Desflurane preconditioning in coronary artery bypass graft surgery: a double-blinded, randomised and placebo-controlled study

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Received 1 February 2007; received in revised form 1 May 2007; accepted 7 May 2007; Available online 15 June 2007

Abstract

Background: Recent clinical and experimental data indicate that volatile anaesthetics may precondition myocardium against ischaemia and infarction. The present clinical trial was designed to verify the cardioprotective effects of desflurane in patients undergoing elective coronary artery bypass surgery. It was hypothesized that desflurane preconditioning would decrease postoperative release of troponin I and brain natriuretic peptide (NT-proBNP). Besides, we have hypothesized that desflurane preconditioning would preserve the myocardium from the dysfunction following cardioplegic arrest. Methods: Twenty-eight patients were randomly divided into two groups: Control group (14 patients) and Desflurane group (14 patients). In Desflurane group (DS) patients, preconditioning was elicited after the onset of cardiopulmonary bypass via a 5-min exposure to desflurane (2.5 minimum alveolar concentration), followed by a 10-min washout before aortic cross-clamping and cardioplegic arrest. The control group (C) patients underwent an equivalent period (15 min) of pre-arrest desflurane-free bypass. Haemodynamic measurements were obtained at six different times. The biochemistry markers of cellular damage and myocardial dysfunction (troponin I, NT-proBNP) were determined. Left ventricular (LV) function was assessed using tissue Doppler imaging (TDI) of mitral annulus. Two-factor repeated-measures analysis of variance was used to evaluate differences over time between groups for all parameters determined in plasma samples and for all TDI-derived variables. Results: After surgery, both the troponin I values (2.04 ± 1.09 ng/ml vs 1.44 ± 0.77 ng/ml, p < 0.01 after 24 h and 1.62 ± 0.96 ng/ml vs 1.00 ± 0.24 ng/ml, p < 0.01 after 72 h respectively) and those of the NT-proBNP (2187 ± 282.9 ng/l vs 885.4 ± 117.35 ng/l, p < 0.01 after 24 h and 3097.9 ± 226.2 vs 1393.6 ± 312.07 ng/l, p < 0.01 after 72 h respectively) were less in the desflurane-treated patients. The values of TDI of mitral annulus were constantly better in desflurane-treated patients. Conclusions: We can conclude that the use of desflurane in these patients provides a pharmacological preconditioning so as to reduce myocardial necrosis and improve the cardiac performance in the postoperative period.

Keywords: Heart; Coronary artery bypass; Myocardial preservation; Anaesthetics volatile; Desflurane

1. Introduction

In 1986, Murry et al. [1] found that four cycles of 5-min left circumflex coronary artery occlusions, before 40-min occlusion, reduced myocardial infarction by 75%. This phenomenon was named ‘ischaemic preconditioning’ and has been extensively investigated. Clinically, ischaemic preconditioning might play a role in successive exercise-induced ischaemia (warm-up phenomenon) and in mediating the protective effect in preinfarction angina pectoris. The volatile anaesthetics have been shown to directly precondition or indirectly enhance ischaemic preconditioning in studies of cardioprotection against myocardial infarction and irreversible myocardial dysfunction [2,3].

In this study, we assumed that the exposure to desflurane, before aortic cross-clamping, could give a better protection to the heart in patients undergoing elective coronary artery surgery with extracorporeal circulation.

In order to verify this hypothesis, we considered the increase in troponin I in the postoperative period as a direct marker of myocardial cellular damage and primary outcome. Furthermore to evaluate the postoperative myocardial function, we used both postoperative levels of N-terminal pro brain natriuretic peptide (NT-proBNP) and postoperative measurement of the tissue Doppler imaging (TDI) of mitral annulus.

The NT-proBNP was chosen because it has been demonstrated to be easily correlated with the myocardial function and for its prognostic role to foretell short- and long-term
risks of infarction, cardiac impairment and death due to heart failure [4, 5].

To evaluate the effects of desflurane exposure on LV systolic function, we used the recently validated TDI-derived acceleration rate during isovolumic contraction (IVA). This index, which embodies one of the earliest events in systole, and is therefore much less affected by loading conditions, was recently validated in an animal model [6].

To evaluate the effects of desflurane exposition on LV diastolic function, we used the TDI-derived mitral annulus velocity during early diastole (Ea).

2. Materials and methods

We have listed in our study 28 patients undergoing elective coronary artery bypass grafting.

The experimental protocol was approved by our ethical committee and all patients signed an informed consent.

The criteria of exclusion were the following: concomitant aortic or valvular surgery, elevated troponin I concentration within 24 h before surgery, unstable angina, angina within 24 h before surgery, haemodynamic instability with the need for medical or mechanical inotropic support, administration of adenosine-triphosphate-sensitive potassium channel agonists or antagonist such as diazoxide, nicorandil, sulfonylurea, or theophylline, left main disease, reintervention, preoperative hepatopathy, emergencies. Patients were randomly divided by opening of a sealed envelope the evening before the surgical procedure, then allocated to receive either desflurane (group DS) or placebo (group C).

The randomisation management was delegated to a person unconnected to the clinical experimentation. No operator involved in the care of the patient in every phase had any knowledge of the group to which each single patient belonged, apart from the person who collected the data and the individual who carried out the statistical analysis.

All patients were anaesthetized with a combination of fentanyl, midazolam, propofol and pancuronium, taking care to use the same quantities of drugs per kilogram of body weight in each patient.

All patients were fully monitored in the preoperative period with the insertion of a pulmonary artery catheter to measure the right ventricle ejection fraction connected to a Vigilance monitor system (Edwards Lifesciences, Irvine, CA, USA) for the continuous monitoring of the right ventricular systemic and pulmonary resistances indexes.

Furthermore, we determined the plasma values of troponin I from the coronary sinus before the aortic clamp and 10 min after clamp removal, and from peripheral venous blood after 24 and 72 h after surgery.

Blood samples to evaluate NT-proBNP were obtained from peripheral venous blood preoperatively 24 and 72 h after the end of surgery.

All postoperative complications were recorded.

2.1. Tissue Doppler imaging

All measurements were obtained preoperatively 12 and 24 h after the intervention.

All echocardiograms were obtained with a Sonos 550 system (Philips Medical Systems, Best, The Netherlands) according to current guidelines [7]. A 1.8–2.1/3.6–4.1 MHz probe was used for transthoracic echocardiography (preoperative measurements, and after 72 h measurements), and a 4–7 MHz multiprobe plane was used for transesophageal echocardiography (after 12 h measurements).

Two- and four-chamber views were obtained by the parasternal and apical views for TTE, and by standard midoesophageal and transgastric views for TOE. All echocardiographic measurements, which were performed by a single
investigator blinded to patients’ group (MM), were obtained by averaging three cardiac cycles.

For recordings of pulse-wave tissue Doppler imaging, the sample volume was placed at septal and lateral sites of the mitral annulus.

Mitrail annulus early diastolic (Ea) velocity and mitral annulus late diastolic (Aa) velocity at the septal and lateral areas of the mitral annulus were measured to assess the LV diastolic function.

Systolic function was assessed using peak velocity signals (at septal and lateral sites of mitral annulus) during isovolumic contraction (Sivc) and systolic ejection (Sa) as well as isovolumic acceleration rate (IVA). Systolic IVA rate was calculated as the difference between baseline and peak velocity during isovolumic contraction divided the time interval between them [6].

2.2. Statistical analysis

The sample size was calculated on cardiac troponin I and NT-proBNP levels post-CPB as primary outcomes.

The sample size for troponin I levels was calculated based on data reported by De Hert et al. [8]; with an expected difference of 50% between group means, 60% SD of the means, and alpha = 0.05 and beta = 0.8, a simple size of eight patients per group was necessary. The sample size for NT-proBNP concentration was calculated based on the data reported by Julier et al. [9]; with an expected difference of 40% between group means, 50% SD of the means, alpha = 0.05 and beta = 0.8, a simple size of 14 patients per group was necessary.

All values did not show a normal distribution; therefore, a logarithmic transformation was necessary.

Two-factor repeated-measures analysis of variance was used to evaluate differences over time between groups for all parameters determined in plasma samples and for all TDI-derived variables. Multiple paired t-tests were used to compare the parameters at each time point with the respective preoperative baseline measurements within groups, and unpaired t-tests were used to compare these parameters at each time point between groups.

All other data were analysed using unpaired t-tests for parametric data or Mann—Whitney tests for nonparametric data.

Categorical data were analysed using the two-tailed Fisher exact test or $\chi^2$, as appropriate.

All data are presented as mean ± standard deviation. Statistical significance was accepted at $p < 0.05$. All p-values were two tailed.

3. Results

The preoperative and operative characteristics did not differ substantially in the two groups (Table 1).

All patients received a complete revascularization.

3.1. Biochemical markers of myocardial necrosis

Preoperative plasma concentrations of troponin I were similar in placebo and desflurane-treated patients.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients’ characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo group $(n = 14)$</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.9 ± 3.1</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/4</td>
</tr>
<tr>
<td>Mean preoperative ejection fraction (%)</td>
<td>54.2 ± 8</td>
</tr>
<tr>
<td>Mean postoperative ejection fraction (%)</td>
<td>55 ± 7.8</td>
</tr>
<tr>
<td>No. of patients</td>
<td>2 vessels with &gt;70% stenosis</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>7 8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 12</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8 6</td>
</tr>
<tr>
<td>Current medication</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>14 14</td>
</tr>
<tr>
<td>Ca²⁺-blocker</td>
<td>3 5</td>
</tr>
<tr>
<td>Nitrates</td>
<td>11 12</td>
</tr>
<tr>
<td>ACEI</td>
<td>0 1</td>
</tr>
<tr>
<td>Statins</td>
<td>8 6</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0 0</td>
</tr>
<tr>
<td>Mean bypass time (min) ± SD</td>
<td>61.6 ± 14.4</td>
</tr>
<tr>
<td>Mean cross-clamp time (min) ± SD</td>
<td>35.9 ± 11.3</td>
</tr>
<tr>
<td>Mean no. of grafts ± SD</td>
<td>3.1 ± 0.7</td>
</tr>
<tr>
<td>Mean total opioid use (mg) ± SD</td>
<td>1980 ± 722</td>
</tr>
<tr>
<td>AST peak values (U/l)</td>
<td>22.2 ± 4.83</td>
</tr>
<tr>
<td>ALT peak values (U/l)</td>
<td>9.50 ± 1.08</td>
</tr>
<tr>
<td>LDH peak values (U/l)</td>
<td>352 ± 22.31</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± standard deviation. ACEI: angiotensin converting enzyme inhibitor; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactic dehydrogenase.

A significant postoperative increase in concentrations of troponin I was observed in the placebo and desflurane-treated groups (time effect for all parameters, $p < 0.001$) (Fig. 1).

Postoperative plasma concentrations were lower in desflurane-treated patients (group effect, $p < 0.001$; group—time interaction, $p < 0.001$).

In addition, postoperative peak plasma troponin I concentrations were lower in desflurane-treated patients than in placebo patients (Fig. 1).

3.2. Biochemical markers of myocardial function

Preoperative values of NT-proBNP were similar in both groups (Fig. 1).

As for troponin I values, a significant postoperative increase in NT-proBNP plasma concentrations was observed in the placebo and in desflurane-treated patients (time effect for all parameters, $p < 0.01$) (Fig. 1).

Postoperative plasma concentrations were lower in desflurane-treated patients (group effect, $p < 0.001$; group—time interaction, $p < 0.001$).

In addition, postoperative peak plasma NT-proBNP concentrations were markedly lower in desflurane-treated patients (Fig. 1).
3.3. Tissue Doppler imaging and haemodynamic data

Postoperative early diastolic mitral valve annular velocity (Ea) was higher in desflurane group both at septal and lateral sites of mitral annulus (Table 2).

All indexes of systolic performance showed better post-operative values in desflurane-treated patients.

Postoperative systolic myocardial velocity (Sa) was higher in desflurane-treated patients both at septal and lateral sites of mitral annulus (Table 2).

In the postoperative period, the systolic isovolumic acceleration rate (IVA) was higher in desflurane-treated group both at septal and lateral sites of mitral annulus (Table 2).

Preoperative haemodynamic data did not differ between the two groups (Table 3).

There were no statistically significant differences between the two groups in mean arterial and mean pulmonary pressures.

Cardiac index was higher in patients treated with desflurane in all measurements obtained after cardiopulmonary bypass (Table 3).

Systemic vascular resistances were lower in desflurane-treated patients after 8 and 24 h from surgery (Table 3).

Left ventricular stroke work index was higher in desflurane-treated patients (Table 3).

No patients died in both groups. No patients had serious complications. One of the patients of the control group needed amiodarone treatment for an atrial fibrillation. No patient needed intra-aortic balloon pump or inotropic support.

Average intensive care therapy admission times were less in the group of patients treated with desflurane (48 ± 16 h vs 36 ± 12 h, p < 0.02).

One patient in the desflurane group had new Q waves on the electrocardiogram with a modest rise (maximum peak of 3.0 ng/ml after 12 h from the surgical procedure) of postoperative values of troponin I. Nevertheless, this patient was included in the study and had a normal outcome. An echocardiogram carried out 15 days after the operation demonstrated normal left ventricle function without evident signs of dyskinesia or akinesia. All desflurane-treated patients showed a rise of postoperative hepatic enzymes values, without clinical consequences. Hepatic enzyme peak postoperative values of the two groups are reported in Table 1.

4. Discussion

As far as we know, this is the first double-blinded, randomised and placebo-controlled clinical study on the preconditioning effects of desflurane.

The results of the present study indicate that desflurane is able to decrease myocardial necrosis markers and to enhance...
After 16 h from ICU arrival; DS: desflurane group; CVP: central venous pressure (mmHg); PCWP: pulmonary capillary wedge pressure (mmHg); CEDVI: continuous CVP (mmHg); CI: cardiac index (l/min/m²); L VSWI: left ventricle stroke work index (g-m/beat/m²); SVRI: systemic vascular resistances (dyn/cm/s⁵/m²).

Functional recovery of the myocardium in the postoperative period.

Our study shows that the postoperative values of troponin I was lower in the group treated with desflurane than in the control group, indicating that the necrosis area in these patients was less than in the placebo-treated patients. The NT-proBNP values were always lower in the desflurane group compared to patients treated with placebo. One patient in the desflurane group had new Q waves. The postoperative course of this patient was free of complications and an echocardiogram distanced in time from the surgical procedure has shown that the ventricular function was conserved. All this would reasonably presuppose that this was a surgical technique problem and should not to be attributed to the exposure to desflurane.

Tissue Doppler imaging (TDI) has been reported to be a powerful modality that enables assessment of ventricular wall motion with a high temporal and spatial resolution.

Measurement of mitral annulus displacement along the LV long axis has been proposed as a method for assessment of LV systolic and diastolic function [10]. The early diastolic mitral valve annular velocity (Ea) observed by TDI, is related to LV diastolic function and tends to decrease with impaired myocardial relaxation [11]. Relaxation velocity of the mitral valve annular velocity (Ea) observed by TDI, is related to LV diastolic function and correlates with conventional measures derived from LV filling patterns and the time constant of isovolumic relaxation (τ). Moreover, there is evidence that diastolic tissue velocities are less influenced by the changes in preload which commonly compensate for diastolic dysfunction and which confound assessment by standard measures based on LV filling patterns. Further evidence of the relative preload independence of Ea velocity was presented by Oki et al. [12], who reported that the time constant of isovolumic relaxation (τ) correlated well with Ea velocities regardless of LV filling pressure.
Sohn et al. [13] also demonstrated that manipulation of LV filling dynamics produced alterations in LV Doppler inflow patterns, but with no significant changes in the Ea velocities.

Recently, ultrasound-derived myocardial acceleration rate during isovolumic contraction (IVA) has been reported to be a good index for evaluation of ventricular function [6].

TDI measurements show better systolic and diastolic postoperative function in desflurane-treated patients.

Our findings confirm those from previous studies. De Hert et al. [8] compared the effects of sevoflurane and propofol on myocardial function during and after coronary artery surgery.

Before cardiopulmonary bypass (CPB), all haemodynamic variables were similar between the two anaesthetic treatment groups. However, after CPB, patients who received sevoflurane had preserved cardiac performance, which was evident from a preserved stroke volume, dp/dt max, and length-dependent regulation of myocardial function.

This was confirmed in a subsequent study by the same authors in a group of elderly high-risk patients with documented impaired myocardial function [14].

Sevoflurane and desflurane preserved myocardial function after CPB with less evidence for myocardial damage and better postoperative myocardial function compared with an intravenous anaesthetic regimen.

It should be noted that in these studies the halogenated agents were given during the whole time of extracorporeal circulation, whereas in our study the halogenated anaesthetic was given only before the cardiopлегic arrest.

This makes the two studies extremely different.

While in our study we used the halogenated agent as the only promoter of preconditioning phenomenon, with exposure exclusively before the ischaemic insult, in the above study, the exposure continued. This does not allow us to determine whether the beneficial effect was due to pharmacological preconditioning or decrease in the ischaemia-reperfusion damage.

There were no important differences between the two groups as regard to preoperative and operative data, we are therefore entitled to conclude that the difference observed in our study between the two groups of patients relates exclusively to (or not to) the exposure to desflurane.

Opioids were shown to mimic the cardioprotective effect of ischaemic preconditioning [15].

In the present study, dosages of fentanyl were similar in both groups.

In the placebo group, the increase in troponin I values, just above the cut-off value of 2 ng/ml, is comparable with the 5.2 ng/ml value as shown by Sadony et al. [16] in those patients classified as having a minor myocardial damage. There is increasing evidence that the volatile anaesthetics are able to protect the myocardium against the reversible and irreversible damages of ischaemia [17].

This phenomenon is called ‘anaesthetic-induced preconditioning’ (APC) and it is defined by a short phase of memory very similar to that observed during ischaemic preconditioning.

Up to now, the adenosine type 1 (A1) receptors, the protein kinase C (PKC), inhibitory guanine nucleotide binding (Gi) proteins, reactive oxygen species (ROS), and mitochondrial and sarcolemmal KATP (mito KATP and sarc KATP, respectively) channels have been demonstrated to be mediators of the APC [18,19].

Hanouz et al. [20] demonstrated that 15 min of exposure to desflurane prior to 30 min of simulated ischaemia enhanced contractile recovery of isolated human myocardium during the reoxygenation period. In addition, the same authors showed that this effect was blocked by glibenclamide, indicating that the opening of the KATP channels was implicated in the protection induced by desflurane and even the blocking of the α and β adrenoceptors cancelled the cardioprotection.

Toller et al. [21] showed that both mito KATP and sarc KATP channels were implicated in desflurane-induced preconditioning. The mechanism of mito KATP-induced cardioprotection may involve alterations in mitochondrial Ca2+ handling, the optimisation of energy production and modulation of reactive oxygen species during ischaemia or reperfusion. The stimulation of α and β adrenoceptors plays a role in desflurane-induced preconditioning. In contrast to other volatile anaesthetics, desflurane has been reported to induce sympathetic activation in healthy volunteers but also to release intracellular stores of catecholamines in isolated rat and human myocardium [22,23].

Pirou et al. [24] demonstrated that in rats, desflurane exhibited the best cardioprotective effect by comparison with isoflurane and sevoflurane.

The NT-proBNP values and the cystatin C values in the post-operative period were lower in patients treated with sevoflurane, but the post-operative values of CK-MB and troponin I were not different in the two groups, and this indicated that pharmacological preconditioning with sevoflurane reduced postoperative myocardial dysfunction and decreased CPB-induced renal dysfunction, but not the amount of myocardial necrosis markers.

The results of our study demonstrated that a single brief exposure to desflurane immediately prior to cardiopлегic arrest reduced the postoperative NT-proBNP concentration, a biochemical marker of myocardial dysfunction, and the postoperative troponin I concentration, a biochemical marker of myocardial necrosis.

4.1. Limits of the study

Our study was carried out on patients at a low preoperative risk to clinically demonstrate the pharmacological preconditioning effects of the exposure to desflurane. The method used for this purpose, however, lengthens the CPB times and we do not think of proposing this as a method for routine. Other research studies should be necessary to value the impact of the pharmacological preconditioning with desflurane also in patients at high preoperative risk. Furthermore, the protection offered by desflurane against the damage caused by ischaemia-reperfusion should be taken into consideration in the clinical decision to use this agent possibly for the whole duration of the operation.

Even if there is the possibility of using desflurane during the whole operation, this could lead to an increase in the cardiac frequency due to the adrenergic stimulus. In their study, De Hert et al. [14] used the administration of desflurane during the entire operation and do not refer to inconveniences linked to the use of a volatile anaesthetic.
References


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