Effect of Aortic Root Infusion of Sufentanil on Ischemia-Reperfusion Injury in Patients Undergoing Mitral Valve Replacement

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Objective: This study investigated the effects of aortic root infusion of sufentanil on myocardial ischemia/reperfusion injury in patients undergoing elective mitral valve replacement (MVR) with cardiopulmonary bypass (CPB).

Design: A prospective, randomized, clinical study.

Setting: A university-affiliated teaching hospital.

Participants: Fifty-three adult patients undergoing elective MVR with CPB.

Interventions: Bolus infusions of sufentanil (0.2 μg/kg, n = 24) or normal saline (n = 29) were administered through the aortic root cardioplegia perfusion catheter 5 minutes before aortic unclamping.

Measurements and Main Results: Plasma concentrations of CK-MB and cTnI and variables including heart rate, mean arterial pressure, central venous pressure, cardiac output, stroke volume, duration of mechanical ventilation, length of ICU stay, length of hospital stay, and 24-hour postoperative inotropic scores were recorded. Plasma concentrations of CK-MB and cTnI were significantly lower 4 and 8 hours after aortic unclamping in the sufentanil postconditioning group compared to control ($p < 0.05$). Inotropic drug use, duration of mechanical ventilation, and length of ICU and hospital stays were reduced significantly in the sufentanil postconditioning group compared to control ($p < 0.05$).

Conclusions: The present study demonstrated that sufentanil can attenuate myocardial ischemia-reperfusion injury in patients undergoing elective MVR with CPB.

KEY WORDS: cardiopulmonary bypass, cardiac surgery, sufentanil, postconditioning, ischemia, reperfusion

ISCHEMIC POSTCONDITIONING, which refers to multiple brief periods of ischemia/reperfusion (I/R) that occur after prolonged ischemic insult, was first described by Zhao et al[1] in a dog model. Ischemic postconditioning provides myocardial protection by reducing reperfusion injury[2] and can also reduce myocardial injury induced by cardiopulmonary bypass (CPB) surgery.[3] However, it is difficult to apply intermittent I/R and some adverse consequences, such as aortic injury, left ventricular distention, and malignant arrhythmia, have been documented. Pharmacologic postconditioning, using drugs at the beginning of reperfusion, may be readily applied to mimic ischemic postconditioning during myocardial I/R.[4] Extensive experiments have demonstrated that opioids, including morphine and remifentanil, have similar cardioprotective effects to postconditioning.[5–7]

Zhang et al[7] demonstrated that aortic root cardioplegia needle infusion of morphine may provide enhanced cardioprotection against I/R injury in children undergoing correction of tetralogy of Fallot (TOF). The authors' preliminary study also suggested that aortic root infusion of remifentanil imitated ischemic postconditioning and attenuated myocardial I/R injury in patients with congenital heart disease.[8] Pharmacologic postconditioning via the aortic root is a new administration method, which can deliver the drug directly to the myocardium and avoid dilution effects due to cardiopulmonary bypass (CPB) and lag effects caused by central venous or peripheral vein administration.

Sufentanil, a specific μ-opioid-receptor agonist, is used widely as anesthesia for patients undergoing cardiac surgery. The authors and others have confirmed that sufentanil postconditioning confers powerful cardioprotection from I/R injury in rats, similar to ischemic postconditioning.[9,10] Until now, sufentanil postconditioning has not been investigated in adult cardiac surgery. Whether sufentanil could induce cardioprotective effects in the clinic remains unknown.

The purpose of this study was to test the hypothesis that aortic root infusion of sufentanil could provide enhanced cardioprotection against I/R injury in patients undergoing mitral valve replacement (MVR) with CPB. The primary outcome was to evaluate the plasma creatine kinase-MB(CK-MB) and cardiac troponin l(cTnI) levels as severity markers of myocardial injury response to the surgery. The secondary outcome was to evaluate inotropic scores, the duration of mechanical ventilation, and the lengths of intensive care unit and postoperative hospital stay.

METHODS

Ethical approval (Ethical Committee NO. 2012-022) was provided by the Ethical Committee of the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China in December 2012. This trial has been registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-12002949).Written informed consent was obtained from all the participants. Sixty American Society of Anesthesiologists physical status II to III patients aged 18 to 65 years old and undergoing elective MVR surgery were included in this prospective, randomized study. Patients with infective valve disease, valve disease with coronary artery disease, hypertension, diabetes mellitus, and previous heart surgeries were excluded. None of the patients received preoperative inotropic support.

A computer-generated allocation program randomly assigned 30 patients to receive sufentanil and 30 patients to receive normal saline. Randomization results were concealed in sealed envelopes until after informed consent had been obtained. All patients received a left radial arterial catheter, a central venous catheter, an electrocardiogram, and pulse oximetry. During the surgical procedure, anesthesia was induced with an IV bolus of midazolam (0.05 mg/kg), sufentanil (1μg/kg), target-controlled infusion (TCI) of propofol (effect-site concentration [Ce] starting at 1.0 μg/mL increasing to 2.0 μg/mL by 0.5 μg/mL), and

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rocuronium (0.9 mg/kg). For maintenance, a continuous infusion of propofol with TCI (Ce1.5-2.0 μg/mL) and sufentanil (1.0 μg/kg/h) were administered. Complete muscle relaxation was maintained with pipecuronium until the end of surgery. In all patients, bispectral index monitoring (BIS) (A2000 system, Aspect Medical Systems, Leiden, Netherlands) was used to maintain BIS values between 40 and 60 and adapt propofol infusion rates and midazolam doses. In non-CPB periods, mean arterial pressure (MAP) was maintained at 65 mmHg to 95 mmHg, heart rate (HR) 70-100 beats/min; during CPB, MAP was maintained at 50 mmHg to 80 mmHg.

All procedures were performed by the same surgical team using moderate hypothermic CPB (28-32°C) with bicaval cannulation and left heart venting via the right superior pulmonary vein. The myocardium was protected with intermittent perfusion of cold blood cardioplegic solution. The initial dose of cardioplegia was infused at 20 mL/kg; thereafter, cardioplegia solution was reinfused every 30 minutes at 10 mL/kg. Patients were separated from CPB when conditions were appropriate. Weaning from CPB followed a standardized protocol, including optimization of filling pressures and hemodynamics using volume and vasoactive drugs as needed. Modified ultrafiltration was used following separation from CPB. After surgery, patients were transferred to the intensive care unit and weaned from ventilation when hemodynamic stability was achieved. All patients received standard postoperative care. Dopamine and/or dobutamine were first-line inotropes, and epinephrine or norepinephrine were second-line inotropes for hemodynamic support as needed.

In the sufentanil postconditioning group, 5 minutes before aortic cross-clamp removal patients received a dose of sufentanil (0.2 μg/kg) injected via a cardioplegia catheter into the aortic root for direct and focused delivery to the heart within 1 minute. In the control group, the same protocol was performed with the same volume of normal saline.

HR, MAP, central venous pressure (CVP), cardiac output (CO), and stroke volume (SV) were recorded before induction of anesthesia (before CPB), at weaning from CPB (end of CPB), 30 minutes after weaning from CPB (30 min after CPB), 60 minutes after weaning from CPB (60 min after CPB), and at the end of the surgery (end of surgery). The Vigileo/FloTrac system (software version 1.01; Edwards Lifesciences, Irvine, CA), a device based on arterial pressure waveforms, was used to detect CO and SV at different time points.

Preoperative, intraoperative and postoperative data were collected and analyzed. Preoperative information included age, gender, weight, left ventricular ejection fraction (LVEF), and atrial fibrillation (AF). Intraoperative variables included duration of aortic cross–clamping (ACC) and CPB, time of surgery, and resumption of cardiac activity/rhythm. Postoperative data included the first 72-hour postoperative drainage volume, the first 24-hour postoperative inotrope score, duration of mechanical ventilation, lengths of intensive care unit (ICU) and postoperative hospital stay, and in-hospital mortality. The first postoperative 24-hour quantitative measures of inotropes were evaluated by inotrope score with the following formula: ([dopamine +dobutamine] × 1) + (milrinone × 15) + ([epinephrine + norepinephrine + isoproterenol] × 100).[11] All patients were followed for at least 30 days.

Blood samples for CK-MB and cTnI measurements were obtained from the jugular vein before induction of anesthesia (baseline) and at 4 hours, 8 hours, 24 hours, and 48 hours after aortic unclamping. Samples were centrifuged immediately for 10 minutes at 3000 g and stored at −80 °C until use. The CK-MB and cTnI were measured using commercially available enzyme-linked immunosorbent assays according to the supplier's recommendations (\Jidan Biotechnology Company, Nanjing, China). The values were expressed as U/L and ng/mL, respectively (normal reference values were ≤24 U/L and 0.15 ng/mL, respectively).

The sample size of the study was calculated based on the difference in peak cTnI concentration measured after reperfusion in a previous study of patients receiving normal saline (0.75 [standard deviation, 0.20] ng/mL) and morphine (0.57 [0.15] ng/mL)[7]. A power of 0.8 and an α of 0.05 were used to determine that 20 patients in each group would be appropriate. Statistical analysis was performed using the SPSS 13.0 statistical software package. Normally distributed data are presented as mean ± standard deviation for continuous variables, and frequencies were measured for categoric variables. The Student t test according to tests of variance was applied to compare differences, and Fisher exact test was used to compare categoric data. Values measured repeatedly within a group were tested by 1-way analysis with repeated measurements. $P < 0.05$ was considered statistically significant.

RESULTS

From April to October 2013, 60 patients were divided randomly into a sufentanil postconditioning group (n = 30) or a control group (n = 30). Seven patients were excluded due to aortic reclamping (3 patients), coronary artery disease (3 patients), and constrictive pericarditis (1 patient), leaving 24 patients in the sufentanil postconditioning group and 29 patients in the control group.

Preoperative clinical data are shown in Table 1. No significant differences in age, gender, weight, LVEF, or AF were detected between the groups. Operative and postoperative data are shown in Table 2. Patients from the 2 study groups were similar with regard to duration of CPB and ACC, surgical time, and first postoperative 72-hour drainage volume. The dose of inotropes used during the first 24 postoperative hours in the sufentanil postconditioning group patients was significantly lower than in the control group (7.6 ± 2.8 *v* 10.3 ± 3.9 μg/kg/min, p = 0.03). Patients who received sufentanil postconditioning had shorter duration of mechanical ventilation, length of ICU stays, and postoperative hospital stays compared to control patients (12 ± 4 *v* 14 ± 4 h, p = 0.03;34 ± 11 *v* 44 ± 14 h, p = 0.01, and 10 ± 3 *v* 13 ± 4 days, p = 0.00, respectively). One patient in the control group died of cardiac failure 6 days after surgery.

Intraoperative hemodynamics was displayed in Table 3. The HR, MAP, and CVP were not significantly different between the groups at any time point. Moreover, the CO and SV in the sufentanil group also had no significant difference compared to the control group.

Preoperative plasma CK-MB concentrations were within normal limits for all patients and were not different between the groups. Significant postoperative increase in CK-MB activity was observed in the control and postconditioning groups. Differences between the groups occurred at 4- and 8-hour

Table 1. Patient Demographic and Clinical Features

	S_{post} (n = 24)	Control (n = 29)	p Value*
Age (y)	47 ± 12	52 ± 10	0.08
Gender (female/male)	15/9	21/8	0.44
Weight (kg)	55 ± 9	55 ± 12	0.99
LVEF (%)	62 ± 5	63 ± 6	0.54
AF (with/without)	9/15	15/14	0.30

NOTE. Data are presented as numbers (percentages) or mean ± standard deviation. There were no significant differences between the 2 groups ($p > 0.05$).

Abbreviations: S_{post}, sufentanil postconditioning; LVEF, left ventricular ejection fraction; AF, atrial fibrillation.