The controversy of right ventricular systolic pressure: is it time to abandon the pulmonary artery catheter?

In this issue of *Anaesthesia* there are two papers that contribute to the growing controversy as to whether Doppler echocardiography can be used to diagnose pulmonary hypertension. Cowie et al. [1] and Soliman et al. [2] have sought to determine the role of transoesophageal echocardiography (TOE) in estimating right ventricular systolic pressure (RVSP) and systolic pulmonary artery pressure (sPAP), compared with the gold standard of pulmonary artery catheter measurements.

**History of the controversy**

Doppler echocardiography has been used to estimate sPAP since the early 1980s. Using transthoracic echocardiography (TTE), Skjaerpe and Hatle were the first to demonstrate that the peak velocity of blood flow across a tricuspid regurgitant jet could be used to estimate RVSP [3]. Furthermore, Yock and Popp found a good correlation between the Doppler-derived RVSP and the measurements from direct right heart catheterisation, subsequent studies produced conflicting results [6, 7]. In a recent meta-analysis, Taleb et al. [8] found a wide range of correlations between these two measurements; however, even in the studies with a high degree of correlation, the diagnostic accuracy (defined as the ability to predict sPAP within 10 mmHg of the value measured by right heart catheterisation) was only in the range of 75–78%. While overall Doppler echocardiography is a fairly sensitive indicator of pulmonary hypertension (sensitivity 88%), the specificity is low (56%) [8]. Consequently, most current guidelines recommend that outpatient Doppler echocardiography should be used as a screening tool for pulmonary hypertension, whilst the definitive diagnosis should be reserved for right heart catheterisation [9, 10].

The next reason for the controversy is a question of measures. Traditionally, pulmonary hypertension is defined by a mean pulmonary artery pressure (mPAP) > 25 mmHg. This value is either measured directly during right heart catheterisation or calculated from the peak systolic and diastolic pulmonary artery pressures. The RVSP, however, is an estimation of sPAP and not mPAP. There are several ways of estimating mPAP using echocardiography. Most commonly, mPAP can be assessed by using the peak velocity of a jet of pulmonic insufficiency. This parameter, however, is rarely obtained in clinical practice because most patients do not have sufficient pulmonic insufficiency to allow a complete Doppler envelope. With mixed results, several authors have used other methods of estimating mPAP from Doppler TTE [11–13]. None of these alternative techniques have made it to the mainstream echocardiography laboratory.

The last aspect of this controversy is a problem of semantics. The World Health Organization (WHO) and the American College of Chest Physicians make a clear distinction between pulmonary hypertension and pulmonary arterial hypertension [9, 10]. WHO group 1 pulmonary hypertension, formerly known as primary pulmonary hypertension, is a disease of the pre-capillary pulmonary vasculature resulting in pulmonary arterial hypertension. The diagnosis of pulmonary arterial hypertension requires not only a
mPAP > 25 mmHg, but also a pulmonary capillary wedge pressure or left atrial pressure (LAP) < 15 mmHg, and a pulmonary vascular resistance (PVR) > 3 Wood units. Furthermore, with WHO group 2 pulmonary hypertension, pulmonary artery pressures are elevated due to post-capillary hypertension or pulmonary venous congestion, usually from left-sided disease such as mitral stenosis, mitral regurgitation or left ventricular diastolic failure. The distinction between pulmonary hypertension and pulmonary arterial hypertension is important because although left-sided heart disease is the most common cause of pulmonary hypertension, only pulmonary arterial hypertension will respond to afterload reduction with a pulmonary vasodilator [9]. In other words, an elevated RVSP found by TOE in the operating theatre may represent pulmonary hypertension, but if that pulmonary hypertension is caused by pulmonary venous congestion from severe left-sided disease, then the addition of pulmonary vasodilators would be of little value. Echocardiography yields clues to the presence of left-sided disease and there are echocardiographic means of estimating both LAP [14] and PVR [15, 16]. Recent studies, however, have shown that intra-operative echocardiographic estimates of LAP are not accurate enough to be clinically useful [17, 18]. Consequently, the diagnosis of true pulmonary arterial hypertension cannot be made on the estimation of RVSP alone.

TOE versus TTE

The majority of the previously discussed studies compared Doppler-derived RVSP and right heart catheterisation in outpatients, using TTE. Because of the close proximity of the oesophagus to the heart, the major advantage of TOE is the ability to capture high-resolution images. The disadvantage of TOE, however, is the limited ability to manipulate the angle of the interrogating Doppler beam. This is important for the estimation of RVSP because the accuracy of Doppler echocardiography depends upon a near-parallel alignment of the ultrasound beam and the direction of blood flow being measured. Misalignment of more than 20-30° will lead to gross underestimation of blood flow velocities and pressure gradients.

The advantage of the studies of Cowie et al. [1] and Soliman et al. [2] over prior TTE studies is that the TOE was performed in the operating theatre with simultaneous pulmonary artery catheter readings, while the majority of TTE studies compared measurements that were taken hours and sometimes even days apart [8]. The sPAP is dependent on cardiac output, and the variation in cardiac output over time could easily account for the reported discrepancy between RVSP estimates and direct right heart catheter measurements in these studies.

The calculation of RVSP also depends upon an accurate estimate of right atrial pressure. Echocardiographic estimations of right atrial pressure are often inaccurate [19] and this may account for the majority of the error in RVSP estimation [6]. Cowie et al. [1] and Soliman et al. [2] used direct central venous pressure measurements as their real-time estimate of right atrial pressure. This method avoids the error of right atrial pressure estimation inherent in the prior TTE-based studies.

TOE and RVSP

With simultaneous measurements and accurate estimation of right atrial pressure, it is surprising that these two studies have opposite results. Cowie et al. [1] found that the measurement of RVSP was achievable in 100% of their patients, and that it correlated closely with pulmonary artery catheter-derived parameters of sPAP (r = 0.98). In addition, there was a very narrow limit of agreement (−5 to +5 mmHg) across a wide range of pulmonary pressures. On the other hand, Soliman et al. [2] found that adequate Doppler signals were only acquired in 56% of their patients, and that Doppler-derived measurements were accurate (within 10 mmHg of pulmonary artery catheter measurements of sPAP) only 75% of the time. Part of the discrepancy between these two studies may be explained by different methodological approaches. Cowie et al. [1] measured the correlation between RVSP and sPAP, while Soliman et al. [2] evaluated the accuracy or the ability of RVSP to predict sPAP within 10 mmHg. It is certainly possible that two variables can correlate closely but not agree. An example of this would be the close correlation between systolic blood pressure and mean arterial pressure. These two measures correlate because one is dependent on the other, but their values are different. A similar discrepancy...
between correlation and accuracy has been described in the TTE studies of RVSP reported over the last 40 years [7, 8].

In addition, these two studies had vastly differing success rates in obtaining adequate RVSP estimations (100% vs 56%). Both groups used multiple TOE views to look for optimal alignment of the tricuspid regurgitant jet. Soliman et al. [2] defined an adequate tricuspid regurgitant jet as having < 20° alignment with the Doppler beam, but misalignment was never a cause for exclusion in their study. Instead, the most frequent cause of inadequate Doppler signal was the lack of complete tricuspid regurgitant jet envelope. By definition, this approach automatically excludes patients with trivial tricuspid regurgitation, as the inability to produce a complete Doppler envelope is what distinguishes trivial from mild tricuspid regurgitation. The 56% success rate found by Soliman et al. [2], however, is in close agreement with previous work by Taleb et al. [8], who found that adequate Doppler signals for RVSP estimation could only be obtained in 52% of patients overall. Cowie et al. [1] did not specify how they determined an adequate Doppler tricuspid regurgitant jet signal.

The value of RVSP vs the pulmonary artery catheter

Despite all the controversy surrounding Doppler-derived estimates of RVSP, even those that argue against its accuracy acknowledge that the estimation of RVSP in clinical practice should not be abandoned [7, 20]. Because of the non-invasive nature of TTE, the biggest risk involved in the estimation of RVSP is the risk of misinterpretation. It is for this reason that TTE-derived RVSP is often the only measure of pulmonary artery pressure to which outpatient clinicians have access. Although TOE is certainly more invasive than TTE, its use during cardiac surgery is becoming a part of routine practice. In the operating theatre and in the intensive care unit, TOE measurements of RVSP may be an important screening tool for pulmonary hypertension, particularly if this information is combined with the patient’s history and other echocardiographic findings such as right ventricular hypertrophy and dysfunction, left ventricular diastolic failure, and/or valvular disease. Estimation of sPAP can be confirmed using pulmonary artery acceleration time, a measure of pulmonary haemodynamics that is completely independent of the tricuspid transvalvular gradient and can therefore be calculated in the setting of inadequate tricuspid regurgitation [21].

There are many causes of pulmonary hypertension; however, an elevated RVSP finding during TOE examination does not provide a definitive diagnosis. A patient with an elevated RVSP in the setting of sepsis, may have elevated sPAP due to increased cardiac output that may not represent pulmonary arterial hypertension. A patient with severe mitral regurgitation may have elevated RVSP but mitral valve repair is more likely to improve their pulmonary haemodynamics than an intra-operative administration of pulmonary vasodilators. On the other hand, a patient with idiopathic pulmonary fibrosis may benefit from these therapies because their elevated RVSP represents true pulmonary arterial hypertension. The benefit of the pulmonary artery catheter in these complex patients is that pulmonary artery pressure trends can be monitored during surgery and into the immediate post-operative period.

Conclusions

The placement of a pulmonary artery catheter may not be necessary in patients with normal biventricular function undergoing cardiac surgery. In complex patients, however, with known pulmonary hypertension, severe right or left ventricular dysfunction, or severe valvular disease, the pulmonary artery catheter and the TOE provide complimentary information. Accordingly, both monitoring modalities still hold a valuable place in the cardiac operating theatre.

Competing interests

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N. Silverton
Fellow, Cardiovascular Anesthesia and Intensive Care
M. Meineri
Associate Professor of Anesthesia & Director of Perioperative Echocardiography
G. Djaiani
Associate Professor of Anesthesia & Director of Cardiac Anesthesia Fellowship Research
Toronto General Hospital
University of Toronto
Toronto, Canada
Email: george.djaiani@uhn.ca
The myth of the difficult airway: airway management revisited

For years, anaesthetists have tried to predict the difficult airway using various clinical signs and prediction models. In this issue of Anaesthesia, Norskov et al. present a study of a large cohort of 188 064 patients in Denmark and come to a disappointing conclusion: we are not good at it [1]. Of 3391 difficult intubations, 3154 (93%) were unanticipated. When difficult intubation was anticipated, only 229/929 (25%) had
Ischaemic conditioning: intervening to protect; before, after, and at a distance

First love is a kind of vaccination, which saves a man from catching the complaint the second time

— Honore de Balzac

Safety is part of the business of being a good anaesthetist, and has been a guiding principle for the Association of Anaesthetists of Great Britain and Ireland (AAGBI). Indeed, despite the increasing age and unhealthiness of patients requiring surgery and anaesthesia, the mortality attributable solely to anaesthesia continues to decrease, from a rate of 357 (95% CI 324–394) per million before what might be termed the modern era of anaesthesia, beginning in the 1970s, to a rate of 34 (95% CI 29–39) per million in the 1990s–2000s (p < 0.00001) [1]. Now that we are becoming truly safe, however, we increasingly need to focus on quality of care, and on interventions that alter outcomes outside of the peri-operative period. Our thinking here has been remarkably introspective to date, with little consensus as to how best to judge outcomes following major surgery, and a paucity of large, well-conducted randomised controlled trials (RCTs), compounded by significant heterogeneity, so that even meta-analysis and pooling of data from these studies are difficult. The period over which outcomes are reported, too, is short by the standards of other specialities, in particular those relating to cardiology. It is from there that we need to learn, for it is in that field, too, where a vast burden of future health outcomes will be realised. Cardiovascular disease is still the leading cause of death worldwide, killing more than 17 million people in 2008 [2]. This is of great relevance to us, given the high incidence of undetected and unreported peri-operative myocardial ischaemia in a variety of non-cardiac surgical settings, let alone in cardiac anaesthesia. For example, the CHASE investigators demonstrated an incidence of otherwise undetected myocardial injury in 19% of patients undergoing non-cardiac surgery in whom troponin was measured, with an increased relative risk of death of 2.4 (95% CI 1.3–4.2; p < 0.01) for even ‘minor’ rises in troponin levels, increasing to 4.2 (95% CI 2.1–8.6; p < 0.01) if the rise was 10–100 fold [3].

Preconditioning

What if we within anaesthesia were uniquely placed to do something about that? We have long been at the forefront of resuscitation and optimisation; perhaps by using the tools already available to us, we can profoundly alter our patients’ cardiovascular outcomes. A series of three reviews published in Anaesthesia – the first one in this issue [4] – focuses on ischaemic preconditioning, and examines whether we have the ability and evidence base to do just that. The concept seems simple – a small ‘dose’ of tissue ischaemia, delivered either before, during or after a larger ischaemic...
insult, can protect the heart from that subsequent insult, in essence rather like a vaccination. It may protect not only from the effects of ischaemia, but also from those of reperfusion following therapeutic interventions, which can induce a secondary cardiac injury.

The good news for anaesthetists is that this is an active and promising avenue of investigation, with most trials, unsurprisingly, conducted in the cardiac surgery population. In the first review of the series, Kunst and Klein [4] provide a careful assessment and critique of the underlying mechanisms and cellular pathways involved in so-called ‘anaesthetic preconditioning’, before discussing the clinical evidence available to guide our practice. Many will be familiar with the idea that volatile anaesthetic agents are potentially cardioprotective, following early reports in the 1970s and 1980s, though fewer may be aware that propofol and opioids, our other routine tools, may also confer benefit. What is less certain, however, is the way in which these agents should be used. As ever, it seems to be mostly about dose and timing, and the various experimental models continue to expand our understanding of the basic science that underpins anaesthetic preconditioning. However, uncertainty remains. Preconditioning using volatile anaesthetic agents appears to work less well in animal models of hyperglycaemia and hypercholesterolaemia [5, 6], precisely those situations in which we perceive the greatest peri-operative risk. However, do rabbits and cardiac myocytes adequately model the metabolic syndrome? Do we not need more clinical evidence?

The biggest limitation of most trials is that they recruit patients undergoing elective coronary artery bypass grafting (CABG), who are not representative of most patients undergoing surgery and anaesthesia, even in cardiac anaesthesia! Cardioplegia strategies during cardiopulmonary bypass (CPB) may influence results, as can intermittent cross-clamping during surgery, both of which have ‘preconditioning’ effects. In addition, the low incidence of hard clinical endpoints, such as postoperative death, means that to demonstrate reductions in such outcomes from preconditioning would require very large sample sizes. Virtually all the trials conducted to date are proof-of-concept studies, with widely varying anaesthetic techniques, ‘doses’ of preconditioning and patterns of administration. This includes whether the volatile anaesthetic agent was delivered continuously or interrupted with periods of ‘washout’, which the basic science suggests is important to achieving the protective effect [7]. The use of surrogate markers of outcome, such as elevated troponin levels, is almost universal. Nonetheless, the results of meta-analyses of these studies are generally encouraging, with reductions in markers of harm, including troponin levels and requirements for inotropic support [8]. However, Landoni et al.’s meta-analysis, which included 3642 patients from 38 RCTs, and demonstrated a two-fold increase in mortality in patients undergoing cardiac surgery when anaesthesia was maintained using propofol infusions compared with volatile anaesthetic agents [9], may alarm proponents of total intravenous anaesthesia. The caveats to such meta-analyses are of course well known: the small sample size of the included studies; the heterogeneity of secondary surrogate endpoints; and the variations in technique.

Two large retrospective studies approach the numbers we would expect to be at least hypothesis-generating. In an Italian study of 34 310 patients undergoing CABG, use of volatile anaesthetic agents was associated with a lower 30-day mortality [10]. This appears to be corroborated by a Danish study of 10 535 patients having cardiac surgery, with similarly reduced mortality in the volatile anaesthesia group [11]. These results are encouraging, but we would wish for outcome reporting such as that being suggested for all major surgery. The recent publication of European standards for reporting peri-operative outcomes [12] lays down a challenge to those conducting such studies; mortality data should include follow-up to at least 90 days following surgery, and ideally one year. Pragmatic studies of sufficient size will be essential to allow adoption of the techniques already familiar to anaesthetists.

Postconditioning

The mechanisms and strategies discussed above presuppose that we know that there will be an ischaemic insult, and can prepare our patients for it. However, for a different cohort – those who suffer from acute myocardial infarction – this may not be the case; they too, however, are at risk from both the initial ischaemic burden and the reperfusion injury consequent on
our interventions, e.g. primary percutaneous coronary intervention (PCI) or thrombolysis, aimed at re-establishing blood flow to ischaemic myocardial tissue. What if it was possible to provide protection to this group by ischaemic conditioning, but after the event? This concept is addressed by Jivraj et al. in the second review in the series, with a focus on interventions at the time of PCI [13].

Ischaemic postconditioning involves alternating cycles of cardiac ischaemia and reperfusion, usually by cyclical inflation of balloon catheters within coronary arteries, before reflow of blood following PCI. There is a large body of animal research that is suggestive of benefit, although again with significant variation in the algorithms used and the outcomes measured. There are three key elements to any postconditioning algorithm: the time to the first interruption of reperfusion; the number of cycles of ischaemia; and the duration of ischaemia-reperfusion within each cycle. The idea is promising, as the larger the area of myocardium at risk, the greater the benefit of postconditioning seems to be in reducing infarct size. The difficulty lies in assessing the area at risk in patients presenting acutely, and outside of research studies, as the corollary is that one might exacerbate damage by applying postconditioning protocols if the infarct is small. The clinician also needs to judge the duration of ischaemia: if it has been too short, the injury may be exacerbated by postconditioning techniques, while if the period of index ischaemia was very prolonged, it may make no difference. There is also an increased understanding of the importance of microvascular flow following PCI, with much poorer outcomes in situations of ‘no-reflow’; a postconditioning algorithm has been shown to reduce microvascular obstruction as demonstrated by contrast-enhanced cardiac magnetic resonance imaging [14]. In addition, the patients we most wish to benefit – the old, the sick, those with diabetes, and those taking antiplatelet medications – may not, as a result of alterations in the signal transduction pathways involved in postconditioning caused by those conditions and treatments. This is the conundrum facing enthusiasts, and it will only be addressed by larger RCTs. The DANAMI-3 (NCT01435408) study is aiming to recruit 2000 patients, and will report patient-centred outcomes, including heart failure and cardiovascular death, over a three-year period. Trials such as this may begin to answer the clinically relevant questions at which studies reporting surrogate markers can only hint.

Various pharmacological agents mimic endogenous postconditioning pathways, and may become significant to anaesthetists and intensivists in managing patients following primary PCI. Again, timing and dose are crucial. Candidate drugs include cyclosporine, adenosine and erythropoietin, and large clinical trials currently underway (cyclosporine (CIRCUS; NCT01502774); erythropoietin (EPO-AMI-II (UMIN000005721)) may determine their role in cardiac protection following myocardial infarction and PCI.

Remote conditioning
There is also an alternative (or additive) technique to consider: one that is non-invasive, effective, and free of both cost and side-effects. Remote ischaemic conditioning, using a tourniquet to cause intermittent limb ischaemia, has been widely studied; Sivaraman et al. [15] provide an elegant description of the complex neurohumeral pathways involved in this phenomenon, with the conditioned limb producing small, thermolabile proteins, most likely adenosine, and requiring an intact autonomic nervous system and opioid pathways for the conditioning effect. The fact that it is simple to apply, and can be done before, during or after the initial episode of ischaemia, makes it attractive both to study and to consider for clinical use.

Remote preconditioning, applying the ischaemic stimulus before the insult, has a protocol of three episodes of five-minutes’ cuff inflation-deflation on the upper limb, that is broadly accepted in the literature. Unsurprisingly, it has been assessed in CABG surgery, both on- and off-pump, in major non-cardiac surgery, and before elective PCI. Study design remains a significant confounder, with small sample sizes in single centres, and the use of surrogate endpoints and varying protocols. The technique’s relative ease of use and great promise means that it has been rapidly introduced into clinical practice, often without systematic assessment of the effects and outcomes. As is usual, early proof-of-concept trials were positive, but those with a
more clinical focus have proved disappointing. Length of follow-up is also problematic, with the CRISP trial in elective PCI one of few that reported major adverse cardiovascular and cerebrovascular events (MACCE) at six months and six years [16]. These were lower in the group that underwent remote ischaemic conditioning, and studies like this provide a tantalising hint of the promise that remote conditioning holds. Two large studies hope to build on this. The ERRICA (Effect of Remote Ischaemic pre-Conditioning on clinical outcomes in patients undergoing Coronary Artery bypass graft surgery) (NCT01247545) and RIPHear (Remote Ischaemic Preconditioning for Heart surgery) (NCT01067703) trials are studies with real clinical endpoints of value to patients, as they include truly important considerations of quality of life and exercise tolerance. Likewise, De Hert et al. (NCT01107184) are recruiting 660 patients for a multicentre study comparing a control group having CABG with a study population undergoing remote ischaemic pre-conditioning, remote ischaemic postconditioning, and a combination of both, with the incidence of postoperative atrial fibrillation the primary endpoint. Secondary endpoints include length of ICU and hospital stay, and MACCE. This study may be particularly important, as it introduces a new concept. It is possible that we need to extend our search for benefit from single interventions, to investigating ischaemic conditioning ‘bundles’, as it is almost certain that ‘one size’ will not fit all patients. For example, remote ischaemic conditioning pre-hospital appears to confer real clinical benefit, while if instituted in the cardiac catheterisation laboratory, it currently does not, unless combined with opioids. Will we need to consider remote ischaemic conditioning plus volatile anaesthesia, remote ischaemic conditioning plus high-dose propofol, or other combinations of techniques?

And this may be the nub of the issue – the treatment effect of ischaemic conditioning strategies may not be large, and given the number of confounding variables that reduce it, it may be difficult to dissect out the truly useful manoeuvres, or combinations of them. The size of the clinical problem, however, makes it essential that we do just that, as even a small degree of benefit has the potential to alter outcomes for the better in the many thousands of people who annually suffer the effects of myocardial ischaemia. Maybe we should no longer be thinking of a ‘vaccine’ against injury, but rather, as in other areas of perioperative care, take inspiration from Dave Brailsford’s “aggregation of marginal gains” approach [17]. As a speciality, we have unique access and ability to use the drugs and ischaemic conditioning techniques discussed in this series to alter the outcomes of patients with myocardial ischaemia who are under our care. Our increased understanding of the biological pathways involved, and the ability to use similar tools in other areas of surgery that also carry a risk of ischaemia-reperfusion injury, such as transplantation and neurosurgery, mean that it ought to be the business of all anaesthetists to consider the evidence base, and how it applies to their practice. Trials with clinically-focused endpoints and agreed protocols that are currently underway have the potential to impact on the growing burden of cardiovascular morbidity and mortality, and change our anaesthetic practice.

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A. Vercueil
Consultant in Anaesthesia and Intensive Care Medicine
King’s College Hospital NHS Foundation Trust
King’s Health Partners
London, UK
Email: editor-vercueil@aagbi.org

References
Emergence delirium in children

Emergence delirium was first described in the 1960s [1] and, in the paediatric setting, has been defined as “a disturbance in a child’s awareness or attention to his/her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate post anesthesia period” [2]. This ‘dissociated state of consciousness’ can occur in adults as well as children – sometimes with dramatic effects [3] – but it is much more common in the paediatric population, and so it is on emergence delirium in children that we will concentrate for the rest of this editorial. Emergence delirium is manifest on recovery of consciousness and usually lasts for 5–15 min; the child is typically irritable, uncooperative and inconsolable, with crying, moaning, writhing, kicking and exhibiting generally inappropriate behaviour. Children of pre-school age are most commonly affected and they may not recognise or identify family members or familiar objects. Although usually self-limiting, it causes distress to patients, parents and staff, and may result in physical harm to the child, particularly at the site of surgery, dressings and intravenous cannulae. Agitation and regressive behaviour lasting up to two days has been described [4] and long-term psychological effects remain unknown. The term ‘emergence agitation’ is often used interchangeably with ‘emergence delirium’ but agitation is excessive motor activity, is more common than emergence delirium in the postoperative period.

Cardiac anaesthesia has historically been associated with a higher incidence of unintended awareness compared with other anaesthetic subspecialties [1, 2], but the incidence in modern practice is less certain. The incidence in thoracic anaesthesia is also unclear, mainly because so few studies have addressed this issue at all [3, 4]. The recent publication of the 5th National Audit Project (NAP5) report [5] now provides cardiothoracic anaesthetists with a useful point for reflection on current practice.

The reported incidence of unintended awareness in cardiac practice ranges from less than 1% to over 20%, depending on the definition of awareness, the size of the study and the method of detection (Table 1). The early studies [6–8] included fewer than 60 patients each, so were subject to sampling error, and were carried out during the era of high-dose opioid anaesthesia. The later studies were prospective, used a balanced anaesthesia technique, and included 600-900 patients, finding an incidence of 0.3-1.14% [11–13]. The incidence in the cardiac cohort of a large US multicentre study was similar, at 0.44% [2]. Cardiac anaesthesia was thus associated with a two- to tenfold higher risk of unintended awareness than that reported for the general population [2, 16].

The more recent B-Aware [3], B-Unaware [14] and BAG-RECALL [15] studies specifically recruited patients considered to be at high risk of awareness, so a third to a half of these cohorts were cardiac patients. However, they were not specifically cardiac studies, leading to a relatively small cardiac cohort in B-Unaware (525/1941 patients overall). The incidence of unintended awareness in cardiac patients in these studies varied from

Editorial

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0.1% to 0.8% [3, 14, 15], the lowest incidence occurring with protocolised monitoring of end-tidal agent concentrations [14].

Why is there an almost tenfold variation in the reported incidence of unintended awareness in cardiac cohorts, and is there still a problem in cardiac anaesthesia, given that the lowest rate so far achieved (0.1% [14]) is similar to that in the large general studies [2, 16]? Part of the problem may be sampling error, since the largest dedicated cardiac studies thus far include only one tenth the number of patients of Sandin et al.’s landmark study [16]. Other issues may be a reluctance both to adopt a more balanced anaesthetic technique for cardiac patients, and to use conventional doses of anaesthetic drugs in cardiovascularly fragile patients [17]. In an audit feedback study, Ranta et al. reduced the incidence of unintended awareness during cardiac anaesthesia in their unit from 4% to 1.5%, the main change being more frequent continuous administration of volatile anaesthetic agents [10]. A later study from the same group found that lower doses of midazolam were given to those cardiac patients who had unintended awareness [11]. Regular audit and feedback, within a protocol-guided anaesthetic dosing schedule, may be all that is required to reduce the incidence of awareness in cardiac patients to that seen in the general population.

### Pharmacokinetics of anaesthetic agents on bypass

Causes of unintended awareness during cardiac anaesthesia may include reliance on traditional high-dose opioid techniques [18] in combination with altered pharmacokinetics during cardiopulmonary bypass (including haemodilution, changes in acid-base status, and drug sequestration).

Fentanyl in particular is sequestered on the plastics of the bypass circuit [19] and in the lungs [20], leading to the risk of subtherapeutic analgesia in the context of light anaesthesia. Whilst there is a decrease in total blood concentrations of midazolam and propofol with the onset of bypass, there is a concomitant increase in the free fractions as a result of both haemodilution and a heparin-induced decrease in protein binding. In addition, metabolism and elimination are reduced during the hypothermic phase of bypass [21].

For halogenated volatile anaesthetics, the blood:gas partition coefficients decrease with crystalloid haemodilution and increase with hypothermia [22]. Wash-in and wash-out of volatile agents administered via the oxygenator of the bypass circuit are inversely proportional to blood:gas solubility, so that relatively insoluble agents are more rapidly taken up or eliminated than

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Maintenance technique</th>
<th>Incidence of awareness</th>
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<tr>
<td>Maunuksela (1977) [6]</td>
<td>44</td>
<td>Opioid, N₂O</td>
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<tr>
<td></td>
<td>45</td>
<td>Opioid, droperidol</td>
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<td></td>
<td>42</td>
<td>Halothane</td>
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<td>Kim (1978) [7]</td>
<td>55</td>
<td></td>
<td>9%</td>
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<tr>
<td>Goldman et al. (1987) [8]</td>
<td>30</td>
<td>Fentanyl, ± N₂O, ± halothane</td>
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<td>Robinson et al. (1987) [9]</td>
<td>100</td>
<td>Fentanyl, lorazepam, ± isoflurane</td>
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<td>Ranta et al. (1996) [10]</td>
<td>99</td>
<td>Various</td>
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<td></td>
<td>204</td>
<td>Various</td>
<td>1.5%</td>
</tr>
<tr>
<td>Ranta et al. (2002) [11]</td>
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<td>Phillips et al. (1993) [12]</td>
<td>700</td>
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<td>Dowd et al. (1998) [13]</td>
<td>608</td>
<td>Fentanyl, midazolam, isoflurane, propofol</td>
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<td>Sebel et al. (2004) [2]</td>
<td>605</td>
<td>Unspecified</td>
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<td>Balanced volatile, ETAC monitored</td>
<td>0.1%</td>
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<tr>
<td></td>
<td>1004</td>
<td>Balanced volatile, BIS monitored</td>
<td>0.5%</td>
</tr>
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BIS, bispectral index; ETAC, end-tidal anaesthetic concentration.

Table 1 Incidence of definite unintended awareness in studies of cardiac anaesthesia.
more soluble agents [21]. The wash-in of isoflurane has an initial rapid phase if there is no isoflurane present in the circulation, with a much slower late phase, and the wash-out half-life is around 13-19 min [22, 23]. Blood concentrations of isoflurane are around a half to a third of vaporiser settings [24]. Increasing oxygenator sweep gas flow increases the uptake of volatile anaesthetics, whilst changes in pump flow rate have no effect on uptake [21]. However, uptake of volatile anaesthetics is virtually non-existent with the newer ‘plasma-tight’ polymethylpentane (PMP) membranes (designed to reduce microbubble formation, blood trauma and plasma leakage), compared with polypropylene [25]. When oxygenators with PMP membranes are used, it is important to ensure that blood concentrations of volatile anaesthetics are adequate before going on bypass, since monitoring of exhaust gas concentrations does not reflect blood concentrations [24, 25].

In summary, for propofol, midazolam, and isoflurane, the effects of mild hypothermia and haemodilution at the onset of bypass tend to cancel each other out. With the increasing trend towards ‘fast-track’ management, and balanced anaesthetic techniques with moderate doses of fentanyl (or other opioid) for cardiac surgery, the use of high-dose opioid-only anaesthesia has waned. So, where does that leave us?

**Impact of NAP5**

The estimated incidence of spontaneous reports of awareness in the UK in the NAP5 study was 1:15 000 in the baseline survey [26] and 1:19 000 in the main study [5], remarkably less than in the formal studies with a Brice interview [2, 16]. The possible reasons for this have been addressed elsewhere [27, 28], and it is important to stress that NAP5 does not provide a definitive incidence of unintended awareness during cardiothoracic anaesthesia. The NAP5 project received five or four spontaneous reports of unintended awareness during cardiac anaesthesia, depending on whether one reads Chapter 11 or Chapter 14, and four reports during thoracic anaesthesia (Table 2). However, only two of the four cardiac reports originated during the primary surgical procedure, with one of these having occurred quite a few years previously. One case occurred during re-operation for bleeding, and one case in a child in the catheter laboratory; this latter case could arguably be classified as paediatric or cardiological, rather than cardiac surgical.

The situations causing unintended awareness during cardiothoracic anaesthesia were similar to those in the general population, with the majority occurring at induction. The thoracic cases were qualitatively different to the cardiac ones (Table 2), in that the cardiac cases were mainly due to (deliberately?) light anaesthesia, while the thoracic cases were mainly cognitive or technical failures of anaesthetic delivery. The overall incidence of reports of 1:8600 for cardiothoracic practice is similar to the 1:8200 incidence when neuromuscular blocking drugs are used, perhaps indicating a similar root cause. Co-morbidity is high in both cardiac and thoracic practice, leading to reluctance to use conventional doses of the primary anaesthetic agent, although there were no episodes of awareness specifically linked to the cardiothoracic procedure (e.g. during cardiopulmonary bypass).

**Table 2** Reports of awareness in cardiothoracic practice from the NAP5 report.

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Thoracic</th>
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<tbody>
<tr>
<td>Light anaesthesia at induction</td>
<td>Failure to turn on vaporiser – induction</td>
</tr>
<tr>
<td>Pre-bypass – light anaesthesia</td>
<td>Failure to turn on vaporiser – maintenance</td>
</tr>
<tr>
<td>Re-operation – light anaesthesia</td>
<td>Tissed cannula during total intravenous anaesthesia for bronchoscopy</td>
</tr>
<tr>
<td>Catheter study (child) – light anaesthesia</td>
<td>Inadequate reversal of neuromuscular blockade</td>
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**Depth of anaesthesia monitoring**

The National Institute for Health and Care Excellence (NICE) has suggested the use of depth of anaesthesia monitoring, particularly bispectral index (BIS), where there is a high risk of unintended awareness [29]. Though the definition of ‘high risk’ remains unclear, the increased incidence of awareness in cardiothoracic anaesthetic practice suggests that this is a risk category. A potential problem in cardiac anaesthesia is that the electrodes used for depth of anaesthesia monitoring...
will often compete for space with the near-infrared spectroscopy devices that are also increasingly used, suggesting a potential market for an integrated monitor. Using a depth of anaesthesia monitor may be useful during rigid bronchoscopy [30], and may be the only feedback of adequacy of anaesthesia during cardiopulmonary bypass. However, the impact of BIS monitoring in cardiac practice is variable, with a reduction in unintended awareness in cardiac patients in B-Aware [3], no effect in B-Unaware [14], and a higher incidence in the monitored group in BAG-RECALL [15]. Part of the problem could be that BIS varies widely during fentanyl-midazolam anaesthesia, which is commonly used for cardiac patients, and may be unreliable with this drug combination [31].

On the other hand, cardiothoracic may be the most appropriate specialty for evaluating depth of anaesthesia monitors. Patients with multiple co-morbidities may be compromised by the side-effects of excessive administration of anaesthetic agents. Conversely, abnormal cardiovascular physiology provides an unreliable surrogate for assessing adequate depth of anaesthesia. Anaesthetic requirements also differ before, during and after bypass. A lower concentration of isoflurane is required to maintain a BIS of 40-50 during mild hypothermic bypass with fentanyl than in the pre-bypass period [32, 33]. In addition, BIS is higher in normothermic patients than during mild hypothermia at 32°C [34]. These studies suggest that standard cardiac anaesthetic recipes may err on the light side for the current trend of ‘tepid’ bypass, particularly during the re-warming phase at the end of bypass. On the grounds of the risk of both underdosing and overdosing anaesthetic agents, perhaps there should be more habitual use of depth of anaesthesia monitoring in cardiothoracic cases.

Back to the future
Cardiothoracic patients remain at risk of light anaesthesia, compounded by the potential for distraction in a complex surgical setting. The risk in cardiac anaesthesia is mainly in the pre-bypass period, which might be minimised by normalisation of practice to balanced anaesthesia techniques.

While the findings of NAP5 are instructive, there are too few reports of unintended awareness during either cardiac or thoracic anaesthesia for us to be confident that we have a robust incidence of awareness during the primary procedure in either subspecialty, a point made in the cardiothoracic chapter of the NAP5 report. This is important to cardiothoracic patients and their anaesthetists, because of the persisting historical perception that cardiac anaesthesia in particular constitutes a high risk for unintended awareness. We suggest that a prospective subspecialty project be undertaken to evaluate the incidence of both spontaneously reported and Brice-elicited awareness in cardiothoracic practice.

Competing interests
DS was NAP5 Moderator (independent of the NAP5 Project Team and Review Panel), and a Specialist Committee member for the NICE diagnostic guidance document on depth of anaesthesia monitoring.

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D. Smith
Consultant in Cardiac Anaesthesia
Email: david.smith@uhs.nhs.uk

N. G. Goddard
Clinical Fellow in Cardiothoracic Anaesthesia
University Hospital Southampton
NHS Foundation Trust
Southampton, UK
Email: david.smith@uhs.nhs.uk

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Stroke volume optimisation: is the fairy tale over?

Advanced haemodynamic monitoring is espoused as a means to achieve optimisation of cardiac stroke volume during surgery. It is believed that individuals are ‘normovolaemic’ when their stroke volume is at the plateau of the Frank-Starling curve in the supine position [1]. This definition by Truijen et al. appears reasonable since when stroke volume is thus located in awake subjects, cardiac output and oxygen delivery are such that maximal venous oxygen saturation is established [2]. Since the curve is flat here, an increase in preload will not increase stroke volume. According to the same model, patients are hypovolaemic when their stroke volume is on the steeper, ascending leftward part of the Frank-Starling curve. Proponents of goal-directed therapy believe it is possible to exploit this clinically with a fluid challenge: a minimal response suggests that stroke volume is on the plateau. The terminology used to describe goal-directed therapy in the literature is inconsistent and confusing [4]. For the purposes of this editorial, we use the term ‘stroke volume optimisation’ to indicate simple interventions with fluid and/or vasopressors to maintain stroke volume; ‘goal-directed therapy’ is a broader term that encompasses stroke volume optimisation as well as a wide variety of therapies aimed at increasing global oxygen delivery.

The stroke volume optimisation paradigm is as follows. Metabolic demands of surgery create a growing oxygen demand that drives an increasing cardiac output requirement, and conventional haemodynamic signs fail to reveal the deficit [5]. In the absence of adequate peri-operative fluid loading, occult hypovolaemia results: a circulating volume deficit of as little as 10% may lead to splanchnic vasoconstriction and reduced oxygen delivery [6]. Accordingly, intestinal complications are amongst the most common after major surgery [7].

Minimally invasive technology is therefore used continuously throughout surgery to monitor for any deficit in functional circulating volume. Most ‘flow based’ monitors derive stroke volume: some use the pulse power or contour of the arterial waveform, others use Doppler ultrasound to measure blood velocity in the descending thoracic aorta. Algorithms incorporating fluid challenges are used to maintain stroke volume throughout, thereby providing incremental benefit through the avoidance of postoperative oxygen debt.

All the early fluid responsiveness studies were positive: protocol patients had substantially better outcomes than controls [5, 8–11], even though the primary intervention differentiating the groups appeared to be marginal: the infusion of about 500 ml colloid during surgery, with no postoperative intervention at all. Endorsement of this technology by the National Institute for Health and Care Excellence (NICE) on the basis of this initial evidence base may have been premature [12, 13].

Contemporary surgical outcomes have been improved by the systematic delivery of peri-operative care known as ‘enhanced recovery’
Provenance and Peer Review
This editorial was commissioned for publication and peer reviewed.

The association of the ‘newer’ respiratory arterial waveform variation parameters to diagnose fluid responsiveness has been rather more rigorously quantified [3]. Where the pulse pressure variability signal is concerned, there is a ‘grey’ zone, in other words a range of values (9–13%) within which we cannot be certain whether an individual patient will be fluid responsive or not. This is seen in around 25% of patients receiving mechanical ventilation under general anaesthesia before major surgery [28]. It appears also that the concordance between different monitors when used to measure stroke volume in anaesthetised adult patients is rather modest [29].
Limitations

However, there are several important caveats to consider when appraising Godfrey et al.’s paper [23]. First, it does not refute that one might see an stroke volume improvement > 10% in hypovolaemic patients. It is likely that participants in earlier studies of goal-directed therapy in colorectal, cardiac and orthopaedic trauma surgery were relatively hypovolaemic at the time of induction of anaesthesia – so current evidence supports stroke volume optimisation in such patients. In acutely ill patients with the potentially disordered haemodynamics and ‘leaky capillaries’ of a systemic inflammatory response, cardiac output measurement to judge fluid resuscitation remains an attractive proposition. In individual patients who are at risk of major intra-operative haemorrhage, it is reassuring to have access to flow-based monitoring. However, evidence is scarce in these settings due to methodological difficulties.

Second, most current stroke volume optimisation algorithms incorporate parameters such as central venous pressure or corrected flow time to show that the intravascular volume is replete, and to help the user avoid fluid excess. No such stopping thresholds are tested in Godfrey et al’s experiment.

Third, it is not clear how much can be inferred about haemodynamic physiology in anaesthetised patients receiving intermittent positive pressure ventilation from a study conducted on awake volunteers. The authors make the intriguing point that most patients having major surgery are allowed to wake at the conclusion of surgery, and that fluid therapy should be aimed at having them in the normovolaemic state when they do so.

Finally, Godfrey et al’s work does not actually tell us whether passive leg raise increases stroke volume in normovolaemic patients. The difference between mean baseline and mean peak stroke volume is not statistically significant so it remains possible that the apparent increase seen was due to the play of chance.

The authors emphasise, though, that five of 11 subjects had an stroke volume response > 10%, and suggest that such a response to fluid challenge intra-operatively would prompt an unnecessary further bolus. However, preload was not the sole cardiovascular variable that changed. The statistically significant increase in heart rate and cardiac index seen, uncoupled from the stroke volume, suggests that the leg raise manoeuvre may not be a suitable experimental model for an isolated increase in preload. The act of lifting a conscious patient’s legs is likely to trigger at least some contribution from adrenergic pathways, with potential changes in vasomotor tone, venous capacitance and cardiac contractility, none of which were directly measured but all of which may also have an effect on stroke volume. It is striking that previous physiology studies [30, 31] are at odds with Godfrey et al.’s observation, and instead show that under normovolaemic conditions, stroke volume does not increase in response to fluid.

In truth, all we can reasonably conclude is that intra-operative haemodynamics are complex. The notion that we are manipulating a static Starling curve is almost certainly an oversimplification. Such pure manipulation of stroke volume is extremely difficult to achieve in vivo. Frank’s original observations on the relationship between diastolic filling and the strength of ventricular contraction were made in an isolated, denervated frog heart [32]. Individual patients in fact have not one but two ventricles, moving serially between a family of ventricular function curves (Fig. 1) – depending on cardiac contractility and afterload [33]. If the passive leg raise manoeuvre transfers the awake subject on to a more ‘dynamic’

![Figure 1](https://example.com/figure1.png)

**Figure 1** A family of Frank-Starling curves (‘Sarnoff curves’), showing simultaneously obtained left and right ventricular function curves (adapted and redrawn from Sarnoff et al. [33]).
Starling curve then the stroke volume for a given preload will increase – but this is not ‘fluid responsiveness.’ Of course, the same applies during surgery. Painful stimuli, endogenous catecholamine levels, vasodilatory effects of neurexin blockade and anaesthesia and tissue oxygen demand may vary considerably, such that it is difficult to be sure what the optimum stroke volume is at a particular moment.

Find the hidden meaning
There are no large randomised controlled trials investigating the clinical effectiveness of individualised intra-operative fluid therapy to improve outcomes, but many small efficacy studies. The most current Cochrane meta-analysis includes 31 studies comprising 5292 participants. Systematic reviews of the literature consistently support goal-directed therapy [16, 34–36]; however, all these meta-analyses combine evidence from a multiplicity of settings. Fluid therapy is delivered with or without inotropes, pre-, intra- and postoperatively, to patients with and without co-morbidities and guided by an array of different advanced haemodynamic monitors. When interpreting this literature, it is important to appreciate the distinction between these two clinical questions:

- In genuinely high-risk patients, do interventions to increase global oxygen delivery during the peri-operative period (goal-directed therapy) produce clinical benefit?
- For all patients having major surgery, is the use of additional monitoring to measure fluid responsiveness beneficial? – i.e. does stroke volume optimisation work?

Evidence for goal-directed therapy shouldn’t be extrapolated to answer questions about stroke volume optimisation. To illustrate this, consider that in the landmark trial by Shoemaker et al., the first to target supranormal oxygen delivery in surgical patients, only 101 of 2086 screened (4.8%) were considered sufficiently high-risk to be included in the study [37]. Further, this work was based on measurement and targeting of supranormal values of oxygen delivery and cardiac index for around 48 hours after surgery, while minimally invasive devices derive stroke volume rather than directly measuring it. Even then, stroke volume is a surrogate – in the real world theatre environment, we hope that our haemodynamic interventions will optimise oxygen delivery but we make no direct measurement of tissue perfusion or oxygen utilisation. Algorithms guide fluid (including transfusion), vasopressor and possibly inotropic therapy, but these haemodynamic therapies all interact with one another in complex ways.

The definitive Cochrane review on peri-operative goal-directed therapy [36] reports several secondary outcomes. From subgroup analyses it is possible to pick out six randomised controlled intra-operative stroke volume optimisation trials, comprising 573 patients. Stroke volume optimisation is clearly associated with a reduction in the number of patients with complications, but – as previously discussed – most of these studies were not conducted within enhanced recovery pathways.

Not too much or too little, but just right
Is it time to tailor our approach to this differently? We and others [13, 20, 22, 38] have previously suggested that stroke volume optimisation provides no marginal benefit for aerobically fit patients having elective surgery within a contemporary enhanced recovery pathway. However, it is possible that the fidelity of the underlying algorithm has been wrong. The relationship between ‘fluid responsiveness’ and stroke volume derived by an advanced haemodynamic monitor could be more precisely elucidated with further translational studies: if we are to achieve bespoke fluid therapy then we need to be confident that the monitors can adequately characterise functional circulating volume for the individual. Then suitable algorithms need to be tested in adequately powered trials to investigate whether they achieve a better clinical outcome than ‘standard’ practice in the setting of contemporary surgery. The frog may yet turn back into a prince, but at this point in time the happy ending seems a long way away.

Competing interests
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G. Minto
R. Struthers
Consultant Anaesthetists & Honorary Senior Lecturers
Plymouth Hospitals NHS Trust
Plymouth, UK
Email: gary.minto@nhs.net
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Airway management – ‘spinning silk from cocoons’
(抽丝剥茧 – Chinese idiom)

Ultrasound technology is evolving rapidly. It is relatively non-invasive and harmless, and is becoming more accessible as costs decrease and once cumbersome devices become more portable and user-friendly. It has now infiltrated many aspects of peri-operative anaesthesia practice. From monitoring of cardiac function to vascular cannulation and regional anaesthesia, it has become a core component of many postgraduate training programs. In this issue of Anaesthesia, Hui and Tsui [1] have shown that the inability to detect the hyoid bone by ultrasound with a probe on the floor of the mouth often indicates difficult laryngoscopy. The authors have, therefore, proposed another possible bedside airway assessment test. Could yet another innovative use of ultrasound improve airway management?

Their study confirms previous work by Riley and colleagues [2], who performed cephalometric analysis showing that a long hyo-mandibular distance is associated with obstructive sleep apnoea because if the hyoid is unusually low in the neck, a large portion of the tongue mass lies in the hypopharynx rather than in the oral cavity [3, 4]. Similarly, difficult laryngoscopy has also been shown to occur in patients with an increased submandible angle [5], probably due to difficulty in displacing a large hypopharyngeal tongue.

Chou and Wu [6] have stated that “Basic geometric principles show that... a caudal larynx... necessitate(s) a greater degree of tongue displacement. If the submandibular tissue compliance is sufficient to compensate for these unfavourable factors, tongue displacement is not difficult; otherwise, difficulty may be anticipated.” They postulated that a short mandibular ramus, obtuse mandibular angle and caudal hyoid causes a ‘hypopharyngeal tongue’ [6, 7]. Such displacement from the normal position of the tongue may create significant difficulties in laryngoscopy.

How a hypopharyngeal tongue causes difficult direct laryngoscopy may be explained by the work of Charters and colleagues [8, 9]. During laryngoscopy, the tip of the Macintosh blade should be in the vallecula and, therefore, behind the hyoid. In this position, the tip lifts the hyoid, stretches the hyoepiglottic ligament and, in turn, lifts the epiglottis. However, the curvature of the blade may make optimal placement of the tip difficult [10]. In a small study of patients with difficult laryngoscopy scores, the blade tip “did not come near the hyoid even though it was obviously far enough down to do so”. This failure to elevate the epiglottis during laryngoscopy refocuses our attention on the need to control the base of the tongue with the blade’s tip [11].

Videolaryngoscopes, including the C-MAC® (Karl Storz, Tuttlingen, Germany) and GlideScope®...
Capabilities of a mobile extracorporeal membrane oxygenation service for severe respiratory failure delivered by intensive care specialists*

P. B. Sherren,¹ S. J. Shepherd,¹ G. W. Glover,² C. I. S. Meadows,² C. Langrish,² N. Ioannou,² D. Wyncoll,² K. Daly,³ N. Gooby,⁴ N. Agnew⁴ and N. A. Barrett²

1 Specialist Trainee, 2 Consultant, 3 Consultant Nurse, Department of Critical Care, 4 Clinical Perfusionist, Department of Clinical Perfusion, St. Thomas’ Hospital, London, UK

Summary
We conducted a single-centre observational study of retrievals for severe respiratory failure over 12 months. Our intensivist-delivered retrieval service has mobile extracorporeal membrane oxygenation capabilities. Sixty patients were analysed: 34 (57%) were female and the mean (SD) age was 44.1 (13.6) years. The mean (SD) PaO₂/FIO₂ ratio at referral was 10.2 (4.1) kPa and median (IQR [range]) Murray score was 3.25 (3.0–3.5 [1.5–4.0]). Forty-eight patients (80%) required veno-venous extracorporeal membrane oxygenation at the referring centre. There were no cannulation or extracorporeal membrane oxygenation-related complications. The median (IQR [range]) retrieval distance was 47.2 (14.9–77.0 [2.3–342.0]) miles. There were no major adverse events during retrieval. Thirty-seven patients (77%) who received extracorporeal membrane oxygenation survived to discharge from the intensive care unit and 36 patients (75%) were alive after six months. Senior intensivist-initiated and delivered mobile extracorporeal membrane oxygenation is safe and associated with a high incidence of survival.

Correspondence to: G. W. Glover
Email: guyglover@doctors.org.uk
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Introduction
Despite a wide variety of available technologies to support patients with acute respiratory distress syndrome (ARDS), mortality remains high [1]. The use of lung-protective ventilation, early neuromuscular blockade, mechanical ventilation of the lungs in the prone position, conservative fluid strategies and low-dose corticosteroids have all been shown to improve outcomes in patients with ARDS [2–7]. Beyond these therapies, the use of extracorporeal membrane oxygenation (ECMO) has shown promising results in patients with severe respiratory failure [8–13], while other rescue therapies such as high-frequency oscillatory mechanical ventilation and inhaled nitric oxide have shown no demonstrable mortality benefit [14–17]. In England, five severe respiratory failure centres have been commissioned to deliver complex respiratory support, including ECMO. Transfer to an ECMO-capable
severe respiratory failure centre is associated with improvement in disability-free survival in adult patients with potentially reversible pathology [8, 9].

The centralisation of ECMO services may improve patient outcomes, but it presents a significant logistical challenge. The secondary inter-hospital transfer of severely hypoxaemic and hypercarbic patients is not without risk, and mobile ECMO during retrieval is only indicated in a select group of patients [18–20]. Although the use of mobile ECMO is well established, the ideal composition of the retrieval team remains unclear. The majority of retrieval services and trials to date include surgeons and a large multidisciplinary team [18–20].

There is a lack of literature regarding the feasibility and safety of senior intensivist-only initiated and delivered mobile ECMO. We describe the characteristics, logistics and outcomes of patients transferred by a team with mobile ECMO capabilities led by a senior intensivist (non-surgeon) for patients with severe respiratory failure.

Methods
The need for ethical approval was waived by our institutional review board, patients’ data were anonymised and formal consent was not deemed necessary. This is a retrospective, observational study of our nationally commissioned quaternary severe respiratory failure service, which is part of a 78-bed critical care department. The service can accommodate up to six patients receiving ECMO at any one time, and primarily accepts referrals from South East England. During times of increased demand, referrals and transfers from the rest of England are also undertaken. To facilitate safe transfer from the referring hospital, our institution operates a consultant-delivered retrieval service with mobile ECMO capabilities. The retrieval team comprises a consultant intensivist, ECMO specialist nurse and perfusionist. All consultant intensivists covering the retrieval service have joint accreditation in anaesthesia and intensive care medicine.

Indications for referral to St. Thomas’ hospital’s severe respiratory failure service are in keeping with those in the CESAR trial [8] and UK national recommendations for referral to a specialist ECMO centre. Referral is recommended for patients with potentially reversible disease and refractory severe respiratory failure, where respiratory failure is defined as: hypoxaemia with a PaO2/FIO2 ratio < 13.3 kPa; uncompensated hypercarbia with pH < 7.20 despite optimal conventional treatment; inability to maintain lung-protective mechanical ventilation; or a Murray score of 3 or more [21]. The Murray score ranges from 0 to 4, and is composed of four variables including PaO2/FIO2 ratio, positive end-expiratory pressure (PEEP), compliance and chest radiograph quadrant infiltrates [21]. Relative exclusion criteria for ECMO include: mechanical ventilation of the lungs > seven days with either peak inspiratory pressure > 30 cmH2O or FIO2 > 0.8; signs of intracranial bleeding; other contraindication to limited heparinisation; or any contraindication to continuation of active treatment.

Following assessment at the referral hospital by the retrieval team, a process of on-site optimisation is attempted. In addition to continuous neuromuscular blockade and addressing underlying pathology, a number of mechanical ventilatory strategies may be attempted, including: recruitment manoeuvres; reverse inspired:expired ratio; optimised PEEP; prone positioning; and a variety of mechanical ventilation modes. If an appropriate response, in terms of oxygenation and lung-protective mechanical ventilation, cannot be achieved with the above measures, and there are no contraindications, veno-venous ECMO is initiated at the referring site to facilitate safe transfer. The patients’ femoral vessels are usually cannulated in the operating theatre of the referring hospital, guided by ultrasound, echocardiography and fluoroscopy. We usually use a 25-F multi-stage cannula and a 23-F single-stage return cannula (BioMedicus, Medtronic Inc, Minneapolis, USA). Although jugular-femoral cannulation is occasionally undertaken if necessary, it is our opinion that bi-femoral cannulation offers logistical advantages for insertion and retrieval. Bi-femoral cannulation allows rapid single-site cannulation and secure anchorage of the cannulae and circuit to the legs, and minimises the risk of a long circuit becoming displaced during transport as our ECMO pump sits below the patient’s feet on the retrieval stretcher. Occasionally, we may use a 27–31-F dual-lumen Avalon cannula (Maquet, Rastatt, Germany) if there are venous access issues in the groin. The ECMO pump, regardless of cannulation site, is a Maquet
Cardiohelp (Maquet, Rastatt, Germany). The retrieval team uses a bespoke trolley, specifically designed for the requirements of inter-hospital transport of the patient with severe respiratory failure, including ECMO.

All patients retrieved by the service between February 2013 and January 2014 were identified. Patients were not studied if, on review at the referring hospital, they were deemed not for escalation of therapy, they had died before the arrival of the retrieval team, or they had incomplete datasets. Patients were identified from a locally developed and prospectively completed database. This database and the electronic patient record were used to extract data related to referral, retrieval and critical care, including any adverse events.

Patients were compared using the means of continuous variables and a permutation test version of a two-sample t-test; discrete data were analysed using Fisher’s exact test. Analysis of data was performed using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and program R (R Foundation for Statistical Computing, Vienna, Austria).

Results
During the study period, 152 patients were referred to our service. Forty-eight patients (32%) were deemed inappropriate for escalation of therapy and 33 (22%) improved after advice from our team. Of the remaining 71 patients (47%), three were transferred to another centre because of lack of capacity, one was an internal referral, two died before the arrival of the retrieval team, and three were assessed at the referring centre and deemed inappropriate for escalation of therapy. Due to incomplete datasets, two further patients were not studied, leaving 60 patients (39%) available for analysis (Fig. 1).

Patients’ characteristics are presented in Table 1. The commonest causes of respiratory failure were community acquired pneumonia and viral pneumonitis (Table 2). Only ten (17%) patients were receiving lung-protective ventilation according to criteria [2] at the time of referral. Other therapies already in place at the time of referral included: neuromuscular blockers administered in 47 (78%) patients; eight (13%) patients were in the prone position; two (3%) were receiving high-frequency oscillatory ventilation; three (5%) were receiving inhaled nitric oxide; and 41 (68%) were receiving vasopressors or inotropes. At the time of referral, 11 (18%) patients were receiving renal replacement therapy.

Twelve patients (20%) responded to optimisation by the retrieval team, with significant improvements in PaO₂ and PaO₂/FIO₂ ratio (Table 3). All these patients were safely transported while receiving conventional mechanical ventilation of the lungs. The remaining 48 patients (80%) required veno-venous ECMO before transportation. Of these, 35 (73%) received a bolus of unfractionated heparin bolus before cannulation with a median (IQR [range]) dose of 2500 (2500–3500 [500–5000]) IU. Activated clotting times post-heparin were documented in nine patients before initiation of ECMO and the median (IQR [range]) time was 222 (192–240 [156–250]) s. There were no cannulation failures or immediate bleeding complications; 41 patients (85%) had bi-femoral venous cannulation; five (10%) femoral-jugular; and two (4%) dual-lumen jugular. One patient died following arrival of the retrieval team after starting ECMO at the referring hospital. This patient had established multi-organ failure with multiple cardiac arrests that failed to improve, and was not deemed appropriate to escalate to veno-arterial ECMO. One patient’s return cannula was advanced further into the right atrium following ECMO initiation as the tip was in close proximity to the drainage cannula, resulting in blood recirculation and failure to oxygenate. There was no other significant cannulation or ECMO-related complications. Mean (SD) pump blood flow and sweep gas flow during transport were 4.5 (0.7) and 4.4 (1.7) Lmin⁻¹, respectively.

The median (IQR [range]) retrieval distance was 47.2 (14.9–77.0 [2.3–342.0]) miles and 58 patients were retrieved by road. Only one patient required retrieval by a fixed-wing aircraft. The mean (SD) time from referral to arrival back at our institution was 571 (207) min. There were no serious adverse medical, monitoring or technical events during the retrieval of the remaining 59 patients. Eighteen patients (31%) suffered at least one minor adverse event. These minor adverse events were transient and included: 14 cases of arterial oxygen desaturation < 88%; seven with systolic blood pressure < 80 mmHg; and two non-malignant arrhythmias. The mean (SD) lowest arterial oxygen saturation and systolic blood pressure were 91 (6) % and 105 (19) mmHg, respectively.
On arrival back at our centre, the median (IQR [range]) Acute Physiology And Chronic Health Evaluation (APACHE) II and maximum Sequential Organ Failure Assessment (SOFA) scores were 17 (14–21 [8–31]) and 12 (9–15 [5–20]), respectively. After transfer on ECMO, there were significant improvements in PaO₂/FIO₂ ratio, ventilator FIO₂, plateau mechanical ventilation pressure, pH and arterial PCO₂ (Table 3). Compared with before starting ECMO, once it had been started there was no difference in the number of patients receiving noradrenaline (31 vs 35 patients, respectively, \( p = 0.51 \)) or the mean (SD) infusion dose (0.38 (0.39) vs 0.41 (0.41) \( \mu g.kg^{-1}.min^{-1} \), respectively, \( p = 0.76 \)). Infusions of adrenaline in one patient, dobutamine in one patient and vasopressin in three patients were weaned off after starting ECMO. Milrinone was continued in one patient and started in two others, while three other patients had levosimendan started after initiation of ECMO.

The mean (SD) duration on ECMO, requiring mechanical ventilation of the lungs, and critical care stay were 12.9 (22.0) days, 17.6 (20.3) days and 20.9 (20.6) days, respectively. Six patients (12.7%) suffered an intracerebral haemorrhage, detected by routine admission CT scan. The majority were minor but one patient died as a result of a severe intracerebral haemorrhage.
Thirty-seven patients (77%) who received ECMO and nine patients (75%) retrieved conventionally survived to discharge from critical care. Thirty-six patients (75%) who were initiated and retrieved on ECMO were alive at six months.

**Discussion**

This study describes the activity and outcomes of an intensivist-delivered retrieval service with mobile ECMO capabilities. Despite the lack of surgical involvement common to other studies [18–20], there were no cannulation failures or significant ECMO complications. There were also no major adverse events during transfer. We have also shown a high survival rate in patients who received ECMO – this exceeds those seen in an earlier randomised prospective trial and the CESAR trial [8, 23], and is similar to that seen in more recent studies [18–20]. The use of newer veno-venous circuits, oxygenators and centrifugal pumps, and the improved biocompatibility and systemic anticoagulation requirements of heparin-bonded circuits, may go some way to explain these differences [24, 25].

Twelve patients (20%) reviewed by the retrieval team responded to on-site optimisation and did not require ECMO immediately. These patients were safely transferred while receiving conventional mechanical ventilation of the lungs and had a survival to discharge comparable to those retrieved on ECMO. Despite the clear benefits of lung-protective mechanical ventilation [2], intensive care units consistently fail to deliver this intervention [26]. At referral, only a small proportion of patients were receiving lung-protective ventilation. The inability to provide lung-protective ventilation in these patients with significant lung injury scores, hypoxaemia and hypercarbia is likely to represent a failure of conventional mechanical ventilation rather than simply bad practice. The value of using the published lung-protective ventilation cut-offs [2] could be questioned, and there is an increasing awareness of the importance of limiting plateau pressures well below 30 cmH2O, and using ultra-protective mechanical ventilation of the lungs to limit lung injury and biotrauma [27, 28].

**Table 1** Patients’ characteristics at referral and on arrival back at ECMO centre (n = 60). Values are mean (SD), number (proportion) or median (IQR [range]).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>44.1 (13.6)</td>
</tr>
<tr>
<td>Women</td>
<td>34 (57%)</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>83.9 (23.2)</td>
</tr>
<tr>
<td>Body mass index; kg.m⁻²</td>
<td>29.4 (7.7)</td>
</tr>
<tr>
<td>Murray score</td>
<td>3.25 (3.0–3.5 [1.5–4.0])</td>
</tr>
<tr>
<td>Berlin definition [22] of ARDS, PaO₂/FO₂ ratio</td>
<td>Moderate, 13.3–25.7 kPa 5 (8%)</td>
</tr>
<tr>
<td>Duration of tracheal intubation at referral; days</td>
<td>1.7 (0.8–4.0 [0.25–14.5])</td>
</tr>
<tr>
<td>PaO₂/FO₂ ratio; kPa</td>
<td>10.2 (4.1)</td>
</tr>
<tr>
<td>FO₂</td>
<td>1.0 (0.9–1.0 [0.5–1.0])</td>
</tr>
<tr>
<td>Plateau pressure; cmH₂O</td>
<td>32.8 (5.7)</td>
</tr>
<tr>
<td>PEEP; cmH₂O</td>
<td>11.7 (4.6)</td>
</tr>
<tr>
<td>pH</td>
<td>7.14 (0.16)</td>
</tr>
<tr>
<td>PaCO₂; kPa</td>
<td>10.5 (4.4)</td>
</tr>
<tr>
<td>Mechanical ventilatory support</td>
<td></td>
</tr>
<tr>
<td>Prone positioning</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>High-frequency oscillatory ventilation</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Airway pressure release ventilation</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Neuromuscular blockade</td>
<td>47 (78%)</td>
</tr>
<tr>
<td>Vasoactive infusion</td>
<td>41 (68%)</td>
</tr>
<tr>
<td>Noradrenaline dose; µg.kg⁻¹.min⁻¹</td>
<td>0.37 (0.38)</td>
</tr>
<tr>
<td>Adrenaline dose; µg.kg⁻¹.min⁻¹</td>
<td>0.35 (0.22)</td>
</tr>
<tr>
<td>Vasopressin dose; µU.min⁻¹</td>
<td>0.04 (0)</td>
</tr>
<tr>
<td>Dobutamine dose; µg.kg⁻¹.min⁻¹</td>
<td>0.05 (0)</td>
</tr>
<tr>
<td>Milnirone dose; µg.kg⁻¹.min⁻¹</td>
<td>15 (2%)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>APACHE II score on arrival</td>
<td>17 (14–21 [8–31])</td>
</tr>
<tr>
<td>Maximum SOFA on arrival</td>
<td>12 (9–15 [5–20])</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

**Table 2** Aetiology of severe respiratory failure (n = 60).

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquired pneumonia</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Legionella</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Unknown organism</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Aspiration pneumonitis</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Status asthmatic</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Extrapolmonary acute respiratory distress syndrome</td>
<td>11 (18%)</td>
</tr>
</tbody>
</table>
Serious adverse events have long been of concern in the transfer of critically ill patients [29]. Specialist retrieval services have been shown to offer safe transfer even in severely ill patients [18–20, 30, 31]. Our service employs strict clinical governance and utilises a multidisciplinary team with specialist and standardised equipment. In keeping with other services offering mobile ECMO, no major adverse events were identified [18, 20] and the incidence of minor adverse events was comparable [31].

The possibility of delaying the start of ECMO until arrival back at the specialist centre poses a significant retrieval challenge in this population of hypoxaemic and hypercarbic patients. In the CESAR trial, three patients died before transfer and two died during conventional retrieval [8]. Boedy et al. also described a significant number of deaths before and during transfer of neonates transported for ECMO: of the 167 patients transported for ECMO, 18 deaths were associated with the transfer [32]. The safety of mobile ECMO has been previously described [18–20], and our non-surgeon, intensivist-delivered service has demonstrated a satisfactory safety profile with no deaths during transfer on ECMO. The patient who died of multi-organ failure following successful initiation of ECMO highlights possibly not only a futile application of this technology but also perhaps the need for earlier referral.

In England, the National Specialist Commissioning Service held a tender process in 2011 to establish five severe respiratory failure centres. To qualify as one of the centres, the capability of mobile ECMO was a prerequisite, and the retrieval service had to conform to national standards of governance and audit. We feel that mobile ECMO started in the referring institution should be the standard of care for a select group of patients with severe respiratory failure, although the exact group remains to be properly defined. The improving safety profile and increasing demand for ECMO will inevitably result in further expansion of services beyond the five current severe respiratory failure centres [33].

The present study is a retrospective, observational, uncontrolled, single-centre cohort study and has limitations that are intrinsic to this study design. Consequently, it is possible that adverse events may not have been documented. Only APACHE II and maximum Sequential Organ Failure Assessment (SOFA) scores following retrieval to our severe respiratory failure centre were available. These scores will be heavily influenced by the significant improvements in the pH and PaO$_2$/Fi$_O$$_2$ ratio after starting ECMO. Although

### Table 3 Comparison of ventilation parameters before and immediately after retrieval. Values are mean (SD), median (IQR [range]) or number (proportion).

<table>
<thead>
<tr>
<th>Patients retrieved on ECMO (n = 47)</th>
<th>At referral</th>
<th>Immediately following retrieval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$/Fi$_O$$_2$ ratio; kPa</td>
<td>10.1 (3.8)</td>
<td>28.9 (15.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ventilator Fi$_O$$_2$</td>
<td>1.0 (0.9–1.0 [0.6–1.0])</td>
<td>0.3 (0.2–0.45 [0.3–1.0])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pplat, cmH$_2$O</td>
<td>32.8 (5.8)</td>
<td>21.1 (4.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PEEP, cmH$_2$O</td>
<td>11.8 (5.3)</td>
<td>10 (4.1)</td>
<td>0.053</td>
</tr>
<tr>
<td>pH</td>
<td>7.13 (0.17)</td>
<td>7.34 (0.09)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaO$_2$; kPa</td>
<td>9.22 (3.25)</td>
<td>10.26 (3.87)</td>
<td>0.180</td>
</tr>
<tr>
<td>PaCO$_2$; kPa</td>
<td>10.97 (4.55)</td>
<td>6.27 (1.87)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients receiving lung-protective ventilation</td>
<td>7 (15%)</td>
<td>47 (100%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients retrieved conventionally (n = 12)</th>
<th>At referral</th>
<th>Immediately following retrieval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$/Fi$_O$$_2$ ratio; kPa</td>
<td>11.1 (5.1)</td>
<td>17.2 (11.1)</td>
<td>0.043</td>
</tr>
<tr>
<td>Ventilator Fi$_O$$_2$</td>
<td>1.0 (0.875–1.0 [0.5–1.0])</td>
<td>0.8 (0.725–1.0 [0.5–1.0])</td>
<td>0.22</td>
</tr>
<tr>
<td>Pplat, cmH$_2$O</td>
<td>32.6 (5.2)</td>
<td>30.3 (2.0)</td>
<td>0.076</td>
</tr>
<tr>
<td>PEEP, cmH$_2$O</td>
<td>11 (4.2)</td>
<td>11 (5.9)</td>
<td>1</td>
</tr>
<tr>
<td>pH</td>
<td>7.23 (0.1)</td>
<td>7.26 (0.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>PaO$_2$; kPa</td>
<td>9.37 (2.39)</td>
<td>13.61 (7.47)</td>
<td>0.031</td>
</tr>
<tr>
<td>PaCO$_2$; kPa</td>
<td>8.94 (3.72)</td>
<td>7.71 (2.24)</td>
<td>0.36</td>
</tr>
<tr>
<td>Patients receiving lung-protective ventilation</td>
<td>3 (25%)</td>
<td>8 (67%)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

ECMO, extracorporeal membrane oxygenation; Pplat, plateau airway pressure; PEEP, positive end-expiratory pressure.
the majority of ECMO survivors have satisfactory mental health, a significant number report physical and emotional difficulty at six months and these data are not available for this cohort [34].

In conclusion, we have shown that intensivist-delivered veno-venous cannulation and mobile ECMO can be safely undertaken without surgical support. A high-volume, severe respiratory failure retrieval service with mobile ECMO capabilities can deliver safe transfers and excellent survival rates, even in patients with severe lung injury.

Competing interests
No external funding and no competing interests declared.

References


Haemoconcentration of residual cardiopulmonary bypass blood using Hemosep®: a randomised controlled trial*

M. Hogan,1 A. Needham,2 E. Ortmann,3 F. Bottrill,4 T. J. Collier,5 M. W. Besser6 and A. A. Klein7

1 Clinical Research Fellow, 2 Fellow, 7 Consultant, Department of Anaesthesia and Intensive Care, 4 Clinical Research Coordinator, Department of Research and Development, Papworth Hospital, Cambridge, UK
3 Consultant Anaesthetist, Department of Anaesthesia and Intensive Care, Kerckhoff-Klinik, Bad Nauheim, Germany
5 Lecturer, Department of Statistics, London School of Hygiene and Tropical Medicine, London, UK
6 Consultant Haematologist, Cambridge University Hospitals, Cambridge Biomedical Campus, Cambridge, UK

Summary
Cardiac surgery and cardiopulmonary bypass are associated with haemodilution, activation of haemostasis and blood transfusion. We undertook a randomised controlled trial that included 53 patients in order to compare autotransfusion of residual cardiopulmonary bypass blood with residual blood concentrated using the novel Hemosep® device. There was no difference in patients’ mean (SD) haemoglobin concentration after autotransfusion of unprocessed blood compared with Hemosep; 103.5 (10.2) g.l\(^{-1}\) vs 106.2 (12.4) g.l\(^{-1}\), respectively, \(p = 0.40\). The mean (SD) change in haemoglobin concentration after autotransfusion was 5.9 (5.3) g.l\(^{-1}\) in the control group compared with 4.9 (6.3) g.l\(^{-1}\) in the Hemosep group, \(p = 0.545\). Adjusted for baseline haemoglobin concentrations, the estimated mean (95% CI) difference in change in haemoglobin concentration (control vs Hemosep) was 0.57 (−2.65 to 3.79) g.l\(^{-1}\), \(p = 0.72\). This was despite Hemosep’s reducing the weight of the blood from a mean (SD) of 778.7 (243.0) g to 607.3 (248.2) g, \(p < 0.001\). The haemoglobin concentration in the processed blood increased from a mean (SD) of 87.0 (15.1) g.l\(^{-1}\) to 103.7 (17.4) g.l\(^{-1}\), \(p < 0.001\). We conclude that Hemosep is capable of haemoconcentration when employed to process residual cardiopulmonary bypass blood, but that this is insufficient to increase patient haemoglobin.

Correspondence to: M. Hogan
Email: mauricehogan@yahoo.com
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Accepted: 4 January 2015

Introduction
Peri-operative anaemia [1, 2], bleeding [3] and blood product transfusion [4] are all associated with increased morbidity and mortality after cardiac surgery. Patients who undergo cardiopulmonary bypass have their fluid balance and homeostasis challenged as a consequence of both haemodilution and the induction of a systemic inflammatory response [5]. Haemodilution during bypass directly reduces haemoglobin concentration and impairs coagulation, and can predispose patients to bleeding and subsequent transfusion of blood products. Many techniques have been investigated with a view to minimising the haemodilution caused by bypass (e.g. small prime
circuits, vacuum-assisted venous return with retrograde autologous priming) [6], or partially reversing the dilution either during or after bypass (e.g. ultrafiltration, cell salvage) [7]. Concentrating residual cardiopulmonary bypass blood after cardiac surgery, using modified haemofiltration, is associated with lower requirements for blood transfusion requirement and reduced early morbidity [8, 9], and the use of cell salvage systems may reduce the need for allogeneic blood transfusion [10].

Hemosep® (Brightwake, Nottingham, UK) is a novel cell salvage system that can be applied to concentrate residual bypass blood after surgery. The Hemosep device consists of a blood bag which employs a chemical sponge technology, and a mechanical agitator to concentrate blood-containing fluid, in this case, the fluid drained from the tubing and bypass machine. Hemosep has been shown to increase the haematocrit and concentration of platelets, white cells, albumin and factor VII of residual bypass blood after a treatment period of 40 min [11]. In the single study published to date, it was associated with reduced postoperative bleeding and red cell transfusion. However, residual blood from the bypass reservoir and circuit was discarded in the control group in this study, whereas in our institution and in many others in the UK and worldwide, it is standard practice to autotransfuse this fluid. We therefore decided to study the effect of the Hemosep system in clinical practice and whether its ability to concentrate residual bypass blood was associated with increased haemoglobin concentration after autotransfusion, compared with simply autotransfusing residual untreated bypass blood.

Methods
The study was approved by the local Research Ethics Committee and written informed consent was obtained from all participants. Adult patients scheduled to undergo elective or urgent coronary artery bypass graft (CABG) surgery, valve surgery, or combined CABG and valve surgery, utilising bypass, were approached to participate. Exclusion criteria were emergency surgery, a contra-indication to either heparin, protamine or tranexamic acid, or inability to understand the study protocol.

Full blood count (FBC), prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured pre-operatively. All patients received 2 g tranexamic acid intravenously before institution of bypass [12]. Porcine mucosal heparin was given as a bolus intravenous dose of 300 IU.kg⁻¹, and anti-coagulation was assessed by the activated clotting time (ACT); target ACT during bypass was > 450 s. The bypass circuit was primed with 1.5 l Hartmann’s solution (Macopharma, Twickenham, Middlesex, UK) and 350 ml of 10% mannitol (Fresenius Kabi, Runcorn, Cheshire, UK). The blood transfusion trigger in our institution is a haemoglobin concentration < 70 g.l⁻¹ during bypass and a haemoglobin concentration < 80 g.l⁻¹ after bypass. After discontinuation of bypass, intravenous protamine sulphate (1 mg per 100 IU heparin that had been given) was administered slowly to reverse the effects of heparin, and if the ACT value after protamine was > 110% of the pre-bypass value, further protamine aliquots of 50 mg were given.

After weaning from bypass and administration of protamine, FBC, PT and aPTT were measured. Randomisation was performed after induction of general anaesthesia; patient allocation was determined by computer-generated software, and the research team were informed of the patient’s treatment group by a telephone call from the hospital research department. The research department had no other direct involvement in the conduct of the study. For patients randomly allocated to the control group, residual heparinised bypass blood was drained from the machine tubing and reservoir into a 1-L bag, and the amount was quantified by weighing and corrected for the weight of the collection bag and tubing by taring the weighing scales. A sample of blood from the bag was sent to the laboratory for FBC. The blood was re-transfused to the patient at a rate determined by the anaesthetist, but within 60 min after collection from the bypass machine. For patients allocated to the Hemosep group, blood from the bypass reservoir and tubing was drained into two Hemosep treatment bags, with approximately half the volume in each. The Hemosep bags had already each been primed with 100 ml sodium chloride 0.9%. The residual blood was also quantified by weighing, and a sample was sent for FBC. The two Hemosep collection bags were then placed on the Hemosep orbital shaker device for a fixed 20-min time period. After processing, a further sample was taken from each bag and sent for FBC,
and the blood was then administered to the patient at a rate determined by the anaesthetist. While waiting for the blood to be processed, the anaesthetist was allowed to transfuse Hartmann’s solution or colloid (Gelofusine®; B Braun Medical Ltd., Sheffield, Yorks, UK), and all administered fluid was recorded. In all patients, FBC, PT and aPTT were repeated after completion of autotransfusion.

After surgery, all patients were transferred to the intensive care unit (ICU), where they were managed according to institutional protocols by medical and nursing staff who were all independent of the study team and unaware of the patient’s treatment group. All fluids and blood products administered and blood loss from chest drains were recorded.

From pilot data obtained before the start of the study we determined that the mean (SD) haemoglobin concentration in patients after autotransfusion of residual bypass blood was 100 (10) g.l⁻¹, and decided that a clinically significant difference in haemoglobin concentration produced from haemoconcentration would be 10 g.l⁻¹, i.e. an increase of 10% in the patient’s haemoglobin concentration. We calculated that 24 patients would be required in each group, using the Wilcoxon rank-sum test of two groups at a significance (alpha) level of 0.05 with 90% probability. We therefore planned to enrol 53 patients to allow for a 10% dropout rate. Comparisons between groups at each time point were made using two-sample student’s t-tests or two-sample Wilcoxon rank-sum (Mann–Whitney) tests, depending on the distribution. The change from post-bypass to post-autotransfusion was analysed using a two-sample t-test and ANOVA, adjusting for the baseline value. We plotted the individual patients’ haemoglobin concentration trajectories over the course of the study by treatment group overlaid with the group mean value. We used IBM SPSS Statistics (IBM Ltd, Armonk, NY, USA) software for all calculations, and a p value < 0.05 was considered statistically significant.

**Results**

Sixty-nine patients gave consent for inclusion in the study and 16 were not studied due to lack of research staff or equipment (nine patients), change in surgical procedure or bypass technique (six patients), or the procedure was cancelled (one patient). Twenty-eight patients received standard treatment (control group), and 25 received Hemosep blood concentration. The logistic EuroSCORE was higher, and there were more patients who had not stopped taking aspirin or clopidogrel, in the control group compared with the Hemosep group (Table 1).

For the primary outcome measure, there was no difference in the patients’ haemoglobin concentration after autotransfusion in the control group compared with the Hemosep group (Table 2 and Fig. 1). In both groups, haemoglobin concentration increased after autotransfusion, but by a similar amount whether or not Hemosep was used. The mean (SD) increase in haemoglobin concentration after autotransfusion was 5.9 (5.3) g.l⁻¹ in the control group compared with 4.9 (6.3) g.l⁻¹ in the Hemosep group, p = 0.545. Adjusted

<table>
<thead>
<tr>
<th>Table 1 Baseline and surgical characteristics of patients included in the study. Values are mean (SD), number (proportion) or median (IQR [range]).</th>
<th>Control</th>
<th>Hemosep</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age; years</strong></td>
<td>70.5 (10.2)</td>
<td>67.7 (10.2)</td>
</tr>
<tr>
<td>Male/female</td>
<td>24 (86%)/4 (14%)</td>
<td>19 (76%)/6 (24%)</td>
</tr>
<tr>
<td>BMI; kg.m⁻²</td>
<td>28.5 (4.7)</td>
<td>30.0 (6.6)</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
<td>6.0 (2.5–8.0 [0.9–41.6])</td>
<td>4.2 (2.3–6.9 [0.9–18.8])</td>
</tr>
<tr>
<td>Aspirin not stopped</td>
<td>17 (61%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Clopidogrel not stopped</td>
<td>5 (18%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>CABG</td>
<td>23 (81%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Single valve</td>
<td>3 (11%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>CABG + valve procedure</td>
<td>2 (7%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>CPB duration; min</td>
<td>79.8 (20.6)</td>
<td>86.6 (27.9)</td>
</tr>
<tr>
<td>Aortic cross clamp time; min</td>
<td>50.7 (16.9)</td>
<td>57.0 (21.3)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CABG, coronary artery bypass grafts; CPB, cardiopulmonary bypass.
for baseline haemoglobin concentration, the estimated mean (95% CI) difference in change in haemoglobin concentration (control vs Hemosep) was 0.57 (−2.65 to 3.79) g\text{L}^{-1}, p = 0.72.

Hemosep processing of residual blood led to a mean (SD) decrease in the weight of the processed blood from 778.7 (243.9) g to 607.3 (248.2) g, p < 0.001, and a corresponding mean (SD) increase in the haemoglobin concentration of the processed blood from 87.0 (15.1) g\text{L}^{-1} to 103.7 (17.4) g\text{L}^{-1}, p < 0.001. The mean (95% CI) weight reduction attributable to processing of the blood with Hemosep was 171.4 (157.3–185.5) g, and the mean (95% CI) difference in haemoglobin concentration was 16.7 (12.1–21.3) g\text{L}^{-1}. However, the decrease in weight of the processed blood was not related to the original weight (Fig. 2). There was also no correlation (R = −0.03) between the change in haemoglobin concentration of the processed blood and the change in the patients’ haemoglobin concentration (Fig. 3).

There was no difference between the groups in red cell or blood product transfusions, total fluid administration or blood loss in the first 12 h (Table 3). Median (IQR [range]) ICU length of stay was 2 (2–2 [1–4]) days in the control group and 2 (2–2 [1–6]) days in the Hemosep group. There were no deaths.

**Table 2** Haemoglobin concentrations (Hb), platelet counts and clotting profiles of patients in the control and Hemosep groups. Values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative Control (n = 28)</th>
<th>Hemosep (n = 25)</th>
<th>After CPB Control (n = 28)</th>
<th>Hemosep (n = 25)</th>
<th>p value*</th>
<th>After autotransfusion Control (n = 28)</th>
<th>Hemosep (n = 25)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb; g\text{L}^{-1}</td>
<td>136.4 (15.3)</td>
<td>138.9 (14.5)</td>
<td>97.6 (10.0)</td>
<td>101.3 (12.0)</td>
<td>0.24</td>
<td>103.5 (10.2)</td>
<td>106.2 (12.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Platelets; \times 10^9\text{L}^{-1}</td>
<td>268.1 (70.8)</td>
<td>214.3 (41.0)</td>
<td>140.2 (47.4)</td>
<td>141.8 (38.7)</td>
<td>0.89</td>
<td>169.0 (57.4)</td>
<td>144.3 (34.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>PT; s</td>
<td>11.7 (0.9)</td>
<td>11.7 (0.9)</td>
<td>15.6 (1.4)</td>
<td>14.6 (1.3)</td>
<td>0.01</td>
<td>13.8 (1.4)</td>
<td>13.9 (1.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>aPTT; s</td>
<td>31.9 (6.7)</td>
<td>31.0 (4.7)</td>
<td>44.4 (14.6)</td>
<td>31.9 (7.0)</td>
<td>0.10</td>
<td>32.5 (5.6)</td>
<td>31.8 (4.8)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; PT, prothrombin time; aPTT, activated partial thromboplastin time.
p values are given for comparison between groups after CPB, and between groups after autotransfusion (control vs Hemosep groups in both cases).
The p values refer to the comparison between pre-operative and after cardiopulmonary bypass (CPB)*, and between after CPB and after autotransfusion†.

**Figure 1** Individual trajectories in haemoglobin concentration (Hb) over time in a) control and b) Hemosep groups. Grey line – individual patients. Red line – mean values. CPB, cardiopulmonary bypass.
Discussion
We have shown that there is no difference between autotransfusion of the remaining blood after bypass, which is standard practice in most cardiac surgical units, and concentration of the same blood using the Hemosep device before autotransfusion. Therefore, we cannot recommend use of the Hemosep for this indication in cardiac surgery. Although we have shown that the Hemosep device does reduce the weight, and therefore volume, of blood in a 20-min processing cycle, the reduction was less than that expected from the manufacturers’ data and from previously published work [11]. The increase in haemoglobin concentration within the bag of blood was also less than expected because the concentrating effect did not appear to be as efficient as previously thought. More importantly, once this blood was administered to the patient, although the patients’ haemoglobin level did increase, the increase was similar to that seen after administering unprocessed blood; therefore, there was no advantage in using the device. Although there was some reduction in perioperative allogeneic red cell transfusion, this did not reach statistical significance and the study was not powered to detect a difference in this outcome; a study including more patients would be required to confirm or refute this finding.

After discontinuation of bypass, the dead space of the reservoir and tubing remains filled with a mixture of the patient’s blood, prime volume and any fluid added during the bypass period. Consequently, this fluid contains many useful substances, including red cells, platelets, white cells, proteins and hormones; however, it may also contain detrimental substances such as inflammatory mediators and debris from the surgical field [13]. Nevertheless, it is currently recommended that this blood be salvaged and administered back to patients as part of a blood conservation strat-

Figure 2 Individual weights of blood before (○) and after (●) processing with Hemosep.

Figure 3 Bland–Altman plot of difference in haemoglobin concentration (Hb) value in the bags of blood and patients’ haemoglobin concentration after processing with Hemosep.
egy [14]. Our standard protocol is to transfuse this blood directly back to the patient, although techniques such as cell salvage or haemofiltration are also used to haemoconcentrate the blood. Haemofiltration in particular may be beneficial by increasing the red cell and platelet count and coagulation factor concentrations directly, but also by reducing the amount of inflammatory mediators transfused back into the patient, and has been associated with improved haemodynamic, haemostatic and pulmonary function [15]. Haemofiltration was first introduced during cardiac surgery as a protective strategy against bypass-induced inflammatory response and subsequent tissue oedema [16]. In spite of the overall clinical benefits associated with haemofiltration [8, 9], it is still not routinely applied in clinical practice. This is most likely to be related to cost, and also to the availability of specially trained staff, usually perfusionists, to remain in the operating room following discontinuation of bypass in order to process the blood. Cell salvage during cardiac surgery has also been shown to reduce the exposure to allogeneic blood products and red cell transfusions [17, 18].

Hemosep can be described as a combination of a cell salvage system and a haemofiltration device, although its mechanism of action is unique and distinct from both conventional cell salvage and haemofiltration systems. The Hemosep device consists of a blood bag that employs a chemical sponge technology, and a mechanical agitator to concentrate blood-containing fluid, in this case, the fluid drained from the tubing and bypass machine. Hemosep is marketed as being capable of concentrating all cell species, preserving platelets, white cells and red cells for subsequent transfusion. The Hemosep device relies on two main constituent elements for its primary function of concentrating blood cells from diluted blood: a control membrane and a super-absorber. The control membrane is the filter component of the system and has a pore size of 1 μm, which prevents cells from passing through it. Plasma passes freely through this filter, and will be absorbed by the polycarbonate absorber membrane. The rate of absorption, and therefore concentrating effect, is dependent on contact between plasma and the unsaturated polycarbonate membrane, which is the reason why mechanical agitation increases absorption and the haemoconcentration effect.

Hemosep has already been evaluated in the setting of cardiac surgery, demonstrating an increase in the haematocrit of processed blood from 0.23 to 0.28 after 15 min, and to 0.37 after 40 min of treatment [11]. This was associated with significantly reduced postoperative bleeding and reduced transfusion of blood products after surgery. However, the residual bypass blood was discarded in the control group, which is not standard practice, and is therefore the major difference between Gunaydin et al.’s study and ours. Our study was not blinded because untreated blood was returned to the anaesthetist, and the Hemosep-treated blood was returned in its own collection bag. Outside the operating theatre, however, e.g. in the ICU and blood transfusion laboratory, staff were unaware which patients had been allocated to which group.

We autotransfused the residual blood in our control group patients, and found that the patients’ haemoglobin concentration was the same as in those patients treated with Hemosep. The concentrating effect of the Hemosep was not as effective as we had hoped; this may have been due to the 20-min processing time, and it is possible that extending this to 40 min would have led to improved haemoconcentration, as demonstrated

<table>
<thead>
<tr>
<th>Transfused red cells</th>
<th>Hemosep</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfused platelets</td>
<td>2 (7%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Transfused FFP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total fluid given in 12 h; ml</td>
<td>3101 (2640–3527 [2341–6027])</td>
<td>3006 (2869–3611 [2002–4884])</td>
</tr>
<tr>
<td>Blood loss in 12 h; ml</td>
<td>300 (275–475 [150–1046])</td>
<td>325 (250–450 [125–1150])</td>
</tr>
</tbody>
</table>

FFP, fresh frozen plasma.
by Gunaydin et al. However, we were advised by the manufacturers that recent improvements in technology meant that prolonging the processing time was no longer necessary. In addition, the anaesthetist often has to administer fluid in the post-bypass period; the 800 ml or so of unprocessed blood is usually administered over 30–60 min. In the Hemosep group, the anaesthetists had to wait a further 20 min until the processed blood was available, and often administered additional fluids while waiting for the processed blood. There was no difference between the two groups in total fluid administered over 12 h, and we therefore conclude that any reduction in fluid volume gained by the Hemosep was offset by administration of extra (non-blood) fluid, which explains the lack of difference in haemoglobin concentration. In only one case was it deemed necessary to discontinue the treatment process and re-transfuse the blood back to the patient before the 20-min treatment period was completed. In over half of all cases (13 out of 25), the attending anaesthetist reported the need to administer extra crystalloid or colloid solution to patients while waiting for the blood to be processed. Given that the concentrating effect of the device is approximately 170 ml on average, it is clear that administration of even a small volume of fluid while waiting for the processing would obviate its potential advantages. We consider the inefficiency of the Hemosep (low concentrating effect per unit time) compared with conventional cell salvage or ultrafiltration systems to be the overwhelming weakness of the system, and the lack of apparent clinical benefit is not surprising given the low absolute volumes obtained.

The concentration effect of the Hemosep observed in our study was approximately 20%, with a mean (SD) reduction in total blood mass from 779 (243) g to 607 (248) g. We chose to quantify the blood by weighing it and taring the measurement for the weight of the fluid bags, rather than by estimating the volume, as accurate volumetric analysis of fluid contained in bags is difficult. Although we demonstrated that this concentration is of statistical significance, it did not translate into a clinical benefit, as no difference was found in any of the haematological or coagulation variables measured. Of note, there was no increase in the patient’s platelet concentration in the Hemosep group; therefore, we have not been able to confirm the manufacturer’s claim regarding the ability of the device to increase platelet numbers after treatment.

Residual bypass blood from the circuit is still anticoagulated at the time of collection, as bypass must have ended before protamine can be safely administered. This implies that the blood returned to the patient contains some heparin. It is not clear from our study what effect Hemosep has on this residual heparin, as we did not measure heparin concentration. The attending anaesthetist was allowed to administer further doses of protamine on the basis of the patient’s ACT result, if they felt that this was indicated.

Our study was not powered adequately to determine whether use of Hemosep vs control reduces allogeneic blood product usage, and consequently, it is not possible to perform a cost–benefit analysis of the system in terms of its blood product sparing effect. We failed to demonstrate an observable primary clinical benefit and therefore believe that no cost savings could be possible. We did not compare Hemosep with cell salvage or haemofiltration because, despite demonstrations of their efficacy and benefit [19], we consider that widespread clinical practice remains autotransfusion of untreated residual bypass blood [20]. Indeed, our findings seem to have validated this approach because the Hemosep was not superior to simple autotransfusion. In addition, we did not explore whether the use of Hemosep had any effect on visco-elastic tests of functional coagulation [21], heparin concentration or serum levels of inflammatory mediators. Finally, we did not power the study for blood transfusion requirements or length of stay in the ICU or hospital, and to do so would require a study including many more patients. A larger study may be indicated if the haemoconcentrating effect of the Hemosep was improved by technological or manufacturing changes. With regard to blood transfusion, the non-significant decrease we observed in patients in whom the Hemosep was used could be employed to power a future study, which would mean that 176 patients per group would be required with 80% power. Further studies directly comparing haemofiltration, cell salvage, Hemosep and autotransfusion should also be considered.

We conclude that Hemosep is easy to use, and is capable of producing a statistically significant haemoconcentrating effect when used to treat residual bypass
blood. However, the system as currently applied is too inefficient because the concentrating effect per unit time is too low to translate into clinical benefit. It is possible that efficiency can be improved in order for the system to be clinically relevant in the future, or there may be other clinical situations where these factors do not limit its applicability.

Acknowledgements
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Competing interests
No other competing interests or external funding declared.

References
The utility of transoesophageal echocardiography for estimating right ventricular systolic pressure

B. Cowie,1,2 R. Kluger,1 S. Rex2 and C. Missant3

1 Staff Anaesthetist, Department of Anaesthesia, St. Vincent’s Hospital, Melbourne, Victoria, Australia
2 Associate Professor and Staff Anaesthetist, 3 Professor and Staff Anaesthetist, Department of Anesthesiology, University Hospitals Leuven, Belgium

Summary
With the reduction in use of the pulmonary artery catheter, alternative methods of pulmonary pressure estimation are required. The use of echocardiographically-derived right ventricular systolic pressure has recently been questioned, but this technique has not been validated in anaesthetised surgical patients with transoesophageal echocardiography. One hundred measurements of right ventricular systolic pressure with transoesophageal echocardiography were compared with the pulmonary artery systolic pressure obtained simultaneously from a pulmonary artery catheter in patients undergoing cardiac surgery. Simultaneous right ventricular systolic pressure and pulmonary artery systolic pressure measurements were possible in all patients, and these measurements were strongly correlated \( r = 0.98, \ p < 0.001 \), with minimal bias and narrow limits of agreement (approximately \(-5\) to \(+5\) mmHg), across a broad range of pulmonary pressures. Measurement of right ventricular systolic pressure using transoesophageal echocardiography is readily achievable and closely correlates with pulmonary artery systolic pressure, with minimal bias, in cardiac surgical patients undergoing general anaesthesia and positive pressure mechanical ventilation of the lungs.

Correspondence to: B. Cowie
Email: brian.cowie@svhm.org.au
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Introduction
The use of the pulmonary artery catheter to monitor pulmonary artery pressure in cardiac surgical patients has been fundamental in peri-operative care. However, its use has decreased recently as no clear outcome benefits have been demonstrated in the literature for any group of critically ill patients [1]. Echocardiography can be used to estimate the pulmonary artery pressure non-invasively. Most commonly, this is achieved using the tricuspid regurgitant jet velocity and the simplified Bernoulli equation to obtain a right ventricular to right atrial pressure gradient. Adding this tricuspid valve pressure gradient to the right atrial pressure gives an estimate of right ventricular systolic pressure. In the absence of pulmonary stenosis or right ventricular outflow obstruction, right ventricular systolic pressure equals pulmonary artery systolic pressure [2].

Recently, the use of right ventricular systolic pressure to estimate pulmonary artery pressure has been questioned, with both under- and over-estimation reported compared with right heart catheterisation [3]. Some of these discrepancies can be explained by variations in the way right atrial pressure is estimated. Many researchers report non-simultaneous measurements of right ventricular systolic pressure compared with those
obtained by right heart catheterisation, sometimes days or weeks apart [4]. In addition, initial validation studies of right ventricular systolic pressure and almost all subsequent published data have been in awake patients using transthoracic echocardiography.

There are several reasons why many of the assumptions used in calculations for awake patients using transthoracic echocardiography may not be valid in patients undergoing general anaesthesia using transoesophageal echocardiography. These include the effects of positive pressure ventilation of the lungs, changes in intrathoracic pressure, and the effects of general anaesthesia on pulmonary vascular resistance, preload, afterload and contractility [4]. Transthoracic echocardiography parameters are not necessarily interchangeable with transoesophageal echocardiography. There are recent examples where suggested benefits from transthoracic echocardiography-derived echocardiography quantification could not be demonstrated with transoesophageal echocardiography under general anaesthesia [5, 6].

As many centres do not routinely insert a pulmonary artery catheter during cardiac surgery, the ability to estimate pulmonary artery pressure less invasively is required. We aimed to assess the feasibility and accuracy of calculated right ventricular systolic pressure measured using transoesophageal echocardiography compared with pulmonary artery pressure measured simultaneously with a pulmonary artery catheter, in cardiac surgical patients under general anaesthesia.

**Methods**

This study was approved by the Human and Research and Ethics Committee and undertaken at the University Hospital, Leuven. Informed consent was waived, since transoesophageal echocardiography and pulmonary artery catheterisation are routinely performed in patients undergoing cardiac surgery in our institution. Consecutive patients undergoing cardiac surgery, where one of the authors was available, were included. Patients were not studied if, for whatever reason, both transoesophageal echocardiography and a pulmonary artery catheter were not used as part of their intraoperative care.

The transoesophageal echocardiographic examination included assessment of the tricuspid valve for tricuspid regurgitation in the mid-oesophageal and transgastric views, looking for optimal alignment of the tricuspid regurgitant jet. When the tricuspid regurgitant jet was as near to parallel to the direction of the probe as possible, a continuous-wave Doppler was placed through the jet to obtain the peak regurgitant velocity. The highest continuous-wave Doppler envelope and tricuspid regurgitant velocity were obtained and recorded according to published guidelines [2], and the right ventricular systolic pressure determined using the simplified Bernoulli equation:

\[
\text{Pressure gradient} = 4 \times \text{peak velocity}^2
\]

Tricuspid valve pressure gradient
\[
= 4 \times \text{peak tricuspid regurgitant velocity}^2
\]

Right ventricular systolic pressure
\[
= 4 \times \text{peak tricuspid regurgitant velocity}^2 + \text{right atrial pressure}
\]

Simultaneously, pulmonary artery and central venous pressures were recorded from the pulmonary artery catheter waveform (Edwards Lifesciences Swan Ganz CCOmbo, Irvine, CA, USA). The central venous pressure was used as the right atrial pressure for the right ventricular systolic pressure calculation. All measurements were taken at end-expiration, before the institution of cardiopulmonary bypass and during a haemodynamically stable period, after sternotomy in the majority of patients.

All patients were in the supine position, and the pressure transducers were located in the mid-thoracic position, halfway between the sternum and bed, as recommended in recent guidelines [7, 8]. Severity of tricuspid regurgitation was graded qualitatively as trace, mild, moderate and severe, as per published guidelines [2]. All measurements were performed by experienced cardiac anaesthetists, with expertise and qualifications in transoesophageal echocardiography, blinded to invasive pulmonary artery catheter measurements, as part of a comprehensive transoesophageal echocardio-
graphic study. Two different machines were used, depending on availability: Vivid S6 with the 6Tc probe (GE Vingmed Ultrasound, Horten, Norway); and iE33 with the X7-2t probe (Philips Healthcare, Best, the Netherlands).

Bland–Altman analysis was used to compare simultaneous calculations and measurements, and correlation was analysed using the Pearson correlation coefficient ($r$). We used Stata 12.1 (StataCorp, College Station, TX, USA), taking $p < 0.05$ to indicate statistical significance.

**Results**

We were able to measure right ventricular systolic pressure and pulmonary artery systolic pressure in all 100 patients studied, regardless of the severity of the tricuspid regurgitant jet. A total of 39 patients underwent coronary artery bypass graft surgery, 28 valvular surgery, 20 combined coronary and valvular surgery, eight aortic surgery, and five others (pulmonary endarterectomy, septal defect repair and aneurysmectomy). Baseline characteristics and measurements are presented in Table 1.

Right ventricular systolic pressure as calculated using transoesophageal measurements and pulmonary artery systolic pressure as measured directly were strongly correlated, with $r = 0.98$, $p < 0.001$. Bland–Altman analysis (Fig. 1) revealed narrow limits of agreement (approximately $-5$ to $+5$ mmHg) across a wide range of pulmonary pressures. Hence, the percentage error ($5 \times 100$; pulmonary artery systolic pressure) fell as the pulmonary artery systolic pressure increased. At the median pulmonary artery systolic pressure, the percentage error was 15%, but this fell to under 10% at a pulmonary artery systolic pressure of 50 mmHg.

Most patients had trivial (65 patients) or mild (28 patients) tricuspid regurgitation, with seven patients having moderate or severe tricuspid regurgitation. There was only a weak relationship between the severity of regurgitation and the pulmonary artery systolic pressure (Fig. 2) and many patients with mild tricuspid regurgitation had high pulmonary artery systolic pressures.

**Discussion**

This study confirms that right ventricular systolic pressure accurately reflects pulmonary artery systolic pressure in cardiac surgical patients and is achievable in all patients. It strongly correlates with invasive measurements across a range of normal to severely elevated pulmonary pressures.

Pulmonary hypertension is defined as a mean pulmonary artery pressure $> 25$ mmHg, but in general, elevated right ventricular systolic pressure and pulmonary artery pressure are present when the tricuspid regurgitant peak jet velocity is $> 2.8–2.9$ m.s$^{-1}$, which correlates with a pulmonary artery systolic pressure of 36 mmHg [2]. Pulmonary hypertension increases the risk of peri-operative and long-term mortality, and intensive care and hospital length of stay in cardiac surgical patients [9]. It also influences the peri-operative use of inotropes, vasopressors and pulmonary vasodilators [10]. Hence, its estimation is fundamental in cardiac anaesthesia.

While a pulmonary artery catheter is the gold standard for the measurement of pulmonary artery pressure, systolic pulmonary artery pressure can be obtained less invasively with transoesophageal echocardiography. Increasingly, pulmonary artery catheters are not routinely inserted in many cardiac surgical centres, with insertion rates of $< 10\%$ in some institutions. A central line is inserted in almost all centres [11].
Despite right ventricular systolic pressure estimation’s being a routine part of most formal cardiology echocardiograms, its accuracy has been recently questioned [12]. This has been attributed to the many potential pitfalls in the calculation, including non-simultaneous measurements, inadequate tricuspid regurgitation, excessive or inadequate adjustment of the gain, malalignment of the Doppler beam and inaccurate estimation of right atrial pressure [12]. Limitations in the simplified form of the Bernoulli equation may also play a role [13].

Figure 1 Bland–Altman plot of agreement between right ventricular systolic pressure (RVSP) and pulmonary artery systolic pressure (PASP); ULA, upper limits of agreement; LLA, lower limits of agreement.

Figure 2 Plot of pulmonary artery systolic pressure (PASP) vs grade of tricuspid regurgitation. Each dot represents one patient, horizontal lines represent group medians. Tricuspid regurgitation is graded as trivial (0), mild (1), moderate (2) and severe (3).
In formal transthoracic echocardiography, right atrial pressure and central venous pressure is estimated using inferior vena caval diameter and collapsibility. However, this relationship is being increasingly questioned, and traditional estimates of central venous pressure based on caval size and collapsibility are poor [14]. When an inaccurate estimate of central venous pressure is combined with the estimate of tricuspid valve pressure gradient obtained with echocardiography, the potential for error is magnified [12]. In the setting of cardiac surgery, in which central venous catheterisation is routinely performed, simultaneous invasive measurement of the central venous pressure allows this variable to be measured accurately, without the errors associated with measurement of inferior caval diameter. Furthermore, as both the right atrial pressure and pulmonary artery pressure transducers were at the same level, our measurement of right ventricular systolic pressure plus right atrial pressure was independent of transducer position.

The strengths of this study include the simultaneous measurement of both right ventricular systolic pressure and pulmonary artery systolic pressure. In most of the cardiology literature using transthoracic echocardiography, the measurements were obtained at different time points, at hours and often days apart [4]. Pulmonary pressures vary on a beat-to-beat basis, and depend on changes in cardiac output, volume status, positioning and pulmonary vascular resistance. Pressures can differ dramatically by more than 25 mmHg on an hourly basis [15]. Accurate measurement of the central venous pressure, when used in the modified Bernoulli equation for estimation of right ventricular systolic pressure, we believe, is a key to reliable estimation of this parameter. With the declining use of the pulmonary artery catheter but almost ubiquitous use of a central line, and the frequent employment of transoesophageal echocardiography, we suggest that estimation of right ventricular systolic pressure using this combination is accurate, reliable, feasible and commensurate with current clinical practice.

Some degree of tricuspid regurgitation was present in all patients. The cardiology-based transthoracic echocardiography literature suggests the feasibility of Doppler-derived right ventricular systolic pressure measurement to be 70–90% [4]. With a pulmonary artery catheter in situ, the incidence of tricuspid regurgitation increases by 48%, as does its severity, which may account for our ability to find at least some tricuspid regurgitation in all patients [16].

This is a pragmatic and real-world study performed by experienced cardiac anaesthetists in cardiac surgical patients, under routine operating room conditions. Limitations of our study include the possibility that right ventricular systolic pressure measurement may be less feasible in patients without a pulmonary artery catheter in situ, where no tricuspid regurgitation jet is visible. Despite being unaware of the invasive pulmonary artery pressure measurements on the screen, it is possible that the echocardiographer was aware of the general clinical state of the patient and spent more time analysing the tricuspid regurgitation jet. The anaesthetist performing the transoesophageal echocardiogram could spend time optimising multiple views, increasing colour gain and zooming in on the tricuspid valve to obtain a tricuspid regurgitation envelope in patients with otherwise trivial and clinically insignificant tricuspid regurgitation.

Estimated right ventricular systolic pressure is routinely obtained in the echocardiography laboratory, and is recommended in all patients in international guidelines. Estimation of pulmonary artery diastolic pressure is recommended only in specific circumstances, and is not routine practice pre-operatively or in the operating room [2]. Therefore, we did not estimate pulmonary diastolic pressure using the pulmonary regurgitation jet. This estimates transpulmonary valve gradient and uses right atrial pressure measurement as a surrogate for right ventricular end-diastolic pressure estimation. We are unaware of any studies looking specifically at pulmonary artery diastolic pressure in any group of patients, nor how this would assist in management decisions of our patients. Mean pulmonary artery pressure can be reliably estimated from the right ventricular systolic pressure and both systolic and mean pressures have prognostic significance [2, 17].

In conclusion, measurement of right ventricular systolic pressure using transoesophageal echocardiography in cardiac surgical patients under general anaesthesia and receiving positive pressure ventilation of the lungs was achievable in 100% of study patients, and closely agrees with pulmonary artery systolic pressure.
Competing interests
No external funding or competing interests declared.

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Evaluation of the utility of the Vigileo FloTrac™, LiDCO™, USCOM and CardioQ™ to detect hypovolaemia in conscious volunteers: a proof of concept study*

E. O’Loughlin,1,2 M. Ward,1 A. Crossley,3 R. Hughes,4 A. P. Bremner5 and T. Corcoran6,7

1 Consultant, 3 Research Fellow, Department of Anaesthesia, Fremantle Hospital, Perth, Western Australia
2 Clinical Senior Lecturer, School of Medicine and Pharmacology, 5 Associate Professor, 6 Clinical Professor, School of Population Health, University of Western Australia, 4 Research Fellow, 7 Consultant, Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Perth, Western Australia, Australia

Summary
It is important to detect and treat hypovolaemia; however, detection is particularly challenging in the conscious, spontaneously breathing patient. Eight healthy male volunteers were monitored using four minimally invasive monitors: Vigileo FloTrac™; LiDCOrapid™; USCOM 1A; and CardioQ™ oesophageal Doppler. Monitor output and clinical signs were recorded during incremental venesection of 2.5% estimated blood volume aliquots to a total of 20% blood volume removed. A statistically significant difference from baseline stroke volume was detected after 2.5% blood loss using the LiDCO (p = 0.007), 7.5% blood loss using the USCOM (p = 0.019), and 12.5% blood loss using the CardioQ (p = 0.046) and the FloTrac (p = 0.028). Receiver operator characteristic curves for predicting > 10% blood loss had areas under the curve of 0.68–0.82. The minimally invasive cardiac output devices tested can detect blood loss by a reduction in stroke volume in awake volunteers, and may have a role in guiding fluid replacement in conscious patients with suspected hypovolaemia.

Introduction
Detection of blood loss and hypovolaemia in conscious patients is difficult, yet important [1]. Clinical signs [2], central venous and pulmonary capillary wedge pressures [3, 4], and haemoglobin and lactate levels [5–7] all correlate poorly with intravascular volume status. Occult hypovolaemia is associated with poor clinical outcomes postoperatively [8, 9]. Clinicians seek to prevent the development of such hypovolaemia by restricting pre-operative fasting times and paying close attention to intravenous fluid replacement intra-operatively. Such fluid replacement may be guided by minimally invasive cardiac output monitors [10–12]. There is some evidence that such devices can detect small (4%) degrees of blood loss in patients receiving controlled ventilation intra-operatively [13]. A pertinent
question is whether these monitors can assist in the detection of hypovolaemia in the postoperative period, which would be a useful extension of their application in at-risk patients. More broadly, can these monitors detect occult hypovolaemia in any spontaneously breathing patient at risk of blood loss, potentially facilitating timely treatment?

This study tests the hypothesis that minimally invasive cardiac output monitors can detect the physiological changes associated with hypovolaemia in conscious, spontaneously breathing patients at lower levels of blood loss and hence at an earlier time point than changes in clinical signs. In addition, the utility of a dynamic challenge, a passive leg raise, was also assessed.

Methods
This trial received ethical approval from the South Metropolitan Health Service, and all volunteers provided written informed consent. Eight healthy male anaesthetists, who were not taking any medications, were recruited from the anaesthetic departments of Fremantle and Royal Perth Hospitals. A pre-procedure physical examination was conducted and electrocardiogram (ECG) performed. Participant’s blood volumes were estimated using the Nadler formula [14]. Subjects were instructed not to eat solid food for at least 6 h before the start of the study, but to maintain clear fluid intake until 2 h before venesection, to be as close as possible to euvoelastic status for the start of the study.

Four minimally invasive hemodynamic monitoring devices that were commercially available in Western Australia at the time of this study were assessed: Vigileo FloTrac™ (Edwards Lifesiences, Irvine, CA, USA); LiDCOrapid™ (LiDCO, London, UK); USCOM 1A (USCOM, Sydney, NSW, Australia); and CardioQ™ oesophageal Doppler (Deltex Medical, Chichester, West Sussex, UK). Device names are subsequently abbreviated to FloTrac, LiDCO, USCOM and CardioQ, respectively.

Heart rate, intra-arterial blood pressure, oxygen saturation and time were recorded from the monitor of an Aisys® (GE Healthcare, Madison, WI, USA) anaesthetic machine. Data recorded from all the minimally invasive devices were stroke volume (SV). The FloTrac and LiDCO also measured SV variation. The USCOM and CardioQ recorded peak velocity and time-corrected flow (FTc: duration of systolic flow corrected for a heart rate of 60 bpm), and the CardioQ also recorded maximum amplitude.

The study was conducted in the operating theatres at Fremantle Hospital over a one-week period. A 20-G intravenous cannula was inserted in the right hand, a 20-G cannula was placed in the left radial artery, and a short 14-G intravenous cannula was placed in the left antecubital fossa for venesection. A CardioQ nasal oesophageal Doppler probe was inserted by an experienced operator after application of topical anaesthesia using 4% lidocaine viscous gargle and 10% lidocaine nasal spray. Continuous pulse oximetry and three-lead ECG were also used.

The arterial cannula was connected via a transducer to the anaesthetic monitor and zeroed. Invasive arterial pressure, ECG-measured heart rate and oxygen saturation were displayed. LiDCO and FloTrac monitoring was established using this arterial cannula; the USCOM Doppler signal was acquired by an experienced operator using the device-specific probe in the sternal notch; and the CardioQ was adjusted to obtain an optimal signal. All individuals who were recording data were blinded to the other monitors and to the stage of venesection via drapes concealing the patient’s arm. The investigator performing venesection acted as the timekeeper.

The operator of each device was asked to record data specific to their monitor at baseline (time point 0). Following this, each operator recorded two sets of observations at 5-min intervals, one before and one after a passive leg raise. Venesection was commenced at a random time point during the first 30 min to maintain blinding of the operators.

Once venesection commenced, 2.5% of estimated blood volume was removed over 5 min. Collection was into citrate-phosphate-dextrose bags weighed using electronic scales tared to the weight of the bag. Total venesection was 20% of estimated blood volume over a period of 40 min. Re-infusion of venesected blood was commenced immediately after the measurements taken at maximal blood loss: 5% of blood volume was returned every 10 min with device measurements continued every 5 min to maintain blinding. Arterial blood gas samples were taken at baseline and at
maximum blood loss to assess haemoglobin and lactate concentrations.

A sequential approach to assessing changes in recorded data was used. Paired t-tests or Wilcoxon signed-rank tests for paired data were conducted, as appropriate, to compare first baseline with 20% blood loss, then baseline with 10% blood loss. If the results of these tests were statistically significant, up to two further tests were conducted to define the percentage blood loss at which observed changes were likely to occur with an unadjusted probability of < 0.05. These tests were also used to assess changes before and after passive leg raise and during the re-infusion of blood.

Receiver operator characteristic (ROC) curve analysis was used to compare detection of a known 10% blood loss using clinical signs and the SV output of the monitors. As clinical signs and monitored variables had different baselines and scales, data were converted to ratios. Area under the curve was computed, and the optimal cut-off point, defined as the point that maximised sensitivity and specificity for detection of > 10% blood loss, was identified for each variable. For each optimal cut-off point, the positive predictive value, negative predictive value and positive signal, which describes the magnitude and direction of change in variable from baseline, were calculated. Positive likelihood ratios were calculated for the change in SV and heart rate modelled in the ROC curve analysis for > 10%, 15% and 20% blood loss. We used SPSS for Windows (Version 20.0.0; IBM SPSS Chicago, IL, USA) for statistical analysis. Significance was set at 5%.

Results

All eight participants confirmed they were fasted for solids but had had variable oral intakes determined by thirst as instructed, and all completed the protocol of venesection and blood re-infusion. Mean (SD) age was 36.5 (2.0) years, height 1.79 (0.03) m and weight 77.1 (6.8) kg. Mean estimated blood volume was 5.20 (0.33) l and 1.04 (0.07) l blood was venesected in eight aliquots. The CardioQ Doppler probe could not be used in two subjects; the probe would not pass the nose in one, and the other complained of recurrent regurgitation due to the presence of the probe. All subjects experienced discomfort from the CardioQ probe after the local anaesthetic used to facilitate insertion wore off. This discomfort was often coincident with the period of blood re-infusion and was worst when the USCOM probe was used.

One subject developed a supraventricular tachycardia at maximal (20%) blood loss. This was self-terminating after re-infusion of approximately 5% of his blood volume. The results for this participant have been analysed excluding the period of tachyarrhythmia.

There was a fall in haemoglobin concentration from a mean (SD) of 143.9 (7.8) g.l\(^{-1}\) to 138.8 (5.3) g.l\(^{-1}\) (mean (95% CI) decrease 5.1 g.l\(^{-1}\) (2.2–8.0) g.l\(^{-1}\), \(p = 0.004\)) over the course of the venesection, but no other significant changes in arterial blood gas analysis were detected.

Mean (SD) heart rate increased from 70.6 (5.2) bpm at baseline to 77.2 (7.2) bpm after 17.5% blood loss (mean (95% CI) increase 6.6 (2.9–10.1) bpm, \(p = 0.004\)). Mean (SD) systolic blood pressure was lower after venesection of 2.5% blood volume (144.0 (18.6) mmHg) compared with baseline (153.5 (18.4) mmHg), mean (95% CI) difference 9.5 (5.8–13.2) mmHg, \(p < 0.001\), but following this the blood pressure remained stable (Fig. 1).

Graphical representations of the change in the monitored variables with increasing blood loss are presented in Figs. 2–5, with the first instance of a variable’s being significantly different from baseline marked. Statistically significant changes in SV from baseline were detected by all four monitors: at blood loss levels of 2.5% with the LiDCO; 7.5% with the US-
Figure 2 Mean stroke volume (red; ml) and stroke volume variation (green; ml) measured using the FloTrac in eight volunteers as blood loss increased up to 20%. Error bars = SD. *First point at which \( p < 0.05 \) from baseline.

Figure 3 Mean stroke volume (red; ml) and stroke volume variation (green; ml) measured using the LiDCO in eight volunteers as blood loss increased up to 20%. Error bars = SD. *First point at which \( p < 0.05 \) from baseline.

Figure 4 Mean stroke volume (red; ml), peak velocity (green; cm.s\(^{-1}\)) and time-corrected flow (blue; ms) measured using the USCOM in eight volunteers as blood loss increased up to 20%. Error bars = SD. *First point at which \( p < 0.05 \) from baseline.

Figure 5 Mean stroke volume (red; ml), peak velocity (green; cm.s\(^{-1}\)) and time-corrected flow (blue; ms) measured using the CardioQ in eight volunteers as blood loss increased up to 20%. Error bars = SD. *First point at which \( p < 0.05 \) from baseline.
COM; and 12.5% with the CardioQ and the FloTrac. The absolute magnitude of these changes ranged from 3.25 ml with the LiDCO to 17 ml with the FloTrac (Figs. 2–5). The only variable to change significantly from baseline apart from SV was peak velocity, as measured by the CardioQ; this fell from 116.2 cm.s\(^{-1}\) to 106 cm.s\(^{-1}\) after 10% blood loss (95% CI of difference 1.8, 18.6, \(p = 0.026\)). The monitor-specific change in SV for predicting >10% blood loss is shown in Fig. 6.

The sizes of the changes in SV and clinical signs used for constructing the ROC curves, areas under the curves, and positive and negative predictive values are presented in Table 1. Of note, the optimal change modelled to predict blood loss is different for each monitor. The positive likelihood ratios for the whole number changes in heart rate (3 bpm) or SV (7–12 ml) modelled for the ROC curves by device are presented in Table 2.

The only significant haemodynamic changes in response to a passive leg raise were seen after 20% blood volume venesection. Mean (SD) heart rate fell by 3.7 (3.6) bpm (95% CI 0.35–7.7 bpm), \(p = 0.036\). The CardioQ demonstrated an increase in mean (SD) SV from 70.5 (12.2) ml to 82 (8.2) ml (mean (95% CI) difference 11.5 (2.7–20.3) ml, \(p = 0.02\)) and peak velocity rose from 96.6 (17.3) cm.s\(^{-1}\) to 103.7 (17.7) cm.s\(^{-1}\) (\(p = 0.012\)).

During re-infusion of the blood, heart rate did not return to baseline. Mean heart rate at restoration of blood volume was unchanged compared with maximal hypovolaemia (mean (95% CI) difference 1.8 (–8 to 4.5) bpm, \(p = 0.53\)) but higher than pre-venesection (mean (95% CI) difference 9.3 (2.5–16.1) bpm, \(p = 0.015\)). Mean (SD) blood pressure was unchanged compared with that at maximal blood loss for both systolic (respectively 148 (15) mmHg vs 144 (17) mmHg, mean (95% CI) difference 3.6 (–9.3 to 16.5) mmHg, \(p = 0.53\)) and diastolic (respectively 80 (10) mmHg vs 83 (11) mmHg, mean (95% CI) difference 3.0 (–6.2 to 12.2) mmHg, \(p = 0.54\)).

Table 1 Changes in clinical signs and stroke volume (SV) measured using four minimally invasive monitors in eight volunteers during venesection of 20% blood loss in 2.5% aliquots.

<table>
<thead>
<tr>
<th>Monitor</th>
<th>AUC Baseline</th>
<th>Change modelled</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate;</td>
<td>0.783 70.8</td>
<td>+2.6</td>
<td>71.0%</td>
<td>69.7%</td>
</tr>
<tr>
<td>bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP;</td>
<td>0.598 153.5</td>
<td>–8.7</td>
<td>62.5%</td>
<td>62.5%</td>
</tr>
<tr>
<td>mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP;</td>
<td>0.563 72.5</td>
<td>–2.8</td>
<td>61.3%</td>
<td>60.6%</td>
</tr>
<tr>
<td>mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FloTrac SV;</td>
<td>0.821 138.9</td>
<td>–11.8</td>
<td>71.0%</td>
<td>80.8%</td>
</tr>
<tr>
<td>ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LiDCO SV;</td>
<td>0.712 106</td>
<td>–7.4</td>
<td>74.2%</td>
<td>72.7%</td>
</tr>
<tr>
<td>ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USCOM SV;</td>
<td>0.684 96.2</td>
<td>–9.4</td>
<td>66.7%</td>
<td>67.7%</td>
</tr>
<tr>
<td>ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CardioQ SV;</td>
<td>0.788 90.8</td>
<td>–10.7</td>
<td>73.9%</td>
<td>70.8%</td>
</tr>
<tr>
<td>ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Positive likelihood ratios for change from baseline in heart rate or stroke volume measured using four minimally invasive monitors in eight volunteers during venesection of 20% blood loss in 2.5% aliquots.

<table>
<thead>
<tr>
<th>Change modelled</th>
<th>10% blood loss</th>
<th>15% blood loss</th>
<th>20% blood loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate; bpm</td>
<td>–3</td>
<td>5.7</td>
<td>14.0</td>
</tr>
<tr>
<td>FloTrac; ml</td>
<td>–12</td>
<td>6.0</td>
<td>9.5</td>
</tr>
<tr>
<td>LiDCO; ml</td>
<td>–7</td>
<td>5.0</td>
<td>3.3</td>
</tr>
<tr>
<td>USCOM; ml</td>
<td>–9</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>CardioQ; ml</td>
<td>–11</td>
<td>6.2</td>
<td>8.8</td>
</tr>
</tbody>
</table>

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produced a study in non-fasted volunteers in which a 45 to redistribution of blood volume is supported by a recent [19]. The possibility that a 30 to redistribution of blood to the central circulation was only observed with the CardioQ. The literature in this area is limited [18], but the method of passive leg raise used in this study, from supine to 30°, rather than to 45°, may be associated with a reduced to redistribution of blood to the central circulation [19]. The possibility that a 30° leg raise is insufficient to redistribute blood volume is supported by a recent study in non-fasted volunteers in which a 45° leg raise produced a > 10% change in SV in nearly half of those studied [20].

Without the dynamic challenge to the circulation of positive pressure ventilation, it is not surprising that SV variation was not altered with the levels of blood loss assessed in this study. This is consistent with published studies demonstrating a lack of change in peripheral measures of cardiovascular status with normal breathing [21], or patterned breathing [22], despite simulated hypovolaemia. Other dynamic manoeuvres, such as a Valsalva manoeuvre, may warrant further investigation.

The strength of this study is the methodology of measuring actual blood loss rather than a surrogate or alternative method of cardiac output or SV. This has allowed a small study to demonstrate that a moderate degree of blood loss (> 10%) was predicted better using these monitors than by changes in invasive arterial blood pressure. Heart rate change generated a reasonable area under the ROC curve and positive likelihood ratios during venesection; however, the small size of the change in heart rate and the failure of heart rate to return to normal with re-infusion of blood raise questions about its utility. All of the minimally invasive monitors, with the exception of USCOM, had greater than 70% positive and negative predictive values for detecting blood loss. The magnitudes of the changes in SV (8.5–11.8% of baseline, or 7–12 ml) were big enough to be clinically detectable. It may be possible to improve the predictive value of these devices by utilising additional clinical or computed information [23, 24].

There are a number of limitations to this study. The study participants were young, healthy males who took no medication and had minimal discomfort and no pathological process occurring to cause the blood loss. This state is fundamentally different from the state of intense sympathetic stimulation, systemic inflammatory activation and immunomodulation [25] that may be associated with injuries or surgery causing similar or larger degrees of blood loss. Despite this lack of major trauma, it is possible that the small increases in heart rate observed may be related to nociception from the study technique rather than the level of blood loss, as heart rate failed to return to baseline values despite complete volume restoration.

A consequence of the small study size is the inability to apply repeated measures modelling, beyond the paired analysis conducted. The sequential

2.0 mmHg, p = 0.172) and diastolic (72.5 (5.0) mmHg vs 70.5 (4.9) mmHg, mean (95% CI) difference 2.0 (–5.1 to 1.1) mmHg p = 0.174).

Over the period of blood re-infusion, SV recovered to pre-venesection levels. The first statistically significant increase in SV was seen after 10% blood had been re-infused with the CardioQ (mean (95% CI) 14.7 (6.1–23.2) ml, p = 0.007) and the FloTrac (11.4 (0.5–22.2) ml, p = 0.042), 15% with the LiDCO (7.1 (1.6–12.6) ml, p = 0.018) and 20% for USCOM (15.8 (5.6–25.6) ml, p = 0.008). Passive straight leg raise during re-infusion of venesected blood was not associated with any significant changes in clinical signs at any level of blood loss.

**Discussion**

This study illustrates the potential of minimally invasive cardiac output monitors to aid detection of blood loss in the conscious patient. The change in SV tracks blood loss and restoration of blood volume better than other variables monitored by these devices, or indeed clinical signs.

This study affirms a number of previous studies that highlight the poor utility of clinical signs in predicting blood loss or hypovolaemia [2, 4, 15, 16], and challenges the classical teaching of the presence of tachycardia with more than 15% blood loss [17]. The participant who developed supraventricular tachycardia at 20% blood loss stated subsequently that he had not maintained an oral intake of clear fluids until 2 h pre-procedure (he had fasted for over 12 h), and was therefore likely to have been dehydrated by the time of the study.

Surprisingly, passive leg raise did not aid immediate detection of hypovolaemia until maximal blood loss; even then, a significant change from the supine state was only observed with the CardioQ. The literature in this area is limited [18], but the method of passive leg raise used in this study, from supine to 30°, rather than to 45°, may be associated with a reduced to redistribution of blood to the central circulation [19]. The possibility that a 30° leg raise is insufficient to redistribute blood volume is supported by a recent study in non-fasted volunteers in which a 45° leg raise produced a > 10% change in SV in nearly half of those studied [20].
approach to paired statistical testing, to minimise the number of tests performed, resulted in different numbers of tests to detect changes applied for each device. This made it impossible to apply a consistent reduction in the statistical significance cut-off, so our results need to be interpreted with caution. The study is small, and although it has defined likely levels of detection of blood loss in conscious patients, a larger study would facilitate in-depth statistical modelling and greater precision. This could allow for improved detection of blood loss by incorporating clinical signs and monitor output, or by modelling multiple monitor outputs into a single ‘chance of blood loss’ score. The ROC curves and positive and negative predictive values generated from this study also need validating in another setting.

Our experience suggests that the utility of the devices may vary according to the clinical setting. The nasal oesophageal Doppler probe was poorly tolerated in the unmedicated patient after 45–60 min, and only successfully placed in six of eight motivated participants. This is a different situation to that where the CardioQ is used intra-operatively and inserted during anaesthesia.

The question of how much blood loss is important before consequences of hypovolaemia are seen has not been answered by our study. An interplay of patient and surgical factors will influence this for an individual patient. The issue of SV optimisation is a related but different issue [26]. It may be that the monitors we tested have their ideal role in the detection of hypovolaemia as measured by a fall in SV from baseline, rather than attempting to maximise SV. These technologies offer at least the chance for better detection of hypovolaemia in the conscious patient, potentially improving fluid replacement, avoiding the adverse consequences of blood loss and possibly facilitating timely surgical intervention in these patients. We hope that this proof of concept study stimulates further clinical work in this area.

Acknowledgements
The authors acknowledge Drs Roger Browning, Nigel Hamilton, Anton Van Niekerk, Will Fellingham and Alex Swann for volunteering to be venesected and monitored for this research project.

Competing interests
Edwards Lifesciences provided partial funding support for the study. All devices studied were loaned by the manufacturers for the duration of the study. USCOM provided a technician to operate its device for the duration of the study. No competing interests declared.

References


Conditioning out-of-date bank-stored red blood cells using a cell-saver auto-transfusion device: effects on numbers of red cells and quality of suspension fluid*

M. S. Read, P. Coles, M. Pomeroy, E. Anderson and M. I. Aziz

1 Consultant Anaesthetist, 3 Core Trainee in Paediatrics, University Hospital of Wales, Cardiff, UK
2 Consultant Anaesthetist, Morriston Hospital, ABMU Health Board, Swansea, UK
4 Consultant Anaesthetist, Prince Charles Hospital, Merthyr Tydfil, UK

Summary
We investigated the utility of a cell-saver device for processing out-of-date red blood cells, by washing twenty bags of red blood cells that had been stored for between 36 and 55 days. The volume of recovered cells, and the characteristics of the suspension fluid, were measured before and after treatment. The ratio of free haemoglobin to total haemoglobin was up to 0.02 before processing, and up to 0.011 afterwards, changing by between −0.013 and +0.003. This ratio met the current standard for free haemoglobin (less than 0.008 in more than 75% of samples), both before and after processing. Ninety-three percent of red blood cells survived the process. Potassium ion concentration fell from above 15 mmol.l⁻¹ in all cases, to a mean of 6.4 mmol.l⁻¹ (p < 0.001). The pH rose to a mean value of 6.44 (p = 0.001). Lactate ion concentration fell to a mean value of 14 mmol.l⁻¹ (p < 0.001). Sodium ion concentration rose from a mean value of 93 mmol.l⁻¹ to a mean value of 140 mmol.l⁻¹ (p < 0.001). A useful proportion of out-of-date red blood cells remained intact after conditioning using a cell-saver, and the process lowered concentrations of potentially toxic solutes in the fluid in which they were suspended.

Correspondence to: M. S. Read
Email: martyn.read@wales.nhs.uk
Accepted: 26 April 2014

Introduction
Bank-stored red blood cells (RBCs) are discarded after a prescribed number of days in storage (35 in Britain, 42 in the USA) because of concerns about deterioration and resulting toxicity. Even for in-date RBCs, some authors have expressed concerns about high concentrations of potassium ions in the suspension fluid [1–3], and concentrations of hydrogen ions, lactate ions and free haemoglobin are potentially also of concern as storage time increases. During storage, RBCs develop a ‘storage lesion’ during storage, the early stages of which include suboptimal oxygen carriage and red cell deformability, and effects on the recipient’s vascular tone and on immune system [4, 5]. In the late stages, changes to the RBCs are evident on microscopy. Ideally, laboratory testing would be able to differentiate between bags of RBCs that are in good condition, transfusion of which will benefit the patient, and those that have deteriorated over time and will therefore do more harm than good. However,
there is no universally accepted test or criterion for this [6].

Cell-savers are used routinely in operations with significant blood loss. Placing RBCs into a cell-saver that is already in use would involve almost no additional effort or cost compared with transfusing them directly, and it may be that this strategy would convert out-of-date RBCs from being unsafe for transfusion to being safe. Doing this in a blood bank would require extra equipment and training, and would introduce further concerns regarding the safe storage of the RBCs after processing.

Investigating whether out-of-date RBCs can be made safe for transfusion into patients if they are processed by a cell-saver immediately before transfusion means determining: (1) the fraction of the original RBCs that survive the cell-saver washing process; (2) the toxicity of the resulting suspension fluid; (3) the fraction of transfused RBCs that survive for 24 h after transfusion; (4) physiological, biochemical, immunological or haematological changes in recipients; and (5) clinically relevant outcomes such as mortality, infection rates, etc. This article reports our investigation into the first two of these.

Methods
We obtained confirmation from the local research and development committee that this study did not require formal ethical approval.

Twenty bags of leucocyte-depleted RBCs suspended in ‘SAG-M’ (adenine, glucose and mannitol in saline) that had been refrigerated and stored for between 36 and 55 days were included in the study.

Before being processed, each bag of bank-stored RBC suspension was first gently mixed, and then sampled by collecting 15 ml into a universal container and 1 ml into a heparinised blood gas syringe. The RBC suspension was then transferred from the storage bag into the bowl of a BRAT 2 (Baylar Rapid Autologous Transfusion, model 2) cell-saver system (COBE Cardiovascular Inc., Arvada, CO, USA) through a UHS Maxi Set Blood Infusion Set (Universal Hospital Supplies Ltd, Enfield, UK). These sets contain a 200-μm filter.

The recommended volume of wash fluid during cell-saver processing differs according to circumstance. Larger volumes are used in obstetric and orthopaedic surgery than in general or urological surgery. Since we were unable to predict the ideal wash volume in this novel use of the cell-saver, we chose to end the washing process when the emerging fluid appeared clear to the naked eye.

This process produced RBCs suspended in wash fluid (0.9% saline). Volumes of RBC suspension put in, wash fluid used and RBC suspension produced were displayed by the cell-saver, and note was taken of these. After gentle mixing, samples of the resulting RBC suspension were again taken, 15 ml in a universal container and 1 ml in a heparinised blood gas syringe. The universal container samples were kept refrigerated before being analysed within three hours. An ABZ 800 Flex blood gas analyser (ABX Horiba Diagnostics, Montpellier, France) was used to measure pH and concentrations of bicarbonate, lactate, potassium and sodium ions. These analyses were done within 15 min of sampling.

The haematocrit and the haemoglobin concentration of the RBC suspension in the universal containers was measured using a Pentra 120 blood analyser (ABX Horiba Diagnostics) and a Beckmann DU-640 spectrophotometer (Beckmann Coulter, Brea, CA, USA), respectively. The suspension fluid in the samples was isolated by centrifugation using a Heraeus Labofuge 400-R Centrifuge (Heraeus, Hanau, Germany), and the haemoglobin concentration of this supernatant was measured using the same spectrophotometer.

Haemoglobin concentration was calculated from the spectrophotometer readings in the manner described in the extract from Welsh Blood Service Standard Operating Procedure CCQ-099, included below as Appendix 1.

The two-way paired Student’s t-test was used to assess the significance of the haemoglobin concentration results. The Wilcoxon signed-rank test was used to analyse the pH, bicarbonate, lactate, potassium and sodium results.

Results
The median (IQR [range]) age of the bags of RBC suspensions was 46 (36–48 [36–530]) days, and the volume of saline used for washing was 2000 (1013–2056 [1005–2542]) ml.
The volume of the bags was changed little by processing, from a mean of 234 ml to a mean of 241 ml. The mean difference was +7.2 ml (SD 42 ml, 95% CI 18.6 ml [range -103 to +70 ml]). Total haemoglobin in the bags also changed little, from a mean of 42.1 g to a mean of 39.1 g. The mean difference was -3.0 g (SD 6.8 g, 95% CI 3.0 g [range -23.9 g to +6.3 g]). Because the fraction of haemoglobin that was extracellular was very small compared with the intracellular fraction, calculation of the amount of intracellular haemoglobin in the bags after processing produced very similar results. There was a change from a mean of 41.8 g to a mean of 38.9 g. The mean difference was -3.0 g (SD 6.5 g, 95% CI 2.7 g [range -23.9 g to +6.3 g]).

The percentage of bags with free haemoglobin less than 0.8% of total haemoglobin was 85% before processing and 90% after processing.

Pre- and post-processing ratios of free to total haemoglobin concentrations, pH and concentrations of bicarbonate, lactate, potassium and sodium ions are shown in Table 1 and in Figs 1–6. Among the pre-processing samples, some readings were outside the range for which the blood gas analyser could give values. Thus, some pre-processing bicarbonate, lactate,
potassium and pH readings were recorded as $< 4 \text{ mmol}^{-1}$, $> 30 \text{ mmol}^{-1}$, $> 15 \text{ mmol}^{-1}$ and $< 6.3$, respectively. For the purposes of comparison and statistical testing, these were replaced with values of exactly $4 \text{ mmol}^{-1}$, $30 \text{ mmol}^{-1}$, $15 \text{ mmol}^{-1}$ and $6.3$, respectively, which increased the likelihood of a type-2 error (failing to show a significant difference when in fact there was one). Non-parametric tests of significance were used for these parameters because this assumption would mean that the data were not normally distributed.
Figure 7 demonstrates that there was no relationship between the concentration of free haemoglobin (before processing) and the storage time of the RBCs.

The effect of the cell-saver on the ratio of extracellular-to-total haemoglobin concentration is shown in Fig. 8. The mean change of this ratio was \(-0.0012\). Of the ten bags in which the ratio was initially below the median, it rose in seven. Of the ten bags in which it was initially above the median, it fell in eight.

**Discussion**

Guidelines for permitted levels of haemolysis for bank-stored RBCs in Britain (Appendix 2) stipulate that in more than 75% of bags of RBCs, fewer than 0.8% of the red cells should have undergone haemolysis [7]. In the context of RBCs that have been processed with a cell-saver, the number of cells that have lysed is not of interest: the washing process is able to remove the resulting debris. What is still of interest is the ratio of extracellular haemoglobin (the unwanted fraction) to total haemoglobin. The standard, expressed above as less than 0.8% of RBCs, can equally be expressed as a ratio of extracellular-to-total haemoglobin of \(<0.008\).

Guidelines from the US Food and Drugs Administration (Appendix 3) stipulate that survival of RBCs at 24 h after transfusion should be greater than 75% [8]. In one study in 2008, RBCs 25–35 days old only just met this standard, and younger RBCs performed much better [9]. Most of the removal of what the authors of this article termed ‘removal-prone’ RBCs occurred in the first hour after transfusion.

It has been suggested by many authors that RBCs in the first part of the maximum permitted storage time are safer than older RBCs, implying that the current maximum permitted storage time may be too long. This has been refuted recently in an observational study in adults [10] and a randomised controlled trial in infants [11]. Three further randomised controlled trials investigating this question are currently under way: the

![Figure 6](image-url)  
**Figure 6** Sodium ion concentration before and after processing.

![Figure 7](image-url)  
**Figure 7** Extracellular/total haemoglobin ratio in bags of RBCs (before processing) according to number of days of storage.
Age of Blood Evaluation (ABLE) trial in the resuscitation of critically ill patients; the Red Cell Storage Duration (RECESS) study; and the Red Cell Storage Duration and Outcomes in Cardiac Surgery study.

There are thus three types of evidence indicating the relationship between the age of bags of stored RBCs and their toxicity: (1) laboratory studies, with an uncertain relationship between laboratory measurements and clinical outcomes; (2) studies of physiological, biochemical, immunological or haematological changes in transfusion recipients, including the survival of RBCs after transfusion, again with an uncertain relationship between observed variables and clinical outcomes; and (3) epidemiological evidence that looks specifically at clinical outcomes, without concerning itself with mechanisms of toxicity. Current practice standards are based on some of this evidence, but none of it definitively indicates a safe maximum storage time.

Rather than simply transfusing stored RBCs, some workers have tried processing (referring to it as ‘rejuvenating’) them before transfusion. In a study that involved washing 35–39 day-old RBCs with a specific mixture designed to replace lost substances and functions, the 24-hour post-transfusion survival value was 80% [12].

Others have processed in-date RBCs with a cell-saver and demonstrated a reduction in the toxicity of the suspension fluid [1–3]. However, this has been shown to induce some haemolysis, both at the time of processing and (when stored in vitro) for some hours afterwards [13]. A study using RBCs up to 49 days old also found that processing with a cell-saver reduced the toxicity of the suspension fluid, and that some haemolysis occurred, but the number of bags of RBCs was smaller than in the present study, and the authors did not measure the fraction of RBCs that survived [14].

The propensity for RBCs to haemolyse may be assessed using the mechanical fragility index, the haemolysis rate caused by a standardised mechanical stress applied to RBCs. Compared with fresh blood, this is raised in in-date RBCs [15] and in fresh blood processed by a cell-saver [16]. It is higher in in-date RBCs that have been processed by a cell-saver than in unprocessed, in-date RBCs [17].

The analysis of our results of the pH, bicarbonate, lactate and potassium concentrations included a risk of a type-2 error. Despite this fact, the differences were statistically significant for all four parameters, as well as for the sodium results. Therefore, it is reasonable to conclude that after processing with the cell-saver, reductions were seen in concentrations of potassium and lactate ions; sodium ion concentration rose from sub-physiological levels to physiological ones. Bicarbonate ion concentration fell, but pH rose slightly, in keeping with the fall in lactate ion concentration.

Figure 8 Extracellular/total haemoglobin ratio before (■) and after (□) processing, ranked in order of increasing pre-processing ratio.
The concentration of free haemoglobin was somewhat high in a number of bags, but within the standard for in-date stored RBCs. Processing did not affect this proportion. There was a trend for the free haemoglobin concentration to rise in bags in which the initial concentration was low, and for it to fall when the initial concentration was high. The fact that it rose in some bags suggests that haemolysis occurred during processing, and that the haemoglobin released by this mechanism had been imperfectly removed.

It may be that the final free haemoglobin concentration was determined more by the equilibrium of haemolysis and haemoglobin removal than by the initial free haemoglobin concentration. This would account for the ‘reversion towards the mean’ pattern we observed in changes in free haemoglobin concentration during processing.

The small changes in volume of bags and the haemoglobin concentration within them imply that this haemolysis made little difference to the total number of RBCs. During the study, it was noted that fluid volumes measured by the cell-saver could be slight overestimates. This was because the rotary pump within the cell-saver sometimes made a small but variable number of extra turns after fluid had been replaced by air in the tubing at the point of the air sensor. The cell-saver is in daily use at our institution, and clinical decisions are made on the basis of its measurements of fluid volumes. We consider these measurement errors to be small. It may explain the fact that in some cases there appeared to be a small increase in the amount of haemoglobin in the bag.

Recent studies (published or ongoing) address whether the maximum permitted storage time is appropriate or whether it is too long. This study has shown that RBCs that have been stored for longer than the currently accepted maximum time can be processed by a cell-saver autotransfusion device to improve the safety profile of the fluid in which they are suspended. This process causes haemolysis, but the number of RBCs lost through this is small. It also washes out free haemoglobin. The balance of these two effects produces an acceptably low concentration of free haemoglobin in the suspension fluid.

We surmise that washing the RBCs for longer, with a larger volume of wash fluid, may have further reduced the concentrations of toxic chemicals, may have caused fewer RBCs to survive the process, and may have caused more haemolysis, with an unpredictable effect on the free haemoglobin concentration in the suspension fluid.

Further work is warranted to investigate the characteristics of the RBCs that remain after processing. We postulate that the removal-prone RBCs would be lysed by the cell-saver, selecting out robust RBCs that remained intact.

Acknowledgements
We gratefully acknowledge the help of Christopher Lee, Biomedical Scientist, University Hospital of Wales, for invaluable help in measurement of light absorption for haemoglobin concentration.

Competing interest
No external funding and no competing interests declared.

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### Appendix 1

Calculations of free haemoglobin in the supernatant and of ‘percent haemolysis’ specified in the Welsh Blood Service standard operating procedures.

\[
\text{Fr-Hb} \left( \text{mg.}100 \text{ ml}^{-1} \right) = \left( 115 \times 576 \text{ nm-A} \right) - \\
\left( 102 \times 623 \text{ nm-A} \right) - \\
\left( 39.1 \times 700 \text{ nm-A} \right) \times \text{dilution factor}
\]

where Fr-Hb is the haemoglobin concentration of the supernatant, and 576 nm-A, 623 nm-A and 700 nm-A are absorbance measurements at light wavelengths of 576, 623 and 700 nm, respectively. The dilution factor is used to produce a useful range of absorbances measurable at the above wavelengths.

\[
\% \text{ Haemolysis} = \left( \frac{100 - \% \text{ HCT} \times \text{supernatant Hb}}{\text{Total Hb}} \right)
\]

where HCT is the haematocrit.

### Appendix 2

British guidelines for permitted levels of haemolysis for bank-stored RBCs: “Haemolysis measurements on red cell components are performed at the end of the component shelf life. Due to intermittent availability of outdated red cell components, each primary process should be validated to give haemolysis of < 0.8% of the red cell mass at the end of component shelf life in > 75% of components with a minimum of 20 components tested” [7].

### Appendix 3

Levels of RBC survival expected by the US Food and Drugs Administration: “Radiolabelling studies should be performed in at least two separate centres (laboratories) with a total of 20–24 healthy donors. The mean recovery at 24 hours for each unit should be > 75% with SD < 9%; and the one sided 95% lower confidence limit for the population proportion of successes > 70%” [8].
Does individual experience affect performance during cardiopulmonary resuscitation with additional external distractors?

R. Krage,1 L. Tjon Soei Len,2 P. Schober,1 M. Kolenbrander,2 D. van Groeningen,3 S. A. Loer,4 C. Wagner5 and L. Zwaan6

1 Consultant Anaesthetist, 2 Anaesthesia Resident, 3 Anaesthesia Nurse, 4 Professor of Anaesthesia, Department of Anaesthesia, VU University Medical Centre, Amsterdam, The Netherlands
5 Professor of Patient Safety, 6 Psychologist, Research Fellow, Department of Public and Occupational Health, EMGO Institute for Health and Care Research, Amsterdam, The Netherlands

Summary
Cardiopulmonary resuscitation is perceived as a stressful task. Additional external distractors, such as noise and bystanders, may interfere with crucial tasks and might adversely influence patient outcome. We investigated the effects of external distractors on resuscitation performance of anaesthesia residents and consultants with different levels of experience. Thirty physicians performed two simulated resuscitation scenarios in random order, one scenario without additional distractors (control) and one scenario with additional distractors (noise, scripted family member). Resuscitation performance was assessed by a score based on European Resuscitation Council guidelines, presented as median (IQR [range]). We found that performance scores were lower under experimental conditions (11.8 (9.0–19.5 [−9.0 to 28.5])) than under control conditions 19.5 (14.0–25.5 [5.0–29.5]), p = 0.0002). No interaction was observed between additional distractors and experience level (p = 0.4480). External distractors markedly reduce the quality of cardiopulmonary resuscitation. This suggests that all team members, including senior healthcare providers, require training to improve performance under stressful conditions.

Correspondence to: R. Krage
Email: r.krage@vumc.nl
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Introduction
Cardiopulmonary resuscitation (CPR) is perceived as a stressful task by medical teams [1, 2]. Stress is defined as a non-specific response of the body to an event or stimulus (stressor), and it has been suggested that stress can interfere with the performance of technical skills in critical situations [2, 3]. Stressors vary in form and include factors regularly encountered during CPR, such as high workload and time pressure. Additional external distractors, such as noise and presence of family members or bystanders during resuscitation, may also distract from crucial tasks and may have a negative impact on teamwork, and hence might adversely influence overall patient outcome.

Previous data on the effect of external distractors on human performance during CPR are conflicting [1, 2]. Moreover, to our knowledge, there are no data on whether the experience of a healthcare provider has an influence on performance during CPR when affected by additional distractors. Although it seems plausible
that more experienced providers – who may often serve as the leader of a resuscitation team – can better focus on their tasks and may get distracted less easily than inexperienced providers, this might not necessarily be true. Therefore, we investigated whether external distractors influence performance during a standardised simulated CPR scenario in general, and specifically tested the hypothesis that performance during CPR with external distractors depends on the level of experience of healthcare providers.

Methods
The study was conducted at the ADAM simulation centre of the VU university medical centre in Amsterdam, the Netherlands. The institutional ethical review board approved the study. Every participant gave written informed consent to take part in this study. Thirty physicians with different levels of clinical experience (group 1: 1st and 2nd year anaesthesia residents; group 2: 4th and 5th year anaesthesia residents; group 3: consultant anaesthetists; n = 10 per group) participated on a voluntary basis. All participants were part of our hospital resuscitation team and were trained in advanced life support (ALS). Volunteers were informed that their CPR performance during two simulated scenarios would be evaluated in the context of a scientific investigation, but they were not aware that we were specifically interested in the effects of external distractors.

Before commencing the study, each participant received a 15-min structured familiarisation with both the simulator and the environment (available equipment and drugs, logistics and communication pathways to get further assistance). A full-scale patient simulator (SimMan™; Laerdal Medical Corporation, Stavanger, Norway) was used to simulate CPR scenarios as described below. Features of this simulator include palpable pulses and spontaneous breathing with visible thoracic excursions. The simulator was placed on an emergency room stretcher in our simulation centre, and was connected to a monitor that displayed all common vital signs such as ECG, non-invasive blood pressure, capnography and temperature. A peripheral intravenous cannula was in place to allow for intravenous administration of drugs. All drugs and equipment necessary to perform CPR according to current guideline recommendations, including a manual defibrillator, were available in the simulating room.

In this randomised crossover study, each volunteer participated in two simulated CPR scenarios. One ‘standard’ resuscitation scenario without external distractors served as the control condition, and one scenario with additional distractors as described below served as the experimental condition. Participants were assigned the role of leader of the resuscitation team, and were provided with three additional team members, who were part of the research group: a first-year anaesthesia resident; a medical student; and an emergency room nurse. The team was instructed to act with helpful attitude, but to be active on commands of the participant only. All scenarios were recorded on video to allow for accurate rating of CPR performance.

Using exactly the same scenario twice for each participant (except for the fact that one scenario contains additional distractors) might lead to carry-over effects in the way that participants could instantaneously recognise that they are confronted with the same situation, and that they would basically have to perform the same actions as in the first scenario. We therefore developed two ‘standard’ simulation scenarios that could be presented either with or without additional distractors (i.e. both scenarios could serve as ‘control’ or ‘experimental’ condition, depending on whether distractors were added or not). One scenario featured ventricular tachycardia (VT) without cardiac output and the other ventricular fibrillation (VF). To create a different mind-set for the study participants when entering the simulator room, the case briefing described different medical histories (patient with chest pain vs patient who collapsed). Note that although two different scenarios and medical histories were chosen to create a different mind-set and to minimise carry-over effects, both scenarios required exactly the same treatment during CPR, allowing direct comparison of performance.

For each participant, additional external distractors were randomly added to either the first or second scenario. The external distractors consisted of a scripted family member of the patient (role-play) who was talking to the physician during the procedure at predefined crucial moments (such as the start of resuscitation, defibrillation, re-assessment) and a constant static radio noise at approximately 70 decibels.
Randomisation of the sequence in which the scenarios (VT vs VF) and the distractors (external distractors vs no external distractors) were presented was performed using a sealed envelope technique.

We developed a scoring protocol based on recommendations in the European Resuscitation Council (ERC) guidelines to assess and summarise individual CPR performance in a single score. The score ranges from $-12$ to $+34$ (negative scores were assigned for omission of defibrillation, chest compressions and drug administration) and represents a weighted sum of a number of elements that are considered crucial for efficient resuscitation. This includes recognition of cardiac arrest, calling for assistance, recognition of a shockable heart rhythm, time to defibrillation, start of chest compressions, checking quality of chest compressions and time to administration of adrenalin. The score was developed in an audit process within the study group in close collaboration with the hospital’s resuscitation board and experienced non-investigator physicians. After data collection, two reviewers watched the recorded videos and independently rated the technical performance.

Since timely defibrillation in shockable rhythms and initiation of chest compressions are considered crucial events during CPR with a proven impact on outcome [4], we specifically considered time to first defibrillation and time to starting of chest compressions as secondary outcome parameters. These times were dichotomised depending on whether participants started chest compressions and performed defibrillation within clinically acceptable limits (60 and 90 s, respectively).

Results were analysed by the STATA 13.0 statistical package (StataCorp, College Station, TX, USA). Performance scores showed a marked skewed distribution. To allow for parametric analysis, the score was transformed to a normal probability distribution using a Box-Cox transformation with a transformation parameter of 1.7 after re-centring of the original score to non-negative values [5]. Normal distribution of the transformed variable was confirmed by the Shapiro–Wilk test and normality plots. Differences between experimental and control conditions (additional distractors vs no additional distractors) were assessed by multifactorial ANOVA. Additional factors included in the ANOVA model were the sequence in which scenarios were presented (potential carry-over effect), time period (potential learning effect), participant identification number (to account for repeated measurements), scenario type and experience group, as well as the interaction between experienced group and distractors (to assess whether the effects of distractors depend on the level of experience).

Dichotomous parameters were compared with Pearson’s chi-squared tests. A p value $< 0.05$ was considered statistically significant.

The intraclass correlation (ICC) was calculated to assess the inter-rater agreement between the two reviewers who individually assigned CPR performance scores.

Power calculations were performed with SAS 9.2 (SAS Institute Inc, Cary, NC, USA). Since the performance score was exclusively developed for this study, no literature was available for a priori estimations of mean differences, standard deviations and correlations between repeated measurements. Calculations using different plausible estimates suggested that a sample size of around 20–30 pairs would be necessary to detect a mean difference of 5 in the performance score between stress and no-stress conditions at a two-sided alpha level of 0.05 and with a power of 0.8. We therefore empirically chose a sample size of 30 pairs.

Results

All participants completed the study. Their characteristics and experience are shown in Table 1.

Overall performance scores were significantly lower when additional external distractors were present than under control conditions (Fig. 1). No interaction was observed between additional distractors and experience level ($p = 0.448$), indicating that the effect of distractors does not depend on the experience level. Figure 2 shows the effects of additional distractors per group of experience. There were no overall significant differences in median (IQR [range]) performance scores between groups of different experience (1st/2nd year residents: 17 (11.8–20.0 [−3.5 to 28.5]), 4th/5th year residents: 19.8 (11.8–21.8 [−9.0 to 29.5]), consultant anaesthetists 14.3 (9.3–20.5 [−2.0 to 29.0]), $p = 0.519$). This was equally true under control conditions (1st/2nd year residents: 17.8 (16.0–21.0...
Table 1 Characteristics of participants performing cardiopulmonary resuscitation with and without external distractors stratified by level of experience. Values are number (proportion), mean (SD) or number.

<table>
<thead>
<tr>
<th>Level of experience</th>
<th>1st and 2nd year residents (N = 10)</th>
<th>4th and 5th year residents (N = 10)</th>
<th>Consultant anaesthetists (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (60%)</td>
<td>6 (60%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Age; years</td>
<td>30.1 (2.6)</td>
<td>33.4 (3.8)</td>
<td>39.8 (6.9)</td>
</tr>
<tr>
<td>Work experience; years</td>
<td>2.7 (1.1)*</td>
<td>5.5 (1.1)*</td>
<td>12.3 (7.1)</td>
</tr>
<tr>
<td>Number of resuscitations performed (in categories)</td>
<td>&lt; 10 = 2</td>
<td>&lt; 10 = 0</td>
<td>&lt; 10 = 0</td>
</tr>
<tr>
<td></td>
<td>10–50 = 8</td>
<td>10–50 = 5</td>
<td>10–50 = 2</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 = 0</td>
<td>&gt; 50 = 5</td>
<td>&gt; 50 = 8</td>
</tr>
<tr>
<td>Number of simulation sessions performed</td>
<td>0 = 2</td>
<td>0 = 0</td>
<td>0 = 0</td>
</tr>
<tr>
<td></td>
<td>1 = 3</td>
<td>1 = 7</td>
<td>1 = 2</td>
</tr>
<tr>
<td></td>
<td>2 = 3</td>
<td>2 = 2</td>
<td>2 = 3</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 = 2</td>
<td>&gt; 3 = 1</td>
<td>&gt; 3 = 3</td>
</tr>
</tbody>
</table>

*In the Netherlands residents obtain work experience before their official residency.

Figure 1 Overall effect of additional distractors on performance during CPR scenarios. The horizontal line inside the box depicts the median, the box itself represents the IQR and the whiskers show the full range of data.

Figure 2 Effects of additional distractors on CPR performance in different groups of experience. White boxes indicate conditions without distractors, grey boxes with distractors.

When external distractors were present, significantly fewer participants defibrillated within predefined acceptable clinical time limits (8 participants (26.7%) vs 18 participants (60.0%), p = 0.009). We also observed a trend that fewer participants started chest compressions within the predefined time limit in the scenarios with additional distractors (16 participants (53.3%) vs 22 participants (73.3%), p = 0.108). The type of scenario (VF or VT) was not associated with performance (p = 0.735), suggesting that the type did not confound the relationship between performance and distractors or experience, respectively. The sequence in which the scenarios were presented (first experimental, then control vs first control, then experimental) was also not associated with performance (p = 0.588), suggesting that there were no carry-over effects. However, participants scored
significantly better during the second scenario compared with the first scenario (median (IQR [range]) 19.0 (16.0–21.5 [8.0–29.0]) vs 11.8 (5.0–20.0 [−9.0 to 29.5]), respectively, p = 0.0007), suggesting a learning effect.

A high inter-rater agreement between the two reviewers who individually assigned CPR performance scores was observed (ICC = 0.938).

Discussion

We tested the hypothesis that external distractors influence performance of physicians during CPR, and assessed whether this depends on the physician’s level of experience. The addition of external distractors during CPR markedly reduced the overall quality of performance of anaesthesia residents and anaesthesiologists and significantly delayed the first defibrillation. This is particularly critical because early defibrillation is crucial for survival in patients with VF or pulseless VT [5]. The effects of external distractors on CPR performance scores were independent of the level of experience.

Healthcare professionals usually experience management of cardiac arrest as a high-stress situation [2, 3]. This is even more prominent when bystanders such as family members are present [2]. However, current literature is conflicting on whether such additional distractors actually impair CPR performance. Consistent with our data, Fernandez et al. observed that the presence of distracting family members during a simulated CPR scenario did have an adverse impact on CPR performance in emergency medicine residents [1]. In contrast, Bjørshol et al. did not observe effects of external distractors on CPR quality [2]. In that study, experienced paramedics performed simulation-based resuscitation scenarios with and without distractors. Participants did experience a significant increase in the subjective workload and frustration level when external distractors were present, but CPR performance was not affected. There are several possible reasons for the difference between the findings from that study and our data. First, Bjørshol defined ‘quality of CPR’ as measuring chest compression depth, chest compression rate and no-flow ratio, as well as time to first shock and time to intubation. Our scoring protocol focused more on the adhesion to the ERC CPR guidelines.

This could create a different interpretation of the term ‘performance’. Second, the participants in that study were paramedics, whereas our participants were anaesthesiologists. Bjørshol et al. argued that paramedics face socio-emotional stress quite frequently. Paramedics are used to working in public places with bystanders and external distractors, and may therefore be more ‘resistant’ to such factors than anaesthesiologists, who primarily respond to emergency situations in a confined hospital setting.

Another hypothesis of our study was that medical personnel with more work experience would be less affected by external distractors. Based on the results of our study, we cannot confirm this. No association between the level of distraction and the level of experience was observed, and there were no significant differences in performance between the three experience groups under experimental and control conditions. Common belief and older studies suggest that more experience is associated with better performance [6], whereas accumulating evidence suggests that there is only a weak relationship between the two factors [7]. This is particularly important because more experienced personnel often serve as leaders of resuscitation teams, and are expected to maintain oversight and take correct decisions even under stressful conditions. However, our data suggest that experience neither guarantees good performance during CPR nor is associated with decreased susceptibility to distraction. Rather than solely relying on experienced team leaders, all team members, including senior healthcare providers, require training to improve performance under stressful conditions. This is especially important because external distractors cannot always be eliminated during CPR.

In this context, ample evidence shows that multidisciplinary simulation training improves technical and non-technical skills in medical teams [8–21]. Non-technical skills including communication, leadership, workload and task distribution have been shown to play a pivotal role in mastering stressful clinical situations [3, 8, 10, 22–30]. Therefore, training sessions that particularly address non-technical skills and stress management might help individuals and teams to be better prepared for CPR with a high level of external distractors.
We used a full-scale simulator to assess the effects of external distractors on CPR performance. Performing a similar study in real resuscitations raises several logistic, technical and ethical issues. First, cardiac arrests are acute events in a heterogeneous patient population in different settings and handled by varying resuscitation teams, making it impossible to achieve standardised conditions. Second, assessment of human performance during CPR is a logistic challenge, as it is unlikely that trained observers or a video system arrive at the scene from the very beginning of the arrest. Third, it would be unethical to experimentally introduce distractors with a potentially adverse effect on CPR performance during actual resuscitations. In contrast, use of the simulator allowed for a randomised crossover design under standardised study conditions and in which each participant served as his/her own control. Cardiac arrest scenarios could be run under identical conditions for all participants, distractors could be reproducibly manipulated and CPR performance could reliably be recorded and assessed. Due to these properties, simulator-based studies are broadly accepted as research instruments for CPR performance [12]. Nonetheless, resuscitation on a simulator differs from conditions encountered in actual resuscitation settings. In particular, the level of stress may be higher during an actual resuscitation, but since conditions are alike for all participants, simulation does allow comparisons of experimental vs control conditions.

Our study goal was to assess the impact of distractors on performance. However, to our knowledge no standard scoring protocols are available to assess overall individual human performance of the resuscitation team leader during CPR. Guided by similar scoring protocols used in the aviation industry to score pilot performance, we identified all relevant tasks outlined in the ERC resuscitation algorithm. In an internal audit process, we assigned weights to each task depending on its relevance, and assigned negative scores for omission of tasks that play a pivotal role in the algorithm for shockable rhythms, such as defibrillation, chest compressions and administration of adrenaline. Subsequently, our weighting method was discussed with non-investigator experts in the field from our hospital’s resuscitation commission, and was readjusted until consensus was reached. The overall performance score is the sum of the individual weighted scores, and hence reflects how well the algorithm was followed by the resuscitation team leader, while giving more emphasis on aspects deemed to play a more critical role in the algorithm. Our data show an excellent inter-rater agreement, suggesting good reproducibility of the score that we have developed. Beside the performance score, we also used time to chest compressions and time to defibrillation as outcome parameters. Although there is a broad consensus that both events should be commenced as early as possible, maximum acceptable time limits are not defined in the literature. We consider delays > 60 s unacceptable for starting with chest compressions, and delays > 90 s unacceptable for defibrillation (we allowed extra time for defibrillation because defibrillation pads need to be attached first). Hence, we defined 60 and 90 s, respectively, as cut-off-points for dichotomising response times.

We used two different types of scenarios (VT and VF) to minimise carry-over effects, and our data indeed do not provide evidence for carry-over effects. Moreover, the data demonstrate that using two different scenario types did not confound the relationship between performance and distractors or experience, respectively. However, we did observe a learning effect in the way that performance scores were on average higher in the second than in the first scenario. Due to balanced randomisation, an equal number of participants started with either the control or experimental scenario, and hence the learning effect did not systematically bias the relationship between distraction and performance in our study. In fact, the learning effect is a central goal of simulator teaching sessions, and although it was not a focus of our investigation, this observation does underline the potential of simulation-based training to improve skills that might be beneficial to patient care and safety. We conclude that human performance during CPR is altered when external distractors are added. The effects on performance do not depend on general work experience. It is likely that non-technical skills such as teamwork and leadership skills play an important role. Healthcare should invest more effort into training the non-technical skills of individuals and teams who are working in a high-stress environment.
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Competing interests
No competing interests are declared.

References
The minimally invasive MitraClip™ procedure for mitral regurgitation under general anaesthesia: immediate effects on the pulmonary circulation and right ventricular function

E. Kottenberg,1 M. Dumont,2 U. H. Frey,1 T. Heine,1 B. Plicht,3 P. Kahlert,3 R. Erbel4 and J. Peters5

1 Staff Anaesthetist, 5 Professor, Department of Anaesthesia and Intensive Care Medicine, 2 Medical Student, 3 Staff Cardiologist, 4 Professor, Department of Cardiology, Universität Duisburg-Essen and Universitätsklinikum Essen, Essen, Germany

Summary

A relatively new minimally invasive cardiological procedure, called the MitraClip™, does not require sternotomy and may have a number of advantages compared with open mitral valve surgery, but its acute impact on the pulmonary circulation and right ventricular function during general anaesthesia is unclear. We prospectively assessed the effects of the MitraClip procedure in 81 patients with or without pulmonary hypertension (defined as mean pulmonary artery pressure > 25 mmHg), who were anaesthetised using fentanyl (5 μg.kg⁻¹), etomidate (0.2–0.3 mg.kg⁻¹), rocuronium (0.5–0.6 mg.kg⁻¹) and isoflurane. Placement of the MitraClip led to a 60% increase in mean (SD) right ventricular stroke work index (from 512 (321) to 820 (470) mmHg.ml.m⁻²,p < 0.0001), while mean (SD) pulmonary vascular resistance index decreased by 24% (522 (330) to 399 (244) dyn.s.cm⁻⁵, p < 0.0001), and mean (SD) pulmonary artery pressure decreased by 10% (30 (8) to 27 (8) mmHg, p < 0.0001). Patients with pulmonary hypertension experienced a similar decrease in mean pulmonary artery pressure compared with those without, and they also had a slight reduction in mean (SD) pulmonary artery occlusion pressure (22 (6) down to 20 (6) mmHg, p = 0.044). We conclude that successful MitraClip treatment for mitral regurgitation acutely improves right ventricular performance by reducing right ventricular afterload, regardless of whether patients have pre-operative pulmonary hypertension.

Introduction

The MitraClip™ (Abbot, Wetzlar, Germany) procedure is a recently introduced percutaneous transcatheter technique for the treatment of severe mitral valve regurgitation (MR) [1–3]; it is especially attractive in high-risk patients, as cardiopulmonary bypass, sternotomy, bleeding and tissue trauma may be avoided [1–4]. A major concern after mitral valve surgery is increased left ventricular afterload following elimination of the low-impedance regurgitant pathway into the left atrium; this may result in impaired left ventricular systolic performance [5] and low cardiac output [6]. Patients with MR also have varying degrees of pulmonary hypertension [7] and increased pulmonary vascular resistance, a major risk factor for mortality and worse outcome after both cardiac and non-cardiac surgery [8].
The MitraClip procedure is most often conducted under general anaesthesia with mechanical ventilation of the lungs, therefore the acute effects of the procedure are of particular importance to the anaesthetist. However, data on the acute haemodynamic consequences of the MitraClip procedure during anaesthesia are scarce [9–11] and, to our knowledge, its effects on right ventricular performance and pulmonary hypertension, and their mutual relationship, have not been reported to date.

We therefore investigated the immediate effect of MitraClip placement in high-risk patients under general anaesthesia on the pulmonary circulation and right ventricular performance. Specifically, we hypothesised that right ventricular stroke work index would immediately improve in response to successful MitraClip implantation, and that the haemodynamic effects would be different in patients with and without pulmonary hypertension.

Methods

Following approval of the local ethics committee and with written informed consent for data collection and publication, we enrolled all patients consecutively from March 2009, when our MitraClip programme started, until April 2013. All patients were either symptomatic (dyspnoea) with moderate to severe (3+) or severe (4+) MR, or asymptomatic with the same severity of MR and abnormal left ventricular systolic function (left ventricular ejection fraction < 60% or left ventricular end-systolic diameter > 40 mm), in accordance with the American College of Cardiology/American Heart Association guidelines for mitral valve surgery for MR [12]; this was graded according to the criteria of the American Society of Echocardiography [13]. Pulmonary hypertension was defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mmHg.

After premedication with 0.5–1 mg oral flunitrazepam, both on the evening before and the morning of the procedure, a five-lead electrocardiography system was applied to monitor heart rate, rhythm and ST-segments (leads II and V5). A pulse oximeter was attached and peripheral venous and radial arterial cannulae placed. We administered fentanyl (5 μg·kg⁻¹), etomidate (0.2–0.3 mg·kg⁻¹) and rocuronium (0.5–0.6 mg·kg⁻¹) before tracheal intubation. Patients’ lungs were mechanically ventilated with oxygen in air so as to achieve normocarbia, which was confirmed by arterial blood gas analysis. Anaesthesia was maintained by additional fentanyl boluses and inhaled isoflurane in end-tidal concentrations of 0.6–0.8%. A gastric tube and a urinary catheter were also placed. A triple-lumen catheter and a pulmonary artery catheter were inserted into the right internal jugular vein.

All MitraClip procedures were performed by a single senior cardiologist specialising in this technique. Technical aspects of procedure have been described before in detail [1–3]. Briefly, access to the right atrium is established via a femoral vein; with echocardiographic and fluoroscopic guidance, the inter-atrial septum is crossed and a steering device is advanced through the mitral valve into the left ventricle. The mitral valve leaflets are grasped and the arms of the MitraClip are closed. Mitral valve function and severity of residual MR is then assessed by transoesophageal echocardiography. If further reduction in MR is required, a second device may be placed. If the residual iatrogenic atrial septal defect is thought to be causing deleterious haemodynamic effects, immediate closure is performed using an Amplatzer Septal Occluder (St. Jude Medical, St. Paul, MN, USA). After the procedure, patients were transferred to the intensive care unit.

Cardiac output was derived using the thermodilution technique at end-expiration and over several cardiac cycles, resulting in < 10% variation [14]. Systemic and pulmonary vascular resistance were calculated as the ratio between the pressure drop along the respective vascular beds and the cardiac output, and converted to metric units. Right ventricular stroke volume index, systemic vascular resistance index and pulmonary vascular resistance index were calculated from measured variables using standard formulae. Right ventricular stroke work index was calculated as right ventricular stroke volume index multiplied by the difference between mPAP and mean central venous pressure (CVP). All measurements were taken after induction of general anaesthesia, before and 5 min after device placement.

Data were tested for distribution using the Kolmogorov–Smirnov test. Normally distributed data were compared using Student’s t-test for paired and unpaired
samples. Pearson’s correlation was used to assess the relationship between continuous variables. Non-continuous data were compared using the Wilcoxon test. The null hypothesis was that there was no difference in mean haemodynamic variables before and after MitraClip placement, and that these were the same in patients with and without pulmonary hypertension.

**Results**

A total of 94 patients were studied (Table 1), and data from 81 were analysed; thirteen patients were not studied, nine because of insufficient or missing data that could not be retrieved from the anaesthesia recording system and four because the MitraClip procedure failed. Acute procedural success was defined as a reduction in MR to moderate or less (grade ≤ 2+) following MitraClip placement and this was achieved in 81 (95%) patients. Septal closure was necessary in 21 patients (22%).

Complications were rare and there were no procedural deaths. The failed procedures were due to a technical defect of the delivery system (n = 1), and inability to deploy the clip at the target region (n = 3). One patient developed a haematoma following puncture of a subclavian artery. Another patient underwent emergency mitral and tricuspid valve surgery because of a technical defect of the delivery system.

Following successful device deployment, there was a significant reduction in MR from pre-operative values (Table 1). There was no effect on tricuspid valve regurgitation. Five minutes after device deployment, right ventricular stroke work index increased by 60%, pulmonary vascular resistance index decreased by 24% and mPAP decreased by 10% (Table 2). In addition, there was a 68% increase in cardiac index, and right ventricular stroke volume index increased by 38%, whereas CVP and pulmonary artery occlusion pressure remained unchanged.

There was a significant inverse association between right ventricular stroke volume index and pulmonary vascular resistance index both before (r = −0.4352, p < 0.0001) and after (r = −0.4866; p < 0.0001) successful MitraClip implantation (Fig. 1a,b). However, pulmonary vascular resistance index was less for the same right ventricular stroke volume index. In contrast, right ventricular stroke volume index and mPAP were not correlated either before (r = −0.15, p = 0.18) or after (r = −0.21, p = 0.08) MitraClip implantation (Fig. 1c,d).

**Table 1** Characteristics and, peri-operative and post-operative data from 85 patients undergoing MitraClip placement under general anaesthesia. Values are mean (SD), number (proportion) or median (IQR [range]).

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>72 (12)</td>
</tr>
<tr>
<td>Men</td>
<td>52 (61%)</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>76 (19)</td>
</tr>
<tr>
<td>Height; cm</td>
<td>171 (9)</td>
</tr>
<tr>
<td>Aetiology of MR</td>
<td></td>
</tr>
<tr>
<td>Degenerative</td>
<td>47 (55%)</td>
</tr>
<tr>
<td>Functional (ischaemic/dilated)</td>
<td>35 (42%)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>30 (35%)</td>
</tr>
<tr>
<td>3–4</td>
<td>57 (66%)</td>
</tr>
<tr>
<td>Morbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26 (31%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80 (94%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>27 (32%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>55 (65%)</td>
</tr>
<tr>
<td>Previous coronary stent implantation</td>
<td>37 (44%)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>26 (31%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44 (52%)</td>
</tr>
<tr>
<td>Previous cerebral ischaemic event</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>Severely impaired left ventricular function</td>
<td>23 (27%)</td>
</tr>
<tr>
<td>Peri-operative variables</td>
<td></td>
</tr>
<tr>
<td>Total operation time; min</td>
<td>196 (57)</td>
</tr>
<tr>
<td>Anaesthesia induction time; min</td>
<td>38 (14)</td>
</tr>
<tr>
<td>Total anaesthesia time; min</td>
<td>348 (78)</td>
</tr>
<tr>
<td>MR grade</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>3.0 (2.5–3.0 [2.0–3.0])</td>
</tr>
<tr>
<td>After</td>
<td>1.5 (1.0–2.0 [0.5–3.0])*</td>
</tr>
<tr>
<td>TR grade</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>2.0 (1.0–2.0 [0.5–3.0])</td>
</tr>
<tr>
<td>After</td>
<td>2.0 (1.0–2.8 [0.5–3.0])</td>
</tr>
<tr>
<td>Postoperative variables</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>85 (100%)</td>
</tr>
<tr>
<td>Postoperative mechanical ventilation</td>
<td>51 (60%)</td>
</tr>
<tr>
<td>Mechanical ventilation &gt; 48 h</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Length of ICU stay; days</td>
<td>2.8 (7.5)</td>
</tr>
<tr>
<td>Length of hospital stay; days</td>
<td>16.4 (11.7)</td>
</tr>
</tbody>
</table>

MR, mitral regurgitation; NYHA, New York Heart Association; ASD, atrial septal defect; TR, tricuspid regurgitation; ICU, intensive care unit.

*p < 0.0001 compared with before.
Significant pulmonary hypertension was diagnosed in 47 (58%) patients pre-operatively; in 2 (2%) patients this was severe (mPAP ≥ 50 mmHg).

Pulmonary vascular resistance index, right ventricular stroke work index, pulmonary artery occlusion pressure, CVP, and mean arterial pressure were all decreased pre-operatively in patients without pulmonary hypertension compared with those with (Table 3). After MitraClip placement, patients without pulmonary hypertension experienced a 96% increase in right ventricular stroke work index compared with only 44% (p < 0.001) in patients with pulmonary hypertension (Table 3). There was a similar reduction in pulmonary artery pressure in both groups. However, pulmonary artery occlusion pressure was only reduced in patients with pre-operative pulmonary hypertension. In these patients, mPAP, CVP, pulmonary artery occlusion pressure and pulmonary vascular resistance index all remained higher than in patients without pre-operative pulmonary hypertension.

There were no differences in dosages of inotropic or vasopressor drugs before and after MitraClip placement, and patients without or with pre-operative

### Table 2

Haemodynamic data in 81 patients undergoing successful MitraClip placement under general anaesthesia. Values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVSWI; mmHg.ml.m⁻²</td>
<td>512 (321)</td>
<td>820 (470)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PVRI; dyn.s.cm⁻５.m⁻²</td>
<td>522 (330)</td>
<td>399 (244)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>mPAP; mmHg</td>
<td>30 (8)</td>
<td>27 (8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCWP; mmHg</td>
<td>18 (6)</td>
<td>18 (6)</td>
<td>0.348</td>
</tr>
<tr>
<td>MAP; mmHg</td>
<td>69 (12)</td>
<td>72 (12)</td>
<td>0.027</td>
</tr>
<tr>
<td>CVP; mmHg</td>
<td>14 (5)</td>
<td>14 (5)</td>
<td>0.384</td>
</tr>
<tr>
<td>RVSVI; ml.m⁻²</td>
<td>32 (12)</td>
<td>44 (17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CI; l.min⁻¹.m⁻²</td>
<td>1.9 (0.7)</td>
<td>3.2 (1.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SVRI; dyn.s.cm⁻５.m⁻²</td>
<td>2699 (1425)</td>
<td>1651 (759)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HR; beats.min⁻¹</td>
<td>63 (17)</td>
<td>74 (18)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adrenaline; μg.kg⁻¹.min⁻¹</td>
<td>0.035 (0.028)</td>
<td>0.044 (0.055)</td>
<td>0.091</td>
</tr>
<tr>
<td>Noradrenaline; μg.kg⁻¹.min⁻¹</td>
<td>0.045 (0.038)</td>
<td>0.048 (0.042)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

RVSWI, right ventricular stroke work index; PVRI, pulmonary vascular resistance index; mPAP, mean pulmonary artery pressure; PCWP, pulmonary artery wedge (occlusion) pressure; MAP, mean arterial pressure; CVP, central venous pressure; RVSVI, right ventricular stroke volume index; CI, cardiac index; SVRI, systemic vascular resistance index; HR, heart rate.

**Figure 1** Association between pulmonary vascular resistance index (PVRI) and right ventricular stroke volume index (RVSVI) (a and b) and between mean arterial pulmonary artery pressure (mPAP) and RVSVI (c and d) in patients undergoing successful MitraClip implantation procedure (n = 81); (a and c) before the MitraClip implantation procedure, and (b and d) after the MitraClip implantation procedure.
Discussion

We have shown that the MitraClip procedure in high-risk patients with severe MR immediately improves right ventricular performance, presumably by relieving the right ventricle from the increased afterload evoked by an increased pulmonary vascular resistance and pressure secondary to the leaking mitral valve. This effect was seen whether patients had pre-operative pulmonary hypertension or not. This contrasts with the postoperative course after cardiac surgery and open mitral valve repair or replacement, which may be associated with cardiac failure, marked postoperative pulmonary hypertension, and the need for vasopressors, nitric oxide, or other inhaled pulmonary vascular dilators so as to decrease pulmonary artery pressure and maintain cardiac output. However, there is no consensus about the outcome of patients with pulmonary hypertension after mitral valve surgery in the literature. While some studies have reported that severe pulmonary hypertension was associated with worse outcome and increased mortality [15], other have shown that severe pulmonary hypertension did not increase risk after mitral surgery [16], or was actually associated with improved haemodynamics [17].

The presence of MR in patients with heart failure and impaired left ventricular ejection fraction is associated with an adverse prognosis and increased morbidity as well as mortality; this is directly related to the severity of the MR [18]. Pulmonary hypertension is a common and serious complication of chronic MR [19], and an indicator of poor prognosis in patients with dilated cardiomyopathy and functional MR [20]. Classically, pulmonary hypertension in patients with cardiomyopathy has been attributed to increased left ventricular filling pressures, reactive pulmonary arterial vasoconstriction and pulmonary vascular remodelling [21]; this is also associated with functional MR [22]. Since pre-operative pulmonary hypertension is a major risk factor for right ventricular failure and peri-operative mortality in patients undergoing mitral valve surgery [15], percutaneous mitral valve repair techniques have recently been developed [1–3], and are particularly attractive in high-risk surgical patients [4]. Although percutaneous repair may be less effective in reducing MR than conventional surgery, the MitraClip procedure has been shown to be effective in both

| Table 3 Haemodynamic data from 81 patients with and without pre-operative pulmonary hypertension (mPAP > 25 mmHg), who underwent the MitraClip procedure under general anaesthesia. Values are mean (SD). |
|---------------------------------|----------------|----------------|----------------|
| **No pulmonary hypertension**   | **Pulmonary hypertension**<br>(n = 47) |
| **Before**                      | **After**      | **p value**    | **Before**     | **After**      | **p value**    |
| **RVSWI; mmHg.ml.m⁻²**          | 379 (181)      | 742 (448)      | < 0.001        | 612 (366)*     | 880 (483)      | < 0.001        |
| **PVRI; dyn.s.cm⁻⁵.m⁻²**        | 711 (149)      | 271 (109)      | 0.002          | 644 (384)*     | 503 (274)†     | 0.006          |
| **mPAP; mmHg**                  | 23 (3)         | 21 (3)         | 0.009          | 35 (6)*        | 32 (7)†        | < 0.001        |
| **PCWP; mmHg**                  | 14 (3)         | 15 (5)         | 0.107          | 22 (6)*        | 20 (6)†        | 0.044          |
| **MAP; mmHg**                   | 66 (12)        | 71 (14)        | 0.020          | 71 (11)*       | 72 (10)        | 0.426          |
| **CVP; mmHg**                   | 11 (4)         | 12 (5)         | 0.155          | 16 (5)*        | 15 (5)†        | 0.714          |
| **RVSVI; ml.m⁻²**               | 35 (13)        | 51 (18)        | < 0.001        | 29 (12)        | 40 (14)†       | < 0.001        |
| **CI; l.min⁻¹.m⁻²**             | 1.9 (0.6)      | 3.5 (1.5)      | < 0.001        | 1.9 (0.7)      | 2.9 (1.1)      | < 0.001        |
| **SVRI; dyn.s.cm⁻⁵.m⁻²**        | 2642 (1510)    | 1517 (678)     | 0.001          | 2740 (1376)    | 1749 (807)     | < 0.001        |
| **HR; beats.min⁻¹**             | 57 (14)        | 72 (17)        | < 0.001        | 67 (19)*       | 76 (19)        | 0.001          |
| **Adrenaline; µg.kg⁻¹.min⁻¹**   | 0.033 (0.026)  | 0.039 (0.045)  | 0.232          | 0.040 (0.030)  | 0.037 (0.030)  | 0.209          |
| **Noradrenaline; µg.kg⁻¹.min⁻¹**| 0.045 (0.028)  | 0.048 (0.032)  | 0.241          | 0.046 (0.044)  | 0.049 (0.048)  | 0.198          |

mPAP, mean pulmonary artery pressure; RVSWI, right ventricular stroke work index; PVRI, pulmonary vascular resistance index; PCWP, pulmonary artery occlusion pressure; MAP, mean arterial pressure; CVP, central venous pressure; RVSVI, right ventricular stroke volume index; CI, cardiac index; SVRI, systemic vascular resistance index; HR, heart rate.

*p < 0.0001 vs mPAP < 25 mmHg before MitraClip.
†p < 0.0001 vs mPAP < 25 mmHg after MitraClip.
organic and functional MR with suitable anatomy. It has been associated with increased safety, reduced left ventricular size and clinical improvement in both dyspnoea and quality of life [1–3]. Mechanically, the MitraClip technology is a percutaneous adaption of the surgical Alfieri approach to mitigate MR by suturing together the midpoint of the two mitral valve leaflets so as to create a bow-tie or double orifice configuration [23, 24].

The right ventricle has long been termed the ‘forgotten’ half of the heart [25], yet it is vitally important in a variety of clinical situations. Right ventricular stroke work index, as a measure of right ventricular function, can readily be calculated during right heart catheterisation and represents the pressure-volume work of the right ventricle, although, in this age of echocardiography, little appears to be known about its usefulness for prognosis in patients with pulmonary hypertension [26]. We explored the association between improvements in right ventricular performance following successful MitraClip implantation with other haemodynamic variables. The major determinant of right ventricular stroke work index appeared to be a decrease in pulmonary vascular resistance. This is supported by our data showing that pulmonary vascular resistance in patients with MR has a strong inverse association with the right ventricular stroke volume, both before and after successful MitraClip implantation.

Little is known about the acute response of the right ventricle to MitraClip implantation in anaesthetised patients with pulmonary hypertension. We have shown that right ventricular stroke work immediately increased while pulmonary vascular resistance and mPAP decreased after a successful procedure. While the decrease in pulmonary artery occlusion pressure achieved statistical significance only in patients with pulmonary hypertension, this may be explained by reduced pulmonary vascular compliance in patients with chronically high pulmonary artery pressure. Our measurements, however, do not allow us to pinpoint the mechanisms for these differences.

The principal mechanisms implicated in the development of pulmonary hypertension in the setting of MR include: passive retrograde transmission of increased left atrial pressure resulting from MR and chronic volume overload; reactive pulmonary vasoconstriction; and pulmonary vascular remodelling altering the difference between pulmonary artery occlusion pressure and actual left atrial pressure [27]. Therefore, the right ventricle of patients with pulmonary hypertension is accustomed to working against a high pulmonary artery pressure and vascular resistance, and decreased pulmonary vascular resistance is thought to improve right ventricular function by decreasing right ventricular afterload. This is supported by our finding of increased right ventricular stroke work associated with acutely decreased pulmonary vascular resistance but a reduction in the regurgitant fraction into the left atrium following successful MitraClip implantation.

In our study, an increase in cardiac index was seen in all patients, consistent with other reports [9, 10]. This contrasts with the EVEREST trial [11] addressing acute effects of MitraClip placement in patients with haemodynamic decompensation, where an increase in cardiac index was only observed in patients with a low baseline cardiac index (< 2.5 l.min\(^{-1}\).m\(^{-2}\)), or increased left ventricular end-diastolic pressure (≥ 15 mmHg), mean pulmonary artery occlusion pressure (≥ 15 mmHg), or systolic pulmonary artery pressure (> 40 mmHg), using transthoracic echocardiography for stroke volume measurements. Moreover, in contrast to our data, a reduction in pulmonary artery pressure was only seen in patients with a baseline pressure above 30 mmHg. Furthermore, an acute, significant increase in CVP was observed while pulmonary vascular resistance and mPAP were unchanged [9]. These discrepancies may or may not be related to a different anaesthetic regimen. Unfortunately, while interventions and haemodynamic evaluation in the EVEREST trial were apparently performed under anaesthesia, no information was provided about the anaesthetic technique or agents used. Furthermore, another study showed a decrease in pulmonary artery occlusion pressure of 20% when performed under continuous infusion of propofol and remifentanil [10]. This may be due to a direct effect of propofol on the systemic vasculature or to differences in patients’ baseline characteristics [28, 29]. While the latter group [10] included mainly patients with functional MR and impaired left ventricular function, our cohort included patients with both degenerative and functional regurgitation. In addition, the degree of intravenous hydration
in patients who had fasted overnight and received radiopaque contrast media at the beginning of the procedure is uncertain. It is possible that patients in the EVEREST trial [9, 11] were deliberately overhydrated during the procedure, and that this in part accounted for the apparent increase in pulmonary artery occlusion pressure and mPAP. Finally, in our study, doses of inotropes and vasopressors were similar before and after MitraClip implantation. This may also be important, since other studies [9–11] did not provide information about cardiovascular drug infusions, and such drugs may evoke vasoconstriction on their own [9].

Our study has a number of limitations. First, while it appears to be the first to address the response of the right ventricle to MitraClip implantation during fentanyl-isoflurane anaesthesia, we only studied a relatively small number of patients. Second, right ventricular stroke work index alone is a less than perfect measure of right ventricular function and reflects both afterload- and preload-related variables. It does not account for right ventricular systolic wall stress, which is hard to measure even in an anatomically normal right ventricle. Third, variables such as regurgitant volume into the left atrium or changes in pulmonary vascular compliance were not assessed. Fourth, in the setting of right ventricular dilation, tricuspid valve regurgitation is common and an important consideration in right ventricular function. Importantly, some publications indicate that tricuspid valve regurgitation can affect thermodilution measurements of stroke volume, with both over- and underestimation described. However, the amount of tricuspid valve regurgitation before and after MitraClip implantation in our study was similar. Finally, given the importance of the transpulmonary pressure gradient in calculating both pulmonary vascular resistance and right ventricular stroke work index, interpretation of our data is complicated by the potential disparity between pulmonary artery occlusion pressure and actual left atrial pressure. The EVEREST trial measured left atrial pressure via a trans-septal catheter but these data were not presented [11]. Instead, they reported left ventricular end-diastolic pressure which, in the absence of significant mitral valve stenosis, should have been close to mean left atrial pressures. Vascular remodelling can alter the difference between pulmonary artery occlusion pressure and actual left atrial pressure. In any case, however, the haemodynamic profile following MitraClip implantation has been reported before, and this was much improved compared to the often troublesome haemodynamic course of patients undergoing open surgical mitral valve surgery [30].

In conclusion, successful MitraClip implantation during general anaesthesia and mechanical ventilation of the lungs immediately improves right ventricular performance in high-risk patients both with and without pulmonary hypertension, at least partly by relieving right ventricular afterload. These effects do not support the hypothesis that cardiac failure may be precipitated by an acute decrease in MR, and rather support the view that interventional procedures to mitigate MR under anaesthesia such as the MitraClip can be considered to be a good and low-risk alternative to surgical mitral valve repair, particularly in high-risk patients.

Competing interests
BP has received honoraria for lectures from Abbot, Wetzlar, Germany. No other competing interests declared.

References


Intra- and inter-centre standardisation of thromboelastography (TEG®)

C. Quarterman,1 M. Shaw,2 I. Johnson3 and S. Agarwal4

1 Specialist Registrar. 4 Consultant, Department of Anaesthesia, 2 Senior Clinical Information Analyst, 3 Senior Clinical Perfusionist, Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, UK

Summary
Thromboelastography is used for assessment of coagulation and to guide administration of blood products peri-operatively. There is currently no method of standardisation in the UK, nor an approved method of proving quality. We investigated the reproducibility of thromboelastography by testing whole blood with no coagulation abnormality in three phases. Where a single operator performed multiple assays on the same blood sample at a single location, we found considerable variation, with 21% of R- and 25% of K-time measurements lying outside a set tolerance range (median ± 20%). Where samples were analysed by different operators in a single location, this finding was repeated. Where blood was transported in a citrated form for simultaneous analysis in multiple locations, results were more consistent, suggesting improved stability. Across all phases of testing there was good reproducibility of the maximum amplitude. Further examination of the results indicated less variation where analysis was performed on blood taken from the same kaolin vial compared with results from different vials. Our preliminary study indicates that R- and K-times may be highly variable, which we hypothesise may be due to variable mixing of blood and kaolin. We intend to repeat this study in the context of coagulopathy, where variability in results could potentially impact upon transfusion practice.

Correspondence to: S. Agarwal
Email: seema.agarwal@lhch.nhs.uk
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Introduction
Major surgery, in particular cardiac and liver surgery, is often associated with significant derangement of coagulation [1]. Point-of-care testing can be used to assess coagulopathy in the peri-operative setting, and its use as part of a transfusion algorithm has been shown to reduce the administration of blood and blood products [2, 3]. This in turn leads to a reduction in transfusion-related adverse events, and studies have suggested there may also be reduced patient morbidity and six-month mortality [4].

Thromboelastography (TEG®, Haemonetics, Braintree, MA, USA) is one point-of-care method of assessing coagulation. A sample of whole blood is pipetted into a cup into which a torsion wire is suspended. The cup oscillates, and as the blood begins to clot, the oscillation is conducted to the wire. With increasing clot strength, there is increasing conduction of oscillation...
tion. The kinetics of the change in the oscillation of the wire are recorded graphically as the thromboelasto- 

Standardisation of laboratory tests is essential to ensure the results of investigations are reliable and comparable, regardless of where the analysis is actually conducted. Currently, the United Kingdom National External Quality Assessment Service (NEQAS) takes responsibility for external quality control of the majority of laboratory tests, but there is no external quality control within the UK and Europe for the TEG system [6]. The NEQAS assessments involve the circulation of a series of blood samples to multiple laboratories, each of which submits the results of their testing. The results of these are collated by NEQAS and the median value determined. A percentage tolerance above and below the median is used to create a median tolerance range. Laboratories that return results within the tolerance range are deemed to have returned an acceptable result. Those that return results outside the tolerance range may undergo repeat assessment.

The aim of the current study was to assess the reproducibility of the TEG within an individual centre and between centres, using whole patient blood.

Methods

Ethical approval was granted by the East Midlands (Nottingham) Ethics Committee, on behalf of the National Research Ethics Service. Patients over the age of 18 years who gave written informed consent for blood sampling and underwent cardiac surgery at Liverpool Heart and Chest Hospital were recruited. Exclusion criteria included patients with a pre-existing coagulation abnormality, and those receiving recent treatment with any medication influencing coagulation or platelet function.

All TEG machines were compliant with the manufacturer-delivered servicing programme, and passed the full internal quality control procedure for instrument qualification before undertaking tests. This included internal electrical control and a two-stage liquid quality control, which consisted of testing standard solutions representing blood with both normal and abnormal coagulation. Across each set of tests, and across each test centre, consumables with the same batch number were used. Within the theatre complex of the base investigating hospital, there are eight TEG machines, each with two channels, allowing up to 16 simultaneous assays to be performed.

Testing was divided into three phases, and each phase was performed on a different blood sample. All TEG assays were performed by experienced, trained operators. In phase-one, a single operator performed multiple TEG assays across all available channels at our centre, with the same blood sample. In phase-two, a blood sample was immediately analysed by multiple operators in our centre. Phase-three involved transportation of blood samples to four other locations at two hospitals in the north-west region (University Hospital of South Manchester NHS Foundation Trust and Central Manchester University Hospitals), to allow simultaneous testing by different operators in different locations. Phase-one testing was performed on five occasions with blood from five different patients; phases two and three were each performed on one occasion only.

In all patients, an arterial line was inserted before induction of anaesthesia. The line was flushed with 0.9% sodium chloride and transduced to ensure adequate intra-arterial positioning. Five millilitres of fluid were aspirated from the arterial line and discarded before obtaining the blood sample for analysis to ensure that an undiluted blood sample was obtained. The blood was then aliquoted into 1-ml vials containing kaolin. Mixing of blood and kaolin by an inversion technique was performed by the operator conducting
the TEG assay, and a measured 360-μl blood/kaolin mix was then pipetted into the cup and the TEG assay commenced. In phases one and two, the TEG was started within 5 min of obtaining the blood sample. In phase-three, where transportation of the blood was required, 3 ml whole blood was injected into a citrated coagulation blood bottle and transported along with all consumables to the other locations, where they were received by an experienced operator. Tests were started 1 h after the blood was taken from the patient. At this time, the samples were recalcified by transferring 20 μl 0.2 M calcium chloride to the cup, followed by 340 μl of the blood/kaolin mix. Analysis then proceeded as for phases one and two. Blood from a different patient was used for each phase of testing and also where phases were repeated.

Five TEG measurements were recorded: the R-time (time until first evidence of clot is detected, in minutes); the K-time (time from the end of R until the clot reaches 20 mm); the alpha angle (angle of the slope between R and K); the maximum amplitude (MA); and the LY30 (% clot lysis after 30 min). The median value of all of the obtained measurements was calculated and a range of acceptable values, 20% above and below the median value, was created. Results returned outside this range were deemed to be outside the tolerance limits, with an unacceptable degree of variability. This technique of assessing the acceptability of results was adopted following review of the techniques employed by NEQAS [6].

One additional analysis was performed to investigate the variability with respect to kaolin activation. For the standard method of performing a TEG assay, 1 ml whole blood is added to a single kaolin tube; this therefore contains enough blood/kaolin mix to allow two TEG assays to be performed. It is accepted practice that two samples are taken from this one tube – generally in cardiac surgery, that is a plain and a heparinase cup as an otherwise matched pair. The additional analysis looked at the variability between two samples taken from the same kaolin tube, run on the same machine simultaneously, both within plain cups. This was termed the within-vial variation and was compared with the between-vial variation using the Wilcoxon signed-rank test.

**Results**

In phase-one, blood from five separate patients was tested (Table 1): 21% of measurements of the R-time, 25% of the K-time, 4% of the alpha angle and 79% of the LY30 lay outside the tolerance range. All measurements of the MA were within the tolerance range. With regards to the paired assays from a single tube (within-vial variation), there was greater similarity between the pairs of results (Table 2). When compared with results from unpaired samples (between-vial variation), differences between values were significantly reduced (p = 0.002, Fig. 2).

In phases two and three, only one blood sample was tested on each occasion. In phase-two, where multiple operators performed TEG assays with the same blood simultaneously at the same location, there was even more marked variability in the R- and K-times, with 60% falling outside the tolerance range for each measurement; the MA results were again consistent (Table 3). During phase-three, where five operators at five separate TEG machine locations performed testing simultaneously with the same citrated blood sample, results were more consistent, with 22% of R-times and 11% of K-times falling outside the tolerance range.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>R-time</th>
<th>K-time</th>
<th>Alpha angle</th>
<th>MA</th>
<th>LY30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>2 (n = 16)</td>
<td>8 (50% [25–75%])</td>
<td>8 (50% [25–75%])</td>
<td>1 (6% [2–30%])</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>3 (n = 15)</td>
<td>4 (27% [8–55%])</td>
<td>7 (47% [21–73%])</td>
<td>2 (13% [2–40%])</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>4 (n = 12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>5 (n = 16)</td>
<td>3 [19 (4, 46)]</td>
<td>3 [19 (4, 46)]</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Overall (n = 73)</td>
<td>15 (21% [12–32%])</td>
<td>18 (25% [15–36%])</td>
<td>3 (4% [1–12%])</td>
<td>0</td>
<td>58</td>
</tr>
</tbody>
</table>

MA, maximum amplitude; LY30, % decrease in amplitude 30 min after MA.
assays are performed by either single or multiple operators. The same level of reproducibility is not found when measuring the R- and K-times. Examination of one group of assays performed by a single operator (within-vial variation) suggests that variability may arise secondary to inconsistent activation of coagulation when the blood sample is combined with kaolin. There was improved reproducibility with recalcified citrated blood, possibly as a result of improved stability of the sample. These are preliminary data and further testing would be required to confirm this; however, our study suggests that, even with use of whole blood, there is the potential for wide variation in results. Testing involved use of blood from patients who had normal clotting and platelet function, and the results suggest that clinicians should exercise caution in the use of TEG assay results in algorithm-guided treatment of coagulopathy.

There were limitations to this study and until further data are available, these findings merely serve to highlight the potential for variation and emphasise the importance of clinical judgement when interpreting results and guiding transfusion. Measurements could only be performed on TEG channels that were not in use, thereby limiting the extent of data that could be acquired. While all TEG assays were started within 5 min of obtaining the blood sample, there was some variability in the exact start time of each assay by virtue of the practicalities of a single operator’s performing several assays simultaneously. The possibility that this introduced some variation cannot be excluded, although this was considered as part of the data analysis, which showed no evidence to indicate that those assays performed later had a tendency to longer or shorter measurements compared with those started earlier. Testing involving multiple operators at both a single and multiple sites was only performed on one occasion due to the logistical challenges of identifying experienced TEG operators not engaged in clinical

Table 3 Results outside the 20% tolerance range during phase-two testing – multiple operators, single location. Values are number (proportion [95% CI]).

<table>
<thead>
<tr>
<th>Patient</th>
<th>R-time</th>
<th>K-time</th>
<th>Alpha angle</th>
<th>MA</th>
<th>LY30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 10)</td>
<td>6 (60% [26–88%])</td>
<td>6 (60% [26–88%])</td>
<td>0</td>
<td>0</td>
<td>8 (80% [44–97%])</td>
</tr>
</tbody>
</table>

MA, maximum amplitude; LY30, % decrease in amplitude 30 min after MA.
work and available to perform the analysis at the required time, and sample transportation. A 20% tolerance range to produce a range of acceptable results for each parameter was adopted on each occasion of testing. This was based on the system used by NEQAS for assessment of simple tests of coagulation, but with more data the suitability of this approach should be considered further.

Currently, the manufacturer recommends a number of operating conditions and internal quality control procedures in an attempt to ensure the accuracy of results. Accurate conduct of the TEG assay requires the machine to be on a stable and level surface. The upper aspect of the machine has a clear window and the enclosed bubble must be positioned within a central circular target. An e-test is initiated by the operator via the attached TEG computer to ensure correct electronic functioning. Bubble and e-tests are performed daily to ensure correct electronic functioning. Two quality control standard samples of reconstituted lyophilised plasma are provided for use on a daily basis. One standard is designed to be comparable with and reflect the properties of a blood sample with normal coagulation, and the other to have properties of a sample with abnormal coagulation. The operator runs TEG assays using these controls on a daily basis, with the expectation of obtaining results within the range specified by the manufacturer, to ensure satisfactory performance of the instrument.

A validation guide is disseminated by the manufacturer and widely used in the USA as part of local quality assurance programmes [7]. Verification of TEG reference ranges is advised for each centre, and is achieved by performing TEG assays on blood samples from 20 healthy volunteers with normal coagulation. Results are compared with the reference ranges provided by the manufacturer, and where no more than two results lie outside this range, the machine and accompanying reference ranges are deemed acceptable. The manufacturer does not, to our knowledge, regularly disseminate information of the verification process within the UK. While its inclusion in the quality control process could further improve identification of poorly performing devices, the two-stage liquid control assays should also identify this. Successful completion of the verification process does not guarantee reproducible results, only that normal blood will return a result within the normal range the majority of the time.

Use of TEG as a point-of-care test of coagulation is increasing in popularity. Although it has been used for many years in the management of coagulopathy during cardiac and liver surgery, its scope of use is widening to include, among others, orthopaedic surgery and obstetrics [8, 9]. Casey et al. report the use of TEG to guide the management of a paediatric patient undergoing scoliosis surgery following use of low-molecular weight heparin bridging anticoagulation [8], indicating the significant advantage that the rapid return of results can have for patient care in many contexts. Platelet mapping assays have been developed for use with TEG equipment to allow the specific assessment of platelet function, a new application of this equipment that can highlight patients with an acceptable platelet count who may still be at risk of peri-operative bleeding [10]. As the application of this technology expands, it is essential that clinicians are able to have confidence in the accuracy and consistency of results. Studies performed by the TEG-ROTEM working group [11] and NEQAS [12], have indicated considerable variability. The TEG-ROTEM group, when considering the TEG analysis results, utilised platelet-rich plasma and found significant variability between laboratories, ranging from 7 to 60%. Interestingly, this group identified variability in the R-time and the MA as being lowest, with both below 20%, whereas the K-time showed the most variability [11]. The National External Quality Assessment

<table>
<thead>
<tr>
<th>Patient</th>
<th>R-time</th>
<th>K-time</th>
<th>Alpha angle</th>
<th>MA</th>
<th>LY30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 9)</td>
<td>2 (22% [3-60%])</td>
<td>1 (11% [1-48])</td>
<td>0</td>
<td>0</td>
<td>5 (56% [21-86%])</td>
</tr>
</tbody>
</table>

MA, maximum amplitude; LY30, % decrease in amplitude 30 min after MA.
Service utilised lyophilised plasma as an alternative to whole blood, and identified a wide range in the coefficient of variance for returned results of 7.1–39.9%. The National External Quality Assessment Service analysis also found, on one occasion, that three out of the 11 sites involved reported a normal blood sample to display abnormal coagulation [12]. Our study also shows that potentially significant variation in results can occur, but specifically highlights the R- and K-times as the most inconsistent, with good reproducibility of the MA.

Research assessing the effect of citrate on the thromboelastogram indicates that, when kaolin is used to activate coagulation, analysis of a recalcified citrated blood sample gives similar results to non-citrated fresh blood [5]. Where other activators are used, the thromboelastogram is consistent with a hypercoagulable state. Other groups have identified a period of instability if the citrated sample was analysed within the first 30 min of storage [13, 14], and for this reason, analysis in this part of our study was not started until 1 h after storage began. However, after 30 min, reproducibility was greater. In our study, analysis of citrated samples suggested greater consistency, although further testing would need to be performed to confirm this. Although it could be suggested that all blood samples should therefore be citrated routinely to improve accuracy, the value of TEG as a point-of-care device would be compromised to accommodate a mandatory 30-min delay in analysis. This may, however, be considered justified if results can be considered to be more meaningful and to offer a better guide to clinical care.

Initiation of clot formation, as represented by the R- and K-times, is based on the activation of clotting factors. In the context of the TEG assay, this is often—as it was for this study—initiated by the combination of the blood sample with kaolin. This accelerates the acquisition of results of the TEG to aid clinicians in the prompt management of patients with a potential coagulopathy. The R-time of the TEG represents the reaction time, from initiation of the TEG assay to first fibrin formation and usually ranges from 5 to 7 min where kaolin is used as an activator. The K-time represents the time taken for subsequent fibrin cross-linkage to occur, and for a clot strength to be reached that equates to an amplitude of 20 mm. This would usually lie in the range of 1–3 min for a kaolin-activated TEG assay [15]. In this study, the R- and K-times were highly variable, suggesting that results may be very operator-dependent, and potentially limiting their clinical usefulness. Assays started from blood taken from the same blood/kaolin vial showed far greater consistency. While mixing of blood and kaolin was performed by the same operator during phase-one of the study, with the same technique, variability in blood/kaolin mixing remains a potential explanation for the observed variability in the R- and K-times. Previous studies have found differences in the degree of variability depending on the type of coagulation activator used. Ganter et al. found that variability was lower following extrinsic activation with tissue factor, but substantially higher when kaolin was used. This group also found that variability was least for the MA [16].

The alpha angle gives a measure of the gradient of the rise of the TEG trace, and represents the speed of clot strengthening via fibrin cross-linking. This is usually in the range of 53–67° for a kaolin-activated TEG assay of a normal blood sample. The MA gives an indication of platelet aggregation and integration of fibrin, ultimately representing the strength of the fibrin clot that forms, and normally ranges from 59 to 68 mm in a kaolin-activated blood sample [15]. Our results suggest that there is good intra-operator consistency in the measurement of the alpha angle and the MA. Other groups have demonstrated potential inaccuracies in the identification of the alpha angle by the TEG device. This was thought possibly to be due to incorrect identification of the split point in the trace, and thus incorrect calculation of the alpha angle, due to the presence of air bubbles in the blood following pipetting into the cup before analysis [17]. This was not found in our study, but TEG operators should be aware of this potential cause of variability.

In recent years, models of coagulation have evolved from the clotting cascade that was originally described. Hoffman and Monroe describe a series of overlapping stages ranging from initiation on an appropriate cell surface, through amplification involving activation of platelets and co-factors, to propagation and a thrombin burst at the platelet surface [18]. If variable initiation of coagulation occurred, secondary to variable mixing of blood with kaolin,
this may explain the observed variability in the R- and K-times. Furthermore, the alpha angle and MA may be more consistent as these measurements represent the amplification and propagation phases that are initiated by widespread platelet and co-factor activation, not influenced by the presence of kaolin, thus leading to more consistent interaction of platelets and fibrin.

The LY30 represents fibrinolysis in the 30-min period following the achievement of the MA, and normally lies between 0 and 7.5% [15]. We found that assessment of the LY30 was the most inconsistent variable in this study, with the majority of measurements lying outside the tolerance range in all phases of testing. Clot retraction has been hypothesised to occur due to the dissociation of fibrin strands from the cup wall when the interaction of fibrin and the platelet glycoprotein IIb/IIIa receptor is intense [19]. It is therefore thought to be greater in the presence of a higher platelet count. As our patients all had normal platelet counts and presumed normal function (given the lack of history of bleeding or antiplatelet medication), and the same blood sample was used across each phase of testing, it is unclear how this would influence the degree of clot retraction and therefore measurement of the LY30.

All operators involved in the study were regularly performing TEG assays as part of routine management of patients in whom a coagulopathy was suspected. Training was delivered by the manufacturer, and the individuals who were originally trained have continued to use it regularly. Despite this, the question remains whether the variability we have shown arises from a training or a device issue. We also examined the results of the liquid quality control tests performed immediately before our study started, using the same methods as the study itself. All results lay within the tolerance range that we set. The inconsistency when testing whole blood in our study suggests that the root cause may lie in the mixing of kaolin and blood before the actual TEG assay is started, despite performing the mixing exactly as recommended by the manufacturer. The latter suggests an inversion technique, but it is possible that this is insufficient to ensure consistent mixing and activation of coagulation on all occasions, suggesting a flaw in this stage of the recommended standard operating procedure.

The findings of this study suggest inadequate reproducibility of the current TEG assay, and if the quality of mixing of blood with kaolin is indeed the reason for the variability we have demonstrated, it will be necessary to establish a more consistent method of activation of coagulation in the future. To offer better guidance to clinicians and avoid either unnecessary TEG-directed therapy, or failure to treat patients who might have benefited from therapy, further studies are warranted. Improvements in TEG testing could be expected to increase the cost-effectiveness of this service.

Acknowledgements
We thank Dr K. Pendry ( Consultant Haematologist, Central Manchester University Hospitals) and Dr S. Haynes ( Clinical Scientist, University Hospital of South Manchester NHS Foundation Trust) for their involvement in co-ordinating testing in their hospitals.

Competing Interests
No external funding or competing interests declared.

References


A randomised controlled trial comparing incentive spirometry with the Acapella® device for physiotherapy after thoracoscopic lung resection surgery


1 Clinical Fellow, 2 Assistant Professor, 3 Resident, 6 Clinical Professor, 7 Professor, 8 Associate Professor, Department of Anaesthesiology and Pain Medicine, 4 Associate Professor, 5 Professor, Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul, South Korea

Summary

Lung resection surgery has been associated with numerous postoperative complications. Seventy-eight patients scheduled for elective video-assisted thoracoscopic lung resection were randomly assigned to receive standard postoperative care with incentive spirometry or standard care plus positive vibratory expiratory pressure treatment using the Acapella® device. There was no significant difference between incentive spirometry and the Acapella device in the primary outcome, forced expiratory volume in 1 s, on the third postoperative day, mean (SD) 53% (16%) vs 59% (18%) respectively, p = 0.113. Patients treated with both devices simultaneously found incentive spirometry to be less comfortable compared with the Acapella device, using a numeric rating scale from 1 to 5 with lower scores indicating higher comfort, median (IQR [range]) 3 (2–3 [2–4]) vs 1 (1–2 [1–3]) respectively, p < 0.001. In addition, 37/39 patients (95%) stated a clear preference for the Acapella device. Postoperative treatment with the Acapella device did not improve pulmonary function after thoracoscopic lung resection surgery compared with incentive spirometry, but it may be more comfortable to use.

Introduction

Airway clearance is a major concern during the care of patients after thoracic surgery, and postoperative pain can interfere with the effective removal of airway secretions. Failure to clear secretions from the respiratory tract can lead to atelectasis, pneumonia, and increased mortality [1].

Manual percussion with chest wall vibration is a widely accepted method for respiratory physiotherapy to assist in airway clearance. However, it is labour-intensive, operator-dependent and time-consuming. Moreover, it can be painful for patients in the immediate postoperative period.

There are several reports that alternative types of vibration and oscillation can facilitate airway clearance and improve lung function in various clinical settings [2–6]. However, no clinical trial to date has evaluated the efficacy of vibratory positive expiratory pressure
using the Acapella® device (Acapella DH Green, Smiths Medical ASD Inc., Keene, NH, USA; Fig. 1), in patients undergoing lung resection surgery. The Acapella consists of a counterweighted plug and metal strip attached to a lever, and a magnet. Airflow oscillation is created by breaking and reforming of a magnetic attraction by the plug as it intermittently occludes air passing through the device [7]. The device is available either in blue, for patients who cannot maintain their expiratory flow above 15 l.min\(^{-1}\) for 3 s, or green, for patients who can maintain an expiratory flow equal to or above 15 l.min\(^{-1}\) for at least 3 s [8, 9]. We hypothesised that treatment with the Acapella device after thoracoscopic lung resection surgery would enhance pulmonary function and provide more comfort than conventional chest physiotherapy.

**Methods**
The study was approved by Seoul National University Hospital’s Institutional Review Board, and all participants provided written informed consent before enrolment. From January to August 2013, patients who were scheduled for elective video-assisted thoracoscopic pulmonary resection surgery for the treatment of lung cancer were screened for eligibility. Inclusion criteria were: age 20–75 years; thoracoscopic surgical resection of less than two entire lobes planned; extubation of the trachea in the operating room; admission to the intensive care unit (ICU) at the end of surgery; and postoperative administration of intravenous patient-controlled analgesia (PCA). Exclusion criteria were: body mass index < 15 kg.m\(^{-2}\) or > 30 kg.m\(^{-2}\); a history of respiratory tract infection within three months; pre-operative treatment with supplemental oxygen or tracheal intubation; baseline arterial partial pressure of oxygen (P\(_{aO_2}\)) < 70 mmHg or arterial partial pressure of carbon dioxide (P\(_{aCO_2}\)) > 50 mmHg; baseline forced expiratory volume in 1 s (FEV\(_1\)) < 30% of predicted; unconsciousness; presence of neuromuscular disease; emergency surgery; bilateral pulmonary resection; and any other physical or psychological condition not compatible with the use of the Acapella device. After completion of surgery, patients who required open thoracotomy or were not admitted to the ICU were not studied. At the time of admission to the ICU, patients were randomly assigned to receive standard care (incentive spirometry) or standard care plus Acapella treatment. Block randomisation was conducted using an automated computer randomisation system performed by a clinician not involved in this study.

Each patient underwent baseline pulmonary function tests measuring FEV\(_1\) and forced vital capacity (FVC), and arterial blood gas analysis, pre-operatively. All measures of FEV\(_1\) and FVC are expressed as percentages of the predicted value. Standardised surgical and anaesthetic protocols were followed. Video-assisted thoracoscopic surgery with a working window and two or three ports was performed. General anaesthesia was induced and maintained with a continuous infusion of remifentanil and propofol using a target-controlled infusion system without pre-treatment. The bispectral index was kept between 40 and 60. Patients’ lungs were mechanically ventilated with a tidal volume of 6–8 ml.kg\(^{-1}\) and positive end-expiratory pressure of 5–8 cmH\(_2\)O. Respiratory rate and fractional inspired oxygen were adjusted to maintain a P\(_{aCO_2}\) of 5.3–6.0 kPa and a P\(_{aO_2}\) of more than 12.0 kPa, respectively. Intravenous PCA consisted of a combination of fentanyl 10–20 µg.ml\(^{-1}\) and morphine 0.4–0.7 mg.ml\(^{-1}\) at a continuous infusion rate of 0.5 ml.h\(^{-1}\) and a bolus of 1 ml with a lockout interval of 10 min.

Patients in the control group were treated with incentive spirometry (HS-IM-1200, Hyupsung Medical Co. Ltd., Yangju, Korea; Fig. 2), which is routinely used after thoracic surgery in our institution. Incentive spirometry is designed to facilitate the patient taking a deep breath, mimicking spontaneous yawning or sighing [8], increasing or maintaining inhaled lung volume and improving sputum expectoration [10]. Patients

![Figure 1 Acapella device.](image-url)
were instructed to take ten deep inhalations with their lips sealed around the mouthpiece – this was motivated by the visual feedback provided by the balls rising with active inhalation. They were encouraged to use incentive spirometry every 2 h, in a tolerable sitting position while awake.

Patients in the Acapella group were treated with the green device because we excluded patients with impaired pulmonary function pre-operatively. Patients were instructed to inhale deeply and hold their breath for 2–3 s before each use. They were allowed to control a dial on the bottom of the device to set the expiratory resistance of the device. Acapella treatment included ten active slow exhalations causing oscillation through the device followed by active coughs in a set cycle repeated at least every 2 h while awake. Patients were also instructed to use the incentive spirometer every 2 h along with the Acapella device. Education about the use of each device was provided by two investigators (YJC and JL).

A portable spirometer was used to measure FEV$_1$ and FVC (MS01; Micro Medical Ltd., Kent, UK) pre-operatively, 1 h and 6 h after surgery and on the first, second and third postoperative days. Patients were instructed on how to use the spirometer pre-operatively and the best value of three consecutive measurements was recorded. The P$_{a}$O$_2$/F$_{i}$O$_2$ ratio was measured before, immediately and 6 h after surgery, and on the first postoperative day. We applied a Venturi mask (MM061; MOW Medical, Wonju, Korea) to patients at least 30 min before arterial blood sampling to ensure an accurate F$_{i}$O$_2$ for each blood gas analysis. An F$_{i}$O$_2$ in the range of 0.35–0.5 was delivered to maintain adequate peripheral oxygen saturation via pulse oximetry; if supplemental oxygen was not required, room air F$_{i}$O$_2$ was assumed to be 0.21.

Patients’ comfort was assessed with a visual analogue scale used by previous investigators [11]: 1 = comfortable with treatment; 2 = uncomfortable, but able to tolerate treatment; 3 = painful, more uncomfortable, but is willing to continue treatment; 4 = severe pain, but can tolerate treatment; and 5 = intolerable pain. Patients in the Acapella group were asked whether they preferred the incentive spirometer or the Acapella. Postoperative pain was evaluated using a visual analogue scale from 0 (free of pain) to 10 (worst pain imaginable) immediately and 6 h after surgery, and on the first, second, and third postoperative days. The total amount of analgesia administered in the first three days after surgery was recorded in terms of equivalent intravenous morphine dose.

The primary endpoint was FEV$_1$ on the third postoperative day. This study was designed to have 80% power to detect a treatment difference of 10% in FEV$_1$ on the third postoperative day between the two treatment groups. Assuming a standard deviation of 13%, from a previous study [12] and significance at the two-sided 5% level, a sample size of at least 39 patients in each group was required (Power and Sample Size Calculation software, version 3.0.43, Vanderbilt University Medical Center, Nashville, TN, USA). All analyses were conducted on an intention-to-treat basis. Data were compared using the independent t-test, the Mann–Whitney U-test, Pearson’s chi-squared test or Fisher’s exact test. A two-sided p value of < 0.05 was considered to indicate statistical significance. For data analysis, we used SPSS (version 19.0.0; SPSS, Inc., IBM, Chicago, IL, USA).

Results
We assessed 559 patients for study eligibility between January and August 2013. Of the 145 patients who were screened as eligible, 78 were enrolled in the study and were randomly assigned to incentive spirometry (n = 39) or Acapella (n = 39) (Fig. 3). The high rate
of enrolment failure was due mainly to admission to the postanaesthetic care unit instead of the ICU, which was a predetermined exclusion criterion. Baseline characteristics were similar (Table 1); however, total surgical and anaesthesia times were shorter in the incentive spirometry group. There was no difference in preoperative pulmonary function and oxygenation parameters (Fig. 4).

With regards to the primary outcome measure, FEV₁ on the third postoperative day was similar (mean (SD) 53% (16%) in the incentive spirometry group vs 59% (19%) in the Acapella group, p = 0.113) (Fig. 4). Four patients (one in the incentive spirometry group and three in the Acapella group) were discharged before the third postoperative day; therefore, data from day two were included. There were no other differences in terms of lung function or oxygenation (Fig. 4), and there was also no significant difference in terms of pain scores or analgesic requirements (Table 2). Patients in the Acapella group, who used both devices according to our study methods, reported significantly higher comfort scores than those treated only with incentive spirometry (Table 2). In addition, most patients in the Acapella group preferred using the Acapella device compared with the incentive spirometry device (Table 2). One patient in the incentive spirometry group was diagnosed with postoperative pneumonia using clinical and radiological criteria, treated with conventional antibiotics and discharged from hospital on the eighth postoperative day. Packed red cells were transfused to two patients in the Acapella group. There was no difference between the two groups with regard to the volume of fluid drained by the chest tubes in the first 24 h after surgery or how long the chest tubes were left in situ (Table 3). Heart rate on the third postoperative day was higher in the Acapella group (Fig. 5); however, no haemodynamic instability was observed in either group.
Table 1 Baseline characteristics of patients randomly assigned to standard care with incentive spirometry or the Acapella device. Values are number (proportion) or mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Incentive spirometry (n = 39)</th>
<th>Acapella (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>21 (54%)</td>
<td>22 (56%)</td>
</tr>
<tr>
<td>Age; years</td>
<td>56.5 (9.8)</td>
<td>56.4 (10.5)</td>
</tr>
<tr>
<td>Body mass index; kg.m⁻²</td>
<td>23.2 (3.0)</td>
<td>23.8 (2.5)</td>
</tr>
<tr>
<td>Tobacco history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>20 (51%)</td>
<td>25 (64%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7 (18%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>2 (31%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>ASA status 1</td>
<td>20 (51%)</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>ASA status 2</td>
<td>19 (49%)</td>
<td>22 (56%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (28%)</td>
<td>15 (39%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (8%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chronic obstructive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulmonary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Previous pulmonary</td>
<td>6 (15%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous anti-platelet</td>
<td>3 (8%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of previous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>14 (36%)</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other surgery</td>
<td>23 (59%)</td>
<td>22 (56%)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>23 (59%)</td>
<td>32 (82%)</td>
</tr>
<tr>
<td>Bronchioloalveolar</td>
<td>4 (10%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>carcinoma</td>
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<tr>
<td>Squamous cell</td>
<td>5 (13%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>6 (15%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Benign</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Extent of operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>27 (69%)</td>
<td>29 (74%)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>5 (13%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>4 (10%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Metastasectomy</td>
<td>3 (8%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Surgical time; min</td>
<td>132.1 (46.0)</td>
<td>157.0 (56.4)</td>
</tr>
<tr>
<td>Anaesthetic time; min</td>
<td>188.2 (47.2)</td>
<td>213.3 (55.9)</td>
</tr>
</tbody>
</table>

Discussion

In our study, postoperative Acapella treatment did not improve postoperative lung function compared with incentive spirometry. However, patients preferred using the Acapella device and found it more comfortable.

In a recent publication [13], enhanced postoperative physiotherapy was recommended to reduce complications and length of hospital stay after thoracic surgery. Various different types of chest physiotherapy have been developed and some favourable findings have been reported. The combination of expiratory positive pressure with high-frequency oscillation has been shown to increase successful expectoration of sputum in patients with bronchiectasis [2, 4, 5] and in patients whose lungs are mechanically ventilated [6]. However,
the Acapella device has not been specifically studied after thoracic surgery up to now, to our knowledge. Park et al. [3] reported that high-frequency chest wall oscillation improved postoperative lung function and oxygenation in pulmonary lobectomy patients. The Acapella device is described by the manufacturer as performing a similar manoeuvre, hence we hypothesised that it would facilitate airway clearance and enhance pulmonary function after thoracoscopic lung surgery.

The fact that patients preferred using the Acapella device to incentive spirometry is consistent with previous studies comparing Acapella therapy with inspiratory muscle training [2] or other airway clearance techniques [4, 7]. Indeed, several patients in our study requested that they be allowed to extend their treatment with the Acapella beyond the original schedule. We were concerned that postoperative pain might be an issue; however, pain scores were generally low in both groups, which was reassuring. Additionally, use of the Acapella device did not increase the volume of chest tube drainage. This compares with a previous study that showed high-frequency chest wall oscillation after pulmonary lobectomy was associated with increased chest tube drainage [3]. We hypothesise that Acapella treatment does not irritate or stimulate the chest wall or wound directly; rather, it delivers vibration to the secretions stuck in the airways. Internally transmitted vibration through the Acapella device may provide a safer method of secretion mobilisation than external chest wall percussion or vibration therapy.

A previous study of high-frequency chest wall oscillation [3] showed significantly improved FEV₁ and PaO₂ in single lobectomy patients, compared with conventional chest physiotherapy. We included lobectomy as well as segmentectomy, wedge resection, and metastasectomy, in our study. One possible explanation for the lack of effect in our study may have been the variety of surgical procedures studied. Another explanation may be the increased anaesthetic and surgical times in the

---

**Table 2** Comfort, preference, pain and analgesic requirements of patients randomly assigned to incentive spirometry or Acapella device. Patient comfort was evaluated by a scoring system ranging from 1 to 5, with lower scores indicating greater comfort. Pain scores were measured by means of a visual analogue scale ranging from 0 (free of pain) to 10 (the worst pain imaginable). Intravenous morphine requirements were the total amount administered during the first three days after surgery. Values are median (IQR [range]), number (proportion) or mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Incentive spirometry (n = 39)</th>
<th>Acapella (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comfort score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acapella</td>
<td>3 (2–3 [2–4])</td>
<td>1 (1–2 [1–3])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Incentive spirometry</td>
<td></td>
<td>37 (95%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Preference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acapella</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incentive spirometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h postoperatively</td>
<td>8 (6–8 [2–10])</td>
<td>8 (7–9 [4–10])</td>
<td>0.211</td>
</tr>
<tr>
<td>6 h postoperatively</td>
<td>6 (3–7 [0–10])</td>
<td>6 (3–8 [0–10])</td>
<td>0.377</td>
</tr>
<tr>
<td>POD 1</td>
<td>5 (3–6 [0–10])</td>
<td>5 (3–7 [0–9])</td>
<td>0.774</td>
</tr>
<tr>
<td>POD 2</td>
<td>3 (3–5 [2–8])</td>
<td>3 (3–5 [1–8])</td>
<td>0.791</td>
</tr>
<tr>
<td>POD 3</td>
<td>3 (2–4 [0–8])</td>
<td>3 (2–5 [0–7])</td>
<td>0.339</td>
</tr>
<tr>
<td><strong>Total dose of morphine; mg</strong></td>
<td>203.2 (125.0)</td>
<td>182.7 (82.0)</td>
<td>0.395</td>
</tr>
</tbody>
</table>

POD, postoperative day.

**Table 3** Safety outcomes of patients randomly assigned to incentive spirometry or Acapella device. Values are number (proportion) or mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Incentive spirometry (n = 39)</th>
<th>Acapella (n = 39)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wound dehiscence</strong></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Chest tube</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dislodgement</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Arrhythmia</strong></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumonia</td>
<td>1 (3%)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Transfusion</strong></td>
<td>0</td>
<td>2 (5%)</td>
<td>0.494</td>
</tr>
<tr>
<td>First 24 h chest</td>
<td>309.4 (201.7)</td>
<td>360.6 (183.7)</td>
<td>0.245</td>
</tr>
<tr>
<td>tube drainage; ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of chest</td>
<td>4.7 (2.8)</td>
<td>5.1 (2.9)</td>
<td>0.553</td>
</tr>
<tr>
<td>tube; days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>5.0 (2.9)</td>
<td>5.5 (3.9)</td>
<td>0.466</td>
</tr>
<tr>
<td>length of stay; days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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On closer inspection, this occurred due to increased surgical complexity in six patients in whom anaesthesia and surgery was greatly prolonged. These included three patients in whom pulmonary wedge resection was followed by lobectomy after frozen section. In the other three patients, the main procedure was followed by an additional wedge resection of another lobe. Such an extended period of surgery and anaesthesia may have adversely affected the postoperative course, which could have obscured any beneficial effect of Acapella treatment in our study. However, adjustment for duration of anaesthesia did not affect our results. Although the heart rate on day three differed statistically between the two groups, pain scores and other haemodynamic parameters were similar and it seemed to have no clinical significance.

We did not study patients who went to the post-anaesthetic care unit instead of the ICU post-operatively, because the arterial cannula could only be left in situ postoperatively in our centre when patients are looked after in the ICU, which we considered to be essential to allow arterial blood sampling as included in the study protocol. Although this led to the exclusion of a large number of patients, we do not believe it affected our results, as patients were randomly assigned to a treatment group after ICU admission. Another possible limitation of our study is related to the incompleteness of the data obtained. We could not determine lung function parameters in four patients on the third postoperative day because they were discharged from hospital earlier than we expected. We did use values determined on the second postoperative day instead, and included these in the final analysis. We also failed to obtain arterial blood from eight patients on the first postoperative day due to removal of the arterial cannula, which may have affected our PaO2/FIO2 data.

In conclusion, postoperative Acapella treatment did not alter lung function after thoracoscopic lung resection surgery in this study; however, it was more comfortable to use than incentive spirometry.

**Acknowledgements**

The Medical Research Collaborating Center is acknowledged for their advice concerning the statistical analyses.

**Competing interests**

No external funding or competing interests declared.

**References**


Pulse pressure variation to predict fluid responsiveness in spontaneously breathing patients: tidal vs forced inspiratory breathing

D. M. Hong,1 J. M. Lee,2 J. H. Seo,1 J. J. Min,3 Y. Jeon4 and J. H. Bahk5

1 Assistant Professor, 4 Associate Professor, 5 Professor, Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, Korea
2 Clinical Instructor, Department of Anesthesiology and Pain Medicine, Seoul City Boramae Hospital, Seoul, Korea
3 Clinical Instructor, Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Seoul, Korea

Summary
We evaluated whether pulse pressure variation can predict fluid responsiveness in spontaneously breathing patients. Fifty-nine elective thoracic surgical patients were studied before induction of general anaesthesia. After volume expansion with hydroxyethyl starch 6 ml.kg−1, patients were defined as responders by a ≥ 15% increase in the cardiac index. Haemodynamic variables were measured before and after volume expansion and pulse pressure variations were calculated during tidal breathing and during forced inspiratory breathing. Median (IQR [range]) pulse pressure variation during forced inspiratory breathing was significantly higher in responders (n = 29) than in non-responders (n = 30) before volume expansion (18.2 (IQR 14.7–18.2 [9.3–31.3])% vs 10.1 (IQR 8.3–12.6 [4.8–21.1])%, respectively, p < 0.001). The receiver-operating characteristic curve revealed that pulse pressure variation during forced inspiratory breathing could predict fluid responsiveness (area under the curve 0.910, p < 0.0001). Pulse pressure variation measured during forced inspiratory breathing can be used to guide fluid management in spontaneously breathing patients.

Correspondence to: J. H. Bahk
Email: bahkjh@snu.ac.kr
Accepted: 11 March 2014

Introduction
Adequate assessment of intravascular volume and appropriate fluid management are essential during the peri-operative period. Fluid administration is usually the first line therapy for hypotension during anaesthesia. Although fluid administration usually improves cardiac output and blood pressure, excessive fluid therapy leads to interstitial oedema, which may worsen the patient outcome [1, 2].

Many haemodynamic variables have been evaluated to determine the predictors of fluid responsiveness. Static variables such as pulmonary artery occlusion pressure and central venous pressure are poor at predicting fluid responsiveness [3–6]. However, dynamic variables, such as systolic pressure variation, pulse pressure variation (PPV), and stoke volume variation can help optimise fluid management during mechanical ventilation [5, 7–9].

Contrary to the cardiac-respiratory interactions during mechanical ventilation [10, 11], the interactions during spontaneous breathing are reversed. Passive inspiration produces negative intrathoracic pressures, thereby increasing the capacitance of the pulmonary vasculature; this in turn may lead to a decreased left
ventricular stroke volume and consequent decreased systemic arterial pressure. Increased capacitance of the pulmonary vasculature during inspiration leads to an expiratory increase in the left ventricular stroke volume and systemic arterial pressure after the pulmonary transit time [12, 13]. These changes could be exploited as indices of fluid loading, but the usefulness of dynamic variables for assessment of fluid responsiveness during spontaneous breathing remains to be determined. A few previous studies have reported that the arterial pressure waveform changes in spontaneously breathing patients are not reliable predictors of fluid responsiveness [14–16]. However, these studies were conducted in critically ill patients with haemodynamic instability. Thus, data for the reliability of dynamic variables are limited in relatively healthy spontaneously breathing patients.

Tidal volume is known to be important in predicting fluid responsiveness during mechanical ventilation [17–19]. Low tidal volumes probably do not induce sufficient changes in stroke volume to make PPV useful as a measure of fluid responsiveness. We thus hypothesised that forced inspiration during spontaneous breathing would better induce cardiovascular changes that enhanced the predictive value of dynamic variables.

Methods
After approval from the Institutional Review Board of Seoul National University Hospital, written informed consents were obtained from the patients. This study was registered in clinicaltrials.gov (NCT01402934). From July 2011 to February 2012, we enrolled patients aged 18–80 years scheduled for elective thoracic surgery. Patients with pre-operative arrhythmias, intracardiac shunts, a left ventricular ejection fraction of <40%, valvular heart disease, right ventricular dysfunction, chronic obstructive pulmonary disease and pulmonary hypertension were not studied.

When the patient arrived in the operating room, midazolam 1 mg was administered intravenously for premedication. Patients were studied in the supine position. Pulse oximetry, non-invasive blood pressure, and three-lead ECG monitoring were commenced. After local anaesthetic infiltration, radial artery cannulation was performed using a 20-G catheter, and the FloTrac/Vigileo system (Edwards Lifesciences Corp., Irvine, CA, USA) was connected for cardiac output and index monitoring.

All measurements were performed at baseline before volume expansion and immediately after volume expansion. Baseline haemodynamic variables were measured 5 min after arterial cannulation without fluid administration. Static variables such as heart rate, arterial pressure and cardiac index were collected using the Solar™ 8000M monitor (GE Healthcare, Milwaukee, WI, USA). First, haemodynamic data were collected during tidal breathing. After 1 min, patients were instructed to take a few forced inspiratory breaths, each cycle of which consisted of deep inspiration immediately followed by slow passive expiration. After training, patients were encouraged to perform forced inspiratory breathing for three cycles. During both tidal and forced inspiratory breathing, a tightly fitting face mask was applied to record capnography. Arterial and capnography waveforms were recorded by data acquisition software (CIC; GE Healthcare).

For volume expansion, hydroxyethyl starch solution was infused at 6 ml.kg⁻¹ ideal body weight for 10 min. After volume expansion, haemodynamic variables were recorded during tidal breathing for 1 min, and during three cycles of forced inspiratory breathing. All haemodynamic variables and arterial and capnography waveforms were also recorded during both tidal breathing and forced inspiratory breathing after volume expansion.

The recorded arterial pressure and capnography waveforms were analysed manually by a researcher blinded to the study protocol. Pulse pressure (PP) was determined by the difference between the systolic arterial pressure and diastolic arterial pressure. Maximal PP (PP_max) and minimal PP (PP_min) values were determined over a single respiratory cycle. Pulse pressure variation was calculated as follows:

\[
PPV = \left( \frac{PP_{max} - PP_{min}}{PP_{max} + PP_{min}} \right) \times 100\%
\]

The measurements were repeated over three respiratory cycles and averaged. Pulse pressure variation was measured under two conditions: during tidal breathing and during forced inspiratory breathing. As in previous studies [14–16], ‘responders’ to fluid loading were classified as those patients who...
demonstrated a ≥ 15% increase in cardiac index after volume expansion; ‘non-responders’ were those with < 15% increase in cardiac index. To evaluate the effects of volume expansion, haemodynamic variables before and after volume expansion were compared using paired t-tests or the Wilcoxon signed-rank test after normality test. Haemodynamic variables between responders and non-responders were compared using Student t-test or Mann–Whitney U-test where appropriate. To assess correlations between haemodynamic variables, Spearman’s rank correlation coefficient was used. A receiver-operating characteristic (ROC) curve for each variable was generated and an area under the ROC curve was calculated. Using this analysis, the optimal threshold value, sensitivity and specificity of each indicator could be determined. The sample size was determined by considering that an area under the ROC curve ≥ 0.8 is clinically reliable to predict fluid responsiveness. To detect a 0.3 difference from the null hypothesis of 0.5, 28 patients were required in each group with 5% significance and 80% power area under the ROC curve. A value of p < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 9.0.1 (MedCalc Software bvba, Ostend, Belgium).

Results

Of the 96 patients scheduled for elective thoracic surgery, 62 patients were enrolled in the study and 59 patients were finally analysed (Fig. 1). After volume expansion began, the responder group (n = 29) demonstrated a ≥ 15% increase in cardiac index and the non-responder group (n = 30) had a < 15% increase in cardiac index.

**Table 1 Patients’ characteristics.** Values are mean (SD) or median (IQR [range]).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 59)</th>
<th>Responders (n = 29)</th>
<th>Non-responders (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>60 (12)</td>
<td>57 (13)</td>
<td>62 (10)</td>
</tr>
<tr>
<td>Male; n</td>
<td>38 (64%)</td>
<td>20 (69%)</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>62 (11)</td>
<td>62 (13)</td>
<td>63 (10)</td>
</tr>
<tr>
<td>BMI; kg.m(^{-2})</td>
<td>23 (3)</td>
<td>23 (3)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Infused volume; ml</td>
<td>350 (305–400)</td>
<td>370 (330–410)</td>
<td>335 (300–380)</td>
</tr>
<tr>
<td></td>
<td>(230–530)</td>
<td>(230–530)</td>
<td>(250–430)</td>
</tr>
<tr>
<td>Type of surgery; n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VATS</td>
<td>45</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Open thoracotomy</td>
<td>13</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

BMI, body mass index; VATS, video-assisted thoracoscopic surgery.

![Figure 1](image-url)  
*Figure 1* Flowchart of patient recruitment. COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; CI, cardiac index.
expansion, there were 29 responders and 30 non-responders. The patients’ characteristics are presented in Table 1.

Haemodynamic variables before and after volume expansion are presented in Table 2. Volume expansion increased the cardiac index in both responders and non-responders ($p < 0.0001$). In the responders, volume expansion significantly increased systolic arterial pressure, mean arterial pressure, and PP. Pulse pressure variation during tidal breathing (PPV$_{TB}$) and PPV during forced inspiratory breathing (PPV$_{FB}$) decreased significantly after volume expansion. The heart rate was not changed in either group. In responders, PPV$_{FB}$ before volume expansion was significantly higher than in non-responders; however, PPV$_{TB}$ before volume expansion was comparable between responders and non-responders Table 2.

Baseline PPV$_{FB}$ was correlated with the volume expansion-induced changes in the cardiac index (Fig. 2). In contrast, there were no relationships between the volume expansion-induced changes in the cardiac index and the baseline values of other haemodynamic variables such as systolic and mean arterial pressures, PP, heart rate, and PPV$_{TB}$.

The area under the ROC of a PPV$_{FB}$ was 0.910 (95% CI 0.806–0.969, $p < 0.0001$), and a PPV$_{FB}$ of 13.7% predicted fluid responsiveness with a sensitivity of 89.7% and specificity of 86.7% (Fig. 3). The area under the ROC of a PPV$_{TB}$ was 0.618 (95% CI 0.482–0.741), and it did not predict fluid responsiveness ($p = 0.112$).

Discussion

We found that PPV during forced inspiratory breathing in spontaneously breathing patients can predict fluid responsiveness: a threshold PPV$_{FB}$ of 13.7% could discriminate responders from non-responders. In contrast, PPV during tidal breathing failed to predict fluid responsiveness in spontaneously breathing patients.

Our results contradict previous reports, in which PPV could not discriminate responders from non-responders after volume expansion among critically ill patients with spontaneous breathing activity [14, 15]. However, those patients were not strictly breathing spontaneously, but received some mechanical ventilator support. In patients triggering the ventilator, inspiration generates both positive and negative intrathoracic pressures. Heart–lung interactions may be unpredictable because the intrathoracic pressure and the capacitance of the pulmonary vasculature are influenced by the intensity of both the inspiratory effort and the positive pressure support. This complicated breathing may explain the lack of predictive value of PPV in those studies.

Soubrier et al. [16] recruited only patients spontaneously breathing without tracheal intubation, and investigated whether dynamic variables could predict fluid responsiveness. They also assessed the predictive value of dynamic variables during deep inspiration followed by deep expiration. In their responders, PPV and systolic pressure variations were significantly higher than in non-responders, but the dynamic variables did not reliably predict fluid responsiveness because of a lack of sensitivity. Interestingly, their

Table 2 Haemodynamic variables. Values are mean (SD) or median (IQR [range]).

<table>
<thead>
<tr>
<th>Haemodynamic variables</th>
<th>Responders (n = 29)</th>
<th>Non-responders (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After volume expansion</td>
</tr>
<tr>
<td>HR; beats.min$^{-1}$</td>
<td>70 (14)</td>
<td>71 (14)</td>
</tr>
<tr>
<td>SAP; mmHg</td>
<td>139 (20)</td>
<td>144 (19)$^*$</td>
</tr>
<tr>
<td>MAP; mmHg</td>
<td>95 (12)</td>
<td>98 (11)$^*$</td>
</tr>
<tr>
<td>PP; mmHg</td>
<td>72 (18)</td>
<td>74 (18)$^*$</td>
</tr>
<tr>
<td>CI; l.min$^{-1}$</td>
<td>3.4 (0.9)</td>
<td>4.0 (1.0)$^*$</td>
</tr>
<tr>
<td>PPV$_{TB}$; %</td>
<td>6.2 (4.1–7.5 [2.3–22.0])</td>
<td>4.3 (2.8–6.1 [1.3–13.2])$^*$</td>
</tr>
<tr>
<td>PPV$_{FB}$; %</td>
<td>18.2 (14.7–18.2 [9.3–31.3])</td>
<td>8.3 (6.7–8.3 [4.3–24.0])$^*$</td>
</tr>
</tbody>
</table>

HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; PP, pulse pressure; CI, cardiac index; PPV$_{TB}$, pulse pressure variation during tidal breathing; PPV$_{FB}$, pulse pressure variation during forced inspiratory breathing.

*p < 0.05 baseline vs after volume expansion.

$^+$p < 0.05 responders vs non-responders.

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forced respiratory manoeuvre decreased the predictive value of PPV and systolic pressure variation. This is contradictory to our findings, in which the increased tidal volume by forced inspiratory breathing resulted in better sensitivity and specificity of the prediction of fluid responsiveness. This can be explained by the difference between forced expiratory effort (which they used) and passive expiration (which we employed). The former might have increased the abdominal pressure and left ventricular afterload, which may have limited the increase in left ventricular stroke volume.

The forced inspiratory breathing is a simple method that requires little training. We only encouraged full inspiration followed by passive expiration for this manoeuver. Knowing the fluid responsiveness from PPV during forced inspiratory breathing before induction of anaesthesia can help predict the fluid administration requirements during induction of anaesthesia. Patients who undergo regional anaesthesia with spontaneous breathing may also benefit, although this remains to be determined by more studies.

The present study has some limitations. First, we did not use thermal dilution for cardiac output measurement. However, the accuracy of the Vigileo system is generally believed to be good and allows for continuous rather than intermittent measurement [20]. We could not utilise the stroke volume variation obtained by the Vigileo system [20, 21] because three cycles of forced inspiratory breathing were not sufficient to record stroke volume variation which is calculated over

Figure 2 Relationships between the percentage changes in cardiac index (CI) and the initial values of pulse pressure variation during forced inspiratory breathing (PPVFB). Initial PPVFB was correlated with the volume expansion-induced changes in the cardiac index (r = 0.50, p < 0.001). Patients are displayed as responders (●) and non-responders (○).

Figure 3 Receiver-operating characteristic curves of pulse pressure variation during forced inspiratory breathing (■) and pulse pressure variation during tidal breathing (○) before volume expansion. p = 0.0002 for the difference in area under the two curves.
a 20-s time frame. Second, respiratory variables such as tidal volume and intrathoracic pressure could not be accurately controlled in the present study. Although all the patients were trained to perform forced inspiratory breathing followed by slow passive expiration, standardisation of breathing volume might further improve the accuracy of PPV FR to predict fluid responsiveness in spontaneously breathing patients. Lastly, the use of hydroxyethyl starch is now suspended in many countries because of published evidence which shows that there is an increased risk associated with the use of hydroxyethyl starch products [22, 23]. However, hydroxyethyl starch was widely used for fluid responsiveness study until these trials and this study was performed from July 2011 to February 2012.

In conclusion, PPV during forced inspiratory breathing appears to predict fluid responsiveness in spontaneously breathing patients. By means of forced inspiration followed by passive expiration, PPV can be used as a simple bedside test to guide fluid management even in spontaneously breathing patients such as before the induction of general anaesthesia.

Competing interests
No external funding or competing interests declared.

References
A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass*

W. F. Kok,1 A. E. van Harten,2 B. M. J. A. Koene,3 M. A. Mariani,4 J. Koerts,5 O. Tucha,6 A. R. Absalom7 and T. W. L. Scheeren7

1 PhD student, 2 Resident, 7 Professor, Department of Anaesthesiology, 3 Staff Surgeon, 4 Professor and Chair, Department of Cardiothoracic Surgery, University Medical Centre Groningen, 5 Neuropsychologist and Assistant Professor, 6 Professor and Chair, Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, the Netherlands

Summary
Coronary artery bypass surgery, performed with or without cardiopulmonary bypass, is frequently followed by postoperative cognitive decline. Near-infrared spectroscopy is commonly used to assess cerebral tissue oxygenation, especially during cardiac surgery. Recent studies have suggested an association between cerebral desaturation and postoperative cognitive dysfunction. We therefore studied cerebral oxygen desaturation, defined as area under the cerebral oxygenation curve < 40% of > 10 min.%, with respect to cognitive performance at 4 days (early) and 3 months (late) postoperatively, compared with baseline, using a computerised cognitive test battery. We included 60 patients, of mean (SD) age 62.8 (9.4) years, scheduled for elective coronary artery bypass grafting, who were randomly allocated to surgery with or without cardiopulmonary bypass. Cerebral desaturation occurred in only three patients and there was no difference in cerebral oxygenation between the two groups at any time. Among patients who received cardiopulmonary bypass, 18 (62%) had early cognitive decline, compared with 16 (53%) in the group without cardiopulmonary bypass (p = 0.50). Three months after surgery, 11 patients (39%) in the cardiopulmonary bypass group displayed cognitive dysfunction, compared with four (14%) in the non-cardiopulmonary bypass group (p = 0.03). The use of cardiopulmonary bypass was identified as an independent risk factor for the development of late cognitive dysfunction (OR 6.4 (95% CI 1.2–33.0) p = 0.027. In conclusion, although cerebral oxygen desaturation was rare in our population, postoperative cognitive decline was common in both groups, suggesting that factors other than hypoxic neuronal injury are responsible.

Correspondence to: T. Scheeren
Email: t.w.l.scheeren@umcg.nl
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Introduction

Coronary artery bypass graft surgery (CABG) is frequently associated with a systemic inflammatory response [1] and injury and dysfunction of several organs, including the brain [2–4]. Diffuse cerebral injury after CABG may result in delirium and/or cognitive decline. Previously, many postoperative complications after heart surgery were attributed to cardiopulmonary bypass (CPB). In recent years, however, doubt has been cast on this theory because retrospective and prospective studies have failed to demonstrate that CABG without CPB is associated with a reduction in the incidence of early mortality and major complications [5–7]. Indeed, although CABG without CPB does not involve the inherent risks of extracorporeal circulation, aortic manipulation is often still required, and can be the cause of cerebral micro-emboli and infarction. However, the number of micro-infarcts is thought to be greater when CPB is used [8]. Perhaps more importantly, cardiac surgery without CPB may introduce other potentially harmful risks, including temporary reduction in cardiac output during periods when the beating heart is manipulated. This variation in blood supply may reduce oxygen delivery and cause hypoxic tissue damage in vulnerable tissues, particularly the brain.

Postoperative cognitive dysfunction may be difficult to diagnose, and results in changes in performance scores in cognitive function tests focused on domains such as attention, concentration, memory and executive function, without evidence of focal neurological damage. Sceptics claim that postoperative cognitive dysfunction is a statistical aberration arising from methodological weaknesses, or from other temporary factors such as fatigue and lethargy caused by residual drug effects and the stress response to surgery [9]. If, however, one accepts that postoperative cognitive dysfunction exists and is the result of diffuse neuronal injury, then there are two possible conclusions. The first is that CPB is not harmful, and that neuronal injury arises with both techniques (with and without CPB) as a result of common responses to surgery and anaesthesia (such as a priming-induced exaggerated inflammatory response) [2]. A second possibility is that both techniques have adverse effects on the brain with similar cognitive consequences, but via different mechanisms.

Near-infrared spectroscopy is commonly used to assess regional tissue oxygen haemoglobin saturation in the frontal cortex of the brain [10, 11]. It gives an indication of the balance between oxygen delivery and oxygen consumption, which may have prognostic value. A recent study showed that pre-operative cerebral oximetry values predicted various postoperative outcomes after coronary surgery using CPB [12]. Other studies have shown a correlation between the severity and duration of cerebral desaturation, with or without CPB, and subsequent postoperative cognitive dysfunction [13, 14], although the evidence is somewhat weak [15]. To our knowledge, there have been no randomised trials comparing cerebral saturation during surgery with and without CPB to date.

The aim of our randomised pilot study was to compare the incidence and severity of cerebral oxygen desaturation during coronary artery surgery with and without CPB. In addition, we sought to explore further the correlation between surgical technique, cerebral oxygenation and postoperative cognitive dysfunction. We hypothesised that significant cerebral desaturation occurs less commonly during surgery without CPB than with CPB, and that cognitive dysfunction would also be less common in this cohort of patients. We also hypothesised that postoperative cognitive dysfunction is associated with intra-operative cerebral hypoxia, but that the pattern would be different depending on whether CPB was used or not.

Methods

This study was performed at the University Medical Centre Groningen, the Netherlands, between June 2011 and May 2012, after institutional review board approval and with written informed consent. A sealed envelope technique was used to randomise eligible patients to undergo coronary artery surgery either with or without CPB. Inclusion criteria were age > 18 years and considered suitable for surgery with or without CPB by both the operating surgeon and the responsible anaesthetist. Patients were not studied if they were likely to experience difficulty completing cognitive testing because of impaired hearing or eyesight, problems understanding the Dutch language, or impaired
function of the dominant hand or arm. Other exclusion criteria included: history of head trauma, stroke or neurosurgery; severe or symptomatic carotid artery disease; systemic steroid therapy; and pre-existing acute or chronic renal impairment (creatinine concentration > 200 \mu mol.l^{-1}).

Anaesthetic management followed a strict protocol. Anaesthesia was induced with sufentanil 0.5 \mu g.kg^{-1} and propofol target-controlled infusion 2 \mu g.ml^{-1}, adjusted thereafter to keep the bispectral index in the range of 30–50 throughout the procedure. Tracheal intubation followed the administration of either 0.1 mg.kg^{-1} pancuronium or 0.6 mg.kg^{-1} rocuronium. During the procedure, a continuous infusion of sufentanil and additional sufentanil boluses of 10 \mu g were given at the discretion of the anaesthetist. During surgery, standard monitoring included mean arterial pressure, heart rate, oxygen saturation, central venous pressure and central venous oxygen saturation. Patients were transferred postoperatively to the intensive care unit (ICU) and sedated with propofol by infusion until they were considered ready for tracheal extubation.

Patients allocated to surgery using CPB received heparin 300 IU.kg^{-1}, after which their ascending aorta and right atrium were cannulated. Cardiopulmonary bypass was non-pulsatile and mean arterial pressure was maintained around 60 mmHg. Patients’ temperature was allowed to drift passively to 34 °C. Cold blood cardioplegia (200 ml) was administered both antegrade (aortic root) and/or retrograde (coronary sinus) and repeated every 20 min. Patients randomly allocated to surgery without CPB also received heparin but at a dose of 200 IU.kg^{-1}; cardiac stabilisation and displacement was obtained using the Acrobat and XPOSE-4 devices (both Maquet, Rastatt, Germany). Coronary anastomoses were facilitated by intracoronary shunts (Medtronic, Minneapolis, MN, USA) and a carbon dioxide with warm saline blower (Blower Mister; Maquet). Side-clamping of the aorta was required in 27 (90%) of patients operated without CPB when anastomosing the top end of the coronary grafts, whereas in 3 (10%) patients, a no-touch aorta technique was used.

Cerebral tissue oxygenation was measured by near-infrared spectroscopy using both the INVOS® Cerebral Oximeter 5100C (Covidien, Dublin, Ireland) and the ForeSight® Cerebral Oximeter (CASMED, Branford, CT, USA) simultaneously [16]. As the two cerebral oximeters showed a similar time course in most patients, with mean ForeSight values uniformly 15–20 percentage points higher than respective INVOS values, we will present only measurements from one device, the INVOS. Immediately after arrival in the operating theatre, the cerebral oximetry sensors were applied bilaterally to the patient’s forehead and cerebral oximetry measurement was commenced. The anaesthetist responsible for the care of the patient remained blinded to the cerebral oximetry measurements throughout anaesthesia and surgery.

With regard to neuropsychological testing, depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) [17] before the start of each cognitive test session. A cut-off HADS score of ≥ 8 was defined to identify patients with pre-existing depression or anxiety. Cognitive function was assessed using the CogState brief computerised cognitive test battery (Cogstate Ltd, Melbourne, Vic., Australia), consisting of the detection task, the identification task, the one card learning task and the one back task [18]. These tests assess psychomotor speed, selective attention, long-term memory and working memory, respectively. Two sets of cognitive tests were performed on the day before surgery. The first set was a practice test and the second was used as the baseline test, as practice effects have been shown between the first and second set of tests [19]. Follow-up tests were then performed at 4 days and 3 months postoperatively. The testing required approximately 15 min per session. Each task was explained to the participants by an investigator using standardised written instructions.

For each postoperative cognitive test, a standardised change Z-score was calculated. This score, equivalent to a reliable change score, takes into account the test–retest variability among an age-matched normal control population. The standardised change scores of the individual tests were summed to generate a composite Z-score. Postoperative cognitive dysfunction was defined as a standardised change Z-score less than −2 in two or more individual tasks or a composite Z-score of less than −2 [20]. The evaluators were blinded to the patient’s group assignment.
The primary outcome of this pilot study was significant cerebral desaturation, defined as cerebral oximetry AUC$_{40}$ > 10 min.%; this was calculated from the integral of the cerebral oximetry signal over time, of the portions of the signal when the cerebral oximetry was < 40% (i.e. AUC$_{40} = \sum [\int (40 - rSO_2) \, dt]$ for all periods where 40 - rSO$_2$ > 0). Secondary outcomes were the incidence of postoperative cognitive dysfunction at 4 days and 3 months postoperatively, the incidence of major complications, and the duration of ICU and hospital admission. Analyses were performed using SPSS statistics software version 20 (IBM, New York, NY, USA). The Kolmogorov–Smirnov test was used to assess distribution of the data. Continuous data were analysed using Student’s t-test and non-continuous data using the Mann–Whitney U-test. Nominal data were analysed using the Pearson chi-squared test or Fisher’s exact test as appropriate. In all cases, a two-sided p value < 0.05 was considered statistically significant. Univariate and multivariate logistic regression models were used to evaluate risk factors that may influence the occurrence of postoperative cognitive dysfunction, such as age, use of CPB, cerebral desaturation and neuropsychological state.

Results

A total of 60 patients undergoing elective CABG were enrolled (Fig. 1). Exclusion of eligible patients due to logistic reasons was quite common; these included the inability to schedule the operation of a consenting patient with a participating surgeon and anaesthetist, and the inability to record data from different patients having surgery at the same time. Mean (SD) age was 62.8 (9.4) years and 54 (90%) patients were men; baseline characteristics between patients randomly allocated to surgery with or without CPB were similar (Table 1). Data from one patient randomly allocated to surgery with CPB were excluded from analysis because he received surgery without CPB as he was found to have a 'porcelain' aorta, and after discussion, it was felt that avoidance of aortic cross-clamping was in his interests. Mean (SD) CPB time was 82.6 (22.6) min and aortic cross-clamp time was 53.1 (14.5) min. Mean arterial pressure at the end of surgery was significantly lower in patients who underwent surgery with CPB compared with those without CPB; other haemodynamic and systemic oxygenation variables were similar (Table 2).

Cerebral oximetry values were similar between the two groups (Table 3). The primary outcome (AUC$_{40}$ > 10 min.%) was reached in only three patients; one who received CPB and two who did not. One of these patients (AUC$_{40}$, 87 min.%, Fig. 2), from the CPB group, suffered a peri-operative stroke. The other two patients fulfilled the criteria for both early and late postoperative cognitive dysfunction. Because of the low incidence of our predefined primary outcome, we performed a broader analysis using other cut-off points in cerebral oximetry values (Table 3). We calculated AUC parameters using less stringent absolute and relative desaturation thresholds, and also recorded the number of patients in whom cerebral oxygen saturation declined below 70% of baseline value, regardless of duration. There were no significant differences in any of these parameters between the two groups of patients. Median (IQR [range]) length of stay in ICU and in hospital was 1 (1–1 [1–12]) and 9 (6–12 [3–29]) days, respectively, in the CPB group, and 1 (1–1 [1–8]) and 8 (6–11 [4–15]) days for patients in the no-CPB group (p = 0.840 and p = 0.552, respectively).

Pre-operatively, 16 (26%) patients scored above the cut-off HADS score of 8, suggesting the presence...
of depression or anxiety. At the first postoperative assessment, median (IQR [range]) scores were 10 (6–15 [0–30]) and 8 (4–11 [0–18]) in CPB and no-CPB groups, respectively (p = 0.116). At 3 months, the scores decreased to 5 (2–8 [0–22]) vs 3 (1–7 [0–17]) in CPB and no-CPB groups, respectively (p = 0.243). Depression and anxiety were not associated with an increased risk of developing postoperative cognitive dysfunction (p = 0.19) (Table 4).

Early postoperative cognitive tests were performed a median (IQR [range]) of 4 (4–6 [2–16]) days after surgery and compliance with tests was high. One patient who received CPB suffered a peri-operative stroke, and could not complete the tests at day 4, but was regarded as having early cognitive dysfunction. Two patients were only able to complete two of the four tests but fulfilled the cognitive dysfunction criteria based on these tests. The remaining patients completed all tests. Among patients who received CPB, 18 (62%) fulfilled the criteria for cognitive dysfunction, compared with 16 (53%) in the no-CPB group, p = 0.50 (Figs 3 and 4).

Further cognitive testing after 3 months was performed a median (IQR [range]) of 93 (92–102 [88–126]) days after surgery. Two patients refused to participate, one from each group, neither of whom had early cognitive dysfunction. Eleven patients (39%) in the CPB group displayed cognitive dysfunction (one of these was the patient who had suffered

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**Table 1** Baseline characteristics in patients randomly allocated to surgery with or without CPB. Variable are number (proportion), mean (SD) or median (IQR [range]).

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 59)</th>
<th>With CPB (n = 29)</th>
<th>Without CPB (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>53 (90%)</td>
<td>26 (90%)</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>Age; years</td>
<td>62.8 (9.4)</td>
<td>62.6 (9.9)</td>
<td>63.0 (9.0)</td>
</tr>
<tr>
<td>Educational status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower education</td>
<td>45 (76%)</td>
<td>21 (75%)</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>Higher education</td>
<td>13 (22%)</td>
<td>7 (21%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>2.5 (1.8)</td>
<td>2.3 (1.7)</td>
<td>2.7 (1.9)</td>
</tr>
<tr>
<td>Smokers</td>
<td>42 (70%)</td>
<td>22 (79%)</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>BMI; kg.m⁻²</td>
<td>27.8 (3.5)</td>
<td>28.1 (4.0)</td>
<td>27.5 (2.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (23%)</td>
<td>6 (21%)</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (29%)</td>
<td>10 (35%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Pre-operative LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-70%</td>
<td>30 (501%)</td>
<td>17 (59%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>40-55%</td>
<td>25 (42%)</td>
<td>10 (35%)</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>&lt; 40%</td>
<td>4 (67%)</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>HADS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.6 (5.7)</td>
<td>9.2 (6.2)</td>
<td>8.0 (5.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.5 (3.9)</td>
<td>5.8 (4.3)</td>
<td>5.2 (3.5)</td>
</tr>
<tr>
<td>Depression</td>
<td>3.2 (2.6)</td>
<td>3.4 (2.8)</td>
<td>2.9 (2.3)</td>
</tr>
<tr>
<td>Duration of surgery; min</td>
<td>188.0 (46.3)</td>
<td>189.0 (31.6)</td>
<td>186.0 (57.7)</td>
</tr>
<tr>
<td>Aortic clamp time; min</td>
<td></td>
<td>53.1 (14.5)</td>
<td></td>
</tr>
<tr>
<td>CPB time; min</td>
<td>–</td>
<td>82.6 (22.6)</td>
<td>–</td>
</tr>
<tr>
<td>Grafts per patient</td>
<td>3.3 (0.8)</td>
<td>3.2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Pre-operative testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes; ×10⁹.l⁻¹</td>
<td>8.1 (2.3)</td>
<td>8.0 (2.3)</td>
<td>8.1 (2.3)</td>
</tr>
<tr>
<td>Hb; g.dl⁻¹</td>
<td>9.0 (0.8)</td>
<td>9.1 (0.8)</td>
<td>8.9 (0.8)</td>
</tr>
<tr>
<td>CRP; mg.l⁻¹</td>
<td>0 [0–6 [0–65])</td>
<td>0 [0–3 [0–20])</td>
<td>0 [0–8 [0–65])</td>
</tr>
<tr>
<td>Urea; mmol.l⁻¹</td>
<td>6.2 (1.9)</td>
<td>6.6 (2.0)</td>
<td>5.9 (1.8)</td>
</tr>
<tr>
<td>Creatinine; μmol.l⁻¹</td>
<td>90.0 (21.5)</td>
<td>90.4 (24.0)</td>
<td>89.2 (19.3)</td>
</tr>
<tr>
<td>eGFR; ml.min⁻¹.1.73 m²</td>
<td>75.0 (18.6)</td>
<td>76.0 (20.4)</td>
<td>74.0 (16.8)</td>
</tr>
<tr>
<td>NT-proBNP; ng.l⁻¹</td>
<td>488.5 (94–1086 [53–1639])</td>
<td>296 (93–586 [72–635])</td>
<td>572 (114–1538 [53–1639])</td>
</tr>
<tr>
<td>Troponin T; ng.l⁻¹</td>
<td>85 (23–736 [9–5325])</td>
<td>70 (9–294 [9–294])</td>
<td>389 (25–977 [18–5325])</td>
</tr>
</tbody>
</table>

CPB, cardiopulmonary bypass; BMI, body mass index; LVEF, left ventricular ejection fraction; HADS, hospital anxiety and depression score; Hb, haemoglobin concentration; CRP, C-reactive protein; GFR, glomerular filtration rate; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide.
Table 2 Peri-operative haemodynamic and systemic oxygenation variables in patients randomly allocated to surgery with or without CPB. Values were taken at baseline, intra-operatively at sternotomy, and at sternal closure indicating the end of the procedure. Values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>p value</th>
<th>Intra-operative</th>
<th>p value</th>
<th>End of surgery</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate; beats.min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CPB</td>
<td>66.7 (12.2)</td>
<td>0.738</td>
<td>63.2 (11.3)</td>
<td>0.336</td>
<td>80.7 (28.9)</td>
<td>0.163</td>
</tr>
<tr>
<td>Without CPB</td>
<td>66.6 (9.7)</td>
<td></td>
<td>60.2 (10.5)</td>
<td></td>
<td>81.9 (14.9)</td>
<td></td>
</tr>
<tr>
<td>MAP; mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>With CPB</td>
<td>102.0 (14.3)</td>
<td>0.131</td>
<td>88.2 (14.8)</td>
<td>0.328</td>
<td>69.2 (15.7)</td>
<td>0.044</td>
</tr>
<tr>
<td>Without CPB</td>
<td>95.6 (18.1)</td>
<td></td>
<td>83.5 (15.6)</td>
<td></td>
<td>73.0 (10.2)</td>
<td></td>
</tr>
<tr>
<td>CVP; mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CPB</td>
<td></td>
<td>0.618</td>
<td></td>
<td>0.11 (4.7)</td>
<td></td>
<td>0.343</td>
</tr>
<tr>
<td>Without CPB</td>
<td></td>
<td></td>
<td></td>
<td>11.7 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO₂; %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CPB</td>
<td>98.6 (1.5)</td>
<td>0.633</td>
<td>98.6 (1.5)</td>
<td>0.459</td>
<td>98.1 (1.9)</td>
<td>0.805</td>
</tr>
<tr>
<td>Without CPB</td>
<td>98.5 (1.3)</td>
<td></td>
<td>99.5 (1.4)</td>
<td></td>
<td>98.2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>SaO₂ central venous; %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CPB</td>
<td></td>
<td>0.310</td>
<td></td>
<td>69.3 (6.7)</td>
<td></td>
<td>0.288</td>
</tr>
<tr>
<td>Without CPB</td>
<td></td>
<td></td>
<td></td>
<td>64.8 (13.0)</td>
<td></td>
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</tr>
</tbody>
</table>

Table 3 Pre- and intra-operative cerebral oximetry saturations in patients randomly allocated to surgery with and without CPB. Values are mean (SD), median (IQR [range]) or number (proportion).

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 59)</th>
<th>With CPB (n = 29)</th>
<th>Without CPB (n = 30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline; %</td>
<td>67.1 (9.4)</td>
<td>67.2 (10.1)</td>
<td>67.0 (8.8)</td>
<td>0.627</td>
</tr>
<tr>
<td>Increase after</td>
<td>14.7 (6.0)</td>
<td>15.4 (6.6)</td>
<td>14.0 (5.2)</td>
<td>0.409</td>
</tr>
<tr>
<td>pre-oxygenation; %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-operative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC &lt; 60%; min.%</td>
<td>117 (12-806 [0-3397])</td>
<td>131 (13-1165 [0-3397])</td>
<td>113 (5.3-817.5 [0-2178])</td>
<td>0.665</td>
</tr>
<tr>
<td>AUC &lt; 50%; min.%</td>
<td>0 (0-26 [0-1077])</td>
<td>0 (0-120 [0-1077])</td>
<td>0 (0-22.5 [0-434])</td>
<td>0.496</td>
</tr>
<tr>
<td>AUC &lt; 40%; min.%</td>
<td>0 (0-0 [0-87])</td>
<td>0 (0-0 [0-87])</td>
<td>0 (0-0 [0-24.5])</td>
<td>0.638</td>
</tr>
<tr>
<td>AUC decrease from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10%; min.%</td>
<td>201.1 (38.3-521.4 [0-2981])</td>
<td>227 (188.45-576.5 [1-2981])</td>
<td>145.5 (3.5-507.1 [0-2024])</td>
<td>0.124</td>
</tr>
<tr>
<td>&gt; 15%; min.%</td>
<td>60 (4.1-217 [0-1964])</td>
<td>87 (11.1-239.9 [0-1964])</td>
<td>35.6 (0.206.2 [0-1140])</td>
<td>0.148</td>
</tr>
<tr>
<td>&gt; 20%; min.%</td>
<td>6.4 (0.59.4 [0-1039])</td>
<td>9.8 (0.91 [0-1039])</td>
<td>2.4 (0.37 [0-439.2])</td>
<td>0.185</td>
</tr>
<tr>
<td>&gt; 30%; min.%</td>
<td>0 (0-0 [0-142])</td>
<td>0 (0-0.75 [0-142])</td>
<td>0 (0-0 [0-75.6])</td>
<td>0.319</td>
</tr>
<tr>
<td>Cerebral saturations &lt; 70% of baseline at any time</td>
<td>14 (24%)</td>
<td>9 (31%)</td>
<td>0 (0-17%)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

Discussion

In this randomised pilot study, we found a very low overall incidence of significant cerebral desaturation, with no differences between patients in whom CPB was used and those in whom CPB was avoided. Despite this, a high proportion of patients fulfilled the criteria for cognitive dysfunction, which was more common in patients in whom CPB was used, although the study was not powered for this outcome.
Although not a direct measure of brain tissue oxygen tension, cerebral oximetry is thought to give an indication of the balance between oxygen delivery and utilisation [10, 11]. Delivery may be impaired by arterial hypoxaemia and/or impaired cerebral blood flow, and utilisation depends on diffusion, oxygen requirements and intact cerebral metabolic processes. Cerebral oximetry measurements mostly reflect venous oxygen haemoglobin saturation, and thus give an indication of tissue oxygen tension. A lower than normal cerebral oximetry value indicates an adverse balance between supply and demand, and in a surgical setting with general anaesthesia usually indicates insufficient cerebral perfusion.

Although there is no agreement of what reduction in cerebral oximetry from baseline is abnormal in cardiac surgery [15], the low incidence of marked desaturation found in our study is discordant with previous literature [21, 22]. The primary outcome for our study was based on a previously published study [14], which showed lower overall baseline and peri-operative cerebral oximetry levels, and deeper dips in cerebral oximetry saturations than our study population. Other studies have also suggested that significant desaturations could be expected in 30–40% of patients [13, 21].

A likely explanation of this difference is that our study population was particularly low-risk and undergoing coronary artery surgery alone, with a mean (SD) EuroSCORE of 2.5 (1.8), whereas other studies
included older and higher-risk patients, and also some patients undergoing valve surgery. As a consequence, a properly powered follow-up study would require a much larger group of low-risk patients or a selected sub-set of higher-risk patients.

The validity of cerebral oximetry measurements has been the subject of debate and controversy, with particular concerns about contamination of the signal by extracranial or scalp blood flow [23]. However, evaluation of the INVOS device has shown reasonable correlation with measured oxygen saturation levels [24]. The effects of signal disturbance by extracranial contamination have been evaluated in an innovative recent clinical trial, which showed that this was present with all existing monitors [25]. Nonetheless, in the presence of constant arterial oxygen tension and normal systemic haemoglobin oxygen saturation, trends and changes in cerebral oximetry values are still likely to provide a useful indication of changes in regional cerebral tissue oxygenation, at least in the frontal cortex.

The overall incidence of cognitive dysfunction among our patients was 56% shortly after surgery and 26% after 3 months. The incidence of cognitive dysfunction is highly sensitive to the nature, timing and interpretation of test results [20, 26]. Different techniques may be used; however, the incidence among our patients is generally comparable with the range of 26–71% reported after major surgery in elderly patients [27], although there is some evidence that patients may recover more quickly after coronary artery surgery [28]. There is also some evidence that the incidence of cognitive dysfunction after coronary surgery may have been overestimated in the past [3, 29, 30].

We did show a small but statistically significant reduction in the incidence of cognitive dysfunction after 3 months in patients who had not received CPB, compared with those who had. Although our study was not powered for this outcome and no correction was made for multiple testing, this is in keeping with other studies specifically designed to investigate this outcome [31–33].

Among the patients studied, significant intra-operative cerebral oximetry desaturation, albeit of low incidence, was associated with neurological consequences, namely stroke or cognitive dysfunction, in all cases. However, the majority of patients who fulfilled the criteria for cognitive dysfunction had normal or at least acceptable intra-operative cerebral oximetry values. This finding is in contrast to that of other groups who reported an association between cerebral desaturation and postoperative cognitive dysfunction [13, 14, 21, 22]. The causes of cognitive dysfunction are likely
to be different when tested for at an early stage compared with later after surgery. For example, it is probable that at the stage of our early tests (median postoperative day 4), factors such as residual opioid effects, sleep deprivation, lethargy and depression may have played a role. Anxiety and depression are also known to influence cognitive outcome [34], and indeed our data do show a non-significant trend towards an association between the pre-operative and early postoperative hospital anxiety and depression scores and early cognitive dysfunction.

While cerebral hypoxia appears not to have been a problem in the majority of our patients, it remains possible, but unproven, that surgery, anaesthesia and/or CPB initiate a number of pathophysiological processes, such as systemic and cerebral inflammation, that cause neuronal injury and result in persistent or late-onset cognitive dysfunction. However, a recent meta-analysis suggested that, despite early cognitive dysfunction, cognitive function might even improve in the first year after coronary artery surgery [30]. In the absence of a gold standard method of assessing cognitive function, it remains unclear whether the finding of a high incidence among our patients represents true neuronal dysfunction.

A limitation of our pilot study is the small sample size, making it difficult to draw firm conclusions. In addition, we chose to study low-risk cardiac surgical patients, which may limit the applicability of the findings to the broader cardiac surgery population. The postoperative cognitive tests should ideally have been performed at exactly the same time point in all patients, but this was not practically and logistically possible. We used total intravenous anaesthesia with propofol and sufentanil, as this is routinely used for cardiovascular surgery in our department. Our decision to exclude the patient with a porcelain aorta from further analysis may be subject to criticism; however, inclusion of the data from this patient in the analyses, whether on an intention-to-treat basis or on a per-protocol basis, does not alter the main findings.

In conclusion, we found that significant cerebral oximetry desaturation was uncommon among low-risk patients undergoing coronary artery surgery, and that the incidence of desaturation, using a range of threshold criteria, was not different among patients randomly allocated to surgery with or without CPB. We therefore cannot recommend that cerebral oximetry should be routinely monitored in low-risk patients undergoing coronary surgery. Nonetheless, the incidence of cognitive dysfunction among our patients was rather high in both groups, similar to that found in other published studies with higher incidences of intra-operative cerebral desaturation, suggesting that factors other than intra-operative hypoxic neuronal injury are responsible for the observed cognitive decline.

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A prospective observational study of stroke volume responsiveness to a passive leg raise manoeuvre in healthy non-starved volunteers as assessed by transthoracic echocardiography

G. E. P. Godfrey, S. W. Dubrey and J. M. Handy

1 Specialist Registrar, Department of Anaesthesia, 2 Consultant, Department of Cardiology, Hillingdon Hospital, London, UK
3 Consultant, Department of Cardiology, Royal Brompton and Harefield NHS Trust, London, UK
4 Honorary Senior Lecturer, Imperial College, London, UK
5 Consultant, Magill Department of Anaesthesia, Pain and Intensive Care Medicine, Chelsea and Westminster Hospital, London, UK

Summary

Current guidelines for intra-operative fluid management recommend the use of increments in stroke volume following intravenous fluid bolus administration as a guide to subsequent fluid therapy. To study the physiological premise of this paradigm, we tested the hypothesis that healthy, non-starved volunteers would develop an increment in their stroke volume following a passive leg raise manoeuvre. Subjects were positioned supine and stroke volume was measured by transthoracic echocardiography at baseline, 30 s, 1 min, 3 min and 5 min after passive leg raise manoeuvre to 45°. Stroke volume was measured at end-expiration during quiet breathing, as the mean of three sequential measurements. Seventeen healthy volunteers were recruited; one volunteer in whom it was not possible to obtain Doppler measurements and a further five for reasons of poor Doppler image quality were not included in the study. Mean (SD) percentage difference from baseline to the largest change in stroke volume was 5.7 (9.6)% (p = 0.16). Of the 11 volunteers evaluated, five (45%) had stroke volume increases of greater than 10%. Mean (SD) maximum percentage change in cardiac index was 14.8 (9.7)% (p = 0.004). A wide variation in baseline stroke volume and response to the passive leg raise manoeuvre was seen, suggesting greater heterogeneity in the normal population than current clinical guidelines recognise.

Correspondence to: J. M. Handy
Email: j.m.handy@imperial.ac.uk
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Introduction

Despite decades of study and research, identifying and achieving the optimal fluid strategy for patients undergoing high-risk surgery remain a challenge. Both hypervolaemia and hypovolaemia can be detrimental during the peri-operative period [1–3], and in recent years, the concept of targeting ‘normovolaemia’ has gained increasing popularity as an endpoint for ‘optimising’ intra-operative fluid therapy. However, ‘normovolaemia’ and ‘fluid optimisation’ are poorly defined clinical entities, making their use as clinical endpoints challenging. In their review of the normovolaemic state, Truijen and colleagues state that “for supine healthy humans, the heart is operating on the plateau of the
Frank-Starling curve since further expansion of the central blood volume does neither increase stroke volume nor cardiac output" [4]; they conclude that "the plateau of the Starling curve for the heart is reached when humans are supine and that observation may be applied to define normovolaemia of consequence for monitoring of volume treatment of patients". This paradigm – that normovolaemia and 'optimal filling' exist when the plateau of the Frank-Starling curve is achieved – forms the physiological basis of current recommendations on intra-operative goal-directed fluid therapy [5]. According to these recommendations, normovolaemia and optimal blood volume are clinically considered to be achieved once stroke volume increments of 10% are no longer identified following intravenous fluid boluses. While some clinical studies have demonstrated improved patient outcomes using such goal-directed therapy over 'standard' fluid regimes [6–8], others have shown potentially detrimental effects [9–11]; the result has been contentious debate [12].

Surprisingly, the evidence base to support the physiological premise of normovolaemia as described above is less robust than might be expected. While some studies support that the normovolaemic state exists at the plateau of the Frank-Starling curve [13–15], others suggest that this is not the case [16, 17]. To test the relationship between stroke volume and preload (left ventricular end diastolic volume) in normovolaemic healthy individuals, two conditions are required. First, preload must be manipulated accurately as the single cardiovascular variable; second, stroke volume must be measured accurately at appropriate time points relative to the change in preload.

Only two methods have been used in healthy non-starved volunteers to manipulate preload: head-up and head-down tilting [15, 16], and the administration of peripheral intravenous fluid boluses [13]; both have limitations. Head-down tilt produces a less persistent increase in cardiac output than the passive leg raise manoeuvre [18] and the effect on preload does not seem to be consistent. In their study of healthy volunteers, Jans et al. found that performing head-down tilt resulted in no increase in stroke volume when compared with supine baseline measurements [15]. Interestingly, central venous pressure did not increase either, suggesting that if an increase in right ventricular end diastolic volume (and, by inference, preload) occurred, it was insufficient to support their conclusions that the subjects were functioning at the plateau of the Frank-Starling curve. Conversely, Nixon et al. [16] found a sustained increase in stroke volume and cardiac output following the head-down tilt manoeuvre, although central venous pressure was not measured. Head-down tilt causes direct and immediate stimulation of the carotid baroreceptors; as such, the immediate cardiovascular responses cannot be attributed to a change in preload alone.

The main limitation of using peripherally administered intravenous fluid to increase preload is the time taken for the fluid to be infused and the impact of venous capacitance on any increase in central venous and right atrial pressures. Various techniques have been used to measure stroke volume in a variety of patient and volunteer studies [13, 15–17, 19–25]. However, accuracy and 'range of uncertainty' are wide-ranging for these devices, resulting in potential inaccuracies in stroke volume measurement; also, a number of these studies have not included the stroke volume/preload relationship in their primary hypotheses and may therefore be underpowered or inappropriately designed. Of all the techniques used to measure stroke volume, transthoracic echocardiography has been repeatedly used and has been shown to be accurate [26].

Given the inconsistencies and limitations described above, we believe that the normovolaemic state has yet to be satisfactorily described in physiological terms. We propose that normovolaemia should be defined clinically by the non-starved supine state, and that understanding fluid responsiveness during this state is important from both clinical and physiological perspectives. Therefore, we undertook a prospective study to test the hypothesis that stroke volume, as assessed by transthoracic echocardiography, would increase after increasing cardiac preload by performing a passive leg raise manoeuvre in non-starved supine (normovolaemic) healthy volunteers.

Methods
Before undertaking the study, 12 sequential, supine, resting stroke volume measurements were made on one of the authors (GG) to establish satisfactory variability in sequential measurements and to provide
data with which to calculate an appropriate sample size.

After receiving approval from the local Research Ethics Committee, a circular email was distributed to staff at Hillingdon Hospital in London describing the study and inviting volunteers to take part. Participants aged 18–50 years were included. Participants were not taken into the study if they reported a history of cardiac, vascular or autonomic disease, use of medication to treat cardiovascular disease, any acute illness in the seven days before the study, or any condition or symptoms that could be exacerbated by the passive leg raise manoeuvre, or due to inadequate transthoracic echocardiographic views. Participants were instructed to eat and drink normally, but to abstain from alcoholic or caffeinated drinks in the 12 h before testing; we considered this non-starved state to be as near the normal ‘ideal’ intravascular state as possible, thus defining ‘normovolaemia’ for the purposes of this study.

On the day of testing, participants were interviewed by a study investigator to ensure that the inclusion/exclusion criteria were met and to gain written consent. The time elapsed since last food and drink was recorded and a check was made to ensure that the volunteers had abstained from alcohol and caffeine. Demographic characteristics were also recorded. Transthoracic echocardiography was performed by one of three trained echocardiographers, each with more than ten years’ experience. The echocardiographers were independent of the study. Echocardiographic images were obtained using a Healthcare Vivid E9 echo machine with an M5S-D Active Matrix Single Crystal Phased Array Probe (GE, Fairfield, CT, USA). All participants were positioned supine with a slight left lateral tilt to facilitate image acquisition. Stroke volume was calculated by measuring the left ventricular outflow tract diameter from the parasternal long axis window and the velocity time integral using pulsed-wave Doppler from the apical five chamber window. Baseline stroke volume measurements were recorded at the end of expiration during normal tidal volume breathing. The participant’s legs were then passively raised from the supine position to 45° by a second investigator; stroke volume was measured as the mean of three sequential beat measurements at end-expiration during tidal volume breathing, with measurements taken at a resting baseline and 30 s, 1 min, 3 min and 5 min after the passive leg raise manoeuvre. Measurements were simultaneously taken for pulse rate at each time period. Maximal change was defined as the value with the greatest deviation from baseline irrespective of the time point at which this occurred.

All cardiac images underwent a quality review by a consultant cardiologist independent of the image acquisition to assess whether the images were of adequate quality to allow subsequent analysis. Images of inadequate quality were excluded from data analysis. Data were recorded for offline analysis. Body surface area was calculated from subjects’ weight and height according to the formula described by Mosteller [27] and was used to calculate cardiac index.

Using the mean (SD) stroke volume values of 118.7 (7.3) ml obtained from our 12 sequential measurements, with an alpha-error of 0.05 and a power of 0.8, a sample size of six was calculated as being needed to identify a 10% change in stroke volume using G*Power analysis (version 3.1.7) [28]. A similar calculation performed using population data acquired after a previous study of stroke volume response following a passive leg raise manoeuvre predicted a sample size of two [16]. However, when this calculation was performed using published data on echocardiographic changes following a passive leg raise manoeuvre in critically ill spontaneously breathing patients [29], a sample size of 12 was calculated as being needed. Allowing for this variation and a 25% attrition rate due to difficult echocardiographic views, we chose to recruit 17 individuals to the study.

After establishing normal distribution, statistical analyses were performed using SPSS version 21 (SPSS Inc, Chicago, IL, USA). Due to the anticipated transient nature of the responses to increased preload, the potential variation in the time periods at which these occurred, and the fact that peak change in stroke volume is proposed as a clinical endpoint in assessing hypovolaemia, we compared the stroke volumes of maximal change with the baseline values using t-test analysis. While repeated measure ANOVA could be considered an appropriate analysis in this situation, with time as the repeated measure, there is a risk that such an approach could miss significant, transient
changes in physiological values. Comparisons were made between the actual values of maximal change (regardless of the time point after passive leg raise manoeuvre) and the respective baseline value for each parameter. Stroke volume data are also presented as percentage change from baseline as this format is commonly used in clinical guidance and monitoring systems.

Results
Seventeen subjects were recruited; testing was abandoned in one subject with difficult echocardiographic windows in whom no Doppler measurements were possible. Overall, 35% of Doppler images were excluded due to suboptimal image quality for accurate stroke volume measurement. This resulted in the exclusion of five further subjects from statistical analysis due to inadequate baseline data (Fig. 1). None of the 11 remaining subjects had drunk alcoholic or caffeinated drinks for 12 h. Data from these volunteers were used for analysis (Table 1).

Changes in stroke volume after the passive leg raise manoeuvre are shown in Table 2. Five of the 11 volunteers (45%) had a maximal change in stroke volume of greater than 10%, with the greatest increase being 19.1% (Fig. 2).

Discussion
In our study in healthy, supine, non-starved volunteers, a passive leg raise manoeuvre to $45^\circ$ did not result in a statistically significant change in stroke volume. However, five of the 11 participants (45%) experienced a percentage increase in stroke volume of more than 10%, with the greatest increase being 19.1%. The lack of statistical significance indicates that, within our study population, any increase in stroke volume following passive leg raise manoeuvre could have occurred by chance. However, our findings are clinically significant in highlighting that using stroke volume responsiveness alone to guide fluid management could result in a normovolaemic individual’s receiving unnecessary fluid therapy and being exposed to the detrimental effects of hyper-volaemia. Also, the overall spread of data for change in stroke volume after passive leg raise manoeuvre was wide, with a standard deviation of 9.6%; this suggests greater heterogeneity in the normal population than current clinical guidelines recognise. This could explain the contradictions in outcomes observed in clinical studies of goal-directed therapy [6–11].

Our findings differ from those of previous studies in healthy volunteers, which found no significant changes in stroke volume, cardiac index or pulse rate following an increase in preload [13, 15]. Basic physics dictates that if flow into the heart increases (even transiently), then either flow out must also increase, or the heart volume must increase. If neither occurs, then there has either been no increase in preload or the physiological compensations to the increase have diminished the changes by the time of measurement. Interestingly, our results also differed from those of Nixon et al. [16], who showed significant increases in end-diastolic volume, stroke volume and cardiac

Table 1 Baseline characteristics in 11 volunteers. Values are number (proportion) or mean (SD).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Age; years</td>
<td>32.6 (9.0)</td>
</tr>
<tr>
<td>Height; m</td>
<td>1.73 (0.12)</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>73 (15.0)</td>
</tr>
<tr>
<td>BMI; kg.m$^{-2}$</td>
<td>24.0 (1.9)</td>
</tr>
<tr>
<td>Time to last food; h</td>
<td>3.0 (3.0)</td>
</tr>
<tr>
<td>Time to last drink; h</td>
<td>2.4 (3.1)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Figure 1 Flow diagram.
output and a significant decrease in pulse rate following head-down tilt manoeuvres in healthy volunteers; cardiac volumes were assessed using transthoracic echocardiography, although the time period for assessment was 90 min after the increase in preload.

There are several possible reasons for these observed differences. The time period at which the stroke volume is measured after preload manipulation is crucial. In the study by Jans et al. [15], cardiovascular and oxygenation variables were recorded and blood samples were drawn 10 min after postural change, whereas Bundgaard-Nielsen recorded changes 5 min after an intravenous fluid bolus. It is possible that transient changes in stroke volume may no longer be present or detectable at these time periods. However, our data suggest that this is not the case; of the five subjects with a stroke volume increase of greater than 10%, two (27%) exhibited their maximum change at 5 min. This suggests that even this long after an increase in preload, significant increases in stroke volume can persist in healthy, non-starved individuals.

We performed our analysis at set points within the respiratory cycle (end-expiration during tidal volume breathing), to avoid respiratory variations in stroke volume confounding our findings. To our knowledge, no previous study has used this technique and level of methodological precision. We used the passive leg raise manoeuvre to increase preload as we believe it to be superior to head-down tilt in sustaining increased central volume [18]. It avoids the direct and immediate baroreceptor stimulation that will occur during head-down tilting and has been shown to result reliably in rapid 'autotransfusion', which can be used to predict fluid responsiveness in a variety of clinical situations [19–22]. Also, the rapid central redistribution of blood that follows a passive leg raise manoeuvre reduces the influence of venous capacitance on preload that may be associated with much slower peripheral administration of intravenous fluid. The method of monitoring physiological responses to increases in preload is vital for accurate assessment. A myriad of monitoring devices have been used to assess

<table>
<thead>
<tr>
<th>After passive leg raise</th>
<th>Baseline</th>
<th>30 s</th>
<th>1 min</th>
<th>3 min</th>
<th>5 min</th>
<th>Maximum Change</th>
<th>% change*</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV; ml</td>
<td>69.8 (19.6)</td>
<td>75.1 (16.3)</td>
<td>74.1 (16.7)</td>
<td>72.5 (19.5)</td>
<td>70.0 (18.9)</td>
<td>2.9 (6.4)</td>
<td>5.7 (9.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>HR; .min⁻¹</td>
<td>67.2 (10.0)</td>
<td>71.1 (10.1)</td>
<td>69.8 (11.9)</td>
<td>70.3 (11.7)</td>
<td>71.5 (13.2)</td>
<td>5.1 (8.5)</td>
<td>7.7 (11.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>CI; l.min⁻¹.m⁻²</td>
<td>2.4 (0.4)</td>
<td>2.7 (0.4)</td>
<td>2.6 (0.5)</td>
<td>2.7 (0.5)</td>
<td>2.5 (0.6)</td>
<td>0.3 (0.2)</td>
<td>14.8 (9.7)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

*Comparing maximum measured value with baseline values.
SV, stroke volume; HR, heart rate; CI, cardiac index.
preload and fluid physiology [13, 15, 23–25], with each device possessing differing accuracies and ‘ranges of uncertainty’. We used transthoracic echocardiography as it has been shown to provide extremely reliable and reproducible real-time measurements [16, 26, 30]. This finding was supported by the low variations in sequential stroke volume measurements from the same subject identified to calculate the necessary sample size for the study. The Doppler principle used to measure stroke volume in transthoracic echocardiography probably makes this technique the least derived measure of cardiac output and stroke volume available. We felt that this device was as near to a gold standard as could be achieved within the constraints of a healthy volunteer study.

Consistent with the Bainbridge reflex, all but one of our volunteers showed an increase in heart rate in response to the passive leg raise manoeuvre. Overall, our findings suggest that the contribution of heart rate to the change in cardiac index following increased preload is greater than that of stroke volume, although this was not found to be the case in all individuals. Our findings suggest that while some patients may demonstrate ‘volume responsiveness’ (as assessed by stroke volume increments) in a variety of clinical circumstances, this does not mean that fluid administration is necessarily the correct clinical response. Our data suggest that if the stroke volume is assessed too soon after a fluid bolus (within 5 min), an increase of more than 10% could be erroneously interpreted as indicating hypovolaemia.

Given the well-documented physiological impact of general anaesthetic agents on cardiovascular physiology, this approach should be used with caution as the sole guide for fluid management in anaesthetised patients. A ‘normovolaic’ state achieved under general anaesthesia is unlikely to be the same when the patient wakes up in the recovery room; alterations in sympathetic tone, peripheral arterio-venous shunt, venous capacitance and peripheral vascular resistance at any time will alter the apparent ‘volaoicaic’ state as assessed by cardiac volumes alone. Variables including pain, temperature, and the use of regional anaesthetic/analgesic techniques will influence further the patient’s cardiac parameters during the postoperative period, a period during which meticulous fluid management is likely to be as crucial, if not more so, as during the intra-operative period. The variation in the stroke volume changes seen in our study following the passive leg raise manoeuvre raises the question whether we should be assessing stroke volume responsiveness of patients during the pre-operative period to characterise their normal physiological status. Such an approach may allow us to develop bespoke fluid strategies more appropriate to an individual’s physiology that can be applied during the postoperative period. If validated appropriately, the increasing armamentarium of non-invasive cardiac output and stroke volume monitors may allow such an approach in the future.

There are limitations to our study. While our volunteers were advised that they could eat and drink as they wished while abstaining from alcohol or caffeine before the study, their oral intake was not as strictly controlled as in the study by Bundgaard-Nielsen et al. [13]; their ‘normovolaic’ state can therefore be brought into question. However, we do not believe that this would have influenced our findings as all volunteers were permitted to drink freely up to the time of the study. The mean (SD) time since last fluid intake was 2.4 (3.1) h, making hypovolaemia extremely unlikely.

It is possible that inter-observer variability may have influenced the stroke volume measurements. However, only three experienced echocardiographers undertook the measurements and all images were assessed for adequacy by a blinded consultant cardiologist before analysis. Our pilot data from sequential measurements showed low standard deviation and we believe that our sample size was generous, given the calculations made a priori. Several previous studies have shown that the variability in stroke volume as measured by transthoracic echocardiography is very low [16, 30].

We did not measure central venous or right atrial pressures to infer left ventricular end-diastolic pressure (and thus volume/preload) accurately. Such pressure measurements would require invasive instrumentation in a volunteer population and, given the increases in cardiac index and pulse rate seen, we believe that an appropriate increase in preload was achieved to address adequately the study hypothesis.

It is possible that our study was underpowered, given the unpredicted wide variation seen in stroke volume changes; retrospective sample size calculation...
using the mean (SD) values obtained results in a sample size of 520 being needed to provide appropriate inferences about the study population. To attempt such a large study in healthy volunteers seems unrealistic; we believe that our existing data provide sufficient data of clinical relevance to challenge current thinking.

Our study addressed a very specific physiological question: the stroke volume response to a passive leg raise manoeuvre in normovolaemic healthy individuals. While we believe this question to be directly clinically relevant, our clinical comments are simply inferences based on extrapolation of this principle; with increased clinical research, it is possible that despite our findings, stroke volume-guided fluid therapy may be conclusively shown to improve peri-operative outcome. However, at present, the situation remains contentious [12].

In conclusion, our findings show that in response to an increase in preload produced by passive leg raise manoeuvre, a statistically significant increase in stroke volume was not observed. The stroke volume response to this manoeuvre was varied, suggesting that our normovolaemic study population functioned at a variety of points on the Frank-Starling curve. An increase in stroke volume of more than 10% was observed in 45% of points on the Frank-Starling curve. An increase in to this manoeuvre was varied, suggesting that our normovolaemia was not observed. The stroke volume response to this manoeuvre and target were used as the sole guide to fluid management.

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Competing interests
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The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients


1 Fellow, 2 Associate Professor and Staff Anaesthetist, 3 Assistant Professor and Staff Anaesthetist, 5 Research Manager, Department of Anaesthesia and Pain Management, 4 Fellow, 6 Professor and Staff Surgeon, Division of Cardiac Surgery, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada

Summary
Because of a lack of contemporary data regarding seizures after cardiac surgery, we undertook a retrospective analysis of prospectively collected data from 11 529 patients in whom cardiopulmonary bypass was used from January 2004 to December 2010. A convulsive seizure was defined as a transient episode of disturbed brain function characterised by abnormal involuntary motor movements. Multivariate regression analysis was performed to identify independent predictors of postoperative seizures. A total of 100 (0.9%) patients developed postoperative convulsive seizures. Generalised and focal seizures were identified in 68 and 32 patients, respectively. The median (IQR [range]) time after surgery when the seizure occurred was 7 (6–12 [1–216]) h and 8 (6–11 [4–18]) h, respectively. Epileptiform findings on electroencephalography were seen in 19 patients. Independent predictors of postoperative seizures included age, female sex, redo cardiac surgery, calcification of ascending aorta, congestive heart failure, deep hypothermic circulatory arrest, duration of aortic cross-clamp and tranexamic acid. When tested in a multivariate regression analysis, tranexamic acid was a strong independent predictor of seizures (OR 14.3, 95% CI 5.5–36.7; p < 0.001). Patients with convulsive seizures had 2.5 times higher in-hospital mortality rates and twice the length of hospital stay compared with patients without convulsive seizures. Mean (IQR [range]) length of stay in the intensive care unit was 115 (49–228 [32–481]) h in patients with convulsive seizures compared with 26 (22–69 [14–1080]) h in patients without seizures (p < 0.001). Convulsive seizures are a serious postoperative complication after cardiac surgery. As tranexamic acid is the only modifiable factor, its administration, particularly in doses exceeding 80 mg.kg⁻¹, should be weighed against the risk of postoperative seizures.

Correspondence to: V. Sharma
Email: vivek.sharma@stgeorges.nhs.uk

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Introduction
The reported incidence of seizures after adult cardiac surgery is 0.5–7.6% [1–8]. The aetiology of postoperative seizures is often multifactorial, and causes range from benign metabolic disturbance to cerebrovascular accident. Previously reported risk factors for seizures include older age, pre-operative neurological disease, open-chamber surgery on the heart, prolonged
cardiopulmonary bypass (CPB) time, previous cardiac surgery, deep hypothermic circulatory arrest (DHCA), aortic calcification or atheroma, and critical pre-operative state [2–4]. There is controversy regarding the association of seizures with tranexamic acid [9–11]. However, apart from the most recent report, studies were limited to a small number of patients, ranging from 24 to 56 cases [1–6, 12].

Furthermore, the burden imposed by postoperative convulsive seizures in cardiac surgical patients in terms of length of stay and mortality has not been clearly defined [1–4]. Most of the studies with a limited sample size have found no significant difference in postoperative outcomes in patients with and without seizures following cardiac surgery [1–4]. More recently, in a larger study, postoperative convulsive seizures have been associated with a higher duration of hospital stay and in-hospital mortality [12].

The relatively low incidence of postoperative seizures requires larger observational studies to delineate the clinical relevance of this particular outcome. We therefore decided to conduct an in-depth analysis of postoperative seizures with respect to diagnostic predictors and associated morbidity and mortality in currently the largest cohort, of 11,529 patients, undergoing adult cardiac surgery.

**Methods**

After formal Ethical Review Board approval, we retrospectively reviewed our database containing records for all patients undergoing cardiac surgery with CPB from January 2004 to December 2010 at Toronto General Hospital.

All patients received premedication with lorazepam 2 mg, 1–2 h before surgery. Anaesthetic technique included fentanyl 10–20 μg kg⁻¹, midazolam 0.1 mg kg⁻¹, pancuronium 0.15–0.2 mg kg⁻¹ and isoflurane 0.5–1.5%. After surgery, patients were transferred to the intensive care unit (ICU) for mechanical ventilation and monitoring. Sedation was maintained with propofol 0.5–4 mg kg⁻¹ h⁻¹ and intermittent intravenous morphine. The patients’ trachea were extubated when standard criteria were met. Transoesophageal echocardiography was used routinely except for patients undergoing elective, isolated coronary artery bypass grafting (CABG) surgery. Patients who underwent surgery before 2008 received either tranexamic acid or aprotinin depending on their risk of peri-operative blood loss. Patients with low risk of bleeding received tranexamic acid as a single bolus of 50 mg kg⁻¹ following induction of anaesthesia. Patients perceived to be at high risk of bleeding received aprotinin (loading dose 2 million KU, followed by an infusion of 500 000 KU h⁻¹ during surgery; an additional dose of 2 million KU was added to the CPB circuit). Following the withdrawal of aprotinin in 2008, all patients who were deemed to be at high risk of bleeding received tranexamic acid instead of aprotinin (bolus of 30 mg kg⁻¹, followed by a 16 mg kg⁻¹ h⁻¹ infusion until chest closure with 2 mg kg⁻¹ added to the CPB circuit prime [13]). Cardiac surgical procedures were divided into open-chamber (valve replacement or repair, major aortic surgery, transplantation and ventricular assist device insertion procedures), and closed-chamber procedures (CABG).

Anticoagulation was achieved with heparin to maintain an activated clotting time > 480 s. The CPB circuit was primed with 1.8 l Ringer’s lactate solution (Braun Medical Inc, Irvine, CA, USA) and 50 ml mannitol 20%. Management of CPB included a slow drift of body temperature to 34 °C, targeted mean perfusion pressure 50–70 mmHg, maintenance of haematocrit > 21% and alpha-stat blood gas management strategy. Myocardial protection was provided by the use of intermittent antegrade and/or retrograde cardioplegia. Deep hypothermic circulatory arrest was achieved by cooling to 20 °C, with antegrade or retrograde cerebral perfusion when required. After separation from CPB, protamine sulphate, 1 mg per 100 U heparin initial dose, was given, to maintain an activated clotting time within 10% of baseline.

A convulsive seizure was defined as a transient episode of disturbed brain function characterised by abnormal involuntary motor movements [14]. Convulsive seizures were classified broadly into two categories: generalised and focal. Myoclonic movements and primary or secondary generalised tonic or clonic movements were categorised as generalised seizures. A repeat seizure was defined as seizure activity occurring after definite termination (spontaneous or in response to therapy) of the first episode. Acute repetitive seizures (cluster seizures) were defined as two or more seizures...
within 24 h with an onset readily recognisable by the caregiver (attending physician or nurse). Status epilepticus was defined as a continuous state of seizures or multiple seizures without return to baseline for at least 30 min [15]. All patients with convulsive seizures underwent neuroimaging, either computerised tomography (CT) scan and/or magnetic resonance imaging (MRI) and were reviewed by a staff neurologist.

Patients’ characteristics, details of pre-operative cardiac and co-morbid conditions, results of pre-operative diagnostics tests and investigations, intra-operative details such as type of surgery, duration of CPB and aortic cross-clamp, employment of DHCA, and postoperative variables including duration of mechanical ventilation, ICU and hospital length of stay and postoperative complications were collected from the cardiac surgical database. After identifying patients with convulsive seizures in the postoperative period, an in-depth analysis of their medical notes was carried out to ascertain the details of the seizure. The attending neurologist’s and/or the on-call ICU physician’s entry in the medical records was used to determine the timing and type of convulsive seizures; the number of episodes; recurrence of convulsive seizures following the initial event; and pharmacological treatment. Additional hemodynamic and metabolic data, including oxygenation, adequacy of ventilation, blood sugar and electrolyte levels in the hours leading up to the convulsive seizure, were recorded. Results of diagnostic tests including EEG were also obtained from the electronic record.

We undertook statistical analysis using chi-squared or Fisher’s exact tests for categorical variables, or two-sample t-tests or Kruskal–Wallis tests for continuous variables. As the aim of this study was to explore the demographic and clinical factors associated with postoperative seizures in cardiac surgery, no formal sample size estimation was performed. Given the dichotomous outcome variable, we selected logistic regression analysis as the primary modelling strategy with a limit of ten events per predictor in the model construction [16]. The effect measure selected for all analyses was the odds ratio. To identify variables associated with postoperative seizures in cardiac surgery, we conducted standard univariate and multivariable logistic regression analyses. Standard postestimation analysis included assessment of co-linearity, Hosmer–Lemeshow goodness of fit and area under the receiver operating characteristic curve estimation. Complementary analyses were performed using logistic regression with bootstrap standard error estimation and fractional polynomials. No multiplicity adjustment was employed. Variables were considered statistically significant at alpha = 0.05 in the univariate and multivariate analyses. However, a threshold of alpha = 0.10 was chosen in the univariate models to select variables for the multivariable models. Bootstrap resampling (n = 632) was used to perform sensitivity analysis and confirm the robustness of the estimates. Statistical analysis was conducted using STATA SE 11 (StataCorp LP, College Station, TX, USA).

Results
A total of 11 529 patients were studied; 100 patients (0.9%) developed postoperative convulsive seizures. Sixty-eight patients experienced generalised and 32 focal seizures. The median (IQR [range]) onset time was 7 (6–12 [1–216]) h and 8 (6–11 [4–18]) h for generalised and focal seizures, respectively. Forty out of 100 patients had a single seizure, while the remaining had cluster seizures. Three (5%) out of 60 patients with cluster seizures had a further episode of convulsive seizures within 24 h of the first episode. Only one patient had a history of epilepsy before surgery; none of the patients had metabolic or electrolyte abnormalities in the hours preceding the seizure activity that could have contributed to development of convulsive seizures. Compared with patients without postoperative seizure, patients with convulsive seizures were on average five years older, had smaller body surface area, were more likely to have class 3 or 4 New York Heart Association symptoms, as well as a history of congestive heart failure, and higher pre-operative creatinine levels (Table 1). Furthermore, patients with postoperative convulsive seizures had a significantly higher incidence of atheromatous disease of the ascending aorta, as well as longer CPB and aortic cross-clamp times.

All patients with convulsive seizures were examined by a staff neurologist and had neuroimaging studies. Computed tomography scanning was performed on all patients with convulsive seizures in the immediate postseizure period. A repeat CT scan and/or MRI
was performed if no organic brain injury was detected on the initial scan or/and if the patient’s neurological status changed.

An initial CT scan was performed within two hours of seizure occurrence. Forty-five (45%) patients required a repeat CT scan based on specialist neurology opinion or continuing neurological impairment. Similarly, MRI was performed when clinically indicated in a total of 22 patients. Based on neuroimaging results, 16 patients had acute cerebral infarcts. Ten out of 16 (63%) acute cerebral infarcts were diagnosed on the initial CT scan, while the other six were diagnosed following MRI. Six patients (19%) with focal seizures and 10 patients (15%) with generalised seizures had evidence of acute cerebral infarct on neuroimaging, respectively, and 13 patients in total had evidence of old cerebral infarcts.

Eighty-two patients had EEG performed within 24 h of the first seizure episode; epileptiform findings were seen in 16/82 (20%) patients, the remainder having either non-epileptiform discharges or diffuse non-specific findings. Anticonvulsant medications (phenytoin and/or benzodiazepines) were administered to 92 patients. After initial treatment, 68/92 (74%) patients continued daily anticonvulsant therapy during their entire hospital stay on the advice of the consulting neurologist.

During the study period, 10 979 patients received tranexamic acid and 550 patients received aprotinin. Convulsive seizures occurred in 99/10 979 (0.9%) and 1/550 (0.2%) patients receiving tranexamic acid and aprotinin, respectively. The median (IQR [range]) dose of tranexamic acid in patients with convulsive seizures was 100 (75–110 [31–175]) mg.kg\(^{-1}\). We identified that the rate of convulsive seizures was 0.58% (45/7721), and 1.44% (55/3808) in patients before and after the withdrawal of aprotinin, respectively (p < 0.0001). This finding was consistent with a 2.5-fold increase in the incidence of convulsive seizures after the withdrawal of aprotinin. When tested in a multivariate regression analysis, tranexamic acid was a strong independent predictor of seizures (OR 14.3, 95% CI 5.5–36.7; p < 0.001).

Of the 10 979 patients who received tranexamic acid, 8132 (74%) were administered a 50 mg.kg\(^{-1}\) bolus, while the remainder received tranexamic acid as an infusion, resulting in a higher cumulative peri-operative dose. Postoperative convulsive seizures occurred in 24 (0.3%) and 75 (2.6%) patients receiving bolus and infusion tranexamic acid, respectively (p < 0.0001).

A total of 5402 (49%) patients underwent closed-chamber cardiac surgery and the remainder open-chamber procedures during the study period. Ninety-four of the 100 patients who experienced postoperative convulsive seizures underwent open-chamber surgery, while only six patients with seizures underwent closed-chamber surgery (p < 0.0001). When tested in a logistic multivariable regression model, patients receiving tranexamic acid whilst undergoing closed-chamber

<table>
<thead>
<tr>
<th>Baseline patient and clinical characteristics in patients with and without seizures. Values are mean (SD) or number (proportion).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures</strong> (n = 100)</td>
</tr>
<tr>
<td>Age; years</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Body surface area; m(^2)</td>
</tr>
<tr>
<td>Past medical history</td>
</tr>
<tr>
<td>NYHA class 3 or 4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 40%</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Left main coronary artery disease</td>
</tr>
<tr>
<td>Three-vessel coronary artery disease</td>
</tr>
<tr>
<td>Carotid artery disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Smokers</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
</tr>
<tr>
<td>Stroke/transient ischaemic event</td>
</tr>
<tr>
<td>Dialysis</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Creatinine; μmol.L(^{-1})</td>
</tr>
<tr>
<td>Surgical characteristics</td>
</tr>
<tr>
<td>Emergency surgery</td>
</tr>
<tr>
<td>Open-chamber surgery</td>
</tr>
<tr>
<td>Redo surgery</td>
</tr>
<tr>
<td>Ascending aortic disease</td>
</tr>
<tr>
<td>Cardiopulmonary bypass; min</td>
</tr>
<tr>
<td>Cross-clamp; min</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association.

Table 1

© 2013 The Association of Anaesthetists of Great Britain and Ireland
surgery were not at risk of developing postoperative convulsive seizures (OR 0.1, 95% CI 0.05–0.27).

Patients with convulsive seizures had 2.5 times higher in-hospital mortality rates compared with patients without convulsive seizures (Table 2). Results of the multivariate analysis identified eight independent predictors of postoperative convulsive seizures: age; female sex; redo cardiac surgery; calcification of the ascending aorta; congestive heart failure; DHCA; duration of aortic cross-clamp; and the use of tranexamic acid (Table 3). The area under the receiver operating characteristic curve for the multivariable model was 0.83 (Fig. 1) and the Hosmer–Lemeshow goodness of fit was non-significant ($p = 1.0$).

Discussion
This study in 11 529 patients shows that tranexamic acid is an independent predictor of postoperative convulsive seizures in cardiac surgical patients. The risk of seizures was significantly higher in patients receiving tranexamic acid as an infusion, which resulted in higher cumulative doses ($> 80 \text{ mg.kg}^{-1}$) of tranexamic acid in the peri-operative period. Only 16% of patients with postoperative convulsive seizures had evidence of acute organic brain injury on neuroimaging. Seizures imposed a significant burden on patients in the postoperative period, resulting in higher morbidity and mortality as well as longer ICU and hospital length of stay.

It is interesting to note that, in our cohort, the majority of patients with postoperative convulsive seizures did not have organic brain injury as revealed by neuroimaging studies. Furthermore, the presence of convulsive seizures could not have been explained by any physiological abnormalities (e.g. electrolyte or acid-base imbalance).

Our findings agree with those of Berman and colleagues who reported an almost threefold increase in the rate of postoperative seizures after pulmonary endarterectomy in patients receiving tranexamic acid vs

### Table 2 Postoperative outcomes in patients with and without seizures. Values are number (proportion) or median (IQR [range]).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Seizures (n = 100)</th>
<th>No seizures (n = 11 429)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>7 (7%)</td>
<td>321 (3%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Low cardiac output syndrome</td>
<td>3 (3%)</td>
<td>368 (3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Use of inotropes</td>
<td>56 (56%)</td>
<td>4139 (36%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1%)</td>
<td>187 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Deep sternal wound infection</td>
<td>1 (1%)</td>
<td>60 (1%)</td>
<td>0.413</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13 (13%)</td>
<td>253 (2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>22 (22%)</td>
<td>170 (2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>47 (47%)</td>
<td>3630 (32%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>2 (2%)</td>
<td>493 (4%)</td>
<td>0.450</td>
</tr>
<tr>
<td>Mechanical ventilation time; h</td>
<td>30 (18–117 [13–144])</td>
<td>7 (5–13 [4–80])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intensive care length of stay; h</td>
<td>115 (50–228 [32–481])</td>
<td>26 (22–70 [14–1080])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospital length of stay; days</td>
<td>14 (8–22 [5–36])</td>
<td>7 (5–9 [4–136])</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 3 Independent predictors of postoperative seizures. Multivariable logistic regression (bootstrap SE model, 632 replications).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>$b$ coefficient</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.031</td>
<td>1.031 (1.012–1.051)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.683</td>
<td>1.980 (1.330–2.950)</td>
<td>0.001</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>1.205</td>
<td>3.335 (2.056–5.410)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ascending aortic disease</td>
<td>1.217</td>
<td>3.376 (2.090–5.452)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.067</td>
<td>2.907 (1.854–4.559)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Deep hypothermic circulatory arrest</td>
<td>0.025</td>
<td>1.025 (1.005–1.047)</td>
<td>0.014</td>
</tr>
<tr>
<td>Cross-clamp time</td>
<td>0.007</td>
<td>1.007 (1.002–1.011)</td>
<td>0.005</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>2.662</td>
<td>14.321 (5.586–36.715)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
In their cohort of 8929 patients, Kalavrouziotis et al. found that as well as older age, open-heart procedures and pre-operative renal failure, a total dose of tranexamic acid $\geq 100 \text{ mg.kg}^{-1}$ was associated with increased risk of postoperative seizures [7]. These findings were supported by those of Manji et al., who reported that exposure to tranexamic acid, along with the other previously reported factors, was associated with a significant increase in the risk of postoperative seizures [4]. In addition, Manji et al. also reported an eightfold increase in the occurrence of seizures using tranexamic acid, and a subsequent decrease in the incidence of seizures after tranexamic acid dose reduction [4, 13].

It is important to note that since the initial restriction of the use of aprotinin, patients at our hospital undergoing complex surgery, such as redo cardiac surgery or requiring DHCA, tend to receive a higher total dose of tranexamic acid. Administration of tranexamic acid via an initial bolus and subsequent infusion results in a total cumulative dose in excess of $100 \text{ mg.kg}^{-1}$ for procedures exceeding 5 h. In addition to the tranexamic acid administered in the operating room, some of these patients received an additional 2–4 g tranexamic acid in the ICU if there was persistent postoperative bleeding. This practice was implemented to reduce the rate of bleeding after complex cardiac surgery, but would have probably contributed to increased postoperative plasma concentrations of tranexamic acid.

Although tranexamic acid has an excellent safety record, there is animal and human evidence suggesting that it may have seizure-inducing or seizure threshold-lowering effects. It is thought that tranexamic acid might induce seizure activity via its dose-dependent antagonism of the central GABA$_A$ receptor and, more recently, glycine receptors [18, 19]. Tranexamic acid doses of 100 mg.kg$^{-1}$ can produce plasma and approximate cerebrospinal fluid concentrations of $600 \text{ mg.l}^{-1}$ and $150–200 \text{ mg.l}^{-1}$, respectively [20, 21]. The potential for CPB-induced disruption of the blood–brain barrier might further facilitate a higher cerebrospinal fluid drug concentration [22]. Additionally, the cerebrospinal fluid concentration would be further exaggerated in patients with renal insufficiency, demonstrating slower clearance of tranexamic acid [19].

More recently, Koster et al. studied the incidence and outcomes of convulsive seizures in patients undergoing open-heart surgery with moderate dose (24 mg.kg$^{-1}$) of tranexamic acid [12]. The authors compared the risk of convulsive seizures in patients receiving moderate doses of tranexamic acid with a control group receiving no tranexamic acid and found a twofold increase in the incidence of convulsive seizures, as well as in-hospital mortality, in patients receiving tranexamic acid. We used considerably higher doses of tranexamic acid and found a significant increase in the incidence of convulsive seizures in patients receiving tranexamic acid compared with those receiving aprotinin. Furthermore, we also found a statistically significant difference in the incidence of seizures in patients receiving a bolus dose (50 mg.kg$^{-1}$) and an infusion (resulting in cumulative dose $> 80 \text{ mg.kg}^{-1}$) of tranexamic acid. This finding strengthens the association of administration of tranexamic acid and the risk of seizures after cardiac surgery.

Our study has several limitations. First, its retrospective nature points to an association rather than a causal relationship between the risk factors and postoperative seizures. Second, the diagnosis of seizures was based on clinical appearance. It is possible that the incidence of asymptomatic seizure activity diagnosed by EEG could have been considerably higher. However, EEG is not part of our routine peri-operative monitoring and further studies would
be required to explore the clinical significance of asymptomatic seizure activity in adult cardiac surgery patients. Finally, we did not ascertain the possible synergistic effect of drugs such as cefalosporins, which were the first-line antibiotics used during surgery during the study period. However, the doses of cefalosporins used during the peri-operative period were consistent with common clinical practice.

In conclusion, our study confirmed that convulsive seizures are a serious postoperative complication associated with increased morbidity and mortality. As tranexamic acid was the only identified modifiable risk factor, its administration, particularly in dosage > 80 mg.kg⁻¹, should be weighed against an increased risk of postoperative seizures.

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Competing interests
No external funding and no competing interests declared.

References
Therapeutic effect of inhaled budesonide (Pulmicort® Turbuhaler) on the inflammatory response to one-lung ventilation

N. Y. Ju,1 H. Gao,2 W. Huang,1 F. F. Niu,1 W. X. Lan,1 F. Li1 and W. Gao3

1 Attending Physician, 2 Vice-Professor, Department of Intensive Care Medicine, The Third Affiliated Hospital of Harbin Medical University, Harbin, China
3 Staff Anaesthetist, Department of Anaesthesiology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China

Summary
This prospective, double-blind trial was designed to evaluate the effect of inhaled budesonide on lung function and the inflammatory response to one-lung ventilation. One hundred patients scheduled for lobectomy were allocated randomly to pre-operative nebulised budesonide or saline. Bronchoalveolar lavage fluid samples were collected from either the collapsed or the ventilated lung both before one-lung ventilation and 30 min after re-expansion of the lung. The concentrations of serum and bronchoalveolar lavage fluid cytokines were determined. Budesonide treatment, compared with saline, reduced both peak (mean (SD) 3.7 (0.4) vs 2.5 (0.2) kPa) and plateau (mean (SD) 3.1 (0.2) vs 2.2 (0.1) kPa, respectively, p < 0.001 for both) ventilatory pressures. Thirty minutes after re-expansion, lung compliance increased in the budesonide group compared with saline (57.5 (4.1) vs 40.1 (3.5) ml.cmH2O⁻¹, respectively p < 0.001). Budesonide also reduced the concentrations of tumour necrosis factor-α, interleukin-1β, interleukin-6 and interleukin-8 in bronchoalveolar lavage fluid, but increased interleukin-10 30 min after re-expansion (p < 0.05 for all measures). Pre-operative nebulisation of budesonide may be effective in improving ventilatory mechanics and reducing the inflammatory response to one-lung ventilation during thoracic surgery.

Correspondence to: W. Gao
Email: gaowei20055@126.com
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One-lung ventilation (OLV) is widely used in thoracic surgery, but may lead to serious lung injury in both the ventilated and collapsed lungs [1, 2]. During OLV, inflammation can be induced by many factors, including: hypoxia; hypoxic pulmonary vasoconstriction-induced low perfusion [3]; collapse and re-opening of alveoli [4]; oxidative stress-related injury [5]; and over-distension and compression of alveolar vessels in the ventilated lung [1, 6]. Furthermore, inflammation can also be triggered by surgical manipulation itself. Inflammation is characterised by increased numbers of inflammatory infiltrates, such as alveolar macrophages, granulocytes and elevated concentrations of pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-8 (IL-8), and the anti-inflammatory cytokine interleukin-10 (IL-10) [7–9].

In clinical practice, patients with lung injury and oedema induced by inflammation may be treated with glucocorticoids. Treatment with methylprednisolone has been shown to improve lung function and decrease the systemic pro-inflammatory response during OLV.
Budesonide (AstraZeneca Pharmaceuticals, Luton, Herts, UK), a glucocorticoid drug that is administered by inhalation, is licensed for the treatment of asthma, non-infectious rhinitis and chronic obstructive pulmonary disease [11–13]. We hypothesised that budesonide inhaled before OLV might improve lung function and mitigate the inflammatory response to OLV in patients undergoing thoracic surgery.

Methods
This prospective, double-blind, randomised study was approved by the Ethical Committee of The Harbin Medical University and was conducted in compliance with the ethical recommendations of the Declaration of Helsinki. Informed written consent was obtained from all patients before enrolment. Between September 2012 and February 2013, patients who were scheduled for thoracic surgery (lobectomy for lung cancer) were recruited. Inclusion criteria were ASA physical status 1–2 and age 20–60 years. Exclusion criteria were as follows: smoking; body mass index > 35 kg.m⁻²; immune dysfunction (history of a common autoimmune disease, such as type-1 diabetes or rheumatoid arthritis); abnormal lung function (forced expiratory volume in 1 s < 40% of predicted value, forced vital capacity < 40% of predicted value, residual volume/total lung capacity > 50% of predicted value, maximal oxygen consumption < 20 ml.kg⁻¹.min⁻¹); acute upper airway infection; chronic lung disease (chronic pneumonia, chronic obstructive pulmonary disease, bronchitis, pneumoconiosis, silicosis); adrenal insufficiency; radiotherapy or chemotherapy; pleural effusion; hypoproteinaemia (serum albumin < 25 g.l⁻¹ or serum total proteins < 40 g.l⁻¹); and asthma. Patients whose oxygen saturation as recorded by the pulse oximeter (SpO₂) fell below 90% during OLV were also not studied.

Patients were randomly allocated to budesonide or saline according to a random number table. The doctor who prepared the study drug was not involved in the care of the patient; a second doctor who was blinded to the group allocation administered the nebuliser, and was responsible for inducing anaesthesia, tracheal intubation and performing fibroptic bronchoscopy and bronchoalveolar lavage. A third study doctor collected blood samples and other data while the same surgical team performed the lobectomy in all cases.

All patients received oral midazolam 0.5 mg.kg⁻¹ before arrival in the intensive care unit, where they were treated with 1 mg nebulised budesonide or saline over 20 min using a separate nebuliser (OMRON Global, Tokyo, Japan). They were then transferred to the operating room, where cannulation of the radial artery was performed with a 22-G catheter and arterial blood gases were measured. A thoracic epidural was then sited at the T5–T6 to T7–T8 epidural interspace. After induction of anaesthesia using lidocaine 1 mg.kg⁻¹, fentanyl 4 µg.kg⁻¹, rocuronium 0.6 mg.kg⁻¹ and propofol 1.5 mg.kg⁻¹, a left or right double-lumen endobronchial tube (Broncho-Cath, 35–41 Ch; Mallinckrodt Medical Ltd, Athlone, Ireland) was inserted depending on the side of surgery. Fibroptic bronchoscopy was then performed (Olympus Europe, Volketswil, Switzerland). Anaesthesia was maintained with sevoflurane and a mixture of lidocaine 1% and ropivacaine 0.5% was administered via the epidural catheter at 6 ml.h⁻¹.

During surgery, the patients’ lungs were ventilated using volume-controlled ventilation at a rate of 12–15 breaths per min with 5 cmH₂O positive end-expiratory pressure and a tidal volume of 8 ml.kg⁻¹, followed by a tidal volume of 6 ml.kg⁻¹ during OLV. Before and after OLV, a manual functional capacity manoeuvre was carried out bilaterally – a pressure of 30 cmH₂O was applied for 10 s. The fraction of inspired oxygen (F₁O₂) was set at 0.5–0.7 to maintain S₉O₂ > 95%, and then adjusted during OLV to 0.8–1.0 to maintain SₒO₂ > 90%. Bronchoalveolar lavage was only carried out in either the collapsed or the ventilated lung as opposed to both lungs, as the ethical committee did not allow us to perform this procedure on both sides. Specimens were collected before OLV and 30 min after re-expansion of the lung from two separate bronchial segments using 50 ml saline 0.9% and an aspiration pressure of 5 kPa, which allowed approximately 50% of the injected volume to be aspirated.

After surgery, morphine 2 mg and ropivacaine 37.5 mg in 150 ml saline 0.9% was infused via the epidural catheter for postoperative analgesia. After turning off the sevoflurane, both lungs were manually ventilated four times each for 10 s at a pressure of 30 cmH₂O. The trachea was then extubated, provided...
SpO$_2$ was $>95\%$ breathing air, and patients were subsequently transferred to the post-anaesthesia care unit.

The bronchoalveolar lavage sample was filtered and immediately centrifuged at $4^\circ$C, 1600 g for 15 min. Blood samples were centrifuged at $4^\circ$C, 2400 g for 20 min immediately after collection, and after centrifugation, both serum and lavage fluid were immediately stored at $-80^\circ$C.

The primary study outcomes were peak airway pressure, plateau pressure, lung compliance and oxygen index (the ratio of partial pressure of arterial oxygen to $F_1O_2$) during OLV. Secondary outcomes were the inflammatory response to OLV, measured by the concentration of serum and bronchoalveolar lavage cytokines. All data were recorded and blood samples collected at six time points: before administration of the nebulised drug (T0); before OLV (T1); 30 min after re-expansion of the lung (T2); 24 h after surgery (T3); 48 h after surgery (T4); and 72 h after surgery (T5).

Serum and bronchoalveolar lavage concentration of TNF-$\alpha$, IL-1$\beta$, IL-6, IL-8 and IL-10 were determined by enzyme-linked immunosorbent assay.
ELISA in a blinded manner using specific kits, according to manufacturers’ instructions (Wuhan Boster Bio-Engineering Limited Company, Wuhan, Hubei, China). The minimum concentration that could be detected was as follows: TNF-α, 3.8 pg.ml⁻¹; IL-1β, 1.56 pg.ml⁻¹; IL-6, 2.5 pg.ml⁻¹; IL-8, 7.8 pg.ml⁻¹; IL-10, 3.4 pg.ml⁻¹.

A power analysis of oxygen index 30 min after OLV in a pilot study of 10 patients indicated that a sample size of 42 patients per group with a standard deviation of 30 would reach approximately 80% power to reject the null hypothesis. Data were analysed using repeated-measures ANOVA with post-hoc Bonferroni correction, the non-parametric Friedman test and the Kruskal–Wallis H-test as appropriate. We used the Statistical Package for Social Sciences (SPSS 11.5; IBM, Chicago, IL, USA) and a p value of < 0.05 was considered statistically significant.

Results

One-hundred patients (67 men) were initially recruited; six were not studied pre-operatively because of upper airway infection, and intra-operatively six patients in the budesonide group and four in the saline group were not studied because lobectomy was not performed (Fig. 1). There was no difference in baseline characteristics between the two groups (Table 1), and there were no adverse events during the study period.

There was no difference between the two groups in peak airway pressure, plateau pressure and dynamic compliance before OLV. However, after lung re-expansion, peak airway pressure and plateau pressure were lower in the budesonide group compared with the saline group, while dynamic compliance was higher (Table 2). There was also no difference in the oxygen index between the two groups until the patients returned to the ward, when it was higher in the budesonide group compared with the saline group (Fig. 2). However, there was no difference in the partial pressure of arterial carbon dioxide or oxygen saturation on pulse oximetry.

Cytokine levels in the bronchoalveolar lavage fluid were similar between the two groups before OLV (Fig. 3). However, 30 min after lung re-expansion, the levels of TNF-α, IL-1β, IL-6 and IL-8 were significantly decreased, but IL-10 was significantly increased in the budesonide group compared with the saline group. In contrast, serum cytokine levels were similar between the two groups intra-operatively; however, TNF-α, IL-1β, IL-6 and IL-8 were lower and IL-10 was higher postoperatively in the budesonide group compared with the saline group (Fig. 4).

Discussion

In this study, we found that pre-operative treatment with nebulised budesonide improved respiratory mechanics, increased the anti-inflammatory cytokine IL-10, and decreased pro-inflammatory cytokines in bronchoalveolar lavage fluid in patients undergoing thoracic surgery. To the best of our knowledge, this is

Table 1 Baseline characteristics and surgical data for patients receiving nebulised budesonide or saline. Values are mean (SD), number (proportion) or median (IQR [range]).

<table>
<thead>
<tr>
<th></th>
<th>Budesonide (n = 42)</th>
<th>Saline (n = 42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>51.6 (9.6)</td>
<td>49.5 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Height; cm</td>
<td>164.4 (7.9)</td>
<td>167.7 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Weight; kg</td>
<td>61.4 (8.6)</td>
<td>63.8 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>26 (62%)</td>
<td>29 (69%)</td>
<td></td>
</tr>
<tr>
<td>FVC; % predicted</td>
<td>89% (56–119 [45–126])</td>
<td>88% (50–117 [44–124])</td>
<td></td>
</tr>
<tr>
<td>FEV1; % predicted</td>
<td>74% (55–96 [47–114])</td>
<td>77% (53–98 [45–112])</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;O2&lt;/sub&gt;; kPa</td>
<td>10.4 (7.9–12.8 [7.4–14.2])</td>
<td>10.1 (8.0–13.4 [7.3–14.3])</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;CO2&lt;/sub&gt;; kPa</td>
<td>4.5 (3.9–5.8 [3.7–6.6])</td>
<td>4.7 (4.2–6.2 [4.0–6.9])</td>
<td></td>
</tr>
<tr>
<td>Duration of one-lung ventilation; min</td>
<td>168 (44)</td>
<td>159 (33)</td>
<td>0.29</td>
</tr>
<tr>
<td>Total volume of fluids infused; ml</td>
<td>1550 (170)</td>
<td>1630 (190)</td>
<td>0.19</td>
</tr>
<tr>
<td>Blood loss; ml</td>
<td>410 (55)</td>
<td>390 (60)</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of mechanical ventilation; min</td>
<td>226 (29)</td>
<td>218 (36)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; P<sub>O2</sub>, arterial partial pressure of oxygen; P<sub>CO2</sub>, arterial partial pressure of carbon dioxide.
the first clinical trial to test the therapeutic effect of pre-operative budesonide in this patient group, which provides a proof of principle for this treatment.

Lung injury is a serious respiratory response to OLV, and acute lung injury/acute respiratory distress syndrome occurs in approximately 3.7% of patients after lobectomy [14]. Lung oedema may be caused by an inflammatory response to surgery, and, in response to OLV, may be associated with ischaemia/reperfusion injury induced by hypoxic vasoconstriction [15], oxidative stress injury [4, 5] or injury caused by mechanical ventilation [16–18].

Previous research has showed that glucocorticoids may attenuate the acute inflammatory response to mechanical ventilation of the lungs, [19, 20] and to ischaemia-reperfusion injury [21, 22]. Furthermore, treatment with a low dose of methylprednisolone can reduce local and systemic inflammation during OLV [10]. Inhaled budesonide is widely used to treat patients with asthma and chronic lung disease, and it is particularly effective because it is delivered locally to the lungs, minimising systemic side-effect [23, 24]. A recent study has shown that inhaled budesonide reduces lung injury induced by chlorine gas in animals [25].

Bronchospasm is a common intra-operative complication during open thoracic surgery and OLV, and may be associated with surgical injury and hypoxaemia; it may persist until the re-expansion of the col-

Table 2 Ventilatory parameters for patients receiving nebulised budesonide or saline, before and 30 min after one-lung ventilation. Values are mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Before one-lung ventilation</th>
<th></th>
<th>p value</th>
<th></th>
<th>Budesonide</th>
<th>Saline</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak pressure; cmH2O</td>
<td>14.9 (1.2)</td>
<td>16.2 (1.9)</td>
<td>0.067</td>
<td>18.8 (1.3)</td>
<td>27.4 (2.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Plateau pressure; cmH2O</td>
<td>11.2 (1.2)</td>
<td>13.1 (1.7)</td>
<td>0.058</td>
<td>16.4 (0.9)</td>
<td>23.2 (1.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dynamic compliance; ml.cmH2O⁻¹</td>
<td>62.0 (4.1)</td>
<td>56.6 (4.5)</td>
<td>0.075</td>
<td>57.5 (4.1)</td>
<td>40.1 (3.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Comparison of arterial blood analysis for patients receiving nebulised budesonide (-----) or saline (→) before lung resection surgery using one-lung ventilation. Data are expressed as the mean, with error bars the SD. T0, before administration of the nebulised drug; T1, before one-lung ventilation; T2, 30 min after re-expansion of the lung; T3, 24 h after surgery; T4, 48 h after surgery; T5, 72 h after surgery. #p < 0.05 vs the saline group.
Figure 3  Cytokine concentrations in the bronchoalveolar fluid of patients receiving nebulised budesonide (■) or saline (■) before lung resection surgery and 30 min after one-lung ventilation. The central line represents the median, the box is the IQR and the error bars are the range. T1, before one-lung ventilation; T2, 30 min after one-lung ventilation. The black dots indicate outliers. #p < 0.05 vs the saline group. TNF, tumour necrosis factor; IL, interleukin.
lapsed lung. Bronchospasm, together with OLV-related decrease in lung compliance [26], may increase airway resistance, decrease ventilatory capacity and aggravate lung injury during OLV. We postulate that treatment with inhaled budesonide pre-operatively may mitigate the lung injury associated with surgery. The therapeu-

Figure 4  Mean cytokine concentrations in the serum of patients receiving nebulised budesonide (→) or saline (←) before and after lung resection surgery using one-lung ventilation. Error bars are SD. T0, before administration of the nebulised drug; T1, before one-lung ventilation; T2, 30 min after re-expansion of the lung; T3, 24 h after surgery; T4, 48 h after surgery; T5, 72 h after surgery. #p < 0.05 vs the saline group. TNF, tumour necrosis factor; IL, interleukin.
tic effect of budesonide may be mediated by down-regulating airway resistance and enhancing the efficacy of ventilation, leading to expansion of the bronchi and promotion of compliance [27–31].

We have also shown that inhaled budesonide may down-regulate the inflammatory response to surgery. During OLV, mechanical ventilation and ischaemia/reperfusion injury can activate the nuclear factor kappa-B (NF-κB) pathway in alveolar epithelial cells and vascular endothelial cells of both the collapsed and the ventilated lungs, inducing inflammatory molecule expression [32]. The increased levels of inflammatory cytokines and chemokines, as well as adhesion molecules, may damage epithelial and endothelial cells, leading to an increase in vascular permeability and albumin leakage [33]. These chemokines can also recruit neutrophils and alveolar macrophages [34, 35], worsening lung injury. Previous studies centre on the intra-operative inflammatory response to OLV [36, 37]. In this study, we measured cytokine levels both during and after surgery, and it was in the days after surgery that serum pro-inflammatory cytokine levels were reduced in response to budesonide. It is possible that the glucocorticoid inhibits NF-κB activation and protein-1 expression, thus decreasing pro-inflammatory cytokine expression in epithelial and endothelial cells as well as inflammatory infiltrates [38, 39]. Indeed, budesonide can inhibit T cell-mediated epithelial inflammation in vitro [40]. In addition, budesonide may also inhibit the recruitment of inflammatory neutrophil and alveolar macrophage infiltration in the lung during OLV [41, 42]. We are interested in further investigating the molecular mechanisms by which budesonide down-regulates inflammation in the lung during OLV.

Interestingly, we found that nebulised budesonide increased the concentration of IL-10 soon after lung re-expansion and during the postoperative period, which is consistent with other studies of methylprednisolone and budesonide [43–45]. The cytokine IL-10 is secreted by many types of cells, including regulatory T and B cells, and has been shown to inhibit inflammation in a number of diseases. It can antagonise the effect of TNF-α, IL-1β, IL-6 and IL-8, and inhibit inflammatory cell migration [46]. Hence, increased levels of local and systemic anti-inflammatory IL-10 may contribute to the therapeutic effect of budesonide on the inflammatory response to OLV. The elevated levels of IL-10 may arise from systemic feedback regulation, or budesonide may directly modulate inflammatory cell activation and deviate activated cells from pro-inflammatory towards anti-inflammatory (IL-10) secretion. The precise mechanisms underlying the action of budesonide in increasing IL-10 response remain to be further investigated. We acknowledge the potential limitations of this study, including limited sample size and failure to study the molecular mechanisms by which local and systemic inflammation may have been reduced.

In summary, we have shown that inhaled budesonide pre-operatively has a beneficial effect on respiratory and ventilatory mechanics after OLV for thoracic surgery, and is also associated with a decrease in pro-inflammatory cytokines and an increase in the anti-inflammatory cytokine IL-10. Thus, budesonide may be a promising candidate for reducing OLV-related lung injury and inflammation in patients undergoing thoracic surgery.

Acknowledgements

Dr Yong-Hui Dong (Department of Intensive Care, the Third Affiliated Hospital of Harbin Medical University) assisted with the study.

Competing interests

No external funding and no competing interests declared.

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Correlation between supra-sternal Doppler cardiac output (USCOM) measurements and chest radiological features

L. Huang,1 L. A. H. Critchley,2 R. L. K. Lok3 and Y. Liu4

1 PhD Student, 2 Professor & Honorary Consultant, Department of Anaesthesia and Intensive Care, and
3 Resident, Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of
Hong Kong, Hong Kong, China
4 Attending Doctor, Department of Radiology, Peking University Third Hospital, Beijing, China

Summary
Cardiac output can be measured non-invasively using supra-sternal Doppler (USCOM, Sydney, NSW, Australia). However, scanning can be difficult in practice in older patients, the reason for which has not been elucidated previously. Chest radiographs from 60 previously studied anaesthetised patients were reviewed and scored for aortic unfolding, enlargement and calcification, and cardiac enlargement. Corresponding supra-sternal Doppler scans were graded as easy or difficult using the Cattermole scoring system. Twenty patients who were difficult to scan, aged 60–88 years, had mean (SD) radiological scores of 5.9 (2.5) out of 12, while 20 adult controls, 40–60 years, and 20 older patients who were easy to scan, 60–80 years, had radiological scores of 0.9 (1.1) and 1.7 (1.4), respectively (p < 0.001). Over 75% of the patients who were difficult to scan had two or more radiological features suggestive of aortic unfolding and cardiac enlargement. Morphological or anatomical changes associated with ageing within the upper chest play an important part in the success of using supra-sternal Doppler in older patients.

Correspondence to: L. Huang
Email: huanglibd@gmail.com
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There is a growing interest among practising anaesthe-
tists in point-of-care, minimally invasive cardiac out-
put monitoring for high-risk surgery [1]. Several
technologies that can provide continuous readings
have recently been developed [2]. One of the more
promising technologies that can be used in anaes-
thesised patients is external Doppler via the supra-sternal
route. This technology may have advantages such as
its reported ability to reflect accurately serial changes
in cardiac output when used correctly, the fact that the
probe does not enter the body and its low running
costs [3]. However, supra-sternal Doppler does have
its weaknesses, for example accuracy may depend on
calibration, which uses body height to predict aortic
valve diameter and assumes that all patients have a
stereotypical body build [4]. In addition, skill and
experience may be needed to insonate the aortic valve,
focus the beam and capture the optimum flow signal.
In some patients, access to the sternal notch, the win-
dow for aortic valve insonation, may be difficult
because of the type of surgery being performed, and in
patients over 50 years of age, it can be very difficult,
and in some cases impossible, to detect a reliable flow
signal [3, 5].

In 2013, the only commercially available supra-stern-
al Doppler cardiac output monitor was the USCOM
USCOM Ltd., Sydney, NSW, Australia). In a previously published study, we found that the quality of USCOM scans declined with the age of the patient studied [3]. In many of the more difficult cases, we noted that the chest X-ray of the patient showed significant morphological changes to the aorta and the heart. We therefore hypothesised that age-related aortic unfolding and calcification, and cardiac enlargement, could explain why older patients were often more difficult to scan using the USCOM. Thus, a retrospective review of chest X-rays from those patients over 60 years of age from this previous study was performed. A scoring system was devised to categorise aortic changes and cardiac enlargement, which was compared with the existing assessments of USCOM scan quality [6, 7].

Methods

The Chinese University of Hong Kong and New Territories East Cluster Joint Clinical Ethics Committee approved the previous study and written informed consent was obtained [3]. This included permission to access and use clinical data for research and publication purposes pertaining to the study. Following publication of the original study of 180 patients, we decided to investigate the problems pertaining to difficult USCOM scans further, which included review of the chest X-rays of the original patients, and further ethical permission was deemed unnecessary. As age was the major predictor of unsuccessful or poor USCOM scan in our previous study, we chose to analyse radiographic data from the older and higher-risk groups. Sixty patients were selected from the previous 180 for further analysis. Patients were divided into three groups: 20 elderly patients (over 60 years) in whom USCOM scan had been difficult (Old/difficult); 20 elderly patients in whom the scan had been easy (Old/easy); and a control group of 20 younger patients (40–60 years of age) who were selected because USCOM scanning had been easy. The ability to insonate the aortic valve and obtain a reliable USCOM scan was recorded in the original study and assessed using the Cattermole scoring system, with a score of 5 or below indicating that the scan had been difficult [7]. The Cattermole score assesses the quality of the USCOM scan Doppler flow profiles [8].

Chest X-rays from the selected patients were studied by two specialist qualified radiologists (A and B).

Results

Data from 60 patients were analysed (Table 1). The Control group was mainly composed of healthy patients with a predominance of female patients scheduled for gynaecological surgery, whereas the other two...
The ease of USCOM scanning was scored using the Cattermole scoring system, with a low score indicating a more difficult scan. Mean (SD) Cattermole scores were lower in the Old/difficult group compared with the Old/easy and Control groups. In the Old/difficult group, the mean score was below the accepted 5-point threshold for reliable USCOM scan quality (Table 2).

The scores based on chest X-ray evaluation were higher in the Old/difficult group compared with the Old/easy and Control groups (Table 2). Radiologist A scored the chest X-rays on average 0.35 points higher than her counterpart radiologist (p < 0.001). A more detailed breakdown of the chest X-ray scoring by the two radiologists is provided (Table 3). Radiologist A was more likely to report abnormal aortic findings. The interclass coefficient between the two radiologist’s scores was $r = 0.85$. As the quality of the USCOM scan decreased, the radiologist’s X-ray assessment scores increased. There was a strong relationship between the Cattermole and chest X-ray score for all patients ($R^2 = 0.78$, $p < 0.001$). To show this relationship to better effect, a box plot was drawn where the Cattermole scores of the USCOM scan were grouped into excellent (score of 10–12), good (score of 9), fair (score of 6–8) and poor (score of 5 and below). The Old/easy and Control group patients were all excellent to fair, while the Old/difficult group patients were all poor. In the latter, 15 patients (75%) had a combined X-ray score of 4 or more, whereas in the other two groups, no patient scored more than 4 (p < 0.001, Fig. 2).

**Discussion**

Our main finding was that when USCOM scans were more difficult to perform, morphological changes were often found on the routine pre-operative chest X-ray, which indicated that the aorta was unfolded, enlarged and/or calcified and that the heart was enlarged. These chest X-ray changes were mainly present in patients over the age of 60 years, and provided an explanation as to why USCOM scanning becomes more difficult as patients become older when the supra-sternal window and aortic valve are used.
The USCOM may also be used to measure cardiac output by interrogating the pulmonary valve via the left parasternal window, and this may provide a useful alternative in problematic cases. However, left lateral positioning, as is required to obtain a good quality scan in this area, may not be feasible because of ongoing surgery, and scanning may be made more difficult if the edge of the lung overlies the area being interrogated.

When planning this study, we could not find a published method for scoring aortic elongation, dilatation and unfolding on a standard posterior–anterior chest X-ray. Hence, we developed our own scoring system based on morphological changes of the aorta and cardiac enlargement, as both these may alter the anatomical position of the aortic valve and thus make it more difficult to interrogate the aortic valve from the supra-sternal notch. To reduce discrepancies between the two radiologists, their scores were combined. Thus, if a radiological feature was marginal, it was more likely to be identified by at least one of the radiologists. We decided to use the Cattermole scoring system for USCOM scan quality as it has been shown to provide a more sensitive assessment compared with its predecessor, the 6-point Fremantle score [6, 7].

Pathological changes can be found in almost all parts of the human body as it ages, and the cardiovascular system is no exception with very typical and well-recognised changes. When a person ages, the ascending aorta increases in length by approximately 12%, and its diameter by 3%, for each decade of life. This phenomenon is described as aortic unfolding and dilatation, and the pathological mechanism is the loss of elastic tissue from the wall of the aorta [9, 10]. It is also commonly associated with calcification of the aorta, and is rare in patients less than 45 years of age. However, above 60 years, the incidence of aortic calcification is 15%, and this increases sharply to 50% by the age of 80 [11]. Left ventricular hypertrophy and left atrial enlargement are also common with ageing [12–14].

It is well known from echocardiographic studies that the patient’s position and the movement of their lungs, especially during mechanical ventilation, can affect the quality of ultrasound scans of the heart [15–17]. The supra-sternal window for ultrasonic scanning of the aortic valve relies on an unobstructed passage of the ultrasound beam, and this is provided by the fat and thymus-filled anterior mediastinum in front of the trachea and the ascending part of the aorta as it passes upwards (superiorly) and before it curves backwards (posteriorly) over the left main bronchus. However, any intervening air-filled space or bone will interrupt and attenuate the ultrasound signal. Occasionally, if the trachea in the thoracic inlet is prominent and lies anteriorly, it may prove difficult to insert the USCOM probe deep enough into the supra-sternal notch to get a good signal, and its beam may be partially obstructed by the sternum. However, we propose another, more subtle, problem associated with ageing. As the aorta unfolds and the heart enlarges, this alters the position of the aortic valve in the mediastinum, making it more difficult to interrogate because of interference by other structures such as the lungs. This phenomenon becomes very obvious when computerised tomography (CT) scans of the upper thorax are studied in relation to the passage of the ultrasound waves. Calcification of the ascending aorta may also play a role in attenuating the USCOM signal.

The correlation between the ability to perform successful supra-sternal USCOM scans and chest...
radiographical evidence of aortic unfolding and heart enlargement shown by this study provides an explanation as to why USCOM scanning can be difficult in some elderly anaesthetised patients. Therefore, we recommend reviewing the chest X-ray before deciding whether to use the USCOM device in older patients. Users of the USCOM should be familiar with the radiological features that may cause problems and be able to relate them to probe use. Further useful applied anatomical data can be obtained from a CT or magnetic resonance imaging scan of the upper thorax if available.

In conclusion, supra-sternal use of the USCOM is affected by age-related changes in the aorta (unfolding, enlargement and calcification) and cardiac enlargement. These changes can be identified on the routine pre-operative chest X-ray. Routinely reviewing the X-ray pre-operatively may help guide the use of USCOM during surgery.

Acknowledgements

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References

The effects of prolonged inspiratory time during one-lung ventilation: a randomised controlled trial


1 Professor, 2 Clinical Assistant Professor, 3 Assistant Professor, 4 Resident, 6 Clinical Fellow, Department of Anaesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
5 Assistant Professor, Department of Anaesthesia and Pain Medicine, Hallym University College of Medicine, Suwon, Korea

Summary

We evaluated the effects of a prolonged inspiratory time on gas exchange in subjects undergoing one-lung ventilation for thoracic surgery. One hundred patients were randomly assigned to Group I:E = 1:2 or Group I:E = 1:1. Arterial blood gas analysis and respiratory mechanics measurements were performed 10 min after anaesthesia induction, 30 and 60 min after initiation of one-lung ventilation, and 15 min after restoration of conventional two-lung ventilation. The mean (SD) ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen after 60 min of one-lung ventilation was significantly lower in Group I:E = 1:2 compared with Group I:E = 1:1 (27.7 (13.2) kPa vs 35.2 (22.1) kPa, respectively, p = 0.043). Mean (SD) physiological dead space-to-tidal volume ratio after 60 min of one-lung ventilation was significantly higher in Group I:E = 1:2 compared with Group I:E = 1:1 (0.46 (0.04) vs 0.43 (0.04), respectively, p = 0.008). Median (IQR [range]) peak inspiratory pressure was higher in Group I:E = 1:2 compared with Group I:E = 1:1 after 60 min of one-lung ventilation (23 (22–25 [18–29]) cmH2O vs 20 (18–21 [16–27]) cmH2O, respectively, p < 0.001) and median (IQR [range]) mean airway pressure was lower in Group I:E = 1:2 compared with Group I:E = 1:1 (10 (8–11 [5–15]) cmH2O vs 11 (10–13 [5–16]) cmH2O, respectively, p < 0.001).

We conclude that, compared with an I:E ratio of 1:2, an I:E ratio of 1:1 resulted in a modest improvement in oxygenation and decreased shunt fraction during one-lung ventilation.

Deterioration in pulmonary gas exchange results in serious adverse effects during one-lung ventilation (OLV) [1, 2], with significant hypoxaemia occurring in 5–10% of patients. The pathophysiology of gas exchange disturbance during OLV is attributed to intrapulmonary shunt due to collapse of the non-ventilated lung and ventilation/perfusion (V/Q) mismatch due to an increase in atelectasis in the dependent lung [2–4]. We hypothesised that oxygenation during OLV would be improved by applying inverse-ratio ventilation (IRV), with the resultant increase in mean airway pressures reducing atelectasis in the dependent lung and thus reducing V/Q mismatch. Inverse-ratio ventilation is a prolonged inspiratory time compared with expiratory time and is known to be effective for increasing oxygenation and reducing peak airway pressures.
pressures in adults with respiratory distress syndrome [5] and respiratory failure [6]. Previous studies evaluating the effect of IRV during general anaesthesia revealed no muscle-sparing [7] or only a marginal improvement in gas exchange [8, 9]; however, there have been no studies investigating the effectiveness of IRV in subjects undergoing OLV for lung surgery. The aim of our study was to evaluate whether a prolonged inspiratory time improves gas exchange and respiratory mechanics in patients undergoing lung surgery with OLV compared with conventional ventilatory settings. However, a considerable amount of auto-positive end-expiratory pressure (PEEP) develops during OLV [10] and IRV may aggravate this. Thus, we decided to evaluate the effect of an I:E ratio of 1:1, rather than 2:1, to avoid further increases in auto-PEEP.

Methods
Following local research ethics committee approval, this prospective, randomised trial was performed at a single University Hospital between February and October 2012. Patients scheduled to undergo elective lung lobectomy were considered eligible for inclusion in the study and all patients provided written informed consent. Exclusion criteria were a history of pneumothorax, asthma or ischaemic heart disease.

Routine monitoring included electrocardiography, pulse oximetry (SpO2), capnography, oral temperature, radial artery pressure and urine output. Anaesthesia was induced with 5 mg kg⁻¹ thiopental, 2 μg kg⁻¹ fentanyl and 0.6 mg kg⁻¹ rocuronium. After intubation with a single-use disposable 35-Fr or 37-Fr double-lumen tube (Broncho-Cath; Mallinckrodt Medical Ltd, Athlone, Ireland) under direct vision using fibreoptic bronchoscopy, mechanical ventilation of the lungs was instituted. A disposable CO₂/flow sensor was connected to a CO₂SMO plus® respiratory profile monitor (Novametrix Medical Systems Inc., Wallingford, CT, USA) and attached to the proximal end of the double-lumen tube.

During two-lung ventilation, the protocol consisted of volume-controlled ventilation with FIO₂ of 0.5, tidal volume (VT) of 8 ml kg⁻¹ predicted body weight, an inspiratory pause of 30%, and an I:E ratio of 1:2. Patients were randomly assigned to one of two treatment groups using an internet-based computer-generated random number table (www.randomizer.org) and sealed envelope method. During OLV, patients in Group I:E = 1:2 underwent volume-controlled ventilation with FIO₂ of 0.5, VT of 6 ml kg⁻¹ predicted body weight, an inspiratory pause of 30%, an I:E ratio of 1:2 and PEEP of 5 cmH₂O. Patients allocated to group I: E = 1:1 underwent the same ventilation protocol as Group I:E = 1:2 except with an I:E ratio of 1:1. Respiratory frequencies were adjusted to maintain an end-tidal CO₂ of 4.7–6.0 kPa. The maximal allowable peak inspiratory pressure (PIP) was 30 cmH₂O and if the pressure exceeded this, then volume-controlled ventilation was changed to pressure-controlled mode. Peak inspiratory pressure was adjusted to achieve the same V₅. If it was still not possible to reduce PIP to less than 30 cmH₂O, then the target VT was reduced in increments of 1 ml kg⁻¹ until the pressure was less than 30 cmH₂O. If S₉O₂ decreased to less than 95%, the FIO₂ was increased to 1.0 and if it remained less than 95%, then continuous positive airways pressure or intermittent two-lung ventilation was instituted.

Anaesthesia was maintained with an end-tidal sevoflurane concentration of 1 MAC in a 50:50 oxygen:air mixture. Remifentanil was infused intravenously to control haemodynamic responses. A muscle-sparing thoracotomy or video-assisted thoracoscopic surgery was performed. Lobectomies were performed by four surgeons, each of whom perform more than 100 major lung resections per year. Intravenous fluid therapy consisted of lactated Ringer’s solution at a rate of 6 ml kg⁻¹ h⁻¹. If mean arterial pressure was less than 60 mmHg for more than 5 min, an additional fluid challenge of 10 ml kg⁻¹ hydroxyethyl starch was administered.

After surgery, all patients underwent tracheal extubation in the operating theatre and received supplementary oxygen at 5 l min⁻¹ via a facemask for 30 min. This was continued if S₉O₂ was less than 95% whilst breathing room air. Postoperative analgesia was provided by continuous wound infusion (Baxter PAINfusor® catheter 15; Baxter LV5 INfusor®; Baxter Healthcare, Zurich, Switzerland) of 0.2% ropivacaine at 5 ml h⁻¹ for 48 h postoperatively or intravenous patient-controlled analgesia (Accufuser Plus®; Woo-young Healthcare, Seoul, Korea) consisting of 1500 μg fentanyl diluted in 70 ml saline 0.9%, set to deliver a bolus of 1 ml, with a lockout time of 15 min and
background infusion of 1 ml·h⁻¹. Patients were transferred to the intensive care unit and monitored for at least 24 h, the attending physician being blinded as to group allocations.

Arterial blood gases were analysed (Rapidlab 1265; Bayer Healthcare, Leverkusen, Germany) at four time intervals: 10 min after anaesthetic induction (baseline); after 30 min of OLV; after 60 min of OLV; and 15 min after reinstitution of two-lung ventilation. The following respiratory variables were measured: expiratory V₅ (Vₑ₅), minute ventilation (MVₑ), PIP, plateau inspiratory pressure (Pplat), mean airway pressure, PEEP, dynamic compliance (Cdyn) and static compliance (Cstag).

Mixed-expired CO₂ (PₑCO₂) was calculated by dividing the volume of CO₂ in a minute by the total expired volume during that same interval. The ratio of physiological dead space (V₅) to Vₑ₅ (Vₑ₅/V₅) was calculated using (PₑCO₂ - PₑCO₂)/PₑCO₂ [11]. The PₑO₂/FₑO₂ ratio and alveolar-arterial oxygen difference (A–aDO₂) were calculated [12]. Intrinsic PEEP was recorded by observing the time-flow curve, intrinsic PEEP occurring when inspiration began before expiration was complete [13].

Arterial blood gas analysis was performed 2 h after arrival in the intensive care unit. Chest radiographs were taken each morning, and a radiologist blinded to the study group allocation evaluated each radiograph. The incidence of atelectasis, pulmonary infiltration or acute lung injury [14] was recorded. Acute lung injury was diagnosed by: (i) sudden onset of respiratory distress; (ii) diffuse pulmonary infiltrates on the chest radiograph consistent with alveolar oedema; (iii) a PₑO₂/FₑO₂ ratio < 40 kPa; (iv) absence of hydrostatic pulmonary oedema due to cardiac insufficiency or fluid overload, on the basis of pulmonary arterial catheterisation, ECG, laboratory data (creatine kinase-MB, troponin), clinical evaluation, or a combination of these [15, 16].

Primary outcome measures were the PₑO₂, the PₑO₂/FₑO₂, and the PₑCO₂. A power analysis (α = 0.05, β = 0.20) indicated that at least 47 patients were required in each group. For this calculation, we used data obtained from a pilot study and assumed a PₑO₂/FₑO₂ ratio difference of 6.7 kPa between the groups to be significant. To allow for a 10% dropout rate, we aimed to recruit 52 patients in each group.

The Kolmogorov–Smirnov test with Lilliefors correction was used to assess the normality of data distribution. Patient and surgical characteristics were compared using an unpaired t-test or Mann–Whitney U-test for continuous variables and chi-squared test or Fisher’s exact test for categorical data. Comparison of gas exchange and other respiratory data was performed using ANOVA. Comparisons between each pair of time intervals within a group were made using a paired t-test or Wilcoxon signed-rank test. Intergroup differences in gas exchange and respiratory mechanics at each time point were determined using a t-test or Mann–Whitney U-test. The Bonferroni correction was performed to reduce the likelihood of false-positive results. Multiple logistic regression analysis was performed to find independent predictors of improved oxygenation at 60 min of OLV compared with 30 min of OLV. For this, univariate logistic regression analysis was used for patients’ and surgical characteristics and gas exchange parameters at baseline. The multivariate model included variables that were significant on univariate analysis. Data were analysed using SPSS software (SPSS version 20.0, Chicago, IL, USA) and a P value of less than 0.05 was considered statistically significant.

Results

Of 119 patients considered eligible for the study, nine were not studied due to a history of pneumothorax, asthma or ischaemic heart disease (Fig. 1). One hundred and ten patients were included in the study and the data from 100 patients were analysed. Patients’ and surgical characteristics are shown in Table 1.

Intra-operative gas exchange and respiratory mechanics are shown in Figs 2 and 3, and Table 2. Mean (SD) PₑO₂/FₑO₂ ratio after 60 min of OLV was significantly lower in Group I:E = 1:2 compared with Group I:E = 1:1 (27.7 (13.2) kPa vs 35.2 (22.1) kPa, respectively, p = 0.043. Mean (SD) Vₑ₅/V₅ was significantly higher in Group I:E = 1:2 compared with Group I:E = 1:1 after 60 min of OLV (0.45 (0.05) vs 0.42 (0.02), respectively, p < 0.001). Median (IQR [range]) PIP and plateau pressures were significantly higher whilst median (IQR [range]) mean airway pressure, dynamic compliance and static compliance were significantly lower in Group I:E = 1:2 compared with
Group I:E = 1:1 at 30 and 60 min of OLV. Two patients in Group I:E = 1:2 required a change in ventilation mode due to an increase in PIP of > 30 cmH2O compared with none in Group I:E = 1:1. There were no differences between the groups in terms of mean arterial pressure or heart rate changes.

Postoperative gas exchange was similar in both groups. Six patients in each group suffered atelectasis.
lung infiltration or acute lung injury and there were no differences between the groups in the lengths of intensive care unit or hospital stay.

We compared PaO\textsubscript{2} at 30 and 60 min of OLV and found that there were 44 patients with improved oxygenation (>20% increase in PaO\textsubscript{2} at 60 min, compared with 30 min of OLV) in both groups. We compared patients whose oxygenation improved with those whose oxygenation did not improve. There were fewer Group I:E = 1:2 patients than Group I:E = 1:1 patients in the improved group (11 (22%) vs 33 (66%), respectively, p < 0.001). The patients’ height, pre-operative functional residual capacity (FVC), and PaO\textsubscript{2}/FiO\textsubscript{2} ratio at baseline and at 15 min after reinstitution of conventional ventilation were significantly higher in the improved group than in the unimproved group. The A-aDO\textsubscript{2} at baseline and at 15 min after reinstitution of conventional ventilation were significantly lower in the

Figure 2 Partial pressure of arterial oxygen/fraction of inspired oxygen (P_{aO_2}/F_{iO_2}) ratios of patients who received I:E = 1:2 (□) or I:E = 1:1 (■) during one-lung ventilation (OLV) measured at baseline (10 min after anaesthesia induction), 30 min after initiating OLV, 60 min after initiating OLV, and 15 min after restoration of two-lung ventilation (TLV). Error bars indicate SD. *p < 0.05, Group I:E = 1:2 vs Group I:E = 1:1. †p < 0.05 compared with baseline. I:E, inspiratory to expiratory time ratio.

Figure 3 Physiological dead space/tidal volume (V\textsubscript{D}/V\textsubscript{T}) ratios of patients who received I:E = 1:2 (□) or I:E = 1:1 (■) during one-lung ventilation (OLV) measured at baseline (10 min after anaesthesia induction), 30 min after initiating OLV, 60 min after initiating OLV, and 15 min after restoration of two-lung ventilation (TLV). Error bars indicate SD. *p < 0.05 Group I:E = 1:2 vs Group I:E = 1:1. †p < 0.05 compared with baseline. I:E, inspiratory to expiratory time ratio.
Table 2: Intra-operative respiratory mechanics and hemodynamic parameters in patients who received I:E = 1:2 or I:E = 1:1 during one-lung ventilation (OLV). Values are median (IQR [range]) or mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>I:E = 1:2</th>
<th>I:E = 1:1</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>TOLV30</td>
<td>TOLV60</td>
</tr>
<tr>
<td>Dynamic compliance; ml.cmH2O⁻¹</td>
<td>28.3 (2.5)</td>
<td>18.5 (3.9)</td>
<td>18.1 (3.7)</td>
</tr>
<tr>
<td>Static compliance; ml.cmH2O⁻¹</td>
<td>32.8 (2.3)</td>
<td>24.6 (2.2)</td>
<td>25.1 (3.6)</td>
</tr>
</tbody>
</table>

Baseline, 10 min after anaesthetic induction with two-lung ventilation; TOLV30, 30 min after the initiation of one-lung ventilation (OLV); TOLV60, 1 h after the initiation of OLV; TTLV15, 15 min after the restoration of two lung ventilation.

*p value < 0.05 Group I:E = 1:2 vs Group I:E = 1:1.
improved group compared with the unimproved group. Multiple logistic regression analysis of the predictors for improved oxygenation revealed that an I:E ratio of 1:1 and an A-aDO2 at baseline of < 8.7 kPa were independently associated with improved oxygenation after 60 min of OLV (Table 3).

### Discussion

We compared the effects of two I:E ratios on gas exchange and respiratory mechanics during OLV for lung surgery. Oxygenation after 60 min of OLV was better, and $V_D/V_T$ was significantly lower, in patients in Group I:E = 1:1 compared with those in Group I:E = 1:2. Peak inspiratory pressures and peak plateau pressures were significantly lower, and mean airway pressures were significantly higher, in Group I:E = 1:1 compared with Group I:E = 1:2. As the improvement in oxygenation was only modest, we performed a subgroup analysis to identify factors that might predict those patients who would benefit from a prolonged inspiratory time. When we compared $P_{A\text{O}_2}$ values at 30 min with those at 60 min of OLV, 44 patients had improved oxygenation at 60 min. Multiple logistic regression analysis demonstrated that an I:E ratio of 1:1 and A-aDO2 at baseline of < 8.7 kPa were independent predictors of improved oxygenation. Increased inspiratory time improved oxygenation at 60 min of OLV in patients with normal baseline pulmonary function and we speculate that this beneficial effect may be mediated by an increase in mean airway pressure and decrease in $V_D/V_T$ during OLV in Group I:E = 1:1.

The effect of increasing the inspiratory time is useful only when a significant number of lung units are recruitable. Those patients with improved oxygenation at 60 min of OLV were taller, had a greater FVC and $P_{A\text{O}_2}/F_{I\text{O}_2}$ ratio, and a significantly lower A-aDO2 at baseline compared with those whose oxygenation did not improve. These variables correlate because taller patients have a greater physiological $V_D$, a previous study reporting that $V_D$ increases by 17 ml for every 10 cm increase in patients’ height [15]. The differences in $P_{A\text{O}_2}/F_{I\text{O}_2}$ ratios, and A-aDO2 at baseline between the improved and unimproved groups suggest that those with improved oxygenation had relatively good baseline gas exchange status.

The main differences in respiratory mechanics in Group I:E = 1:1 compared with Group I:E = 1:2 were increases in mean airway pressure and decreases in PIP. Mean airway pressure is considered a major determinant of oxygenation because it affects alveolar pressure and thus alveolar recruitment [16, 17]. Sustained alveolar inflation appears to decrease dead space, facilitating the mixing of inhaled gases and enhancing the efficacy of collateral ventilation. However, the beneficial effects of a prolonged inspiratory time cannot be explained solely by an increase in mean airway pressure because a previous study demonstrated that increasing PEEP to produce an increase in mean airway pressure did not result in a corresponding increase in oxygenation [18, 19]. The improved oxygenation in Group I:E = 1:1 could also be explained by an increase in total PEEP. Total PEEP was not measured accurately in our study because it requires a period of flow interruption and pressure equalisation in the ventilator circuit [20].

Although mean airway pressures were elevated, patients in Group I:E = 1:1 had reduced peak inspiratory and plateau pressures compared with Group I:E = 1:2. As high plateau pressures are considered a risk factor for acute lung injury and poor postoperative prognosis [14, 21], the prolonged inspiratory time may reduce the incidence of lung injury. Further studies measuring pulmonary inflammatory markers are required to investigate any potential benefit of prolonged inspiratory time on clinical outcomes.

### Table 3

<table>
<thead>
<tr>
<th>Covariate</th>
<th>$\beta$-coefficient</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
<th>AUC for single variable (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:E ratio of 1:1</td>
<td>1.48</td>
<td>4.38</td>
<td>1.54–12.47</td>
<td>&lt; 0.006</td>
<td>0.72 (0.62–0.83)</td>
</tr>
<tr>
<td>A-aDO2 at baseline &lt; 8.7 kPa</td>
<td>2.49</td>
<td>12.00</td>
<td>4.20–34.25</td>
<td>&lt; 0.001</td>
<td>0.78 (0.69–0.88)</td>
</tr>
<tr>
<td>Constant</td>
<td>–2.54</td>
<td>0.079</td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under receiver operating characteristic curve; A-DO2, alveolar-arterial oxygen difference.
There have been reports of using IRV during general anaesthesia. Whilst IRV had no beneficial effects when patients were placed in the supine position [7], arterial oxygenation increased slightly when patients were placed in the Trendelenburg position [8]. Another study reported that IRV reduced intra-operative A-aDO₂ [9]. A prolonged inspiratory time may be beneficial only when a significant number of recruitable lung units exist. One-lung ventilation in the lateral position causes a cephalad shift of the diaphragm with closure of small airways and increases the number of recruitable lung units in the dependent lung [2, 22]. Thus, increases in dead space and impaired V/Q mismatch in the dependent lung should be improved by an increased inspiratory time. Collapsed alveoli with prolonged ventilatory time constants [23] would theoretically require a prolonged inspiratory time to inflate fully.

There may be an interaction between externally applied PEEP [1], auto-PEEP developing during OLV [10, 24, 25], and auto-PEEP developing due to an increased inspiratory time. The same level of PEEP [26, 27] was applied to all patients’ lungs in our study to compare the effect of inspiratory time only, but auto-PEEP may occur in patients with emphysema or in the elderly [24]. The beneficial effects, or otherwise, of applying external PEEP in the presence of auto-PEEP during OLV depend on the individual’s lung mechanics [1, 28]; if the application of PEEP shifts the expiratory equilibration position on the compliance curve towards the lower inflection point of the curve, then external PEEP will be beneficial. We did not measure individual compliance curves and so it is not clear how the increased inspiratory time influenced the expiratory equilibration position.

There could be adverse effects related to increasing the inspiratory time; although it does maintain similar tidal volumes at lower peak airway pressures, excessive end-expiratory gas trapping may occur [20]. Excessive gas trapping may exacerbate the tendency for lung rupture, although the incidence of pneumothoraces is reported to be rare [5, 6]. In addition, the increased mean airway pressure may impede venous return and result in a reduced cardiac output [29, 30]; however, these effects only occurred with ventilation set at a 3:1 I:E ratio [31], with another study reporting no significant decrease in cardiac index [6].

Our study has several limitations. First, we applied the prolonged inspiratory time only after the initiation of OLV, which may have delayed any beneficial effects. If applied immediately after induction of anaesthesia, the oxygenation may have improved during the early period of OLV, when arterial desaturation most often occurs. Second, we did not compare lung injury or inflammation by measuring alveolar cytokines [32] and different ventilation strategies can affect postoperative clinical outcomes [33]. Third, we did not use tomodensitometric evaluation of alveolar recruitment [34]. This method could not be justified clinically in our study and calculating dead space is still considered an acceptable method to assess the efficacy of ventilator settings [35]. Fourth, auto-PEEP was not measured accurately because it requires an end-expiratory hold [20], which was not practical in our study. We concede that, because arterial oxygenation during OLV may be affected by the presence of pulmonary hyperinflation [10, 36], measurement of auto-PEEP is desirable when comparing oxygenation levels.

In conclusion, adjusting the I:E ratio by prolonging the inspiratory time showed an improvement in oxygenation and decreased shunt fraction after 60 min of OLV. It resulted in an elevated mean airway pressure, but reduced peak and plateau airway pressures. The improvement in oxygenation was most noticeable in those patients with normal pre-operative lung function, although the clinical advantages of a prolonged inspiratory time appear to be limited.

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Competing interests
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References


Evaluation of cardiac output in intensive care using a non-invasive arterial pulse contour technique (Nexfin™) compared with echocardiography*

O. Taton,1 D. Fagnoul,2 D. De Backer3 and J.-L. Vincent4

1 Resident, 2 Registrar, 3 Consultant, 4 Head, Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium

Summary
In this prospective study, cardiac output was measured in 38 intensive care unit patients before and after a fluid challenge, using both pulse contour analysis (Nexfin™; BMEYE, Amsterdam, the Netherlands) and transthoracic echocardiography. The ability of the Nexfin device to detect significant changes in the velocity–time integral was evaluated. The pulse wave could not be detected by the Nexfin device in five patients (13%), leaving 33 patients for analysis. The Nexfin device adequately tracked changes in the velocity–time integral in 20 (61%) patients. Using a cut-off of a 10% increase in cardiac output estimated by the Nexfin or by echocardiography, the sensitivity of the Nexfin device to detect a response to fluid challenge was 47%, with specificity 81% and accuracy 64%. The percentage error between the Nexfin and echocardiography was 448%; lower limit of agreement −62% (95% CI −62 to −36%) and upper limit of agreement, 32% (95% CI 20–45%). We conclude that the Nexfin device does not adequately track changes in cardiac output in critically ill patients.

Correspondence to: J. L. Vincent
Email: jlvincen@ulb.ac.be

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Providing adequate oxygen delivery to prevent tissue hypoperfusion is a fundamental goal in acutely ill patients [1]. After oxygen administration, optimisation of cardiac output (CO) is the next step in early resuscitation, and fluid administration is often the first method used to increase CO [2, 3]. However, CO is rarely measured in the early resuscitation period because it usually requires the use of an invasive device. The ability to measure CO non-invasively would, therefore, be welcome. Echocardiography can be used for this purpose, but may be time-consuming, requires specific training and is not continuous [4]. In the early resuscitation setting, the ideal device would provide continuous CO monitoring without requiring puncture of a vessel.

The Nexfin™ device (BMEYE, Amsterdam, the Netherlands) has recently been introduced for continuous non-invasive CO measurement. The technique used is derived from the volume-clamp method described by Penaz in 1973 [5]. This device is currently used for ambulatory blood pressure monitoring [6] and has been proposed more recently for CO monitoring in the intensive care setting.
monitoring. Its use to monitor CO has been validated during coronary artery bypass graft surgery [7–9], but use in acutely ill patients has not been well studied.

Assessment of changes or trends in CO is more useful than absolute values, particularly for evaluation of the response to therapy. Acutely ill patients frequently require administration of fluids or vasoactive drugs to increase CO, with the aim of improving tissue perfusion. Indeed, excessive administration of intravenous fluids may be harmful [10], so that monitoring the response to fluids is essential.

The purpose of our study was to evaluate the feasibility and accuracy of the Nexfin device to track changes in CO after fluid administration in acutely ill patients, compared with echocardiography.

**Methods**

The study was approved by the ethical committee of Erasme University Hospital, which waived the need for written informed consent. All adult patients admitted to the intensive care unit (ICU) between February 2011 and February 2012 with signs of tissue hypoperfusion requiring fluid challenge within the first few hours of admission were prospectively included in the study. Patients less than 18 years of age, patients for whom the quality of the echocardiographic pictures was considered likely to be insufficient to obtain an adequate evaluation of CO (e.g. postoperative care after thoracic or cardiac surgery) and patients in whom it was impossible to apply the finger strap were not included.

The cuff of the Nexfin device was placed on the middle phalanx of the third finger for at least 15 min for calibration of the device. Measurements were always performed on the opposite hand if an arterial line was in place. The Nexfin cuff is composed of an inflatable ring, in which a photo-electric plethysmograph is incorporated. The ring inflates during systole and deflates during diastole, which is said to maintain the diameter of the artery constant [5]. The aortic stroke volume is extrapolated from the pressure measured at the finger artery using an algorithm based on several parameters, including the age of the patient, weight, height, sex and mean arterial pressure (MAP) [11]. Cardiac output is then calculated by multiplying the stroke volume by the heart rate. The external calibration function of this device, which can be used to adjust the parameters of the Nexfin to another technique that estimates the CO, was not used in this study.

At the same time as the Nexfin CO measurements, transthoracic echocardiography (Toshiba Xario SSA-660A, Tokyo, Japan) was performed, which was used as the reference technique. Stroke volume was determined as the product of the velocity–time integral of aortic flow at the left ventricular outflow tract and left ventricular outflow area obtained in the parasternal long-axis view [12, 13]. The mean value of three measurements was determined. If the patient had an arrhythmia, we selected heart beats that had a constant P-R interval. Transthoracic echocardiography was performed according to our standard practice by an experienced user and reviewed by a senior echocardiographer [13, 14].

All measurements were taken before and after a fluid challenge, which was defined as an infusion over a short period of time (15–30 min) of a crystalloid (500–1000 ml) or colloid (300–500 ml) solution, according to our standard practice [15]. During the fluid challenge, respiratory (positive end-expiratory pressure) and haemodynamic (dose of vasopressor or inotropic agents) parameters were kept unchanged. Total systemic vascular resistance was calculated before the fluid challenge by dividing the MAP by the CO estimated by the Nexfin.

The primary endpoint of this descriptive study was to evaluate the correlation between the Nexfin and transthoracic echocardiography for evaluating the response to a fluid challenge; the secondary endpoint was to assess the agreement between the two methods. A Pearson correlation coefficient test was performed to assess the relationship between changes in CO values obtained by the Nexfin and by transthoracic echocardiography. Patients with an increase in CO using either technique of at least 10% were defined as fluid responders. We used Fisher’s exact test to evaluate the agreement of the two techniques to characterise fluid response, using two cut-offs of 10% and 15%, as these are both described in the literature to identify responders to fluid challenge [16, 17]. Exploratory analyses were also conducted in subgroups of patients according to their lactate levels (≤ and >2 mmol.l⁻¹), use of vasopressor agents, and total systemic vascular resistance...
values (\textless{} and \textgeq{} 970 dyn.s\(^{-1}\).cm\(^{-5}\) \cite{18}). Bland-Altman analysis was performed to determine the limits of agreement between the techniques \cite{19}. Statistical tests were two-tailed and a p-value \textless{} 0.05 was considered statistically significant. Analyses were performed using SPSS Statistics Version 19 (IBM Corp, New York, NY, USA).

Results

Thirty-eight patients met the inclusion criteria during the study period; 23 were men and mean (SD) age was 63 (15) years (Table 1). Nine patients (24%) had a diagnosis of respiratory failure, 6 (16%) cardiac failure, 9 (24%) sepsis and 14 (36%) were admitted after elective surgery. The arterial pulse wave could not be obtained by the Nexfin device in five (13%) patients; these patients had a similar central temperature to those in whom an arterial pulse wave was detected. Fluid challenge was performed with crystalloids in 31 (82%) patients (mean (SD) volume 741 (150) ml), colloids in 6 (15%) patients (408 (100) ml) and blood products in 1 (3%) patient (482 ml). In 19 patients (50%), the fluid challenge was given to increase MAP, and in the remaining patients, it was given in response to a low urine output.

The fluid challenge increased CO measured with the Nexfin by mean (SD) 0.3 (0.9) l.min\(^{-1}\) (n = 33), compared with 2.3 (2.8) measured using echocardiography in the same patients (p \textless{} 0.001). Correlation between the two measurement methods was poor, r = −0.025, p = 0.89 (Fig. 1). Using a cut-off of a 10% increase in CO, a positive response to a fluid challenge was identified by the Nexfin in 11 (33%) patients and by echocardiography in 17 (52%). Among the 11 patients classified as responders by Nexfin, 8 (73%) were true responders by echocardiography (Table 2).

Table 1 Baseline characteristics of 38 patients before a fluid challenge. Values are mean (SD) or number (proportion).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or Number (Proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td>20 (7)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Noradrenaline; ( \mu \text{g.min}^{-1} ) (13 patients)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Dobutamine; ( \mu \text{g.kg}^{-1}.\text{min}^{-1} ) (6 patients)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Lactate level; mmol.l(^{-1})</td>
<td>2.4 (1.9)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>14 (37%)</td>
</tr>
<tr>
<td>PEEP; cmH(_2)O</td>
<td>6.0 (1.6)</td>
</tr>
<tr>
<td>SVR; Wood units</td>
<td>1228 (352)</td>
</tr>
<tr>
<td>Technical failure of Nexfin</td>
<td>5 (13%)</td>
</tr>
</tbody>
</table>

Figure 1 Correlation between the percentage of variation in the cardiac output estimated by the Nexfin device (% \( \text{CO}_{\text{Nexfin}} \)) and that evaluated by transthoracic echocardiography (%\( \text{CO}_{\text{Echo}} \)) during a fluid challenge. The Pearson correlation coefficient, r, was −0.025 (p = 0.89). Dotted lines define the areas where the results from the two methods are in agreement with a cut-off of variation at (a) 10% or (b) 15%.
The results from the two techniques agreed in 20 (61%) patients (Fig. 2). Agreement was slightly better with a cut-off of 15% compared to 10% (64% vs 61%, respectively), with fewer responders identified (Fig. 2). However, the sensitivity of the Nexfin to identify responders to a fluid challenge correctly remained low regardless of the cut-off used (Table 2). The percentage error between CO measurements made by the Nexfin and echocardiography was 448% (Fig. 3); the lower limit of agreement was −48% (95% CI −62 to −36) and upper limit of agreement, 32% (95% CI 20–45).

In the subgroup of 21 patients with normal lactate levels and using the 10% cut-off, results between the two methods of measurement agreed in 16 (76%) patients, compared with only 4 (33%) of the 12 patients who had elevated (> 2 mmol.l\(^{-1}\)) lactate concentrations (\(p = 0.015\)). In the subgroup of the 10 patients with low initial systemic vascular resistance (< 970 dyn.s\(^{-1}\).cm\(^{-5}\)), results agreed in 9 (90%) patients compared with only 12 (52%) of the 23 remaining patients (\(p = 0.038\)). Noradrenaline was administered to 13 patients because of haemodynamic instability. For both the 10% and 15% cut-offs, there were no significant differences in agreement between the techniques according to whether the patient received noradrenaline or not.

### Discussion

Our results show that the Nexfin and transthoracic echocardiography do not agree with each other when they are used to measure changes in cardiac output when a fluid challenge is administered to ICU patients. This resulted in frequent discrepancy in the interpretation of the response to fluid, and as we consider transthoracic echocardiography to be the gold standard in this regard, we have shown that the Nexfin may not be used in this setting.

The poor correlation between the two techniques may be due to peripheral vasoconstriction, which directly influences arterial blood pressure in the finger where the Nexfin device is applied and on which the non-invasive pulse wave contour analysis is based. This is supported by the observation that agreement

<table>
<thead>
<tr>
<th>Table 2 Agreement between cardiac output values measured using the Nexfin and those measured by transthoracic echocardiography.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cut-off 10%</strong></td>
</tr>
<tr>
<td>Agreement</td>
</tr>
<tr>
<td>Responders (no of patients)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Accuracy</td>
</tr>
</tbody>
</table>

![Figure 2](image-url) Evolution of the cardiac output evaluated by Nexfin (CO\(_{\text{Nexfin}}\)) and that evaluated by transthoracic echocardiography (CO\(_{\text{Echo}}\)) using a cut-off of (a) 10% or (b) 15%. Each arrow represents one patient. The base of each arrow is positioned according to the CO\(_{\text{Nexfin}}\) (x value) and the CO\(_{\text{Echo}}\) (y value) before the fluid challenge; the arrowhead is positioned according to the CO\(_{\text{Nexfin}}\) and the CO\(_{\text{Echo}}\) after the fluid challenge. Solid arrows represent patients for whom cardiac output values obtained by the two techniques were in agreement and dashed arrows represent patients in whom values did not agree. Asterisks indicate the patients considered as responders by transthoracic echocardiography.
between the two techniques was better in patients with a low systemic vascular resistance and worse in patients with high lactate levels, a marker of peripheral hypoperfusion [20]. Hence, it seems that the Nexfin is less reliable in the presence of vasoconstriction. However, as previously reported by Imholz et al. [5], we observed that the use of vasopressors did not affect the ability of the Nexfin device to evaluate the CO.

Transthoracic echocardiography was used as the reference technique in our study for several reasons. First, it has been well validated [21, 22], and can reliably estimate aortic flow, particularly change in flow during various interventions, whereas measurement of left ventricular outflow area is more subject to error [12]. Secondly, the assessment of CO was performed in the early resuscitation period and most of the patients were still awake, ruling out the use of transoesophageal echocardiography. The limitations of transthoracic echocardiography are related to patient factors (e.g. presence of chest drains, obesity), clinical conditions (e.g. imaging difficulties following cardiothoracic surgery due to pneumomediastinum) and the skill of the practitioner in performing and interpreting the images [13, 14].

Stoke volume is a good measure for assessing haemodynamic changes after vascular filling [23, 24]. In our study, we measured velocity–time integral using echocardiography to calculate stroke volume to evaluate the response to a fluid challenge. The velocity–time integral represents a good approximation of stroke volume because it has been found to be reproducible in clinical studies [25]. The main source of error in the evaluation of CO with echocardiography is due to errors in the measurement of the diameter of the left ventricular outflow tract, but this does not change following a fluid challenge, so tracking changes in CO is not affected by this source of error. In addition, pulse-wave Doppler facilitates the measurement of the velocity–time integral when the echocardiographic window is of poor quality.

Only a few studies have evaluated the accuracy of measurements of CO using the Nexfin device. In 23 patients undergoing cardiac resynchronisation therapy, van Geldorp et al. [26] reported that stroke volume as assessed by the Nexfin device and by transthoracic echocardiography showed good agreement. In 10 patients with circulatory shock, Stover et al. [8] reported quite a good correlation between Nexfin and thermodilution, but, because of the high standard deviation in their study, they concluded that it could not be used in place of an invasive monitoring system. Another report [9] compared the Nexfin and thermodilution in patients who underwent coronary artery bypass graft surgery. After using the external calibration function of the Nexfin device for the thermodilution technique, results obtained by the two methods were interchangeable. Good correlation in
CO measurement between the Nexfin and transthoracic echocardiography was also reported in patients undergoing routine echocardiography [27]. Broch et al. [7] showed good correlation between the Nexfin and transcardiopulmonary thermodilution (PiCCO, Pulsion Medical Systems, Munich, Germany) during coronary artery bypass graft surgery, but the evaluation was limited to patients with good cardiac function and therefore the results cannot be extrapolated to other patient populations. Another study compared the Nexfin and PiCCO in critically ill patients who received a fluid challenge [28]. They showed similar results to those of our study, but slightly better agreement between the two techniques. Finally, Fischer et al. [29] found a good correlation between Nexfin and PiCCO in postcardiac surgery patients; however, because of the high percentage error between the two methods, they concluded that the measurements were not interchangeable.

Our data are less encouraging than these previous studies. This difference may be explained in part by the reference method used to validate the Nexfin measurements, which has its own limitations as discussed earlier [4, 13]. Our population was also more heterogeneous than that in previous studies, but there was no difference in the level of agreement according to the reason for admission. Furthermore, we did not use the calibration function of the Nexfin device because the objective was to obtain reliable assessment without the need for calibration using another technique. The main cause of error when using the Nexfin is that it is directly dependent on vascular flow in arteries in the finger; we were unable to detect the arterial pulse wave in five (13%) patients, which represents the technical failure rate of this method. The manufacturer advises heating the hand to avoid vasoconstriction, but this process may, in our experience, affect the results of the values measured by the device.

Limitations of this study include the assessment of vasoconstriction using systemic vascular resistance, which was calculated from the CO measured by the Nexfin, and we only measured lactate as a surrogate marker. Capillary refill time, hourly diuresis or neurological status may be other ways to demonstrate vasoconstriction [30, 31]. Secondly, in addition to the limitations of transthoracic echocardiography discussed earlier, we selected only patients in whom we anticipated that good echocardiography images could be obtained, so that we probably overestimated the ability of echocardiography to assess CO. Finally, our patient cohort was relatively small, but we do not see how increasing the size of the population would substantially alter the results.

In conclusion, although the Nexfin finger plethysmography system is easy to use and non-invasive, we have shown that it does not accurately assess CO in critically ill patients and in particular does not accurately track changes following fluid challenge; its routine use in these patients therefore cannot be recommended.

**Competing interests**

No external funding and no competing interests declared.

**References**


The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery: a systematic review and meta-analysis

C. Corredor,1 M. Wasowicz,2 K. Karkouti2 and V. Sharma3

1 Specialist Registrar, 3 Consultant Anaesthetist, Department of Anaesthesia, St. George’s Hospital, London, UK
2 Associate Professor and Staff Anesthesiologist, Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Ontario, Canada

Summary
This systematic review and meta-analysis appraises the utility of point-of-care platelet function tests for predicting blood loss and transfusion requirements in cardiac surgical patients, and analyses whether their use within a transfusion management algorithm is associated with improved patient outcomes. We included 30 observational studies incorporating 3044 patients in the qualitative assessment, and nine randomised controlled trials including 1057 patients in the meta-analysis. Platelet function tests demonstrated significant variability in their ability to predict blood loss and transfusion requirements. Their use within a blood transfusion algorithm demonstrated a reduction in blood loss at longest follow-up (mean difference $-102.9$ ml (95% CI $-149.9$ to $-56.1$ ml), $p < 0.001$), and transfusion of packed red cells (RR 0.86 (95% CI 0.78–0.94), $p = 0.001$) and fresh frozen plasma (RR 0.42 (95% CI 0.30–0.59), $p < 0.001$). Viscoelastic methods used in combination with other platelet function tests achieved greater reduction in blood loss (mean difference $-111.8$ ml (95% CI $-174.9$ to $-49.1$ ml), $p = 0.0005$) compared with their use alone (mean difference $-90.6$ ml (95% CI 166.1–15.0 ml), $p = 0.02$). We conclude that incorporation of point-of-care platelet function tests into transfusion management algorithms is associated with a reduction in blood loss and transfusion requirements in cardiac surgery patients.

Introduction
Bleeding following cardiac surgery is a commonly encountered complication that accounts for up to 20% of all hospital blood transfusions [1]. Massive bleeding and subsequent requirement for blood product administration and mediastinal re-exploration is associated with significant morbidity and mortality [2]. Furthermore, administration of blood products is linked with worse outcomes after cardiac surgery [3, 4]. The development of strategies to reduce blood loss following cardiac surgery is therefore imperative and continues to be explored.

Postoperative, non-surgical bleeding in cardiac surgical patients is often multifactorial, and causal
mechanisms involve a complex interaction of all aspects of the coagulation cascade and regulatory pathways [5]. Platelet dysfunction, excessive fibrinolysis, hypothermia, pre-operative anaemia and deficiency of coagulation factors or their dilution are all suggested aetiologies of postoperative bleeding [6]. Among these, the most important is thought to be platelet dysfunction, which occurs as a result of the interplay of acquired and pharmacologically-induced factors [7, 8]. Cardiopulmonary bypass directly affects platelet function, and the associated use of heparin contributes to defects in platelet activation [9]. The interaction between protamine and platelets also inhibits thrombin-induced platelet aggregation [10]. Additionally, patients frequently undergo cardiac surgery while on or under the residual effects of antiplatelet medications, which further impair platelet aggregation [11].

Rapid and accurate identification of peri-operative platelet dysfunction would allow for targeted therapy, thereby potentially reducing blood loss and alleviating the need for further transfusions. The use of a point-of-care testing-guided transfusion algorithm, first described more than a decade ago, has been associated with reduced blood transfusion and blood loss in cardiac surgery [12]. Since then, there has been significant advancement in the understanding of platelet dysfunction in cardiac surgical patients, and new methods of point-of-care platelet function testing have been developed.

Platelet aggregometry using platelet-rich plasma is the gold standard for assessment of platelet function. However, complexity and a long turnaround time make this technique unsuitable for regular peri-operative use. Point-of-care platelet function tests overcome these limitations and allow for rapid peri-operative assessment of platelet function. Table 1 summarises the characteristics of common point-of-care tests currently available.

Despite a variety of commercially available point-of-care platelet function monitors, there is very little consensus on the optimal test for the best prediction of blood loss and transfusion requirements and their performance when incorporated as part of a blood transfusion management algorithm. We performed a systematic review to characterise point-of-care platelet function tests, and performed a meta-analysis to appraise quantitatively their influence on blood loss and transfusion requirements when included in peri-operative blood transfusion management algorithms.

Methods
We conducted this review following the methods suggested by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. The Patient, Intervention, Comparison, Outcome, Time (PICOT) framework was used to select studies by constructing a two-part question [14]:

- Which point-of-care platelet function test best detects platelet dysfunction and predicts blood loss and/or blood product utilisation following cardiac surgery?
- Does the inclusion of point-of-care platelet function testing as part of a blood management algorithm lead to improved outcomes in patients with significant bleeding following cardiac surgery?

The first question was addressed by performing a qualitative analysis of observational studies. Quantitative analysis of observational studies was not possible due to the wide variation in the reported variables used to describe the predictive ability of these tests. We defined point-of-care platelet function devices as those that could provide bedside information on qualitative and/or quantitative platelet function. We excluded studies that incorporated the use of point-of-care devices that are no longer commercially available such as HemoSTATUS™ (Medtronic, Parker, CO, USA).

The next part of the review addressed the second question and investigated only randomised controlled trials that incorporated point-of-care platelet function testing as part of a blood management algorithm. We included trials that compared point-of-care platelet function testing with standard coagulation tests, standard institutional practice and/or clinical judgement.

We performed a systematic search of the MEDLINE (via OvidSP), EMBASE (via OvidSP) and the Cochrane Central Register of Randomised Controlled Trials (CENTRAL) (issue 4 of 12, April 2014) databases. There was no date restriction and we limited the search to articles published in the English language.

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The search was last updated in October 2014. Search terms were entered into electronic databases using the search filters for observational studies developed by the Scottish Intercollegiate Guidelines Network (SIGN) and the Cochrane highly sensitive strategies for randomised controlled trials [15, 16]. The following terms were used: cardiac surgery; coronary artery bypass graft; platelet function test; point-of-care test; aggregometry; thromboelastography TEG (TEG®; Haemonetics Corporation, Braintree, MA, USA); thromboelastogram; RapidTEG™ (Haemonetics Corporation, Braintree, MA, USA); rotational thromboelastometry ROTEM® (TEM International GmbH, Munich, Germany); Sonoclot (Sienco Inc., Arvada, CO, USA); Plateletworks® (Helena Laboratories, Beaumont, TX, USA); VerifyNow® (Accumetrics, Inc., San Diego, CA); Impact-R (CPA; DiaMed, Cressier, Switzerland); Platelet Mapping Assay™ (Haemoscope Corporation, Niles, IL, USA); Multiplate™ (Dynabyte Medical, Munich, Germany); and platelet function analyser PFA-100® (Siemens Corporation, Munich, Germany). Table 2 illustrates examples of search strategies used.

Table 1 Currently used clinical tests of platelet function.

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet–platelet aggregation</td>
<td>Historical gold standard</td>
<td>Large sample volume, complex sample preparation, time-consuming</td>
</tr>
<tr>
<td>Turbidometric aggregometry</td>
<td>Whole blood assay</td>
<td>Large sample volume, expensive, time-consuming</td>
</tr>
<tr>
<td>Impedence aggregometry</td>
<td>Whole blood assay, small sample volume, simple and rapid, no sample preparation</td>
<td>Limited range of haematocrit and platelet count</td>
</tr>
<tr>
<td>VerifyNow</td>
<td>Whole blood assay, minimal sample preparation</td>
<td></td>
</tr>
<tr>
<td>Plateletworks</td>
<td>Whole blood assay, minimal sample preparation</td>
<td>Limited studies</td>
</tr>
<tr>
<td>Activation-dependent changes in platelet surface</td>
<td>Whole blood assay, low sample volume</td>
<td>Complex sample preparation, expensive, needs experienced technician, lack of commercial availability</td>
</tr>
<tr>
<td>Platelet surface P-selectin, platelet surface-activated GP IIb/IIIa, leucocyte-platelet aggregates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activation-dependent signalling</td>
<td>Whole blood assay, small sample volume, most specific for P2Y12 blockers effect</td>
<td>Complex sample preparation, expensive (flow cytometry), needs experienced technician</td>
</tr>
<tr>
<td>VASP phosphorylation</td>
<td>Whole blood assay, platelet clot formation and lysis data</td>
<td>Limited studies</td>
</tr>
<tr>
<td>Viscoelastic tests: platelet contribution to clot strength</td>
<td>Whole blood assay, clot information</td>
<td></td>
</tr>
<tr>
<td>TEG</td>
<td>Whole blood assay, platelet clot formation and lysis data</td>
<td></td>
</tr>
<tr>
<td>Platelet mapping assay</td>
<td>Whole blood assay, clot information</td>
<td>Limited studies, not a true point-of-care device</td>
</tr>
<tr>
<td>ROTEM</td>
<td>Whole blood assay</td>
<td>Not approved in USA</td>
</tr>
<tr>
<td>Activation-dependent release from platelets</td>
<td>Evaluation of cyclo-oxygenase 1 inhibition (aspirin target)</td>
<td>Indirect, not platelet specific, cannot monitor thienopyridine and GP IIb/IIIa inhibitor effect</td>
</tr>
<tr>
<td>Seum thromboxane-B2</td>
<td>Evaluation of cyclo-oxygenase 1 inhibition (aspirin target)</td>
<td>Indirect, not platelet specific, cannot monitor thienopyridine and GP IIb/IIIa inhibitor effect</td>
</tr>
<tr>
<td>Urinary 11-dehydro thromboxane-B2</td>
<td>Whole blood assay, small sample volume, no sample preparation, simple, tests the effect of shear stress</td>
<td>Not widely used, requires pipetting, not recommended for monitoring GP IIb/IIIa inhibitors</td>
</tr>
<tr>
<td>Shear-induced platelet adhesion</td>
<td>Simple, rapid, low sample volume and no sample preparation</td>
<td>Dependent on von Willebrand factor and haematocrit, not recommended for monitoring thienopyridines</td>
</tr>
<tr>
<td>Impact cone and plate(let) analyzer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shear-induced platelet aggregation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFA-100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GP, glycoprotein; VASP, vasodilator-stimulated phosphoprotein; PFA-100, Platelet Function Analyser-100.
Two investigators (CC, VS) independently screened titles and abstracts produced by the search strategies, and non-relevant titles were excluded. Relevant full-text articles were then analysed against the pre-determined selection criteria and data were extracted from individual studies using pre-designed data collection tables. Two investigators (CC, VS) independently collected data using a standardised data collection method.

### Table 2 Example of search strategies used.

<table>
<thead>
<tr>
<th>Ovid Medline SIGN search strategy for observational studies</th>
<th>Ovid Medline CHSS for randomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Epidemiologic studies/</td>
<td>1 randomized controlled trials as a topic/</td>
</tr>
<tr>
<td>2 exp case control studies/</td>
<td>2 randomized controlled trials/</td>
</tr>
<tr>
<td>3 exp cohort studies/</td>
<td>3 random allocation/</td>
</tr>
<tr>
<td>4 Case control.tw.</td>
<td>4 double blind method/</td>
</tr>
<tr>
<td>5 (cohort adj (study or studies)).tw.</td>
<td>5 single blind method/</td>
</tr>
<tr>
<td>6 Cohort analy$.tw.</td>
<td>6 clinical trial/</td>
</tr>
<tr>
<td>7 (Follow up adj (study or studies)).tw.</td>
<td>7 controlled clinical trial.pt.</td>
</tr>
<tr>
<td>8 (observational adj (study or studies)).tw.</td>
<td>8 randomized controlled trial.pt.</td>
</tr>
<tr>
<td>9 Longitudinal.tw.</td>
<td>9 multicenter study.pt.</td>
</tr>
<tr>
<td>10 Retrospective.tw.</td>
<td>10 clinical trial.pt.</td>
</tr>
<tr>
<td>11 Cross sectional.tw.</td>
<td>11 exp clinical trial as topic/</td>
</tr>
<tr>
<td>12 Cross-sectional studies/</td>
<td>12 or/1-11</td>
</tr>
<tr>
<td>13 or/1-12</td>
<td>13 (clinical adj trial).tw.<strong>chr(13)</strong>((singl$ or doublortreb or tripl$)adj(blind3 or mask$3)).tw.</td>
</tr>
<tr>
<td>14 exp cardiac surgery/</td>
<td>14 randomly allocated.tw.</td>
</tr>
<tr>
<td>15 cardiac surgery.tw.</td>
<td>15 (allocated adj2 random$).tw.</td>
</tr>
<tr>
<td>16 cardiac surgery.mp.</td>
<td>16 or/13-16</td>
</tr>
<tr>
<td>17 14 or 15 or 16</td>
<td>17 12 or 17</td>
</tr>
<tr>
<td>18 exp coronary artery bypass graft/</td>
<td>18 case report.tw.</td>
</tr>
<tr>
<td>19 coronary artery bypass graft.tw.</td>
<td>19 letter/</td>
</tr>
<tr>
<td>20 coronary artery bypass graft.mp.</td>
<td>20 historical article/</td>
</tr>
<tr>
<td>21 18 or 19 or 20</td>
<td>21 or/19-21</td>
</tr>
<tr>
<td>22 17 or 21</td>
<td>22 18 not 22</td>
</tr>
<tr>
<td>23 exp platelet function test/or platelet function test.tw. or platelet function test.mp.</td>
<td>23 exp cardiac surgery/</td>
</tr>
<tr>
<td>24 exp point of care test/or point of care test.tw. or point of care test.mp.</td>
<td>24 cardiac surgery.tw.</td>
</tr>
<tr>
<td>25 exp aggregometry/or aggregometry.tw. or aggregometry.mp.</td>
<td>25 cardiac surgery.mp.</td>
</tr>
<tr>
<td>26 exp thromboelastography/or thromboelastography.tw. or thromboelastography.mp.</td>
<td>26 24 or 25 or 26</td>
</tr>
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<td>27 exp thromboelastogram/or thromboelastogram.tw. or thromboelastogram.mp.</td>
<td>27 exp coronary artery bypass graft/</td>
</tr>
<tr>
<td>28 exp TEG/or TEG.tw. or TEG.mp.</td>
<td>28 coronary artery bypass graft.tw.</td>
</tr>
<tr>
<td>29 exp rapidTEG/or RapidTEG.tw. or RapidTEG.mp.</td>
<td>29 coronary artery bypass graft.mp.</td>
</tr>
<tr>
<td>30 exp plateletworks/or plateletworks.tw. or plateletworks.mp.</td>
<td>30 28 or 29 or 30</td>
</tr>
<tr>
<td>31 exp VerifyNow/or VerifyNow.tw. or VerifyNow.mp.</td>
<td>31 27 or 31</td>
</tr>
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<td>36 exp thromboelastogram/or thromboelastogram.tw. or thromboelastogram.mp.</td>
</tr>
<tr>
<td>37 exp TEG/or TEG.tw. or TEG.mp.</td>
<td>37 exp TEG/or TEG.tw. or TEG.mp.</td>
</tr>
<tr>
<td>38 exp RapidTEG/or RapidTEG.tw. or RapidTEG.mp.</td>
<td>38 exp RapidTEG/or RapidTEG.tw. or RapidTEG.mp.</td>
</tr>
<tr>
<td>39 exp plateletworks/or plateletworks.tw. or plateletworks.mp.</td>
<td>39 exp plateletworks/or plateletworks.tw. or plateletworks.mp.</td>
</tr>
<tr>
<td>40 exp VerifyNow/or VerifyNow.tw. or VerifyNow.mp.</td>
<td>40 exp VerifyNow/or VerifyNow.tw. or VerifyNow.mp.</td>
</tr>
<tr>
<td>41 exp Impact-R/or Impact-R.tw. or Impact-R.mp.</td>
<td>41 exp Impact-R/or Impact-R.tw. or Impact-R.mp.</td>
</tr>
<tr>
<td>42 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42</td>
<td>42 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42</td>
</tr>
<tr>
<td>43 23 and 32 and 43</td>
<td>43 23 and 32 and 43</td>
</tr>
</tbody>
</table>

SIGN, Scottish Intercollegiate Guidelines Network; CHSS, Cochrane highly sensitive search strategy.
collection form and a third author (MV) resolved discrepancies. The references in selected articles were manually searched. In addition to the results obtained via a search of electronic databases, review articles on point-of-care platelet function testing were hand-searched for further references. We excluded abstracts, doctoral dissertations, letters and randomised controlled trials that were not peer-reviewed.

The ability of point-of-care platelet function tests to detect platelet dysfunction and predict postoperative bleeding in cardiac surgical patients was assessed in observational studies, and is summarised in Table 3 [17–46].

Primary outcome for meta-analysis of randomised controlled trials was postoperative blood loss at longest follow-up. Secondary outcomes were: blood loss at 6 h and 12 h postoperatively; overall mortality at longest follow-up; blood products administered; hospital and intensive care unit length of stay; and surgical re-exploration rates. We performed subgroup analyses of these outcomes comparing studies that involved the use of TEG or ROTEM only, with studies using TEG/ROTEM in combination with other point-of-care platelet function tests, as observational studies suggested that non-viscoelastic platelet function tests were able to detect platelet dysfunction and predict blood loss.

Methodological quality of observational studies was assessed using the SIGN framework and checklists [16]. Studies were classified into high-quality (+++), acceptable (+) and unacceptable (−), according to the risk of bias and methodological quality of the study. Risk of bias for randomised controlled trials was assessed independently by two investigators using the Cochrane collaboration tool [47]. Analysis of risk of bias was performed for the following domains: selection; performance; detection; attrition; reporting; and other potential sources of bias. A randomised controlled trial was considered to be at high risk of bias if one or more domains were deemed to be high-risk.

Meta-analysis of randomised controlled trials was performed using Review Manager 5.3 (Revman version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A Mantel–Haenszel model was used for dichotomous outcomes, and results are reported as risk ratios (RR), 95% CI and p values. Differences in continuous outcomes were analysed using an inverse variance method and values reported as mean difference (MD), 95% CI and p values. The p values were two-tailed and considered statistically significant if p < 0.05. Heterogeneity amongst studies was assessed using a univariate chi-squared analysis and was quantified using I² statistics. A random effect models was used if the I² value was higher than 0%. Publication bias was assessed both by visual analysis of a funnel plot and by using Egger’s regression test, using comprehensive meta-analysis version 2.2.064 [48, 49].

Results

Eight-hundred and seventy-nine potential titles were identified after entering the SIGN search filters for observational studies. Thirty-five articles were obtained for full-text assessment after screening abstracts and titles against our inclusion criteria. Thirty observational studies were included in the final qualitative assessment [17–46, 50]. Appraisal of the full-text titles produced the following exclusions: point-of-care platelet function tests no longer commercially available; non-cardiac surgery; and no predictive ability of blood loss analysed [51, 52] (Fig. 1).

The search strategy for randomised controlled trials produced 2468 potential titles. Following removal of duplicates and screening of titles and abstracts against our inclusion criteria, 23 full-text titles were selected for assessment. Nine trials [12, 53–60] (Table 4) were identified for quantitative analysis, and the following titles were excluded: no randomised controlled trials [61–65]; desmopressin trials [66, 67]; no blood transfusion management algorithm used [68]; non-cardiac surgery [69–71]; and paediatric patients [72, 73] (Fig. 1).

Thirty observational studies incorporating 3044 patients, investigating the ability of point-of-care platelet function tests for predicting postoperative bleeding in cardiac surgery, were analysed. Characteristics of studies are summarised in Table 3. The majority of studies were deemed to have acceptable methodological quality with only three considered being of high quality.

Studies using TEG as the sole point-of-care test found that TEG failed or had very limited ability to predict blood loss and transfusion requirements [17, 19, 23]. Using ROTEM was found to have a poor
Table 3 Summary of observational studies of point-of-care (POC) platelet function test.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>No of patients</th>
<th>POC assay</th>
<th>Timing of POC test</th>
<th>SIGN</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorman et al. [17]</td>
<td>60</td>
<td>TEG</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>TEG failed to predict blood loss. ( r &lt; 0.25, \ p = 0.78 )</td>
</tr>
<tr>
<td>Wahba et al. [18]</td>
<td>40</td>
<td>Hepcon Haemostasis Management System + PFA-100</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>Significant correlation between pre-operative PFA-100 and blood loss ( r = 0.41, \ p = 0.022 ). No correlation with Hepcon.</td>
</tr>
<tr>
<td>Dietrich et al. [19]</td>
<td>16</td>
<td>TEG, impedance aggregometry, PFA-100</td>
<td>Pre-, intra-, postoperative</td>
<td>(+)</td>
<td>None of the methods predicted postoperative blood loss</td>
</tr>
<tr>
<td>Lasne et al. [20]</td>
<td>146</td>
<td>PFA-100</td>
<td>Pre-operative, 5 min and 5 hours post protamine</td>
<td>(+)</td>
<td>No correlation between blood loss and pre- or postoperative PFA-100 values</td>
</tr>
<tr>
<td>Slaughter et al. [21]</td>
<td>76</td>
<td>PFA-100</td>
<td>Pre-, intra-, postoperative</td>
<td>(+)</td>
<td>Low positive predictive value (18%) for post-bypass collagen/adenosine diphosphate closure times. Negative predictive value (96%)</td>
</tr>
<tr>
<td>Forestier et al. [22]</td>
<td>45</td>
<td>PFA-100/Haemostatus</td>
<td>Postoperative</td>
<td>(+)</td>
<td>No correlation between POC testing and chest drain output</td>
</tr>
<tr>
<td>Ti et al. [23]</td>
<td>40</td>
<td>TEG</td>
<td>Ten and 60 min post-protamine</td>
<td>(+)</td>
<td>Limited predictive ability. Positive predictive value 58% at 10 min and 55% at 60 min</td>
</tr>
<tr>
<td>Fattorutto et al. [24]</td>
<td>70</td>
<td>PFA-100</td>
<td>Pre- and post-bypass</td>
<td>(+)</td>
<td>Weak correlation between pre-bypass collagen/adenaline closure time and 2 h mediastinal blood loss ( r = 0.34, \ p = 0.01 )</td>
</tr>
<tr>
<td>Cammerer et al. [25]</td>
<td>255</td>
<td>TEG + PFA-100</td>
<td>Pre-, during and post-bypass</td>
<td>(+)</td>
<td>High negative predictive value for bleeding post-bypass. ROTEZ ( \alpha )-angle 82%, PFA-100-adenosine diphosphate 76%</td>
</tr>
<tr>
<td>Lennon et al. [26]</td>
<td>50</td>
<td>Plateletworks</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>Poor correlation with postoperative blood loss ( r = 0.14, \ p = 0.34 )</td>
</tr>
<tr>
<td>Chen et al. [27]</td>
<td>90</td>
<td>PFA-100</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>Adenosine diphosphate aggregometry was a better predictor of blood loss and platelet and/or red cell transfusion than PFA-100</td>
</tr>
<tr>
<td>Gerrah et al. [28]</td>
<td>18</td>
<td>Cone and Platelet Analyzer</td>
<td>Pre- and peri-operative</td>
<td>(+)</td>
<td>Pre-operative average size and surface coverage values correlated with postoperative bleeding ( r = 0.7, \ p = 0.01 )</td>
</tr>
<tr>
<td>Ostrowsky et al. [29]</td>
<td>35</td>
<td>Plateletworks/TEG</td>
<td>Pre-operative, Post-protamine and 24 h postoperative</td>
<td>(+)</td>
<td>Plateletworks collagen tubes correlated with postoperative bleeding ( r = -0.324, \ p = 0.048 ). No correlation with TEG</td>
</tr>
<tr>
<td>Patient population</td>
<td>No of patients</td>
<td>POC assay</td>
<td>Timing of POC test</td>
<td>SIGN</td>
<td>Summary of findings</td>
</tr>
<tr>
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</tr>
<tr>
<td>Kotake et al. [30] Cardiac surgery with bypass</td>
<td>26</td>
<td>Whole blood aggregometry, Sonoclot</td>
<td>Pre-, post-bypass</td>
<td>(-)</td>
<td>No correlation between postoperative blood loss and reduced platelet aggregation</td>
</tr>
<tr>
<td>Hertfelder et al. [31] Coronary artery bypass grafting</td>
<td>49</td>
<td>PFA-100, impedance aggregometry, TEG</td>
<td>Pre-, post-bypass</td>
<td>(-)</td>
<td>PFA-100 and impedance aggregometry do not predict postoperative blood loss</td>
</tr>
<tr>
<td>Reinhofer et al. [32] Cardiac surgery with bypass</td>
<td>150</td>
<td>ROTEM</td>
<td>Pre-, post-bypass</td>
<td>(+)</td>
<td>Positive predictive value and specificity for &gt; 600 ml blood loss. EXTEM clot formation time (71%/94%) and maximum clot firmness FIBTEM (73%/95%)</td>
</tr>
<tr>
<td>Davidson et al. [33] Coronary artery bypass surgery</td>
<td>58</td>
<td>ROTEM</td>
<td>Pre- and postoperative 1–3 h</td>
<td>(+)</td>
<td>Poor positive predictive value 14.8% for predicting postoperative bleeding</td>
</tr>
<tr>
<td>Rahe-Meyer et al. [34] Cardiac surgery with bypass</td>
<td>60</td>
<td>Multiplate</td>
<td>Pre- and postoperative</td>
<td>(+)</td>
<td>Pre- and postoperative adenosine diphosphate test predicts risk of platelet transfusion (area under the curve 0.74 p = 0.001). No relationship between decreased platelet aggregation and postoperative blood loss</td>
</tr>
<tr>
<td>Velik-Salchner et al. [35] Coronary artery bypass grafting</td>
<td>70</td>
<td>Multiplate, LTA</td>
<td>Pre-operative, 15 min and 3 h post-protamine</td>
<td>(++)</td>
<td>Multiplate and LTA detect bypass-induced platelet dysfunction but they do not predict blood loss</td>
</tr>
<tr>
<td>Alstrom et al. [36] Coronary artery bypass grafting receiving dual antiplatelet therapy</td>
<td>60</td>
<td>VerifyNow/TEG 5000+, platelet mapping</td>
<td>Pre- and postoperative</td>
<td>(+)</td>
<td>Weak correlation between pre-operative platelet inhibition measured by VerifyNow and postoperative blood loss. (r = 0.29, p = 0.03). No significant correlation observed with TEG 5000</td>
</tr>
<tr>
<td>Kwak et al. [37] Off pump coronary artery bypass grafting receiving clopidogrel</td>
<td>100</td>
<td>TEG + platelet mapping</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>Association between 70% platelet inhibition and postoperative transfusion requirements (AUC = 0.77, 95% CI 0.67–0.87, p &lt; 0.001)</td>
</tr>
<tr>
<td>Preisman et al. [38] Coronary artery bypass grafting receiving dual antiplatelet therapy</td>
<td>59</td>
<td>TEG + platelet mapping</td>
<td>Pre-operative</td>
<td>(++)</td>
<td>Only maximum amplitude adenosine diphosphate predicts excessive postoperative blood loss. Sensitivity 78%, specificity 84%</td>
</tr>
<tr>
<td>Patient population</td>
<td>No of patients</td>
<td>POC assay</td>
<td>Timing of POC test</td>
<td>SIGN</td>
<td>Summary of findings</td>
</tr>
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</tr>
<tr>
<td>Reece et al. [39] Coronary artery bypass grafting</td>
<td>44</td>
<td>Multiplate</td>
<td>Pre-/post-bypass</td>
<td>(+)</td>
<td>Patients requiring blood transfusion had significantly reduced platelet aggregation compared with non-transfused patients. Adenosine diphosphate (18U vs 29U, p = 0.01) and thrombin receptor agonist peptide-6 (65U vs 88U, p = 0.01)</td>
</tr>
<tr>
<td>Ranucci et al. [40] Cardiac surgery exposed to thienopyridines</td>
<td>87</td>
<td>Multiplate</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>Multiplate adenosine diphosphate (cut-off value 31U) predicts postoperative bleeding risk. Sensitivity 72%, specificity 66%</td>
</tr>
<tr>
<td>Dalen et al. [41] Coronary artery bypass grafting receiving dual antiplatelet therapy</td>
<td>50</td>
<td>Plateletworks</td>
<td>Pre-operative</td>
<td>(+)</td>
<td>Correlation between adenosine diphosphate-induced aggregation and postoperative blood loss (r = -0.83, p &lt; 0.01)</td>
</tr>
<tr>
<td>Lee et al. [42] Cardiac surgery with bypass</td>
<td>321</td>
<td>ROTEM</td>
<td>Pre- and postoperative</td>
<td>(+)</td>
<td>ROTEM did not improve performance of statistical model predicting blood loss Abnormal adenosine diphosphate test and thrombin receptor agonist peptide test significantly predict postoperative blood transfusion requirements</td>
</tr>
<tr>
<td>Schimmer et al. [43] Mixed cardiac surgery with bypass</td>
<td>223</td>
<td>Multiplate</td>
<td>Pre- and postoperative</td>
<td>(+)</td>
<td>Abnormal adenosine diphosphate test and thrombin receptor agonist peptide test significantly predict postoperative blood transfusion requirements</td>
</tr>
<tr>
<td>Petricevic et al. [44] Coronary artery bypass grafting</td>
<td>211</td>
<td>Multiplate</td>
<td>Pre-op, bypass, post-protamine</td>
<td>(+)</td>
<td>Multiple values correlated with 24-h chest tube output. Arachidonic acid &lt; 20 and adenosine diphosphate &lt; 73 were ‘bleeder’ determinants Functional platelet count increase associated with high blood loss. Rewarming RR 0.89 95% CI 0.82–0.97, p 0.006. Post-protamine RR 0.87, 95% CI 0.78–0.98, p = 0.02</td>
</tr>
<tr>
<td>Orlov et al. [45] Cardiac surgery with cardiopulmonary bypass</td>
<td>100</td>
<td>Plateletworks</td>
<td>Pre-bypass, postoperative</td>
<td>(+++)</td>
<td>Functional platelet count increase associated with high blood loss. Rewarming RR 0.89 95% CI 0.82–0.97, p 0.006. Post-protamine RR 0.87, 95% CI 0.78–0.98, p = 0.02</td>
</tr>
<tr>
<td>Ranucci et al. [46] Cardiac surgery exposed to P2Y2 receptor inhibitors</td>
<td>435</td>
<td>Multiplate</td>
<td>Pre-operative</td>
<td>(+++)</td>
<td>Adenosine diphosphate test and thrombin receptor agonist peptide-6 test significantly associated with postoperative bleeding (p = 0.001)</td>
</tr>
</tbody>
</table>

SIGN, Scottish Intercollegiate Guidelines Network; PFA-100, Platelet Function Analyser-100; LTA; light transmission aggregometry.
positive predictive value for predicting blood loss in patients undergoing primary coronary artery re-vascularisation [33]. The addition of ROTEM did not improve the performance of a model for prediction of postoperative chest drain output in patients undergoing cardiac surgery with bypass [42]. The performance of ROTEM was better in a different study of patients undergoing cardiac surgery with bypass, demonstrating good positive predictive values and specificity for predicting postoperative blood loss in both EXTEM and FIBTEM assays [32].

A study including patients undergoing cardiac surgery with bypass found the Sonoclot analyser to be inferior to whole blood aggregometry for detection of platelet dysfunction post-bypass, and no correlation was found between chest drain output and defects in haemostasis detected by Sonoclot [30].

Thromboelastography platelet mapping was predictive of excessive blood loss in patients undergoing coronary artery bypass grafting who were taking concurrent aspirin and clopidogrel therapy [38]. Another study investigating patients who received clopidogrel within five days of coronary artery bypass grafting surgery without bypass found that a cut-off value of 70% platelet inhibitory response to clopidogrel predicted increased postoperative blood loss and transfusion requirements [37].

Pre-operative abnormalities in platelet function detected by Impact Cone and Plate(let) Analyzer, in patients undergoing off-pump coronary artery bypass grafting, were found to be an independent risk factor for excessive postoperative bleeding [28].

The ability of the Platelet Function Analyser-100 (PFA-100) to predict postoperative blood loss has been tested in several studies with mixed results. A study in patients undergoing cardiac surgery with bypass found a significant correlation between pre-operative PFA-100 values and total blood loss.
However, great variability in individual results was observed [18]. Conversely, pre- and postoperative values of PFA-100 were found to have no correlation with postoperative blood loss in two other studies of patients undergoing cardiac surgery with bypass [19, 22]. Slaughter et al. found PFA-100 post-bypass collagen/adenosine diphosphate closure times to have a good negative predictive value but a very poor positive predictive value for prediction of bleeding in coronary artery bypass grafting surgery patients [21]. Low positive predictive value and sensitivity were also found when the PFA-100 was used to predict bleeding in a group of patients undergoing mixed cardiac surgery with cardiopulmonary bypass [24]. Chen et al. used the PFA-100 together with aggregometry and conventional coagulation function tests as part of a transfusion algorithm aimed at minimising transfusions in patients undergoing coronary artery bypass grafting with recent exposure to clopidogrel. While PFA-100 was found not to be a good predictor of blood loss or transfusion requirements, it was also inferior to aggregometry [27]. Platelet Function Analyser-100 values failed to predict postoperative blood loss in patients with ‘low risk’ of bleeding following coronary artery bypass grafting. However, the PFA-100 demonstrated high specificity for detecting adequate platelet function post-bypass [31]. In a study comparing the ability of modified thromboelastography (ROTEM®, Pentapharm, Munich, Germany) and PFA-100 to predict postoperative blood loss, post-bypass modified TEG was found to be a better predictor of blood loss than PFA-100. However, the addition of the PFA-100 increased the predictive value of modified TEG, with the combined test demonstrating a high negative predictive value [25].

VerifyNow, TEG platelet mapping and flow cytometry of vasodilator-stimulated phosphoprotein phosphorylation assay were used in a study to assess the correlation between platelet inhibition and postoperative blood loss in patients with dual antiplatelet treatment scheduled for coronary artery bypass grafting surgery. A weak correlation was found between pre-operative platelet inhibition measured by VerifyNow P2Y12 and postoperative blood loss [36].

Table 4 Characteristics of randomised controlled trials included in the quantitative analysis.

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Type of procedure</th>
<th>Point-of-care test</th>
<th>Longest reported blood loss</th>
<th>Duration of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shore-Lesserson et al. [12]</td>
<td>105</td>
<td>High-risk (CABG + valvular, valve replacement single or multiple, thoracic aorta, redo operations)</td>
<td>TEG</td>
<td>24 h</td>
</tr>
<tr>
<td>Royston et al. [57]</td>
<td>60</td>
<td>High-risk (heart transplant, Ross procedure, multiple valve + CABG)</td>
<td>TEG</td>
<td>12 h</td>
</tr>
<tr>
<td>Nuttall et al. [56]</td>
<td>92</td>
<td>Mixed CABG + valvular heart surgery requiring bypass</td>
<td>TEG + Coaguchek Plus and Coulter-MD II</td>
<td>24 h</td>
</tr>
<tr>
<td>Avidan et al. [54]</td>
<td>102</td>
<td>Elective CABG</td>
<td>TEG + PFA-100</td>
<td>24 h</td>
</tr>
<tr>
<td>Ak et al. [53]</td>
<td>224</td>
<td>Elective CABG</td>
<td>TEG</td>
<td>12 h</td>
</tr>
<tr>
<td>Westbrook et al. [59]</td>
<td>69</td>
<td>Mixed cardiac procedures</td>
<td>TEG + platelet mapping</td>
<td>12 h</td>
</tr>
<tr>
<td>Giarduskas et al. [55]</td>
<td>56</td>
<td>High-risk aortic surgery with deep hypothermic circulatory arrest</td>
<td>ROTEM</td>
<td>24 h</td>
</tr>
<tr>
<td>Weber et al. [58]</td>
<td>100</td>
<td>Complex surgery (CABG + valve, ≥ 2 valve, aortic surgery, redo procedures)</td>
<td>ROTEM + Multiplate</td>
<td>24 h</td>
</tr>
<tr>
<td>Agarwal et al. [60]</td>
<td>249</td>
<td>CABG (including emergency and urgent procedures)</td>
<td>TEG + Multiplate and TEG + platelet mapping</td>
<td>12 h</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass grafting; PFA-100, Platelet Function Analyser-100.
Pre-operative measurement of platelet aggregation with Plateletworks, compared with light transmission aggregometry, was found to correlate poorly with post-operative mediastinal blood loss in a prospective study of patients undergoing elective coronary artery bypass grafting or valve replacement [26]. However, a different study found a correlation between chest drain output and Plateletworks collagen tube values [29]. A prospective study of patients on antiplatelet therapy undergoing coronary artery bypass grafting surgery, 66% of whom were receiving clopidogrel, observed a significant correlation between Plateletworks adenosine

![Figure 2](image1.png)

**Figure 2** Effect of point-of-care platelet function test-guided transfusion algorithm vs control group on bleeding after cardiac surgery at longest follow-up, grouped by studies using TEG/ROTEM alone and TEG/ROTEM plus other point-of-care platelet function test.

![Figure 3](image2.png)

**Figure 3** Effect of point-of-care platelet function test-guided transfusion algorithm vs control group on proportion of patients receiving red cells, grouped by studies using TEG/ROTEM alone and TEG/ROTEM plus other point-of-care platelet function test.
diphosphate-induced platelet aggregation values and postoperative blood loss [41]. In a recent prospective observational study, Orlov et al. used Plateletworks to measure platelet dysfunction in 100 patients undergoing cardiac surgery with bypass, and showed an independent association with high blood loss both during rewarming and after administration of protamine [45].

Multiple electrode platelet aggregometry using Multiplate was used by Rahe-Meyer et al. to demonstrate that pre- and postoperative adenosine diphosphate tests identified patients at higher risk of requiring a postoperative platelet transfusion. However, there was no correlation between Multiplate values and postoperative blood loss [34]. Multiplate was compared with light transmission aggregometry in studies of patients scheduled for coronary artery bypass grafting surgery. Both Multiplate and light transmission aggregometry were able to detect platelet dysfunction induced by bypass. However, neither Multiplate nor light transmission aggregometry were found to correlate with postoperative blood loss [35, 39]. Using multivariable linear regression analysis in a study of patients exposed to thienopiridines, Ranucci et al. found that the Multiplate adenosine diphosphate test was independently associated with postoperative bleeding. The best cut-off value for the adenosine diphosphate test was determined to be 31U [40]. The same author studied the postoperative bleeding predictive ability of Multiplate in a retrospective cohort of patients undergoing cardiac surgery while receiving P$_2$Y$_{12}$ receptor antiplatelet agents. High-negative and low-positive predictive values were demonstrated in both the adenosine diphosphate test and thrombin receptor agonist peptide-6 test [46]. Schimmer et al. also found a correlation between abnormal adenosine diphosphate and thrombin receptor agonist peptide-6 test and requirement for blood products [43]. A significant correlation between pre-operative arachidonic acid test and adenosine diphosphate test values and postoperative chest tube output was found in a study of patients undergoing coronary artery bypass grafting surgery [44].

Quantitative analysis of platelet function testing as part of blood transfusion management algorithm

The nine randomised controlled trials chosen for quantitative analysis include a total of 1057 patients. Publication dates ranged from 1999 to 2014. Five studies [12, 53, 55–57] used viscoelastic methods only (TEG/ROTEM) to guide the transfusion algorithm, and four studies [54, 58–60] used a combination of TEG/ROTEM and other point-of-care platelet function tests. Six studies [12, 55–57, 59, 60] applied the transfusion algorithm during the peri-operative period only, while three others [53, 54, 58] extended the use of the transfusion algorithm to up to 24 h postoperatively. Five studies contained at least one high risk of bias domain, and
Therefore were deemed at overall high risk of bias [54–56, 58, 60]. Only one study was judged to be at low risk of bias in all domains [12]. The remaining studies contained at least one unclear risk of bias domain [53, 57, 59].

All nine randomised controlled trials reported postoperative bleeding outcomes [12, 53–60]. We analysed postoperative bleeding at 6 h, 12 h and at longest follow-up time. There was a statistically significant reduction in the amount of bleeding at all three time points, favouring the patients in whom platelet function was analysed via point-of-care methods. Subgroup analysis according to the type of point-of-care test at the longest follow-up time demonstrated a larger effect size for bleeding reduction in trials using TEG/ROTEM in combination with other point-of-care platelet function tests (MD −111.8 ml (95% CI −174.5 to −49.1 ml), p = 0.0005), compared with TEG/ROTEM alone (MD −90.6 ml (95% CI −166.1 to −15.0 ml), p = 0.02) (Fig. 2).

Point-of-care platelet function testing was associated with a statistically significant reduction in the proportion of patients receiving packed red blood cells (RR 0.86 (95% CI 0.78–0.94), p = 0.001) and fresh frozen plasma (RR 0.42 (95% CI 0.30–0.59), p < 0.00001). There was no significant difference in the rate of platelet transfusions (RR 0.81 (95% CI 0.55–1.18), p = 0.27). Subgroup analysis demonstrated that the combination of TEG/ROTEM and other platelet function tests (RR 0.84 (95% CI 0.73–0.97), p = 0.02) was associated with a statistically significant reduction in the proportion of patients receiving packed red blood cells compared with TEG/ROTEM alone (RR 0.88 (95% CI 0.75–1.03), p = 0.10) (Fig. 3). Conversely, the proportion of patients receiving platelets in the TEG/ROTEM-only subgroup (RR 0.59 (95% CI 0.44–0.80), p = 0.007) was significantly lower than that of patients in whom a point-of-care platelet function test was performed in addition to TEG/ROTEM (RR 1.16 (95% CI 0.73–1.85), p = 0.52).

Six studies reported mortality outcomes [12, 53, 55, 57, 58, 60]. There was no overall mortality benefit at longest follow-up favouring a point-of-care platelet function testing-guided transfusion algorithm when compared with a control group (RR 0.66 (95% CI 0.31–1.39), p = 0.27).

Surgical re-exploration rates were reported by all nine studies [12, 53–60]. Point-of-care platelet function testing did not confer any benefit in terms of proportion of patients requiring surgical re-exploration compared with the control group (RR 0.68 (95% CI 0.36–1.26), p = 0.22). Subgroup analysis according to type of point-of-care platelet function test also failed to show any benefit in surgical re-exploration rates over the control group.

Intensive care unit and hospital length of stay was reported by four trials [53, 55, 58, 59]. Point-of-care platelet function testing did not confer statistically significant benefit in terms of hospital (MD −2.1 days (95% CI −4.3 to 0.2 days), p = 0.08) or intensive care unit length of stay (MD −2.1 days (95% CI −4.3 to 0.2 days), p = 0.08).

Visual analysis of the funnel plot and results of the Egger’s regression test performed for primary outcome of blood loss at longest follow-up did not suggest the presence of publication bias (Fig. 4).

Discussion
This systematic review and meta-analysis has found that point-of-care platelet function tests can indeed detect platelet dysfunction in the peri-operative setting in cardiac surgical patients. In addition, their incorporation into a blood transfusion management algorithm is associated with reduced blood loss and transfusion requirements. The systematic review of observational studies revealed a wide range of platelet function tests available for use in the peri-operative management of cardiac surgical patients. The point-of-care platelet function tests reviewed differ greatly in their assay principle and the way their performance and clinical data were obtained and analysed. Comparison of clinical outcomes is thus limited by heterogeneous methodologies and poor agreement between tests [74]. Therefore, it is difficult to establish the superiority of one method over the other objectively for risk stratification of bleeding in the cardiac surgical patient.

Viscoelastic methods (TEG and ROTEM) alone appear to have limited ability for prediction of blood loss and transfusion requirements after cardiac surgery. This limitation is particularly apparent in patients receiving antiplatelet medications, as conventional
viscoelastic methods are unable to detect the effect of antiplatelet medications on platelet function [75]. Modifications of TEG, such as platelet mapping, attempt to overcome these limitations, demonstrating improved predictive ability for blood loss and transfusion requirements in patients on antiplatelet therapy undergoing coronary artery bypass grafting with or without the use of bypass.

Platelet function tests based on the principle of aggregometry, incorporating the use of a platelet agonist, appear to be particularly useful for detection of platelet dysfunction induced by the use of antiplatelet medications and bypass. Multiple electrode aggregometry exhibits high negative predictive values, which, when incorporated into a transfusion algorithm, can suggest a surgical cause of bleeding when multiple electrode aggregometry values are normal. Disappointingly, positive predictive values remain very low.

The quantitative analysis of randomised control trials revealed that the use of point-of-care platelet function tests as part of a blood transfusion algorithm is associated with a reduction in our primary outcome of postoperative blood loss. The meta-analysis demonstrated an overall statistically significant reduction in blood loss in patients in whom platelet function was analysed with the use of point-of-care testing. The combination of viscoelastic and other platelet function testing methods (PFA-100, multiple electrode aggregometry, platelet mapping) achieved a larger effect size in terms of blood loss reduction compared with viscoelastic methods alone.

Transfusion of allogeneic blood products has been associated with significant morbidity and an increased mortality [76, 77]. Reduction in transfusion requirements is therefore highly desirable, and this has been incorporated within international guidelines for the management of severe peri-operative bleeding [78,79]. The proportion of patients receiving blood and fresh frozen plasma in our study was significantly lower when point-of-care testing was used to guide transfusion. This analysis was, however, limited by the fact that only six studies reported these data.

Subgroup analysis based on the type of point-of-care test revealed that the reduction in the proportion of patients transfused red blood cells was greater in those who were tested with point-of-care platelet function tests in combination with TEG/ROTEM, compared with those patients in whom platelet function was analysed by TEG/ROTEM alone. Interestingly, the opposite was true for platelet transfusion, with a significant reduction in transfusion in the subgroup of studies that used TEG/ROTEM alone. This may be attributed partially to the variation in the transfusion triggers incorporated within different algorithms used in the trials we studied. It can also be explained by a possible higher detection rate of peri-operative platelet dysfunction in studies using a combination of TEG/ROTEM and a point-of-care platelet function test. Higher detection of platelet dysfunction may have led to increased platelet transfusion in this subgroup.

The reduction in blood loss and blood transfusion rates found in our analysis did not have an impact on mortality. We chose mortality as a secondary outcome as none of the included trials were powered to detect a difference in peri-operative mortality. Powering of trials including cardiac surgery patients is notoriously difficult, owing to the low rates of postoperative mortality experienced by this group of patients. Additionally, the follow-up period was possibly too short for any benefits of reduced blood loss and transfusion requirements to surface.

Our systematic review and meta-analysis focused on cardiac surgical patients with study outcomes relevant to this patient population. Previous reviews, however, have included non-cardiac patient populations [80]. We appraised both the ability of individual point-of-care platelet function tests for detecting platelet dysfunction and predicting postoperative bleeding, and the impact of their incorporation into transfusion algorithms. We acknowledge several limitations of our study. All the included trials are single-centre, with a limited number of patients. Data were extracted from studies rather than using data from individual patients, and the lack of data for some of the outcomes limited further the amount of patients available for subgroup analyses. Most of the trials were deemed to have a significant risk of bias. None of the included studies in the meta-analysis were powered to detect differences in mortality, which limits the interpretability of our mortality analysis. Finally, data regarding volume of blood products were incomplete and inconsistently
reported, and definitions of blood loss and transfusion triggers also varied between studies, hence the proportion of transfused patients in these studies as an indicator of blood transfusion requirements should be interpreted with caution.

In summary, evidence suggests that point-of-care platelet function tests have not consistently been shown to predict the risk of bleeding in the cardiac surgical patient. The multifactorial nature of postoperative bleeding in cardiac surgery may necessitate a need for the use of combinations of point-of-care tests. The incorporation of point-of-care platelet function tests into blood transfusion management algorithms is associated with a reduction in blood loss and transfusion requirements. The use of a combination of viscoelastic methods and platelet agonist assays achieved the greatest reduction in blood loss and blood transfusion requirements. We suggest that future randomised studies should incorporate accepted thresholds to identify peri-operative platelet dysfunction. Additionally, agreement on the proposed definition of massive blood loss is required to define better the role of point-of-care platelet function testing in cardiac surgical patients and conclude on the utility and cost-effectiveness of the generalised application of this strategy.

Competing interests
No external funding and no competing interests declared.

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54. Avidan MS, Alcock EL, Da Fonseca J, et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of


Review Article

Peri-operative anaesthetic myocardial preconditioning and protection – cellular mechanisms and clinical relevance in cardiac anaesthesia

G. Kunst¹ and A. A. Klein²

¹ Consultant, Department of Anaesthetics, King’s College Hospital NHS Foundation Trust, London, UK
² Consultant, Department of Anaesthesia and Intensive Care, Papworth Hospital, Cambridge, UK

Summary
Preconditioning has been shown to reduce myocardial damage caused by ischaemia–reperfusion injury peri-operatively. Volatile anaesthetic agents have the potential to provide myocardial protection by anaesthetic preconditioning and, in addition, they also mediate renal and cerebral protection. A number of proof-of-concept trials have confirmed that the experimental evidence can be translated into clinical practice with regard to postoperative markers of myocardial injury; however, this effect has not been ubiquitous. The clinical trials published to date have also been too small to investigate clinical outcome and mortality. Data from recent meta-analyses in cardiac anaesthesia are also not conclusive regarding intra-operative volatile anaesthesia. These inconclusive clinical results have led to great variability currently in the type of anaesthetic agent used during cardiac surgery. This review summarises experimentally proposed mechanisms of anaesthetic preconditioning, and assesses randomised controlled clinical trials in cardiac anaesthesia that have been aimed at translating experimental results into the clinical setting.

Correspondence to: G. Kunst
Email: gudrun.kunst@kcl.ac.uk
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Introduction
In the UK, about 34 760 adult cardiac surgical procedures were carried out in 2011, including 17 070 coronary artery bypass graft (CABG) procedures, and 17 690 valvular repairs or replacements, many of which also required concurrent CABG. Overall mortality was 2.97% (see http://bluebook.scts.org). The population requiring surgery is older than before, with more patients presenting with multiple co-morbidities, including obesity, diabetes, chronic renal failure, and peripheral vascular disease [1], which increase the risk of postoperative complications [2, 3].

Extensive evidence from experimental studies has shown that volatile anaesthetics protect the heart from ischaemic myocardial injury in animal models, and that they also have the potential to provide renal and cerebral protection. Clinical proof-of-concept studies and meta-analyses based on small clinical studies have supported these experimental results, but inconclusively. However, whereas surgical myocardial protec-
tion and cardioplegic strategies are routinely employed to improve organ protection during cardiac surgery [4], management of general anaesthesia has remained basically unchanged over the last 20 years, with some anaesthetists using intravenous propofol only for maintenance, and others volatile anaesthetics alone, or volatile anaesthetics plus propofol in combination. This variation in clinical practice stems from a lack of evidence as to which type of anaesthetic is superior, and it demonstrates the potential for more protective anaesthesia if best practice could be conclusively demonstrated.

This article will provide a review of the current literature on mechanisms of anaesthetic protection by preconditioning in cardiac anaesthesia, and an overview of clinical trials assessing potentially protective anaesthetic regimens.

Methods
We performed a comprehensive literature review using MEDLINE and EMBASE, accessed via the National Health Service Healthcare Databases Advanced Search (HDAS) link. Articles from 2004 until 2014 were accessed with the following terms: volatile anaesthetics OR inhalation anaesthetics OR isoflurane OR sevoflurane AND myocardial protection OR preconditioning OR myocardial reperfusion injury OR cardiac protection OR myocardial ischaemia. Only studies written in the English language were considered. A total of 886 studies were identified, and based on their relevance to cellular mechanisms and clinical applications of myocardial conditioning by volatile anaesthetics in cardiac anaesthesia, we selected 97 for inclusion in this review.

Experimental evidence
Myocardial preconditioning describes the experimentally observed phenomenon that an intervention or a trigger, before a prolonged ischaemic insult to the myocardium, results in a reduction in the infarcted area. The preconditioning trigger can either be an ischaemic intervention or a pharmacological stimulus, such as volatile anaesthetics. Ischaemic preconditioning was first described in 1986 by Murry et al., who demonstrated in a dog model that four short episodes of 5 min of myocardial ischaemia, followed by 5 min of reperfusion, before a prolonged ischaemic period of 40 min, produced a ‘memory’ effect in the myocytes, that led to a 75% reduction in infarct size [5]. The pathophysiology of this phenomenon has subsequently been well described [6].

In addition to an immediate window of protection 1–2 h after the preconditioning stimulus, a delayed phase of protection from preconditioning, that persists for 2–3 days, has been described as late preconditioning [7]. Furthermore, the myocardium can also be protected by a stimulus that is applied after ischaemia–reperfusion injury [8]; this phenomenon is called post-conditioning, and has been reviewed elsewhere in this journal [9]. If the ischaemic stimulus for myocardial protection is applied at a distant organ or tissue such as a limb, the technique is called remote preconditioning, and is included in this thematic series [10].

The first experimental evidence of myocardial protection from ischaemia–reperfusion injury by volatile anaesthetics was obtained using halothane in a dog model, in the 1970s [11]. This protective effect was subsequently confirmed in the 1980s using halothane [12], enflurane [13] and isoflurane [14]. Volatile anaesthetic agents, however, have also been shown to induce the harmful phenomenon of ‘coronary steal’ in experimental models [15]. This describes the phenomenon where by vasodilation results in the shunting of blood flow away from the ischaemic myocardium, which then worsens myocardial ischaemia. Conflicting results in subsequent studies meant that by the early 1990s, the proposed phenomenon of coronary steal had been largely refuted [16]. More than 10 years after the first experimental description of preconditioning by an ischaemic trigger, preconditioning by an anaesthetic stimulus was described in 1997 by three independent groups, in rabbit models [17, 18] and in a dog model [19].

Two main intracellular signal transduction pathways, directing cardioprotection from cell surface receptors to convergent targets in the mitochondria, have been proposed as models to explain preconditioning: the reperfusion injury salvage kinases (RISK) pathway [20] via G-protein-coupled cell surface receptors; and the survivor-activating factor enhancement (SAFE) pathway [21]. The latter operates mainly through the tumour necrosis factor (TNF)-alpha receptor and signal transducer, and activator of transcription
In the mitochondria, protection is triggered by inhibition of the opening of the mitochondrial permeability transition pore (mPTP) [22], and by activating the opening of the ATP-dependent potassium (KATP) channel [23]. Mitochondria supply ATP to cardiomyocytes, but they have also recently been identified as activators of cell death pathways; cell death can be inhibited by mitochondrial autophagy and pro-survival pathways, and mPTP plays an important role in modulating the balance of pro-survival over cell death pathways [24]. A recent study demonstrated that drug-induced activation of autophagy in rabbits before ischaemia, or during reperfusion, protected the myocardium from ischaemia–reperfusion injury [25].

The intracellular signal transduction proteins and molecules that are candidates for interactions with volatile anaesthetic agents are listed in Table 1 [26–57]. These interactions have been demonstrated in a number of experimental models in animals, in isolated perfused hearts (the so-called Langendorff heart apparatus), and also in human atrial myocardium and human embryonic stem cells. This body of evidence demonstrates that all three volatile anaesthetics currently in use (isoflurane, sevoflurane and desflurane), have the ability to protect myocardium not only in vivo in mammals, but also in vitro in human and animal myocardial tissue and cells.

In addition to protection in cardiac myocytes, direct endothelial protection by volatile anaesthetic agents has also been described, which may be of relevance for myocardial protection (Table 2 [58–64]).

It has been recently demonstrated that isoflurane (and also morphine) provides endothelial protection by preventing TNF-alpha-induced adhesion molecule expression in human umbilical vein endothelial cells [60], and more recently in volunteers anaesthetised with sevoflurane [61]. More detailed interactions and the individual signal transduction pathways of anaesthetic conditioning have been reviewed previously [8, 65–70].

Experimental investigations suggest that the ability of volatile anaesthetics to protect the myocardium by anaesthetic preconditioning significantly increases from isoflurane to sevoflurane to desflurane [71]. Not only the type of volatile anaesthetic, but also the duration and frequency of exposure to the volatile anaesthetic before ischaemia, have been shown to be of potential relevance in in-vitro experiments. In guinea pig hearts, exposure to sevoflurane for two periods of 5 min before a period of ischaemia, with a 5-min washout period in-between, showed improved protection compared with one single 15-min exposure to sevoflurane before ischaemia [72].

In addition to volatile anaesthetic agents, other drugs used in the peri-operative period may have an effect on anaesthetic preconditioning. In-vivo experiments in rabbits suggest that propofol may block preconditioning attributed to desflurane [73]. On the other hand, propofol may protect rat myocardium from ischaemia–reperfusion injury by up-regulation of nitric oxide synthase activity [74]. Interestingly, the combination of isoflurane preconditioning before cardiopulmonary bypass (CPB), and propofol during and after CPB, provided significantly improved myocardial protection in a dog model, compared with either agent alone [75]. Experimental data show that morphine enhances pharmacological preconditioning of isoflurane [76]. In addition, opioid infusions of remifentanil and sufentanil have been shown to protect human right atrial muscle from ischaemia–reperfusion injury in vitro [77]. Sulfonylureas are KATP channel blockers, and prevent myocardial preconditioning [78], and the beta-blocker metoprolol has been shown to block desflurane-induced preconditioning [79].

Experimental data have also suggested that co-morbidities such as diabetes/hyperglycaemia and obesity may attenuate the protective effects of volatile anaesthetics. Hyperglycaemia prevents isoflurane preconditioning in dogs in vivo, and also in human cardiomyocytes derived from induced pluripotent stem cells [80]. Sevoflurane-induced preconditioning was prevented by obesity [81] and reduced in isolated hypercholesterolaemic hearts from rats exposed to a high cholesterol diet, and in hypertrophied rat hearts, induced by transverse aortic constriction [82, 83]. Advanced age reduces myocardial protection provided by volatile anaesthetic agents, as demonstrated in guinea pig hearts [84] and also in human atrial cardiomyocytes [85].

The experimental evidence supports several hypotheses of molecular interactions by volatile anaesthetics resulting in potential myocardial protection;
Table 1 Effects of volatile anaesthetic preconditioning on signal transduction proteins in cardiomyocytes.

<table>
<thead>
<tr>
<th>Myocyte</th>
<th>Protein</th>
<th>Experimental model</th>
<th>Volatile anaesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytosol PKC</td>
<td>PKC-delta activation preceded by ROS release</td>
<td>Rat myocardial trabeculae in vitro</td>
<td>Isoflurane [26]</td>
</tr>
<tr>
<td></td>
<td>PKC-delta and PKC-epsilon translocation, and Src PTK activation</td>
<td>Rat heart in vivo</td>
<td>Isoflurane [27]</td>
</tr>
<tr>
<td></td>
<td>PKC-epsilon and ERK1/2</td>
<td>Rat heart in vivo</td>
<td>Desflurane [28]</td>
</tr>
<tr>
<td></td>
<td>PKC-delta activation depends on modulation of Na+/Ca2+ exchanger</td>
<td>Right ventricular rat trabeculae in vitro</td>
<td>Sevoflurane [29]</td>
</tr>
<tr>
<td></td>
<td>PKC-epsilon activation</td>
<td>Rat cardiomyocytes</td>
<td>Isoflurane [30]</td>
</tr>
<tr>
<td></td>
<td>PKC-alpha and -epsilon translocation and activation</td>
<td>Guinea pig hearts in vitro</td>
<td>Sevoflurane [31]</td>
</tr>
<tr>
<td></td>
<td>PKC-delta, and -alpha activation, phosphorylation of Akt and GSK-3 beta, ERK1/2 activation</td>
<td>Human right atrial appendages, 3 cycles of preconditioning in vivo</td>
<td>Isoflurane and sevoflurane [32]</td>
</tr>
<tr>
<td>ERK1/2</td>
<td>ERK1/2 triggered HIF-1alpha and VEGF up-regulation</td>
<td>Rat hearts in vivo</td>
<td>Isoflurane [33]</td>
</tr>
<tr>
<td>PI3K/Akt</td>
<td>PI3K/Akt activation and attenuation of myocardial apoptosis</td>
<td>Rabbit heart in vivo</td>
<td>Isoflurane [34]</td>
</tr>
<tr>
<td>S'AMP PK</td>
<td>S'AMP-activated protein kinase, ROS induced</td>
<td>Rat hearts in vitro</td>
<td>Sevoflurane [35]</td>
</tr>
<tr>
<td>Cyclooxygenase</td>
<td>Cyclooxygenase-2: critical mediator</td>
<td>Dog hearts in vitro</td>
<td>Isoflurane [36]</td>
</tr>
<tr>
<td>Caveolin-3</td>
<td>Caveolin-3 expression and caveoleae are critical mediators</td>
<td>Caveolin-3-knockout mice, hearts in vivo and cardiomyocytes in vitro</td>
<td>Isoflurane [37]</td>
</tr>
<tr>
<td></td>
<td>Caveolin-3-dependent cyclooxygenase-2 inhibition</td>
<td>Caveolin-3-knockout mice in vivo</td>
<td>Sevoflurane [38]</td>
</tr>
<tr>
<td>NO</td>
<td>NO release mediated protection</td>
<td>Rabbit hearts in vivo</td>
<td>Desflurane [39]</td>
</tr>
<tr>
<td>NOS</td>
<td>Activation of NOS</td>
<td>Rabbit hearts in vivo</td>
<td>Desflurane [40]</td>
</tr>
<tr>
<td>ROS</td>
<td>ROS generation from electron transport chain complex III</td>
<td>Rabbit hearts in vivo</td>
<td>Isoflurane [41]</td>
</tr>
<tr>
<td></td>
<td>ROS mediates attenuation of mitochondrial respiration complex I</td>
<td>Guinea pig myocardial mitochondria</td>
<td>Sevoflurane [42]</td>
</tr>
<tr>
<td></td>
<td>ROS generated PKC-alpha activation</td>
<td>Rat right ventricular trabeculae in vitro</td>
<td>Sevoflurane [43]</td>
</tr>
<tr>
<td>Mitochondrion mPTP</td>
<td>Improved resistance of mPTP to Ca2+ induced opening</td>
<td>Human atrial trabeculae</td>
<td>Sevoflurane and desflurane [44]</td>
</tr>
<tr>
<td></td>
<td>mKATP activation induced mPTP inhibition</td>
<td>Adult ventricular rat cardiomyocytes</td>
<td>Sevoflurane and desflurane [45]</td>
</tr>
<tr>
<td></td>
<td>Delayed opening of mPTP</td>
<td>Cardiomyocytes from hESC</td>
<td>Sevoflurane [46]</td>
</tr>
<tr>
<td></td>
<td>O-GlcNAc modification of mitochondrial voltage-dependent anion channel inhibits opening of mPTP</td>
<td>Rat cardiomyocytes</td>
<td>Isoflurane [30]</td>
</tr>
<tr>
<td></td>
<td>Activation of mKATP channels</td>
<td>Rabbit hearts in vivo</td>
<td>Isoflurane [49]</td>
</tr>
<tr>
<td>BKCa</td>
<td>Activation of human cardiac mKATP channels</td>
<td>Lipid bilayers</td>
<td>Isoflurane [51]</td>
</tr>
<tr>
<td></td>
<td>Activation of BKCa (PKA mediated)</td>
<td>Mouse hearts in vivo</td>
<td>Desflurane [52]</td>
</tr>
</tbody>
</table>
However, the limitations of the experimental set-ups do need to be considered. For example, in-vivo animal models may experience variable collateral blood flow, which can potentially interfere with the infarct size, and is difficult to control for. This issue is avoided in tissue models such as human atrial trabeculae, and also in single cardiomyocytes. However, human atrial muscle has different subtypes of contractile and metabolic proteins compared with ventricular myocytes, which may alter the response to ischaemia of atrial muscle cells compared with those of ventricular myocytes. Isolated adult cardiomyocytes lose important physiological aspects of myocardial ischaemia–reperfusion injury. In the whole heart, hyper-contraction of myocytes, causing sarcolemmal and cytoskeletal disruption, results in massive enzyme release, influx of calcium ions into broken cells, and interstitial oedema during reperfusion, after an ischaemic insult. Both hyper-contraction and interstitial oedema do not occur during reperfusion in isolated adult cardiomyocytes [86].

On the other hand, embryonic cells (including human embryonic stem cell-derived cardiomyocytes), which have the advantage of a non-animal model, and

<table>
<thead>
<tr>
<th>Myocyte</th>
<th>Protein</th>
<th>Experimental model</th>
<th>Volatile anaesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell nucleus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF-kappa B</td>
<td>Attenuation of NF-kappa B activation at the end of I-R</td>
<td>Rat hearts in vitro</td>
<td>Sevoflurane [53]</td>
</tr>
<tr>
<td></td>
<td>Activation of NF-kappa B, up-regulation of autophagy, decreased apoptosis before I/R</td>
<td>Rat hearts in vitro</td>
<td>Sevoflurane [54]</td>
</tr>
<tr>
<td></td>
<td>Inhibition of NF-kappa B during I/R</td>
<td>Rat hearts in vivo</td>
<td>Sevoflurane [55]</td>
</tr>
<tr>
<td></td>
<td>Up-regulation of NF-kappa B and anti-apoptosis factors before I-R</td>
<td>Rat hearts in vivo</td>
<td>Sevoflurane [56]</td>
</tr>
<tr>
<td>HIF-1 alpha</td>
<td>Activation of HIF-1 alpha</td>
<td>Rabbit hearts in vivo</td>
<td>Isoflurane [57]</td>
</tr>
</tbody>
</table>

PKC, protein kinase C; ROS, reactive oxygen species; Src PTK, sarcoma protein tyrosine kinase; ERK, extracellular signal regulated kinase; Akt, protein kinase B; GSK, glycogen synthase kinase; HIF, hypoxia inducible factor; VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; AMP, adenosine monophosphate; NO, nitric oxide; NOS, nitric oxide synthase; mPTP, mitochondrial permeability transition pore; mKATP channel, mitochondrial ATP-sensitive potassium channel; hESC, human embryonic stem cells; O-GlcNAc, O-linked beta-N-acetylglucosamine; BK<sub>Ca</sub>, large-conductance calcium-activated K<sup>+</sup> channel; PKA, protein kinase A; NF, nuclear factor; I-R, cardiac ischaemia-reperfusion.

Table 1 (continued)

Table 2 Effects of volatile anaesthetic preconditioning on signal transduction proteins in endothelium.

<table>
<thead>
<tr>
<th>Endothelium</th>
<th>Inhibition of endothelial NF-kappa B activation</th>
<th>Human umbilical vein, endothelial cells</th>
<th>Desflurane [58]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of TNF-alpha-stimulated expression of adhesion molecules ICAM-1, VCAM-1 and E-selectin</td>
<td>Human umbilical vein, endothelial cells</td>
<td>Desflurane [59]</td>
<td></td>
</tr>
<tr>
<td>Prevention of TNF-alpha-induced adhesion molecule expression</td>
<td>Human umbilical vein, endothelial cells</td>
<td>Isoflurane [60]</td>
<td></td>
</tr>
<tr>
<td>Inhibition of endothelial leucocyte adhesion</td>
<td>Human volunteers</td>
<td>Sevoflurane [61]</td>
<td></td>
</tr>
<tr>
<td>Preservation of glycoctalis from I-R-induced degradation by attenuation of lysosomal cathepsin B release</td>
<td>Guinea pig hearts in vitro</td>
<td>Sevoflurane [62]</td>
<td></td>
</tr>
<tr>
<td>Endothelial protection against ischaemia mediated by PKCs and mKATP channels NOSs (endothelial NOS and inducible NOS)</td>
<td>Bovine pulmonary arterial endothelial cells NOSs knockout mice</td>
<td>Isoflurane [63]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desflurane [64]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NF, nuclear factor; TNF, tumour necrosis factor; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; I-R, cardiac ischaemia–reperfusion; PKC, protein kinase C; mKATP channel, mitochondrial ATP-sensitive potassium channel; NOSs, nitric oxide synthases.
elimination of collateral blood flow and maintenance of contractility, have a completely different energy metabolism compared with adult cardiomyocytes. One feature is that the fetal heart relies on carbohydrate substrates such as lactate and glucose, thus tolerating a low oxygen environment much better than adult cardiomyocytes [87]. Membrane preparations with membrane proteins and applied patch-clamp techniques can measure and quantify interactions and modulation from volatile anaesthetic agents; however, these interactions cannot be shown to have a causal relationship with myocardial protection from ischaemia–reperfusion injury.

Clinical evidence of anaesthetic preconditioning

The very low incidence of hard clinical endpoints such as mortality and myocardial infarction in the postoperative period means that surrogate endpoints, such as postoperative troponin concentrations, are commonly used in proof-of-concept trials. While serum markers may reflect clinical outcome, their clinical importance as an appropriate endpoint remains open to debate [88].

Raised levels of troponin postoperatively have been shown to correlate strongly with worse clinical outcome [89]. In addition, postoperative troponin I correlates well with the mass of myocyte necrosis diagnosed by serial cardiac magnetic resonance imaging (MRI) after CABG surgery [90].

We have identified a number of small-to-medium-sized, prospective, randomised controlled proof-of-concept trials in which volatile anaesthetics induced a significant reduction in postoperative troponin levels in cardiac surgery [91–103], summarised in Table 3, and other, similarly-sized trials that did not demonstrate reduced postoperative troponin levels with volatile anaesthetics (Table 4 [104–117]).

In coronary surgery, Lee et al. demonstrated that isoflurane, if given at the beginning of CPB at 2.5 minimum alveolar concentration (MAC) before aortic cross-clamping, and with a 5-min washout period after its administration, significantly reduced the postoperative ischaemic marker troponin I at 24 h [92]. However, dose-related effects and application patterns, including several cycles of volatile anaesthetic preconditioning with washout intervals, were not investigated.

Amr and Yassin used the same anaesthetic preconditioning protocol with the application of 2% isoflurane followed by a 5-min washout period, to show that anaesthetic preconditioning reduced postoperative cardiac troponin I as much as the protection conferred by ischaemic preconditioning, and significantly more than in the control group, that received midazolam and no volatile anaesthetic agent [100]. In another small proof-of-concept trial by Meco et al., desflurane, given before CPB, resulted in myocardial protection and reduced cardiac troponin I postoperatively [96]. In contrast to the three trials mentioned above, where volatile anaesthetic agents were administered before placement of the aortic cross-clamp, De Hert et al. described significant reductions in postoperative cardiac troponin I after continuous administration of sevoflurane during surgery [91]. In the same study, sevoflurane was also administered only pre- or post-CBP, and this did not result in significant postoperative troponin changes compared with patients receiving propofol only. These results are confounding when compared with those described by Lee et al., Amr and Yassin and Meco et al., where the volatile anaesthetic was only given before CPB. However, all patients in De Hert et al.’s trial underwent CABG surgery with CPB and intermittent aortic cross-clamping, which potentially provided an additional ischaemic preconditioning stimulus, as well as adding additional reperfusion episodes. The improved myocardial protection may therefore have been a result of the combination of anaesthetic preconditioning during CPB, and ischaemic preconditioning caused by intermittent aortic cross-clamping [91].

Tritapepe et al., in a relatively large trial with 150 patients, demonstrated that the continuous administration of 1 MAC desflurane during CABG surgery, except during CPB, induced significant cardioprotection, as assessed by reduced postoperative cardiac troponin I levels, compared with propofol infusion [97]. In contrast to the study by de Hert et al., anterograde or retrograde cold blood cardioplegia was used to immobilise the myocardium during grafting, thus excluding an additional protective effect by cross-clamp defibrillation. Kawamura et al. showed a similar effect on postoperative myocardial ischaemic markers in a small cohort of 23 patients after continuous
Table 3 Clinical trials comparing volatile anaesthesia with propofol anaesthesia in cardiac surgery that indicated less myocardial injury with volatile anaesthetics, demonstrated by statistically significant reductions in postoperative ischaemic markers.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anaesthetic intervention</th>
<th>Control group</th>
<th>Analgesia</th>
<th>n</th>
<th>Cardiac marker</th>
<th>Findings and effect sizes (reduction in cardiac marker)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>Sevoflurane 0.5–2% pre/post-CPB or continuously</td>
<td>TCI propofol</td>
<td>Remifentanil infusion</td>
<td>200</td>
<td>CtnI</td>
<td>Significantly lower increase in cTnI in the sevoflurane continuous group compared with the propofol group</td>
<td>[91]</td>
</tr>
<tr>
<td>CABG</td>
<td>Isoflurane 2.5 MAC at onset of CPB for 15 min before CC, 5-min washout</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>40</td>
<td>CtnI</td>
<td>Significant reduction in cTnI at 24 h after the surgery in the isoflurane group</td>
<td>[92]</td>
</tr>
<tr>
<td>AVR</td>
<td>Sevoflurane 0.5–1%</td>
<td>TCI propofol</td>
<td>Remifentanil infusion</td>
<td>30</td>
<td>CtnI</td>
<td>Significant reduction in cTnI up to 24 h postoperatively in the sevoflurane group</td>
<td>[93]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Desflurane 0.5–2 MAC during surgery</td>
<td>TCI propofol</td>
<td>Fentanyl</td>
<td>112</td>
<td>CtnI</td>
<td>Significant reduction of the cTnI AUC up to 24 h postoperatively</td>
<td>[94]</td>
</tr>
<tr>
<td>CABG</td>
<td>Sevoflurane 0.5–1.0% during surgery</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>23</td>
<td>CtnT</td>
<td>Significant reduction in peak cTnT up to 3 h after aortic declamping in the sevoflurane group</td>
<td>[95]</td>
</tr>
<tr>
<td>CABG</td>
<td>Desflurane 2.5% for 5 min during CPB before CC, 10-min washout</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>28</td>
<td>CtnI</td>
<td>Significant reduction in peak cTnI at 24 h and 72 h after surgery in the desflurane group</td>
<td>[96]</td>
</tr>
<tr>
<td>CABG</td>
<td>Desflurane 1 MAC during surgery, except during CPB time</td>
<td>TCI propofol</td>
<td>Fentanyl</td>
<td>150</td>
<td>CtnI</td>
<td>47% reduction of the cTnI AUC in the desflurane group</td>
<td>[97]</td>
</tr>
<tr>
<td>CABG</td>
<td>Sevoflurane 1 MAC continuous vs intermittent (10-min washout) before CPB</td>
<td>Propofol</td>
<td>Sufentanil</td>
<td>42</td>
<td>CtnT</td>
<td>Significant reduction in peak cTnT at 24 and 48 h postoperatively in the intermittent sevoflurane group</td>
<td>[98]</td>
</tr>
<tr>
<td>CABG</td>
<td>Sevoflurane 1 MAC × 5 min vs 2 MAC × 5 min with 10-min washout before CPB</td>
<td>TCI propofol</td>
<td>Sufentanil</td>
<td>30</td>
<td>CtnI</td>
<td>Significant reduction in peak cTnT up to 72 h postoperatively in the 2 × 5 min sevoflurane group</td>
<td>[99]</td>
</tr>
<tr>
<td>CABG</td>
<td>Isoflurane 2.5% 10 min before CC</td>
<td>Midazolam</td>
<td>Sufentanil</td>
<td>45</td>
<td>CtnI</td>
<td>Significant reduction in peak cTnI up to 36 h postoperatively in the isoflurane group</td>
<td>[100]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>1–2.5% Isoflurane during surgery</td>
<td>Propofol</td>
<td>N₂O</td>
<td>45</td>
<td>CtnT</td>
<td>Significant reduction in peak cTnT at 6 and 24 h after surgery in the isoflurane group</td>
<td>[101]</td>
</tr>
<tr>
<td>CABG</td>
<td>Isoflurane 1-1.5 MAC until CPB and propofol during and after CPB; or isoflurane only</td>
<td>Propofol or midazolam</td>
<td>Fentanyl</td>
<td>120</td>
<td>CtnI</td>
<td>Isoflurane plus propofol reduced the cTnI AUC by 33% compared with iso only, and 35% compared with propofol only</td>
<td>[102]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Sevoflurane 0.75/1.0/1.5 MAC</td>
<td>Midazolam</td>
<td>Fentanyl</td>
<td>48</td>
<td>CtnI</td>
<td>Significant reduction of cTnI peak levels at 24, 48 and 72 h after surgery in the 1.0 and 1.5 MAC groups</td>
<td>[103]</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; TCI, target controlled infusion; CtnI, cardiac troponin I; MAC, minimal alveolar concentration; CC, aortic cross-clamp; AVR, aortic valve replacement surgery; OPCAB, off-pump coronary artery bypass graft surgery; AUC, area under the curve; CtnT, cardiac troponin T.
administration of sevoflurane during CABG surgery, where patients received anterograde cold blood cardioplegia [95].

The washout period of the preconditioning trigger before the episode of critical ischaemia is part of the classical preconditioning protocol [5]. This technique was assessed by Frassdorf et al. and Bein et al. in patients undergoing CABG surgery with CPB [98, 99]. Their studies showed that only intermittent administration of sevoflurane induced statistically relevant reductions in postoperative ischaemic markers, compared with one single episode of volatile anaesthetic administration before CPB. Bein et al. compared intermittent sevoflurane before CPB, with continuous administration of sevoflurane before CPB, and Frassdorf et al. compared intermittent sevoflurane with a single 5-min period of sevoflurane before CPB. Both trials also included a control group receiving propofol only. However, the intermittent sevoflurane regimen was not compared with sevoflurane-only during the whole procedure, particularly during CPB. Clinical limitations of intermittent sevoflurane applications, with washout periods in-between, include natural limits on the number of these washout periods before CPB, as the beginning of CPB should not be delayed. In addition, during the interruption of sevoflurane, the administration of a different non-volatile anaesthetic regimen needs to be considered.

One recent small proof-of-concept trial by Huang et al. investigated the concept of whether isoflurane plus propofol anaesthesia would result in less myocardial damage during CABG surgery, compared with isoflurane, propofol or midazolam alone [102]. Isoflurane was administered before CPB, and propofol 100 µg.kg⁻¹.min⁻¹ was given during CPB, and until 15 min after aortic declamping, followed by propofol 60 µg.kg⁻¹.min⁻¹ after CPB. The results indicated that a combination of isoflurane preconditioning before CPB, and propofol protection during and after CPB, resulted in a significant reduction in postoperative markers of myocardial ischaemia, in contrast to the effects of either isoflurane or propofol anaesthesia alone. Propofol may protect the myocardium from ischaemia–reperfusion injury by scavenging peroxynitrite [118]. This effect can potentially be synergistic with the preconditioning effect of isoflurane, which generates small amounts of peroxynitrate before bypass that at low levels provides myocardial protection.

During CABG surgery without the use of CPB, isoflurane, desflurane or sevoflurane administered during the whole procedure have been shown to reduce postoperative troponin concentrations [94, 101, 103], while during aortic valve replacement surgery, sevoflurane has also been shown to reduce postoperative troponin levels [93]. Wang et al. investigated different doses of isoflurane during CABG surgery without CPB, and demonstrated that 1 MAC of sevoflurane induced a significant reduction in postoperative troponin levels, whereas a lower dose of 0.75 MAC provided no protection, and a higher dose conferred no additional myocardial protection [103].

In contrast to the evidence presented up to now, there are a number of trials showing that volatile anaesthetic agents in cardiac surgery do not reduce postoperative troponin levels. Xia et al. demonstrated a protective effect of propofol in the clinical setting, when compared with isoflurane alone. High doses of propofol (120 µg.kg⁻¹.min⁻¹), from 10 min before CPB until 15 min after aortic unclamping, resulted in a significant reduction in postoperative troponin I, suggesting that a continuous infusion of high-dose propofol is more protective than either isoflurane or a lower-dose infusion of propofol [106]. One explanation for this confounding finding may be the long aortic cross-clamp time in all groups, which exceeded 80 min. Experimental data have shown previously that the therapeutic timeframe for anaesthetic preconditioning lies between 25 and 40 min [119]. Therefore, protection by the volatile anaesthetic agent may not have been observed in the study conducted by Xia et al. owing to the prolonged CPB and ischaemic time.

Flier et al. investigated a protocol with isoflurane given during the whole procedure [112]. Their results did not reveal any differences in postoperative troponin levels after maintenance of anaesthesia with propofol, in comparison with isoflurane. However, patients taking the K<sub>ATP</sub> channel blocker sulphonylurea were not excluded from the study, and sulphonylureas are known to block the potentially cardioprotective effect of volatile anaesthetic agents. In addition, the intervention had to be discontinued in 13% of patients, and three patients were from the isoflurane group, which led to a potential
Table 4 Clinical trials comparing volatile anaesthesia with propofol anaesthesia in cardiac surgery that indicated the same amount of myocardial injury with volatile anaesthetics and propofol, with similar peri-operative troponin serum concentrations, or less myocardial injury and lower postoperative cardiac serum markers with propofol.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anaesthetic intervention</th>
<th>Control group</th>
<th>Analgesia</th>
<th>n</th>
<th>Cardiac marker</th>
<th>Other findings apart from no difference between postoperative biomarkers</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>Isoflurane 1 MAC for 5 min before CPB plus 5-min washout</td>
<td>Propofol</td>
<td>Sufentanil</td>
<td>34</td>
<td>CTnI</td>
<td>No difference between groups in postoperative CTnI peak values</td>
<td>[104]</td>
</tr>
<tr>
<td>MIDCAB</td>
<td>Sevoflurane 1 MAC during surgery</td>
<td>Propofol</td>
<td>Remifentanil</td>
<td>50</td>
<td>CTnT</td>
<td>No difference in postoperative CTnT values. After LAD occlusion. Preserved myocardial function with sevoflurane</td>
<td>[105]</td>
</tr>
<tr>
<td>CABG</td>
<td>Isoflurane 1–1.5% after induction during surgery</td>
<td>Propofol: 60 μg.kg⁻¹.min⁻¹, 120 μg.kg⁻¹.min⁻¹ during CPB</td>
<td>Fentanyl</td>
<td>54</td>
<td>CTnT and cTnI</td>
<td>Significantly lower CTnI and cTnI levels at 8, 24 and 48 h after surgery in the high-dose propofol group compared with the other groups</td>
<td>[106]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Sevoflurane during surgery</td>
<td>Propofol</td>
<td>Remifentanil</td>
<td>18</td>
<td>CTnI</td>
<td>Similar AUC of postoperative CTnI in sevoflurane and propofol groups (up to 36 h)</td>
<td>[107]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Sevoflurane during surgery</td>
<td>Propofol</td>
<td>Remifentanil</td>
<td>20</td>
<td>CTnT</td>
<td>Similar postoperative cTnT release in sevoflurane and propofol groups. Different transcriptional response in sevoflurane group</td>
<td>[108]</td>
</tr>
<tr>
<td>CABG</td>
<td>Sevoflurane 1 MAC 15 min before CPB</td>
<td>Propofol</td>
<td>Sufentanil</td>
<td>72</td>
<td>CTnI</td>
<td>Similar AUC for postoperative CTnI concentrations (up to 12 h)</td>
<td>[109]</td>
</tr>
<tr>
<td>MVR</td>
<td>Desflurane 0.5–2 MAC pre-CPB</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>120</td>
<td>CTnI</td>
<td>Similar postoperative cTnI release in both groups. Significant difference in subgroup of patients with CAD (n = 20) with reduced CTnI peak levels postoperatively</td>
<td>[110]</td>
</tr>
<tr>
<td>CABG</td>
<td>Desflurane/sevoflurane &gt; 0.5 MAC at least 30 min before CC until at least 10 min after CC</td>
<td>Propofol</td>
<td>Not defined</td>
<td>414</td>
<td>CTnI</td>
<td>No difference in postoperative CTnI peak levels and AUC between groups</td>
<td>[111]</td>
</tr>
<tr>
<td>CABG</td>
<td>Isoflurane 0.5–1 MAC during surgery</td>
<td>Propofol</td>
<td>Sufentanil</td>
<td>84</td>
<td>CTnI</td>
<td>Similar postoperative CTnI peak levels in both groups</td>
<td>[112]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Sevoflurane during surgery</td>
<td>Propofol</td>
<td>Remifentanil</td>
<td>94</td>
<td>CTnI</td>
<td>Similar postoperative CTnI levels in both groups</td>
<td>[113]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Sevoflurane 1.5–2.5%</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>38</td>
<td>CTnI</td>
<td>Similar postoperative CTnI peak levels in both groups. Increased oxidative stress markers in propofol group</td>
<td>[114]</td>
</tr>
</tbody>
</table>
problem with statistical power [112]. Soro et al. compared three groups of patients, with one group receiving propofol only, the second group sevoflurane during surgery and the third receiving sevoflurane during surgery and postoperatively in the cardiac intensive care unit before tracheal extubation [116]. This study was designed as a double-blind trial, with sevoflurane administered using an infusion pump. There was no difference between the groups with regard to postoperative myocardial ischaemic markers. However, nearly half of the patients were diabetic, which might have blocked potential cardioprotective effects, and relatively low doses of sevoflurane (1 MAC) were used postoperatively, which may not have been high enough to induce significant myocardial protection [116]. Wang et al. reported that the administration of 1 MAC of isoflurane for 5 min, plus a 5-min washout before CPB, did not result in reduced postoperative troponin levels [104]. However, only a single application/washout period was included, which may have reduced the effect of the intervention. Similarly, Piriou et al. showed that 1 MAC of sevoflurane for 15 min before CPB had no effect compared with propofol [109]. Potential causes of the negative outcome of this trial include: the dose, which may have been too low; the administration pattern, which was not intermittent; and the administration time, which may have been too short and/or the washout period too long [109].

De Hert et al. assessed a large cohort of patients (n = 414) in a multicentre randomised trial; interestingly, they did not observe a change in postoperative troponin I peak levels in patients receiving volatile anaesthetics, compared with propofol anaesthesia. However, the protocol in this trial allowed the centres to administer sevoflurane or desflurane in different patterns. All patients received the volatile anaesthetic during CPB, and some patients in addition both before and/or after CPB. The type of analgesia was not fixed [111]. In contrast to the troponin I results, however, they observed trends in clinical outcomes in favour of volatile anaesthetics; the 1-year mortality was 12.3% in the propofol group, but only 3.3% in the sevoflurane and 6.7% in the desflurane groups, and the hospital length of stay was reduced in the group receiving volatile anaesthetics.

In contrast to Wang et al., who demonstrated a cardioprotective effect of sevoflurane during CABG without CPB [103], five other study groups did not observe a similar effect [107, 108, 113, 114, 117]. Three of these trials recruited small numbers of patients with n = 18, [107], n = 20 [108] and n = 38 [114], which may have contributed to the negative results, as they are likely to have been statistically underpowered. In addition, the relatively short duration of ischaemia during CABG without CPB, and the low doses of sevoflurane used, may have contributed to the confounding results. Ballester et al. assessed levels of oxidative stress

### Table 4 (continued)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anaesthetic intervention</th>
<th>Control group</th>
<th>Analgesia</th>
<th>n</th>
<th>Cardiac marker</th>
<th>Other findings apart from no difference between postoperative biomarkers</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVR</td>
<td>Sevoflurane 0.5–2 MAC pre- + post-CPB</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>100</td>
<td>CTnI</td>
<td>Similar postoperative CTnI peak levels in both groups</td>
<td>[115]</td>
</tr>
<tr>
<td>CABG</td>
<td>Sevoflurane during surgery and postoperatively, not during CPB</td>
<td>Propofol</td>
<td>Remifentanil</td>
<td>73</td>
<td>CTnI</td>
<td>Similar postoperative CTnI peak levels in both groups</td>
<td>[116]</td>
</tr>
<tr>
<td>OPCAB</td>
<td>Sevoflurane 1–2% or desflurane 4–6% during surgery</td>
<td>Propofol</td>
<td>Fentanyl</td>
<td>139</td>
<td>CTnT</td>
<td>Similar postoperative CTnT levels in all three groups up to 96 h after surgery</td>
<td>[117]</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft surgery; MAC, minimal alveolar concentration; CPB, cardiopulmonary bypass; CTnI, cardiac troponin I; MIDCAB, minimally invasive direct coronary artery bypass surgery; CTnT, cardiac troponin T; LAD, left anterior descending artery; OPCAB, off-pump coronary artery bypass graft surgery; AUC, area under the curve; MVR, mitral valve replacement; CAD, coronary artery disease; CC, aortic cross-clamp.
during CABG without CPB, by analysing lipid peroxidation and nitrosative stress biomarkers from the coronary sinus. These remained constant in the sevoflurane group, but were significantly increased in the control group receiving propofol, suggesting that oxidative stress is reduced with sevoflurane [114]. Suryaparakash et al. studied 139 patients undergoing CABG without CPB, randomly allocated to anaesthesia using sevoflurane, desflurane or propofol [117]. Postoperative troponin levels were similar in all study groups, possibly owing to insufficient statistical power [117].

It is hard to draw firm conclusions from these results, with some studies showing beneficial effects of volatile anaesthetics, others demonstrating beneficial effects of propofol, and one recent study showing that a combination of volatile anaesthetics plus propofol provides optimal myocardial protection. Similarly, different administration patterns of volatile anaesthetics during surgery, and only before CPB, have been shown to be beneficial. This variability may be a result of different anaesthetic and surgical techniques, operations, patient co-morbidities and peri-operative drug administration. Another issue to consider is that troponin release after cardiac surgery does not always indicate irreversible myocardial damage, as has been demonstrated recently by Pegg and colleagues, using delayed enhancement cardio-MRI after CABG surgery [90].

The release pattern of troponin from myocardial tissues occurs in two phases: an initial troponin peak between 1 h and 6 h postoperatively, with non-necrotic/reversible myocardial injury and troponin release from the cytoplasmic compartment, due to CPB; and a delayed and sustained secondary release pattern with a peak after 24 h, caused by degradation of the contractile myofibril apparatus, inducing necrosis. Pegg et al. concluded that either several postoperative troponin measurements resulting in a washout curve (area under the curve), or equally a 24-h post-surgery single measurement of troponin I, correlate best with new postoperative myocyte necrosis. This differential picture of troponin release may further explain contradictory results in the assessment of preconditioning using volatile anaesthetics, with troponin levels as the primary outcome measure.

Apart from ischaemic markers, inflammatory markers may be reduced in patients receiving volatile anaesthetic agents, which may have a beneficial effect on postoperative morbidity and mortality. For example, sevoflurane reduced interleukin (IL)-6 and IL-8 concentrations in patients undergoing CABG surgery compared with propofol [95]. In another clinical trial, sevoflurane 2% was added to the cardioplegia, which resulted in a reduced postoperative inflammatory response, indicated by lower IL-6, CD11b/CD18, and TNF-alpha serum levels postoperatively, compared with a control group receiving only propofol [120].

In summary, it is evident from the above clinical proof-of-concept trials that all three volatile anaesthetics (isoflurane, desflurane and sevoflurane) have the potential to provide myocardial protection, and also that some patterns of administration, e.g. during the whole surgical procedure and intermittently before CPB, may increase the potential protection from volatile anaesthetics. In addition, recent data have suggested that a combination of volatile anaesthetics and a high dose of propofol during bypass and reperfusion might increase myocardial protection [102].

So far, clinical trials have been too small to investigate the effects of volatile anaesthetics on clinical outcomes such as postoperative myocardial infarction and mortality. Nevertheless, clinical outcome has been addressed by two retrospective longitudinal studies and by recent meta-analyses. In the longitudinal studies, a total of 34 310 patients undergoing CABG in 64 Italian cardiac surgery centres, and 10 535 consecutive patients undergoing cardiac surgery in three Danish centres, were studied; both suggested that the use of volatile anaesthetic agents is associated with a decline in 30-day mortality [121, 122]. One meta-analysis of 2979 patients in 27 trials showed that the protective intracellular effects of volatile anaesthetic agents on the myocardium in patients undergoing CABG surgery resulted in reduced postoperative troponin I levels, higher cardiac indices and a lower requirement for inotropic support [123]. However, the authors were unable to demonstrate a significant clinical benefit from volatile anaesthetics on other outcome variables such as myocardial infarction or mortality, predominantly because the studies were small, with low statistical power for clinical endpoints. In another meta-analysis, including 2841 patients from 32 clinical trials, Yu and Beattie found no difference in...
postoperative myocardial infarction or in-hospital mortality [124]. Similarly, Yao and Li, who assessed the potential beneficial effects of sevoflurane on clinical outcome in 696 patients, did not find any differences in postoperative myocardial infarction or mortality [125].

In contrast, another meta-analysis of 1922 patients from 22 clinical trials showed a reduction in postoperative myocardial infarction and mortality with the use of volatile anaesthetics [126]. Only proof-of-concept studies investigating sevoflurane or desflurane were included, and the volatile anaesthetics were mainly administered throughout the cardiac surgery, or before CPB. Recently, Landoni et al. published another meta-analysis with the largest number of patients so far, assessing clinical outcomes and anaesthetic preconditioning [127]. A total of 3642 patients from 38 trials were included. Postoperative mortality was doubled in patients receiving total intravenous anaesthesia, compared with those receiving volatile anaesthetics in cardiac surgery, from 25/1994 (1.3%) in the volatile anaesthetic group to 43/1648 (2.6%) in the group of patients receiving intravenous anaesthesia. Despite the relatively large number of patients, the authors commented that the number of patients enrolled in clinical trials investigating the potential benefits of volatile anaesthetics in cardiac surgery is still low, and that there is a need for large randomised trials. Limitations of the above meta-analyses include the potentially suboptimal quality and heterogeneity of the proof-of-concept trials that were included, as well as the different secondary endpoints.

Conclusions

There is evidence from experimental in-vitro and in-vivo trials that volatile anaesthetics have a beneficial effect, by inducing myocardial protection. This body of evidence includes not only animal studies, but also in-vitro analysis of human myocardial muscle tissue or cells. The translation of the experimental evidence into clinical practice has, to date, resulted in many small-to medium-sized proof-of-concept trials, with only surrogate myocardial ischaemic markers as the primary outcome measure. The results of these trials are promising, with many studies indicating a beneficial effect of volatile anaesthetics in patients undergoing cardiac surgery. However, they remain inconclusive. The evidence has not been convincingly translated from experimental studies into the clinical setting, and there is still a high degree of variability in anaesthetic techniques, with different administration patterns, including volatile anaesthetics and/or propofol [128, 129]. Larger pragmatic, multicentre trials are therefore required to investigate whether volatile anaesthetic agents in cardiac surgery have the potential to reduce the incidence and severity of major adverse clinical endpoints, such as peri-operative cardiac events, or postoperative mortality [130]. The results of these multicentre clinical outcome trials will be necessary to inform the evidence base, and change our clinical practice.

Competing interests

AAK is an Editor of Anaesthesia and this paper has undergone an additional external review as a result. No external funding declared.

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Pulmonary hypertension and its management in patients undergoing non-cardiac surgery

S. A. Pilkington,1 D. Taboada2 and G. Martinez3

1 Specialist Registrar, Department of Anaesthesia, The Queen Elizabeth Hospital NHS Foundation Trust, King’s Lynn, UK
2 Consultant Cardiologist, Pulmonary Vascular Disease Unit, 3 Consultant, Department of Anaesthesia, Papworth Hospital NHS Foundation Trust, Cambridge, UK

Summary
Pulmonary hypertension is a complex disorder of the pulmonary vasculature that leads to increased peri-operative morbidity and mortality. Non-cardiac surgery constitutes a significant risk in patients with pulmonary hypertension. The management of right ventricular failure is inherently challenging and fraught with life-threatening consequences. A thorough understanding of the pathophysiology, the severity of the disease and its treatment modalities is required to deliver optimal peri-operative care. This review provides an evidence-based overview of the definition, classification, pathophysiology, diagnosis and treatment of pulmonary hypertension and focuses on the peri-operative management and treatment of pulmonary hypertensive crises in a non-cardiac setting.

Correspondence to: G. Martinez
Email: guillermo.martinez@nhs.net
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Introduction
Pulmonary hypertension (PH) is a serious condition and, despite advances in treatment, prognosis remains poor [1]. Patients with PH may present for anaesthesia and non-cardiac surgery and there are very few retrospective studies reporting outcome, with postoperative mortality rates varying between 1% and 18% [2–6]. This disparity reflects the wide variation in the methods used to diagnose PH, the severity of the disease and whether or not a control population was included. Peri-operative morbidity appears to be in the range of 14–42% and includes respiratory failure, heart failure, dysrhythmias, sepsis, renal insufficiency and myocardial infarction [2–6]. Although it is clear that PH represents an independent risk factor for peri-operative complications and postoperative death, the actual incidence of these complications is still unknown. In this article, we aim to review studies published in the last decade with emphasis on pre-operative recognition and peri-operative management of adults with PH.

Methods
A comprehensive literature search was performed on MEDLINE and EMBASE using the National Health Service health database, advanced search interface, assessing articles from 2003 to 2014. To achieve maximum sensitivity of the search, the following key words were applied: ‘pulmonary hypertension’; ‘surgical procedures’; ‘cardiac surgical procedures’; ‘anesthesia’; ‘anesthetics’; ‘noncardiac’; ‘non cardiac’; ‘anaesth’; ‘anaesthesia’. The search results included English, Spanish, French, German, Russian and Japanese studies. A total
of 169 articles were initially identified. We excluded cardi- 
cardiac surgery, paediatric surgery, transplantation surgery 
and adults with congenital heart disease. Foreign lan-
guage papers except Spanish articles were excluded. 
Individual case reports and non-systematic reviews were 
also excluded. A total of 44 articles were included fol-
following the initial search. In addition, articles were 
retrieved on scanning bibliographies. The three authors 
examined and graded the articles based on their clinical 
relevance and methodology. Due to the scarce number 
of randomised controlled trials, available case series and 
recommendations based on expert opinion were 
included. Where the evidence found on a particular 
section was considered unsatisfactory, a more specific 
search was performed and older evidence revisited. Epi-
demiological data and information on changing demo-
graphics and survival were obtained from PH registries 
[1, 7]. The current prevalence and survival data in the 
UK were obtained from the National Audit of Pulmo-
Nary Hypertension 2012 [8].

Definition and classification
PH is defined as a mean pulmonary artery pressure 
(mPAP) ≥ 25 mmHg measured by right heart cathe-
terisation at rest [9, 10]. There are multiple aetiologies 
for elevated pressure in the pulmonary circulation and 
PH could be defined as a haemodynamic state rather 
than a single disease entity. A recently updated World 
Health Organization (WHO) clinical classification 
from the Fifth World Symposium 2013 can be found in 
Table 1 [11]. A distinction between pre-capillary 
and post-capillary PH is fundamental to understanding 
the vascular and haemodynamic changes present in 
patients with PH. Throughout this article, pulmonary 
arterial hypertension (PAH) will be used when refer-
ning to WHO group 1 in particular, whilst PH will be 
used for pulmonary hypertension in general. The char-
acterisation of the different haemodynamic profiles is 
summarised in Table 2.

Prevalence
There are no reliable data on the prevalence or aetiol-
ogy of pulmonary hypertension, but an estimation can 
be made by examining individual groups of patients. 
In a major study in France, a prevalence of 15 per mil-
lion inhabitants was observed for PAH between 2002

Table 1 World Health Organization clinical classification 

1. Pulmonary arterial hypertension (PAH) 
   1.1. Idiopathic PAH 
   1.2. Heritable 
      1.2.1. BMPR2 
      1.2.2. ALK1, endoglin,SMAD9,CAV1, KCNK3 
      1.2.3. Unknown 
   1.3. Drug- and toxin-induced 
   1.4. Associated with 
      1.4.1. Connective tissue diseases 
      1.4.2. HIV infection 
      1.4.3. Portal hypertension 
      1.4.4. Congenital heart diseases 
      1.4.5. Schistosomiasis 
1’. Pulmonary veno-occlusive disease and/or pulmonary 
capillary haemangiomatosis 
1”. Persistent pulmonary hypertension of the newborn 
2. Pulmonary hypertension due to left heart disease 
   2.1. Left ventricular systolic dysfunction 
   2.2. Left ventricular diastolic dysfunction 
   2.3. Valvular disease 
   2.4. Congenital/acquired left heart inflow/outflow 
      tract obstruction and congenital cardio-
      myopathies 
3. Pulmonary hypertension due to lung diseases and/or 
hypoxia 
   3.1. Chronic obstructive pulmonary disease 
   3.2. Interstitial lung disease 
   3.3. Other pulmonary diseases with mixed restrictive 
      and obstructive pattern 
   3.4. Sleep-disordered breathing 
   3.5. Alveolar hypoventilation disorders 
   3.6. Chronic exposure to high altitude 
   3.7. Developmental abnormalities 
4. Chronic thromboembolic pulmonary hypertension 
5. Pulmonary hypertension with unclear multifactorial 
   mechanisms 
   5.1. Haematological disorders: chronic haemolytic 
      anaemia, myeloproliferative disorders, splenectomy 
   5.2. Systemic disorders: sarcoidosis, pulmonary 
      histiocytosis, lymphangioleiomyomatosis 
   5.3. Metabolic disorders: glycogen storage disease, 
      Gauchers disease, thyroid disorders 
   5.4. Others: tumour obstruction, fibrosing 
      mediastinitis, chronic renal failure, segmental PH

BMPR2, bone morphogenetic protein receptor type 2; ALK1, 
activin receptor-like kinase type 1; SMAD, SMAD group 
of intracellular proteins; CAV1, Caveolin-1; KCNK, Potassium 
channel subfamily K; HIV, human immunodeficiency virus.

and 2003 [13]. The data from the National Pulmonary 
Hypertension Audit, UK 2013, showed that designated 
centres saw 124 patients per million population in 
Great Britain between 2012 and 2013 [8]. The most 
common diagnosis, was PAH in 45% of patients, 
followed by chronic thromboembolic pulmonary
Hypertension (CTEPH) in 19%. Both left heart disease and lung disease contributed 7% each. Survival of PAH patients in the current treatment era has improved from a median of 2.8 years in the US National Institutes of Health (NIH) registry in 1980, to a 49% survival at seven years from diagnosis reported by the US REVEAL (The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) published in 2012 [7, 14, 15].

Pathogenesis
Although the factors responsible for disease initiation are different depending on the subcategories of PH, various interrelated processes result in endothelial dysfunction favouring vasoconstriction, vascular remodelling with excessive cell proliferation in the presence of reduced cell apoptosis and thrombosis [16, 17] (Fig. 1).

In PAH, levels of prostacyclin (PGI₂) are reduced and thromboxane synthesis is increased [17]. Prostacyclin is a potent vasodilator that inhibits platelet aggregation and smooth muscle cell proliferation [18]. Thromboxane A₂ stimulates vasoconstriction and platelet aggregation.

Nitric oxide (NO) acts via cyclic GMP (cGMP), causes vasodilatation and has antiproliferative properties [17]. All forms of PH are believed to result in a state of reduced NO bioavailability [19, 20]. Phosphodiesterase-5 (PDE-5) breaks down cGMP into inactive 5GMP. There is increased expression of PDE-5 both in the endothelial smooth muscle cells and in the right ventricle [16].

There is also an association between PAH and increased production in the pulmonary vasculature of endothelin-1 (ET-1), which is a potent vasoconstrictor and stimulates smooth muscle cell proliferation [21]. Structural remodelling is seen in PAH and the term ‘mitochondrial remodelling’ is used to describe the metabolic changes that occur in the vascular endothelial cells [22]. There is also a genetic component: mutation of bone morphogenetic protein receptor-2 (BMPR2) leads to loss of inhibitory action of bone morphogenetic protein on growth of vascular endothelial and smooth muscle cells [23]. Ultimately, chronically elevated afterload results in hypertrophy and dilatation of the right ventricle, and a metabolic shift from oxidative mitochondrial metabolism to the less energy efficient glycolytic pathway, which is related to cardiac ischaemia [24].

Diagnosis and treatment
Transthoracic echocardiogram (TTE) remains the method of choice for screening and assessing the likelihood of PH when clinically suspected. Right heart}

Table 2 Haemodynamic definition of pulmonary hypertension [9, 10, 12].

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics (all values at rest)</th>
<th>WHO clinical groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension (PH)</td>
<td><strong>mPAP ≥ 25 mmHg</strong></td>
<td>All</td>
</tr>
<tr>
<td>1) Pre-capillary PH</td>
<td><strong>mPAP ≥ 25 mmHg</strong></td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td></td>
<td><strong>PAWP ≤ 15 mmHg</strong></td>
<td>PH due to lung disease</td>
</tr>
<tr>
<td></td>
<td><strong>PVR &gt; 3 WU</strong></td>
<td>CTEPH</td>
</tr>
<tr>
<td></td>
<td><strong>CO normal/reduced/high</strong></td>
<td>PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>2) Post-capillary PH</td>
<td><strong>mPAP ≥ 25 mmHg,</strong></td>
<td>PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td><strong>PAWP &gt; 15 mmHg</strong></td>
<td></td>
</tr>
<tr>
<td>2a) Isolated post-capillary PH*</td>
<td><strong>PAWP &gt; 15 mmHg</strong></td>
<td>PH due to left heart disease</td>
</tr>
<tr>
<td>2b) Post-capillary PH with pre-capillary component*</td>
<td><strong>DPAP-PAWP &lt; 7 mmHg</strong></td>
<td>PH due to left heart disease</td>
</tr>
<tr>
<td></td>
<td><strong>PAWP &gt; 15 mmHg</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>DPAP-PAWP ≥ 7 mmHg</strong></td>
<td></td>
</tr>
</tbody>
</table>

mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units; CTEPH, Chronic thromboembolic pulmonary hypertension; CO, cardiac output; High cardiac output can be present in cases of hyperkinetic conditions such as systemic to pulmonary shunts (pulmonary circulation only), anaemia, hyperthyroidism, portal hypertension, sepsis etc.; DPAP, Diastolic pulmonary artery pressure.

*Proposed definition by Vachiéry et al.
catheterisation is the gold standard to confirm the diagnosis and establish the severity of PH [9]. Once the diagnosis is confirmed, other diagnostic tools assist in establishing the underlying aetiology and clinical group to which the patient belongs (Table 3).

There is a complex pathophysiology of PAH such that, despite advances in treatment over the last decade, it remains incurable. Treatment with PH-targeted drug therapy is only licensed for patients in WHO group 1. In the UK, drug prescribing is restricted to national PH centres (Fig. 2).

General measures include advice on physical activity and supervised rehabilitation, psychological support, infection control, birth control and pregnancy. Supportive measures include advice on anticoagulation, diuretics and oxygen therapy. For almost 30 years, anticoagulation has been recommended for patients with idiopathic PAH based on pathological findings of thrombotic arteriopathy. The COMPERA registry data showed that the survival improvement at three years remained statistically significant in patients with

**Table 3** Diagnostic tests to establish the aetiology of pulmonary hypertension [9].

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Associated condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>Left ventricular systolic and diastolic dysfunction</td>
</tr>
<tr>
<td>X-ray chest, PFT</td>
<td>COPD, sarcoidosis</td>
</tr>
<tr>
<td>V/Q scan, CTPA</td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>Sleep study</td>
<td>Chronic thromboembolic pulmonary disease</td>
</tr>
<tr>
<td>Serological test (ANA, HIV)</td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Liver ultrasound</td>
<td>Lupus, scleroderma, HIV</td>
</tr>
<tr>
<td>Right heart catheterisation</td>
<td>Portopulmonary hypertension</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td>CHD with systemic to pulmonary shunt</td>
</tr>
</tbody>
</table>

CHD, congenital heart disease; PFT, pulmonary function tests; COPD, chronic obstructive pulmonary disease; V/Q, ventilation/perfusion; CTPA, contrast CT angiography of the pulmonary artery; ANA, antinuclear antibody; HIV, human immunodeficiency virus.
idiopathic PAH. In contrast, the use of anticoagulants was not associated with a survival benefit in patients with other forms of PAH [25]. Decompensated right heart failure leads to fluid retention and although there are no randomised controlled trials comparing diuretics in PAH, clinical experience shows clear symptomatic benefit in fluid-overloaded patients [9]. Oxygen administration has been demonstrated to reduce pulmonary vascular resistance in patients with PAH, but there are no data to confirm that long-term oxygen therapy is beneficial. Guidance is based on evidence of its benefit in patients with chronic obstructive pulmonary disease [26].

Specific drug therapy includes calcium channel blockers that have traditionally been used in the treatment of idiopathic PAH. It has been increasingly recognised that only a small number of patients (<10%) demonstrate a favourable response to acute vasodilator testing at the time of right heart catheterisation, and their use in non-responders can be associated with deleterious effects [27]. Synthetic prostacyclin analogues, such as epoprostenol, iloprost and treprostinil, have shown efficacy in patients with idiopathic PAH. Epoprostenol has a short half-life and is stable at room temperature for only 8 h; hence, it needs to be administered continuously by means of an infusion pump and a permanent tunnelled catheter. It improves exercise capacity and is the only treatment shown to improve survival in idiopathic PAH in a randomised study [28]. Iloprost is available for intravenous, oral, and aerosol administration. Inhaled iloprost in patients with PAH and CTEPH showed an improvement in symptoms and clinical events [29]. Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature and has shown clinical and haemodynamic improvement in PAH patients [30]. Another group of drugs, endothelin receptor antagonists, which include bosentan, ambrisentan and macitentan, are effective in the treatment of PAH. Bosentan is an orally active, dual endothelin-A and endothelin-B receptor antagonist and has been evaluated in PAH. Patient have shown improvement in functional class, haemodynamics and time to clinical worsening [31]. Ambrisentan is an oral selective endothelin-A receptor antagonist that has been shown to improve exercise capacity in PAH patients [32]. Macitentan is a new, orally active drug that has been tested in a large prospective study in PAH patients. A decrease in a composite endpoint has been shown that included worsening PH and death [33]. Phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, are orally active, potent, and selective inhibitors of the PDE-5 enzyme and have been shown to improve exercise
capacity, symptoms and haemodynamics in PAH patients [34, 35]. Riociguat is a new drug that stimulates soluble guanylate cyclase, leading to an increase in cyclic GMP, and has proven to be efficacious in PAH and CTEPH patients [36]. The incidence of transplantation has increased and both heart–lung transplantation and double-lung transplantation improve survival in transplantation candidates with idiopathic PAH [37].

Group 4 CTEPH patients should be referred for consideration of pulmonary endarterectomy. Specific drug therapy is also used in CTEPH patients who are not suitable for surgical treatment or those with residual PH after pulmonary endarterectomy as an unlicensed indication.

In general, treatment of patients in WHO groups 2, 3 and 5 should be focused on the underlying condition.

Pre-operative risk assessment
The peri-operative management of patients with PH should involve a multidisciplinary team. Patients need to be explicitly informed of the possibility of serious complications that can lead to prolonged hospitalisation or even death. The mortality associated with non-cardiac surgery is influenced by the severity of PH and type of surgery. Table 4 summarises the studies in PH patients undergoing non-cardiac surgery. In a 2005 study by Ramakrishna et al., which included 145 surgical patients with PH of varying aetiology, the perioperative mortality rate was 7% [5]. A year later, in a smaller case series of 21 patients with moderate to severe PH, Minai et al. showed an 18% mortality rate [6]. However, both these studies were retrospective in design and included patients treated until 2003, before modern therapies for PAH had evolved. Also, almost 75% of patients in Ramakrishna et al.’s study were in New York Heart Association (NYHA) functional class 1–2 (Table 5) and only 13% of the patients were taking a prostanoid or endothelin antagonist. In contrast, Minai et al. had larger proportions of patients in NYHA class 2–4 and more patients were on PH-targeted therapy. Nevertheless, in both series, right ventricular failure was the contributing cause of death in 50% of the patients [5, 6].

In a case–control study of PH patients undergoing non-cardiac, intermediate- and high-risk surgery, Kaw et al. included 96 patients with PH confirmed with pulmonary artery catheter and compared them with a similar group without PH [2]. The PH group had a higher complication rate (25% vs 2.5%), but mortality was low (1%). Importantly, this study included mainly patients with PH related to left heart failure [2]. Lai et al. found a 9.7% mortality rate in PH patients undergoing non-cardiac surgery; however, PH diagnosis was based on echocardiography [3] and the

Table 4 Summary of studies showing morbidity and mortality associated with pulmonary hypertension (PH) in patients undergoing non-cardiac surgery [2–6, 38]. Values are proportion.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PH due to left heart disease</td>
<td>USA</td>
<td>No</td>
<td>USA</td>
<td>No</td>
<td>Taiwan</td>
<td>Yes</td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>100%</td>
<td>79%</td>
<td>58%</td>
<td>50%</td>
<td>57%</td>
<td>7%</td>
</tr>
<tr>
<td>Major surgery</td>
<td>7%</td>
<td>18%</td>
<td>9.7%</td>
<td>57%</td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td>Mortality</td>
<td>7%</td>
<td>14%</td>
<td>24%</td>
<td>Retrospective</td>
<td>Retrospective</td>
<td>Controlled</td>
</tr>
<tr>
<td>Morbidity</td>
<td>42%</td>
<td>36%</td>
<td>24%</td>
<td>Retrospective</td>
<td>No control</td>
<td>Doppler ECHO criteria</td>
</tr>
<tr>
<td>Study type/limitations</td>
<td>Retrospective</td>
<td>No control</td>
<td>ECHO criteria to define PH</td>
<td>Retrospective</td>
<td>Control</td>
<td>Doppler ECHO criteria</td>
</tr>
</tbody>
</table>

ECHO, echocardiography; RHC, right heart catheterisation; THR/TKR, total hip/knee replacement; NIS, National Inpatient Sample.

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increased mortality could be due to selection bias by the inclusion of patients with untreated severe PAH. There were no right heart catheterisation data and the contribution of left sided disease could not be accurately assessed.

More recently, Price et al. studied 28 PH patients having surgery under general or regional anaesthesia. At the time of surgery, 75% of patients were in NYHA functional class 1–2. Deaths occurred in 7% of patients and peri-operative complications, all related to PH, occurred in 29% of patients \( [4] \). Risk factors associated with complications were emergency surgery \( (p < 0.001) \), major surgery \( (p = 0.008) \) and a long operative time \( (193 \text{ vs } 112 \text{ min}; \ p = 0.003) \) \[4\]. Memtsoudis et al. matched 3302 PH patients who underwent total hip or knee arthroplasty with non-PH controls from the national database. The PH group showed a 4 to 4.5-fold increase in the adjusted risk of mortality after hip or knee arthroplasty compared with patients without PH, and that the PAH subgroup had the highest mortality. The overall mortality was lower compared with previous studies, possibly due to spanning only the immediate peri-operative period \[38\].

With regard to patients undergoing pre-operative evaluation, a distinction should be made between those patients with an established diagnosis of pulmonary hypertension and those who have not been formally assessed. Patients ‘suspected’ of having PH with an uncertain underlying cause and ungraded severity are subject to poorer pre-operative optimisation and are exposed to a higher risk of peri-operative complications. In these circumstances, elective surgery must be postponed and the patient referred to a specialised PH service before surgery.

The pre-operative evaluation of a patient with established pulmonary hypertension should be based on a risk assessment that takes into account their functional state, severity of the disease and type of surgery proposed. A detailed history and physical examination should be complemented with relevant investigations. Patients’ symptoms range from general fatigue, dyspnoea and chest pain on exertion to syncope in advanced PAH. Syncope is an ominous sign and, in most cases, is related to the inability to increase cardiac output on exertion and places the patient in the advanced functional class \[39\]. NYHA functional class at diagnosis is an important predictor of survival in patients with PAH and improvement from functional class 3/4 to 1/2 with treatment is associated with a better prognosis \[14\]. The six-minute walking distance (6MWD) is used to assess exercise capacity in patients with PH and a reduced total distance is associated with a higher mortality \[40\].

Pre-operative investigations include laboratory tests, electrocardiography, echocardiography, chest radiography and a recent right heart catheterisation. Blood tests to assess haemoglobin level and renal function and to measure pro-brain natriuretic peptide (pro BNP) and/or its terminal fraction are requested. Although a high BNP level is an independent predictor for postoperative cardiac mortality in patients undergoing non-cardiac surgery, its use in stratifying postoperative risk has not been established in PH patients \[41\]. Transthoracic echocardiography is non-invasive and readily available to evaluate right ventricular function in patients with PH. Echocardiographic predictors of poor prognosis in patients with PAH are right atrial enlargement, reduced tricuspid annular plane systolic excursion (TAPSE) and pericardial effusion \[42\]. Right

### Table 5: Functional classification of pulmonary hypertension (modified after the New York Heart Association (NYHA) functional classification according to the WHO 1998) \[9\].

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>2</td>
<td>Pulmonary hypertension resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary hypertension resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>4</td>
<td>Pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

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heart catheterisation establishes the diagnosis and type of PH and provides essential information regarding the severity of the disease and right heart function [43]. It also allows differentiation between pre- and post-capillary PH, which is particularly relevant in patients with risk factors for left heart disease [44].

Before surgery, medications should be reviewed and altered depending on recent investigation results. Examples include: initiation or augmentation of PAH-specific therapies for patients in WHO Group 1; diuretics and systemic vasodilators and appropriate heart failure therapies for patients in WHO group 2; administration of oxygen, bronchodilators, antibiotics and steroids in patients with chronic obstructive pulmonary disease; and use of bi-level positive airway pressure for obstructive sleep apnoea [45]. Established PAH therapies should be continued in the peri-operative period and when oral formulations cannot be used, temporary administration of inhaled (NO, nebulised prostacyclin) or intravenous (prostacyclin, sildenafil) therapy should be considered. Warfarin should be discontinued before the procedure without the need for bridging with heparin unless there is another indication (e.g. pulmonary embolism, CTEPH, mechanical heart valve). Patients should receive prophylactic anticoagulation to prevent deep vein thrombosis and pulmonary thromboembolism.

The type of surgery is also relevant in the pre-operative risk assessment. High-risk surgery includes that associated with major blood loss, significant peri-operative systemic inflammatory response, venous air, carbon dioxide, fat or cement embolism, and loss of lung blood vessels [45]. Table 6 summarises patient and surgical risk factors that are associated with increased morbidity and mortality in patients with PH.

Table 6 Patient and surgical risk factors associated with increased morbidity and mortality in patients with pulmonary hypertension [2–6].

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Surgical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA/WHO functional class ≥ 2</td>
<td>Emergency surgery</td>
</tr>
<tr>
<td>6MWD &lt; 300 m</td>
<td>Intermediate-/high-risk surgery</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>ASA physical status &gt; 2</td>
</tr>
<tr>
<td>History of pulmonary embolism</td>
<td>Duration of anaesthesia &gt; 3 h</td>
</tr>
<tr>
<td>History of chronic renal insufficiency</td>
<td>Intra-operative use of vasopressors</td>
</tr>
<tr>
<td>RVH with severe systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Higher mean pulmonary artery pressure</td>
<td></td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; WHO, World Health Organization; 6MWD, six-minutes walking distance; RVH, right ventricular hypertrophy.

Principles of anaesthetic management

Prevention of PH crisis and right ventricular failure relies on the optimal mechanical matching of the right ventricle and pulmonary circulation. A variety of intra-operative events, both surgical and anaesthetic, can affect the right ventricular oxygen supply–demand relationship.

The transition from spontaneous breathing to intermittent positive pressure ventilation, addition of positive end-expiratory pressure (PEEP), patient positioning, pneumoperitoneum or diaphragmatic compression can significantly increase right ventricular afterload and precipitate a pulmonary hypertensive crisis. In addition to the pulmonary vascular effects of hypoxia and hypercarbia, patients may also be subjected to venous emboli arising from air, thrombi or particulate matter forced into the circulation.

Right ventricular contractility in PH patients can range from normal through varying degrees of systolic dysfunction. Ventricular wall hypertrophy and chamber dilatation are common, the latter being more significant in the advanced stages of PH. Right ventricular contractility can be affected directly or indirectly by either depression from anaesthetic drugs or acute changes in the sympathetic/parasympathetic balance. Table 7 shows the effect of various anaesthetic agents on right ventricular contractility and afterload. Inhaled anaesthetics such as isoflurane and desflurane have a marked dose-dependent effect in reducing right ventricular contractility and some negative impact on right ventricular afterload; hence, they significantly impair right ventricle pulmonary artery coupling [46, 47]. Sevoflurane causes significant depression of global right ventricular function associated with a qualitatively different effect on inflow and outflow tracts, without any modification of pulmonary vascular
resistance. The use of nitrous oxide should be restricted because it increases pulmonary vascular resistance.

With regard to intravenous anaesthetic agents, thiopental reduces right ventricular contractility and systemic vascular resistance, but does not affect pulmonary vascular resistance. Etomidate has been advocated as the induction agent of choice in patients with right ventricular dysfunction, although there are no comparative data. Ketamine increases pulmonary vascular resistance in adults, although this has not been observed in children. Propofol sedation in patients with acute respiratory failure or neurological disease receiving critical care was found to decrease right ventricular contractility and this effect was reversed by dobutamine. Interestingly, in a comparison study of propofol and isoflurane in patients undergoing one-lung ventilation, there was a greater reduction in the mean cardiac index and right ventricular ejection fraction with propofol, but propofol was not associated with a significant increase in shunt fraction, whereas isoflurane was associated with a three-fold increase in shunt fraction. Fentanyl and sufentanil have minimal effects on pulmonary haemodynamics. Remifentanil produces minor pulmonary vasodilatation, which is mediated by histamine release.

Although central neuraxial blockade has been used safely in patients with PH, blocking cardiac sympathetic fibres in the upper thoracic region disrupts right ventricular homeometric autoregulation. Homeometric autoregulation is an adaptive mechanism that allows the right ventricle to tolerate acute increases in afterload but preserves the mechanical coupling between right ventricle and the pulmonary circulation. When inhibited (e.g. by central neuraxial blockade), it can lead to a critical reduction in cardiac output and right heart failure that is not due to impaired right ventricular coronary flow dynamics or systemic vasodilation.

The balance between myocardial oxygen supply and demand is affected by several events that occur during anaesthesia and surgery. The altered pattern of increased right ventricular pressures and systolic wall tension with limited coronary blood flow occurring mainly in diastole has a greater impact on right ventricular perfusion during systemic hypotension.

### Intra-operative anaesthetic management

There is a lack of evidence-based guidelines on the peri-operative management of patients with PH, and the recommendations in this section are based on literature review and the authors’ experience.

All patients should be given supplementary oxygen. In addition to preventing hypoxia, oxygen is a direct pulmonary vasodilator. It is good practice to remove air from intravenous syringes and lines. Hypothermia can cause pulmonary vasoconstriction and \(V/Q\) mismatch and it should be prevented by using forced air-warming blankets, heat and moisture exchangers and warmed intravenous fluids.

### Airway and ventilation

When using conscious sedation techniques, it is vital to ensure a patent airway and easy access to it, in case ventilation becomes compromised. During induction of general anaesthesia, there is a period of susceptibility until the airway is secured and ventilation controlled. An adequate depth of anaesthesia should be ensured before attempting laryngoscopy and tracheal intubation, as sympathetic stimulation has deleterious
effects on right ventricular afterload. Hypercarbia, acidosis, high inspiratory pressures and high levels of PEEP should also be avoided.

Monitoring
There is no strong evidence to suggest that any specific type of monitoring has an influence on patient morbidity and mortality. Nonetheless, invasive arterial monitoring before anaesthetic induction can facilitate early recognition of haemodynamic instability and allows intermittent arterial blood gas sampling to check adequacy of ventilation. Right atrial pressure measurement reflects the relationship of blood volume to the capacity of the venous system and also reflects the functional capacity of the right ventricle. Intra-operative monitoring with transoesophageal echocardiography (TOE) and/or a pulmonary artery catheter should be considered in all patients with severe PH or mild-to-moderate PH with existing right-sided heart failure [60]. Monitoring with TOE allows continuous measurement of systolic pulmonary artery pressure, valuable information on right ventricular performance and guidance for fluid management [61]. Studies have shown that the use of TOE triggered a change in the overall therapeutic management in between 30% and 50% of high-risk patients undergoing non-cardiac surgery [62, 63]. However, several factors limit the routine use of TOE; the image acquisition and interpretation of findings are dependent on the operator’s training and personal experience, and the probe is not well tolerated in awake patients undergoing regional anaesthesia [62].

The intra-operative use of a pulmonary artery catheter is controversial. Many studies have failed to demonstrate any benefit in its use for intra-operative monitoring; however, in most of the studies, a pulmonary artery catheter was used for measurement and guiding optimisation of cardiac output and left ventricular end-diastolic pressure [64]. Despite there being no robust data for the use of pulmonary artery catheter monitoring in patients with PH undergoing non-cardiac surgery, its use in the peri-operative setting provides unique direct, consistent and continuous measurement of pulmonary artery pressure, pulmonary vascular resistance and dynamic changes that occur in response to fluid administration, drug therapy or unexpected events that raise pulmonary artery pressure [9]. All authors point out that the insertion of a pulmonary artery catheter is associated with certain risks, which must be considered before insertion is attempted [65].

Circulation
In general, patients with PH have low systemic arterial pressures as a result of both their disease and specific medical therapy, rendering them susceptible to decompensation. The goal is to maintain the pre-anaesthetic haemodynamic condition. Therefore, invasive monitoring before induction is often required. Permissive hypotension is not applicable to high-risk PH patients; in contrast, the use of a low dose of vasoconstrictor to compensate for the reduction in systemic vascular resistance caused by anaesthetic drugs is a safe and effective approach. Blaise et al. recommended intra-operative management that allows the mean pulmonary artery pressure to fluctuate in the range of 15% of the initial value [66]. However, a pulmonary artery catheter is not always placed before induction of anaesthesia and placement whilst awake is distressing for the patient and can negatively impact the pulmonary vascular resistance. A practical approach would include siting an arterial line awake followed by a balanced anaesthetic induction that aims to maintain the baseline blood pressure; See Table 8 for proposed haemodynamic goals. Intra-operative fluid therapy should be relatively restricted and in a targeted manner based on the central venous pressure.

Vasoconstrictors, inotropes and inodilators
Maintaining the gradient between aorta and right ventricle is achieved by using sympathomimetic and non-sympathomimetic vasopressors. Noradrenaline and vasopressin improve perfusion of the right coronary artery, reduce the pulmonary/systemic vascular resistance ratio, enhance right ventricular performance and marginally improve cardiac output [67, 68]. However, the evidence of their impact on mortality related to right heart failure is weak [69]. Inotropes that enhance right ventricular performance, such as adrenaline, dobutamine and levosimendan are effective in treating right-sided heart failure. The
Table 8  Peri-operative haemodynamic goals.

<table>
<thead>
<tr>
<th>Systolic blood pressure $\geq$ 90 mmHg and/or 40 mmHg above sPAP</th>
<th>MAP $\geq$ 65 and/or 20 mmHg above mPAP</th>
<th>mPAP &lt; 35 mmHg or 25 mmHg lower than MAP</th>
<th>PVR/SVR ratio &lt; 0.5 or aim for pre-operative PVR/SVR ratio</th>
<th>RAP the lowest possible that maintains</th>
<th>MAP &gt; 65 mmHg</th>
<th>Cardiac index $\geq$ 2.2 l.min$^{-1}$.m$^{-2}$</th>
</tr>
</thead>
</table>

sPAP, systolic pulmonary artery pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PVR/SVR ratio, pulmonary vascular resistance/systemic vascular resistance ratio; RAP, right atrial pressure.

Inhaled prostacyclin in the operating theatre and intensive care unit [72]. Iloprost has a longer half-life than prostacyclin and is less likely to cause rebound phenomena after discontinuation. It can be administered peri-operatively via both controlled and spontaneous ventilation. Evidence with iloprost in patients undergoing non-cardiac surgery is scarce and limited to case reports [73]. Inhaled treprostinil is stable at room temperature and has been shown to benefit patients with PAH, but its use peri-operatively is also limited to a few case reports [74]. Table 9 outlines the management of a pulmonary hypertensive crisis.

**Postoperative management**

Patients with PH should be fully monitored in the intensive care unit postoperatively. There should be a robust plan for pain management, including regional blocks and non-opioid medications. Postoperative clinical deterioration and death are due to fluid shifts, pulmonary vasoconstriction, arrhythmias and pulmonary thromboembolism. Respiratory failure (60%) and right ventricular failure (50%) are the most frequent contributing causes to death [5]. Atrial tachyarrhythmias are associated with right ventricular failure and death [75]. Beta-blockers should be avoided as they are poorly tolerated in these patients [76] and amiodarone would be the drug of choice, although dronedarone or flecainide should be considered if amiodarone is contraindicated or not tolerated [75]. In patients in whom sinus rhythm cannot be restored, digoxin should be considered for rate control [75]. Post-surgical complications such as bleeding and infection must be promptly controlled and treated. Right ventricular function in PH is ‘preload-dependent’ but at the same time, fluid overloading is detrimental. Maintenance of systemic pressures with vasopressors and inotropes, along with replacement of blood volume when necessary, is of paramount importance. Vasodilator therapies that were started intraoperatively must be continued and slowly transitioned back to the patient’s pre-operative regimen.

**Pregnancy**

Historically, it is well known that pregnancy poses an immense risk to women with PAH. Avoidance of pregnancy is still strongly advocated and early termi-
Selective pulmonary vasodilation is recommended for PAH patients. With regards to the specific medical management of PAH, endothelin receptor antagonists are contraindicated during pregnancy due to their teratogenic effect, but epoprostenol, treprostinil, nebulised iloprost, sildenafil and inhaled nitric oxide can be used [77]. Calcium channel blockers are recommended for responders to the vasodilatory testing.

Weiss et al. reported a mortality rate of 30% in patients with idiopathic PAH and 56% in patients with PH associated with other conditions [78]. A more recent systematic review concluded that mortality was reduced to 17% in idiopathic PAH and 33% in PH associated with other conditions [79]. Vaginal delivery is associated with less blood loss and a lower risk of maternal infection; however, labour without effective analgesia is associated with stress, pain and increased sympathetic tone, which are deleterious in patients with severe PH. Elective caesarean section allows for better planning, a multidisciplinary team approach and optimal pain control. Although the majority of leading centres favour elective caesarean section over vaginal delivery, the optimal anaesthetic technique remains controversial. In two recently published series, elective caesarean section was the mode of delivery in more than 95% of cases. In Jaïs et al.’s. series [80], 80% of patients received regional anaesthesia, while in Rosengarten et al.’s. series, up to 80% of caesarean sections were performed under general anaesthesia [81]. Interestingly, the maternal mortality rate was similar in both cohorts (20% and 22%, respectively). In a retrospective review, Bedard et al. found that general anaesthesia was associated with a four-fold increase in maternal mortality; however, it could be possible that patients who underwent emergency caesarean section, and those who received general anaesthesia, had more severe disease [79]. The majority of deaths in pregnant patients with PAH occur in the peripartum period, mainly due to right heart failure and pulmonary thromboembolism. The practice of thromboprophylaxis in pregnant patients with PH is not standardised. Most case reports describing pregnant patients with PH placed patients on thromboprophylaxis during pregnancy and through the postpartum period with only a brief interruption around the time of delivery. Exceptions are for those who had a history of thromboembolic disease and idiopathic PAH where higher levels of anticoagulation may be required [77, 79].

Conclusions
Recent advances in our understanding of PH and the availability of new treatment modalities have resulted in improved survival. There are an increasing number of patients presenting for non-cardiac surgery. Their successful management requires a multidisciplinary team approach and thorough pre-operative risk assessment. Correct diagnosis, optimisation of the patient’s functional status and haemodynamics and management of co-morbidities are vital. Anaesthetic management is dependent on an understanding of pathophysiology and avoidance of a pulmonary hypertensive crisis. The presence of an experienced anaesthetist and surgeon in a specialist centre is advocated. Further studies on patients with PH undergoing non-cardiac surgery are required to provide guidance on the optimal management of this rare and complex disease.

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Haemostatic management of cardiac surgical haemorrhage

M. W. Besser,1 E. Ortmann2,3 and A. A. Klein4

1 Consultant, Department of Haematology, 2 Locum Consultant, 4 Consultant, Department of Anaesthesia and Intensive Care, Papworth Hospital, Cambridge, UK
3 Consultant, Department of Anaesthesia and Intensive Care, Kerckhoff Klinik Heart and Lung Centre, Bad Nauheim, Germany

Summary

Almost 30 000 cardiopulmonary bypass operations are performed in the UK every year, consuming a considerable portion of the UK blood supply. Each year, in cardiac surgery, 90% of blood products are used by only 10% of patients, and over the past 25 years, much innovation and research has gone into improving peri-operative diagnosis and therapy for these patients. Visco-elastic tests performed at the bedside, with modifications to allow direct quantification of fibrinogen levels, are probably the biggest advancement. There is no clear advantage of thromboelastometry over thromboelastography, and the published literature remains scarce. Visco-elastic testing has recently been coupled with the systematic replacement of clotting factors by means of factor concentrates, with objective improvement in terms of blood loss, red blood cell usage and surgical re-exploration. The National Institute for Health and Care Excellence has reviewed the available evidence and recommended visco-elastic tests as cost effective in cardiac surgery. Factor concentrates, however, carry significant risks, particularly unnecessary donor exposures, potential selective over-correction of partial deficiencies and the possibility that the postoperative risk of venous thromboembolism is increased; as yet there are no data on risk–benefit analysis. There are a number of promising drugs used in topical haemostasis, but the requirement to apply these before major bleeding is manifest limits their use considerably. Hyperfibrinolysis is less important than in the past due to the wide spread adoption of antifibrinolytic agents and close intra-operative monitoring of heparin effect.

Introduction

Cardiothoracic surgery uses approximately 10% of the blood supply of the National Blood Service in the UK; 90% of these products are consumed by only 10% of patients operated on. Over 30 000 cardiac surgical procedures are performed every year in the UK [1, 2]. Transfusion rates vary widely, and seem directly proportionate to the expertise of the centre when measured by the number of cases per year [3]. A number of blood products and pharmacological agents are available to minimise coagulopathy associated with excessive bleeding. Although there is no internationally agreed management protocol for patients bleeding after cardiac surgery, it has been shown repeatedly in the last 25 years that algorithm-based transfusion protocols are superior to individualised decisions [4]. Currently, there is a major trend to replace laboratory-based testing with point-of-care-based tests. Clear evidence for the benefit of individual products is lacking, as well as for the benefits of individual tests in isolation [5]. A number of topical agents are available which, in combination with intravenous administration...
of products, are useful to reduce microvascular bleeding [6]. This review will give an overview on causes, diagnosis, treatment and current state-of-the-art treatment based on available evidence.

Pathophysiology of the coagulopathy of cardiopulmonary bypass

Patients undergoing cardiopulmonary bypass (CPB) are subjected to a number of challenges which are unique to cardiothoracic surgery. The patient receives a large dose of heparin (300 IU.kg\(^{-1}\)), and is haemodiluted as soon as they are connected to the bypass circuit. All their blood comes into contact with the plastic tubing of the bypass circuit, which causes a variable degree of contact activation. Blood is then propelled to an oxygenator, where it is trickled through fine capillaries with secondary flow and a high dwell-time, and past a semi-permeable membrane to allow oxygen absorption, and then re-injected into the arterial system [7]. Propagation of blood can be with either roller or centrifugal pumps, which vary in their degree of platelet activation, with the latter increasing the degree of platelet activation and risk of clot formation [8]. Typically, a portion of the blood is cooled to 4°C and mixed with potassium chloride and local anaesthetic to deliver cardioplegia solution to the heart, allowing safe temporary cardiac arrest. The patient emerges at the end of CPB with reduced coagulation factor levels but high thrombin levels, which is different to other forms of surgery. Despite immediate reversal of heparinisation after CPB, inadvertent re-heparinisation from heparin-sequestering storage sites in the patient’s body is not unusual, due to the high heparin doses involved [9], especially in obese patients or when unusually large doses of heparin were administered during CPB due to heparin resistance [10, 11]. Despite the high heparin levels employed during CPB, platelets are activated, consumed and show selective loss of alpha granules in response to being exposed to foreign material and the flow conditions in the extracorporeal circuit [9].

Chest drain blood losses of up to 400 ml are to be expected in adults in the first 6 h after surgery. Excessive bleeding is usually defined as > 2 ml.kg\(^{-1}\).h\(^{-1}\), and high volume transfusion and/or surgical re-exploration may be required. Excessive bleeding is associated with a tripling of mortality, up to 10–15% overall [12]. In addition to coagulation changes outlined above, inflammation by complement activation through contact activation via the alternative pathway, IL-6 production and white cell activation also takes place, which causes a prolonged inflammatory response [9, 13].

Activation of fibrinolysis

At the same time as activating the clotting cascade, thrombin is also an activator of fibrinolysis. The action of thrombin during CPB and the release of by-products of thrombin activity, activate endothelial cells to release tissue plasminogen activator. This in turn converts plasminogen to plasmin, which acts on fibrin clots that have formed and releases split products such as D-dimers and fibrin degradation products. The activity of tissue plasminogen activator increases by at least three logarithmic scales in proximity to fibrin, helping to minimise the chance of systemic hyperfibrinolysis in response to a localised complication.

Historically, this mechanism accounted for a significant proportion of postoperative bleeding, but it is less important since the introduction of frequent ACT monitoring during CPB in the 1970s to prevent under-heparinisation. Activation of the fibrinolytic system is usually self-limiting and rarely extends into the post-operative recovery period. Excessive fibrinolysis would require overcoming the endogenous scavenger molecules that serve to inactivate plasmin, or an overwhelming release of tissue plasminogen activator, such as in exogenous administration of pharmacological doses. Where it gains pathological significance, the mechanism is usually two-fold: premature breakdown of cross-linked fibrin clots, and impairment of new fibrin polymerisation due to soluble fibrin and high fibrin degradation products [14].

Causes of excessive bleeding

There are three main causes of excessive postoperative bleeding in cardiothoracic surgery:

1. Surgical; half of patients who bleed have a surgical cause that can be identified at the time of re-sternotomy.
2. Coagulopathy; patients subjected to prolonged sternotomy, intra-operative hypothermia, or disseminated
intravascular coagulation, may exhibit microvascular bleeding in the absence of a surgical cause.

3 Pre-operative undiagnosed or untreated coagulopathy; due to anticoagulants, antiplatelet agents, congenital bleeding diathesis, thrombocytopenia or reversible platelet dysfunction.

Surgical bleeding can be due to a number of factors, for example residual chest wall bleeding, bleeding suture lines or, in extremis, graft dehiscence. If not recognised in a timely fashion, surgical bleeding can lead to inappropriate transfusion and delay in re-sternotomy, with protracted high blood loss. Recurrent factors associated with increased bleeding risk are underweight patients, re-do and complex procedures (e.g. multiple valve replacements or operations involving the aortic arch), as well as emergency operations [1, 15, 16].

Coagulopathy, on the other hand, needs to be corrected to ensure optimal haemostasis as this will exacerbate surgical bleeding. Abnormal haemostasis may be diagnosed in the absence of bleeding, and in this instance, correction will have no benefit to the patient and carry a potential risk of transfusion-transmitted infection, acute lung injury and immune modulation [5, 17].

Diagnosis

During chest closure, the experienced surgeon may be able to distinguish between micro-angiopathic and surgical bleeding. Subjective assessment of the type and degree of bleeding, however, may lead to over- or under-treatment. Current standard of care is the integration of laboratory-based results into the treatment algorithm, such as platelet count, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time. Increasingly, point-of-care testing is advocated, such as thromboelastometry (ROTEM®; TEM International, Munich, Germany), thromboelastagography (TEG®; Haemonetics Corp., Braintree, MA, USA) or impedance platelet aggregometry (Multiplate®; Roche Diagnostics Ltd, Rotkreuz, Switzerland) [5, 9, 17, 18]. In an attempt to quantify the volume of bleeding when the chest is still open, the chest may be packed with swabs for exactly five minutes before weighing the swabs and subtracting their dry weight [19].

Viscoelastic assays, such as TEG and ROTEM, have evolved from the simple addition of heparinase to allow haemostatic assessment during CPB while the patient is fully heparinised. Further refinements of in vitro conditions now produce values corresponding to the aPTT (INTEM (ROTEM) or kaolin-based TEG); PT (EXTEM (ROTEM) or rapid-TEG) and fibrinogen (FIBTEM (ROTEM) or functional fibrinogen (TEG)). In the past, a laboratory Clauss (functional) fibrinogen result of < 1 g.l⁻¹ was the trigger for treatment, but recent recognition of the importance of fibrinogen has led to suggested thresholds of 1.5–2.0 g.l⁻¹ [20]. FIBTEM (ROTEM) and functional fibrinogen (TEG) allow the direct assessment of the fibrinogen contribution to clot firmness by blocking platelets through or cytochalasin-D (ROTEM) or abciximab (TEG). In one study, a threshold of 10 mm (FIBTEM) corresponded to a Clauss fibrinogen of 2 g.l⁻¹ [21]. Of note, the result may depend on the exact platelet inhibitor used in the assay, and they are therefore not completely interchangeable [22, 23]. Fibrinogen levels can be corrected, either by the use of cryoprecipitate or fibrinogen concentrates. Some very small studies have suggested that aggressive replacement of fibrinogen with a commercially available concentrate (RiaSTAP™; CSL Behring, King of Prussia, PA, USA) may reduce red cell transfusion and re-sternotomy [24, 25], however further studies are required.

A competing technology is the Sonoclot (Sienco, Denver, CO, USA), where the viscoelasticity of blood is assessed with a vertically vibrating probe. The Clot-Signature trace looks completely different to the ROTEM/TEG trace, but produces very similar information. Modifications are also available to allow differentiated assessment of the coagulation system, and particularly platelet retraction [26].

The National Institute for Health and Care Excellence (NICE) has recently reviewed the available evidence for use of visco-elastic testing in cardiac surgery and concluded that viscoelastic testing improves the use of blood products and factor concentrates, reduces red cell transfusion, and is cost effective. It also concluded that the above was true for intra- and postoperative use, however they did not recommend any particular transfusion algorithm. For ROTEM and TEG, the effect on mortality, length of ICU and hospi-
eral stay, and rate of re-sternotomy was not statistically significant across all studies [26].

Near-patient platelet function testing is not yet widely adopted in cardiac surgery. Platelet concentrate is usually administered if the laboratory platelet count is < 100 x 10^9, but many clinicians administer platelet concentrate whatever the laboratory value, on the basis that platelet function is abnormal due to prior administration of aspirin or clopidogrel. Point-of-care devices such as Multiplate (Roche Ltd) for assessing platelet function using are now available. The evidence for their benefit is limited [27–29] and thresholds for intervention are not yet clearly defined. However, abnormal results for the stimulation of the adenosine diphosphate (ADP) and thrombin receptors (residual aspirin and clopidogrel activity respectively) may be predictive for higher transfusion requirements [30].

Laboratory assays for hyperfibrinolysis are used in clinical trials, but have not yet entered clinical practice. Hyperfibrinolysis may also be apparent on visco-elastic testing, but their sensitivity is low. Both the maximum lysis in 60 min and the time of onset of lysis have been used in research studies. When compared with laboratory tests in trauma patients for fibrinolytic activation (plasmin/antiplasmin complex and D-dimer levels), more than 90% had a normal fibrinolytic pattern in the maximum lysis (ML > 15%) of the ROTEM assay [31–33].

Cardiothoracic postoperative bleeding may be complicated by early coagulopathy due to the high intra-operative dose of heparin, whether due to incomplete reversal with protamine, or inadvertent silent re-heparinisation of the patient from sequestration sites. Consequently, some of the massive blood loss protocols in use by other specialties are of limited benefit in cardiac surgical patients [9]. This means that rapid turnaround and appropriate testing is even more important than in other forms of surgery.

**Treatment**

Available clotting factor concentrates, their relative factor content and cost are compared in Table 1.

**Fibrinogen**

Replacing fibrinogen if levels are low has taken centre stage with regard to the relative importance of coagulation factor replacement in major bleeding, and after CPB in particular. In the 2004 British Committee for Standards in Haematology (BCSH) guidelines [35], a target of 1 g.l^-1 was suggested; in recognition of the changes in major bleeding management. A new guideline is due to be published, and this is likely to set a trigger for giving fibrinogen (in the form of cryoprecipitate) at 1.5–2.0 g.l^-1. The American and Japanese guidelines state a minimum target of 0.8 g.l^-1, and German and Austrian/European trauma guidelines suggest 2 g.l^-1 [36, 37]. Indeed, clot firmness improves up until fibrinogen > 3 g.l^-1, with clot formation rate highest at 2 g.l^-1 [38]. While there is no evidence of harm, raising the transfusion threshold increases the number of eligible patients and, given that factor concentrates expose the patient to 20 000 donations or more, this could be potentially hazardous. The manufacturers quote the resultant extreme dilution of individual donations as an advantage, but history has proven that, dependent on the pathogen, this may or may not be true. While data on overall survival benefit is not available, caution should be exercised, particularly given the cost difference between cryoprecipitate and fibrinogen concentrate on a gram-for-gram basis and the lack of data on risk-benefit and cost effectiveness.

The choice between cryoprecipitate and fibrinogen concentrate varies from country to country, partially due to availability. Non-heat-treated fibrinogen concentrate was withdrawn in the US and replaced with cryoprecipitate to reduce the risk of transmission of non-A, non-B hepatitis, which affected up to 5% of batches in the late 1970s, with a number of countries following suit. Fibrinogen concentrate is now heat-treated, but this has not led to a re-introduction of this product in all countries where the license had been previously withdrawn. Cryoprecipitate itself was not originally designed as a treatment for hypofibrinogenemia, but was intended as a treatment for haemophilia A and von Willebrand disease, and subsequently found to also be rich in fibrinogen and factor XIII [39]. Interestingly, the NICE guidance on viscoelastic testing does not refer to cryoprecipitate at all, and recommends fibrinogen concentrate instead, despite the absence of a UK license for the treatment of acquired coagulopathy [26].
Fresh frozen plasma

There is limited evidence for the therapeutic benefit of fresh frozen plasma (FFP) in postoperative coagulopathy. The main body of evidence is from retrospective data in massive transfusion, where civilian and military trauma studies showed a survival benefit in patients who received higher FFP:red cells ratio (so called 1:1 ratio) [40–43]. However, this data have been criticised in that there was survivorship bias because patients who died on arrival at the emergency centre would not have had time to receive FFP.

The most frequently administered dose of FFP in the UK is 15 ml.kg⁻¹ in adults [44, 45]. This is a dose of convenience, which is tolerable in most patients, taking into account that an adult has between 36 and 38 ml.kg⁻¹ plasma volume, and that, on average, FFP contains 1 U.ml⁻¹ clotting factors. Prothrombin time and aPTT are screening tests which are dependent on the exact reagent–analyser combination, and become prolonged when there is moderate reduction of a single clotting factor below the reference range. Paradoxically, in a patient with multiple coagulation factor deficiencies, this occurs at a higher threshold than in single factor deficiencies [46, 47]. Therefore, a standard dose of FFP can elevate the plasma factor concentration to a level where these tests return to near normal, but the clinical effect may be less pronounced. A dose of 30 ml.kg⁻¹ FFP has been quoted as potentially a more effective therapeutic alternative. While this dose makes sense from a coagulation point of view, the major setback is the large volume of administration (2.25 l for a 75 kg patient), which could potentially nearly double the circulating plasma volume. This could be detrimental in patients exhibiting a degree of myocardial stunning or cardiac failure after cardiac surgery [45]. Given this, and the fact that CPB causes haemodilution, the indication for FFP in patients with mild prolongation of PT, aPTT or visco-elastic parameters is often questionable.

Prothrombin complex concentrates

The two most widely used products in Europe are four-factor prothrombin complex concentrate (PCC) containing protein C and S, as well as factors VII, IX, X and II and traces of heparin. While PCC can replace
the vitamin K-dependent clotting factors regardless of
the cause of clotting factor depletion, the universally
accepted (and licensed) indication remains warfarin
reversal. A dose equivalent in vitamin K-dependent
clotting factor activity to 15 mL.kg⁻¹ FFP in a 70 kg
patient can be given in 40–50 ml of fluid as opposed
to over 1 l in the case of FFP. However, there is little
data as yet comparing PCC with FFP for the treatment
of acute peri-operative haemorrhage, let alone in the
cardiac surgical setting. In addition, published studies
have compared point-of-care with laboratory testing at
the same time as PCC with FFP, making interpretation
of the actual advantages and disadvantages very dif-
cult. Therefore, the main benefit is the speed of
administration, reliable effect, and small treatment
volume, however further research is awaited [48–50].

Platelets

There remains great controversy regarding the platelet
transfusion threshold to be applied in cardiac surgery,
due to the platelet function defect present in all
patients after CPB [51]. Numeric platelet counts from
the laboratory may not be accurate due to clumping,
particularly if the patient is hypothermic or if the sam-
ple was taken during or immediately after CPB, which
can lead to an artifically low platelet count. The
numerical analysis of platelets in the laboratory does
not take into account a variable degree of platelet dys-
function induced by CPB and potentially exacerbated
by pre-operative treatment with platelet antagonists
and/or uraemia [51]. The monitoring of platelet block-
ade with impedance aggregometry (Multiplate), platelet
mapping (TEG) or latex agglutination (Verify Now®,
Accumetrics, San Diego, CA, USA), remains outside
what is considered the standard of care, and the clinical
utility of preserved patient platelet function in vitro
remains to be established. Near-patient platelet function
assessment relies on a minimum number of platelets available in the patient for analysis (50–
100 × 10⁹.l⁻¹), and can be adversely affected by extremes of haematocrit when this is performed on
whole blood. As the platelet count decreases, the
absence of platelet function in vitro is difficult to inter-
pret, whereas preserved platelet function despite thrombocytopenia is considered to confirm normal
platelet function. The problem here also is that aggre-
gation is only one of the functions of platelets. Even
when more than one aggregation response assessment
is performed (e.g. collagen, aspirin, ADP, thrombin
receptor agonist peptide), interpretation becomes more
and more difficult given the complex nature of post-
CPB coagulopathy [5, 52, 53]. Treatment is still trans-
fusion of platelet concentrate, whatever the defect, with
a trend to consider double dose platelets or downward
adjustment of the platelet transfusion threshold to
compensate for reduced function.

The best measure of platelet function postopera-
tively remains unresolved. Currently, platelet function
testing may be more important for pre-operative risk
stratification. Most measures of platelet function
become invalid at platelet counts < 50–100 × 10⁹ in
the test tube [54]. Enriching platelets in vitro to allow
an assessment in this situation introduces signifi-
cant delay, which is why platelet aggregometry, considered
the gold standard of platelet function assessment, has
never become standard in postoperative patients after
cardiac surgery [55].

Antifibrinolytic drugs

There has been a lot of interest in hyperfibrinolysis
since the introduction of aprotinin in 1986 [56]. In
current clinical practice, true hyperfibrinolysis apparent
in vitro by TEG is a rare occurrence. It would appear
that a degree of fibrinolysis is to be expected after car-
diac surgery, but the definition of systemically appar-
ent hyperfibrinolysis is less clear.

Tranexamic acid (TXA), used almost ubiquitously
in UK cardiac surgical practice, and epsilon amino-
caproic acid (EACA), are synthetic lysine-analouges
that reversibly block the lysine binding site of plasmin-
ogen which inhibits the lysis of polymerised fibrin.
They have a plasma half-life of around 2 h, and are
excreted in the urine in high concentrations [53]. The
optimum dose of TXA is unknown despite its wide-
spread international use, with 10 mg.kg⁻¹ bolus fol-
lowed by 1 mg.kg⁻¹.h⁻¹ as a continuous infusion
being the most commonly used regimen, with little
evidence for higher doses [57]. Seizures are the main
reported adverse event with TXA, but thrombotic
events after its use have not been reported. Both agents
have been shown to reduce blood loss, when used pro-
phyactically in cardiac surgery. Tranexamic acid may
be slightly more effective than EACA in reducing blood loss, however there is little evidence to support the exceedingly high doses (up to 10 g) used in some centres [57].

Aprotinin is a bovine-derived serine protease inhibitor which has powerful antiplasmin and antikallikrein effects. In high doses, it reduces bleeding in cardiac surgery [57]. It has a number of additional effects such as reduction in neutrophil activation and interaction with the renin–angiotensin system. The half-life of this drug is more than twice as long as TXA or EACA (5–10 h). Despite a positive effect on red cell transfusion and reduction in blood loss, a retrospective analysis of 4000 patients by Mangano et al. [58] detected an increase in the incidence of renal failure, increased incidence of myocardial infarction and heart failure in the aprotinin group compared with TXA, EACA and placebo. This was confirmed in the randomised controlled BART trial [59], which studied 2331 high-risk cardiac surgery patients. The trial was terminated early due to excess mortality in patients who received aprotinin, despite decreased blood loss and transfusion [59]. This led to the withdrawal of aprotinin.

Currently, aprotinin use in the UK can only be considered in uncomplicated coronary artery bypass graft surgery for named patient use, however this is not ideal because the majority of these cases are not at excessive risk of bleeding. The administration of aprotinin to patients who would probably benefit the most, such as those undergoing surgery for endocarditis, re-sternotomy and complex multiple procedures, is not currently advocated or licensed. Where aprotinin is administered, care must be taken to assess the effect on celite-based coagulation tests such as some activated clotting test cartridges and aPTT reagents, and additional heparin administration may be required. The prolonged aPTT seen postoperatively, given the half-life of 10 h, may lead to inappropriate FFP or protamine administration [57].

Desmopressin
Desmopressin (DDAVP) is a vasopressin analogue which releases endogenous von Willebrand Factor (vWF) stored in the Weibel–Pallade bodies of endothelial cells, as well as factor VIII, prostacyclin and tissue plasminogen activator. Its structure is modified from vasopressin to reduce its vasoactive actions. This reaction is exhaustible, and the drug is typically administered no more frequently than once in 24 h. It is most often used in mild haemophilia A, von Willebrand’s disease and platelet disorders, and it is also a useful adjunct in uraemic and cirrhotic bleeding. Rapid administration can lead to hypotension, and the antidiuretic hormone-like effect can lead to fluid retention [60].

The evidence for the use of DDAVP in cardiac surgery comes from two trials which showed that, in small cohorts of patients undergoing complex cardiac surgery, DDAVP administration led to a reduction in mean 24-h blood loss compared with placebo, and those patients with the lowest vWF levels benefitted the most [61, 62]. Subsequent trials have failed to show a reduction in blood loss following DDAVP administration. Horrow et al. were able to show that co-administration of TXA was necessary in a small group of patients to reduce blood loss, which the authors attributed to concomitant tissue plasminogen activator release [63].

Recombinant factor VIIa
Pharmacological doses of recombinant factor VIIa (rVIIa) concentrate should only be used as a last resort, due to the excess of prothrombotic events and lack of evidence for a reduction in overall mortality [64]. Recombinant factor VIIa contains factor levels in excess of four logs of the physiological concentration of VIIa, which are able to activate factor Xa in the presence of activated platelet surfaces. A recent meta-analysis included 4468 patients, and showed that rVIIa increased the risk of arterial thrombosis (5.5% vs 3.3%), especially in the elderly, whereas the risk of venous thromboembolism remained unchanged [65]. Where rVIIa is used, coagulopathy must be addressed first, as there is a greatly reduced effect in the presence of hypothermia, hypocalcaemia, hypofibrinogenemia or major coagulopathy.

Activated prothrombin complex concentrate
Activated prothrombin complex is plasma-derived, and contains similar quantities of factor VII, IX and X compared with (non-activated) four-Factor PCC. In addition, small quantities of factor VIIa and Xa are
present. It has been shown to be effective in small cohorts of patients, but also produced thrombosis in unusual sites as a side effect, and its use should be restricted in a similar way to rVIIa [66].

**Factor XIII**

Factor XIII concentration is reduced during CPB, consistent with other clotting factors. Over the last 20 years, there have been a few small studies with conflicting results regarding the link between low factor XIII plasma levels and excessive bleeding after cardiac surgery. In a randomised controlled trial of recombinant factor XIII vs placebo, there was no therapeutic benefit on transfusion avoidance, transfusion requirements or operative revision, despite an observed correction of factor XIII levels. Factor XIII administration outside clinical trials should therefore be discouraged [67–71].

**Topical sealants**

The first use of human plasma as a topical haemostatic agent was documented in 1909 [72]. There are a number of situations considered amenable to topical haemostatic agents: diffuse raw surface bleeding or oozing; venous-type bleeds; bone bleeding; and needle-hole bleeding. As a rule of thumb, low-flow situations are most amenable to topical haemostatic agents, meaning that the best time to apply them may be before weaning from CPB, while there is low flow in the wound bed. However, this is suboptimal, as the unselective use of these agents is undesirable. Moreover, the surgeon has to weigh risks and benefits carefully before their application, as some of these topical agents may be inadvertently aspirated by the cell saver or cardioto-my sucker and therefore re-infused to the patient intravascularly. In addition, leakage of these agents through incompletely sealed wounds into the surgical site and embolisation has been described [73].

Topical haemostatic agents rely on the patients’ native platelets and haemostatic system to provide a framework for platelet or clot adhesion. They are mostly isolated or combined animal, or human, plasma-derived clotting proteins, recombinant clotting proteins or other polymers. Broadly, four types of topical agents are in use, even though the nomenclature is somewhat confusing, given the heterogeneity of the components.

**Mechanical**

Mechanical haemostatic agents (microporous polysaccharide, chitin/chitosan-based, collagen, gelatin, cellulose) provide a framework for platelet or red cell adhesion, with little alteration in haemostasis. Examples include Surgicel (Johnson & Johnson Medical Inc, Arlington TX, USA) and Oxycel (Oxycel, Pershore, UK).

**Flowable**

Flowable agents are also based on gelatin from various animal sources but some, such as Surgiflo® (Ethicon, Livingston, UK) or FloSeal® (Baxter, Compton Newbury, UK), contain plasma-derived human thrombin.

**Fibrin/albumin/synthetic sealants**

Fibrin or synthetic sealants are based on the dual action of fibrinogen and thrombin, and contain human pooled thrombin and fibrinogen. Examples include Tisseel® (Baxter) or Evicel®/Quixil® (Ethicon). Synthetic alternatives function by a similar mechanism, but do not contain human or animal plasma derivatives. Examples include cyanoacrylate (Omnex®; Ethicon) and CoSeal® (Proseal, Macclesfield, UK). Tisseel contains a fibrinolysis inhibitor, bovine aprotinin and Quixil contains TXA.

The sealant Bioglue® (Cryolife, Kennesaw, GA, USA) contains bovine serum albumin and glutaraldehyde, making it difficult to categorise as it contains albumin rather than fibrin or synthetic sealant but does not rely on the action of added thrombin.

**Active**

Active topical haemostatic agents are based on bovine (Thrombin JMI®; Pfizer, Walton Oaks, UK), human (Evithrom®; Ethicon) or recombinant thrombin (Recothrom®; The Medicines Company, Parsippany, NJ, USA). A completely synthetic tissue sealant consisting of recombinant fibrinogen, thrombin and factor XIII has recently been described [72].

Evidence for the use of these products is limited, and most of the studies have a considerable risk of bias due to sponsorship by manufacturers [6]. Also, the criteria for determining a response are difficult to standardise, and there are often clinical confounding factors.
Those products that are based on bovine thrombin are associated with a risk of inducing anti-human factor V antibodies due to bovine prothrombin cross-reacting with human factor V (Thrombin–JMI®, Pfizer, New York, USA) [74–77]. Since their first inception in 1943, the purity of the products has improved substantially. The incidence of factor V inhibitor with the currently available bovine thrombin product (Thrombin-JMI), which contains less bovine thrombin product, remains unknown [78].

Patients who refuse blood products would have to be specifically consented with regard to the preferred topical sealant, making particular reference to the bio-source of the components. The benefit of these agents is likely twofold: reduction in allogeneic blood use, which is not clinically significant in many cases as the agents are not applied in low-flow situations; and a reduction in time to chest closure and subsequent transfer to the intensive care unit [6, 73].

**Application**

Patient blood management is a multidisciplinary, evidence-based approach to reduce avoidable blood transfusion as much as possible. All hospitals in the UK have been asked by NHS Blood and Transplant, the UK Department of Health and the UK National Blood Transfusion Committee to establish a patient blood management programme, to include: patient and clinician education and intervention; a review of the frequency and volume of blood testing; use of near-patient haemoglobin testing; adherence to approved indications and transfusion triggers when requesting blood; optimisation of pre-operative anaemia and reversal of pre-operative anticoagulant therapy by using agreed protocols.

**Conclusion**

The optimal transfusion support of the bleeding patient after cardiothoracic surgery remains to be established. A ‘state-of-the-art’ transfusion algorithm should include indicators for residual heparin, measures of haemodilution or coagulation factor consumption, an indicator specific for hypofibrinogenaemia, and a platelet count. The tests should be rapidly available and clinicians should be familiar with their interpretation and limitations. The routine use of platelet function tests cannot currently be recommended. More evidence, particularly from randomised controlled trials, is required to identify the haemostatic agents that are most appropriate to treat postoperative haemorrhage and to identify the optimum postoperative treatment algorithm, including differentiated point-of-care testing. This will allow a more tailored transfusion strategy, with minimal turnaround times in patients with postoperative haemorrhage following cardiac surgery.

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**Competing interests**

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References


A review of echocardiography in anaesthetic and peri-operative practice. Part 1: impact and utility

R. L. Barber¹ and S. N. Fletcher²

¹ Specialty Registrar in Intensive Care Medicine and Anaesthesia, Leicester Royal Infirmary, Leicester, UK
² Consultant Anaesthetist and Intensivist, St George’s Hospital and Honorary Senior Lecturer, St George’s University of London, London, UK

Summary

Echocardiography is migrating rapidly across speciality boundaries and clinical demand is expanding. Echocardiography shows promise for evolving applications in the peri-operative assessment and therapeutic management of patients undergoing non-cardiac surgery, whether it be elective or emergency. Although evidence is limited with regard to significant impact on outcomes from anaesthesia and surgery, there is little doubt about the validity and power of two-dimensional real-time viewing of cardiac anatomy and function. Echocardiography can be used to assist in decision-making along the entire peri-operative pathway, and is increasingly delivered by the previously referring physicians. The discussion around more widespread incorporation of cardiac ultrasound into anaesthetic practice must take into account competency, training and governance. Failure to do so adequately may mean that the use of echocardiography is poorly applied and costly.

Introduction

There is a tipping point at which the uptake of a highly functional technology, such as the mobile phone, can be observed to behave almost like the spread of an epidemic [1]. Arguably, the tipping point for echocardiography was reached well over a decade ago in cardiac anaesthesia and emergency medicine [2–4] and within the last decade in critical care [5, 6]. This pattern of uptake has also occurred with ultrasound for nerve blocks and vascular access in anaesthesia [7–10]. Echocardiography, or cardiac ultrasound, allows the clinician to view heart valves, cardiac chambers, the pericardium and major blood vessels, and also to observe the blood flow within these structures. Historically, this was limited to patients who were safely able to reach the echocardiography department [11]. With the development of compact, portable, high-quality platforms, echocardiography can now be readily performed wherever the patient is located. Clinical demand is now the only driver for an echocardiographic examination rather than the geography of the hospital, and, as referred to above, this clinical demand has continued to expand. Echocardiography is a complex technical skill and the limiting factor in the uptake of echocardiography in these settings is the availability of trained operators. Much has been written about this clinical demand and there are a variety of initiatives in different healthcare systems to supply it.

As anaesthetists demand more widespread use of echocardiography within their practice [12], it is
pertinent to stand back and evaluate the supporting evidence and search for insight into how this may be achieved safely and efficiently.

Methods
In this review, we have searched PubMed and Embase using the terms echocardiography, ultrasound, anaesthesia, anesthesiology, anaesthetist and anesthesiologist. We have also searched the websites of professional bodies related to echocardiography and anaesthetic practice. We have filtered the results to focus particularly on echocardiography in non-cardiac anaesthesia practice, although we have included other publications from related areas of practice, where relevant. We present a narrative review highlighting the best of the available supporting evidence and professional recommendations.

Pre-operative assessment and the undifferentiated murmur
Valvular heart disease is an independent risk factor for peri-operative mortality and morbidity [13]. However, the clinical methods by which murmurs are detected and classified as normal or abnormal can be surrounded by difficulties. Although pre-operative questioning may raise the suspicion of valvular pathology, the lack of symptoms may be falsely reassuring. Early features of symptomatic valvular disease may be non-specific and difficult to separate from co-existent respiratory disease, and some patients may be unaware of a gradual decline in their exercise tolerance. Heart murmurs are commonly detected by anaesthetists during pre-operative assessment, yet the sensitivity of auscultation in this context is unknown [14]. Senior cardiologists fail to detect 10–20% of murmurs, and no physical examination finding has been identified that has both a high sensitivity and a high specificity for the diagnosis of severe aortic stenosis in asymptomatic subjects [15]. It is recommended that echocardiography be performed in patients with known or suspected valvular heart disease to assess its severity and consequences [16].

It comes as little surprise that practice differs between anaesthetists, mostly when it comes to striking a balance between thorough investigation and the need for expedient surgery. A dilemma is commonly encountered for patients with hip fractures, in whom the prevalence of moderate-to-severe aortic stenosis may be as high as 8% [17] and a delay in surgery is associated with an increase in morbidity and mortality [18, 19]. A national postal survey highlighted this dilemma: 20% of respondents would insist on an echocardiogram when confronted with a previously undiagnosed heart murmur; 54% would request an echocardiogram only in the presence of suspicious signs or symptoms; and 26% would proceed with hip surgery in the absence of an echocardiogram [20].

Patients who have echocardiography are more likely to experience a delay in surgery, although this delay may be determined by their overall medical complexity [21]. The institution of a dedicated echocardiography service, among other service changes, can reduce the mean time for transthoracic echocardiography (TTE) and surgery [17]. This is in line with national recommendations that the availability of pre-operative TTE should be prioritised [22]. The authors claimed that the service improved the process of informed consent and increased clinicians’ vigilance, but a major drawback was that the service depended on senior sonographers who were unavailable at weekends. Many hospitals are, in reality, unable to deliver even a weekday service [23, 24]. A focused TTE delivered by the anaesthetist can relieve pressures on echocardiography departments without introducing a delay before surgery [25, 26]. Loxdale et al. undertook TTE in all patients with hip fracture; in contrast, Canty et al. performed a focused TTE examination, designed to take < 10 min only on patients more than 65 years old [17]. This more practical and achievable concept showed a lower 30-day and 12-month mortality in the 64 patients who underwent TTE in comparison with the control group [26]. This proof-of-concept study lacked power, but it showed that anaesthetic-delivered TTE is feasible and an area of promise for future research.

Pre-operative assessment and ventricular function
Major adverse cardiac events are a leading cause of morbidity and mortality following major surgery [27–29]. Pre-operative risk stratification using clinical cardiovascular risk indices are utilised in an attempt to study and
improve these outcomes [30–32]. Resting pre-operative TTE is one non-invasive test that is commonly requested to provide additional prognostic information. It is as yet equivocal whether adding echocardiography values to models of risk prediction improves their predictive strength. This may be either because resting TTE cannot reliably detect coronary artery disease and inducible ischaemia, or because there are limited therapeutic options for poor systolic function. Studies have advanced conflicting views, and there are no randomised controlled trials evaluating the effect of pre-operative echocardiography on postoperative outcomes [33, 34]. It is important to note that left ventricular dysfunction is not purely confined to systolic function. Half of patients with congestive cardiac failure have normal systolic function [35], and the significance of diastolic dysfunction has only recently come to light. Diastolic dysfunction is an independent predictor of adverse outcome after major vascular surgery and can be assessed using TTE [36]. The incorporation of pulse wave and tissue Doppler into modern bedside ultrasound platforms raises the possibility of its inclusion into pre-operative TTE protocols.

It is similarly important to appreciate that the model of cardiac function as a single chamber pump is an oversimplification. The right ventricle has, until recently, received less attention than the left. There are few studies that have specifically examined the risk associated with right ventricular failure and non-cardiac surgery. Right ventricular dysfunction in cardiac surgery significantly increases the resulting morbidity and mortality. Severe pulmonary hypertension is associated with a 7% mortality rate in non-cardiac surgery in which right ventricular failure was a contributing cause of death [37]. Recognition of the condition and directed peri-operative treatment are essential in the management of these patients. Echocardiography is the only practical investigation available for confirmation of the diagnosis of right ventricular failure, and is accurate for the evaluation of pulmonary hypertension [38, 39].

Current evidence-based consensus recommendations do not agree on the use of resting echocardiography for left ventricular assessment in patients undergoing high-risk surgery (level C evidence and IIa recommendation) [16, 40], yet it is the most frequently requested specialised test before non-cardiac surgery. This places a significant burden on busy outpatient echocardiography clinics and introduces a delay to the flow of patients along the surgical pathway. This provides context for the interest in anaesthetist-delivered echocardiography. Echocardiography is surely a powerful tool when in the hands of the person posing the clinical question, who is then in the position of translating the results of the scan into a peri-operative plan.

In the emergency setting, when access to echocardiography may be time-limited, clinical assessment of cardiac disease may be unreliable. Echocardiography has been shown to change the cardiac diagnosis in as many as 67% of patients [41]. Three of the four patients with a clinical diagnosis of cardiac failure made by the anaesthetist were revealed to be incorrect. Two of these patients were found to be hypovolaemic on TTE and administration of fluid boluses was required. Similarly, three of the five patients assessed as hypovolaemic by the anaesthetist had cardiac failure, as was one patient who was diagnosed with normal cardiac function. Focused TTE has been shown to enhance confidence in decision-making with regard to cardiovascular pathology in the emergency department, and it seems plausible to suggest that a similar effect may be seen in peri-operative practice [4]. Although there is doubt regarding the validity of left ventricular assessment with resting TTE to reduce individual mortality and morbidity, a test that improves diagnostic accuracy and clinical management may result in improved clinical outcomes, and further work is needed to capture potential benefits.

Impact on pre-operative management

Transthoracic echocardiography can be used anytime in the period preceding surgery, from the pre-assessment clinic to the anaesthetic room, and it has been shown to influence anaesthetic management [25, 42]. A change in management occurred in 54% of unselected patients, but when applied to a selected group with suspected cardiac disease, this increased to 61% [43]. This compares favourably with the critical care environment, where TTE is more established [44]. Overall, Canty et al. found that there was an escalation in management in 20–33% of patients, and it was scaled down in 8–34% [41–43]. On further examination, a
Significant proportion of this impact related to the requirement for vasopressors or intra-operative invasive monitoring. It is possible to interpret this as merely opinion, but it may indeed represent a vigilant and proactive approach to the prevention of acute cardiovascular decompensation. Cowie et al. found that pre-operative TTE in the operating or anaesthetic room avoided an adverse incident on six occasions (7% of all scans) [25]. Planned non-essential surgery was cancelled or delayed following the diagnosis of hitherto unrecognised severe valvular pathology or pulmonary hypertension. Similarly, on two occasions in an audit of 39 patients, TTE performed in the anaesthetic room revealed cardiac disease of such severity that a conservative management plan was instigated as an alternative to surgery [42]. Effective pre-operative assessment also has a significant impact on hospital efficiency and postoperative resource allocation. With ever increasing demand for critical care beds, there are clinical and economic pressures to use this limited resource as efficiently as possible [44–47]. Pre-operative bed requests may be based on inaccurate information, and result in inappropriate prioritisation or delay in critical care bed allocation. Greater accuracy of pre-operative assessment using TTE can reduce postoperative referral to high-dependency areas, reduce the surgical cancellation rate and also reduce referral rates to allied specialities such as cardiology [42] (Table 1).

Intra-operative haemodynamic monitoring
The ability of multiplane transoesophageal echocardiography (TOE) to influence anaesthetic and surgical decision making in cardiac surgery [52] has made routine TOE not only a clinically beneficial modality but also a cost-effective one [53–59]. The widespread use of TOE in non-cardiac surgery remains controversial. However, there are specific circumstances where the impact of TOE is increasingly recognised, such as haemodynamic failure and optimisation. Transoesophageal echocardiography can alter intra-operative anaesthetic care for a wide range of patients, including minor abdominal to major vascular procedures, and Suriani et al. showed that in 15% of cases, TOE may have a major impact [48]. Impact studies in the context of haemodynamically unstable patients yield much more impressive results: therapy was altered in 60% of patients with life-threatening unexplained intra-operative hypoxia or hypotension in another study [49]. During 22 intra-operative cardiac arrests, TOE established the primary aetiology in 19. This included nine patients with thromboembolic events and two with cardiac tamponade. This gave the clinicians the confidence to proceed rapidly beyond advanced cardiac life support protocols to implement definitive therapy, including pulmonary embolectomy, ventricular thrombectomy, pericardotomy and mechanical support by intra-aortic balloon pump [60]. Assessment of preload and myocardial contractility is an essential accompaniment to the successful modern management of the high-risk surgical patient. Echocardiography can accurately predict fluid responsiveness and enable informed changes in vasoactive drugs [51, 61–65]. Unlike alternative flow-based monitors that display a numerical value, echocardiography can display real-time changes in valvular function or the development of ventricular wall motion abnormality. Segmental wall motion abnormalities are alarmingly common, seen in 20–32% of patients undergoing surgery, and there is a clear association with coronary ischaemia and cardiac events [66]. Prompt detection and treatment can result in the resolution of myocardial ischaemia, and TOE has been demonstrated to be effective when used in this manner [51]. Transoesophageal echocardiography is twice as sensitive to left ventricular wall motion abnormalities when compared with ECG monitoring, although clinical and enzyme correlation with intra-operative findings is currently lacking [67]. A new miniaturised monoplane disposable TOE probe (Imacor Inc, New York, NY, USA) has been recently trialled in critical care and cardiac surgery [68–70]. Whereas it is too early in the development of this technology to recommend its use in non-cardiac surgery, the potential utility and ease of use for the non-expert echocardiographer warrant investigation for non-cardiac surgical intra-operative use.

Emergency and trauma care
There is an increasing body of evidence that advocates the role of echocardiography in the emergency department and in the management of trauma patients [71–78]. Transthoracic echocardiography has been
Table 1 Impact studies of anaesthetist-performed transthoracic and transoesophageal echocardiography in non-cardiac surgery. Level of evidence as per National Institute for Health and Care Excellence (NICE) 2005 levels of evidence for intervention studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Impact</th>
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<tr>
<td>Canty et al. [43]</td>
<td>Observational prospective study of TTE in 100 non-cardiac surgery patients&lt;br&gt;Indication: cardiac risk, suspected cardiac disease or age ≥ 65&lt;br&gt;Level of evidence 3</td>
<td>Management change 54%&lt;br&gt;Step up 20%&lt;br&gt;Step down 34%&lt;br&gt;Monitoring change 30%&lt;br&gt;Anaesthetic technique change 4%&lt;br&gt;Postoperative location 16%</td>
<td>Focused scan performed by a single anaesthetist in the pre-operative clinic&lt;br&gt;In 92% findings consistent with cardiology opinion, and no clinically significant differences in 8%</td>
</tr>
<tr>
<td>Cowie [25]</td>
<td>Observational prospective study of TTE in 170 non-cardiac surgery patients&lt;br&gt;Level of evidence 3</td>
<td>Management change 82%&lt;br&gt;Monitoring change 37%&lt;br&gt;Anaesthetic technique change 12%&lt;br&gt;Postoperative location 7%&lt;br&gt;Cancelled 4%</td>
<td>Focused scan performed by cardiac anaesthetists in the peri-operative setting and requested by the primary anaesthetist&lt;br&gt;Consistency of 91% in those patients that went on to receive formal TTE</td>
</tr>
<tr>
<td>Canty et al. [41]</td>
<td>Observational prospective study of TTE in 99 non-cardiac surgery emergency patients&lt;br&gt;Indication: cardiac risk, suspected cardiac disease or age ≥ 65&lt;br&gt;Level of evidence 3</td>
<td>Management change 44%&lt;br&gt;Diagnosis change 67%&lt;br&gt;Step up in 36% and step down 8%</td>
<td>Focused scan performed by a single anaesthetist pre-operatively</td>
</tr>
<tr>
<td>Canty and Royse [42]</td>
<td>Observational prospective study of TTE in 87 patients: mixed elective and emergency&lt;br&gt;Indication: murmur, structural heart disease, dyspnoea, haemodynamic disturbance chest pain and syncope&lt;br&gt;Level of evidence 3</td>
<td>Management change in 75%&lt;br&gt;Scans performed immediately before emergency surgery and in 43% of elective&lt;br&gt;Haemodynamic changes in 8 of 10 intra-operative TTE</td>
<td>Focused scan performed by a single anaesthetist peri-operatively&lt;br&gt;Adequate intra-operative images in all 10 subjects</td>
</tr>
<tr>
<td>Canty et al. [26]</td>
<td>Retrospective study of TTE in 64 patients with hip fracture and high cardiac risk&lt;br&gt;Level of evidence 3</td>
<td>Management change in 52%&lt;br&gt;Lower mortality at 30 days and 12 months</td>
<td>Pre-operative focused TTE&lt;br&gt;Proof of concept exercise</td>
</tr>
<tr>
<td>Suriani et al. [48]</td>
<td>Retrospective study of TOE in 123 non-cardiac surgery patients&lt;br&gt;Level of evidence 3</td>
<td>Management change 81%&lt;br&gt;Major impact in 15%&lt;br&gt;Minor impact in 48%&lt;br&gt;Limited impact 17%&lt;br&gt;No impact 20%</td>
<td>Intra-operative TOE&lt;br&gt;No complications from TOE</td>
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<td>Denault et al. [49]</td>
<td>Prospective observational study of intra- and postoperative TOE in 214 non-cardiac surgery patients&lt;br&gt;Level of evidence 3</td>
<td>Greater impact in those with haemodynamic instability&lt;br&gt;Category 1 indications: 60% had therapy altered&lt;br&gt;Category 2: 31% had therapy altered&lt;br&gt;Category 3: 21% had therapy altered</td>
<td>Performed during surgery and afterwards in PACU or ICU</td>
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shown to predict unfavourable outcomes in patients with sonographically identified cardiac standstill, regardless of the initial electrical rhythm on arrival at the emergency department [74–76]. Jones et al. used TTE in the assessment of patients with non-traumatic hypotension and shock [71, 78]. They concluded that early echocardiography increased the likelihood of detecting the correct diagnosis for the cause of hypotension from 50% to 80%, and echocardiographic detection of hyperdynamic left ventricular function had a high specificity (93%) for septic shock [71, 78]. Other investigators have successfully used echocardiography to assess cardiac pathology such as chest pain, cardiomegaly and pericardial effusion in the emergency department [73, 74, 79]. Anaesthetists are an essential part of hospital resuscitation and trauma teams. The role of the anaesthetist in a resuscitation and/or major trauma scenario may extend beyond the more conventional requisite of airway management to provision of advanced circulatory support such as establishing invasive monitoring and commencing vasopressors and/or inotropes, if required. Echocardiography thus merits a place in resuscitation protocols and the advanced circulatory management of blunt or penetrating traumatic injury, and could be a vital tool in the decision-making process. It is worth mentioning pleural ultrasound in this context. Pneumothorax occurring intra-operatively is the stuff of anaesthetic nightmares. Radiographic diagnosis is rarely possible, yet an incorrect clinical diagnosis has very serious implications for the physician and patient. A simple ultrasound technique using a linear array ultrasound probe attached to a basic ultrasound machine is a sensitive test to assist in this difficult task [80, 81] and should always be considered.

### Neuroanaesthesia

Operating on patients in the sitting position can improve surgical conditions, by allowing access to deeper structures without excessive cerebellar retraction, as well as aiding the passive drainage of cerebrospinal fluid and blood with gravity, thereby providing a clearer surgical field. However, one of the most serious drawbacks and fundamental reasons for the diminishing use of the sitting position during neurosurgery is the occurrence of venous air embolism [82]. This can complicate as many as 76% of neurosurgical procedures [83], and although it alone can be fatal, when accompanied by the presence of a patent foramen ovale, it can lead to paroxysmal air embolism and severe neurological sequelae. The incidence of asymptomatic probe-patent foramen ovale may be as high as 27% of the population as a whole [84]. Some authors

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**Table 1 (continued)**

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<th>Methodology</th>
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<tr>
<td>Schulmeyer et al. [50]</td>
<td>Prospective observational study of TOE in 42 non-cardiac surgery patients</td>
<td>Helpful in all cases</td>
</tr>
<tr>
<td>Category 1 indication: refractory intra-operative hypotension (systolic &gt; 30% of baseline) unresponsive to fluid replacement and ephedrine</td>
<td>42% of cases were hypovolaemic</td>
<td>42% of cases were hypovolaemic</td>
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<tr>
<td>Level of evidence 3</td>
<td>5 patients: significant emboli</td>
<td>5 patients: significant emboli</td>
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<td>5 patients: low ejection fraction</td>
<td>5 patients: low ejection fraction</td>
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<td>5 patients: segmental wall motion abnormality</td>
<td>5 patients: segmental wall motion abnormality</td>
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<td>5 patients: dynamic LVOT obstruction</td>
<td>5 patients: dynamic LVOT obstruction</td>
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<td>3 patients: tamponade</td>
<td>3 patients: tamponade</td>
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| Hofer et al. [51] | Prospective observational study of TOE in 99 non-cardiac elective surgery patients | 165 new TOE findings | No serious TOE complications |
| Category 2 indication: risk of myocardial ischaemia or haemodynamic instability | 47% changes in drug therapy | Intra-operative TOE performed by two experienced anaesthetists |
| Level of evidence 3 | 24% change in fluid therapy | |

TTE, transthoracic echocardiography; TOE, transoesophageal echocardiography; LVOT, left ventricular outflow tract; PACU, post-anaesthesia care unit; ICU, intensive care unit.

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have taken the position that a patent foramen ovale is an absolute contraindication to surgery in the sitting position [85].

Patients scheduled to undergo neurosurgery in the upright position should have contrast echocardiography pre-operatively or an intra-operative contrast TOE following induction of anaesthesia, to dictate whether the surgery is performed with the patient sitting or supine [86]. Transoesophageal echocardiography is the most sensitive intra-operative monitor to detect air in the right atrium and paradoxical left atrial air [87, 88]. It can also refine the final positioning of a central venous catheter at the junction of the right atrium and the superior vena cava to allow for the aspiration of air in case of air embolism [89]. Most episodes of venous air embolism are preventable, and the use of TOE may lead to the resurgence of this surgical technique before the skills are lost to the new generation of surgeons.

**Vascular anaesthesia**

The use of intra-operative TOE to monitor cardiac function has been previously discussed. In addition, the high-resolution images of the aorta acquired by TOE make it an attractive and complementary modality for endovascular repair of the thoracic aorta. Transoesophageal echocardiography has proven particularly valuable for selecting the landing site for the proximal stent by illustrating areas of atheroma or calcification that would otherwise not be detected by angiography and could interfere with stent adhesion. In one case series, the addition of this information led to a change in the landing site in a third of patients [90]. Transoesophageal echocardiography can indicate accidental placement of the guidewire into the false lumen, allowing for immediate repositioning, and it is also able to detect the position of the guidewire tip in relation to the aortic valve, preventing arrhythmia or damage to the delicate valve cusps. After stent deployment, TOE can detect the presence of endoleaks. The sensitivity of TOE in detecting small amounts of flow into the aneurysmal sac makes it ideal and in many instances it has surpassed angiography [91]. In one case series, angiography failed to detect six of the eight endoleaks found by TOE [92]. However, when endoleaks are observed by TOE and not by angiography, it creates a difficult dilemma. Should immediate remedial action be undertaken in the operating room or should careful follow-up, looking for spontaneous closure with CT imaging, occur in the outpatient setting [91]? In the absence of research, the interpretation of these conflicting findings has relied on clinical judgement and experience.

**Intensive care**

Much has already been written about the utility and uptake of echocardiography into intensive care practice, and readers are referred elsewhere for a more detailed treatment of the evidence round this topic [93–95]. However, as many anaesthetists are also employed in critical care, this article would be incomplete without an examination of some of the main themes.

Patients requiring intensive care commonly exhibit disordered and unstable physiology, which is continuously being manipulated by interventions such as fluid infusion and vasoactive drug administration. Heart–lung interactions are complex, and even small changes in positive pressure ventilation can produce significant haemodynamic effects, impacting on the performance of both ventricles. The response to an intervention is often unclear, and this is of particular concern as untimely [96], overzealous [97–99] or restrained [100] therapy can be detrimental to outcome. Current evidence suggests that central venous pressure monitoring is no better than ‘flipping a coin’ [101], and with the abandonment of right heart catheterisation in general critical care [102, 103], it is inevitable that critical care physicians are turning to echocardiography for answers. Echocardiography has been shown to alter the management of critically ill patients significantly [44, 104, 105], and it is the investigation of choice in cardiac ICU [106]; there is also increasing international recognition of its various applications [107, 108].

The fluid responsiveness of a particular patient’s circulation is a commonly encountered clinical dilemma. Echocardiography can readily identify the causes of shock [71, 109] and there are a number of well-validated echocardiography applications to predict fluid responsiveness [62–64]. Echocardiography can also predict the response to fluid in situations when other methods are not validated, for example, during spontaneous breathing as opposed to mechanical ventilation [110]. For those deemed unresponsive to fluids,
it can guide pharmacological [111] and mechanical [112] support of the cardiovascular system.

In cases of persistent shock, echocardiography is the only bedside test that can identify dynamic left ventricular outflow tract obstruction, right ventricular failure or complications of myocardial infarction such as papillary muscle rupture or ventricular septal defect. Right ventricular dysfunction and pulmonary hypertension are common but often underdiagnosed conditions in critical care. They may be encountered in 25% of patients with acute lung injury [113], and right ventricular dysfunction can be seen in up to 31% of septic patients [114].

The use of echocardiography is moving beyond a limited focused examination and towards uncovering some of the less understood causes of hypoxaemia and failure to wean from mechanical ventilation, such as patent foramen ovale and diastolic dysfunction [115]. As the enthusiasm for echocardiography in the ICU gathers pace and new applications are studied, there will undoubtedly be variation in physicians’ experience and competence. There is a risk that the boundaries between focused and advanced imaging become blurred. To ensure patient safety, it is imperative that the competence of the operator is defined and the endpoints for which the modality is being utilised are clearly laid out.

Obstetric anaesthesia

Cardiac disease is the leading cause of maternal death in developed countries, with an increasing incidence of obstetric patients with congenital heart disease, coronary artery disease, heart transplantation and cardiomyopathies presenting for peripartum care [116]. Symptoms such as dyspnoea are common and can lead to diagnostic dilemmas in the pregnant population, and the challenges of managing these complex patients for anaesthetic and surgical interventions are considerable. Echocardiography is recommended as a first-line investigation in the diagnosis and management in severe chest pain and shortness of breath [116]. Dennis and Stenson describe the assessment of a case of undifferentiated shock within 6 h of caesarean section for antepartum haemorrhage – massive pulmonary embolism and ongoing hypovolaemia were excluded and diagnosis of peripartum cardiomyopathy was made, enabling the commencement of prompt and appropriate medical therapy [117]. There is a similar report of the diagnosis of an unsuspected acute aortic dissection by an anaesthetic echocardiographer performing a focused scan, enabling prompt and life-saving referral for surgical repair of the aorta [118]. While these case reports do not provide hard evidence of broader benefit to obstetric patients, the benefit to these individual critically ill patients was inestimable. Haemodynamically unstable obstetric patients constitute a particularly difficult study group. The predominance of regional anaesthesia in the obstetric setting favours TTE over other invasive modalities, as it is well tolerated by the mothers and the feasibility of intra-operative TTE has been demonstrated [119]. The left lateral position for the avoidance of caval compression is also conducive to the attainment of good acoustic windows and a recent study was able demonstrate good-quality systolic, diastolic and structural information in 100% of the 80 women enrolled [120]. This study also demonstrated that echocardiography is redefining how we think about hypertension in pre-eclampsia. Some pregnant women would appear to have a high cardiac output with mild elevations in systemic vascular resistance [120], while others have a low cardiac output and a high systemic vascular resistance [121]. Although opinions that it may be a heterogeneous condition remain polarised, there is agreement that diastolic dysfunction and pericardial effusions are more common in women with untreated pre-eclampsia. Dennis et al. described two women who were noted to have diastolic compression of the right side of the heart, an early echocardiographic sign associated with cardiac tamponade. Untreated pre-eclamptic women or those who respond poorly to treatment may represent a subset of patients who may benefit from pre-term echocardiography and additional input in the peri-partum period. Clearly, echocardiography during normal deliveries is neither desirable nor cost-effective; however, its use in assessing complicated, unstable or high-risk patients warrants further exploration.

Conclusions

Echocardiography in non-cardiac surgery and obstetric practice is an emerging technological application. The evidence base for its use is somewhat limited at the
moment and is mostly confined to audits, case reports and observational studies produced by a number of pioneers and advocates. A common theme in a number of studies is that the echocardiography examination (both TTE and TOE) is performed by an accredited expert. This will clearly affect the results and make it difficult to extrapolate the conclusions to the current clinical reality where accredited expert anaesthetic echocardiographers are in very limited supply. It also raises the question of manpower and affordability in comparison with cardiology, where echocardiography is delivered by highly trained technicians. Interestingly, the same pattern of development can be observed for echocardiography in cardiac surgery and critical care, for which there is now plenty of evidence of impact, but little evidence of improved outcomes. There is a large number of anaesthetic studies where a mode of monitoring is introduced or two modes of monitoring are compared. The key to the value of the monitor is how the information thus obtained is interpreted and used to change the patient management. Echocardiography in its more focused applications does not provide simple measures such as cardiac index or stroke volume variability. It is therefore more difficult to protocolise an intervention such as fluid or inotropes compared with, for example, oesophageal Doppler. The interpretations and interventions based on echocardiography are multiple and do not readily map to a binary decision-making sequence. A paradigmatic shift is required. The true value of echocardiography lies in its greater applicability and reliability in a wide variety of clinical scenarios and environments. The pulse oximeter and the capnograph were disruptive technological innovations in anaesthesia that revolutionised practice without a large evidence base. The flipside of this is the complexity and technical skill needed for performance and interpretation. Echocardiography as an imaging technology in all its forms is very well validated and used throughout the world – without a great deal of outcome research or economic analysis. We suggest that the barrier to greater use in our field is not so much a lack of evidence, rather the problems associated with establishing large-scale training programmes for anaesthetic specialists, and we shall explore this further in part 2 of our review.

Competing interests
SNF runs echocardiography training courses and teaches on courses organised by a number of national and international professional bodies. He has also received conference and course support from GE and Sonosite Fujifilm. No other competing interests declared.

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