The effect of desflurane and propofol protocols on preconditioning

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Advances in Clinical and Experimental Medicine, ISSN 1899-5276 (print), ISSN 2451-2680 (online) *Adv Clin Exp Med*. 2017;26(5):817–823

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Funding sources
None declared

Conflict of interest
None declared

Received on July 17, 2015
Revised on November 16, 2015
Accepted on December 18, 2015

Abstract

Background. Preconditioning is one of the most powerful mechanisms preventing the myocardial ischemic damage that occurs during coronary artery bypass grafting.

Objectives. We aimed to investigate the effects of different propofol and/or desflurane administration protocols in terms of the prevention of ischaemia-reperfusion damage.

Material and methods. Ninety patients, aged > 18 years, American Society of Anesthesiologists (ASA) category III, scheduled to undergo primary elective coronary artery bypass grafting (CABG), were included in the study. During maintenance, the patients in group 1 (n = 30) received a propofol infusion (5–6 mg/kg/h) combined with a fentanyl infusion (3–5 mcg/kg/h); the patients in group 2 (n = 30) also received a propofol infusion (5–6 mg/kg/h) combined with a fentanyl infusion (3–5 mcg/kg/h), but they were also given 6% desflurane inhalation for 15 min both before cross-clamping of the aorta and after removal of the clamp; the patients in group 3 (n = 30) received a propofol infusion (2–3 mg/kg/h) combined with a fentanyl infusion (3–5 mcg/kg/h) and received the continuous 6% desflurane inhalation. Blood samples were drawn in the preoperative period (S1), during cardiopulmonary bypass, before cross-clamping the aorta (S2), after removal of the cross-clamp (S3) and 24 h after the operation (S4).

Results. All groups were similar in terms of age and BMI ($p > 0.05$). TNF-α levels were higher at S3 compared to S1, S2 and S4 ($p > 0.001$). The TNF-α levels at S4 were lower in group 3 than those in group 1 and group 2 ($p < 0.05$). In all groups, h-FABP levels showed an increase in S3 but were significantly lower at S4 ($p < 0.05$). In group 3, h-FABP levels at S2 and S3 were significantly lower than those in group 1 ($p < 0.05$). There was a moderate correlation between h-FABP and TNF-α levels (Spearman's rho = 0.472, $p < 0.001$).

Conclusions. On the basis of the measurement of h-FABP and TNF-α, low-dose propofol and continuous desflurane inhalation provide more effective preconditioning than propofol alone or a short course of desflurane in patients undergoing CABG.

Key words: preconditioning, propofol, desflurane

DOI
10.17219/acem/61045

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Introduction

Ischemic preconditioning has been defined as the reduction of high energy catabolism by producing short periods of ischemia that are accompanied by a decrease in myocardial contractility, arrhythmia and intracellular acidosis. Thus, ischemia-reperfusion-related contractile dysfunction is prevented, which is crucially important in patients with a hypertrophied ventricle. Preconditioning produces short periods of ischemia that help the heart adapt to ischemia-reperfusion compromise.[1,2]

As demonstrated by experimental and clinical studies, producing short periods of ischemia using pharmacological and perioperative volatile anesthetic drugs has a pre-conditioning effect on the myocardium.[3] Propofol was shown to have antioxidant effects and desflurane and sevoflurane were shown to be associated with lower troponin I levels, which may indicate their potential use for preconditioning.[4,5]

Large amounts of reactive oxygen radicals are created during cardiopulmonary bypass, causing an increase in systemic oxidative stress and lipid peroxidation that alters myocardial function.[6] Tumor necrosis factor alpha (TNF-α), which increases during the creation of oxygen radicals, has been shown to increase following cardiopulmonary bypass.[7] Therefore, TNF-α is thought to play an important role in the inflammatory process that causes cardiac dysfunction.[4]

Heart-type fatty acid binding protein (h-FABP) has been shown to be a sensitive marker in the diagnosis of myocardial infarction. Its use in the assessment of preconditioning during cardiac surgical anesthesia was suggested since it may be detected in venous blood within a couple of hours after myocardial ischemia or infarction.[8,9] TNF-α was also suggested to be a useful marker in the assessment of effectiveness of the preconditioning method used in cardiac surgery.[10,11] Another advantage of TNF-α is its stimulation of the acute phase reaction, which may allow the cardiac protective effects of preconditioning to be traced during cardiac surgery.

In light of the above, we sought to evaluate the effects of different propofol and/or desflurane management protocols on preconditioning during coronary artery surgery, with the assessment being based on TNF-α and h-FABP levels.

Patients and methods

The study was approved by our institutional review board (02-2/6, 20.03.2013). All patients were informed about the study protocol and signed procedure-oriented informed consent forms. Patients aged > 18 years of age, American Society of Anesthesiologists (ASA) category III, scheduled to undergo primary elective coronary artery bypass grafting (CABG) were included in the study. Patients with a left ventricle ejection fraction < 50% and those with unstable angina pectoris, diabetes, renal failure (creatinine ≥ 1.2 mg/dL), or acute or recent (< 2 weeks) myocardial infarction were excluded. Patients with a clear indication for combined valve or aortic surgery and those who had cardiogenic shock or low cardiac output syndrome were also excluded. A total of 90 patients were included in the study.

Study protocol and chemical analysis

The patients were pre-medicated with 5 mg oral diazepam on the night before the operation. All operations were performed by the same surgical team. Standard monitoring was performed with 12-lead electrocardiogram and pulse oximetry. A peripheral venous line was introduced via the right antecubital vein. Invasive arterial monitoring was achieved via the right radial artery. After 5 min of pre-oxygenation with 100% oxygen, anesthesia was induced with 1.5–2.0 mg/kg/min of propofol (Lipuro %1, Braun, Melsungen, Germany) and 5–10 mcg/kg of fentanyl (Fentanyl, Mercury Pharma, London, UK). Neuromuscular blockade was achieved with 1 mg/kg of intravenous rocuronium (Curon, Mustafa Nevzat, Istanbul, Turkey). Patients were intubated and were placed on volume-controlled mechanical ventilation. The respiratory rate was set at 12 times per min, positive end-expiratory pressure at 0 mbar, maximum pressure at 30 mbar and tidal volume at 7–10 mL/kg. End-tidal CO_2 was measured using a Nihon Kohden Life Scope 14. Then, a central venous catheter was introduced via the right internal jugular vein and central venous pressure was recorded during and after the operation. Bispectral index (BIS) monitoring was performed in all patients (Aspect Medical Systems BIS VISTA™ Covidien).

The patients were randomly allocated into 3 groups to receive 1 of 3 different anesthetic maintenance regimens. Randomization was achieved using computer-based software. During maintenance, the patients in group 1 (n = 30) received a propofol infusion (5–6 mg/kg/h) combined with a fentanyl infusion (3–5 mcg/kg/h). Patients in group 2 (n = 30) also received a propofol infusion (5–6 mg/kg/h) combined with a fentanyl infusion (3–5 mcg/kg/h) but they were also given 6% desflurane (Suprane, Baxter, Puerto Rico) inhalation for 15 min both before cross-clamping of the aorta and after removal of the clamp. The patients in group 3 (n = 30) received a propofol infusion (2–3 mg/kg/h) combined with a fentanyl infusion (3–5 mcg/kg/h) plus continuous 6% desflurane inhalation. BIS was kept at 40–50.

Body temperature was monitored using a nasopharyngeal probe and patients' body temperatures were cooled down to 32°C. Blood samples were drawn in the preoperative period (S1), during cardiopulmonary bypass, be-

fore cross-clamping of the aorta (S2), after removal of the cross-clamp (S3) and 24 h after the operation (S4). The samples were preserved in a refrigerator at -80°C. TNF-α (USCN Life Science Inc., USA) and h-FABP levels were measured via ELISA. Creatinine kinase (CK), CK-MB, troponin-I, B-type natriuretic peptide (BNP) and lactate dehydrogenase (LDH) levels were measured from samples drawn in the preoperative period and 24th postoperative hour.

Statistical analysis

All analyses were performed using STATISTICS for Social Sciences (SPSS) v. 19.0. For related measurements, normally distributed data was compared using repeated measures analysis of variance and non-normally distributed data was compared using the Friedman test. For independent measurements, normally distributed data was compared using one-way analysis of variance (ANOVA) and non-normally distributed data was compared using the Kruskal-Wallis test. Spearman's correlation analysis was used to test for any linear relationship among the study variables. A p-value of less than 0.05 was considered statistically significant.

Results

The 3 groups were similar in terms of age and body mass index ($p > 0.05$). CK, CK-MB, LDH, troponin I and BNP levels showed a significant increase in the 24th postoperative hour compared to their baseline values ($p < 0.001$). There were no significant differences among the groups either before or after the operation ($p > 0.05$) (Table 1).

In group 1, 2 and 3, TNF-α levels did not differ among S1, S2 and S4 ($p > 0.05$) whereas S3 was significantly higher than S1, S2 and S4 ($p < 0.001$). There was a significant difference between S2 and S4 in group 1 whereas no such difference was observed in other groups ($p < 0.05$) (Table 2). In almost all groups, TNF-α levels showed a significant increase after removal of the cross-clamp but had decreased 24 h postoperatively. In addition, S3 TNF-α levels showed a marked increase compared to other stages in all 3 groups. S3 TNF-α levels did not differ significantly among the 3 groups ($p < 0.05$). S2 TNF-α levels were significantly lower in group 3 compared to group 1 and group 2 ($p < 0.05$). Similarly, S4 TNF-α levels were significantly lower in group 3 than those in group 1 and group 2 ($p < 0.05$) (Table 2). S2 TNF-α levels were significantly lower in group 2 and group 3 (desflurane administered) than those in group 1 (desflurane not administered) ($p < 0.05$). The most profound reduction by the 24th postoperative hour was that seen in group 3 ($p < 0.05$).

Table 1. Comparison of data from patient groups before and after the operation

	Group 1			Group 2			Group 3			Comparison of groups**
N (female/male)	30 (11/19)			30 (12/18)			30 (10/20)			
Age, year	64.5 ± 8.8			63.8 ± 6.2			64.0 ± 6.8			> 0.05
BMI, kg/m^2	27.1 ± 2.2			27.4 ± 3.4			26.5 ± 3.1			> 0.05
	preopmean ± SD	postop mean ± SD	*p	preop mean ± SD	postop mean ± SD	*p	preop mean ± SD	postop mean ± SD	*p	
CK, U/L	93 ± 60	1115 ± 644	< 0.0001	98 ± 61	1048 ± 673	< 0.0001	109 ± 82	1054 ± 678	< 0.0001	> 0.05
CK-MB, U/L	11.8 ± 3.8	66.7 ± 23.7	< 0.0001	13.9 ± 3.7	65.6 ± 27.2	< 0.0001	13.8 ± 4.7	63.8 ± 31.7	< 0.0001	> 0.05
LDH, U/L	270 ± 133	608 ± 202	< 0.0001	257 ± 145	622 ± 320	< 0.0001	262 ± 129	615 ± 234	< 0.0001	> 0.05
Troponin I, µg/L	0.31 ± 0.59	2.47 ± 1.67	< 0.0001	0.30 ± 0.56	2.51 ± 1.48	< 0.0001	0.27 ± 0.66	2.41 ± 1.60	< 0.0001	> 0.05
BNP, pg/mL	233 ± 114	998 ± 545	< 0.0001	239 ± 185	972 ± 631	< 0.0001	244 ± 153	981 ± 658	< 0.0001	> 0.05

*Paired t-test for intra-group comparison; **one-way analysis of variance (ANOVA), comparison of pre-op and post-op values between groups was not significant.

Table 2. Comparison of the TNF-alpha (pg/mL) data of stages belonging to all groups

n		S1		S2		S3		S4		p-value
		30		30		30		30		
Group 1	mean ± SD	20.06 ± 2.50		19.10 ± 11.02		187.16 ± 138.49		39.34 ± 37.46		[b]< 0.0001
	min.–max.	14.97–26.34		6.89–57.71		14.15–510.86		14.01–183.45		
	95% CI from-to	19.12–20.99		14.98–23.21		135.45–238.86		25.36–53.33		
	comparison	S1 vs S2	S1 vs S3	S1 vs S4		S2 vs S3	S2 vs S4		S3 vs S4	
	p-value**	> 0.05	< 0.001	< 0.05		< 0.001	< 0.05		< 0.01	
Group 2	mean ± SD	21.44 ± 3.67		17.93 ± 3.61		188.54 ± 127.66		27.91 ± 9.80		[a]< .0001
	min.–max.	16.09–31.13		8.94–23.88		12.23–447.43		15.88–55.93		
	95% CI From-To	20.07–22.80		16.58–19.28		140.88–236.21		24.26–31.57		
	comparison	S1 vs S2	S1 vs S3	S1 vs S4		S2 vs S3	S2 vs S4		S3 vs S4	
	p-value*	> 0.05	< 0.001	< 0.05		< 0.001	> 0.05		< 0.01	
Group 3	mean ± SD	19.79 ± 3.49		14.25 ± 4.13		122.54 ± 122.12		22.52 ± 8.57		[a]< 0.0001
	min.–max.	12.58–25.93		8.12–26.06		10.31–511.68		14.01–49.44		
	95% CI From-To	18.49–21.10		12.71–15.79		76.94–168.13		19.32–25.72		
	comparison	S1 vs S2	S1 vs S3	S1 vs S4		S2 vs S3	S2 vs S4		S3 vs S4	
	p-value**	> 0.05	< 0.001	> 0.05		< 0.001	> 0.05		< 0.01	
		G1 vs G2		G1 vs G3		G2 vs G3				
Comparison for S1		–		–		–				[c] 0.1164
Comparison for S2**		> 0.05		< 0.05		> 0.05				[c] 0.0260
Comparison for S3		–		–		–				[c] 0.0847
Comparison for S4*		> 0.05		< 0.05		< 0.05				[d] 0.0137

S – stage; G – group; SD – standard deviation; CI – confidence Interval; min.–max – minimum–maximum; [a] – repeated measures ANOVA; [b] – Friedman Test (nonparametric repeated measures ANOVA); [c] one-way analysis of variance (ANOVA); [d] – Kruskal-Wallis Test (nonparametric ANOVA). If p-value obtained by ANOVA is <0.05; *Dunns or **Tukey-Kramer multiple comparisons test (Post-hoc tests) was used to compared all stages (S1,S2 and S3). Post tests were not calculated because the p-value was greater than 0.05.

In group 3, S3 h-FABP levels were significantly higher than S1, S2 and S4 levels ($p < 0.001$) whereas no significant difference was found among S1, S2 and S4 h-FABP levels ($p > 0.05$). In group 1, no significant difference was found between S1 and S2 h-FABP levels whereas the differences among the other stages were statistically significant ($p < 0.001$). In group 2, no significant difference was found between S1 and S2 h-FABP levels whereas the differences among the other stages were statistically significant ($p < 0.001$) (Table 3).

In all groups, h-FABP levels were found to be increased after removal of the aortic cross-clamp and decreased by the 24th hour postoperatively ($p < 0.05$). There was a moderate but significant correlation between h-FABP and TNF-α (Spearman's rho = 0.47, $p < 0.001$).

S1 h-FABP levels did not differ significantly among the groups ($p > 0.05$). S2 h-FABP levels in group 3 were significantly lower compared to group 1 ($p < 0.05$). S3 h-FABP levels in group 3 were also significantly lower compared to group 1 but did not differ significantly from those in group 2 ($p < 0.01$ and $p > 0.05$, respectively). S4 levels in group 3 were significantly lower than those in group 2 ($p < 0.001$) (Table 3).

Discussion

The myocardium is exposed to artificial ischaemia and reperfusion ischaemia during extracorporeal circulation.[12] Myocardial protection against such insults is essential to the success of cardiac surgery. Systemic inflammation plays an important role in the development of reperfusion injury.[13] There is a positive relationship between the degree of systemic inflammation and inflammatory biomarkers.[14] Studies have demonstrated that remote ischemic preconditioning suppresses pro-inflammatory gene transcription in human leukocytes.[15]

Table 3. Comparison of the h-FAPB (ng/mL) data of stages belonging to all groups

n		S1		S2	S3		S4	p-value
		30		30	30		30	
Group 1	mean ± SD	2.24 ± 0.79		3.08 ± 1.77	7.68 ± 3.30		3.76 ± 2.02	
	min.–max.	1.08–3.96		1.16–8.67	1.32 -18.10		1.00–9.86	
	95% CI From-To	1.95–2.54		2.42–3.74	6.45–8.92		3.00–4.51	[b]< 0.0001
	comparison	S1 vs S2	S1 vs S3	S1 vs S4	S2 vs S3	S2 vs S4	S3 vs S4	
	p-value**	> 0.05	< 0.001	< 0.01	< 0.001	> 0.05	< 0.001	
Group 2	mean ± SD	2.51 ± 1.23		2.79 ± 1.20	6.20 ± 3.69		4.60 ± 1.38	
	min.–max.	1.04–5.95		1.04–5.37	2.17–14.74		1.79–6.98	
	95% CI From-To	2.05–2.97		2.34–3.23	4.82–7.57		4.09–5.12	[a]< .0001
	comparison	S1 vs S2	S1 vs S3	S1 vs S4	S2 vs S3	S2 vs S4	S3 vs S4	
	p-value*	> 0.05	< 0.001	< 0.001	< 0.001	< 0.01	< 0.05	
Group 3	mean ± SD	2.10 ± 0.69		2.00 ± 1.26	4.98 ± 2.90		3.06 ± 1.09	
	min.–max.	0.89–3.85		0.74–7.95	1.56 -12.74		1.73–6.39	
	95% CI From-To	1.84–2.35		1.53–2.47	3.89–6.06		2.65–3.47	[a]< 0.0001
	comparison	S1 vs S2	S1 vs S3	S1 vs S4	S2 vs S3	S2 vs S4	S3 vs S4	
	p-value**	> 0.05	< 0.001	> 0.05	< 0.001	< 0.05	< 0.001	
		G1 vs G2		G1 vs G3	G2 vs G3			
Comparison for S1		–		–	–			[b] 0.2295
Comparison for S2**		> 0.05		< 0.05	> 0.05			[b] 0.0126
Comparison for S3		> 0.05		< 0.01	> 0.05			[b] 0.0085
Comparison for S4*		> 0.05		> 0.05	< 0.01			[b] 0.0010

S – stage; G – group; SD – standard deviation; CI – confidence Interval; min.–max – minimum–maximum; [a] – repeated measures ANOVA; [b] – one-way analysis of variance (ANOVA). If p-value obtained by ANOVA is <0.05; **Tukey-Kramer multiple comparisons test (post-hoc tests) was used to compared all stages (S1,S2 and S3).

Landoni et al. reported in their randomized meta-analysis that troponin I levels showed greater reduction with the modern volatile agents desflurane and sevoflurane in patients undergoing cardiac surgery.[16] However, we found no difference in troponin I levels between the groups receiving or not receiving desflurane. This finding may be attributed to the dosage of propofol or desflurane or use of intravenous anesthesia as the anesthetic approach. In addition, the cardio-protective effect propofol produced alone may be another reason why troponin I levels were different.

Moreover, our results are supported by others suggesting that there was no difference between propofol and sevoflurane with regard to postoperative mortality and myocardial infarction in patients undergoing CABG. These results, as reported previously, are due to the antioxidant effects of propofol and preconditioning effects of volatile anesthetics.[17] An inverse relationship was noted between the effectiveness of preconditioning and the amount of reactive oxygen species, whilst propofol is known as a reactive oxygen scavenger. On the other hand, Smul et al. reported in their experimental study on rabbits that propofol inhibits desflurane-related preconditioning.[18] However no conclusive evidence exists to justify the relationship of this effect with free radicals.

In their prospective study on 120 patients, Huang et al. reported that TNF-α showed a significant increase within 5 min after removal of the aortic cross-clamp in all groups whilst TNF-α levels were significantly lower after cross-clamping of the aorta in patients receiving propofol and isoflurane compared to other groups.[8] In line with our data, these authors found that an isoflurane and propofol combination was superior to regimens consisting of isoflurane alone or propofol alone.

In our study, we found that TNF-α levels were significantly lower in patients receiving low-dose propofol and continuous desflurane administration than in other groups after removal of the cross-clamp and by the 24th

postoperative hour, when stress and traumatic events (inflammation) reach their maximum. This may be attributable to the cardio-protective effect of volatile agents and their anti-inflammatory properties.[11,17] Moreover, some studies have reported the anti-oxidant effects of propofol. Such studies demonstrated that, as a pro-inflammatory cytokine that increases with the production of oxygen radicals, TNF-α levels decrease after CPB.[10,11] In light of the above, any increase in TNF-α levels should be considered a negative criterion since it is associated with decreased tolerance of ischemic damage and inflammation.

We found lower TNF-α levels in the propofol combined with continuous desflurane group compared to the propofol alone group before cross-clamping of the aorta, which may be due to the early cardio-protective effects of desflurane. The significant decrease in TNF-α levels in group 3 in the postoperative period highlights the effectiveness of the preconditioning effect of low-dose propofol and continuous desflurane administration. A few studies support these findings.[19] Sayın et al. have reported that propofol inhibits lipid peroxidation.[20] In our study, both the cardio-protective and the anti-oxidant effects of propofol and desflurane might have been observed. Unlike previous studies, the present study demonstrated that the addition of desflurane to propofol reduces TNF-α levels following cardiopulmonary bypass. Desflurane and propofol may potentiate the preconditioning effects of each other.

In the present study, h-FABP levels showed an initial increase after cross-clamping of the aorta but they had decreased by the 24th postoperative hour, especially in group 3. The moderate correlation between h-FABP levels and TNF-α levels may be explained by inflammatory and traumatic processes, supporting the view that they may influence the release of each other. Some studies have suggested that h-FABP may be a marker of early ischaemia.[8,9] Moreover, h-FABP has been shown to have an earlier peak compared to CK-MB or cardiac troponin I. In another study[21], h-FABP was demonstrated to be a marker of long-term mortality following acute coronary syndrome, and is capable of defining high-risk patients.[21] In light of the above, the present study demonstrated that low-dose propofol and continuous desflurane administration was more effective than propofol alone or propofol combined with 15 min of desflurane administration when h-FABP levels were considered as the measure of preconditioning. Lower h-FABP levels were observed in the low-dose propofol and continuous desflurane group compared to propofol alone before cross-clamping of the aorta and more profoundly after removal of the cross-clamp, indicating desflurane's favorable effect on myocardial adaptation to ischaemia. Moreover, the lower h-FABP levels observed in the low-dose propofol and continuous desflurane group at the 24th postoperative hour demonstrate that the longer the duration of desflurane administration, the better prepared the myocardium is against ischaemia and reperfusion.

Tomai et al. found no difference between 15 min of isoflurane administration before cardiopulmonary bypass and control groups with regard to myocardial function and cardiac enzyme levels.[22] We found that troponin levels in the continuous or intermittent desflurane administration and non-desflurane groups were similar. In recent years, there has been no detailed data regarding the combined use of propofol and desflurane or their short-course administration. However, there have been many reports suggesting that these drugs inhibit severe inflammation and reduce TNF-α levels as well as their preconditioning effects. Such studies report that ischemic preconditioning inhibits the local myocardial and systemic inflammatory response.[15,23] However, whether the decrease in TNF-α levels occurs due to the preconditioning effects of these drugs or their effects on inflammation is unclear.

Zhang et al. reported that the antioxidant effect of propofol is due to the phenol group it contains, similar to vitamin E.[24] They found that it causes lower neutrophil activation and a lower increase in C5a levels after CABG.

In conclusion, h-FABP and TNF-α levels may be used to assess the effectiveness of ischemic preconditioning practice. On the basis of the measurement of these pro-inflammatory cytokines, low-dose propofol and continuous desflurane provided more effective preconditioning than propofol alone or short-course desflurane in patients undergoing CABG.

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