Effect of sevoflurane combination with epidural anesthesia on myocardial injury in patients with coronary artery disease undergoing non-cardiac surgery

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ABSTRACT

الأهداف: تحديد مدى تأثير السيوفلورين مع التخدير فوق الجافية على تضرر عضلة القلب لدى المرضى المصابين باعتلال شريان القلب التاجي والذين سيخضعون لعملية جراحية اختيارية في البطن.

الطريقة: أُجريت هذه الدراسة في مستشفى تيان جين نان كاي، نان كاي، الصين وذلك خلال الفترة من نوفمبر 2009م إلى مارس 2010م. شملت الدراسة 80 مريضاً مصاباً باعتلال شريان القلب التاجي والذين سيخضعون لعملية جراحية اختيارية في البطن وقد تم تقسيمهم عشوائياً إلى ٤ مجموعات وهي: مجموعة س1 وخضعت للتخدير فوق الجافية مع تخدير السيوفلورين العام، والمجموعة س2 وخضعت لتخدير السيوفلورين العام المتعارف عليه، والمجموعة ب1 وخضعت لتخدير البروبوفول العام مع التخدير فوق الجافية، والمجموعة ب2 وخضعت لتخدير البروبوفول العام المتعارف عليه. لقد قمنا أثناء العلمية بمراقبة متوسط مستويات كلاً من: ضغط الشرايين، والضغط الوريدي المركزي، وصور تخطيط القلب، ومؤشر قياس عمق التخدير. فيما تم قياس مستويات العناصر التالية في مصل الدم وعلى مراحل مختلفة أثناء العملية وهي: إنترليوكين6–، وإنترليوكين–8، وعامل تنخر الأورام ألفا، وتروبونين القلب I، وغليكوجين فوسفوليز ب ب.

النتائج: أشارت نتائج الدراسة إلى أن مستويات ST قد كانت عالية في المجموعة ب1 وس2 مقارنةً بالمجموعة س1 وذلك بصورة واضحة من الناحية الإحصائية (p=0.000)، وكانت هذه المستويات أقل من المجموعة ب2 (p=0.00). كما وكانت مستويات كلاً من: إنترليوكين6–، وإنترليوكين–8، وعامل تنخر الأورام ألفا، وتروبونين القلب I، وغليكوجين فوسفوليز ب ب أعلى بكثير لدى المجموعتين ب1 وس2 بالمقارنة مع المجموعة س1 (p=0.00)، وأقل من المجموعة ب2 (p=0.00).

خاتمة: أظهرت هذه الدراسة بأن جمع التخدير فوق الجافية مع تخدير السيوفلورين قد يحمي من تضرر عضلة القلب لدى المرضى المصابين باعتلال شريان القلب التاجي، ودور هذا التخدير في تخفيض وتنظيم مستويات كلاً من: إنترليوكين–6، وإنترليوكين–8، وعامل تنخر الأورام ألفا، وتروبونين القلب I، وغليكوجين فوسفوليز ب ب قد يساعد في توفير هذه الحماية

Objectives: To determine the effect of sevoflurane combination with epidural anesthesia on myocardial injury in patients with coronary artery disease (CAD) undergoing non-cardiac surgery.

Methods: The investigation was performed in TianJin NanKai Hospital, TianJin, China from November 2009 to March 2010. Eighty patients with CAD undergoing elective abdominal surgery were randomized into 4 groups: group S1- combined sevoflurane general and epidural anesthesia; group S2 - standard sevoflurane general anesthesia; group P1 - combined propofol general and epidural anesthesia; and group P2 - standard propofol general anesthesia. Mean arterial pressure, central venous pressure, electrocardiogram, and bispectral index was monitored throughout the surgery. The serum levels of interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), cardiac troponin I (cTnI), and glycogen phosphorylase BB (GP-BB) was measured at different time points during surgery.

Results: The ST depression in group P1 and S2 was significantly higher than that in group S1 (p=0.000) and lower than that in group P2 (p=0.00). The serum levels of IL-6, IL-8, TNF-α, cTnI, and GP-BB in group P1 and S2 were dramatically greater than that in group S1 (p=0.00), and lower than that in group P2 (p=0.00).

Conclusion: Sevoflurane in combination with continuous epidural anesthesia could protect against myocardial damage in patients with CAD, downregulation of IL-6, IL-8, and TNF-α might contribute to this protection.

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Contemporary medicine shows a trend towards more aggressive surgeries in sicker patients, among whom the prevalence of ischemic heart disease is increasing.[1] Patients with cardiac disease have a higher incidence of cardiovascular events after non-cardiac surgery than those who without such disease,[2] because their reserves to withstand the stress of anesthesia induction and surgery are reduced.[3] Therefore, how to effectively improve perioperative myocardial injury, especially in coronary artery disease (CAD) patients, has become more important. Anesthetic agents are administrated widely in the clinic, including situations where myocardial injury is a threat to patients, especially to CAD patients. Propofol increased the B-cell lymphoma -2/bcl-2 associated X protein expression ratio, and decreased caspase-3 activity in ischemia/reperfusion rat hearts, which resulted in reduction of myocardial apoptosis as evidenced by TUNEL analysis and DNA laddering experiments.[4] Administration of a large dose of propofol during cardiopulmonary bypass attenuated postoperative myocardial cellular damage as compared with isoflurane or small-dose propofol anesthesia.[5] It is reported that the use of sevoflurane reduces the risk for myocardial ischemic lesion during myocardial revascularization both under extracorporeal circulation and on the working heart, and short-term (15 minutes) use of the agent before myocardial ischemia suffices for pharmacological myocardial preconditioning to develop its effect.[6] Many investigations had indicated that continuous epidural anesthesia (CEA) in combination with general anesthesia (GA) could protect vital organs from injury. Bakhtiary and colleagues,[7] studying patients receiving high thoracic epidural anesthesia in combination with GA, demonstrated a reduction in the incidence of perioperative arrhythmias, such as atrial fibrillation. They also observed a significant reduction of serum epinephrine levels in that patient group. The results of their study support that a combination of thoracic epidural anesthesia with GA may lead to improvement of patient outcome, early analgesia and reduction of perioperative complications in off-pump coronary artery bypass procedures. Furthermore, thoracic epidural anesthesia in combination with GA could also preserve cardiac function via increasing expression of vascular endothelial growth factor and inducible nitric oxide synthase, improving hemodynamic function, reducing arrhythmias,[8] and reducing apoptosis[9] after aortic cross clamp release. However, whether sevoflurane in combination with CEA has a protective effect on myocardial injury in CAD patients undergoing non-cardiac surgery has been unconfirmed systematically investigated. Therefore, the present study was designed to learn the effect of sevoflurane in combination with CEA on myocardial injury in CAD patients undergoing non-cardiac surgery.

Methods.

Patient recruitment. The investigation was performed in TianJin NanKai Hospital, TianJin, China from November 2009 to March 2010 according to the principles of the Helsinki Declaration. With patients informed contents and approval from the local Ethics Committee, we studied 80 ASA (American Society of Anesthesiologists Physical Status)[10] II-III patients (50 men, 30 women of age range from 66-70 years old) with CAD undergoing elective abdominal surgery, which was expected to last at least 4 hours were studied. Patients were eligible for enrollment if they had evidence of CAD. Evidence of CAD included a previous myocardial infarction, a history of substernal chest pain precipitated by stress or exercises, and relieved by rest or nitroglycerin, atypical chest pain plus evidence of ischemia on exercise electrocardiograph, or by coronary angiography. Patients who were taking non-steroidal anti-inflammatory drugs (NSAIDs) or hormone drugs, had infectious disease, autoimmune disorders, endocrine disease, bleeding diathesis, or water-electrolyte disturbances were excluded. The patients were also excluded from this study if the duration of surgery was less than 4 hours.

Group assignment. Each patient was randomly assigned to one of the 4 anesthesia groups: group S1 - combined sevoflurane general and epidural anesthesia during surgery; group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery; and group P2 - standard propofol general anesthesia during surgery. Each group consisted of 20 patients, both males and females.

Study protocol. Continuous epidural anesthesia. All patients fasted for 12 hours, but were allowed free access to water 6 hours before the induction of anesthesia. Pethidine 50 mg, promethazine 25 mg, and scopolamine 0.3mg were intramuscularly injected (im) approximately one hour before anesthesia. In the operating room, after placement of the epidural catheter at T8-9, a test dose of 3 mL of 2% lidocaine (group S1 and group P1), or 3 mL of 0.9% normal saline (group P2 and group S2) was administered to exclude intrathecal catheter placement. Ten minutes later, group P2 and group S2 still received 0.9% normal saline, group S1 and group P1 received 0.5% ropivacaine epidurally at 5 mL/h. Fifteen minutes after the test dose, the levels of loss of pinprick sensations were bilaterally determined by a 25-gauge needle in the midclavicular line.

General anesthesia. Induction of GA was induced with etomidate 0.25 mg/kg, sufentanil 1 mg/kg and vecuronium 0.1 mg/kg. The bispectral index score (BIS) was monitored using a BIS sensor (Narcotrend, Schiller, Switzerland). Once the BIS value reached 40-

50, the trachea was intubated. Maintenance ventilation was controlled with a tidal volume of 8-10 mL/kg and respiratory rate adjusted to maintain end-tidal carbon dioxide between 35-40 mm Hg. After endotracheal intubation, the target concentration of sevoflurane and propofol was titrated to maintain BIS between 40 and 50. Maintenance with sufentanil 0.5 mg/kg, and further doses of vecuronium 0.05 mg/kg were given every 30 minutes. Before operation, a flexible 14-French cannula was inserted in the right internal jugular vein to monitor central venous pressure, a flexible 20-gauge cannula was inserted in the radial artery to monitor mean arterial pressure. Inadequate analgesia was defined as an increase of systolic arterial blood pressure and/or heart rate greater than 20% baseline value for more than 5 minutes in response to a surgical stimulus. In cases of inadequate analgesia, 50 ug sufentanil was administrated. Bradycardia, heart rate (HR) <55 bpm, was treated with 0.5 mg of atropine intravenous (IV); hypotension, decrease of systolic arterial blood pressure by more than 30% or less than 90 mm Hg, was treated by infusion of lactated Ringer's solution and/or 6% hydroxyethyl starch 130/0.4, if necessary, with ephedrine 5 mg IV.[11] Mean arterial pressure (MAP), central venous pressure (CVP), HR, BIS, and electrocardiogram (ECG) were monitored continuously throughout the surgery by monitor instruments (Hellige, Freiburg, Germany).

Outcome measures. The changes of MAP, CVP, HR, BIS and ST segment depression (ST depression) were recorded before induction, 2 hours after induction, and at surgery termination. Blood samples were taken from the peripheral vein immediately before induction and 2 hours after surgery termination, then the blood sample (3 ml) was centrifuged at 2,000 rpm for 10 min at 4°C. Interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), cardiac troponin I (cTnI), and glycogen phosphorylase BB (GP-BB) levels presented in serum were determined using commercially available murine-specific sandwich enzyme-linked immunosorbent assay (ELISA) kits. The IL-6, IL-8 and TNF-α assay kits were supplied by Santa Cruz, CA, USA, and the cTnI and GP-BB assay kits were supplied by Beijing Zhongshan Biotechnology Co. Ltd, Beijing, China.

Statistical analysis. All data were expressed as mean ± standard deviation (SD). Comparisons of gender between groups were made by the x^2 goodness of fit test, and intergroup comparisons among the 4 groups were determined by one-way ANOVA. When the F value was significant ($p<0.05$), a post hoc analysis was performed with the Duncan new multiple range test in order to test the difference between means. A p-value <0.05 was considered statistically significant.

Results. ***General data.*** Characteristics of patients and surgery are listed in **Table 1**. There were no significant differences in gender, age, weight, urine volume, duration of surgery and anesthesia, bleeding volume, infusion volume of lactated Ringer's solution and 6% hydroxyethyl starch 130/0.4 among the 4 groups (all $p>0.05$).

Comparisons of MAP, CVP, BIS, HR, and ST-segment depression. The comparisons of MAP, CVP, HR, BIS, and ST segment among the 4 groups are listed in **Table 2**. There were no significant differences in MAP, CVP, and HR among the 4 groups at different time points (all $p>0.05$). The BIS among the 4 groups at the end of surgery was dramatically greater than that at 2 hours after induction, and lower than that at before induction (**Figure 1**, $p=0.000$, **Table 3**). The ST depression at 2 hours after induction among the 4 groups was dramatically lower than that at surgery termination, and higher than that at before induction (**Figure 2**, $p=0.000$, **Table 4**). At surgery termination, the ST depression in group P1 and S2 was dramatically higher than that in group S1, and lower than that in group P2 (**Figure 2**, $p=0.000$, **Table 5**). There were no significant differences in ST depression between group P1 and group S2 (**Figure 2**, $p>0.05$).

Comparisons of serum IL-6, IL-8, TNF-alpha, cTnI, and GP-BB. The comparisons of serum IL-6, IL-8, TNF-alpha, cTnI, and GP-BB among the 4 groups are listed in Table 6. There were no significant differences at before induction of anesthesia in serum IL-6, IL-8, TNF-alpha, cTnI, and GP-BB among the 4 groups (all $p>0.05$). At 2 hours after surgery termination, the serum levels of the 5 indices in group P1 and S2 were dramatically greater than that in group S1, and lower than that in group P2 (**Figure 3**, $p=0.000$, **Table 7**). There were no significant differences in the 5 indices between group P1 and group S2 at 2 hours after surgery termination (**Figure 3**, all $p>0.05$).

Table 1 - Patients and surgical characteristics among the 4 groups (mean±SD, n=20) .

Variables	Group S1	Group S2	Group P1	Group P2
Gender (male/female)	13/7	12/8	14/6	11/9
Age (year)	67±12	69±11	68±9	68±12
Weight (kg)	62±10	60±16	59±13	61±17
Duration of surgery (min)	292±27	283±41	287±38	279±46
Duration of general anesthesia (min)	317±33	307±39	304±47	299±48
Bleeding volume (ml)	232±65	201±96	222±67	213±81
Urine volume (ml)	2165±334	2049±382	2101±355	2002±395
Lactated Ringer's solution (ml)	2203±177	2115±253	2213±263	2197±236
6% Hydroxyethyl Starch 130/0.4 (ml)	1291±137	1163±149	1208±144	1191±168

Table 2 - Comparisons of MAP, CVP, HR, BIS, and ST depression among the 4 groups (n=20). (mean±SD, n=20)

Time point	MAP (mm Hg)	Central venous pressure (cm H_2O)	Heart rate (bpm)	Bispectral index	ST segment depression (mm)
Before induction					
Group S1	97.2 ± 8.9	8.7 ± 1.9	83.4±7.4	94.1 ± 3.6*	-1.15 ± 0.07*
Group S2	96.9 ± 9.7	8.0 ± 1.7	79.7±10.1	94.7 ± 3.1*	-1.12 ± 0.10*
Group P1	94.7 ± 10.6	7.8 ± 2.1	81.5±9.2	95.1 ± 2.4*	-1.14 ± 0.08*
Group P2	93.4 ± 12.9	7.7 ± 2.3	80.2±9.6	93.9 ± 3.8*	-1.13 ± 0.11*
2 hours after induction					
Group S1	88.4 ± 9.3	9.2 ± 1.6	80.9±8.3	40.3 ± 4.9	-1.48 ± 0.09
Group S2	87.1 ± 12.6	8.2 ± 2.3	82.7±10.7	41.2 ± 3.7	-1.51 ± 0.07
Group P1	85.5 ± 10.4	8.6 ± 2.0	79.1±9.8	38.9 ± 5.2	-1.53 ± 0.06
Group P2	90.3 ± 8.6	8.5 ± 1.9	82.5±7.7	39.8 ± 6.1	-1.54 ± 0.04
At the end of surgery					
Group S1	90.9 ± 9.5	9.1 ± 1.7	84.7±9.3	53.5 ± 9.7*	-1.77 ± 0.08*,†,‡
Group S2	92.3 ± 10.8	8.6 ± 1.9	86.4±8.9	52.6 ± 10.8*	-2.15 ± 0.07*
Group P1	88.8 ± 10.1	8.5 ± 2.2	82.4±10.4	50.9 ± 12.3*	-2.11 ± 0.05*
Group P2	91.7 ± 11.3	8.3 ± 2.0	83.4±10.3	51.8 ± 9.9*	-2.54 ± 0.10*,†,‡

MAP - mean arterial pressure, CVP - central venous pressure, HR - ST segment, BIS - bispectral index score; group S1 - combined sevoflurane general and epidural anesthesia during surgery, group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery, group P2 - standard propofol general anesthesia during surgery (*p=0.000 versus 2 hours after induction; †p=0.000 versus group P1; ‡p=0.000 versus group S2) (one-way ANOVA, p<0.05)

Table 3 - Bispectral index comparison among the 4 groups at the end of surgery and at 2 hours after induction.

Bispectral index	Surgery termination (lower) versus before induction	Surgery termination (greater) versus 2 hours after induction
	95% confidence interval	
Group S1	(-44.99, -36.61)	(8.81, 17.19)
Group S2	(-46.43, -37.77)	(7.07, 15.73)
Group P1	(-49.18, -39.22)	(7.02, 16.98
Group P2	(-46.61, -37.69)	(7.49, 16.41)

group S1 - combined sevoflurane general and epidural anesthesia during surgery; group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery; group P2 - standard propofol general anesthesia during surgery

Table 4 - The ST depression among 4 groups at before induction, 2 hours after induction and surgery termination.

ST depression	2 hours after induction versus surgery termination	2 hours after induction versus before induction
	95% confidence interval	
Group S1	(0.239, 0.341)	(-0.381, -0.279)
Group S2	(0.588, 0.692)	(-0.442, -0.338)
Group P1	(0.540, 0.620)	(-0.430, -0.350)
Group P2	(0.944, 1.061)	(-0.466, -0.349)

The ST depression at 2 hours after induction among the 4 groups was dramatically lower than that at surgery termination and higher than that at before induction (p=0.000). group S1 - combined sevoflurane general and epidural anesthesia during surgery; group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery; group P2 - standard propofol general anesthesia during surgery

Table 5 - The ST depression between the 4 groups at surgery termination.

ST depression	95% confidence interval (at surgery termination)	
	Group P1(or S2) versus group S1	Group P1(or S2) versus group P2
P1 versus S1	(-0.389, -0.291)	(-)
S2 versus S1	(-0.429, -0.331)	(-)
P1 versus P2	(-)	(0.381, 0.479)
S2 versus P2	(-)	(0.341, 0.439)

At surgery termination, the ST depression in group P1 and S2 was dramatically higher than that in group S1, and lower than that in group P2 (p=0.000). Group S1 - combined sevoflurane general and epidural anesthesia during surgery; group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery; group P2 - standard propofol general anesthesia during surgery

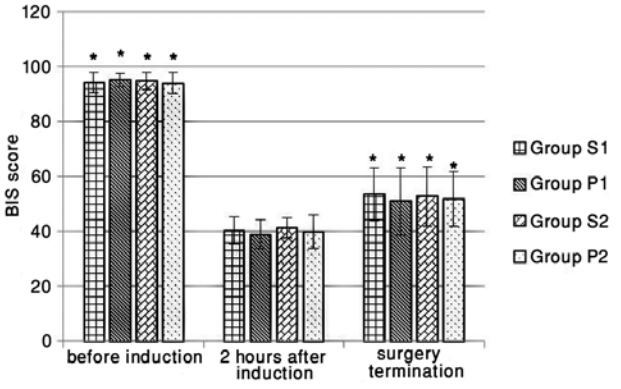

Figure 1 - The bispectral index (BIS) among 4 groups at surgery termination was dramatically greater than that at 2 hours after induction, and lower than that at before induction (p=0.000). *p<0.05 versus 2 hours after induction (1-way ANOVA, p<0.05).

Table 6 - Comparisons of serum IL-6,IL-8, TNF-α, cTnI and GP-BB among the 4 groups (n=20).

Time point	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF- α(ng/ml)	cTnI (ng/ml)	GP-BB (ng/ml)
Before induction of anesthesia					
Group S1	45 ± 6	172 ± 91	0.52 ± 0.13	0.28 ± 0.02	2.62 ± 0.44
Group S2	42 ± 8	167 ± 97	0.60 ± 0.09	0.26 ± 0.08	2.19 ± 0.62
Group P1	43 ± 5	170 ± 88	0.54 ± 0.10	0.29 ± 0.05	2.25 ± 0.76
Group P2	44 ± 7	174 ± 76	0.57 ± 0.11	0.27 ± 0.08	2.46 ± 0.53
2 hours after surgery termination					
Group S1	206 ± 92*	397 ± 99*	0.73 ± 0.16*	1.22 ± 0.14*	4.79 ± 1.54*
Group S2	334 ± 99*,†,‡	569 ± 101*,†,‡	0.99 ± 0.13*,†,‡	1.87 ± 0.21*,†,‡	7.02 ± 1.10*,†,‡
Group P1	321 ± 112*,†,‡	533 ± 112*,†,‡	0.92 ± 0.13*,†,‡	1.78 ± 0.28*,†,‡	6.50 ± 1.32*,†,‡
Group P2	407 ± 116*	711 ± 142*	1.26 ± 0.12*	2.33 ± 0.19*	8.41 ± 0.93*

IL-6 - interleukin-6, IL-8 - interleukin-8, TNF-α - tumor necrosis factor-alpha, cTnI - cardiac troponin I, GP-BB - glycogen phosphorylase BB, group S1 - combined sevoflurane general and epidural anesthesia during surgery, group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery, group P2 - standard propofol general anesthesia during surgery (*p=0.000 versus 2 hours after induction; †p=0.000 versus group P1; ‡p=0.000 versus group S2) (one-way ANOVA, p<0.05)

Table 7 - The 95% confidence interval of serum IL-6, IL-8, TNF-alpha, cTnI, and GP-BB among the 4 groups.

Groups	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF- α(ng/ml)	cTnI (ng/ml)	GP-BB (ng/ml)
	95% confidence interval				
P1 versus S1	(68.34, 161.66)	(71.72, 199.78)	(0.125, 0.275)	(0.4621, 0.6579)	(1.1003, 2.3197)
S2 versus S1	(81.34, 174.66)	(107.94, 236.03)	(0.185, 0.335)	(0.5506, 0.7464)	(1.6203, 2.8397)
P1 versus P2	(-132.66, -39.34)	(-242.28, -114.22)	(-0.405, -0.255)	(-0.6479, -0.4521)	(-2.5197, -1.3003)
S2 versus P2	(-119.66, -26.34)	(-206.03, -77.97)	(-0.345, -0.195)	(-0.5594, -0.3636)	(-1.9997, -0.7803)

IL-6 - interleukin-6, IL-8 - interleukin-8, TNF-α - tumor necrosis factor-alpha, cTnI - cardiac troponin I, GP-BB - glycogen phosphorylase BB, group S1 - combined sevoflurane general and epidural anesthesia during surgery, group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery, group P2 - standard propofol general anesthesia during surgery

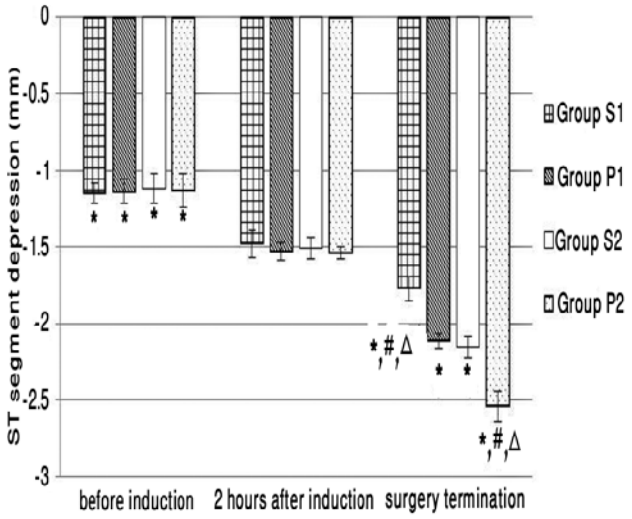

Figure 2 - The ST depression of the 4 groups before and after induction and at surgery termination. Group S1 - combined sevoflurane general and epidural anesthesia during surgery; group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery; group P2 - standard propofol general anesthesia during surgery. (*p=0.000 versus 2 hours after induction; †p=0.000 versus group P1, ‡p=0.000 versus group S2) (one-way ANOVA, p<0.05)

Discussion. Table 2 shows that there were no significant differences in MAP, CVP, and HR among the 4 groups at different points. It indicates that the physiological status of the patients before induction, 2 hours after induction, and surgery termination were stable and similar throughout the surgery. The BIS monitor uses Fourier transformation and bispectral analysis to compute a number (BIS score) ranging from 0 (isoelectric) to 100 (fully awake). The BIS scores of 0 to 40, 40 to 60, 60 to 70, and 70 to 100 are deep hypnotic state, general anesthesia state, deep sedation state, and sedation state.[12] It has been validated in the operating room as an objective measure of sedation depth. In Table 2, the BIS score at surgery termination was greater than that at 2 hours after induction and lower than that at before induction. It implies that, at 2 hours after induction and surgery termination, patients were in a state of general anesthesia, whilst at before induction, in a state of sedation.

The ST interval in the EEG represents the period during which the ventricles depolarize. The ST depression can be caused by ischemia, digitalis, tachycardia, temperature or electrolyte abnormalities.

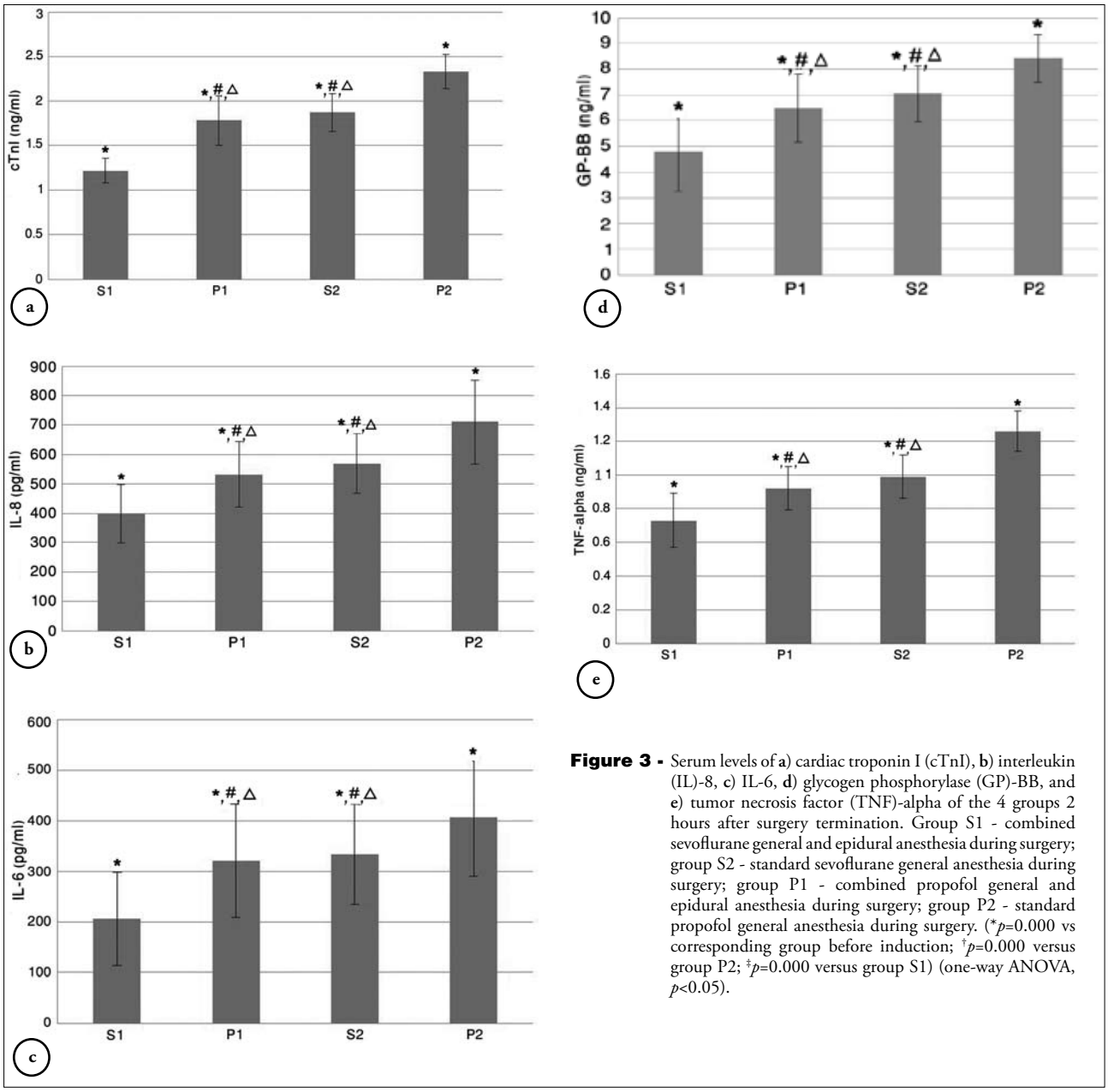

Figure 3 - Serum levels of **a**) cardiac troponin I (cTnI), **b**) interleukin (IL)-8, **c**) IL-6, **d**) glycogen phosphorylase (GP)-BB, and **e**) tumor necrosis factor (TNF)-alpha of the 4 groups 2 hours after surgery termination. Group S1 - combined sevoflurane general and epidural anesthesia during surgery; group S2 - standard sevoflurane general anesthesia during surgery; group P1 - combined propofol general and epidural anesthesia during surgery; group P2 - standard propofol general anesthesia during surgery. (*p=0.000 vs corresponding group before induction; †p=0.000 versus group P2; ‡p=0.000 versus group S1) (one-way ANOVA, p<0.05).

A depression in the ST-segment is associated with increased risk for future cardiac injury. According to **Table 2**, the myocardial risk among the 4 groups at 2 hours after induction was higher than that in the corresponding group before induction, but lower than that in the corresponding group at surgery termination. Furthermore, there were significant differences in ST depression among the 4 groups at surgery termination. The data indicated that the myocardial risk in group P1 was lower than that in group P2, but higher than that in group S1. The myocardial risk in group S2 was lower than that in group P2, but higher than that in group S1. There were no significant differences in myocardial risk between group P1 and group S2. Therefore, both sevoflurane and epidural anesthesia have an effect in reducing myocardial risk according to our study data.

To clarify the effect of sevoflurane in combination with CEA on myocardial injury in patients with CAD receiving non-cardiac surgery, we used cTnI, and GP-BB were used to assess the extent of myocardial injury. The cTnI, the specific and selective proteolysis of the myofilament protein, has been proposed to play a key role in human myocardial ischemia/reperfusion injury, including in stunning and in acute pressure overload.[13] It is the best cardiac biomarker for myocardial damage because it has nearly absolute myocardial tissue specificity

and higher sensitivity than creatine kinase, lactate dehydrogenase, and their isozymes, and myoglobin.[12] Apple et al[14] declared cardiac troponin as the preferred biomarker for myocardial infarct. The GP catalyses the breakdown of glycogen in the sarcoplasmic reticulum. It has been suggested that, after glycogenolysis in ischemic tissue, GP-BB is released into the circulation 2-4 hours after myocardial injury from the sarcoplasmic reticulum into the cytoplasm through the damaged cell membrane, and it is also a highly sensitive marker of myocardial injury.[15] Therefore, GP-BB together with cardiac-specific markers such as cTnI could improve specificity and sensitivity for the early diagnosis of myocardial injury. The ELISA kits used in this study were murine-specific, they can also be used in human serum test according to the product instruction.

In **Table 6**, at 2 hours after surgery termination, the myocardial injury in group P1 was better than that in group P2, but worse than that in group S1; the myocardial injury in group S2 was better than that in group P2, but worse than that in group S1. There were no significant differences in myocardial injury between group P1 and group S2. Therefore, sevoflurane in combination with CEA has an effect in reducing myocardial injury in this study. Furthermore, IL-6, IL-8, and TNF-α in group P1 were downregulated compared with that in group P2, but still greater than that in group S1; the IL-6, IL-8, and TNF-α in group S2 were downregulated compared with that in group P2, but still greater than that in group S1. There were no significant differences in IL-6, IL-8, and TNF-α a between group P1 and group S2. Therefore, sevoflurane in combination with CEA may have an effect in downregulating IL-6, IL-8, and TNF-alpha. All the results imply that sevoflurane in combination with CEA may have myocardial protection, and reducing cytokine release might be associated with this protection. In this study, it was found that sevoflurane in combination with CEA could decrease the ST depression and the levels of serum cTnI and GP-BB, while the levels of IL-6, IL-8, and TNF-α were reduced. These results indicated that sevoflurane in combination with CEA could improve myocardial injury in patients with CAD undergoing non-cardiac surgery. Many studies have investigated the possible protective mechanism. Firstly, it is reported that CEA could attenuate production of IL-6, IL-8, and IL-1RA during the perioperative period.[16] Caputo and colleagues[17] also reported that thoracic epidural anesthesia downregulates the levels of IL-6 and IL-8, and attenuates the surgically mediated sympathetic stress response, thereby preventing the increase in myocardial oxygen demand. Secondly, sevoflurane suppresses the production of IL-8[18] and proinflammatory effects of TNF-α, which is evidenced by attenuated upregulation of proinflammatory cytokine mRNA, such as TNF-alpha, monocyte chemoattractant protein-1(MCP-1), and intercellular adhesion molecule-1 (ICAM-1). Sevoflurane also has an effect in reducing nuclear translocation of the proinflammatory factors nuclear factor- B (NF-κB) and activator protein-1 (AP-1).[19]

This investigation determined that the proper anesthesia method and reasonable drug administration were important to improving myocardial injury. However, whether it is possible to control the degree of myocardial injury by these exact methods is still uncertain. Furthermore, this study could also be explored further by extending the sample population, observing the post-operative effects, and possible long-term complications due to the applied type of anesthesia.

In conclusion, sevoflurane in combination with CEA could protect against myocardial damage in patients with CAD, and downregulation of levels of IL-6, IL-8, and TNF-α might contribute to the protection. However, its precise mechanism of myocardial protection needs further study.

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