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Halothane Inhibits Calcium Accumulation Following Myocardial Ischemia and Calcium Paradox in Guinea Pig Hearts

Sumio Hoka, M.D., Zeljko J. Bosnjak, Ph.D.,† John P. Kampine, M.D., Ph.D.‡*

This study was performed to test the hypothesis that halothane inhibits calcium accumulation associated with myocardial ischemia and calcium paradox. Using a Langendorff preparation in isolated guinea pig hearts, tissue ^{45}Ca was measured after 40 and 60 min of loading with ^{45}Ca, followed by 20 min of washout period. Myocardial ischemia was produced by a 30-min occlusion of the left anterior descending coronary artery (LAD). LAD occlusion caused an increase in ^{45}Ca content in the anterior left ventricular muscle (ischemic area) of 215% compared to that of the posterior left ventricular muscle (normal myocardium). The increase in ^{45}Ca content in the ischemic area was significantly less ($P < 0.05$) in the presence of halothane (1%) compared to the non-halothane group. Halothane did not significantly alter ^{45}Ca content in the non-ischemic myocardium. Myocardial injury associated with calcium paradox, which was produced by a 10-min perfusion of the heart with calcium-free Krebs solution followed by normal calcium repletion, caused a significant increase ($P < 0.05$) in the ^{45}Ca content compared to control. Addition of halothane (1%) significantly depressed ($P < 0.05$) the increase in ^{45}Ca content caused by calcium paradox. It is suggested that halothane might inhibit calcium accumulation associated with myocardial ischemia and calcium paradox under certain experimental situations. The inhibitory effect of halothane on calcium accumulation may be beneficial for the ischemic heart during halothane anesthesia. (Key words: Anesthetics, volatile: halothane. Heart: coronary occlusion; myocardial ischemia. Ions, calcium: efflux; paradox; uptake.)

CALCIUM IONS PLAY a crucial role in the regulation of cardiac function.[1,2] Under various pathophysiological conditions, calcium movement is profoundly affected. For example, a massive entry of calcium into cells was observed when the heart was subjected to post-ischemic perfusion.[3,4] On reperfusion of ischemic myocardium, a rapid net gain of calcium occurs, particularly in the mitochondria, whose function has been impaired.[5,6] The extent in this calcium accumulation is related to the severity and duration of ischemia and the degree of mechanical recovery.[5,7]

Greatly augmented calcium accumulation is also produced when a calcium-containing solution is readmitted to the hearts after a period of calcium-free perfusion,[8–10] a phenomenon called "calcium paradox."[8] Myocardial injury associated with calcium paradox has also been linked to a sudden and massive influx of calcium into the cells upon calcium repletion.[9,10] The calcium accumulation associated with ischemia and calcium paradox has been shown to be due, in part, to increased influx, probably related, not to the gross disruption of the cell membrane, but to a specific abnormality of ionic channels.[7] Part of the total calcium influx into the myocardial cell is through the slow calcium channel of the cardiac action potential, and influx through this channel probably contributes to the calcium accumulation associated with ischemia and calcium paradox. Therefore, inhibition of slow channel calcium influx across the cell membrane of the myocardial cell is of potential benefit in reducing the severity of the cell damage.[11] It has been shown that halothane can depress the slow channel calcium influx and intracellular calcium transients.[12–15] The present study was performed to test the hypothesis that halothane inhibits the calcium accumulation associated with myocardial ischemia and calcium paradox.

Methods

Forty-one guinea pigs (350–550 g) were heparinized (500 IU) and killed by decapitation. The hearts were immediately removed and washed in cold oxygenated Krebs solution. The spontaneously beating hearts were then perfused at constant pressure (40 mmHg) using the Langendorff technique with a freshly prepared, modified Krebs solution (in mM): Na^+, 128; K^+, 5.9; Ca^{++}, 2.5; Mg^{++}, 1.2; Cl^-, 125; HCO_3^-, 15.5; HPO_4^{--}, 1.2; glucose, 11.5 and D-mannitol 16.4. Mannitol was added to reduce extravascular accumulation of fluid. Immediately after aortic cannulation, the pulmonary artery was cut, the left atrium was opened, and the mitral valve was cut. These procedures assured continued closure of the aortic valve so that the heart performed no external work. The fluid was equilibrated in a reservoir with a 97% O_2-3% CO_2 mixture, providing a P_{O_2} of over 400 mmHg and a pH of 7.40 ± 0.10. The perfusate was warmed by a thermostatically controlled heating coil adjacent to the cannula to maintain a constant temperature of 35° C. No correction was made for the osmolarity when calcium was omitted from the normal medium, since this change in osmolarity has been shown

* Visiting Research Professor of Anesthesiology.

† Associate Professor of Anesthesiology and Physiology.

‡ Professor of Anesthesiology and Physiology; Chairman, Department of Anesthesiology.

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Address reprint requests to Dr. Bosnjak: Research Service 151, VA Medical Center, Milwaukee, Wisconsin 53295.

to have no effect on the cardiac performance.[16] Coronary flow rates (flow rates of effluents) were assessed by measuring the effluent flow. In all experiments, preconditioning of the preparation involved a 20-min perfusion to wash out the red blood cells and to stabilize the heart rate and coronary flow.

Calcium accumulation into the myocardium was determined by measuring tissue ^{45}Ca (New England Nuclear) which was loaded for 40 or 60 min followed by a 20-min washout period. The loading solution included 0.5 μCi/ml of ^{45}Ca. At the end of each experiment, hearts were dismounted, and quickly dipped into an inactive Krebs solution to wash away superficially adherent radioactivity. Tissues (20–80 mg each) were removed, gently blotted, and weighed. Following overnight solubilization in NCS solution (tissue solubilizer, Amersham Corp.) at 55° C, tissue ^{45}Ca was determined using a liquid scintillation spectrometer (Packard Tri-Carb). ^{45}Ca content of the tissue was calculated as cpm/100 mg wet weight. The relative ^{45}Ca content of an individual preparation was expressed as tissue [^{45}Ca] divided by the loading solution [^{45}Ca] × 100.

Halothane (1%) was vaporized in a gas mixture (total flow > 3 l/min) using a Fluotec Mark III vaporizer. A dial setting of 1% produced a concentration of 0.40 mM in the Krebs solution measured using a gas chromatograph (Perkin-Elmer) with a flame ionization detector.[17]

Myocardial Ischemia

Seventeen hearts were used in this series of experiments (nine for the non-halothane group and eight for the halothane group). Regional myocardial ischemia was produced by occlusion of the left anterior descending (LAD) coronary artery at a point 2–4 mm from its origin for 30 min, using a modified technique developed by Selye *et al.*[18] The validity of this technique for temporary coronary occlusion and reperfusion was affirmed by adding a small amount of methylene blue in the preliminary experiments. ^{45}Ca was added to the perfusate 10 min before LAD occlusion, and through the reperfusion period of 20 min. Total loading time was 60 min. Halothane, when present, was added 10 min before the loading with ^{45}Ca and was present throughout reperfusion. After a 20-min washout period, tissues were removed from the left anterior wall of the left ventricle representing an ischemic region, and the posterior wall of the left ventricle representing a non-ischemic region.

Calcium Paradox

Nineteen hearts were used in this series of experiments (five for the control, eight for the calcium paradox without halothane, and six for the calcium paradox with halothane). The hearts were subjected to 10 min of calcium-free perfusion followed by calcium repletion. Loading of ^{45}Ca was started with calcium repletion for 40 min followed by a 20-min washout period. Halothane was added 10 min before the calcium-free perfusion and throughout the ^{45}Ca loading period. Tissue samples taken from the heart included right ventricle, left ventricle, and left ventricular papillary muscle.

Calcium Efflux

Calcium efflux was assessed by measuring the washout of ^{45}Ca after the loading period of 60 min in five guinea pig papillary muscle preparations.[19] The papillary muscle was superfused continuously at a rate of 10 ml/min with Krebs solution, as described previously.[14] The muscle was stimulated using a bipolar electrode at 0.5-s intervals. The effluents were collected in 1-min periods in a fraction collector during the 60 min after initiating washout. Each outflow fraction was weighed and radioactivity per 1 ml/min measured in liquid scintillation counter (0.5 ml of superfusate was added to 10 ml of Safty-Solve by RPI), and an efflux curve of the ^{45}Ca was made.

Statistics

Data were expressed as means ± standard error of the mean. The results of repeated measurements and multiple groups were analyzed by one-way analysis of variance. Multiple pairwise comparisons between groups were assessed by a Student's *t* test. Significance was considered at *P* value of less than 0.05.

Results

Myocardial Ischemia

Time courses of the heart rate and coronary flow in response to LAD occlusion are shown in figure 1. Baseline heart rates were 176 ± 5 beats/min in the non-halothane group and 174 ± 4 beats/min in the halothane group. Halothane (1%) caused a significant decrease in the heart rate as compared to the baseline value ($P < 0.05$), as well as the non-halothane group ($P < 0.05$). Baseline coronary flows were 1.76 ± 0.12 and 1.60 ± 0.04 ml/min per gram of tissue in non-halothane and halothane groups, respectively. Halothane caused a significant increase in coronary flow ($P < 0.05$). During the LAD occlusion, the coronary flow was significantly decreased in both groups ($P < 0.05$). Heart rate and coronary flow during the washout period were not significantly different between the two groups. Figure 2 shows relative ^{45}Ca content of anterior LV myocardium

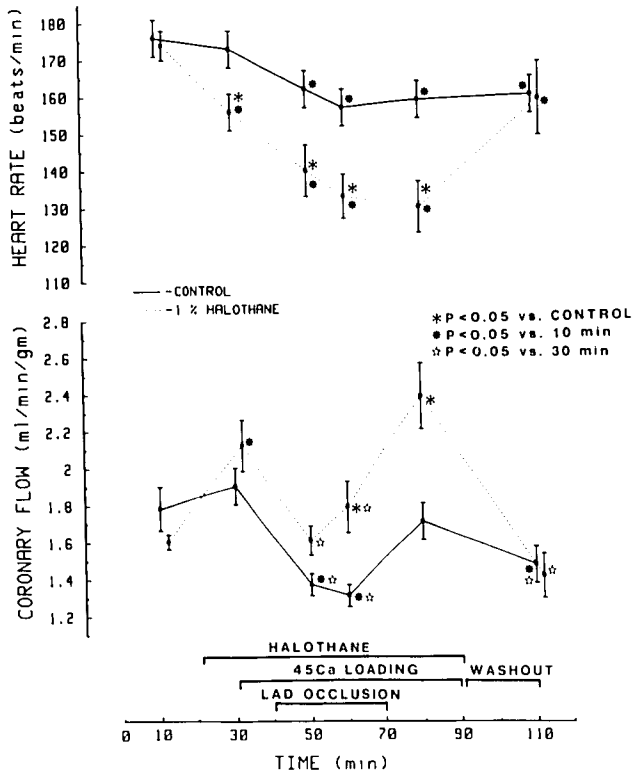

FIG. 1. Time course of the heart rate and coronary flow associated with the left anterior descending coronary artery (LAD) occlusion in the control (n = 9) and halothane (n = 8) groups. During LAD occlusion, the coronary flow was significantly decreased in both groups. Values are means ± SE.

(ischemic region) and posterior LV myocardium (normal, non-ischemic region) in the absence and presence of halothane. Ischemia increased the relative ^{45}Ca content by 215% ($P < 0.05$ *vs.* normal). The per cent change in the relative ^{45}Ca content in the anterior LV was significantly less ($P < 0.05$) in the presence of halothane as compared to that in the non-halothane group. There were no significant differences in the relative ^{45}Ca contents between normal groups (0% halothane *vs.* 1% halothane). These results indicate that halothane can depress calcium accumulation associated with myocardial ischemia.

Calcium Paradox

Time courses of the heart rate and coronary flow in response to calcium paradox (CP) are shown in figure 3. Baseline heart rates were 172 ± 4 beats/min in the control group (non-CP), 177 ± 7 beats/min in the CP group, and 179 ± 6 beats/min in the CP + Halothane (H) group. Halothane (1%) caused a significant decrease in the heart rate as compared to the baseline value ($P < 0.01$) and the control group ($P < 0.01$), as well as the

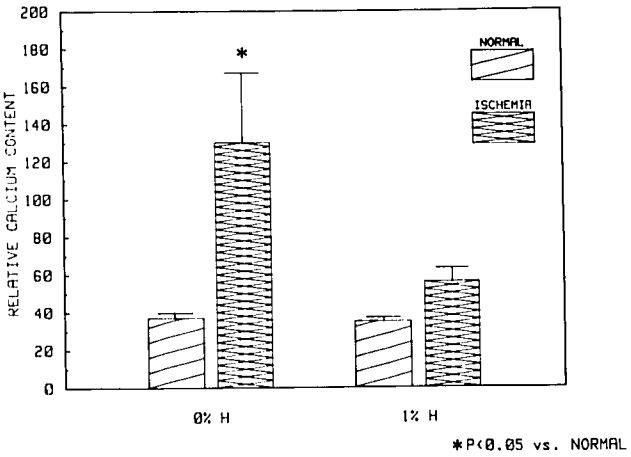

FIG. 2. Relative ^{45}Ca content in the anterior LV myocardium (ischemia) and posterior LV myocardium (normal) during the control (0% H, n = 9) and in the presence of halothane (1% H, n = 8). Ischemia increased relative ^{45}Ca content by 215% in the control group. Halothane depressed the increase of ^{45}Ca content in the ischemic preparations following 30 min LAD occlusion. Values are means ± SE.

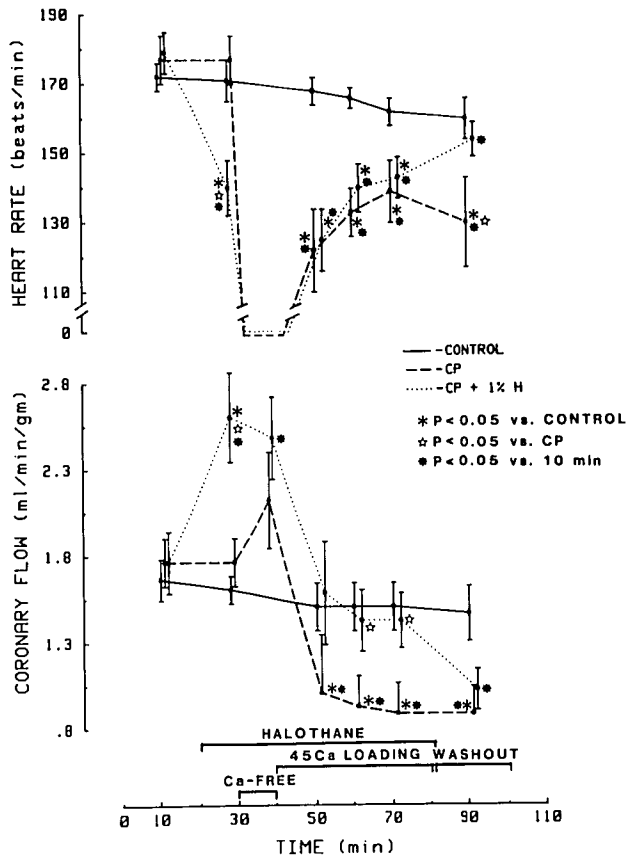

FIG. 3. Time course of the heart rate and coronary flow in the control hearts (CONTROL, n = 5), calcium paradox experiments (CP, n = 8), and calcium paradox in the presence of halothane (CP + 1% H, n = 6). During calcium-free perfusion, the heart ceased beating. Values are means ± SE.

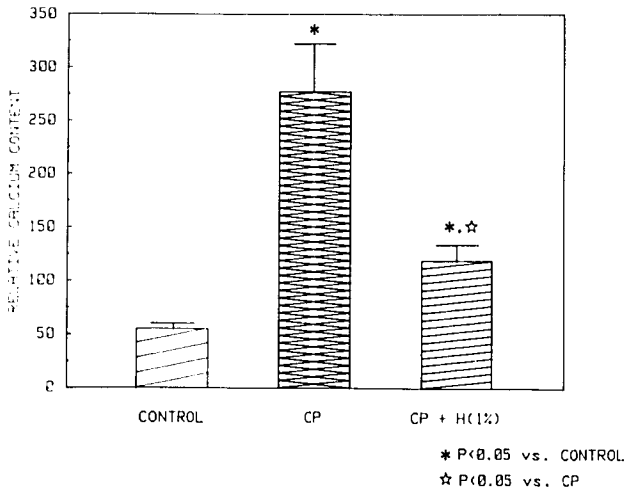

FIG. 4. Relative ^{45}Ca content in the control hearts (CONTROL n = 5), calcium paradox experiments (CP, n = 8), and calcium paradox in the presence of halothane (CP + 1% H, n = 6). CP increased ^{45}Ca content by 350% as compared to the control. Halothane depressed the increase in ^{45}Ca content caused by CP. Values are means ± SE.

CP group ($P < 0.01$). During the calcium-free perfusion, the hearts ceased beating. After initiating calcium repletion, heart rates gradually increased. Baseline coronary flows were 1.66 ± 0.12, 1.76 ± 0.14, and 1.76 ± 0.18 ml/min per gram tissue, in the control, CP, and CP + H groups, respectively. Halothane caused a significant increase in the coronary flow ($P < 0.01$). Calcium-free perfusion tended to increase the coronary flow in the CP group, but not in the CP + H group. Reperfusion with normal calcium medium caused a significant decrease in coronary flow both in CP and CP + H groups ($P < 0.01$). Figure 4 shows relative ^{45}Ca contents in all three groups. The relative ^{45}Ca contents in CP and CP + H groups were significantly greater ($P < 0.05$) than the control group. However, the relative ^{45}Ca content in the CP + H group was significantly less ($P < 0.05$) than the CP group. The results indicate that halothane can depress calcium accumulation associated with calcium paradox.

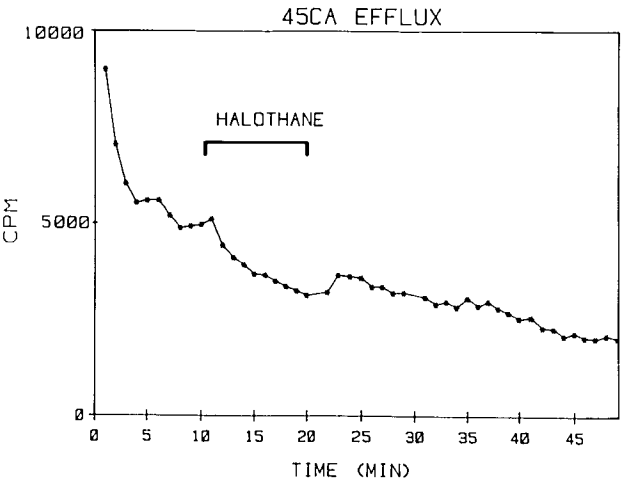

FIG. 5. Efflux of ^{45}Ca in a guinea pig papillary muscle preparation, in which halothane slightly decreased ^{45}Ca efflux. Halothane (1%) was given for 10 min, beginning 10 min after the start of the washout of ^{45}Ca. The half time of the final phase of the efflux curve was approximately 50 min.

EFFLUX OF ^{45}CA

Efflux of the ^{45}Ca was not greatly altered by halothane in four experiments. One experiment showed slight depression of ^{45}Ca efflux during halothane (1%) exposure for 10 min (fig. 5). The half time of the final phase of the efflux curve was approximately 50 min.

Discussion

The present study was designed to examine the effect of halothane on the alteration in calcium homeostasis. This is potentially important, since calcium ions play a prominent role in the cascade of events that terminate in irreversible injury in response to myocardial ischemia. The extent of the calcium accumulation is related to the severity, the duration, and the degree of myocardial recovery.[5,7] The present study showed that halothane depressed ^{45}Ca accumulation associated with myocardial ischemia and calcium paradox. These results suggest that halothane might have a protective effect on myocardial injury associated with ischemia and calcium paradox under certain experimental situations.

Several points should be addressed with respect to the methodology employed in this study. First, we adopted a low perfusion pressure of 40 mmHg using a Langendorff preparation, since it was reported that the severity of myocardial damage in the calcium paradox depends upon perfusion pressure and coronary flow rate.[20] Ohhara *et al.*[21] have shown that verapamil had a protective effect only on mild injury occurring at a perfusion pressure of 30 mmHg, but not on severe injury occurring at a perfusion pressure of 60 mmHg. Therefore, a low perfusion pressure of 40 mmHg was chosen here to produce a moderate myocardial damage instead of a complete and unprotectable damage. Accordingly, the observed protective effect of halothane may not directly apply to the condition of high perfusion pressure. Second, the changes in the tissue calcium content was assessed by means of ^{45}Ca after equilibration of the preparation with solution containing this isotope for 40 or 60 min. Since 60-min exposure to isotope did not result in an increase in the tissue ^{45}Ca content compared to the 40-min exposure (figs. 2, 4), equilibration appears to be complete. Therefore, changes in the tissue ^{45}Ca content

should be equivalent to the changes in the total Ca content. Third, single measurements of tissue ^{45}Ca were performed after 20 min washout, with the assumption that this part of ^{45}Ca efflux originates primarily from an intracellular compartment. This assumption was supported by Pytkowski *et al.*,[22] Lewartowski *et al.*,[23] and Shine *et al.*,[19] who indicated using a kinetic analysis of the ^{45}Ca efflux that any calcium arising from sites at the interstitial space and the rapidly exchangeable intracellular sources were eliminated at the time of 20 min, leaving a more permanently bound intracellular pool. Although it is not clear how the calcium efflux is modified after myocardial injury associated with ischemia and calcium paradox, it seems likely that the measured ^{45}Ca content represents the slowly exchangeable calcium compartment originating from the intracellular space. It has been shown that calcium accumulation occurred in the mitochondria after myocardial ischemia[5] and during reoxygenation after hypoxia.[24]

The decrease in myocardial ^{45}Ca accumulation by halothane can be explained in at least two ways; one is the inhibition of ^{45}Ca influx, and the other is the enhancement of ^{45}Ca efflux. It may be possible that, if a flow rate was greater in the halothane group than the non-halothane group, ^{45}Ca efflux could be increased in the former group. This seems unlikely, however, since the flow rates were not significantly different between these two groups during the washout period (fig. 1). In addition, in the efflux study, halothane did not significantly change the ^{45}Ca efflux rate, and, in one experiment, a slight decrease in the effluent curve was observed (fig. 5). Therefore, it seems unlikely that halothane enhances ^{45}Ca efflux during calcium accumulation. On the other hand, the decrease in ^{45}Ca accumulation by halothane may be due to the inhibition of ^{45}Ca influx.

The mechanism by which halothane could inhibit the augmented ^{45}Ca influx associated with myocardial ischemia and calcium paradox is not clear. It has been shown that halothane can inhibit slow channel calcium influx.[12-15] This may, in part, contribute to the depression of the calcium accumulation, since the slow calcium channel is thought to be one of the major pathways for calcium accumulation.[5,11]

^{45}Ca accumulation in non-ischemic tissue was not different between halothane and non-halothane groups (fig. 2), suggesting that total ^{45}Ca uptake over time is not altered by halothane in a normal beating heart. This is consistent with the results of Porsius and Zwieten,[25] who found that halothane changed the rate of ^{45}Ca uptake but did not alter total ^{45}Ca uptake in guinea pig atria.

The alteration of coronary flow produced by halothane may favor the inhibition of calcium accumulation with myocardial ischemia. Halothane increased coronary flow (fig. 1). During LAD occlusion, the coronary flow decreased by 0.53 ± 0.18 ml/min per gram in the halothane group, and by 0.53 ± 0.08 ml/min per gram in the non-halothane group. Although these values are similar, the amount of coronary flow reduction may not necessarily reflect a similar extent of ischemia, since there may be a difference in the extent of blood supply to the tissue as well as oxygen demand of the tissue between these two groups. Actually, the coronary flow rate during LAD occlusion was not altered in the halothane group when compared to the value before halothane administration. It has been shown that halothane improved myocardial perfusion and oxygenation.[26,27] Verrier *et al.*[27] have shown that halothane increased the coronary vascular reserve, suggesting a possible increase in myocardial oxygen supply in the ischemic heart. Therefore, it seems likely that the decrease in calcium accumulation by halothane might be due in part to the increase in oxygen supply during LAD occlusion.

On the other hand, the increase in coronary flow does not necessarily favor decreased calcium accumulation with the calcium paradox. It has been shown that the higher coronary flow during calcium-free perfusion resulted in a more severe myocardial damage due to a greater calcium accumulation.[20,21] Accordingly, it seems unlikely that the protective effect of halothane on calcium accumulation associated with calcium paradox is due to the increased coronary flow by halothane.

Calcium accumulation could be a primary event leading to cell necrosis in myocardial ischemia and calcium paradox, or the result of damage, or the secondary consequence of lack of tissue ATP to maintain normal calcium homeostasis mechanisms. Therefore, we suggest that halothane is beneficial to an ischemic heart not only because calcium influx is directly inhibited, but also because of its cardiodepressant effect. The reduction in developed tension,[28,29] heart work, and the rate of ATP consumption[30] prevent as rapid a decline of ATP at the onset of ischemia as that which occurs in a non-depressed heart, so that ATP is available to maintain cellular integrity. The inhibitory effect of halothane on superoxide production,[31] which may lead ultimately to a loss of membrane integrity,[32] can also favor the preservation of the ischemic heart by halothane.

In conclusion, the present study indicates that halothane may inhibit calcium accumulation associated with myocardial ischemia and calcium paradox. Since this study was undertaken *in vitro* with the condition of constant perfusion pressure which may be decreased by halothane anesthesia *in vivo*, the results of this study do not directly implicate the clinical benefit of halothane anesthesia to patients who have myocardial injuries.

However, the effect of halothane on calcium accumulation may, under certain conditions, be able to contribute to the preservation of myocardial function.

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