Myocardial ischaemic/ reperfusion injury in the anaesthetized rabbit: comparative effects of halothane and isoflurane

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The effects of halothane and isoflurane anaesthesia on myocardial injury in rabbits subjected to coronary artery ligation and subsequent reperfusion were analyzed. Although halothane and isoflurane (at inspired concentrations of 1.0 and 1.5 per cent, respectively) exerted comparable effects on cardiovascular status during ischaemic and reperfusion phases, greater preservation of subcellular integrity (as assessed by mitochondrial and sarcoplasmic reticular ATPase activities and myocardial ionic alterations) and a lower incidence of ventricular fibrillation and severe hypotension occurred with halothane. Our results indicate that in studies of experimental myocardial ischaemia anaesthetics may, independently of cardiovascular actions, influence the nature and extent of resulting injury, possibly by virtue of their differing effects on subcellular membrane systems.

Key words
MYOCARDIUM: ischaemic/reperfusion injury; ANAESTHETICS, VOLATILE: halothane, isoflurane; BIOCHEMISTRY: subcellular enzyme alterations, ionic compositional changes.

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Acute myocardial ischaemia initiates a complex series of initially reversible and, subsequently, irreversible processes of cellular injury[1] which may continue for some time after the acute episode. It is clear from the extensive literature on experimental myocardial infarction that cellular membrane alternations are a characteristic feature of tissue damage[2–3] and that substances with membrane-active properties are able to limit the extent of necrosis.[4–6]

A major uncertainty in most animal models of acute myocardial infarction relates to the use of anaesthetics (frequently pentobarbitone) whose influence on ischaemia-induced membrane alterations has not been systematically investigated. The direct interaction of general anaesthetics with membrane components[7–9] and their effects on cellular metabolism, myocardial function, and peripheral and coronary vasculature may all modify the extent of myocardial ischaemic injury.

The use of barbiturate anaesthesia in studies of experimental myocardial ischaemia introduces interpretational complexities not only because of the ability of the barbiturates to modify the electrical properties of the myocardium following coronary artery ligation.[10] They have been shown to have protective effects against ischaemia-related damage in several tissues[11,12] including the myocardium,[13,14] but, on the other hand, a recent study by Au *et al.*[15] has shown that in rats subjected to coronary artery ligation under halothane, meperidine or pentobarbitone anaesthesia, the incidence of arrhythmias and

mortality was greatest in the pentobarbitone-treated animals.

It seems likely, then, that anaesthetics are able to influence, to differing degrees, the course of myocardial ischaemic injury, probably as the result of a complex interplay between effects on the cardiovascular system and subcellular alterations at the membrane level. In the present study, we have examined the effects of halothane and isoflurane, two clinically useful inhalational agents with different cardiovascular actions, on the characteristics of myocardial ischaemic/reperfusion injury in rabbits subjected to a 40-min period of ischaemia induced by coronary artery ligation followed by 60 min of reperfusion. A multi-level approach has been utilized wherein the effects of ischaemia and reperfusion were analyzed in terms of alterations in myocardial functon and in biochemical and chemical properties. The results obtained were compared with those we have previously found using pentobarbitone anaesthesia in the same experimental model system.[6]

Methods

Unpremedicated male New Zealand white rabbits weighing between 2–3 kg were anaesthetized with either halothane or isoflurane in oxygen, orally intubated and mechanically ventilated. A Dräger Halothan vaporizer was used to administer both anaesthetic agents. This was felt to be acceptable because of their similarities in vapour pressures, but, to minimize cross-contamination, halothane-treated animals preceded and followed isoflurane-treated animals; for each drug, however, the experimental groups (control, ischaemic and ischaemic/reperfused) were randomized.

Following intubation, needle electrodes were placed for continuous monitoring of the electrocardiogram. An intravenous route for administration of saline was established in a marginal ear vein and the left carotid artery was exposed and cannulated for measurement of arterial pressure using a Statham P23ID transducer connected to a Grass polygraph (model 7 PCPB). A median sternotomy was then performed and a ligature/occluder placed loosely around the major marginal branch of the circumflex coronary artery. A Jelco 20-gauge catheter connected to a Statham pressure transducer was inserted into the left ventricle via the apex and the left ventricular signal together with its differentiated form was recorded using a Grass model 7 P2OC differentiator. When these surgical manipulations had been completed, the inspired concentrations of halothane or isoflurane were reduced to 1.0 and 1.5 per cent, respectively (by dial setting) – concentrations found to just prevent spontaneous movement in all animals. These inspired concentrations were utilized for the remainder of the experiment. The animals rested for at least 15 min before any subsequent procedures were undertaken.

Twenty-six rabbits then underwent 40 min of myocardial ischaemia (induced by tightening the coronary artery occluder) under halothane anaesthesia and half of these underwent subsequent reperfusion (by loosening the ligature) for 60 min. Previous work utilizing microspheres to measure blood flow showed that tightening of the coronary artery occluder in this fashion reduced coronary blood flow to less than five per cent of baseline, while release of the occluder restored flow. Twenty animals were treated similarly under isoflurane anaesthesia of which ten underwent subsequent reperfusion. Sham-operated controls ($n = 8$) were included in each anaesthetic group. Ventricular fibrillation was treated with internal electrical cardioversion and cardiac massage was employed if the systolic blood pressure dropped to below 25 mmHg.

At the conclusion of the experiment (i.e., after 40 min of ischaemia or 40 min of ischaemia with 60 min of reperfusion), the heart was excised and dropped into ice-cold isotonic sucrose. The ligature was tightened for the sham-operated and reperfused samples and the occluded zone identified by lack of blanching following perfusion of the heart with cold isotonic sucrose via the aortic root. Subendocardial tissue samples were taken for ion and ATP analyses, and the remainder of the myocardial tissue was homogenized and fractionated for ATPase marker enzyme analysis. All of these chemical and biochemical characterization procedures have been described in a previous publication.[6]

Statistical analysis

The experimental data were subjected to an analysis of variance and specific group differences were determined using a standardized Tukey's test at a significance level of $p < 0.05$. Chi-squared analysis was applied to the haemodynamic and electrocardiographic data, also at a significance level of $p <$

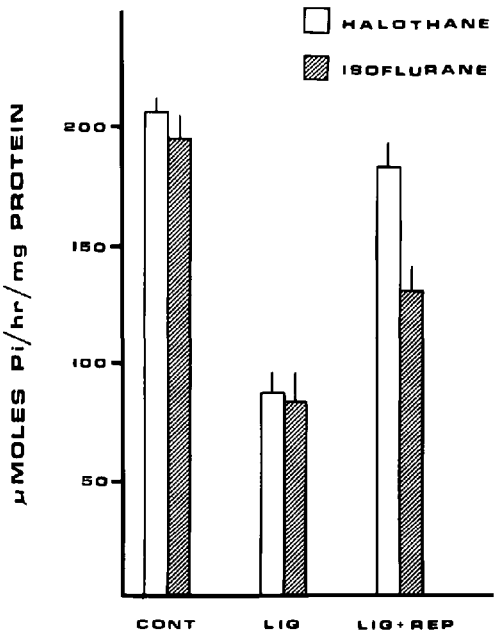

FIGURE 1 Mitochondrial ATPase activities in halothane- and isoflurane-anaesthetized control (cont) rabbits, in animals subjected to 40 min of coronary artery ligation without (lig) or with (lig + rep) subsequent reperfusion for 60 min. (All values are given as mean ± SEM. Numbers of animals in cont, lig and lig + rep groups were 8, 9 and 10, respectively, for halothane and 8, 10 and 10 for isoflurane.)

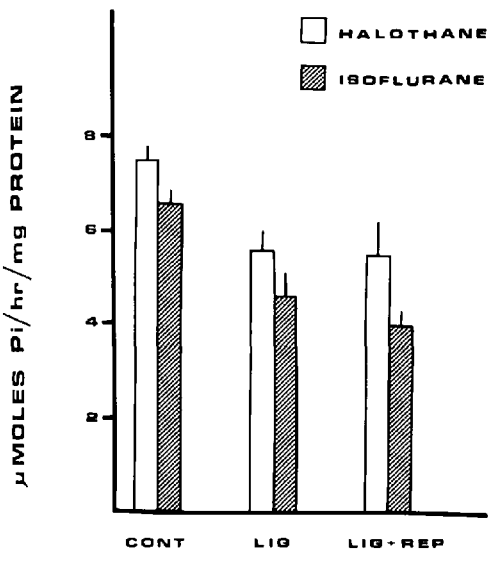

FIGURE 2 Sarcolemmal ATPase activities in halothane- and isoflurane-anaesthetized control, coronary ligated and coronary ligated/reperfused rabbits. (Experimental conditions and abbreviations as in Figure 1.)

0.05. All values are expressed as mean ± standard error. Discrepancies between total numbers of animals used and the numbers reported for biochemical and chemical analyses are due to loss of tissue specimens or errors in the analytical procedures.

Results

The isolated occluded zones, comprising 30–40 per cent of the left ventricular weight, were not significantly different in the two anaesthetic groups and were comparable in magnitude to those observed previously using pentobarbitone as the anaesthetizing agent.[6] Oesophageal temperature dropped by approximately 3° C from baseline by the end of the ligation period, and approximately another 1° C by the end of reperfusion. Again, there were no significant differences between the two inhalational anaesthetics. Estimated blood losses and fluid replacements did not differ significantly for both anaesthetic groups.

Biochemical measurements

Alterations in the integrity of subcellular organelles following ischaemia and reperfusion were analyzed in terms of changes in the activity of specific marker enzymes. Mitochondrial ATPase activity was reduced to approximately 40 per cent of control with both anaesthetics following 40 min of ischaemia. With subsequent reperfusion (60 min) ATPase activity was restored to a value not significantly different from control in the case of halothane but remained significantly depressed ($p < 0.05$) in the isoflurane-treated animals (Figure 1). The sarcolemmal Na^+,K^+-stimulated ATPase exhibited a decrease of approximately 25 per cent relative to control with both anaesthetics during the ischaemic phase and no reversal of this inhibition was apparent with either anaesthetic during reperfusion, reperfusion values being significantly ($p < 0.05$) lower than controls (Figure 2). The Ca^{2+},K^+-dependent ATPase activity of the sarcoplasmic reticulum had

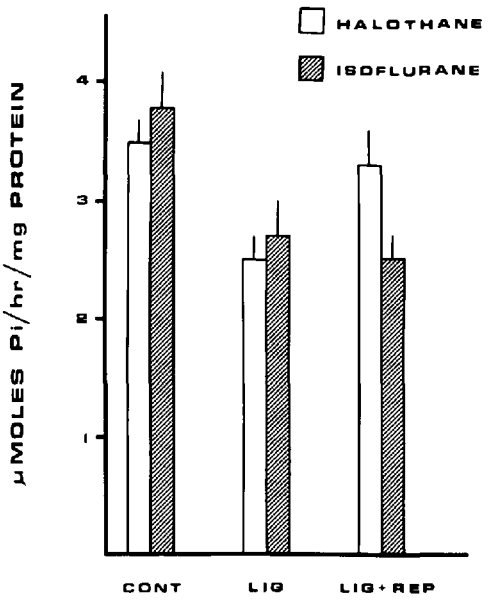

FIGURE 3 Sarcoplasmic reticulum ATPase activities in halothane- and isoflurane-anaesthetized control, coronary ligated and coronary ligated/reperfused rabbits. (Experimental conditions and abbreviations as in Figure 1, except that n = 7 in the control isoflurane group.)

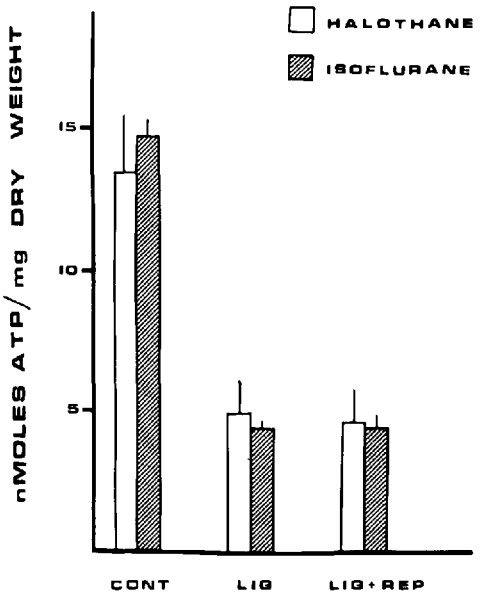

FIGURE 4 Myocardial ATP levels in halothane- and isoflurane-anaesthetized control, coronary ligated and coronary ligated/reperfused rabbits. (Experimental conditions and abbreviations as in Figure 1, except that numbers of animals in cont, lig and lig + rep groups were 8, 11 and 11, respectively, for halothane and 6, 9 and 10 for isoflurane.)

fallen to approximately 70 per cent of control independently of the anaesthetic employed by the end of the ischaemic period but upon reperfusion recovery was apparent in the halothane-anaesthetized animals (activity did not differ significantly from control), whereas the activity of this enzyme showed a further small decrease in the isoflurane group (Figure 3).

Chemical analyses

Tissue ATP content decreased to approximately 30 per cent of control during ischaemia and no restoration was observed with either anaesthetic on reperfusion (Figure 4). Although the levels of major cations in whole myocardial tisue did not change during the ischaemic period, in both experimental groups reperfusion was associated with significant ($p < 0.05$) increases in tissue Na (greater for isoflurane than halothane) and Ca levels; in isoflurane-anaesthetized animals significant decreases ($p < 0.05$) in K and Mg were also present after reperfusion (Table I).

Cardiovascular changes

Preligation systolic blood pressure was significantly higher ($p < 0.05$) in isoflurane-anaesthetized animals, although diastolic blood pressures did not differ significantly between the two groups. Ligation produced approximately 35 per cent reduction in systolic and diastolic pressures with isoflurane as compared with a 25 per cent reduction with halothane (Figure 5). Pressures after ligation in the two groups did not differ significantly and there was no change with either anaesthetic during reperfusion (Figure 5). As with systolic pressure, left ventricular contractility (assessed indirectly by dP/dt_{max}) prior to ligation was also higher ($p < 0.05$) in the isoflurane-anaesthetized animals and there was a greater decline in dP/dt_{max} upon ligation with isoflurane (47 per cent) as compared with halothane (32 per cent), both being statistically significant ($p < 0.05$). However, contractilities after ligation or reperfusion were not significantly different (Figure 6). Variations in heart rate under control or

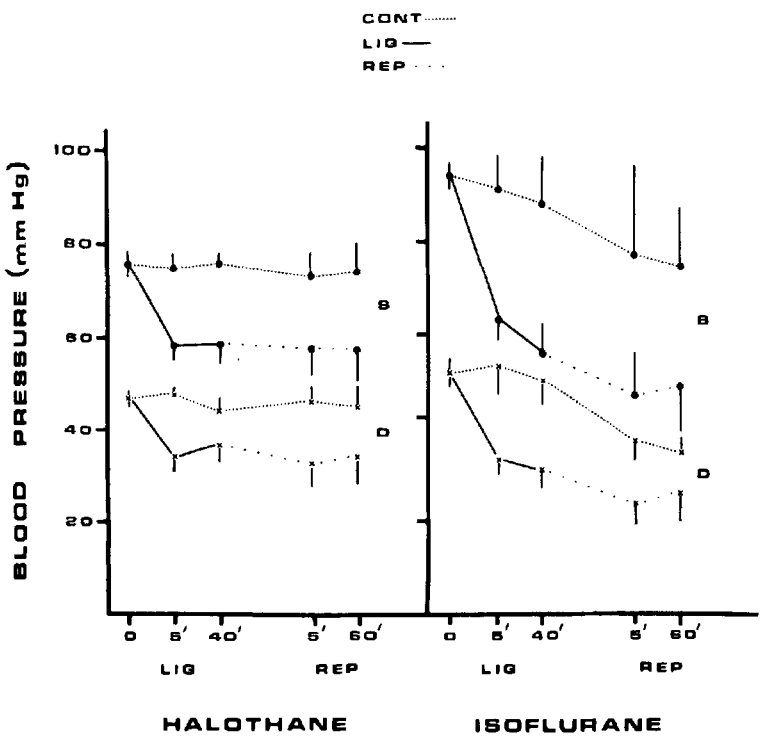

FIGURE 5 Systolic (S) and diastolic (D) blood pressure changes during ligation (lig) and reperfusion (rep) phases in halothane- and isoflurane-anaesthetized rabbits. (Experimental conditions as described in Figure 1.)

TABLE I Cation contents (ng atoms/mg dry weight) of intact myocardial tissue samples from control (CON), ischaemic (ISCH) and ischaemic/reperfused, (REP) hearts of rabbits anaesthetized with halothane or isoflurane

Drug	*n*	*Na*	*K*	*Mg*	*Ca*
Halothane					
CON	8	180 ± 11	336 ± 8	30 ± 0.5	7.4 ± 0.8
ISCH	13	209 ± 11	347 ± 13	29 ± 0.8	5.6 ± 0.5
REP	11	347 ± 38*	291 ± 24	26 ± 2.5	22.3 ± 5.6*
Isoflurane					
CON	8	185 ± 10	381 ± 13	30 ± 0.7	5.8 ± 0.4
ISCH	8	230 ± 31	322 ± 24	28 ± 1.4	6.6 ± 1.0
REP	10	466 ± 31*†	273 ± 15*	22 ± 1.0*	23.9 ± 4.0*

All values are given as mean ± SEM.
*$P < 0.05$, relative to control.
†$P < 0.05$, between halothane and isoflurane.

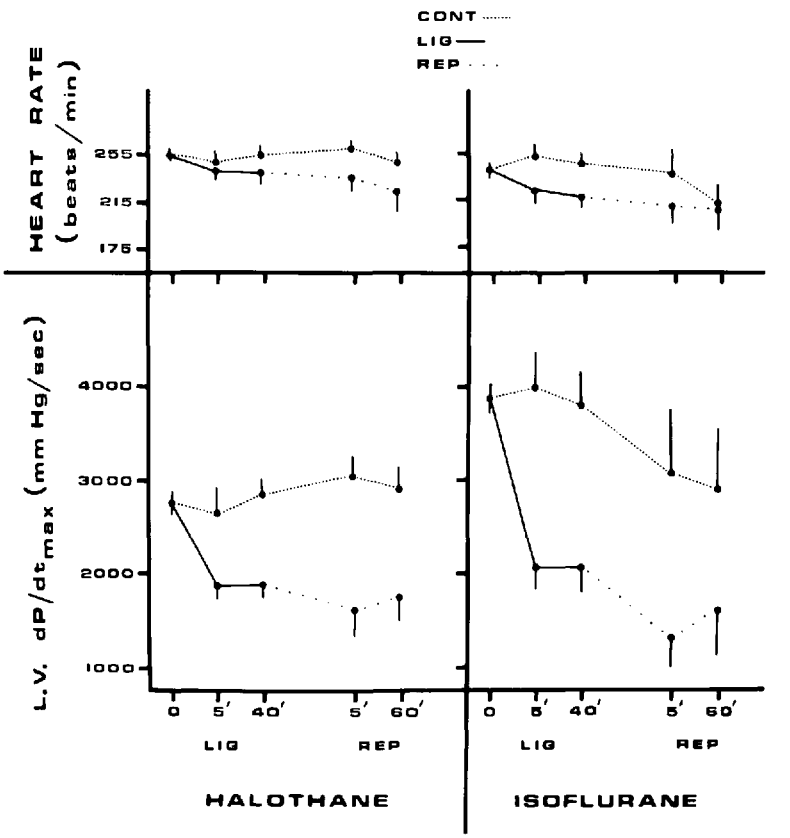

FIGURE 6 Heart rate and left ventricular contractility changes during ligation (lig) and reperfusion (rep) phases in halothane- and isoflurane-anaesthetized rabbits. (Experimental conditions as described in Figure 1.)

TABLE II Incidence of ventricular fibrillation and severe hypotension (systolic bp less than 25 mmHg) during ischaemia and reperfusion in rabbits anaesthetized with halothane or isoflurane

Drug	*Ischaemic phase*	*Reperfusion phase*
Ventricular fibrillation		
Halothane	42% (11/26)	38% (5/13)
Isoflurane	70% (14/20)	30% (3/10)
Severe hypotension		
Halothane	15% (4/26)	31% (4/13)
Isoflurane	25% (5/20)	40% (4/10)

Data are expressed as percentage of the animals showing the abnormality in question.

ischaemic/reperfusion conditions were small and did not differ between the two experimental groups (Figure 6).

The isoflurane group, when compared with the halothane-treated animals, showed a higher incidence of ischaemia-induced ventricular fibrillation, of severe hypotension (systolic pressure less than 25 mmHg, and requiring mechanical support) and of Q-wave appearance (Table II). Although these differences did not attain statistical significance, all are consistent with the indications from our chemical and biochemical studies that halothane affords greater protection to the myocardium from the effects of ischaemia than isoflurane.

Discussion

The present study has compared the influence of two inhalational anaesthetics on the nature and extent of myocardial ischaemic/reperfusion injury following coronary artery ligation in the rabbit. Although the results found with the two inhalational agents were qualitatively similar and parallelled those we have previously reported using pentobarbitone anaesthesia in the same experimental model,[3,6] a number of noteworthy differences were found. By several different criteria, halothane anaesthesia was associated with a lower degree of myocardial damage following 40 min of ischaemia and 60 min of reperfusion than was the case with isoflurane or pentobarbitone. When compared with halothane, isoflurane was associated with less recovery of both mitochondrial and sarcoplasmic reticular ATPase activities on reperfusion, greater alterations in myocardial tissue ions with reperfusion and a consistently higher incidence of cardiac electrical abnormalities and severe hypotension. However, both inhalational anaesthetics led to greater preservations of ATP levels, sarcolemmal ATPase activity and myocardial ionic composition than we have previously noted following coronary artery ligation and reperfusion in rabbits anaesthetized with pentobarbitone.[6]

The ability of halothane to diminish the adverse consequences of myocardial ischaemia has been demonstrated in a number of experimental systems. Halothane was found to decrease ST segment elevation following coronary artery ligation in dogs[16,17] and this effect did not appear to be explainable in terms of haemodynamic alterations.[17] Our results also suggest that the superior protection afforded by halothane as compared with isoflurane is probably not due primarily to differences in haemodynamic status during ischaemia. It has been shown that inhalation of one per cent halothane is able to increase the ratio of oxygen availability/oxygen consumption in a canine model of acute myocardial ischaemia.[14] While this observation may be suggestive of possible alterations in regional blood flow, halothane, when tested under conditions associated with a significant reduction in infarct size in dogs subjected to 30 min of coronary artery ligation, did not detectably alter the endocardial/epicardial flow ratio in the region of ischaemia.[18]

The protective effects of halothane do not appear to necessarily involve a reduction in infarct size. Studies by MacLeod *et al.* in rats have shown that the administration of one per cent halothane beginning 30 min before and for 4 h following coronary artery ligation significantly decreased mortality and electrocardiographic abnormalities relative to conscious or fentanyl-treated animals, without producing any measureable change in occluded or infarcted zones.[19] Indeed, there are reports that halothane under certain conditions may actually increase infarct size,[20] possibly as the result of adverse haemodynamic effects. We have compared the actions of halothane and isoflurane at minimal anaesthetic concentrations which resulted in comparable blood pressure and dP/dt_{max} during ischaemic and reperfusion phases. Our results, therefore, suggest than an important consideration determining the superiority of halothane over a number of other anaesthetics, including pentobarbitone, meperidine and ketamine[15,21] in different models of ischaemic injury, and over isoflurane in the present study may ultimately relate to an inherently greater capacity of halothane to preserve the integrity of sarcolemmal, mitochondrial and sarcoplasmic reticular membrane systems under conditions of ischaemia and subsequent reperfusion.

The disruption of cellular membranes is known to be a critical process determining the onset of irreversible ischaemic injury. Anaesthetics share in common the ability to interact with and perturb biological membranes as manifested, for example, in the stabilization of erythrocytes against hypotonic lysis at concentrations parallelling those producing anaesthesia.[22] Experiments in our laboratory have shown that the red cell membrane perturbational characteristics of various anaesthetic agents, when tested at concentrations producing comparable degrees of antihaemolysis, are critically dependent on the chemical structure of the molecule in question.[8,9,23] Studies of the *in vitro* effects of halothane, ether and chloroform on the behaviour of myocardial sarcolemmal, mitochondrial and myofibrillar ATPases have revealed a complex pattern of stimulatory and inhibitory actions which vary with the agent and the membrane involved.[24,25]

General anaesthetics are known to be capable of modifying the functional properties of mitochondria at anaesthetic concentrations, with electron transport being particularly susceptible.[26,27] In our

present study, cellular levels of ATP in control rabbits anaesthetized with halothane or isoflurane were equivalent and comparable to those previously found in pentobarbitone-anaesthetized animals.[6] Myocardial ATP content following 40 min of ischaemia decreased to approximately 30 per cent of control values with all three agents. In contrast to the further decrease in ATP levels (by approximately 15 per cent) upon reperfusion previously observed in pentobarbitone-anaesthetized animals,[3] no further decline was detected with either halothane or isoflurane. This suggests a protective action of inhalational anaesthetics on some ATP-consuming process occurring during reperfusion. One likely possibility would involve ATP hydrolysis to energize the intracellular sequestration and/or extrusion of calcium, whose increased accumulation during reperfusion has been implicated in the mechanism of ischaemic/reperfusion injury. Myocardial calcium levels following 40 min of ischaemia and 60 min of reperfusion were approximately two-fold greater in rabbits anaesthetized with pentobarbitone[6] as compared with halothane or isoflurane anaesthesia. This difference also suggests that anaesthetic interactions at the level of the sarcolemmal membrane (thus resulting in decreased calcium influx) may be crucial in determining their influence on the course of ischaemic/reperfusion injury. Greater preservation of sarcolemmal integrity by the inhalational anaesthetics is also apparent in the lesser degree of inactivation of sarcolemmal Na^+,K^+-ATPase following ischaemia and reperfusion than we have previously found with pentobarbital.[6]

It may well be, then, that sarcolemmal alterations induced by various pharmacological agents, including anaesthetics, are capable of modifying the course of myocardial ischaemic/reperfusion injury. However, the present findings indicate that the superior protective effects of halothane as observed here and in other experimental studies[15–17,19,21] are not so readily accounted for on this basis. Halothane and isoflurane exerted comparable effects on two indices of sarcolemmal integrity, namely sarcolemmal Na^+,K^+-ATPase activity and myocardial calcium levels, although isoflurane-treated animals did show a significantly greater level of myocardial sodium, suggesting a lower degree of sarcolemmal stabilization. Halothane's greater preservation of mitochondrial and sarcoplasmic reticular ATPase activities during reperfusion indicates that effects of anaesthetics on subcellular organelles may also be crucial in determining their ability to modify the susceptibility of the myocardium to ischaemic/reperfusion injury.

In summary, the results obtained here emphasize that the nature of the anaesthetic used in experimental investigations of myocardial ischaemia may influence, independently of alterations in cardiovascular status, the severity of cellular damage incurred. In particular, biochemical abnormalities are less marked with the two inhalational agents examined than with pentobarbitone, which is commonly employed in animal models of acute myocardial infarction. It is not fully known to what extent the superior protective actions of halothane observed here and in studies by others would be of clinical advantage in patients at risk of developing perioperative myocardial ischaemic injury, although this would seem to warrant more detailed investigation. However, considerable caution must be exercised in extrapolating the results of experiments on acute myocardial infarction in anaesthetized animals, particularly when pentobarbitone is used, to the clinical situation in man.

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Résumé

Les effets de l'anesthésie à l'halothane et l'isoflurane sur les lésions myocardiques chez les lapins ayant subi une ligature d'une artère coronaire et subséquemment reperfusé ont été analysés. Même si l'halothane et l'isoflurane (des concentrations inspirées de 1.0 et 1.5 pour cent respectivement) ont présenté des effets cardiovasculaires comparables durant l'ischémie et la reperfusion, on observa une plus grande préservation de l'intégrité des structures cellulaires (évalué par des altérations des mitochondries et de l'activité de la ATPase du reticulum sarcoplasmique ainsi que des altérations ioniques du myocarde) avec l'halothane. On observa aussi une incidence plus basse de fibrillation ventriculaire et d'hypotension sévère avec l'halothane. Nos résultats indiquent que lors d'études expérimentales sur l'ischémie myocardique, les agents anesthésiques peuvent indépendamment de leurs actions cardiovasculaires influencer la nature et l'étendue des lésions crées possiblement en vertue de leurs effets différents sur le système des membranes intra-cellulaires.