Sevoflurane preconditioning at 1 MAC only provides limited protection in patients undergoing coronary artery bypass surgery: a randomized bi-centre trial

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Background. Volatile agents can mimic ischaemic preconditioning leading to a decrease in myocardial infarct size. The present study investigated if a 15 min sevoflurane administration before cardiopulmonary bypass (CPB) has a cardioprotective effect in patients undergoing coronary surgery.

Methods. Seventy-two patients were randomized in two centres. The intervention group (S) received 1 MAC sevoflurane administrated via the ventilator for 15 min followed by a 15 min washout before CPB, the control group did not. The primary outcome was the postoperative troponin Ic peak. A biopsy of the atrium was taken during canulation for enzyme dosages. Results are expressed as mean (SD).

Results. Neither troponin Ic nor tissular enzyme measurement exhibited any difference between the groups: peak of troponin Ic was 4.4 (5.6) in S group vs 5.2 (6.6) ng ml⁻¹ in control group (ns). Intratissular ecto-5'-nucleotidase activity was 7.1 (4.3) vs 8.5 (11.9), protein kinase C activity was 27.1 (15.7) vs 29.2 (28.7), tyrosine kinase activity was 101 (54.1) vs 98.5 (63.3), and P38 MAPKinase activity was 131.1 (76.1) vs 127.1 (86.8) nmol mg protein⁻¹ min⁻¹ in S group and control group, respectively (ns). However there were fewer patients with low postoperative cardiac index in S group (11% in S vs 35% in control group, P<0.05) when considering the per protocol population. In S group, 25% of patients required an inotropic support during the postoperative period, vs 36% of patients in control group (ns).

Conclusions. This study did not show a significant preconditioning signal after 15 min of sevoflurane administration. The 15 min duration might be too short or the concentration of sevoflurane too low to induce cardioprotection detected by troponin I levels.

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Ischaemic preconditioning is an endogenous defence against ischaemia. Classic or early preconditioning is
defined as a cardioprotective consequence of one or multiple short ischaemia before a sublethal prolonged ischaemia. Several exogenous substances are known to trigger preconditioning, such as adenosine, bradykinin, noradrenaline, delta-opioid agonists, and inhalation halogenated anaesthetics. In animal experimental models, halogenated anaesthetics can produce preconditioning when administered during a short period with a washout period before ischaemia, or post-conditioning when administered after ischaemia during reperfusion, leading to a decrease in myocardial infarct size. Experimental models differ in volatile anaesthetic administration timing, concentration, number of expositions, and washout duration. Recent clinical studies performed on a small number of patients have shown that sevoflurane or desflurane provided a myocardial protection when given throughout coronary artery bypass graft surgery. Sevoflurane administration timing was hypothesized that, as shown in experimental data. We hypothesized that, as shown in preconditioning experimental models, administration of 1 MAC volatile anaesthetic for 15 min followed by a washout period would be sufficient to generate a myocardial protection in coronary surgery.

We conducted a randomized, controlled bi-centre study evaluating the myocardial preconditioning effect of a 15 min sevoflurane inhalation in humans undergoing coronary revascularization under CPB.

Methods
The study was conducted in accordance with the protocol, GCP, ethical principles that have their origin in the Declaration of Helsinki, October 2000 revision and all applicable local and federal regulations. The Lyon B (Hôpital de l’Hôtel-Dieu, Lyon, France) local ethic committee approved this study, and written informed consent was obtained from all patients.

Patients
Patients were included from two french cardiothoracic centres: Hôpital Louis Pradel in Lyon and Hôpital Bichat in Paris. Patients undergoing elective coronary artery bypass graft surgery aged >18 and <80 yr who gave a signed informed consent were eligible. Patients presenting one of the following criteria were excluded: left ventricular ejection fraction <40%, treatment with oral hypoglycaemic sulfonylurea (antagonist of K<sub>ATP</sub> channels), and nicoandil (agonist of K<sub>ATP</sub> channels) within 5 days before surgery, emergency surgery, myocardial infarction, or clinical angina within 7 days before surgery, history of serious adverse event, or serious allergy, or any contraindication to sevoflurane, propofol, midazolam or opioids, and major coagulation disorders.

Intervention
Included patients were randomized into two groups: in the intervention group, the subjects received, in addition to the i.v. anaesthetics, a 15 min period administration of sevoflurane (1 MAC) 15 min before the aortic cross-clamping; in the control group, patients received the i.v. anaesthetics exclusively. Sevoflurane was delivered at a concentration sufficient to reach an end-tidal concentration equivalent to 1 MAC (age-corrected, without nitrous oxide) during 15 min. The administration of sevoflurane was started 30–45 min before the CPB (approximately at the time of mammary retractor placement). The 1 MAC end-tidal concentration was maintained for 15 min. A washout period of at least 15 min was required before the aortic cross-clamping. The absence of sevoflurane in the expired gases was verified before the start of the CPB. Concomitantly with sevoflurane administration, propofol infusion was decreased to maintain stable haemodynamic condition (i.e. a systolic pressure >80 mm Hg) and depth of anaesthesia.

Perioperative procedure
All patients received oral premedication with hydroxyzine 100 mg 60–90 min before induction of anaesthesia. Anaesthesia was induced and maintained with i.v. hypnotics (propofol), cisatracurium, and an opioid (sufentanil). Before the CPB, anaesthesia was maintained with a continuous infusion of propofol (with or without TCI) and boluses or infusion of sufentanil as clinically indicated. Monitoring consisted of radial fluid filled arterial line and Swan-Ganz catheter. Patients were mechanically ventilated with a mixture of air/O<sub>2</sub> (≥60% O<sub>2</sub> as per anaesthesiologist’s judgement). The tidal volume (approximately 10–12 ml kg<sup>−1</sup>) and the ventilatory rate (approximately 8–10 min<sup>−1</sup>) were set to achieve a P<sub>acCO<sub>2</sub></sub> between 28 and 35 mm Hg. Tranexamic acid (15 mg kg<sup>−1</sup>) was used as antifibrinolytic agent.

A median sternotomy and pericardiotomy were performed with harvesting of saphenous veins and internal thoracic arteries as conduits. The right atrium and the ascending aorta were cannulated. After administration of heparin (300 U kg<sup>−1</sup>), standard CPB with a disposable hollow fibre oxygenator was started with a target output of 2.4 litre min<sup>−1</sup>·m<sup>−2</sup> body surface area. Activated coagulation time (using kaolin activator) was kept above 450 s throughout the CPB period. CPB was performed under normothermia or quasi-normothermia (≥35°C). Myocardial protection was achieved by cold Saint Thomas’ Hospital crystalloid cardioplegic solution (4°C) injected into the aortic root immediately after aortic cross-clamping, and every 20 min during clamping. The surgeons performed the coronary bypass, and the heart was defibrillated after aortic unclamping if sinus rhythm did not resume spontaneously. No additional ischaemic preconditioning was employed in any patient. After the weaning of the CPB, anaesthesia was maintained with propofol and sufentanil.
At the end of surgery, the infusion of propofol was continued for ICU sedation purpose until central temperature >35.5°C, mediastinal bleeding <50 ml h⁻¹, and haemodynamic stability were achieved. Therefore, the patients were extubated when pressure support ventilation was well tolerated, usually between 2 and 5 h after the arrival in ICU.

Patients were evaluated during surgery and from H0 (arrival in intensive care unit) to day 3 post-surgery. A final visit or phone call was conducted on D30, to assess the occurrence of any serious adverse events since day 3 post-surgery.

Outcomes

The primary outcome was the postoperative peak level of serum troponin Ic, defined as the highest value observed between 4 h of surgery and the morning of the third day after surgery. Area under the curve (AUC) of troponin Ic, and per cent of patients with a peak of troponin superior to 4, 8, and 12 ng ml⁻¹, was analysed. Secondary outcomes included mortality, haemodynamic data, post-treatment changes in cardiac index, and intracardiac pressures assessed with a thermodilution pulmonary artery catheter, and the tissular 5'-nucleotidase (5'-NT), protein kinase (PKC), and tyrosine kinase activities.

Biological measurements

Troponin I

Blood samples for measurement of troponin Ic were withdrawn after induction of anaesthesia, on the arrival in ICU, 4, 8, 12 h after the arrival in ICU, and on the morning of the three following days. Troponin Ic dosages were performed in a central biochemical laboratory (Bichat Hospital Paris, France) and measured in plasma by chemiluminescence of the specific troponin I isoform using a RxL automate (Dade-Berhing SA). A troponin value <0.4 ng ml⁻¹ was considered normal.

Tissue measurements

During the atrial cannulation, before the CPB and at least 15 min after the discontinuation of sevoflurane administration, a biopsy of the left appendage of the atrium was taken by the surgeon for 5'-NT, PKC, and tyrosine kinase measurements. This biopsy was rapidly frozen and stored under liquid nitrogen at −80°C before examination. All measurements were done in the same centre (Osaka, Japan). Myocardial samples were sent to Japan for measurement. All samples arrived fully frozen. Since we know that PKC activates ecto-5'-nucleotidase, we tested whether the addition of a protein kinase C inhibitor (GF109 203X) modulated the ecto-5'-nucleotidase activity. We found that GF109 203X did not modulate adenosine-related enzymes activity (personal data). We measured adenosine-related enzyme activity using this method, and found considerable activation of ecto-5'-nucleotidase when cardiomyocytes became cardio-protective by ischaemic preconditioning procedure.

Measurement of 5'-nucleotidase and PKC activities

The myocardium was separated into membrane and cytosolic fractions using the following technique: myocardial tissue was homogenized with a Potter–Elvehjem homogenizer (30 strokes) for 5 min in 10 vol of ice-cold 10 mmol litre⁻¹ HEPES–potassium hydroxide (HEPES–KOH) buffer (pH 7.4) containing 0.25 mol litre⁻¹ sucrose, 1 mmol litre⁻¹ MgCl₂, and 1 mmol litre⁻¹ mercaptoethanol at 0°C. The crude homogenate was strained through a double-layered nylon sieve and homogenized again for 1 min. For the preparation of membrane and cytosolic fractions, the homogenate was centrifuged at 1000g for 10 min, and the supernatant was centrifuged at 200 000g for 1 h. After this procedure, we regarded the pellet and supernatant fractions as the membrane and cytosolic fractions, respectively. The membrane and cytosolic fractions were dialysed at 4°C for 4 h against 10 mmol litre⁻¹ HEPES–KOH (pH 7.4) containing 1 mmol litre⁻¹ MgCl₂, 1 mmol litre⁻¹ mercaptoethanol, and 0.01% activated charcoal and were divided into aliquots that were frozen immediately and stored at −80°C. 5'-Nucleotidase activity was assessed by the enzymatic assay technique¹⁰ and was reported as nanomoles per milligram of protein per minute. Protein concentration was measured by the method of Lowry and colleagues¹¹ with bovine serum albumin used as a standard. 5'-Nucleotidase activity of membrane and cytosolic fractions was defined as ecto-5'-nucleotidase and cytosolic 5'-nucleotidase activity, respectively. When cytosolic 5'-nucleotidase activity was measured, AMP-CP (50 μmol litre⁻¹) was added to prevent contamination of ecto-5'-nucleotidase. The activity of PKC was measured by enzyme assay with the RPN 77A kit (Amersham), which provides a simple and reliable method of estimating PKC without extensive purification of the samples.¹² Activity of PKC was expressed as nanomoles per milligram of protein per minute.

Measurement of P38 MAPK and tyrosine kinase activity

One gram of myocardial tissue sample was homogenized, immunoprecipitated, and subjected to in vitro p38 MAPK activity assay as reported previously.¹³ The kinase activity was quantified with a PhosphorImager (Molecular Dynamics). Tyrosine kinase activity was assessed by the enzymatic assay technique¹⁴ ¹⁵ using the AUSA tyrosine kinase assay kit.

Sample size

Calculations were based on assuming a standard deviation of troponin Ic of 2.83 mg ml⁻¹,¹⁶ and considering as clinically relevant a 2 mg ml⁻¹ increase in the mean serum troponin Ic. With a two-sided alpha risk of 5%, and
a beta risk of 17%, calculation using the Casagrande–Pike formula resulted in a sample size of 72 (36 per group).

**Randomization**
A blocked randomization with stratification by centre was performed using sealed envelopes placed in each centre. The study was an open-label study. Outcome evaluation was blinded regarding treatment allocation: laboratory measurements were centralized for troponin Ic (a local measurement was also performed for patient care purposes). Primary and secondary outcome analysis was blinded.

**Statistics**
The *intention to treat* population includes all patients who were randomized to the study. The *per protocol population* includes all subjects who completed the study and have no major protocol deviation (i.e. acute surgical complications <80% or >120% of the targeted sevoflurane exposure and <75% of the required blood samples for troponin Ic available).

Data are expressed as mean (SD). Statistical analysis was performed by independent statisticians (MDS Pharma Services). All statistics were performed using SAS® (8.2 version) software. The primary outcome (postoperative peak level of serum troponin Ic) was compared between the two groups using an analysis of covariance (ANCOVA) with centre (Lyon and Bichat) and treatment as factors (two-tailed test) and H0 value as covariate. The other criteria such as AUC of troponin Ic, ecto 5'-NT, PKC, tyrosine kinase, protein concentration, cytosolic 5'-NT, and P38 MAPK were analysed with an ANOVA with centre and treatment as factors (two-tailed test). For the number of subjects with at least one troponin Ic value after H0≥4 mg ml⁻¹ or ≥8 mg ml⁻¹ or ≥12 mg ml⁻¹, the number of subjects with at least one cardiac index value <2.0 litre min⁻¹ m⁻² after H0 and the number of subjects with at least one inotropic treatment after the end of CPB, the two groups were compared using a χ² test (or Fisher’s exact test, if appropriate).

All results are presented in intent to treat (ITT) analysis. Per protocol analysis was consistent with the ITT analysis for the primary outcome.

**Results**
Between August 1, 2001 and June 12, 2004, 72 patients, 36 patients per group, were enrolled in two university hospital centres in France: the Louis Pradel Hospital in Lyon and the Bichat Hospital in Paris. All patients in the control group and 28 patients in the sevoflurane group completed the protocol. Eight (11%) patients were excluded because of a protocol deviation; all of them were in the sevoflurane group: in five patients, sevoflurane exposure was inadequate (underexposure: n=3, overexposure: n=2); one patient had <75% of the planned troponin Ic assessments, the signed informed consent was missing for one patient, and one patient was lost to follow-up. The patients’ flow is shown in Figure 1.

**Baseline data**
Characteristics of the patients are shown in Table 1. There was no significant difference between the groups. Number
of coronary arterial bypass performed and concomitant medications at inclusion did not differ between the groups.

Outcomes

Primary outcome: troponin Ic

Peak of troponin Ic, defined as the highest postoperative value of troponin Ic, did not differ between the groups, reaching 4.4 (5.6) vs 5.2 (6.6) ng ml\(^{-1}\) for sevoflurane and control groups, respectively. Similarly, the AUC of troponin Ic did not differ significantly, 130.8 (197.1) h mg ml\(^{-1}\) for sevoflurane group and 156.1 (197.0) for control group. Time evolution of troponin Ic level is depicted in Figure 2. The per cent of patients with a peak of troponin Ic >4 ng ml\(^{-1}\), >8 ng ml\(^{-1}\), or >12 ng ml\(^{-1}\) did not differ significantly between the groups (Table 2).

Haemodynamic data

Arterial pressure and heart rate during surgery were not significantly different between the groups (Table 3).

Cardiac index assessed by thermodilution measurement did not reach significant difference between the groups (Table 4). There was no difference between the groups in patients with a low postoperative cardiac index, that is, a cardiac index <2.0 litre min\(^{-1}\)m\(^{-2}\): 12% (7/28) in sevoflurane group vs 35% (12/36) in the control group, \(P=0.136\). The difference was significant when the protocol population was considered [11% (3/28) vs 35% (12/36), \(P=0.025\)]. Fewer patients in the sevoflurane group required inotropic drug during the postoperative period, 25% (9/36) vs 36% (13/36) in the control group, \(P=0.306\). There was no observed in-hospital mortality in any patient of each group.

Enzyme activity

Tissular enzyme measurement (ecto and cytosolic-5'-nucleotidase, PKC tyrosine kinase, and P38MAP kinase activity) did not differ significantly between the groups (Table 5).

Discussion

In the present study, we report that 15 min of sevoflurane pre-administration did not result in a postoperative

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**Table 1** Characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane group, n=36</th>
<th>Control group, n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) [mean (range)]</td>
<td>63 (48–78)</td>
<td>61 (47–78)</td>
</tr>
<tr>
<td>Weight (kg) [mean (sd)]</td>
<td>81 (11)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>Preoperative LV ejection fraction (%)</td>
<td>64 (12)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>CPB time (min) [mean (sd)]</td>
<td>91 (27)</td>
<td>92 (20)</td>
</tr>
<tr>
<td>Aortic cross clamping time (min)</td>
<td>53 (21)</td>
<td>54 (14)</td>
</tr>
</tbody>
</table>

**Table 2** Repartition of patients (%) as a function of peak troponin I value

<table>
<thead>
<tr>
<th>Troponin Ic after CPB H0 [n (%)]</th>
<th>Sevoflurane, n=36</th>
<th>Control, n=36</th>
<th>Test ((\chi^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4 ng ml(^{-1})</td>
<td>10 (28%)</td>
<td>14 (39%)</td>
<td>(P=0.317)</td>
</tr>
<tr>
<td>&gt;8 ng ml(^{-1})</td>
<td>4 (11%)</td>
<td>8 (22%)</td>
<td>(P=0.206)</td>
</tr>
<tr>
<td>&gt;12 ng ml(^{-1})</td>
<td>4 (11%)</td>
<td>2 (6%)</td>
<td>(P=0.674)</td>
</tr>
</tbody>
</table>

**Table 3** Systolic and mean arterial pressure (mm Hg). Before sevoflurane is the time for both groups just before mammary retractor placement, after sevoflurane is the time for both groups 15 min after mammary retractor placement. There was no difference between the groups

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before CPB (opened thorax)</td>
<td>Before CPB (closed thorax)</td>
</tr>
<tr>
<td>Age (yr) [mean (sd)]</td>
<td>40 (15)</td>
<td>41 (16)</td>
</tr>
<tr>
<td>Weight (kg) [mean (sd)]</td>
<td>81 (11)</td>
<td>82 (12)</td>
</tr>
<tr>
<td>Preoperative LV ejection fraction (%)</td>
<td>64 (12)</td>
<td>64 (12)</td>
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<tr>
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</tr>
<tr>
<td>Aortic cross clamping time (min)</td>
<td>53 (21)</td>
<td>54 (14)</td>
</tr>
</tbody>
</table>

**Table 4** Cardiac index (ml min\(^{-1}\) m\(^{-2}\))

<table>
<thead>
<tr>
<th>Groups [mean (sd)]</th>
<th>Before sevoflurane</th>
<th>H0</th>
<th>H4</th>
<th>H8</th>
<th>H12</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane group</td>
<td>2.2 (0.6)</td>
<td>2.4</td>
<td>2.7</td>
<td>2.6</td>
<td>2.7</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Control group</td>
<td>2.3 (0.6)</td>
<td>2.4</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>
troponin Ic decrease compared with control group; however, the number of patients with a low cardiac index was significantly smaller in sevoflurane-treated patients. Troponin Ic is a reliable marker of myocardial ischaemia, and studies have shown that elevated values are a predictor of in-hospital death after cardiac surgery, with a peak occurring between 10 and 20 h after surgery. All recent prospective studies in cardiac surgery have reported positive results with isoflurane or sevoflurane preconditioning. De Hert and colleagues have shown in two groups of 10 coronary patients that sevoflurane administered during all surgical procedure (before, during, and after CPB) produced a decrease in myocardial damage assessed by a decrease in postoperative troponin Ic levels and by an improvement of cardiac function after CPB. Such results have been confirmed by other studies from the same group showing a benefit of sevoflurane anaesthesia, compared with i.v. anaesthesia, on clinical data such as postoperative left ventricular function, ICU, and hospital length of stay and arrhythmias. However, in these studies, sevoflurane administration was continuous, or, when given before CPB much longer than that in the present study. A protective effect has been reported by sevoflurane anaesthesia during off-pump coronary bypass. Interestingly, Julier and colleagues have shown in a randomized multicentre double blinded study that a short time administration, 10 min 4% sevoflurane on the onset of CPB before aortic cross-clamping, did not alter postoperative troponin T, but decreased postoperative release of brain natriuretic peptide, which is a less specific ischaemic marker. However, long-term follow-up of this study has shown that patients included in the sevoflurane group improved cardiovascular free-event survival. To date, no other published clinical study on anaesthetic pre-conditioning reports neutral or negative results, except one non-randomized study showing that isoflurane preconditioning did not decrease postoperative cTnI release and did not alter in-hospital outcome. By testing a similar protocol, Lee and colleagues showed recently, in two groups of 20 patients, that 15 min administration of isoflurane (2.5 MAC) followed by 5 min washout period before aortic clamping resulted in a reduced postoperative troponin I level and in an improvement of postoperative cardiac index. The main factors contributing to explain our conflicting results might be the choice of the volatile anaesthetic and the method of volatile anaesthetic administration. In our study, sevoflurane was administered through the ventilator system before the onset of the CPB, whereas in the study performed by Lee and colleagues, isoflurane was added to the gas mixture in the oxygenator after the start of the administration of CPB. However, in this study, the peak of troponin I in the control group was very high, reaching more than 20 ng ml⁻¹ compared with our study (5.2 (6.6) ng ml⁻¹). The better basal myocardial protection conferred to the patients in our study might contribute to the difficulties to show a protective effect in the treated group.

Although the protocol used in the present clinical study is commonly used in animal experimental studies, it is possible that in the clinical situation, the administration period of sevoflurane was too short, or that the washout period was too long. Another important factor to consider is the concentration of sevoflurane: experimental data have shown that higher concentrations of sevoflurane are more protective than lower concentrations. It is possible that a protective effect would occur if our study was designed with higher concentrations. A limitation of the study is that anaesthetic depth was not monitored, and we cannot exclude a difference in anaesthetic depth between the two groups, contributing to an impact on preconditioning. Alternatively, other factors may have affected the results such as, for example, the observed variance in the present study (SD = 6.125 ng ml⁻¹) compared with the one observed in the study published by Belhomme and colleagues (2.8 ng ml⁻¹), which was used for sample size estimation. The standard deviation in the study published by Belhomme and colleagues was probably unexpectedly low, compared with our study. It is possible that by recruiting more standardized patients (such as high-risk patients), we could have obtained a lower variance. However, our study had a sample size similar to, or higher than, former studies, based on similar hypotheses found in the literature. Results are expressed for the Intention To Treat population; there was no difference with the Per Protocol population for the main endpoint.

Experimental data have shown that halogenated anaesthetics confer a protection against myocardial ischaemia when given before the ischaemic insult, involving different biochemical pathway, such as adenosine receptor, PKC, mitochondrial KATP channel, mitochondrial permeability transition pore opening, and MAP kinases. However, experimental conditions, such as the age of the animals, the number, and the duration of exposition, may affect the extent of sevoflurane preconditioning. Similarly, experimentally, the relative preconditioning potency of the different halogenated agents is

Table 5 Tissular enzyme measurement (atrial sample harvested during atrial canulation)

<table>
<thead>
<tr>
<th>Mean (sd)</th>
<th>Sevoflurane group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecto-5′-nucleotidase (nmol mg protein⁻¹ min⁻¹)</td>
<td>7.1 (4.3)</td>
<td>8.5 (11.9)</td>
<td>0.554</td>
</tr>
<tr>
<td>Cytosolic-5′-nucleotidase (nmol mg protein⁻¹ min⁻¹)</td>
<td>4.1 (2.5)</td>
<td>4.3 (4.4)</td>
<td>0.900</td>
</tr>
<tr>
<td>Protein kinase C activity (nmol mg protein⁻¹ min⁻¹)</td>
<td>27.1 (15.7)</td>
<td>29.2 (28.7)</td>
<td>0.759</td>
</tr>
<tr>
<td>Tyrosine kinase activity (nmol mg protein⁻¹ min⁻¹)</td>
<td>101.0 (54.1)</td>
<td>98.5 (63.3)</td>
<td>0.868</td>
</tr>
<tr>
<td>F38MAP kinase activity (nmol mg protein⁻¹ min⁻¹)</td>
<td>131.1 (76.1)</td>
<td>127.1 (86.8)</td>
<td>0.842</td>
</tr>
</tbody>
</table>
debated.\(^5\)\(^6\)\(^24\) Interestingly, in a dog model, Toller and colleagues showed the lack of effect of 30 min sevoflurane pre-administration when administered after a 30 min washout period, but they demonstrated a protective effect when the washout period was suppressed. However, when a short ischaemic trigger, insufficient by itself to confer a protective effect, was added to the sevoflurane pre-administration followed by the 30 min washout period, a protective effect was observed.\(^31\)

PKC translocation plays a pivotal role in ischaemic\(^32\) and anaesthetic\(^3\) preconditioning. \(^5\)\(^\prime\)-NT, which produces adenosine from AMP, is activated by PKC.\(^33\) Activation of \(^5\)\(^\prime\)-NT is involved in ischaemic preconditioning\(^33\) by increasing adenosine level. Belhomme and colleagues\(^16\) showed in the first ever published clinical study on anaesthetic preconditioning, that 5 min exposure to isoflurane followed by a 10 min washout before aortic cross-clamping, increased ectosolic \(^5\)\(^\prime\)-NT at the end of the preconditioning protocol without any effect on the cytosolic fraction. MAP kinases are the second messenger system. P38 MAPK is involved in ischaemic preconditioning\(^33\), but its role is unclear, being protective, or exacerbating myocardial damage, depending on its activation.\(^34\)\(^–\)\(^36\) In the present study, a 15 min period of the halogenated agent might have been insufficient to trigger an effect and could explain the absence of difference in enzymatic activities between the two groups. Moreover, da Silva and colleagues\(^29\) showed that, conversely to ischaemic preconditioning, anaesthetic preconditioning did not activate p38 MAPK. In a study including 20 patients, Pouzet and colleagues\(^37\) reported that sevoflurane administrated during the CPB did not induce PKC nor P38 MAPK activation, but that the CPB by itself activated the kinases cascade. However, they reported a tyrosine kinase activation by sevoflurane during the CPB. Role of tyrosine kinase in ischaemic preconditioning remains unclear\(^38\) with probably differences between anaesthetic and ischaemic preconditioning.\(^29\)

In summary, in this prospective randomized multicentre study, after a 15 min administration of sevoflurane stopped 15 min before CPB, postoperative troponin Ic peak levels were not significantly lower than that in the control group.

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