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Effects of Inhalation Anesthetics on Cardiac Function and Metabolism after Coronary Ligation in the Isolated Rat Heart

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Abstract and key words

We have evaluated the cardiac effects of inhalation anesthetics on the isolated perfused rat heart after coronary ligation. An isolated rat heart-lung preparation was used. Forty-nine male Wistar rats weighing 300-320g were randomly divided into five groups. All rats except in the control group (they were anesthetized with isoflurane) were anesthetized with each inhalation anesthetic during the preparation and they received no inhalation anesthetic (control), 1 % halothane, 2.2 % enflurane, 1.4 % isoflurane or 2.5 % sevoflurane during the perfusion. The heart was perfused initially at a cardiac output of 30 ml/min and a mean arterial pressure of 70 mmHg. Eight min after the start of perfusion, the left anterior descending coronary artery was ligated. Thirty min after the perfusion, the heart was divided into infarcted and non-infarcted parts and freeze-dried for 6 days. Halothane and enflurane decreased systolic blood pressure significantly when compared with the control after coronary ligation. However, only enflurane reduced cardiac output after coronary ligation. In all groups, myocardial ATP levels in infarcted parts were significantly lower than those in non-infarcted parts. In addition, myocardial ADP, AMP and lactate levels in infarcted parts were significantly higher than those in non-infarcted parts. However, there were no significant differences in high energy phosphates and lactate levels among the groups. Enflurane produced lower blood pressures and lower cardiac output than those seen in the control and other anesthetic agents. Attention should be paid when a patient with ischemic heart disease is anesthetized with enflurane. However, any inhalation anesthetics examined in the present study did not influence the myocardial metabolism.

Key words : Cardiac metabolism, Inhalation anesthetics, Myocardial infarction.

Introduction

Hypoxic coronary perfusion and the sudden onset of myocardial infarction can occur during the course of general anesthesia. Despite many studies of the effects of inhalation anesthetics on the outcome of experimental or clinical myocardial infarction, there is still controversy regarding the relative merits of these anesthetics for patients with coronary artery disease. Several previous investigations have demonstrated that inhalation anesthetics exert cardioprotective effects during myocardial ischemia and reperfusion[1~6]. On the other hand, it has been suggested that these agents may cause coronary steal and lead to exacerbation of myocardial ischemia in patients with coronary artery disease undergoing inhalational anesthesia[7].

The present study was designed to evaluate the cardiac effects of inhalation anesthetics on the isolated perfused rat heart during coronary ligation. This experiment explores the question of whether the choice of anesthetic can influence cardiac function and myocardial metabolism after coronary ligation.

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Materials and Methods

This study was approved by the animal care committee of Yamanashi Medical University. The techniques used were almost identical to those used in an earlier study[8]. Briefly, 49 male Wistar ST rats (300-320g) were randomly divided into 5 groups as follows. 1. Control (C) group (n=10); they received no drugs. 2. Halothane (H) group (n=10); they received 1 % halothane. 3. Enflurane (E) group (n=10); they received 2.2 % enflurane. 4. Isoflurane (I) group (n=9); they received 1.4 % isoflurane. 5. Sevoflurane (S) group (n=10); they received 2.5 % sevoflurane. These were the inspired concentrations that achieved MAC for that agent in rats[9~11]. All rats except in the C group were anesthetized with each inhalation anesthetic in each group. Animals in the C group were anesthetized with isoflurane during the preparation. Tracheotomy was performed, and intermittent positive pressure ventilation was adjusted to maintain $Paco_2$ at 4.7-5.3 kPa and Pao_2 at 40-53 kPa with a 95% O_2+5 % CO_2 gas mixture. The chest was opened and flooded with ice-cold saline and the heart arrested. Cannulas were inserted into the aorta and the superior and inferior venae cavae. The cannula in the superior vena cava was used for the monitor of right atrial pressure.

The heart lung preparation was perfused with a solution containing red blood cells collected from another rat and Krebs-Ringer bicarbonate buffer, with hematocrit and pH of 25 % and 7.4, respectively. The concentrations (mM) of the buffer constituents were: NaCl 127, KCl 5.1, $CaCl_2$ 2.2, KH_2PO_4 1.3, $MgSO_4$ 2.6, $NaHCO_3$ 15, glucose 5.5 and heparin. The perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir kept at 37℃ and then returned to the inferior vena cava. In this model, no other organs except heart and lung were perfused, cardiac output was determined by the inflow as long as the heart did not fail, and mean arterial pressure was regulated by the pneumatic resistance.

Heart rate was recorded with a bioelectric amplifier (AB-621G, Nihonkohden, Japan) and cardiac output was measured with an electromagnetic blood flow meter (MFV-1200, Nihonkohden, Japan). Arterial pressure and right atrial pressure were measured with transducers (TP101T and LPU-0.1A, Nihonkohden, Japan) and carrier amplifiers (AP-601G, Nihonkohden, Japan).

After the preparation was completed, the heart was perfused initially with cardiac output of 30 ml/min and mean arterial pressure of 70 mmHg by regulating the venous return (inflow) and the pneumatic resistance, respectively. In anesthetic groups, each anesthetic was added to the gas mixture using calibrated vaporizers throughout the experiment. Eight min after the start of perfusion, the left anterior descending (LAD) coronary artery was ligated. The site of ligation of the LAD coronary artery located approximately 3 mm from the aortic root. When the right atrial pressure exceeded 60mmHg, we reduced the venous return (inflow) otherwise the heart would fail. Thirty min after the perfusion, the heart was divided into infarcted and non-infarcted parts visibly and immediately freeze dried for 6 days. A part of myocardial tissue was extracted with perchloric acid and centrifuged at 3000 rpm. Myocardial high energy phosphates (ATP, ADP and AMP) were measured by the high liquid performance chromatography[12]. Lactate level was determined spectrophotometrically by standard techniques[13]. The values were expressed as micromoles per gram of dry weight.

Hemodynamic data within groups were analyzed by two-way analysis of variance with repeated measures. The other data were analyzed by one way analysis of variance followed by the Dunnett test for multiple comparisons. A probability of $P<0.05$ was regarded as statistically significant. The data are given as mean ± SEM.

Results

All hearts had no arrhythmias such as ventricular fibrillation or A-V block after coronary ligation. There was no significant difference in heart rate among the groups (Table). Halothane and enflurane decreased systolic blood pressure (SBP) significantly when compared with the control after coronary ligation. In addition, only enflurane reduced cardiac output after

Table. Heart rate changes (beats/min)

Time (min)	5	10	15	20	25	30
Control	267± 5	276±8	272±6	269± 8	273±7	271± 7
Halothane	286± 5	286±6	283±8	278± 5	270±4	268± 6
Enflurane	273± 7	252±7	256±6	264± 4	265±5	240±21
Isoflurane	276±10	271±8	268±8	270± 7	270±7	263± 8
Sevoflurane	266± 7	266±5	271±5	259±10	266±8	261± 6

coronary ligation (Fig. 1). In all groups, myocardial ATP levels in infarcted parts were significantly lower than those in non-infarcted parts. In addition, myocardial ADP, AMP and lactate levels in infarcted parts were significantly higher than those in non-infarcted parts (Fig. 2). However, there were no significant differences in high energy phosphates and lactate levels among the groups.

Discussion

Our results demonstrated that halothane and enflurane decreased SBP after coronary ligation. As the pneumatic resistance is constant in our preparation, the reduced SBP may have resulted from the cardiodepressant effects of both anesthetics. Furthermore, only enflurane decreased cardiac output after coronary ligation. Although several investigators have found enflurane to be more depressant to the myocardium as compared to equipotent concentrations of halothane[14,15], many others have found halothane to be more depressant than enflurane[6,16~18]. These conflicting results may be due to the differences in methods and materials. In addition, the direct negative inotropic effects of halothane and enflurane are reported to be more pronounced than those of isoflurane[19~21] and sevoflurane[22]. The effects of sevoflurane on cardiac function are almost identical to those induced by isoflurane[23,24]. These are consistent with the results that isoflurane and sevoflurane did not change cardiac function significantly when compared with the control hearts.

Acute myocardial infarction induces functional, morphological and biochemical damage to the myocardium which includes ventricular mechanical dysfunction, disturbance of heart rhythm, formation of scar tissue and failure of myocardial energy production. Bester et al.[25] have shown no significant decrease in myocardial high energy phosphates 90 days after left coronary artery ligation in rats, whereas a slight but significant decrease in myocardial high energy phosphates has been observed one week after coronary

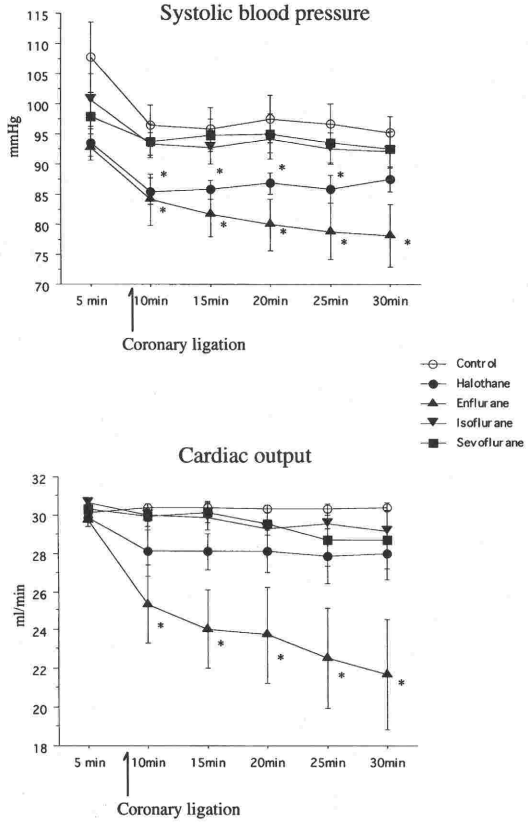

Figure 1. Changes in systolic blood pressure and cardiac output. * $P<0.05$ vs. Control.

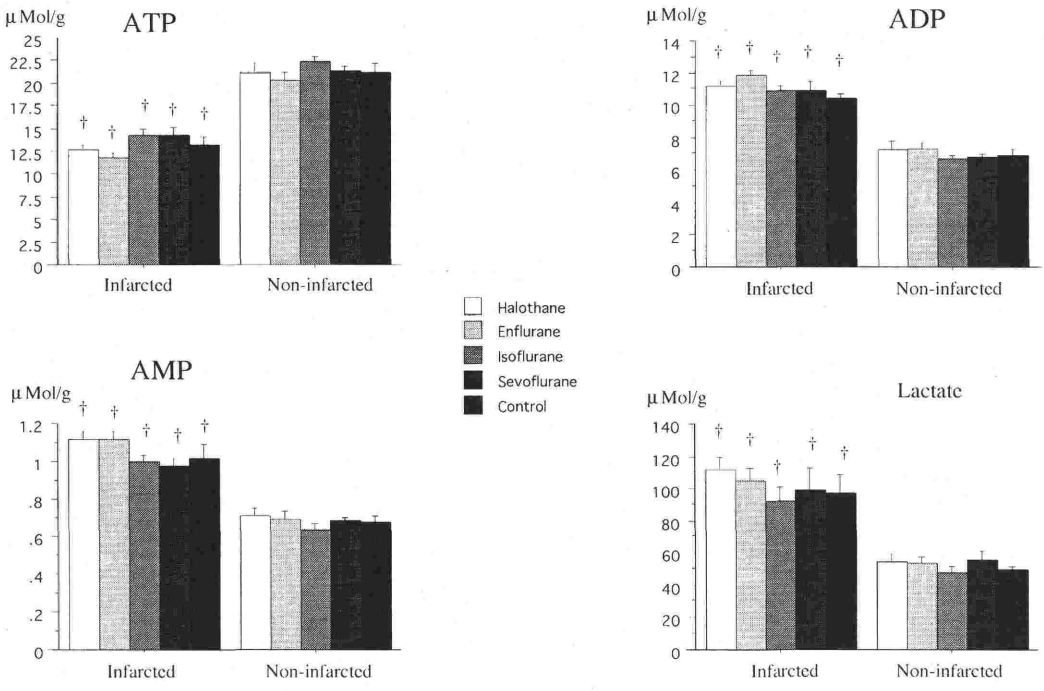

Figure 2. Myocardial ATP, ADP, AMP and lactate concentrations of non-infarcted and infarcted parts.
† $P<0.05$ vs. non-infarcted

artery ligation[26]. In the present study, myocardial ATP levels in infarcted parts were significantly lower than those in non-infarcted parts, and myocardial ADP, AMP and lactate levels in infarcted parts were significantly higher than those in non-infarcted parts, although there were no significant differences among the groups. Sanbe et al.[27] also reported the marked decrease in tissue ATP and increase in lactate levels in the scar tissue after coronary artery ligation in rats, but cardiac output and stroke volume indices were not altered during the first 4 weeks. This is consistent with our result that cardiac output was not altered after coronary artery ligation in the control group.

We did not measure the infacted size because we only divided the infarcted and non-infarcted myocardium visibly which was not probably accurate. However, it has been reported that the occluded and infarcted zones produced by ligation in rats were not influenced by halothane or fentanyl[28]. There is also a clinical report that the specific anesthetic technique does not influence impairment of myocardial oxygen utilization efficiency by anesthesia in patients undergoing coronary bypass surgery[29]. On the other hand, halothane[30] and isoflurane[31] have been reported to decrease the extent of myocardial necrosis produced by LAD occlusion. Concerning to the balance of oxygen supply to demand , halothane[32] and enflurane[33] improve it in acute myocardial ischemia. In the isolated rat heart with a constant preload and afterload, halothane and isoflurane, but not enflurane, increased the myocardial oxygen supply-to-demand ratio[34]. As for metabolism, Sahlman et al.[2] have reported that halothane, but not isoflurane, exerted a direct protective effect against global ischemic injury in the isolated heart. Coetzee et al.[3,4] also have indicated the beneficial effects of inhalation anesthetics on the ischemic hearts. These conflicting observations may result from the differences in methods and materials.

Enflurane depressed cardiac function, but did not

impair myocardial metabolism in the present study. The negative inotropic effect of enflurane and its limiting effect on myocardial oxygen demand may be considered advantageous in the consumption of ATP store. It is reported that enflurane improves the oxygen supply-to-demand balance in the acutely ischemic myocardium[33] and enhances postischemic functional and metabolic recovery in the isolated rat heart[5,6]. Enflurane's protective effects may be, at least in part, to its metabolic sparing effect.

The abrupt occlusion of a coronary artery is well known to be arrhythmogenic. However, all hearts in the present study had no arrhythmias such as ventricular fibrillation or A-V block after coronary ligation. Inhalation anesthetics have antiarrhythmic effects in the coronary ligated models of dogs[35] and rats[36]. In their studies, enflurane was easier to cause hypotension than halothane at the equipotent anesthetic concentration. These are consistent with our results.

In conclusion, enflurane produced lower blood pressures and lower cardiac output than those seen in the control and other anesthetic agents. Extrapolation of in vitro animal studies to human clinical experience is difficult, but attention should be paid when a patient with ischemic heart disease is anesthetized with enflurane. However, any inhalation anesthetics examined in the present study did not influence myocardial metabolism.

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