PRO–CON DEBATE

Administration of ketamine to children with pulmonary hypertension is safe: pro-con debate

PRO ARGUMENT
Glyn D. Williams
Department of Anesthesia, Lucile Packard Children’s Hospital at Stanford Stanford University Stanford, CA, USA

Pulmonary hypertension and perioperative risk in children

Adults vs children
In 2011, recognizing there are significant differences between pediatric and adult pulmonary vascular disease, investigators developed a new (Panama) classification specific for pediatric pulmonary hypertensive vascular disease (1,2). The aim was not to replace the Dana Point Classification of 2008 (3) but rather to augment it for certain pediatric disorders (4). Therefore, because of these differences, it seems prudent to exercise caution when extrapolating adult data regarding the perioperative management of pulmonary hypertension (PAH) to pediatric patients.

PAH and perioperative risk
The estimated prevalence of PAH in children is <10 cases per 1 million (5). Children (n = 216) enrolled in a multicenter PAH registry had, at diagnosis, mean pulmonary artery pressure of 56 mmHg and pulmonary vascular resistance (PVR) index of 17 Wood units per m². Five-year survival from diagnosis for the overall cohort was 74 ± 6%, with no significant difference between the idiopathic PAH/familial PAH and PAH associated with congenital heart disease cohorts. Variables significantly associated with decreased survival were older age, higher PVR, lower-weight z scores, and familial PAH (6).

Children with PAH requiring anesthesia for procedures are at increased risk (7). Perioperative cardiac arrest is more likely in children with cardiac disease (8,9) and PAH (10–14). Some argue that children with PAH should be managed only in institutions that are familiar with the disease and have the resources available to intervene emergently if the situation requires (15). Perhaps this has merit because recent studies from specialized centers reported improved patient outcomes for children with PAH who required anesthesia for cardiac catheterization procedures (16,17).

Right ventricle (RV) decompensation accounts for many of the adverse perioperative outcomes and may result from an acute increase in PVR and/or chronic right heart failure. Of concern, adult data indicate that RV function can deteriorate despite a reduction in PVR from PAH-targeted therapy (18). Published reviews of the anesthetic management of patients with PAH uniformly emphasize strategies that optimize cardiac function and reduce PVR but authors differ in their opinions whether ketamine helps attain those goals. Fischer et al. (19) stated ketamine increases PVR in adults but was little changed in children. Two reviews considered ketamine administration controversial (7,20) and three others regarded it safe or an agent of choice (15,21,22). Strumpher et al. (23) advised against ketamine because it may increase PVR. After this was challenged (24), they replied ‘Thus, although the use of ketamine in patients with PAH remains debatable, it seems that controlling physiologic parameters like oxygenation, ventilation, temperature, acid–base balance, and sympathetic tone may be most important and that the use of ketamine in mechanically ventilated patients is deemed to be safe’ (25).

Ketamine’s effects on human pulmonary vasculature
Clinical experience with ketamine, a phencyclidine derivative discovered in 1962, is substantial (26–31).
Studies of ketamine’s effects on the pulmonary vasculature of humans are summarized in the ‘Con’ article.

In 2001, at the author’s (GDW) institution, there were differences in opinion among the pediatric cardiac anesthesiologists as to whether ketamine increased PVR in children. Now, after two studies (17,32) and a decade of experience, uniform consensus exists within the group that ketamine is an anesthetic drug of choice for children with PAH. The Director of our Center for Pulmonary Vascular Disease agrees that ‘Whatever you are doing seems to work.’ Since 2001, there has not been a surgical procedure or cardiac catheterization-related death in the children with PAH, and a review of the medical records of our pediatric patients with PAH over a 6-year period found ketamine was not associated with perioperative complications (17). Ketamine is used during cardiac catheterizations, cardiac and noncardiac surgical procedures and for sedation/analgesia in the intensive care unit for children with PAH. Occasionally, we employ ketamine as the sole agent but usually combine it with propofol. In a minority of cases, anesthesia is maintained using ketamine and volatile anesthetic agents (sevoflurane or isoflurane). We no longer debate ‘Is ketamine safe?’; instead, we consider ‘Why ketamine is safe?’

Clinical consequences of pulmonary hypertension

The increased risk of perioperative complications in patients with PAH is attributed largely to the adverse consequences of PAH (33), with acute right heart failure being the principal concern (34,35). Several reviews describe the pathophysiology of right heart failure in PAH (23,36–39).

Important features to understand about the normal right ventricle are as follows:

1. The right ventricle is triangular in its long axis and crescent-shaped in cross-section. The RV cavity has inflow, apical, and outflow compartments, with the apex contributing the least to overall ejection fraction (40).

2. The superficial muscle layers are circumferential and intertwine with those of the left ventricle.

3. The deep muscle layers run longitudinally and are continuous with those of the intraventricular septum (IVS). About 40–50% of RV output is due to contraction of the left ventricle (LV) via effects upon the IVS.

4. The two ventricles have different patterns of contraction. The RV squeezes circumferentially (peristaltic action) and lacks the twisting/shortening motion of the LV.

5. Approximately, 60% of RV stroke volume occurs after peak RV systolic pressure because the pulmonary circulation has low impedance.

6. When PVR is normal, RV stroke work is 25% that of the LV.

7. Compared with the LF, the RV is thinner, more compliant, operates at a lower filling pressure, has less contractile reserve and is more sensitive to increases in afterload.

8. Under normal conditions, the pressure–volume loop of the RV is triangular (Figure 1) because it does not take long for RV pressure to exceed pulmonary artery pressure (brief isovolemic contraction time).

9. Because of their anatomy and common enclosure within the pericardium, changes in preload, afterload, and contractility of one ventricle will affect the other ventricle. This is termed ventricular interdependence.

10. Coronary flow to the right ventricle occurs throughout the cardiac cycle.

Tolerance to an increase in RV afterload depends upon several factors:

1. Changes in contractility: There are several mechanisms involved, including (i) the force–frequency relationship (contractile force increases as heart rate increases); (ii) the Frank–Starling mechanism (contractile force increases as muscle fiber length increases); (iii) homeometric autoregulation (contractile force increases as RV afterload increases); (iv) catecholamine release. All these mechanisms become less...
Effective as RV failure increases. RV maximal elastance is a reliable index of RV contractility (Figure 1). Normal ventriculoarterial coupling implies there is adequate flow output at the lowest energy cost. This is disrupted in patients with PAH, who have reductions in RV elastance and pulmonary artery capacitance (41).

2 RV muscle mass: A hypertrophied RV is better able to tolerate afterload than a deconditioned RV. RV adaptation occurs in response to a gradual increase in afterload and is thought to reduce wall stress and maintain an adequate stroke volume. However, these compensatory mechanisms have limitations.

3 Optimal preload: The hypertrophied RV has reduced compliance and requires adequate preload but the dysfunctional RV has a relatively flat Frank–Starling curve. Excessive preload can be deleterious because of volume and pressure effects (see below).

An increase in RV afterload has the following effects:

1 Increase in RV volumes and pressures throughout the cardiac cycle changes ventricular geometry and the position of the IVS. The RV assumes a more cylindrical shape, becomes dysynchronous with loss of peristaltic action and the ejection fraction is reduced (40). During diastole, increased RV volume and pressure shift the IVS leftward, compromising LV filling and elevating LV end-diastolic pressure. If the PVR rises acutely, the IVS shift is exaggerated because there is reduced pulmonary venous return to the left heart. The enlarged, tense right atrium also impinges upon LV filling, especially if the pericardium is intact. Diastolic ventricular interactions contribute significantly to the development of poor biventricular function. During systole, the extent the IVS shifts back rightward (paradoxical septal motion) will depend on the differences between RV and LV pressures. At systemic or suprasystemic RV pressures, the LV remains ‘pancaked’ throughout the cardiac cycle. Increased RV afterload prolongs the duration of systole, thereby increasing RV diastolic pressures and promoting IVS shift leftward. Additionally, the LV’s substantial contribution to RV stroke volume is greatly diminished because the IVS is bulging leftward. Septal shift also realigns the LV muscle fibers, thereby reducing LV ejection by lessening its twisting motion during contraction. Several animal models of PAH have demonstrated that increasing LV afterload pharmacologically (e.g., norepinephrine) or by banding the aorta resulted in an increase in LV volumes and pressures, with IVS movement rightward, allowing an increase in both LV and RV output (42–44).

2 Increased RV pressures and RV dilation result in tricuspid regurgitation, further compromising RV output, increasing volume load and diastolic hypertension.

3 Bradycardia may be poorly tolerated if RV dysfunction results in a relatively fixed stroke volume or if significant tricuspid incompetence is present. Atrial arrhythmia is relatively common with PAH and hemodynamics, may deteriorate rapidly if sinus rhythm is lost.

4 Right coronary artery (RCA) perfusion pressure depends on the difference between aortic root and RV pressures. During a pulmonary hypertensive crisis, RV coronary flow is compromised because RV systolic and diastolic pressures increase and LV output and aortic pressures decrease. It has been shown that most of RCA flow in patients with PAH occurs in diastole. The reduction in systolic RCA flow is related to systolic RV pressure and to RV mass. Subendocardial flow may be insufficient in severe RV hypertrophy (45) and will be further diminished by factors that increase myocardial oxygen demand (e.g., tachycardia).

5 Organ perfusion becomes compromised as a result of decreased aortic pressure and flow, and increased systemic venous pressure. Tissue hypoxia could worsen if the hypertensive, dilated right atrium shunts right-to-left through a patent foramen ovale.

6 In patients with Eisenmenger’s syndrome, an increase in PVR will increase the degree of hypoxia by potentiating right-to-left shunt.

Figure 2 summarizes the pathophysiology of RV failure from PAH.

PVR can be increased perioperatively by many factors. Those relevant to the discussion of ketamine include:

1 Mode of ventilation affects PVR. PVR increases at low lung volumes (extra-alveolar vessel resistance) and high lung volumes (intra-alveolar vessel resistance) and is minimized at lung volumes close to the functional residual capacity. Positive pressure ventilation can aggravate RV failure by diminishing systemic venous return, increasing RV afterload and by ventricular interdependence, decreasing LV output (46).

2 Hypoxia causes pulmonary vasoconstriction and this is potentiated by acidosis.

3 Matching of lung ventilation and perfusion is often abnormal in patients with PAH and may result in poor gas exchange. Mismatch may worsen if hypoxic vasoconstriction is attenuated (e.g., by drugs).

4 Pain and noxious stimuli (e.g., tracheal intubation), by multiple mechanisms, can increase PVR.
Why ketamine is safe

Published literature indicates there are many factors, in addition to PVR, that should be considered when selecting anesthesia drugs for patients with PAH. We argue that ketamine is an appropriate choice because it has the potential to modify many of the adverse consequences of PAH. These are outlined below:

PVR

Obviously, this is controversial and the focus of the debate. Most recent studies indicate it does not increase PVR in children with PAH. Our original study involving 15 patients with PVR index of 11.3 (8.2) Wood units [median (IQR)] reported ketamine does not increase PVR in children undergoing sevoflurane anesthesia and spontaneous ventilation (32). Although, for the purposes of study methodology, patients in the study were maintained on sevoflurane, our usual approach is maintenance with intravenous agents (propofol and ketamine). Volatile agents are typically only administered when an inhalational induction of anesthesia is performed. As mentioned earlier, we found ketamine was not associated with perioperative complications (17).

This suggests ketamine is safe – regardless of the drugs with which it is combined – but does not provide direct evidence regarding effects on PVR. Our enthusiasm for ketamine anesthesia for the PAH population continues, and, to date, we have not observed an increase in PVR that was attributed to ketamine administration.

Systemic vascular resistance

Most pediatric studies report no change or an increase in SVR (32,47–49). This effect is attributed to central sympathetic stimulation and inhibition of the neuronal uptake of catecholamines (30). It is beneficial because:

1. As demonstrated most recently by Apitz et al. (44) an increase in systemic afterload (using norepinephrine or epinephrine) results in improved RV and LV function and increased cardiac output. Proposed mechanisms include ventricular–ventricular interactions, IVS contributions to RV output and alterations in ventricular geometry.
2. In patients with Eisenmenger’s syndrome, stable or increased SVR discourages right-to-left shunt and preserves baseline oxygen saturation.
3. Aortic pressures are stable or increased, thereby maintaining a good driving pressure for coronary flow.

Figure 2 Pathophysiology of right ventricular failure due to pulmonary arterial hypertension. RV, right ventricle; HTN, hypertension; LV, left ventricle; PVR, pulmonary vascular resistance. Reproduced with permission, from Bronicki et al. (36).
Similarly, stable or increased systemic cardiac output and aortic pressure favors satisfactory perfusion of vital organs.

**Contractility**

Although a direct negative inotropic effect has been demonstrated in the laboratory, clinical studies in children have confirmed ketamine’s reputation for hemodynamic stability in patients with compromised cardiac function (30). This is useful because PAH can result in biventricular dysfunction.

**Heart rate**

Patients with PAH and RV dysfunction often have tricuspid regurgitation and limited ability to increase stroke volume. Avoidance of bradycardia is desirable. Marked tachycardia raises the concern of subendocardial ischemia in the hypertrophied RV due to increased myocardial work and decreased coronary flow because diastole is shorter. The tachycardia observed after ketamine is attenuated by the administration of other anesthetic agents such as midazolam (26). Most pediatric studies report minimal or no change in heart rate; the drug fits the preferred profile for PAH.

**Arrhythmias**

It is suggested that ketamine has an indirect arrhythmogenic effect by sympathetic stimulation and a direct antiarrhythmic effect on the myocardium (30). Clinical experience indicates arrhythmia is uncommon. This is useful because atrial arrhythmia and hemodynamic decompensation are a concern in patients with PAH.

**Respiration and airway**

Investigators note ketamine is a mild respiratory depressant with the CO₂ dose-response curve shifted rightward with the slope unchanged. However, it is agreed that the respiratory response to hypercapnia remains intact at clinical doses. Clinical studies in children undergoing cardiac catheterization (some with PAH) reported that blood pH and PaCO₂ remain unchanged (32,47).

1 Ketamine differs from most other anesthetic drugs in that the protective airway reflexes, and the tone and coordination of upper airway muscles are usually preserved.

2 At our institution, we see these properties of ketamine to be advantageous because we are able to permit spontaneous breathing via a native airway during general anesthesia, without the development of respiratory acidosis and hypoxia from hypoventilation or upper airway obstruction. Patients breathe at lung volumes that are close to functional residual capacity and have minimal influence on PVR. Airway instrumentation is avoided which is useful because life-threatening escalation of pulmonary artery pressures has been reported following endotracheal intubation (50).

3 Additionally, positive pressure ventilation is avoided. The adverse effects of positive pressure ventilation on RV function (and thereby, LV function) and pulmonary flow are clinically relevant (51), and special ventilatory modes have been proposed to ameliorate their influence (52).

**Pulmonary hypoxic vasoconstriction**

This physiologic autoregulatory response is abolished by volatile anesthetic agents and may potentiate mismatch of lung ventilation and perfusion. There is some evidence that ketamine usefully preserves pulmonary hypoxic vasoconstriction (26).

**Bronchodilation**

Ketamine is a bronchodilator, probably through β₂ adrenergic receptor and vagal effects. This is useful for the considerable proportion of PAH patients who have reactive airway disease.

**Analgesia**

The analgesic properties of ketamine may diminish the increases in PVR that occur in response to noxious stimuli. Additionally, we have noted a opioid-sparing effect after ketamine administration (17) that may beneficially reduce the risk of narcotic-related respiratory depression.

**Side effects**

Emergence delirium can occur. The incidence is quite low in our practice, probably, because the patients are children, and they also receive other sedative or anesthetic drugs.

Prophylactic antisialogogue administration is often advised to diminish salivary secretions but some members of our group feel it is unnecessary and prefer to preserve the patient’s native heart rate as a useful monitor.

Postoperative nausea and emesis are a concern. Ondansetron is reported to be helpful. The incidence of nausea in one study was 14% (17).
Conclusions

PAH can result from a wide variety of pathological entities and is associated with multisystem dysfunction. Children with PAH have high perioperative risk. It is clear from the literature that formulating a perioperative management plan that is appropriate for the patient’s unique pathophysiology is far more important than the choice of individual anesthetic agents. At our institution, ketamine’s pharmacological properties are in alignment with our philosophical approach regarding the anesthesia care of patients with PAH. There are several unanswered questions regarding ketamine. Is it appropriate for all types of PAH? Does high altitude influence the pulmonary vascular response to the drug?

Conflict of interest

No conflict of interest declared.

References

4 Barst RJ. Classification of pediatric pulmonary hypertensive vascular disease: does it need to be different from the adult classification? *Pulm Circ* 2011; 1: 134–137.
31 Jamora C, Izravani M. Unique clinical situations in pediatric patients where ketamine may be the anesthetic agent of choice. *Am J Ther* 2010; 17: 511–515.
34 Ramakrishna G, Sprung J, Ravi BS et al. Impact of pulmonary hypertension on the outcomes of noncardiac surgery. *Predictors*
Ketamine has a well-deserved reputation for hemodynamic stability. Several investigations have demonstrated stability of systemic blood pressure (BP), systemic vascular resistance (SVR), cardiac output (CO), and heart rate (HR) following ketamine administration. As such, it is an anesthetic agent that is often chosen for patients with hemodynamic instability or poor cardiovascular reserve. The mechanism for this cardiovascular support is centrally mediated by the release of catecholamines and inhibition of neuronal catecholamine uptake (1).

Ketamine does not always support CO. Dose-dependent depression of cardiac contractility has been observed in vitro (2); thus, patients who are catecholamine depleted, such as can be observed in chronic heart failure, may respond to ketamine with a decrease in BP and CO. In critically ill adults receiving inotropic support for heart failure, ketamine infusion was associated with a decrease in CO accompanied by significant increases in SVR, pulmonary artery pressure (PAP), and pulmonary artery wedge pressure (3).

Ketamine does have attributes, as discussed in detail in the ‘Pro’ section of this debate, that make it attractive for use in children with pulmonary arterial hypertension (PAH). Its maintenance of SVR helps to preserve coronary artery perfusion to a hypertensive right ventricle. In vitro, ketamine has mild pulmonary vasodilating effects in isolated rat lung and pulmonary artery preparations (4,5). The administration of ketamine to children with PAH has been advocated in recent studies (6,7). Is it safe to embrace ketamine anesthesia in children
with PAH on the basis of these reports? First, we must examine the evidence provided by the literature more closely.

Quality of the evidence

A portion of the literature regarding ketamine and PAH consists of nonsystematic clinical review articles. These articles are often excellent reading and valuable sources of expert opinion (examples: 8–13) and should not be discounted. However, from the perspective of evidence-based medicine, the strength of evidence that they provide regarding ketamine’s safety in PAH patients is rather weak (14). Level 1 evidence of the safety of ketamine in PAH patients and the effect of ketamine on the pulmonary vasculature in humans is lacking, and case series studies comprise the bulk of the literature.

Prospective case series studies of the pulmonary hemodynamic response to ketamine in adults with and without heart disease (15–19), including one which included patients with PAH (20), have consistently observed significant increases in PAP and/or PVR in response to ketamine. There is variation in study design and details provided among these studies, but their observations of PAP and PVR are generally consistent.

Pediatric studies

The pediatric studies will be reviewed in detail. Investigations of the pulmonary vascular response to ketamine in children have observed widely varying responses—ranging from no change to marked increases—in PAP and PVR (6,21–25), with some concluding that ketamine should not be used in patients with PAH. The conditions under which these investigations took place, including airway management, ventilatory management, altitude, and simultaneous administration of known pulmonary vasodilators, however, have been as variable as their conclusions. This variety of conditions has contributed to a lack of consensus about the safety of ketamine in children with PAH.

Some studies were carried out while subjects breathed spontaneously through a natural airway. This is potentially problematic, as it has been demonstrated that children who are sedated or anesthetized with a variety of drugs, including ketamine, for cardiac catheterization can experience upper airway obstruction or hypventilation resulting in hypoxia or hypercarbia (26), both of which can affect PVR. Controlled ventilation through a secure airway can avoid these changes in SpO₂ and PaCO₂ (26). On the other hand, ketamine has been shown to support maintenance of spontaneous ventilation and patency of the upper airway (27,28), suggesting that significant changes in blood gases may be less common than supposed. PaO₂ and PaCO₂ data were provided in some, but not all, studies of ketamine in children with PAH.

Some studies were conducted at mild elevations of altitude (1600 m), where PaO₂ is lower than at sea level. Although disease states such as altitude sickness and high altitude pulmonary edema are not classically associated with altitude <2500 m, infants with PAH due to ventricular septal defects at 1600 m were shown to have twice the PVR as similar infants with comparable PAP at sea level (29). While this phenomenon may offer some protection against pulmonary overcirculation for these infants, it does introduce a variable to pulmonary hypertension studies.

In other studies, the study drug ketamine was administered while the patient was receiving pulmonary vasodilators such as oxygen, sevoflurane, or therapeutic vasodilating drugs. These are known to affect PVR and could have attenuated an effect of ketamine. All of these potential confounders are considered in the following discussion of the prospective studies that have been carried out in human children.

In 1971, Faithfull and Haider reported a 20% incidence of upper airway obstruction during ketamine anesthesia for cardiac catheterization of children (30). Changes in PAP and PVR were not reported.

In 1974, Gassner and co-authors reported a ‘significant rise’ in PAP following ketamine administration to unpremedicated children undergoing cardiac catheterization that was not observed in children premedicated with droperidol (31). This article was primarily a report of animal experiments, and unfortunately, details of study design and results pertaining to the human part of the study are lacking.

In 1984, Morray and colleagues studied the hemodynamic effects of a 2 mg kg⁻¹ intravenous bolus of ketamine in 20 children undergoing cardiac catheterization (21). Subjects were sedated with rectal thiamylal, and breathed room air spontaneously through their natural airways. PaO₂ and PaCO₂ were measured. Although a 10 mmHg decrease in PaO₂ was observed in one subject with an atrial septal defect, no other significant changes in PaO₂ or PaCO₂ were observed—in individuals or the group as a whole—following ketamine administration. Mean PAP increased from 20.6 to 22.8 mmHg, a statistically significant but clinically insignificant change. The most important observation in this study, however, is that when data from subjects with and without PAH were separated, every subject with PAH (PAP >25 mmHg) at baseline experienced a significant increase in PAP following ketamine, while those without PAH...
generally did not (Figure 1). This study was conducted near sea level.

In 1985, Hickey and colleagues studied the hemodynamic effects of a 2 mg kg$^{-1}$ intravenous bolus of ketamine in 14 infants 1 day following open cardiac operations (22). Subjects were lightly sedated with morphine and sometimes diazepam but judged to be awake and ready for extubation. Subjects breathed spontaneously through endotracheal tubes, but some mechanical support of ventilation was provided with an intermittent mandatory ventilation rate of 4 breaths min$^{-1}$, and FiO2 was 0.3–0.4. ‘Several’ subjects were briefly apneic following ketamine, but mean changes in pH, PaO$_2$, and PaCO$_2$ were insignificant. The mean data for subjects both with and without baseline PAH demonstrated no significant change in PAP or PVR index (PVRI) following ketamine, but one patient with elevated PVRI experienced a 36% further increase in PVRI. Another subject, studied for a second time following extubation, experienced upper airway obstruction and a 300% increase in PVRI following ketamine. The confounding variable in this study is administration of oxygen, a pulmonary vasodilator.

In 1990, Berman and colleagues studied the hemodynamic effects of a 1 mg kg$^{-1}$ intravenous bolus of ketamine in 28 children undergoing cardiac catheterization (23). Subjects were sedated with intramuscular meperidine and droperidol and breathed room air spontaneously through their natural airways. A limitation of this study is that no blood gas data were provided, although the authors reported ‘no effect’ on respiratory pattern, pH, PaO$_2$, or PaCO$_2$. PAP increased by 59% and PVR increased by 69% in response to ketamine, with the greatest changes in subjects having higher baseline PVR. This study took place at 1600-m altitude.

In 1991, Wolfe and colleagues reported hemodynamic measurements during cardiac catheterization of 14 children with baseline elevations of PVR (24). Subjects had undergone surgical repair of left-to-right shunting congenital heart disease at least 1 year earlier, had a history of PAH, and had ongoing risk factors for hyperreactive pulmonary vasculature. Following sedation with intramuscular meperidine and hydroxyzine, subjects spontaneously breathed room air through a natural airway. Measurements were taken in room air, subambient oxygen, 100% oxygen, and (after return to baseline in room air) following a 1 mg kg$^{-1}$ intravenous bolus of ketamine. PaCO$_2$ and pH did not change throughout, and PaO$_2$ did not change from baseline in response to ketamine. In some subjects, only mild responses to subambient oxygen and ketamine were observed, but as baseline PAP, PVRI, and resistance ratio (PVR/SVR) increased, the responses to subambient oxygen and to ketamine became progressively more vigorous (Figure 2). This study was also conducted at about 1600-m altitude.

In 2003, Öklu and colleagues studied the hemodynamic effects of intravenous infusion of ketamine, 50–75 mcg kg min$^{-1}$ during cardiac catheterization of 20 children (25). Following sedation with oral midazolam and intravenous administration of thiopental, subjects spontaneously breathed room air through a natural airway. No significant changes were observed in PaO$_2$, PaCO$_2$, pH, PAP, PVR, or PVR/SVR following an indeterminate duration of ketamine infusion. The results of this study suggest that when ketamine is administered as an infusion rather than a bolus (implying a lower dose and rate of administration), pulmonary hemodynamic effects may be minimal. The failure to report the total dose or duration of ketamine infusion is an important weakness of this study.

In 2007, Williams and colleagues studied the hemodynamic response to intravenous administration of ketamine 2 mg kg$^{-1}$ over 5 min followed by infusion of 10 mcg kg min$^{-1}$ during cardiac catheterization in 15 children with severe PAH (6). Subjects were anesthetized with sevoflurane and breathed spontaneously through a well-fitting facemask. Seven subjects received supplemental oxygen. No significant changes in PaO$_2$, PaCO$_2$, pH, PAP, or PVRI were observed throughout the study, even in subjects with marked elevations in baseline PVRI. Unlike the previous studies discussed, this is the first
to include subjects who were studied while being actively treated with pulmonary vasodilators, including sildenafil, bosentan, prostacyclin analogs, inhaled nitric oxide, and oxygen. This is a significant confounder for this study, as is the administration of the volatile anesthetic, sevoflurane. These pulmonary vasodilators may explain the lack of pulmonary hemodynamic response to ketamine in this study. This is a valid consideration because, as Williams observed in the next study (see below), preoperative pulmonary vasodilator therapy reduced the odds ratio of perioperative complications in children with PAH to 0.31 (7).

Finally, in 2010, Williams and colleagues conducted a retrospective review of the medical records of 68 children with PAH who underwent 192 procedures under general anesthesia (7). This was a study of perioperative complications rather than the pulmonary vascular effects of ketamine. Seventy-seven per cent of patients had moderate to severe PAH. Preoperative treatment with pulmonary vasodilators was provided in 59% of procedures. Ketamine was administered during 78% of procedures, usually combined with propofol [a pulmonary vasodilator (32)] or a volatile anesthetic. One of three patients requiring cardiopulmonary resuscitation experienced a pulmonary hypertensive crisis immediately following administration of ketamine and tracheal intubation, but occurrence of complications was associated with all anesthetic combinations similarly. Limitations of this study are that it was retrospective, and that the distribution of anesthetic drugs among the cases was unequal.

Conclusions

What can we conclude after reviewing these studies? First, none of the studies is perfect; all have potentially confounding variables. Study design is challenging in this population because infants and children require sedation or anesthesia in order to obtain baseline measurements prior to administration of ketamine. Furthermore, modern studies of children with PAH will include subjects who are receiving chronic pulmonary vasodilator therapy, so that is a variable that is here to stay.

Second, although some have argued that studies carried out utilizing the natural airway and spontaneous ventilation are flawed due to hypoventilation, this argument cannot be consistently supported. Elevations of PAP and PVR have been observed in subjects with spontaneous ventilation of room air through a natural airway with documented normal blood gases (15,16,21,24) as well as in those with supported ventilation and oxygen administration (18–20).

Third, the prospective studies that observed no significant effect on pulmonary hemodynamics in response to a ketamine bolus were conducted in the presence of pulmonary vasodilators, including oxygen (22) and volatile anesthetics (6). Along with the evidence that pulmonary vasodilators may reduce the odds of perioperative complications, this suggests that they might also make administration of ketamine safer in children with PAH. Thus, combining ketamine with propofol or sevoflurane may offset the undesired pulmonary vascular effects of ketamine.

Fourth, a consistent conclusion emerges from the prospective observational studies conducted without pulmonary vasodilators, without changes in blood gases, at both sea level and moderate altitude (21,23,24). That conclusion is children with greater severity of PAH at baseline have more severe pulmonary hypertensive responses to ketamine. That conclusion is consistent and irrefutable by current evidence. Until a well designed prospective study is conducted—and I believe that one should be conducted—the safety of ketamine in children with PAH cannot be assumed.

Conflict of interest

No conflict of interest declared.

References


3 Christ G, Mundigler G, Merhaut C *et al.* Adverse cardiovascular effects of ketamine.