Halothane Prevents Postischemic Production of Hydroxyl Radicals in the Canine Heart

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Background: Recent studies indicate that during regional myocardial ischemia and subsequent reperfusion, volatile anesthetics may provide protection against free radical–related injury. The effect of halothane on free radical production during ischemia and reperfusion, in the canine heart, was investigated. The level of hydroxyl radical (·OH)-mediated conversion of salicylate to its dehydrobenzoate derivatives (2,3-DHBA and 2,5-DHBA) was monitored.

Methods: Under general anesthesia, the heart was exposed through median sternotomy. Salicylate (100 mg/kg given intravenously) was administered 30 min before left anterior descending artery occlusion. Six dogs were studied using inhaled halothane (1.6%) 10 min before and during the 10-min ischemic period, followed by 50 min of reperfusion, and then they were compared with seven other dogs used as controls. Blood concentrations of salicylate, 2,3-DHBA and 2,5-DHBA, K+, lactate, oxygen content, and pH were monitored.

Results: An acute increase in the normalized concentrations of 2,3-DHBA and 2,5-DHBA was observed in the control animals during reperfusion. In contrast, halothane inhalation completely inhibited the production of both metabolites (P < 0.02), but 2,5-DHBA concentrations in the halothane-treated group were even less than the basal level (P < 0.05).

The increase in lactate concentrations in the experimental animals was significantly less than that of controls (P < 0.05) and followed the same time-dependent pattern as the changes in K+ and pH. Halothane significantly decreased (P < 0.0001) the difference in oxygen content between coronary sinus and aortic root blood, suggesting decreased oxygen utilization during reperfusion.

Conclusions: Halothane completely inhibited the production of ·OH, and its administration may protect the heart from the deleterious effect of oxygen-derived reactive species, with attenuation of the metabolic response to ischemia. (Key words: Anesthetics, volatile; halothane. Animal: dog. Dihydroxybenzoic acid; high-pressure liquid chromatography; Electrochemical detection; Free radicals; hydroxyl radicals. Heart, coronary circulation: occlusion; regional ischemia. Heart, stunned myocardium: postischemic, reperfusion. Salicylate.)

THE cellular events involved in reperfusion injury after regional ischemia of the myocardium are mainly calcium overload and free radical damage. Several studies indicate that under such circumstances the volatile anesthetics may have properties that protect the heart, which, in turn, could reduce infarct size1 and prevent intracellular calcium accumulation.2,3

Halothane anesthesia is associated with accelerated recovery of myocardial systolic function and with a lower incidence of ventricular dysrhythmias after ischemia in the pig heart.4 Volatile anesthetics also prevented free radical–mediated reduction in both coronary blood flow and in myocardial contractility of the isolated rabbit heart.5 We have shown, in canine heart sarclemoma, that halothane prevented an increase in the number of available voltage-sensitive calcium channels after a short ischemic challenge to the heart.6 An increase in the number of available calcium channels after myocardial ischemia is probably responsible for the increased influx of calcium ions during reperfusion.7

Although the beneficial role of the volatile anesthetics in preventing calcium overload during myocardial stunning has already been shown, the mechanism by which
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they act in physiologic conditions to modulate free radical production in the heart is not clear. Most investigations that implicate the involvement of oxygen-derived radicals in biological injuries are based on indirect evidence. The present study was aimed at clarifying the mode of action of halothane on free radical-generating pathways in the myocardium by using a highly sensitive method to measure in vivo production of hydroxyl radicals.

The present method to monitor free radical-related events in vivo involves chemical trapping of reactive free radicals as they are formed in the tissues. The hydroxyl radical (\(\cdot\)OH) reacts with salicylate to form dihydroxybenzoic acid (DHBA) derivatives, 2,3-DHBA and 2,5-DHBA, which can be resolved from each other, with a high degree of sensitivity by high-pressure liquid chromatography and measured by electrochemical detection.\(^8\)

Although the 2,3-DHBA is a direct product of the reaction of hydroxyl radicals with salicylate, the formation of 2,5-DHBA from salicylate occurs by two independent routes: direct trapping of \(\cdot\)OH and biotransformation mediated by the cytochrome P450 system.\(^9\) Because halothane anesthesia affects the function of cytochrome P450, the present study also sheds light on its influence on cytochrome P450-mediated production of 2,5-DHBA, in the myocardium, during ischemia and reperfusion.

The in vivo generation of free radicals is studied together with other metabolic processes, such as lactate and potassium release, oxygen use, and blood pH, by monitoring arterial and coronary sinus venous blood. The concentrations of these parameters are characteristically modified during ischemia and reperfusion.

Net cellular potassium and lactate efflux occur within 30 s of the onset of myocardial ischemia. Release of both metabolites from the myocyte is enhanced as intracellular pH decreases.\(^10\) The present study examines the timing of the changes during reperfusion in oxygen content, lactate and potassium release, and the role of halothane anesthesia on myocardial metabolism.

Materials and Methods

Preparation of Experiments

A regional myocardial ischemia model in dogs was chosen to examine the injurious effect of a short period of ischemia followed by reperfusion on myocardial metabolism and free radical production. The experiments were done on 13 mongrel dogs weighing 18-24 kg after approval by the institutional committee on animal experimentation. The studies were performed under general anesthesia and continuous electrocardiographic, femoral arterial blood pressure, temperature, and end-tidal carbon dioxide and anesthetic gas concentration monitoring.

Anesthesia was induced with 25 mg/kg intravenous pentobarbital, 30 min after intramuscular injection of 0.5 mg/kg 1% propionylpromazine. At the beginning of the experiment, 15 \(\mu\)g/kg fentanyl was given and the animal was paralyzed with pancuronium (0.1 mg/kg), the trachea was intubated, and ventilation was mechanically controlled using 60% oxygen in air to maintain end-tidal carbon dioxide at 35-40 mmHg. Subsequently, throughout the experiment, additional doses of fentanyl were administered as needed to maintain systolic blood pressure at 120-130 mmHg and heart rate near 100-110 bpm. The mean total dose of fentanyl administered in these experiments was 44 ± 10 \(\mu\)g/kg (means ± SD).

Body temperature was maintained above 35°C using a warm intravenous fluid solution and overhead heating lamp. Stable hemodynamic status was achieved by administering crystalloid intravenous fluid (1-1.5 l) to compensate for the decrease in cardiac output during the ischemic period and administration of inhaled anesthetics.

Seven animals served as controls, whereas in another six dogs end-tidal halothane concentration was maintained at a steady concentration of 1.6 vol% (approximately 2 minimum alveolar concentration) using an anesthetic gas analyzer (Drager Iris, Lubeck, Germany). Administration of halothane from a calibrated vaporizer (Fluotec 3; Cyprane, Keighley, UK) was started 10 min before the coronary occlusion and continued during the 10-min ischemia period. Arterial blood gases were used to confirm adequate ventilation and oxygenation and the absence of metabolic acidosis during the period of ischemia and reperfusion.

The heart was exposed through a median-sternotomy incision, and an atraumatic vascular ligature was applied for 10 min to the left anterior descending artery, distal to the first diagonal artery, to create reversible regional ischemia. For blood sampling, a neonatal coronary sinus cannula was introduced by a pediatric cardiac surgeon into the coronary sinus (DLP Inc., Grand Rapids, MI). Its tip was positioned by palpation 2 cm in depth, which brings it close to the great cardiac vein, the major confluence of the left heart venous system. At each time interval, 2 ml blood, after the first 2 ml dead space
blood was discarded, were withdrawn slowly to avoid retrograde aspiration from the right atrium.

Before coronary occlusion, each animal received, in incremental doses, 25 mg/kg procainamide to reduce the risk of ischemia-induced ventricular dysrhythmia. Intravenous salicylate (100 mg/kg) was given at the beginning of the experiment, and in both groups blood samples for salicylate, 2,3-DHBA, and 2,5-DHBA concentrations were withdrawn slowly from the coronary sinus before, during the ischemic period (at 5 and 10 min), and on reperfusion (at 1, 2, 4, 6, and 10 min and then every 10 min). The blood samples were kept in a −80°C freezer until they were analyzed. Blood samples for blood gases, oxygen content determination, pH, potassium, and lactate analysis were taken simultaneously and were analyzed using the Stat Profile Plus 9 Analyzer (Nova Biomedical, Waltham, MA) immediately after their collection.

Quantitation of Hydroxyl Radicals by Salicylate
Salicylate is a highly effective hydroxyl radical trap that, on scavenging ·OH, forms the stable adducts 2,3-DHBA and 2,5-DHBA by hydroxylation reaction. The 2,3-DHBA and 2,5-DHBA were identified and measured by high-pressure liquid chromatography coupled with electrochemical detection using a Varian 5000 Liquid Chromatograph (Varian, Wallnut, CA) equipped with a Rheodyne 7125 sample injector (20 µl loop) (Rheodyne, Cotati, CA). The column used for separation of salicylate and the DHBA was a 25 cm × 4 mm LiChrospher 100 RP-18, at 5 µm (E. Merck, Darmstadt, Germany). The mobile phase contained 0.03 m citric acid, 0.03 m acetic acid, and 0.2 g/l sodium azide and 2% methanol. It was titrated with solid NaOH to pH 3 followed by titration with CH₃COONa to a final pH of 3.6. The flow rate was 1 ml/min. The system was equipped with two detectors in series. Salicylate was identified and measured fluorimetrically using a model FD-300 detector (SpectroVision, Chelmsford, MA) employing excitation and emission wavelengths of 300 and 412 nm, respectively. Dihydroxybenzoic acids were quantitated using an electrochemical amperometric detector (model 4A, Bioanalytical Systems, West Lafayette, IN) with a plastic cell equipped with a glass carbon electrode operated at +0.80 V, using an Ag/AgCl reference electrode. The signals from the detector were acquired on a Barspec data system (Israel) and subsequently processed.

Analysis of Results
The yield of DHBA derivatives depends on both the flux of hydroxyl radicals generated and the concentration of salicylate. Variation in salicylate concentration was noted and presumably attributed to differences in its renal clearance. It was therefore necessary to normalize the results of the DHBA production to account for the different amounts of salicylate. Thus the concentrations of hydroxyl radicals generated in the heart have been expressed as the ratio of nanograms of DHBA per microgram of salicylate concentrations.

Data are presented as means ± SEM. Consecutive blood concentration data of each study group during reperfusion were analyzed by two-way analysis of variance for each of the parameters examined in the study. An unpaired Student's t test was used to test the differences between the mean values of heart rate, blood pressure, and carbon dioxide arteriovenous (AV) difference at a specific time in the two groups. Differences were significant when the probability value was less than 0.05.

Results
Using the method of salicylate hydroxylation to its DHBA derivatives by ·OH, we found a significant generation of hydroxyl radicals, in vitro, by analyzing the venous effluent coronary blood of a canine heart subjected to 10 min of ischemia followed by 50 min of reperfusion. A representative high-pressure liquid chromatography-electrochemical detection chromatogram (fig. 1) shows the formation of 2,3-DHBA and 2,5-DHBA derivatives at 4 min of reperfusion and the salicylate at that time point. Throughout the period of the experiment, a gradual decrease in salicylate concentrations was evident, from 46 ± 7 µg/ml (means ± SE) to 36 ± 6 µg/ml in the control group. Thus, to overcome these differences in salicylate concentration, the normalized concentrations of DHBA are presented for each time interval.

Throughout the experiment, stable hemodynamic status (table 1), temperature of 36.1 ± 0.6°C, and normal ventilation (S_O₂ 99%, P_O₂ 230 ± 18 mmHg, and P_CO₂ 33 ± 4 mmHg) were maintained in both groups.

In the control experiments (n = 7), an acute increase was observed in normalized 2,3-DHBA concentrations during reperfusion (fig. 2). The first peak was observed at 4 min reperfusion, from 1.3 ± 0.4 to 2.8 ± 1, a 115% increase compared with baseline at time 0 (before

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coronary occlusion). A second and more prolonged increase was observed after 30 min of reperfusion to 3.4 ± 1 (a 162% increase compared with baseline).

The increase in normalized 2,5-DHBA during reperfusion was gradual (fig. 3), from a baseline value of 5.3 ± 2.4 to 8.8 ± 5 at 30 min (67% increase).

In the presence of halothane, there was no evidence of hydroxyl radical production during reperfusion. No change in 2,3-DHBA was observed during the experiments. Thus the mean values of 2,3-DHBA in the halothane group were significantly lower than in the control group (P < 0.02 by analysis of variance) during reperfusion (fig. 2). Figure 3 shows that similar findings were observed for the 2,5-DHBA concentrations, which also were significantly lower in the presence of halothane (P < 0.05).

Simultaneously with the determination of free radical production, blood samples from the coronary sinus were tested for lactate concentration and potassium loss from the myocardial tissue (fig. 4). In each experiment, a concomitant increase in both lactate and potassium concentrations was observed, reaching its peak value at 2 min of reperfusion. Mean lactate concentrations increased from 1 ± 0.3 mmol/l to 4.8 ± 2 mmol/l in control experiments (P < 0.002 compared with baseline by t test) and from 0.6 ± 0.1 mmol/l to 5.4 ± 1.6 mmol/l in the halothane group (P < 0.05). The overall lactate

Table 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Halothane</th>
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<tbody>
<tr>
<td></td>
<td>SBP (mmHg)</td>
<td>DBP (mmHg)</td>
</tr>
<tr>
<td>Baseline</td>
<td>142 ± 17</td>
<td>76 ± 9</td>
</tr>
<tr>
<td>Skin incision</td>
<td>104 ± 8</td>
<td>72 ± 5</td>
</tr>
<tr>
<td>10 min ischemia</td>
<td>92 ± 5</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>15 min reperfusion</td>
<td>98 ± 6</td>
<td>78 ± 8</td>
</tr>
</tbody>
</table>

Values are mean ± SD; there are no significant differences.
SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

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concentrations in the control group were greater than in the presence of halothane anesthesia ($P < 0.05$ by analysis of variance). Potassium blood concentrations in the control experiment increased from a mean baseline value of $3.5 \pm 0.4$ mEq/l to a peak value of $5.7 \pm 2$ mEq/l ($P < 0.03$), whereas the $K^+$ increase in the halothane group (from $5.9 \pm 0.4$ mEq/l to $4.9 \pm 1.5$ mEq/l) was not significant. The differences in potassium blood concentrations between the two groups also were not significant. The changes in potassium and lactate concentrations were accompanied by a decrease in pH, which was maximal at 2 min of reperfusion (fig. 5), from $7.40 \pm 0.1$ to $7.25 \pm 0.1$ ($P < 0.002$) in the control experiments, compared with no change in pH in the halothane group.

Oclusion of the left anterior descending coronary artery in the control group was accompanied by a decrease in oxygen use, as shown by the difference in oxygen content between the aortic root arterial blood and coronary sinus venous blood (table 2). The arteriovenous difference decreased by 55% in the control group from $11.6 \pm 2.8$ mg% to $5.2 \pm 2.7$ mg% at 4 min of reperfusion ($P < 0.01$), and this depression lasted for 30 min. In the halothane group, a decrease of 28.6% was observed at 2 min of reperfusion (from $13.1 \pm 3.1$ to $9.3 \pm 2$), which returned to baseline value within 6 min ($P = NS$). Figure 5 shows the increase in coronary sinus oxygen content (CO$_2$). An increase of 130% in CO$_2$ was noted, from $5 \pm 1.0$ mg/dl at baseline, to $11.4 \pm 2$ mg/dl at 4 min of reperfusion ($P < 0.02$), which lasted 30 min. Under halothane anesthesia there was no change in CO$_2$ during ischemia; the increase in CO$_2$ during reperfusion, compared with the control group, was significantly smaller ($P < 0.001$) and short-lived.

Discussion

This study shows the acute increase in vivo of hydroxyl radicals during early reperfusion. This is demonstrated by the abrupt production of 2,5-DHBA and 2,5-DHBA derivatives from salicylate. At the same time, a marked deterioration in oxygen utilization occurred. Halothane anesthesia administered before and during the period of myocardial ischemia was found to attenuate the production of free radicals and the deleterious effect of ischemia and reperfusion on myocardial metabolism.

The method used in the present study to monitor free radical events, in vivo, involves chemical trapping of reactive free radicals as they are formed in the tissue.
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Fig. 5. Mean oxygen content (solid line) and pH (dashed line) in coronary sinus blood. Each data point represents the mean value in control (square) experiments (n = 7) and halothane (triangle) experiments (n = 6). *Significant difference in mean oxygen content during ischemia (P < 0.05) and during reperfusion (P < 0.001) by analysis of variance.

This method, in which hydroxyl radicals react with salicylate to form DHBAs, provides accurate and direct data on the accumulation of free radical adducts over time.13

Another method to detect free radicals in biological systems is the reaction of free radicals with spin trapping agents to form radical adducts that can be detected and identified by electron spin resonance spectroscopy. An important disadvantage of this method regarding its use in the present study is its inability to measure -OH production in vivo.9

Oxygen free radicals have been implicated as etiologic agents in several clinically important conditions that may contribute to the development of myocardial dysfunction even after a short period of ischemia and subsequent reperfusion. Those conditions include structural alterations in myocytes14 and disturbances in cellular calcium homeostasis,15 with impaired myocardial contractility. Free radicals also affect endothelial-dependent function, and by inactivation of nitric oxide may increase coronary vascular resistance and subsequent reduction in coronary blood flow.5

As part of the mechanism of production of free radicals, they are also generated as a result of activation of the complement system and neutrophil invasion.16 It has been shown that endothelial cells are activated by C5 and other complement components, which resulted within 10 min of reperfusion in the conversion of xanthine dehydrogenase to xanthine oxidase, a response followed by self-amplification of production of free radical species.17 This stage is followed at 90 to 270 min after reperfusion by penetration of neutrophils through the endothelium to the myocardium, where they release free radicals, cytokines, and cytotoxic proteases as part of the inflammatory response to injury.18

In the present study, the time-dependent production of free radicals (fig. 2) showed two peaks in 2,3-DHBA concentrations, which reflect the production of hydroxyl radicals. The first peak might be attributed to the primary surge of free radicals from ischemic myocardium with the reintroduction of oxygen. The second peak might already be related to a release of free radicals from the endothelial cells activated by the complement system.

Several studies have shown previously that an ischemic interval of 10 min is too short to cause irreversible damage to the myocyte.19 The alterations described in the current study in the metabolic parameters, which were reversible with time, indicate that the ischemic insult was minor. This small insult to the myocardial tissue might explain the short duration of hydroxyl radical production, which returned to nearly normal values by 50 min of reperfusion.

In contrast to the production of 2,3-DHBA, 2,5-DHBA can be produced from salicylate via the direct reaction with hydroxyl radical, and via the mediation of the cytochrome P450 system.3 Biotransformation of salicylic acid occurred in the microsomal system and mitochondria, primarily in the liver, but also in many tissues.

Table 2. Arteriovenous Difference in Oxygen Content (mg/dl) between Coronary Sinus and Aortic Root Blood

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control</th>
<th>Halothane</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>11.6 ± 2.8</td>
</tr>
<tr>
<td>Ischemia</td>
<td>5</td>
<td>9.6 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8.5 ± 4.6</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>1</td>
<td>7.9 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.6 ± 3.6*</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5.2 ± 2.2*</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5.6 ± 2.7*</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6.6 ± 2.4†</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>7.3 ± 2.8†</td>
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<td>30</td>
<td>10.2 ± 1.5</td>
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<tr>
<td></td>
<td>40</td>
<td>10.0 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>10.1 ± 1.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* P < 0.01 versus baseline.
† P < 0.05 versus baseline.

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including the heart coronary endothelium. The increase in 2,5-DHBA concentrations observed in the present study probably represents both pathways. The broad peak (fig. 5), which reflects a more prolonged time course, might be explained by the additional and extended contribution of the cytochrome P450 system. Halothane may interfere with the biodegradation of other drugs via the cytochrome P450 system. Thus the present results, which show an acute reduction in 2,5-DHBA production in the presence of halothane, correspond with the hypothesis that the cytochrome P450 pathway contributes to the production of 2,5-DHBA.

The decrease in free radical production in the myocardium in the presence of halothane anesthesia administered before and during the ischemic period is an important finding that might represent an important protective property of volatile anesthetics under these circumstances. Previous studies have also shown the possible protective role of halothane in free radical-mediated events. However, the present results demonstrate a direct, in vivo inhibition of hydroxyl radical production by halothane in the heart during ischemia and reperfusion. These data are complimentary to several previous reports describing the beneficial properties of volatile anesthetics during myocardial ischemia, in preventing deregulation of calcium homeostasis, and its uncontrolled influx through the sarcolemma and sarcoplasmic reticulum of the myocyte. Thus halothane anesthesia administered during vulnerable events such as a short period of reduced oxygen, followed by the massive production of oxygen-derived radicals, might attenuate the mechanism of injury to the heart and preserve its functional status.

The mechanism by which halothane inhibits hydroxyl radical production is not clear. It was previously shown that calcium ions are essential in the induction of superoxide production in neutrophils. Increasing cystolic Ca²⁺ results in protease activation, which causes xanthine dehydrogenase to convert to xanthine oxidase with enhanced superoxide production. In parallel, activation of the phospholipase A₂ by Ca²⁺ activates superoxide anion production via the reduced nicotinamide adenine dinucleotide phosphate oxidase pathway. Thus the volatile anesthetics may reduce intracellular calcium accumulation as part of their mechanism of inhibiting free radical production.

Another possible explanation for the reduction in free radical generation in the presence of halothane might be related to the negative inotropism of halothane, accompanied by reduced requirements for oxygen, and consequently attenuation of the production of free radicals. However, the fact that in the present study major components of myocardial oxygen requirements, such as heart rate and blood pressure, were similar in both groups, may indicate that conservation of energy could not play a major role in the differences observed in free radical production.

The present study supports the theory of conservation of myocardial function by halothane. Blood samples of the effluent venous blood of the left ventricle have shown a decrease in lactate concentration in the presence of halothane, as well as significant improvement in myocardial oxygen utilization in the halothane experiments. The increase in oxygen content immediately after reperfusion and the decrease in the arteriovenous difference of oxygen content probably represent the low use of oxygen by the "stunned" myocardium. It might also be explained by the transient hyperemia characterizing the return of blood flow to ischemic tissue.

The present results show that, in the control studies, lactate and potassium afflux occur on a similar time scale, concomitantly with a decrease in pH. Weiss and Shieh have investigated the link between lactate and potassium afflux. They observed that the release of both species is enhanced as intracellular pH decreases. However, they concluded that no direct link exists between potassium and lactate afflux, and that the relation between the two is indirect. In the current study, halothane clearly attenuated the development of acidosis in the myocardium, with a consequent minor increase in lactate and potassium afflux from the ischemic heart.

In open heart surgery, volatile anesthetics are commonly administered during cardiopulmonary bypass. The clinical use of volatile anesthetics for their beneficial role in preventing reperfusion-related injury during heart surgery has not been reported. The present canine study indicates that, after myocardial ischemia and reperfusion, the protective effect of halothane may warrant investigating the concomitant use of halothane or other volatile anesthetics during the continuous administration of oxygenated blood cardioplegia for myocardial preservation during open heart surgery.

The Dr. William Ganz Chair of Heart Studies at the Hebrew University of Jerusalem was established in 1990. The authors thank Judith Fisher for editorial assistance.
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