Effects of Sevoflurane on Myocardial Metabolism during Postischemic Reperfusion in the Rat

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In experiments on isolated rat heart lung preparation, the effects of sevoflurane on myocardial metabolism during postischemic reperfusion were evaluated with intramyocardial high energy phosphates, lactate and glycogen. Hearts were perfused for 10 min initially and made globally ischemic for 8 min. Afterwards, they were reperfused for 12 min. Sevoflurane was administered from 5 min after the start of perfusion to the end of reperfusion. There was no significant difference in myocardial lactate levels between the sevoflurane (S) and control groups. However, the myocardial ATP level in Group S was significantly higher than that in control (17.45 ± 1.51 vs 15.50 ± 0.87: $P<0.01$). The administration of sevoflurane to the isolated rat heart during pre- and post-ischemia enhanced metabolic recovery in the postischemic state. (Key words: sevoflurane, myocardial metabolism, reperfusion)

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Sevoflurane is a potent inhaled anesthetic having rapid uptake and elimination because of the low blood/gas partition coefficient[1–3].

We reported previously that halothane and enflurane, but not isoflurane, increased the intramyocardial lactate levels when they were administered during pre-as well as postischemic period[4,5]. These indicate that some deterioration in the myocardial oxidation-reduction state is induced by halothane and enflurane.

In the present paper, the effects of sevoflurane on myocardial metabolism during the postischemic reperfusion were investigated.

Materials and Methods

The techniques used were identical to those used in the earlier study[4]. In brief, male Wistar rats (300–310g) were anesthetized, with 50 mg/kg of pentobarbital intraperitoneally. A tracheostomy was performed, and constant volume (3 ml) intermittent positive pressure ventilation was instituted at a rate of 30 breaths/min with 100% oxygen. The chest was opened and flooded with icecold saline and the heart was arrested during preparation. Cannulae were inserted into the aorta and the superior and inferior venae cavae. A pacing wire was placed on the right atrium. The cannula of the superior vena cava was used to monitor central venous pressure.

A heart lung preparation was perfused with modified blood (25 ml), containing red blood cells, which were collected from another rat, and Krebs Ringer bicarbonate buffer, with hematocrit and pH being 25 per cent and 7.4 respectively. The perfusate blood pumped from the aorta, passing

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Table 1. Heart rates, systolic blood pressure, central venous pressure and recovery time (Mean values ± S.D.)

Time (min)	0	5	10	12	14	16	18	R	7	12
		Initial perfusion		Ischemia				Reperfusion		
		Administration of sevoflurane								
Heart rate (beats/min)										
Control		250		156±35	115±61	87±45	75±41	183±78	203±20	198±26
2.3% sevoflurane		250		163±33	109±28	90±13	84±19	238±20	258±17*	256±13*
Systolic blood pressure (mmHg)										
Control		111±6	106±5	0	0	0	0	100±10	99± 2	100± 2
2.3% sevoflurane		110±5	103±6	0	0	0	0	109± 6	102± 6	100± 4
Central venous pressure (KPa)										
Control		0.32±0.06	0.31±0.07	—	—	—	—	0.36±0.08	0.35±0.08	0.34±0.10
2.3% sevoflurane		0.33±0.04	0.34±0.04	—	—	—	—	0.35±0.03	0.32±0.04	0.31±0.03
Recovery time from initiation of reperfusion										
Control		4'15"±3'39"								
2.3% sevoflurane		2'51"± 32"								

R: At recovery time, *P <0.001

Table 2. Myocardial concentration of high energy phosphates, lactate and glycogen after reperfusion (μ mole/g dry tissue), mean values ± s.d.

	control[a] (n = 8)	2.3% sevoflurane (n = 8)	1.5% isoflurane[b] (n = 7)	1% halothane[a] (n = 8)	2% enflurane[a] (n = 9)
ATP	15.50±0.87	17.45±1.51††	17.96±1.31†	16.05±1.99	15.16±2.03
ADP	3.42±0.34	2.59±0.43†	3.41±0.49	2.96±0.42	4.02±0.75
AMP	0.54±0.20	0.26±0.14††	0.45±0.07	0.45±0.08	0.62±0.40
Lactate	28.63±5.98	23.55±3.95	29.79±3.05	44.04±10.54†	40.63±10.34†††
Glycogen	99.30±15.06	80.90±10.80†††	59.25±8.10†	65.04±16.81†	84.12±25.16

†P <0.005, ††P <0.01, †††P <0.05, When compared to control.
a; data from reference[4], b; reference[5]

through a pneumatic resistance, was collected in a reservoir that was warmed at 37°C throughout the experiment by means of a water jacket and then returned to the inferior vena cava. No other organs except heart and lungs were perfused. Hearts were perfused initially at a heart rate of 250 /min, cardiac output of 30 ml/min and mean arterial pressure of 80 mmHg by pacing, regulating the venous return and the pneumatic resistance, respectively. Five minutes after the start of perfusion, 2.3% sevoflurane was administered through a calibrated vaporizer. Sevoflurane was given until the end of experiment (Group S:n=8). Ten minutes after the start of perfusion, the pacing was stopped and the heart was made globally ischemic for 8 min by clamping the venous return and releasing the pneumatic resistance. They were reperfused by regulating the venous return and the pneumatic resistance. The recovery was estimated by the time when the cardiac output and the mean arterial pressure restored to 30 ml/min and 80 mmHg, respectively.

Twelve minutes after the start of reperfusion, hearts were frozen rapidly with precooled, stainless steel, Wollenberger tongs and immediately submerged in liquid nitrogen. Aliquots of tissue were taken for

preparation of perchloric acid extract, and the high energy phosphates (ATP, ADP and AMP) and lactate levels were measured spectrophotometrically using Bergmeyer's techniques[6]. Tissue glycogen level was assayed as glucose equivalents in neutralized potassium hydrated extracts[7]. The values were expressed as μmol/g dry weight.

The data were given as mean $\pm$ s.d. The control study was reported previously using the identical method[4,5]. Statistical significance of differences was determined by variance analysis when $P<0.05$.

Results

Hemodynamic data are shown in table 1. There were no significant differences in systolic blood pressure, central venous pressure and recovery time between both groups. Heart rates in two groups decreased during ischemia, but the heart rates in Group S increased more than those in control during the postischemic reperfusion period.

No significant difference was seen in the lactate level between the two groups. However, the ATP content was significantly greater and the ADP and AMP contents were smaller in Group S than those of control. The glycogen level in Group S decreased more than that of control (table 2). The previous data[4,5] are expressed in table 2 in order to compare with each other.

Discussion

The concentration of sevoflurane was selected according to the MAC[8,9].

The results of this study showed that sevoflurane increased the myocardial ATP content and decreased ADP and AMP at the end of reperfusion. In this experiment, the myocardial oxygen consumption during the preischemic period did not seem to differ between the two groups, in that the mean arterial pressure, heart rates and cardiac output were same. Therefore, there was no evidence that sevoflurane reduced global myocardial oxygen consumption during preischemia. It seems that the administration of sevoflurane during both pre- and post-ischemia could increase myocardial oxygen supply and could increase high energy phosphate product, thus preventing ischemic injury or improving the postischemic myocardial recovery.

Although there is no report about sevoflurane's inhibitory effect of electron transport, volatile anesthetics block electron transport at the NADH-coenzyme Q reductase level in the respiratory chain and increase NADH fluorescense which reflects deterioration in the myocardial oxidation-reduction state[10]. The increase in NADH may produce the accumulation of lactate. However, sevoflurane did not increase the myocardial lactate level at the end of reperfusion, which differs from the results of halothane and enflurane[4]. Isoflurane also did not increase the myocardial lactate level at the end of reperfusion[5]. Sevoflurane may have no effect in the respiratory chain. Otherwise, sevoflurane may have the vasodilating effect like isoflurane[11] and the increased coronary perfusion due to its effect during reperfusion might reduce the accumulated lactate. Manohar et al.[12] have reported that the subendocardial/subepicardial perfusion ratio was well maintained with sevoflurane anesthesia and that the effect of sevoflurane anesthesia on myocardial and other organs blood flow were quite similar to those caused by equipotent isoflurane anesthesia in swine.

Sevoflurane does not affect heart rate in pigs[12] and dogs[13]. In this experiment, the greater increase of heart rate in Group S during the postischemic reperfusion period was consistent with those of halothane and isoflurane in the previous studies[4,5]. This may not be due to a sympathomimetic effect of sevoflurane but due to its direct effect because our preparation is independent of vascular tone and neural reflexes. Myocardial glycogen level in Group S was lower than that in control, which was also consistent with the results of halothane and isoflurane[4,5]. Myocardial glycogen seems to have been metabolized, probably due to the faster heart rates in rats given sevoflurane after ischemia.

In conclusion, the administration of 2.3% sevoflurane to the isolated rat heart during pre- and post-ischemia enhanced metabolic

recovery in the postischemic state. Sevoflurane may give better results than halothane or enflurane when they are administered during the postischemic reperfusion period.

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