特 集 (special edition)

Effects of Inhalation Anesthetics on Myocardial Energy Metabolism in the Ischemic Heart

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Introduction

It has been reported that reperfusion of ischemic myocardium causes reperfusion injury[1,2]. On the other hand, inhalation anesthetics have been reported to exert a protective effect against ischemic myocardium[3-9]. Therefore, we have previously investigated the effects of inhalation anesthetics on myocardial energy metabolism during postischemic reperfusion in the rats[10-12]. The present communication will first give two brief results from the isolated rat's heart. The possible mechanisms of protective effects of inhalation anesthetics will then be discussed.

Methods 1 (Heart-lung preparation)

Forty male Wistar-Kyoto rats were anesthetized with 50 mg/kg of pentobarbital intraperitoneally. A tracheostomy was performed. Cannulae were inserted into the aorta and the superior and inferior venae cavae. This 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 perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir 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, provided the heart did not fail, and systolic arterial pressure was regulated by the pneumatic resistance. All hearts were perfused initially with heart rate of 250 beats/min, CO of 30 ml/min and mean arterial pressure of 80 mmHg. Five minutes after the start of perfusion, 1% halothane, 2% enflurane, 1.5% isoflurane or 2.3% sevoflurane was added to the inspired gas except in the control group. The administration of inhalation anesthetics lasted until the end of the experiment. Ten minutes after the start of perfusion, all hearts were made globally ischemic for 8 min by clamping the venous return and reducing the pneumatic resistance to zero. Afterward, they were reperfused by regulating the venous return and the pneumatic resistance. The recovery time was recorded when the cardiac output and mean arterial pressure returned to the pre-ischemic values.

Twelve min after the start of the reperfusion, the hearts were freeze-clamped and

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freeze-dried for six days. Myocardial ATP, lactate and glycogen were determined by the enzymatic methods[13]. The values were expressed as micromoles per gram of dry weight.

Results 1

The recovery time in the sevoflurane group was significantly shorter than that in the control group (Fig. 1). Myocardial ATP levels in the isoflurane and sevoflurane groups were significantly higher than that in the control group (Fig. 2).

Methods 2 (Working rat heart)

Seventy two male Wistar rats were used. The animals were anesthetized with each inhalation anesthetic and rats in the control group were anesthetized with isoflurane. The heart was then rapidly excised and put into ice-cold saline, which stopped the heart activity within seconds. The aorta was cannulated distal to the aortic valve and the heart was immediately perfused retrogradely through the aorta. Modified Krebs-Henseleit bicarbonate buffer was used as perfusate. During the retrograde perfusion, the left atrium was connected via a pulmonary vein to an angled steel cannula. The remaining pulmonary vein were ligated to avoid leakage. After this preliminary perfusion, the heart was converted to working preparation by perfusing the left atrium and releasing the aortic outflow for a stabilization period of approximately 10 minutes. In the anesthetic groups, each inhalation anesthetic was added to the perfusate (halothane; 1%, enflurane; 2.2%, isoflurane; 1.5% and sevoflurane; 3.3% for 1 MAC). Fifteen minutes after stabilization period, whole heart ischemia was induced by clamping one-way aortic valve bypass for 15 min. Reperfusion of the hearts after this ischemic period of 15 min was performed by declamping the one-way aortic valve bypass tube and lasted for 30 min.

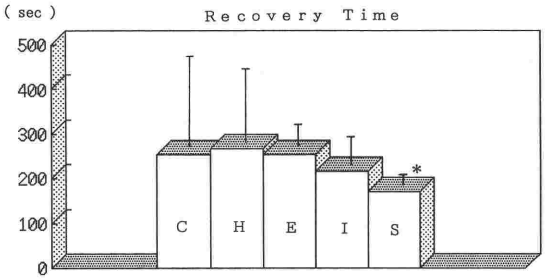

Fig. 1 Recovery time in the rat's heart-lung preparation.
* $p<0.05$ vs control
C; control, H; halothane, E; enflurane, I; isoflurane, S; sevoflurane

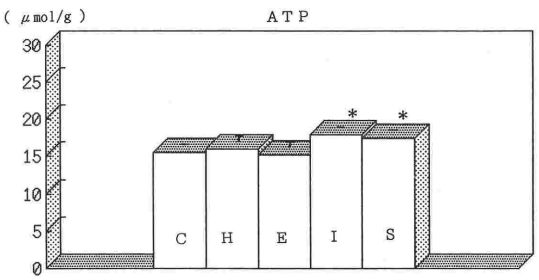

Fig. 2 Myocardial ATP levels after reperfusion.
* $p<0.05$ vs control
C; control, H; halothane, E; enflurane, I; isoflurane, S; sevoflurane

At the end of perfusion, hearts were quickly frozen by clamping with a Wollenberger clamp cooled in liquid nitrogen and freeze-dried for 6 days. Concentrations of ATP, lactate glycogen were measured by enzymatic methods[13].

Results 2

All inhalation anesthetics had an antiarrhythmic effect against ventricular fibrillation induced by ischemia (Fig. 3). Halothane had more negative intropic effect than other inhaslation anesthetics (Fig. 4). In 1 MAC, enflurane and isoflurane showed metabolic recovery concerning with ATP. However, there were no significant differences in ATP levels among the groups with 1.5 MAC (Fig. 5)

Critiques of methods

Both models are isolated hearts and the global ischemia was induced. They are independent of peripheral vascular resistance and have no

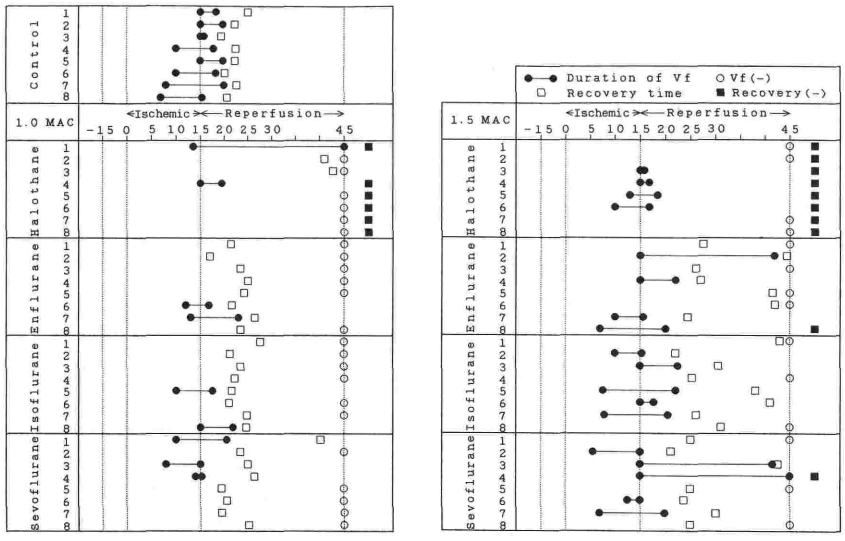

Fig. 3 Incidences of ventricular fibrillation and recovery time in the working rat heart.

neuro-humoral effects. However, 1) the way of administration of anesthetics and concentrations are different. In the heart-lung preparation anesthetics were given by the lung. The concentrations of anesthetics were determined according to the human MAC. In the Working heart, anesthetics were administered directly to the perfusate. Their concentrations were decided by the MAC for rats. 2) Pentobarbital was used in only the heart-lung preparation as a background anesthesia. The influence of basal anesthetics on cardiac function, even in a short period, has been reported[14,15]. 3) The way and the duration of ischemia were different. These differences may be related to the different results of two methods.

Effects of inhalation anesthetics on reperfusion injury

The heart is an aerobic organ which requires an uninterrupted supply of oxygen and metabolic substrates for its survival[16]. Thus, reperfusion of the ischemic myocardium would seem to be desirable and without reperfusion the myocardium cannot recover. Nevertheless reperfusion is not always beneficial. Reperfusion injury has been reported to be associated with oxygen free radicals and calcium paradox[1,2]. The cause of this injury is apparently multifactorial. We don't know whether inhalation anesthetics have a free radical scavenging effect. However, it is likely and reported that inhalation anesthetics might inhibit calcium accumulation associated with myocardial ischemia and calcium paradox under certain experimental situations[17-24]. Less intracellular calcium would be available for uptake by the mitochondria. Thus, mitochondrial function would be preserved and the calcium-induced damage observed during myocardial reperfusion would be diminished.

Effects of inhalation anesthetics on the ischemic heart

The inhalation anesthetics increase atrioventricular conduction time[25,26], and decrease heart rate[25-27] and contractile function[22-26,28-35]. These negative chronotropic, dromotropic, and inotropic effects of inhalation anesthetics are associated with a reduction in oxygen demand. The cardioprotective effect of inhalation anesthetics may involve reducing the severity of

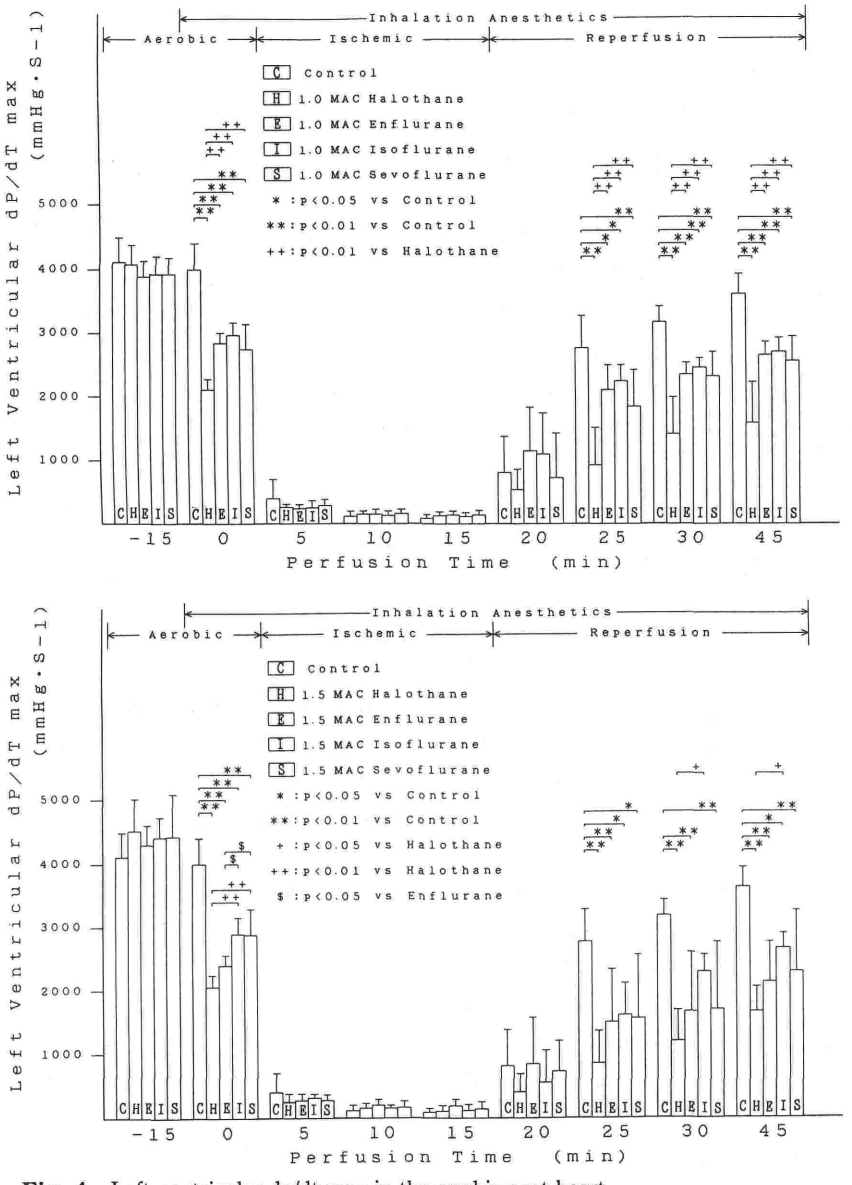

Fig. 4 Left ventricular dp/dt max in the working rat heart.
C; control, H; halothane, E; enflurane, I; isoflurane, S; sevoflurane

ischemia by decreasing myocardial oxygen demand. In other words, the decreased metabolic demand of the myocardium in the presence of anesthetics may slow the metabolism during ischemia, with better maintenance of intracellular calcium control. However, in the working rat model, inhalation anesthetics of 1.5 MAC did not show any metabolic recovery, while 1 MAC enflurane and isoflurane increased myocardial ATP contents at the end of reperfusion. Inhalation anesthetics with higher concentrations may reveal depressant effects rather than protective effects during the recovery from the ischemia.

Antiarrhythmic effect

Inhalation anesthetics can increase the incidence of ventricular ectopic beats[36-38], but they paradoxically can decrease the occurrence of ectopy under certain situations also[39]. In

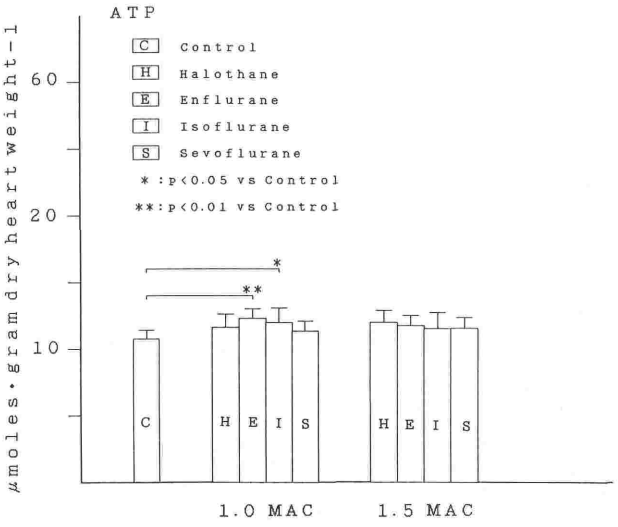

Fig. 5 Myocardial ATP levels after reperfusion in the working rat heart.
* $p<0.05$, ** $p<0.01$ vs control
C; control, H; halothane, E; enflurane, I; isoflurane, S; sevoflurane

the working rat model, inhalation anesthetics with lower concentrations (1 MAC) had an antiarrhythmic effect against ventricular fibrillation induced by ischemia. Lynch[40] has suggested that the antiarrhythmic effects of inhalation anesthetics might be related their actions upon intracellular handling of calcium. However, this cannot explain the fact that higher concentrations (1.5 MAC) of inhalation anesthetics had less antiarrhythmic effect against ventricular fibrillation during and after ischemia.

The abrupt occlusion and reperfusion of a coronary artery is well known to be arrhythmogenic and may result in ventricular fibrillation[41-44]. A variety of mechanisms have been proposed to explain the genesis of reperfusion arrhythmias. These include the stimulation of alpha and beta adrenergic receptors[45-47], the formation of lysophosphatides[48] and toxic free radicals[49-51], the products of the arachidonic acid pathway[52], disturbances of ionic homeostasis[53,54] and the heterogeneity of injury and recovery[43]. Considerable controversy exists as to the relative importance of each of these potential mechanisms. Therefore, studies upon the cellular mechanisms of inhalation anesthetics are necessary to explain the phenomena.

Differences among anesthetics

There are quantitative differences in the degree to which inhalation anesthetics depress electrical[22,26] and mechanical[26,30-35] function and alter coronary flow[7,8,55-58].

When comparing halothane with isoflurane, halothane is more potent than isoflurane in depressing the amount of Ca^{2+} released from the sarcoplasmic reticulum of skinned rabbit cardiac myofibrils[19,23,59]. Halothane is a more potent inhibitor of Ca^{2+} entry than isoflurane based on its depression of slow action potential rate of rise[22]. In addition, halothane is two to three times more potent than isoflurane in depressing the actin-myosin ATPase activity in isolated myofibrillar preparations[60]. These results may responsible for the fact that halothane produced the greatest reductions in cardiac performance when compared with other anesthetics in the working rat heart.

There are also many in vitro reports indicating that isoflurane is less of a cardiac inotropic depressant than is halothane or enflurane[26,30-35,56]. Although isoflurane has been reported to cause ischemia by a "steal" mechanism[61-66], it is a coronary vasodilator in both animal and humans[61,63,67-69]. Less cardiac depressant and coronary vasodilating effects of isoflurane may be related to the metabolic improvements of two different rat's models.

With regard to enflurane, there are comparable data from Freedman et al.[5] showing that the administration of 2% enflurane to the isolated rat heart prior to a severe ischemic insult enhanced metabolic recovery in the postischemic state. This finding agrees with only the result of the working rat heart with 1 MAC. The differences in findings between

ours and Freedman's are likely attributed to differences in study design.

The cardiovascular effects of sevoflurane are comparable to those of isoflurane[70,71]. These reports are consistent with our results of heart-lung preparation, which indicate that 2.3% sevoflurane and 1.5% isoflurane increased myocardial ATP levels after reperfusion. However, sevoflurane did not show any metabolic recovery in the working rat model. This may result from the used concentration of sevoflurane. We used MAC for rats according to Mazze et al.[72] except with sevoflurane. They determined MAC of sevoflurane to be 2.5% in Fischer 344 rats based on unpublished data[73]. We calculated it according to the data of Tamada, et al.[74] which indicated that MAC of sevoflurane was 2.2%, while that of enflurane was 1.45%. As MAC of enflurane is 2.2%[72], 1.45% of enflurane is too low for rats. Thus, 2.2% (sevoflurane MAC in Tamada) was multiplied by 2.2% (enflurane MAC in Mazze) and divided by 1.45% (enflurane MAC in Tamada). So, we determined sevoflurane MAC for rats to be 3.3% because of above reasons. If sevoflurane MAC is 2.5%, 3.3% sevoflurane would have more negative inotropic effect on the heart than other inhalation anesthetics with 1 MAC. This may be the reason why sevoflurane did not show any metabolic recovery in the working rat model.

Conclusions

Although it is inappropriate to translate to humans from animal data, we can conclude from the previous and recent studies that inhalation anesthetics, especially isoflurane, may have protective effects in globally ischemic rat's hearts. However, inhalation anesthetics with higher concentrations may reveal depressant effects rather than protective effects in the ischemic hearts.

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