Isoflurane and Halothane Increase Adenosine Triphosphate Preservation, but Do Not Provide Additive Recovery of Function after Ischemia, in Preconditioned Rat Hearts

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Background: Brief ischemic periods render the myocardium resistant to infarction from subsequent ischemic insults by a process called ischemic preconditioning. Volatile anesthetics have also been shown to be cardioprotective if administered before ischemia. The effect of preconditioning alone and combined with halothane or isoflurane on hemodynamic recovery and preservation of adenosine triphosphate content in isolated rat hearts was evaluated.

Methods: Seven groups of isolated rat hearts (n = 6 each) were perfused in a retrograde manner at constant temperature and pressure. A latex balloon was placed in the left ventricle to obtain isovolumetric contraction. Heart rhythm, coronary flow, left ventricular pressure and its derivative dP/dt (positive and negative), and developed pressure were monitored. The hearts were paced at 300 beats per minute. Each heart was randomly allocated to (1) a time-control group that received no ischemia, (2) an untreated group that received 25 min of normothermic ischemia only, (3 and 4) an isoflurane group and a halothane group that received 40 min of anesthetized (2.2% and 1.5%, respectively) before ischemia; (5) a preconditioning group that received two 5-min periods of ischemia separated by 10 min of reperfusion before ischemia; or (6 and 7) a halothane + preconditioning group and a halothane + preconditioning group that received anesthetized for 10 min at concentrations of 2.2% or 1.5%, respectively, before two 5-min periods of ischemia separated by 10 min of reperfusion. All treated groups received 25 min of normothermic ischemia followed by 30 min of reperfusion.

Results: The time-control group remained hemodynamically stable for the entire experiment, and the adenosine triphosphate content was 18.3 ± 1.7 (SEM) μM/g at the end of 115 min. The untreated group had depressed recovery after 25 min of normothermic ischemia, and the developed pressure was significantly depressed and recovered only 30 ± 9% (P < 0.001) of its preischemic value. There was also a significant increase in the incidence of ventricular fibrillation (P < 0.001). Adenosine triphosphate content was significantly lower in this group than in all other groups. Five minutes of ischemia in the preconditioning group had little effect on hemodynamics and decreased developed pressure only 6.4%. Halothane depressed developed pressure by 16 ± 5% (P < 0.001), and isoflurane increased coronary flow by 145 ± 9% (P < 0.001) but had no significant hemodynamic effect. The treated groups had significantly better recovery of postischemic function than did the untreated group. In the preconditioning group, developed pressure recovered to 85% of control and dP/dt+ to 87% of control. The addition of halothane or isoflurane to preconditioning did not provide additional functional recovery but did increase the level of adenosine triphosphate preservation (13.1 ± 1.1 and 12.4 ± 1.1 μM/g, respectively).

Conclusions: The results indicate that preconditioning, halothane, and isoflurane provide significant protection against ischemia. The combination of preconditioning and halothane or isoflurane did not improve hemodynamic recovery but did increase preservation of adenosine triphosphate. (Key words: Adenosine 5′ triphosphate. Anesthetics, volatile: halothane; isoflurane. Ischemia. Isolated rat heart. Preconditioning.)

PRECONDITIONING is a phenomenon in which a brief period of ischemia renders the myocardium resistant to subsequent ischemia, reduces infarct size, and limits ultrastructural abnormality. This endogenous protective mechanism has been shown to occur in various species, including humans, dogs, rabbits, pigs, and rats. The mechanisms of protection, although not completely understood, involve release of adenosine and activation of A1 receptors that regulate adenylate cyclase activity through guanosine triphosphate, thus binding G-proteins intracellularly. G-proteins have several functions, one of which is to inhibit Ca++ influx.
during ischemia. The G protein pathway also may activate the K<sub>ATP</sub> channel<sup>1</sup> and appears to regulate cellular metabolism, particularly glycolysis.<sup>5</sup> Biochemical analysis indicates that preconditioning also contributes to conservation of adenosine triphosphate (ATP) content during subsequent ischemia.<sup>6</sup> Transient ischemia may occur during anesthesia and surgery. Volatile anesthetics, for example, are often used for patients with coronary artery disease (CAD) who are at risk for having intermittent ischemia during cardiac and noncardiac surgery. Previous reports indicate a beneficial effect of volatile anesthetics given before and during ischemia.<sup>7,8</sup> Halothane decreases the accumulation of intracellular calcium in the postsischemic period,<sup>9</sup> improves functional recovery, and reduces the incidence and duration of dysrhythmias on reperfusion in isolated hearts.<sup>10</sup> It may also decrease the release of adenosine during hypoperfusion and ischemia, producing a favorable condition for reperfusion in isolated guinea pig hearts.<sup>11</sup> Isoflurane enhances the functional recovery of the ischemic myocardium.<sup>12</sup>

We postulated that combining preconditioning with halothane or isoflurane would provide additional protection for hemodynamic recovery and ATP sparing after ischemia in normothermic rat hearts.

**Materials and Methods**

Male Sprague-Dawley rats (weighing 350-425 g) were fed a standard diet and acclimated in a quiet quarantine room for 1 week before the experiments. The protocol was reviewed and approved by the Animal Care and Use Committee of SUNY Health Science Center at Brooklyn. All chemicals were obtained from Sigma Chemical Company (St. Louis, MO).

Forty-two rats were injected with 10 mg ketamine and 500 U heparin intraperitoneally; when they were unresponsive to noxious stimulation, their hearts were rapidly removed through a median sternotomy incision by transecting all the major vessels. The heart was submerged in cold perfusate (4°C) and then attached to the perfusion apparatus via the aorta. Retrograde perfusion was initiated immediately with Krebs-Henseleit bicarbonate (K-H) buffer that had the following composition: 155 mmol/l Na<sup>+</sup>, 5.6 mmol/l K<sup>+</sup>, 138 mmol/l Cl<sup>-</sup>, 2.16 mmol/l Ca<sup>2+</sup>, 1.19 mmol/l PO<sub>4</sub><sup>3-</sup>, 25 mmol/l HCO<sub>3</sub>sup>—</sub>, 0.56 mmol/l Mg<sup>2+</sup>, 11 mmol/l glucose, and 13 mmol/l sucrose. The solution was equilibrated with 95% oxygen and 5% carbon dioxide at 37 ± 0.5°C, achieving a P<sub>O</sub><sub>2</sub> of 560 mmHg, P<sub>CO</sub><sub>2</sub> of 37 mmHg, and a pH of 7.4 ± 0.2. The myocardial temperature was maintained at 37°C throughout the experiment. The perfusion set-up is based on a modification of the system described by Neeley and associates.<sup>13</sup>

The hearts were perfused in the Langendorff mode under constant pressure of 80 mmHg. During the first 20 min of perfusion, the vena cava was ligated, the left atrium was opened, and a fluid-filled latex balloon catheter was introduced into the left ventricle with a microtip manometer placed in the balloon. Balloon volume was adjusted to maintain an end-diastolic pressure of 6–8 mmHg. This preload volume was held constant during the entire experiment to allow continuous recording of the ventricular pressure. The pulmonary artery was cannulated with small-caliber polyethylene tubing and ligated. Coronary flow was measured using the output volume of this tubing into a graduated cylinder at 5-min intervals. Pacing wires were attached to the pulmonary outflow tract and hearts were paced at a cycle length of 200 ms (300 bpm) using a ventrix stimulator. Stimulation was stopped during ischemic periods. Cardiac function (peak left ventricular pressure, developed pressure (end systolic minus end diastolic), and positive and negative dP/dt were continuously recorded with a pressure amplifier and direct differentiator (Astro Med, Boston MA). A three-way stopcock placed above the aortic root was positioned to stop flow and thus produce global ischemia. Pacing was resumed 3 min after reperfusion. Hearts were defibrillated when necessary.

Volatile anesthetics were administered by placing an agent-specific vaporizer between the fresh gas supply and the perfusate. A Dräger infrared gas analyzer continuously controlled the delivered vapor concentration. The concentration of halothane (0.47 ± 0.02%) and isoflurane (0.84 ± 0.03%) in the perfusate was measured using a gas chromatograph (Perkin-Elmer, Norwalk, CT).

**Experimental Design**

All experiments lasted 115 min (fig. 1) beginning with a 20-h period of stabilizing perfusion for equilibration. The time-control group received no ischemia. The untreated group underwent 60 min of perfusion followed by 25 min of ischemia. The halothane and isoflurane groups received 20 min of perfusion, after which halothane or isoflurane was administered for 40 min before ischemia. The preconditioning group had

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Control Group

Unreared group

Drug Treated Groups

Isotrufen 2.2%; Halothane 1.5%

Preconditioned Group

Isotrufen + Preconditioning and Halothane + Preconditioning Groups

Fig. 1. Experimental protocol. I sc = ischemia; Rep = reperfusion.

30 min of perfusion followed by two 5-min periods of ischemia separated by 10 min of reperfusion. The halothane + preconditioning and the isotrufen + preconditioning groups had 20 min of perfusion, followed by 10 min of treatment with either halothane or isotrufen and two 5-min periods of ischemia separated by 10 min of reperfusion. Halothane or isotrufen were present throughout the experiment, except during the equilibration period, the ischemic period, and the reperfusion period. During ischemia, the hearts were enclosed in a water-jacketed container and maintained at 37°C. Reperfusion lasted for 30 min in all groups.

Biochemical Analyses

Ventricular transmural tissue specimens were taken at the end of each experiment. The tissues were frozen immediately in liquid nitrogen and stored at minus 80°C until the time of analysis. After freeze-drying, the tissues were weighed. Adenosine triphosphate was extracted from the tissues by homogenizing in 3N ice-cold perchloric acid and measured, after neutralization, using the firefly Luciferin-Luciferase assay.14

Statistics

All values are expressed as mean ± SEM. Functional parameters at identical time points were compared for the groups by analysis of variance. If the F ratios were significant, a Bonferroni-Dunn post hoc test was applied to assess the significance of individual comparisons (P < 0.05). Recovery parameters within groups were analyzed by repeated-measures (before and after ischemia), single-factor analysis of variance, and multicomparison was tested with Scheffe’s F test. The incidence of ventricular fibrillation in each group was compared using chi squared analysis. We used Stat View 4 (ABACUS, Berkeley, CA) for the statistical analysis.

Results

Preischemic Hemodynamics

Control group hemodynamic values remained stable for the 115 min length of the experiment. Preischemic values of left ventricular end-diastolic pressure (LVEDP), developed pressure, +dp/dt, −dp/dt, and coronary flow for all groups were compared with baseline values and are shown in Table 1. Preconditioning caused a transient increase in coronary flow that was not significantly different from the baseline value. In the isotrufen and isotrufen + preconditioning groups, there were no significant differences in LVEDP, developed pressure, +dp/dt, and −dp/dt; however, the coronary flow increased from 18.8 ± 0.9 to 26.3 ± 2.4 ml/min in the isotrufen group and from 18.5 ± 1.1 to 27.2 ± 2.2 ml/min in the isotrufen + preconditioning group (P < 0.001). Halothane significantly depressed the contractile function, and developed pressure, +dp/dt, and −dp/dt decreased by 16%, 13%, and 16%, respectively (P < 0.01). Halothane did not increase coronary flow significantly. Halothane combined with preconditioning also depressed contractile function, and developed pressure, +dp/dt, and −dp/dt decreased 22%, 33%, and 35%, respectively (P < 0.001). Halothane + preconditioning caused an increase in coronary flow from 18 ± 2 ml/min to 25 ± 2 ml/min (P < 0.001).

Postischemic Hemodynamics

Hemodynamic recovery was severely impaired in rats in the untreated group. Figure 2 shows the time course of changes in LVEDP during reperfusion for all groups. Ischemia produced a significant increase in LVEDP in all groups when compared with baseline values (P < 0.001). The treated groups had a lower LVEDP than did the untreated group (P < 0.001). There was no significant difference in the LVEDP among any of the treated groups at the end of 25 min of ischemia. In the untreated group, LVEDP increased further to reach a maximum value at 5 min of reperfusion and remained high during the rest of the experiment. The treated
groups also showed an increase in LVEDP in the first 5 min of reperfusion, but this decreased subsequently and was significantly lower when compared with the untreated group at the end of reperfusion ($P < 0.001$).

Figure 3 shows the recovery of developed pressure during 30 min of reperfusion. In the untreated group, developed pressure recovered only 30.4% and was significantly different from the preconditioning, isoflurane, and isoflurane + preconditioning groups (85%, 84%, and 90%, respectively; $P < 0.001$). The halothane and halothane + preconditioning groups recovered 83% and 92%, respectively ($P < 0.001$). No significant difference in developed pressure was found among the treated groups.

Figure 4 shows the recovery of $+dP/dt$ during reperfusion. In the untreated group, $+dP/dt$ was 900 ± 108 mmHg/s at the end of reperfusion. In the preconditioning, isoflurane, and isoflurane + preconditioning groups, $+dP/dt$ was 2,766 ± 205, 2,650 ± 219, and 2,775 ± 251 mmHg/s, respectively. In the halothane and halothane + preconditioning groups, $+dP/dt$ was 2,616 ± 216 and 2,816 ± 186 mmHg/s, respectively, which was significantly different from the $+dP/dt$ of the untreated group at the end of reperfusion ($P < 0.001$). There was no significant difference in $+dP/dt$ among treated groups. Similar findings were obtained for $-dP/dt$ (fig. 5). At 30 min of reperfusion, the value for the untreated group was 433 ± 74 mmHg/s, and there was a significant difference between the untreated and treated groups at the end of reperfusion ($P < 0.001$). There was no significant difference in $-dP/dt$ among treated groups.

In the untreated group, coronary flow recovered 76% at 30 min of reperfusion, which was significantly lower than the preconditioning, isoflurane, and isoflurane + preconditioning groups (109%, 111%, and 122%, respectively; $P < 0.001$). The halothane and halothane + preconditioning groups recovered 101% and 120%, respectively ($P < 0.001$). The recovery of coronary flow for halothane-treated hearts was lower than other treated groups ($P < 0.05$), and both anesthetics + preconditioning–treated groups had significantly increased coronary flow recovery compared with preconditioning alone ($P < 0.05$).

### Table 1. Summary of Preconditioning Hemodynamic Variables in Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>LVEDP (mm Hg)</th>
<th>$+dP/dt$ (mm Hg/s)</th>
<th>$-dP/dt$ (mm Hg/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>97 ± 6</td>
<td>8.9 ± 1.5</td>
<td>104 ± 7</td>
</tr>
<tr>
<td>Untreated</td>
<td>11.0 ± 2.1</td>
<td>10.1 ± 2.0</td>
<td>102 ± 7</td>
</tr>
<tr>
<td>Pc</td>
<td>11.1 ± 1.9</td>
<td>9.7 ± 2.1</td>
<td>99 ± 7</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>10.5 ± 1.7</td>
<td>9.5 ± 1.7</td>
<td>99 ± 7</td>
</tr>
<tr>
<td>Halothane</td>
<td>10.3 ± 1.4</td>
<td>9.5 ± 1.7</td>
<td>99 ± 7</td>
</tr>
<tr>
<td>Halothane + Pc</td>
<td>10.5 ± 1.9</td>
<td>10.2 ± 1.7</td>
<td>102 ± 7</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Baseline was recorded at 20 min postischemic state throughout 40 min of reperfusion. Con = control, Pc = preconditioned, Iso = isoflurane, Hal = halothane.

### Adenosine Triphosphate Content

In the time-control group, ATP concentration was 18.3 ± 1.7 μM/g dry weight at the end of 115 min of perfusion without ischemia. Adenosine triphosphate content was better preserved in the preconditioning group (10.8 ± 0.9 μM/g), isoflurane group (11.2 ± 1.2 μM/g).
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Fig. 2. (A) Effects of preconditioning (Pc), halothane (Hal), and halothane + preconditioning on left ventricular end-diastolic pressure, which is plotted as a function of time. Zero time is the beginning of reperfusion. Bars represent SEM. *P < 0.001 for untreated groups compared with preconditioning, halothane, and halothane + preconditioning groups. †P < 0.01 for the preconditioned group compared with the halothane group. No significant difference was found among the preconditioned group and the halothane + preconditioning groups. (B) Effects of preconditioning (preconditioning), isoflurane (Iso), and isoflurane + preconditioning (Iso + preconditioning) on left ventricular end-diastolic pressure, which is plotted as a function of time. Zero time is the beginning of reperfusion. Bars represent SEM. *P < 0.001 for untreated group (U) compared with the preconditioning, isoflurane, and isoflurane + preconditioning groups. No significant difference was found among the treated groups.

μM/g), halothane group (10.2 ± 1 μM/g), isoflurane + preconditioning group (15.1 ± 0.9 μM/g), and halothane + preconditioning group (12.4 ± 0.9 μM/g) than in the untreated group (5.4 ± 1.2 μM/g) (P < 0.001) at the end of the 30-min reperfusion period. The isoflurane + preconditioning group showed greater preservation of ATP content than did the preconditioning and isoflurane groups (P < 0.001 and P < 0.01). The halothane + preconditioning group also showed better preservation of ATP than did the preconditioning and halothane groups (P < 0.05 and P < 0.001). There was no significant difference in ATP sparing among the preconditioning, isoflurane, and halothane groups.

Fig. 3. (A) Effects of preconditioning (Pc), halothane (Hal), and halothane + preconditioning on the recovery of developed pressure in the reperfusion phase. Developed pressure is plotted as a function of time. Zero time is the beginning of reperfusion. Bars represent SEM. *P < 0.001 for untreated groups compared with preconditioning, halothane, and halothane + preconditioning. No significant difference was found among treated groups. (B) Effects of preconditioning (Pc), isoflurane (Iso), and isoflurane + preconditioning on the recovery of developed pressure in the reperfusion phase. Developed pressure is plotted as a function of time. Zero time is the beginning of reperfusion. Bars represent SEM. *P < 0.001 for the untreated group (U) compared with preconditioning, isoflurane, and isoflurane + preconditioning. No significant difference was found among treated groups.
and only one heart in the halothane + preconditioning group (P < 0.01). There was no significant difference among treated groups.

**Discussion**

Our findings indicate that exposure to isoflurane or halothane before an ischemic insult improves recovery of hemodynamic function and has a favorable effect on ATP preservation. This corresponds to previous findings of Kashimoto and coworkers and Wartier and associates. Isoflurane and halothane also decreased the incidence of ventricular fibrillation during reperfusion. Isoflurane produced a better recovery of coronary flow than did halothane.

We also found that ischemic preconditioning can protect the myocardium against injury induced by ischemia–reperfusion, but we failed to show an additive effect, in terms of hemodynamic recovery of pretreatment with halothane or isoflurane combined with preconditioning. We did find a small but statistically significant improvement in the ATP content of hearts that received preconditioning combined with halothane or isoflurane.

Halothane and isoflurane, like ischemic preconditioning, have been shown to activate the K\textsubscript{ATP} channels. Studies suggest that although K\textsubscript{ATP} channels may protect the myocardium during ischemia, how this occurs is still unclear. This mechanism of protection may not be as important in rats as in other species, such as humans, swine, and dogs, because blockade of the K\textsubscript{ATP} channel in rats does not alter the mechanism of preconditioning.

Preconditioned hearts show evidence of ultrastructural damage more slowly than do hearts that have not been preconditioned, and the rate of ATP use is less. Other studies have postulated that the preservation of ATP is responsible for preconditioning as a result of decreased anaerobic glycolysis and glycogen breakdown. Thus intracellular calcium concentrations could decrease as well as ATP use. In this model, the hemodynamic effect of ischemia–reperfusion was severe in the untreated group. The developed pressure was significantly depressed and left ventricular diastolic pressure was elevated, reflecting an increase in left ventricular wall stiffness or contracture. This increase in pressure could be due to an increase in intracellular Ca\textsuperscript{2+} during ischemia. The development of diastolic contracture during ischemia is probably due to persistent, calcium-activated, diastolic contraction secondary to

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Fig. 4. (A) Effects of preconditioning (Pc), halothane (Hal), and halothane + preconditioning on the recovery of the left ventricular positive value of +dP/dt during reperfusion. +dP/dt is plotted as a function of time. Zero time is the beginning of reperfusion. Bars represent SEM. *P < 0.001 for the untreated group (U) compared with preconditioning, halothane, and halothane + preconditioning. No significant difference was found among treated groups. (B) Effects of preconditioning (Pc), isoflurane (Iso), and isoflurane + preconditioning on the recovery of the left ventricular positive value of +dP/dt during reperfusion. +dP/dt is plotted as a function of time. Zero time is the beginning of reperfusion. Bars represent SEM. *P < 0.001 for the untreated group compared with preconditioning, isoflurane, and isoflurane + preconditioning. No significant difference was found among treated groups.

Reperfusion-induced Ventricular Fibrillation

Ventricular fibrillation occurred immediately or within 3 min of reperfusion in all hearts in the untreated group (100%). The incidence of reperfusion-induced ventricular fibrillation was significantly decreased (P < 0.05) in the six hearts of the treated groups compared with those in the untreated group: three hearts in the isoflurane group, two hearts in the preconditioning, isoflurane + preconditioning, and halothane groups;
impaired calcium sequestration by the sarcoplasmic reticulum. An increase in intracellular calcium concentration may activate membrane-located phospholipases, and other enzyme systems involved in energy production, to cause energy depletion with a resultant decrease in contractile function.\textsuperscript{20}

Halothane-decreased myoplasmic calcium concentration, as measured by beat-to-beat changes in bioluminescence of acuronin, is an indicator of free intracellular calcium.\textsuperscript{21} Using a single ventricular cell voltage clamping technique, it was shown that the decrease in intracellular free calcium, with exposure to halothane and isoflurane, is at least due in part to a decrease in calcium flux through voltage-dependent calcium channels.\textsuperscript{22} Isoflurane and halothane decreased the calcium to a similar degree and have at least one effect similar to calcium channel blockers; that is, attenuation of the slow calcium current through voltage-dependent calcium channels. This is meaningful because changes in calcium ion homeostasis play an important role in the events associated with irreversible myocardial injury. In our experiment, this decrease in the intracellular calcium influx was most evident in the lower LVEDP in the treated groups.

Our data show that preconditioning maintained a high concentration of ATP at the end of reperfusion. Richardt and colleagues\textsuperscript{23} have shown that preconditioning with short periods of ischemia, separated by intermittent reperfusion, completely prevented the reperfusion-induced endothelial dysfunction. Adenosine, which accumulates rapidly after the onset of myocardial ischemia, plays a part as a mediator of preconditioning.\textsuperscript{24} Adenosine may hasten repletion of endogenous vasodilator and anti-inflammatory compounds produced by endothelial cells by restoring the metabolic machinery of these cells by replenishing ATP stores or by enhancing oxygen delivery through arteriolar vasodilatation.\textsuperscript{25}

Volatile anesthetics are potent negative chronotropic, dromotropic, and inotropic agents.\textsuperscript{21} Increasing evidence suggests that volatile anesthetics produce negative inotropic effects through mechanisms that affect many steps in the excitation–contraction process. Using the paced isolated rat heart model, we found that 40-min exposure of halothane, but not isoflurane, produced a significant decrease in DP, +dP/dt, and −dP/dt before the onset of ischemia. However, the recovery of DP, +dP/dt, and −dP/dt at the reperfusion period was not significantly different between these two treated groups. Using a guinea pig heart model, Marjić and associates\textsuperscript{20} showed that, before the onset of hypoxia, left ventricular systolic pressure decreased in the halothane and isoflurane groups and reduced the oxygen demand. Volatile anesthetics might act to protect against early hypoxia-induced injury by decreasing the cardiac energy expenditure. Left ventricular diastolic pressure was significantly greater in the halothane group at the end of the 30-min reperfusion period. A greater recovery of left ventricular diastolic pressure in the halothane group compared with the isoflurane group could reflect better protection by an improved oxygen supply-to-demand ratio with halothane than
with isoflurane, because heart rate and left ventricular diastolic pressure, the dynamic determinants of oxygen demand and supply, decreased more with halothane than with isoflurane. It has been shown in the isolated perfused guinea pig model that halothane improves the oxygen supply-versus-demand ratio during hypoxia more by decreasing oxygen extraction than by increasing oxygen supply, and isoflurane improves this ratio more by increasing oxygen delivery and less by decreasing oxygen extraction. The incidence of ventricular fibrillation was significantly decreased in the halothane, isoflurane, and the preconditioning groups. Despite extensive investigation, the mechanisms underlying volatile anesthetic-antiarrhythmic effects are not completely understood. Halothane may have both pro- and antiarrhythmic effects. The accumulation of $[\text{Ca}^{2+}]$, during ischemia and reperfusion may be an important contributing factor to arrhythmogenesis. At the cellular level, volatile anesthetics block the slow inward $\text{Ca}^{2+}$ current, abolish $\text{Ca}^{2+}$-dependent action potentials, decrease intracellular $\text{Ca}^{2+}$ transients, and decrease the amount of $\text{Ca}^{2+}$ available for release from the sarcoplasmic reticulum. Each of these actions can antagonize either abnormal automaticity or triggered activity. The mechanism by which preconditioning acts on arrhythmogenesis is still unknown. Washout of oxygen, blocking of hydrogen ion or other glycolytic products have been proposed as possible mechanisms of the preconditioning effect. Preconditioning has a well-documented capacity to limit proton accumulation during ischemia that would result in a reduction in the trans-sarcolemmal proton gradient after reperfusion. This appears to be very important in the genesis of reperfusion-induced arrhythmias, possibly as a consequence of limiting reperfusion-induced calcium loading. Oxygen free-radical formation by xanthine oxidase could be decreased if preconditioning allowed washout of hypoxanthine. Preconditioning with low-flow ischemia followed by total occlusion reduces ischemia-related arrhythmias by hastening the increase of extracellular potassium. Halothane, isoflurane, and preconditioning independently provide substantial protection against ischemia-reperfusion injury. This protective effect may have a common mechanism via the $K_{\text{ATP}}$ receptors, but this hypothesis requires further investigation. Our premise that inhalational anesthetics combined with ischemic preconditioning may provide greater protection than either one alone could not be proved. However, we did find better preservation of ATP content compared with preconditioning alone or treatment with halothane or isoflurane alone.

References

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