Perioperative Dexmedetomidine Improves Outcomes of Cardiac Surgery

Fuhai Ji, MD; Zhongmin Li, PhD; Hung Nguyen, MD; Nilas Young, MD; Pengcai Shi, MD; Neal Fleming, MD, PhD; Hong Liu, MD

Background—Cardiac surgery is associated with a high risk of cardiovascular and other complications that translate into increased mortality and healthcare costs. This retrospective study was designed to determine whether the perioperative use of dexmedetomidine could reduce the incidence of complications and mortality after cardiac surgery.

Methods and Results—A total of 1134 patients who underwent coronary artery bypass surgery and coronary artery bypass surgery plus valvular or other procedures were included. Of them, 568 received intravenous dexmedetomidine infusion and 566 did not. Data were adjusted with propensity scores, and multivariate logistic regression was used. The primary outcomes measured included mortality and postoperative major adverse cardiocerebral events (stroke, coma, perioperative myocardial infarction, heart block, or cardiac arrest). Secondary outcomes included renal failure, sepsis, delirium, postoperative ventilation hours, length of hospital stay, and 30-day readmission. Dexmedetomidine use significantly reduced postoperative in-hospital (1.23% versus 4.59%; adjusted odds ratio, 0.34; 95% confidence interval, 0.192–0.614; \( P<0.0001 \)), 30-day (1.76% versus 5.12%; adjusted odds ratio, 0.39; 95% confidence interval, 0.226–0.655; \( P<0.0001 \)), and 1-year (3.17% versus 7.95%; adjusted odds ratio, 0.47; 95% confidence interval, 0.312–0.701; \( P=0.0002 \)) mortality. Perioperative dexmedetomidine therapy also reduced the risk of overall complications (47.18% versus 54.06%; adjusted odds ratio, 0.80; 95% confidence interval, 0.68–0.96; \( P=0.0136 \)) and delirium (5.46% versus 7.42%; adjusted odds ratio, 0.53; 95% confidence interval, 0.37–0.75; \( P=0.0030 \)).

Conclusion—Perioperative dexmedetomidine use was associated with a decrease in postoperative mortality up to 1 year and decreased incidence of postoperative complications and delirium in patients undergoing cardiac surgery.


Key Words: cardiovascular surgical procedures ■ complications ■ dexmedetomidine ■ mortality

Approximately 7 million invasive cardiovascular procedures are performed worldwide each year.1 The major complication rates for valve and coronary artery bypass graft (CABG) procedures are as high as 30.1% in Society of Thoracic Surgeons (STS) reports.2 Postoperative delirium, infection, acute renal failure, and major adverse cardiocerebral events (MACEs), which include permanent or transient stroke, coma, perioperative myocardial infarction (MI), heart block, and cardiac arrest, represent major postoperative complications.3–5 These complications translate into increased mortality and prolonged hospital stays with estimated costs exceeding $20 billion annually.6 The reasons for these adverse events are multifactorial, but a major contributing factor is the surgical stress response that results in increasing plasma levels of epinephrine and norepinephrine with consequent myocardial oxygen supply demand imbalance and myocardial ischemia.7 More than 50% of all perioperative complications are related to adverse cardiovascular events.8

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The \( \alpha \)-2 receptor agonists (clonidine, dexmedetomidine) currently used in clinical practice have many desirable effects, including analgesia, anxiolysis, inhibition of central sympathetic outflow, and reduction of systemic norepinephrine release, that improve hemodynamic stability, positively affect myocardial oxygen supply and demand, and may provide myocardial protection.9,10 The most widely studied \( \alpha \)-2 agonist is clonidine, a long-acting partial agonist with an \( \alpha \)-2 to alpha-1 selectivity ratio of 39:1. Dexmedetomidine is a highly selective, shorter-acting intravenous \( \alpha \)-2 agonist with an \( \alpha \)-2...
to alpha-1 selectivity ratio of 1600:1. At our institution, dexmedetomidine is used to transition cardiac surgical patients from the operating room to the intensive care unit (ICU) and to provide sedation before extubation. Studies evaluating the hemodynamic stabilizing and sympatholytic effects have shown that α-2 agonists can potentially reduce postoperative cardiovascular complications. These include studies of clonidine in cardiac surgery patients and dexmedetomidine in vascular and noncardiac surgery patients. However, no studies to date have explored the impact of the α-2 agonists on perioperative outcomes of MI or cardiac death after cardiac surgery. Multiple studies have reported that dexmedetomidine has a protective effect on specific organs, including the heart, brain, kidney, and lungs. In addition, dexmedetomidine has been shown to have anti-inflammatory properties, decreasing mortality and attenuating plasma cytokine concentrations in laboratory animals exposed to endotoxin in a dose-dependent fashion. Therefore, in addition to investigating the more definitive end points of MI and death, this study examined the potential impact of dexmedetomidine on other major end points such as congestive heart failure, myocardial ischemia, arrhythmia, stroke, delirium, infection, and acute renal failure during the postoperative period for patients undergoing cardiac surgery. We hypothesized that dexmedetomidine may provide cardiac, brain, renal, and immune function protection for cardiac surgical patients. The specific aim of this study was to investigate whether the perioperative use of dexmedetomidine was associated with improved outcomes and a decreased incidence in postoperative MACEs or other complications in patients undergoing open heart surgery.

Methods

Study Design

This study was a single-center, retrospective cohort study involving 1260 consecutive patients who underwent cardiac surgery at a university medical center from January 1, 2006, to December 31, 2011. The study was reviewed and approved by the local Institutional Review Board. Patients included in this study met the following criteria: CABG or valve surgery or CABG or valve surgery combined with surgery involving the thoracic aorta or hypothermic circulatory arrest, or surgery involving the thoracic aorta (Figure 1). A total of 1134 patients met the inclusion criteria and were divided into 2 groups: those who received dexmedetomidine (dexmedetomidine group; n=568, 50.08%) and those who did not receive dexmedetomidine (nondexmedetomidine group; n=566, 49.92%) during the perioperative period (Figure 1).

Data Collection

The patient data were collected and organized following the template of the STS National Adult Cardiac Surgery Database and the hospital medical records and included demographics, patient history, medical record information, preoperative risk factors, preoperative medications, intraoperative data, postoperative MACEs, acute renal failure, and in-hospital, 30-day, and 1-year all-cause mortality. Independent investigators prospectively collected the data on each patient during the course of the hospitalization.

For these surgical patients, after standard monitoring, general anesthesia was induced with midazolam, propofol/etomidate, fentanyl/sufentanil, lidocaine, and rocuronium and maintained with oxygen and sevoflurane according to the patient’s hemodynamic responses. Ventilation was controlled to an end-tidal CO₂ of 35 to 45 mm Hg by adjustment of tidal volume and respiratory rate. Arterial catheter, pulmonary artery catheter, and transesophageal echocardiography were used for hemodynamic and cardiac function monitoring. Perioperative dexmedetomidine use was defined as an intravenous infusion (0.24 to 0.6 μg·kg⁻¹·h⁻¹) initiated after cardiopulmonary bypass and continued for <24 hours postoperatively in the ICU. The infusion rate of dexmedetomidine was adjusted according to the manufacturer’s package insert and in response to the patients’ hemodynamic changes in response to stimulation.

Major outcomes of this study were in-hospital, 30-day, and 1-year all-cause mortality and a composite outcome of MACEs, which included permanent or transient stroke, coma, perioperative MI, heart block, and cardiac arrest. Secondary outcomes included postoperative length of mechanical ventilation, postoperative renal failure or new dialysis requirement, length of ICU stay, length of hospital stay, and 30-day readmission. On the basis of the STS criteria, the following definitions were used. Permanent stroke was defined as a postoperative stroke (any confirmed neurological deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 hours. Transient stroke or transient ischemic attack was defined as a loss of neurological function that was abrupt in onset but with complete return of function within 24 hours. The definition of coma was a new postoperative coma that persisted for at least 24 hours secondary to anoxic/ischemic or metabolic encephalopathy, thromboembolic event, or cerebral bleed. Delirium was defined as illusions, confusion, and cerebral excitement in the postoperative period and having a comparatively short course. Perioperative MI (if <24 hours after surgery) was defined as creatine phosphokinase-MB (creatine phosphokinase if MB was not available) ≥5 times the upper limit of normal, with or without new Q waves present in ≥2 contiguous ECG leads, no symptoms required, or (if ≥24 hours after surgery) at least 1 of the following criteria: evolutionary ST-segment elevations, development of new Q waves in ≥2 contiguous ECG leads, new left bundle-branch block pattern on the ECG, or creatine phosphokinase-MB (or creatine phosphokinase if MB was not available) ≥3 times the upper limit of normal. Heart block was defined as new-onset block requiring the implantation of a permanent pacemaker of any type before discharge. Postoperative renal failure was defined as acute or worsening renal failure resulting in 1 or more of the following: an increase in serum creatinine >2.0 mg/dL or 2-fold increase in the most recent preoperative serum creatinine or a new requirement for dialysis. Finally, sepsis was defined as a systemic inflammatory response syndrome when at least 2 of the following criteria were present: hypothermia or hyperthermia (>38.5°C or <36.0°C), tachycardia or bradycardia, tachypnea or leukopenia, or thrombocytopenia. Any complication included all postoperative complications occurring during the hospitalization, including the entire postoperative period up to discharge, even if >30 days (Table I in the online-only Data Supplement).

Statistical Methods

Continuous and categorical variables were reported as mean±SD or percentages and compared by use of the t test or χ² test (2 tailed), respectively. Univariate and multivariate logistic regressions were performed to test the associations of demographic, therapeutic, and clinical outcome variables. To mitigate selection bias in patients who received a dexmedetomidine infusion, we computed the propensity score, that is, the conditional probability of each patient receiving dexmedetomidine, with a multivariable logistic regression model that included patient demographic and clinical risk factors (Table 1 and Figure 1 in the online-only Data Supplement).

To achieve model parsimony and stability, the backward selection procedure was applied with a dropout criterion of P>0.1. The candidate risk factors were selected on the basis of the literature reviews, clinical plausibility, and variables collected in the database. The candidate independent variables included age, sex, race, status of procedure, body mass index, creatinine level, smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, family history of coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, dyslipidemia, renal failure, dialysis, MI, congestive heart failure, intra-aortic balloon pump, β-blockers,
angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, ADP inhibitors, nitrates, anticoagulants, antiplatelet drugs, Coumadin, inotropes, steroids, aspirin, lipid-lowering drugs, glycoprotein IIb/IIIa inhibitors, surgery type, ejection fraction, perfusion time, cross-clamp time, and year of surgery. The parsimonious multivariable propensity model for dexmedetomidine use included status of procedure, preoperative family history of coronary artery disease (CAD), preoperative congestive heart failure, surgery type, ejection fraction, and year of surgery (Figure 2). We then created a propensity-weighted logistic regression model for 1-year mortality in which we used the inverse (estimated) propensity score as weights for patients who received dexmedetomidine and the inverse of 1 minus the propensity score for patients who did not receive dexmedetomidine and then added dexmedetomidine as an independent factor to the model. All models fit analysis was evaluated with the Hosmer-Lemeshow goodness-of-fit statistic. The C statistic was reported as a measure of predictive power. On the basis of the propensity of dexmedetomidine use, we classified all patients into quintiles; quintile 1 contained patients with the lowest propensity scores and quintile 5 contained patients with the highest propensity scores. Then, using a general linear model, we compared the propensity-weighted and risk-adjusted 1-year mortality between the cohort with dexmedetomidine use and the cohort with no dexmedetomidine use for each propensity-matched quintile. The results are reported as percentages and odds ratios (ORs) and with 95% confidence intervals (CIs).

Furthermore, we performed survival analysis and present Kaplan-Meier curves for patients who received dexmedetomidine versus those who did not receive dexmedetomidine. A parsimonious Cox proportional hazards model was created to evaluate the effect of dexmedetomidine for 1-year survival. All reported P values were 2 sided, and values of P<0.05 were considered to be statistically significant. Statistical analysis was performed with SAS version 9.3 for Windows (SAS Inc, Cary, NC).

**Results**

**Baseline and Intraoperative Parameters**

Demographic and clinical data of the patients who did and did not receive perioperative dexmedetomidine therapy are presented in Table 1. There were no significant differences between the 2 groups with respect to age, sex, race, body mass index, medical history (smoking, cerebrovascular disease, chronic lung disease, peripheral vascular disease, diabetes mellitus, or hypertension) and preoperative medical therapy (β-blockers, nitrates, antiplatelet drugs, Coumadin, inotropes, or aspirin). However, the patients in the dexmedetomidine group presented with a greater incidence of a history of previous MI (43.46% versus 32.57%; P=0.0002), congestive heart failure (31.51% versus 7.42%; P<0.0001), low ejection fraction (49.7±13.6% versus 52.5±12.8%; P=0.0004), renal...
failure (5.46% versus 2.47%; \( P = 0.010 \)), dyslipidemia (67.61% versus 44.70%; \( P < 0.0001 \)), and the use of lipid-lowering medications (65.49% versus 52.30%; \( P < 0.0001 \)).

### Procedural Characteristics

Procedural characteristics, including the number of vessels bypassed, and types of surgery were similar in both groups. In contrast, cardiopulmonary bypass time (181.8±76.6 versus 199.8±81.6 minutes; \( P = 0.001 \)) and aortic cross-clamp time (128.9±63.9 versus 144.8±62.5 minutes; \( P < 0.0001 \)) were significantly longer in the nondexmedetomidine group, as was the incidence of intra-aortic balloon pump use (6.87% versus 14.13%; \( P < 0.0001 \)). All surgeries were performed by 1 of 4 experienced cardiovascular surgeons (Table 2).

### Postoperative Complications and Mortality

#### Univariate Analysis

Thirty-three of the total 1134 patients (3.3%) died in hospital, and 39 patients (3.4%) died within 30 days and 63 patients (5.6%) died within 1 year after cardiac surgery. Perioperative infusion of dexmedetomidine was associated with significantly reduced in-hospital, 30-day, and 1-year mortality. In-hospital mortality was 1.23% in the dexmedetomidine group versus 4.59% in the nondexmedetomidine group (OR, 0.26; 95% CI, 0.11–0.60; \( P = 0.008 \)). Thirty-day mortality was 1.76% in the dexmedetomidine group versus 5.12% in the nondexmedetomidine group (OR, 0.33; 95% CI, 0.16–0.67; \( P = 0.002 \)). One-year mortality was 3.17% in the dexmedetomidine group versus 7.95% in the nondexmedetomidine group (OR, 0.38; 95% CI, 0.22–0.66; \( P = 0.0004 \); Figure 3). The perioperative use of dexmedetomidine was associated with a significantly reduced incidence of postoperative sepsis (0.7% versus 2.1%; OR, 0.33; 95% CI, 0.11–1.02; \( P = 0.043 \)) and any complication (47.18% versus 54.06%; OR, 0.76; 95% CI, 0.60–0.96; \( P = 0.0205 \)). No differences were seen in the incidence of MACEs, delirium, postoperative ventilation time (hours), total length of ICU stay (hours), or length of hospital stay (Figure 3 and Table 3).

### Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Yes (n=568)</th>
<th>No (n=566)</th>
<th>( P ) Value</th>
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<tr>
<td>Age, y</td>
<td>63.0 (12.0)</td>
<td>63.5 (11.1)</td>
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<td>Female sex, n (%)</td>
<td>159 (27.99)</td>
<td>166 (29.33)</td>
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<td>White race, n (%)</td>
<td>384 (67.67)</td>
<td>383 (67.61)</td>
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<tr>
<td>BMI, n (%)</td>
<td>29.5 (6.3)</td>
<td>29.9 (6.9)</td>
<td>0.231</td>
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<tr>
<td>Past medical history, n (%)</td>
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<tr>
<td>Current smoking</td>
<td>107 (18.84)</td>
<td>126 (22.26)</td>
<td>0.154</td>
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<tr>
<td>Chronic lung disease</td>
<td>490 (86.27)</td>
<td>476 (84.10)</td>
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<td>Cerebrovascular disease</td>
<td>94 (16.55)</td>
<td>94 (19.61)</td>
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<td>Peripheral vascular disease</td>
<td>80 (14.08)</td>
<td>84 (14.84)</td>
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<td>Family history of CAD</td>
<td>109 (19.19)</td>
<td>168 (29.68)</td>
<td>&lt;0.0001</td>
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<td>Diabetes mellitus</td>
<td>204 (35.92)</td>
<td>204 (31.27)</td>
<td>0.098</td>
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<td>Hypertension</td>
<td>436 (76.94)</td>
<td>437 (77.03)</td>
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<td>Dyslipidemia</td>
<td>384 (67.61)</td>
<td>253 (44.70)</td>
<td>&lt;0.0001</td>
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<td>History of renal failure</td>
<td>31 (5.460)</td>
<td>14 (2.470)</td>
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<td>Dialysis</td>
<td>19 (3.35)</td>
<td>11 (1.94)</td>
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<td>Preoperative MI</td>
<td>245 (43.46)</td>
<td>186 (32.57)</td>
<td>0.0002</td>
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<tr>
<td>CHF</td>
<td>179 (31.51)</td>
<td>42 (7.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF, %</td>
<td>49.7 (13.6)</td>
<td>52.5 (12.8)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Preoperative medication, n (%)</td>
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<td></td>
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<tr>
<td>ACEI</td>
<td>285 (50.18)</td>
<td>326 (57.60)</td>
<td>0.012</td>
</tr>
<tr>
<td>( \beta )-Blockers</td>
<td>394 (69.54)</td>
<td>374 (66.08)</td>
<td>0.212</td>
</tr>
<tr>
<td>Nitrates</td>
<td>16 (2.82)</td>
<td>20 (3.53)</td>
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<td>Antiplatelets</td>
<td>9 (1.58)</td>
<td>6 (1.06)</td>
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<td>Coumadin</td>
<td>42 (7.39)</td>
<td>37 (6.54)</td>
<td>0.571</td>
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<td>Inotropes</td>
<td>2 (0.35)</td>
<td>7 (1.24)</td>
<td>0.093</td>
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<td>Aspirin</td>
<td>456 (77.290)</td>
<td>439 (80.570)</td>
<td>0.176</td>
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<td>Lipid lowering</td>
<td>371 (65.49)</td>
<td>296 (52.30)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Propensity score</td>
<td>0.627 (0.217)</td>
<td>0.376 (0.219)</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitors; BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; EF, ejection fraction; and MI, myocardial infarction. Values are n (%) for categorical variables and mean±SD for continuous variables.
Propensity and Multivariate Analyses

The final multivariate model assessing MACEs included the propensity score, age, body mass index, diabetes mellitus, current smoking, surgical type, intra-aortic balloon pump use, and family history of CAD before surgery. The multivariate model assessing any complication included the propensity score, age, status of procedure, body mass index, creatinine level, smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, family history of CAD, diabetes mellitus, hypertension, renal failure, MI, congestive heart failure, intra-aortic balloon pump, β-blockers, angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelet drugs, steroids, aspirin, surgical type, ejection fraction, perfusion time, and year of surgery. The multivariate model assessing delirium included the propensity score, age, smoking, diabetes mellitus, and surgical type. The multivariate model assessing postoperative renal failure included propensity score, age, status of procedure, family history of CAD, diabetes mellitus, hypertension, surgical type, and angiotensin-converting enzyme. The multivariate model assessing in-hospital, 30-day, and 1-year mortality included the propensity score, age, status of procedure, family history of CAD, surgical type, and perfusion time. The model was calibrated among deciles of observed and expected risks for 1-year mortality (Hosmer-Lemeshow χ²: 13.1039; c= 0.796; P=0.1083) and dexmedetomidine use (Hosmer-Lemeshow χ²: 29.9369; c=0.788; P=0.0002).

Results of the multivariate analysis are summarized in Figure 3. The observed reduction in-hospital (adjusted OR, 0.34; 95% CI, 0.19–0.61; P<0.0001), 30-day (adjusted OR, 0.39; 95% CI, 0.23–0.66; P<0.0001), and 1-year (adjusted OR, 0.47; 95% CI, 0.31–0.70; P=0.0002) mortality in patients receiving perioperative dexmedetomidine persisted after propensity adjustment. The adjusted rates of any postoperative complication (adjusted OR, 0.80; 95% CI, 0.68–0.96; P=0.0136) and delirium (adjusted OR, 0.53; 95% CI, 0.37–0.75; P=0.0030) were also statistically significant between the dexmedetomidine and nondexmedetomidine groups. There is a significant increase in the rate of postoperative renal failure (adjusted OR, 1.5; 95% CI, 1.12–2.51; P=0.00945) in patients receiving perioperative dexmedetomidine. However, there were no statistical differences in the incidence of cardiac arrest (adjusted OR, 0.64; 95% CI, 0.19–2.14; P=0.4681) or sepsis (adjusted OR, 0.70; 95% CI, 0.34–1.45; P=0.3349) between groups after adjustment for differences between groups, although the OR point estimates favor perioperative dexmedetomidine use (Figure 3).

1-Year Mortality and Survival Analysis

On the basis of the propensity of dexmedetomidine use, we classified all patients into quintiles; quintile 1 contained patients with the lowest propensity scores, and quintile 5 contained patients with the highest propensity scores. Patients who received dexmedetomidine in quintiles 1, 3, and 5 had significantly lower 1-year mortality compared with patients in the nondexmedetomidine group (4.99% versus 10.39%, P=0.0495; 2.87% versus 7.89%, P=0.0009; and 3.05% versus 9.88%, P<0.0002, respectively; Table 4).

Survival probability was calculated with Kaplan-Meier methods and compared with the use of a log-rank test (P=0.001). For the duration of 1 year, there were significant differences in survival between the dexmedetomidine and nondexmedetomidine groups (propensity adjusted: 96.74% versus 91.70%; P<0.0001). The absence of overlapping curves from beginning to end suggests that there are obvious differences in survival between the dexmedetomidine and nondexmedetomidine groups (Figure 4).

After risk adjustment, a Cox proportional hazard model analysis revealed that older patients (age >65 years), urgent surgery, and perfusion time significantly increased the 1-year mortality, whereas perioperative dexmedetomidine infusion, CABG only, and CABG plus valve surgery reduced the risk of death during the first year. Preoperative family history of CAD had no relationship with 1-year mortality. Patients who received dexmedetomidine during the perioperative period had a significantly reduced hazard of death (hazard ratio, 47.8%; 95% CI, 0.28–0.81; P=0.007) compared with those in the nondexmedetomidine group at any time within 1 year after cardiac surgery when other risk factors were controlled for (Table 4 and Figure 5).

Discussion

In this analysis of consecutive patients undergoing cardiac surgery at our institution, we found that perioperative dexmedetomidine use is associated with improved survival. We observed significant reductions in in-hospital (1.23% versus 4.59%), 30-day (1.76% versus 5.12%), and 1-year (3.17% versus 7.95%) mortality in the patients who had received dexmedetomidine during the perioperative period. This improvement in survival persisted after statistical adjustment, which included the propensity to have received perioperative dexmedetomidine use. Our results further suggest that perioperative dexmedetomidine use is associated
with a reduced incidence of delirium and overall complications after cardiac surgery. We did not observe an associated statistically significant incremental benefit of perioperative dexmedetomidine use on postoperative MACEs and sepsis; however, the OR point estimates for these outcomes favored perioperative dexmedetomidine use. Our analysis likely lacked sufficient power to detect statistically significant differences in these outcome measures after statistical adjustment. This is the first report of a beneficial effect on outcomes associated with the perioperative use of dexmedetomidine in cardiac surgery patients.

Cardiac surgery is associated with high risks of cardiovascular and other complications, with a reported incidence of 30% for combined valve and CABG procedures that increases up to as high as 86% in higher-risk populations.2,22 These reported postoperative complications include stroke (1.4%–4.6%), cardiac arrest (5.0%), sepsis (4.1%), MI (3.1%), and acute renal failure (3.7%–7.1%).2,4,5,23–25 These complications consequently increase overall morbidity and mortality. The mean of in-hospital mortality in our study (3.41%) is in agreement with previous reports (2.76%–4.4%);26,27; however, in-hospital, 30-day, and 1-year mortality was significantly lower in patients who received dexmedetomidine in our study.

Dexmedetomidine is widely used for anesthetic premedication, sedation, anxiolysis, and analgesia.11 α-2 Agonists have been shown to be beneficial in the setting of noncardiac surgery, where they significantly reduce mortality in patients with coronary artery disease.12 An investigation found that 17% of noncardiac surgery patients received dexmedetomidine preoperatively or intraoperatively between 2007 and 2008.28 Another study found that 11.7% of cardiac surgery patients received intravenous infusion sedation.
after surgery from 2001 to 2007. The perioperative use of dexmedetomidine continues to increase, especially in patients with cardiac disease. In this study, >50% of the cardiac surgery patients received dexmedetomidine. A meta-analysis has indicated that α-2 agonists may reduce cardiac risk, especially during vascular surgery. It would be reasonable to postulate that perioperative dexmedetomidine use might also confer an early postoperative benefit for cardiac surgical patients, given the well-proven benefits of sympatholysis, anti-inflammatory, and antidelirium effects in the setting of cardiac surgery.

Although there is not enough evidence to prove the beneficial effect of dexmedetomidine on myocardial function in our study, the trend of MACEs supports this effect. Studies have shown that dexmedetomidine provides protective effects on the myocardium. α2-Adrenergic agonists have protective effects against myocardial ischemia by increasing the cAMP level and enhancing adenosine-induced coronary vasodilatation effect. Dexametomidine preconditioning has been shown to attenuate myocardial ischemia/reperfusion injury by activating prosurvival kinases.

Surgery and other forms of trauma can activate the sympathetic nervous system, initiating systemic inflammatory responses that can disrupt the function of the central nervous system. Proinflammatory cytokines have been shown to play a key role in mediating surgery-induced neuroinflammation and subsequent postoperative cognitive changes. Dexametomidine attenuates isoflurane-induced neurocognitive impairment and reduces the prevalence of delirium. In a multicenter ICU sedation study, dexmedetomidine-treated patients spent less time on the ventilator and experienced less delirium. Our study also found that those who received dexmedetomidine had a significantly lower incidence of delirium after cardiac surgery, even though the prevalence of delirium in our study was lower than most reported results. The reason for this finding may be that we included only patients with hyperactive delirium in this analysis. Delirium has been observed at higher rates after cardiac surgery, especially in older patients, but the rate of hyperactive delirium seen is far lower than emotional delirium.

By stabilizing the sympathetic nervous system, exerting anti-inflammatory effects, and attenuating ischemia/reperfusion injury, dexmedetomidine produces its protective effects on the functions of heart, brain, lung, kidney, intestine, and immune system. Because cardiopulmonary bypass has adverse effects on all of these same organs, complications inevitably occur after cardiac surgery. Our results indicate that just over 50% of patients experienced some postoperative complications. Dexametomidine reduced the overall incidence of any complication, a measure that includes all postoperative events that occurred during the hospitalization. However, use of dexmedetomidine in this study was associated with an increase in the incidence of postoperative renal dysfunction. Renal protective effects have been reported for α2-adrenoceptor agonists. The contrary results in this study might reflect the timing of dexmedetomidine administration because the beneficial effect may require the administration of the drug before the renal insult. In addition, in this study, the incidence of preoperative renal failure was greater in the dexmedetomidine group. Further studies to confirm this result are required.

**Limitations**

There are several limitations of this investigation. First, this is an observational cohort study. Multivariate regression, in combination with propensity score adjustments, was applied to this study population to reduce evident biases; however, the potential confounding biases associated with a nonrandomized study remain. Second, cardiac surgical patients share...
common risks of postoperative complications involving the heart, brain, and kidneys despite the widely varying types of surgery. Dexmedetomidine may affect the common pathway responsible for these complications by its sympatholytic and anti-inflammatory effects; however, further studies to analyze its impact on different types of cardiac surgery are required and could provide more definitive information about the potential benefits of dexmedetomidine in this setting. Third, although the rate of dexmedetomidine use was much higher in patients undergoing cardiac surgery in this cohort than in a previous cohort study, further prospective, multicenter, randomized studies are required to confirm the benefit demonstrated in this study. Finally, because the data of our study were extracted from STS, which is a voluntary database, the possibility of underreporting or forging adverse outcomes in data submitted to STS is a concern. However, the STS guarantees strict confidentiality, which removes much of the motivation for event underreporting. Moreover, underreporting would unlikely preferentially affect those who were indicated as having received dexmedetomidine compared with those who were not. Recently, the investigations of data quality and outcomes in the STS have demonstrated remarkable similarity between voluntary STS data (eg, percent, age, missing data, incidence, and trend analyses) with audited data and mandatory cardiac databases.39–41

Conclusions
This study is the first to demonstrate that cardiac surgical patients who received an intravenous dexmedetomidine infusion after cardiopulmonary bypass were more likely to have better in-hospital, 30-day, and 1-year survival. The perioperative use of dexmedetomidine is also associated with a significant decrease in the incidence of postoperative complications and delirium. There was no evidence of adverse hemodynamic side effects of dexmedetomidine in patients undergoing cardiac surgery. A prospective, multicenter, randomized study focused on the use of dexmedetomidine in cardiac surgery patients is indicated to confirm these findings.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine (Yes vs. No)</td>
<td>0.48</td>
<td>0.28-0.81</td>
<td>0.0065</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Status (Urgent vs. Elective)</td>
<td>1.84</td>
<td>1.10-3.08</td>
<td>0.0203</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1.63</td>
<td>0.95-2.78</td>
<td>0.0758</td>
<td></td>
</tr>
<tr>
<td>CABG only</td>
<td>0.37</td>
<td>0.19-0.74</td>
<td>0.0045</td>
<td></td>
</tr>
<tr>
<td>CABG+ Valve</td>
<td>0.46</td>
<td>0.24-0.88</td>
<td>0.0187</td>
<td></td>
</tr>
<tr>
<td>Perfusion time</td>
<td>1.01</td>
<td>1.01-1.01</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Cox proportional hazard model for 1-year mortality after cardiac surgery. CABG indicates coronary artery bypass graft; CAD, coronary artery disease; and CI, confidence interval.

Sources of Funding
This work was partially supported by the Department of Anesthesiology and Pain Medicine, Department of Surgery, and Department of Internal Medicine of University of California Davis Health System and National Institutes of Health grant UL1 TR000002. This study was supported by grant from Jiangsu Province by the Key Provincial Talents Program, China (Dr Ji); by the Jiangsu province's 6 Major Peak Talents Program, China (Dr Ji); and by Suzhou Science and Technology Bureau's program No. SYS201111 (Dr Ji), China.

Disclosures
None.

References
Approximately 7 million invasive cardiovascular procedures are performed worldwide each year. Cardiac surgery is associated with a high risk of cardiovascular and other complications that translate into increased mortality and healthcare costs. In this single-center analysis of consecutive patients undergoing cardiac surgery, the perioperative use of dexmedetomidine was associated with improved survival. We observed significant reductions in delirium, overall complications, and in-hospital, 30-day, and 1-year mortality after cardiac surgery in the patients who had received dexmedetomidine during the perioperative period. At the same time, there was no evidence of adverse hemodynamic side effects of dexmedetomidine in patients undergoing cardiac surgery. Dexmedetomidine is a commercially available medication that has been used extensively for sedation. Use of dexmedetomidine as an anesthesia adjuvant was associated with better outcomes in patients undergoing cardiac surgery. This finding further suggests that the use of dexmedetomidine played an important role in mortality and morbidity reduction after cardiac surgery and should be part of the perioperative medication regimen in this patient population.

**CLINICAL PERSPECTIVE**

Perioperative Dexmedetomidine Improves Outcomes of Cardiac Surgery
Fuhai Ji, Zhongmin Li, Hung Nguyen, Nilas Young, Pengcai Shi, Neal Fleming and Hong Liu

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### Supplemental Table 1. The definitions of outcomes in STS (Version 2.73)

<table>
<thead>
<tr>
<th>Postoperative events</th>
<th>Definition</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent stroke</td>
<td>Whether the patient has a postoperative stroke (any confirmed neurological deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 hours.</td>
<td>685</td>
</tr>
<tr>
<td>TIA</td>
<td>A loss of neurological function that was abrupt in onset but with complete return of function within 24 hours.</td>
<td>686</td>
</tr>
<tr>
<td>Coma</td>
<td>A new postoperative coma that persisted for at least 24 hours secondary to anoxic/ischemic and/or metabolic encephalopathy, thromboembolic event or cerebral bleed.</td>
<td>687</td>
</tr>
<tr>
<td>Delirium</td>
<td>Illusions, confusion and cerebral excitement in the post-operative period and having a comparatively short course.</td>
<td>30</td>
</tr>
<tr>
<td>Perioperative MI</td>
<td>&lt;24 hours post-op: CK-MB greater than or equal to 5 times the upper limit of normal, with or without new Q waves present in two or more contiguous ECG leads, no symptoms required; or &gt; 24 hours post-op: at least one of the following criteria: evolution of ST- segment elevations, development of new Q- waves in two or more contiguous ECG leads, new LBBB pattern on the ECG, CK-MB greater than or equal to 3 times the upper limit of normal.</td>
<td>674</td>
</tr>
<tr>
<td>Heart block</td>
<td>New onset requiring the implantation of a permanent pacemaker of any type prior to discharge.</td>
<td>695</td>
</tr>
<tr>
<td>RF</td>
<td>Acute or worsening renal failure resulting in one or more of the following: increase in serum creatinine &gt;2.0 mg/dL or two-fold increase of most recent preoperative serum creatinine or a new requirement for dialysis.</td>
<td>692</td>
</tr>
<tr>
<td>Sepsis</td>
<td>A systemic inflammatory response syndrome is present when at least two of the following criteria are present: hypo- or hyperthermia (&gt;38.5 or &lt;36.0), tachycardia or bradycardia, tachypnea, leukocytosis or leukopenia, and thrombocytopenia.</td>
<td>684</td>
</tr>
<tr>
<td>Any complication</td>
<td>All postoperative complications occurring during the hospitalization, including the entire postoperative period up to discharge, even if over 30 days.</td>
<td>669</td>
</tr>
<tr>
<td>Mort-mortality</td>
<td>Indicate whether the patient has been declared dead within this hospital or any time after discharge from this hospitalization.</td>
<td>702</td>
</tr>
</tbody>
</table>

STS, Society of Thoracic Surgeons National Adult Cardiac Surgery Database; TIA, Transient ischemic attack; MI, myocardial infarction; CK-MB, creatine phosphokinase-MB; ECG, electrocardiograph; RF, Renal failure.  
Supplemental Figure 1. The distribution of propensity score (ps) weight. Dex_YN, patients received dexmedetomidine or those who did not.