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Comparison between sevoflurane and isoflurane anesthesia in pig hepatic ischemia-reperfusion injury

Hiroshi Ishida[1], Yoshitami Kadota[1], Teruko Sameshima[1], Atsushi Nishiyama[1], Toshiyuki Oda[2], and Yuichi Kanmura[1]

[1]Department of Anesthesiology and Critical Care Medicine, Kagoshima University School of Medicine, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
[2]Department of Anesthesiology, Shonan Kamakura General Hospital, 1202-1 Yamasaki, Kamakura 247-0066, Japan

Abstract
Purpose. Sevoflurane and isoflurane have been reported to exert protective effects against ischemia-reperfusion injury (IRI) in various organs. To compare the effect of sevoflurane anesthesia on liver IRI with that of isoflurane anesthesia, we performed the present study in pigs.
Methods. Nineteen pigs were assigned to either the sevoflurane ($n = 9$) or the isoflurane group ($n = 10$). Hepatic warm ischemia was produced by 30-min hepatic artery and portal vein clamping beginning 90 min after the start of the inhalation anesthesia; this was followed by a 240-min reperfusion. To extend our evaluation, we evaluated the degree of IRI using various parameters (plasma α-glutathione-S-transferase [α-GST], lipid peroxide, and lactate concentrations), in addition to the conventionally used liver damage markers.
Results. The lactate level was significantly higher under isoflurane than under sevoflurane at 120 min after reperfusion ($4.0 \pm 0.4\,mmol \cdot l^{-1}$ *vs* $2.5 \pm 0.3\,mmol \cdot l^{-1}$; $P < 0.05$). However, this difference had disappeared after 240 min of reperfusion. No significant differences between the two groups were observed in values for α-GST, lipid peroxides, aspartate aminotransferase, alanine aminotransferase, or lactic dehydrogenase.
Conclusion. The extent of the hepatic IRI seen under sevoflurane anesthesia in pigs did not differ significantly from that seen under isoflurane, as judged from measurements of a number of parameters over a 240-min reperfusion period.

Key words Ischemia-reperfusion injury (IRI) · Sevoflurane · Isoflurane · α-GST · Lipid peroxide

Introduction

Intraoperative temporary interruption of liver blood flow sometimes occurs during various surgical procedures, including resection of hepatic tumor, repair of hepatic trauma, liver transplantation, and thoracic aortic surgery. This hepatic ischemia and the subsequent reperfusion can lead to liver dysfunction or severe hepatic failure, depending on the severity and duration of the ischemia. For some years, data have been accumulating from in vivo and in vitro experiments suggesting that inhalation anesthetics, including commonly used modern agents such as sevoflurane and isoflurane, exert protective effects against ischemia-reperfusion injury (IRI) in various organs [1–9]. In the liver, both isoflurane and sevoflurane are reported to protect against hepatic IRI in vitro [3]. However, Preckel et al. [5] and Schlack et al. [6] suggested that sevoflurane has more prominent protective effects than isoflurane on myocardial reperfusion injury (in vivo and in vitro investigations, respectively).

To our knowledge, no in vivo study has yet been done to compare the influence of sevoflurane anesthesia on liver IRI with that of isoflurane. In this study, we compared sevoflurane and isoflurane in terms of liver IRI in pigs. For this study, we used certain additional parameters besides the conventionally used liver damage markers to extend our evaluation of the injury. These parameters were: (1) plasma α-glutathione-S-transferase (α-GST) concentration, (2) plasma lipid peroxide concentration, and (3) plasma lactate concentration. The plasma α-GST concentration provides a very sensitive index of liver damage [10,11], and the measurement of lipid peroxides has been used both to reveal the existence of oxidative stress, which is one of the mechanisms underlying IRI, and to enable the inhibitory effect of anesthetics on this stress to be evaluated [12,13].

Materials and methods

The study was conducted following guidelines laid down by the Animal Care Committee of Kagoshima

Address correspondence to: Y. Kadota
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University School of Medicine. Nineteen male pigs (specific pathogen-free [SPF], weighing 20–28 kg) were used.

Surgical preparation

The pigs were anesthetized with ketamine 400 mg and atropine 0.5 mg, administered intramuscularly; a 24-gauge catheter was inserted into the ear vein, and tracheal intubation was performed. During the surgical preparation, including the catheterization and laparotomy, anesthesia and muscle paralysis were maintained with a continuous infusion of ketamine 20 $mg \cdot kg^{-1} \cdot h^{-1}$ and pancuronium 0.4 $mg \cdot kg^{-1} \cdot h^{-1}$, with local anesthesia achieved using 0.5% lidocaine. When needed (e.g., if there was an abrupt rise in arterial blood pressure and heart rate), intravenous ketamine (50–100 mg) was given to maintain adequate anesthesia during surgery. One catheter (Medicut-UK-II; outer diameter [OD], 16 G; length, 70 cm; Japan Sherwood, Tokyo, Japan) was inserted into the jugular vein for the administration of drugs and maintenance fluids; another was inserted into the common carotid artery for blood sampling and measurement of arterial blood pressure. The liver was exposed via a midline incision, and both the hepatic artery and the portal vein were isolated. Ventilation was controlled to maintain $PaCO_2$ and PaO_2 at 35 ± 5 mmHg and over 150 mmHg, respectively, using 40%–50% oxygen in nitrogen (total flow, 5–6 l). During the experiment, acetated Ringer's solution, containing 3% glucose, was infused via the venous catheter at a rate of 3–5 $ml \cdot kg^{-1} \cdot h^{-1}$. Arterial pressure and electrocardiogram were monitored, and body temperature, measured with a thermistor probe inserted rectally, was kept at 38 ± 1°C. The pigs were randomly assigned to the sevoflurane group ($n = 9$) or the isoflurane group ($n = 10$).

Experimental protocol

After the surgical preparation, we allowed a no-treatment time of 30 min for stabilization after the stress inherent in the surgery. After this stabilization period, there was a period of baseline inhalation anesthesia (90 min), during which there was no experimental intervention, such as hepatic warm ischemia. In newborn swine (1–2 weeks), the reported values for the 1.0 minimum alveolar concentration (MAC) of sevoflurane and isoflurane are 2.12% and 1.4%, respectively [14]. Our animals were anesthetized using these 1.0 MAC values (that is, sevoflurane 2.1% end-tidal concentration or isoflurane 1.4% end-tidal concentration) for the duration of the experiment. Hepatic warm ischemia was produced by 30-min clamping of the hepatic artery and portal vein beginning 90 min after the start of the inhalation anesthesia; this was followed by a 240-min period of reperfusion. The end-tidal concentration of sevoflurane or isoflurane was determined by infrared spectroscopy (Icorn Anesthetics Agent Monitor, Mera, Tokyo, Japan).

Blood analysis

For the measurement of the liver enzymes α-GST, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH), together with plasma lactate and lipid peroxides, and arterial blood gases, arterial blood samples (18 ml) were withdrawn before and at 90, 120, 122, 150, 180, 240, and 360 min after the start of the period of inhalation anesthesia. The anesthetic concentration in whole blood and the hemodynamic parameters were measured before and at 30, 60, 90, 100, 110, 120, 122, 135, 150, 165, 180, 240, and 360 min after the start of the inhalation anesthesia. Each blood sample was replaced with an equal volume of heparin-saline. The blood samples were centrifuged immediately, and the plasma was separated. The plasma for the measurement of α-GST, lactate, and lipid peroxide was stored at −80°C until analysis. The α-GST concentration in plasma was measured using a Biotrin Hepkit-Alpha, Biotrin, Dublin, Ireland for porcine α-GST (which is based on an enzyme immunoassay). The detection limit was 0.69 $\mu g \cdot l^{-1}$. The intra- and interassay coefficients of variation were 1.83%–5.69% and 4.02%–11.0%, respectively. AST, ALT, and LDH activities in plasma were measured using a TBA-80FR self-analyzer (Toshiba, Tokyo, Japan). The lactate concentration in whole blood was measured by enzymatic analysis [15]. Lipid peroxides were evaluated by measuring malondialdehyde (end metabolite), with the plasma malondialdehyde concentration measured according to the method of Nielsen et al. [16], using high-performance liquid chromatography (HPLC). The detection limit was 0.1 μM. The interassay coefficient of variation was 3.50%. Arterial blood gases were measured using a Stat profile 4 (Nova Biomedical, Tokyo, Japan). The concentrations of sevoflurane and isoflurane in whole blood were assayed by gas chromatography [17].

Statistical analysis

Statistical analysis was performed using Stat-View 4.5 (Abacus Concepts, Berkeley, CA, USA). All data values are expressed as means ± SE. One-way analysis of variance (ANOVA) for repeated measurements, followed by a post-hoc Fisher's test, was used to compare values obtained from a given group at different times. For between-group comparisons, two-way ANOVA was performed. When significant differences were

detected by ANOVA, a post-hoc Scheffé test was used. Body weight was analyzed using one-way ANOVA. Statistical significance was assumed at P values < 0.05.

Results

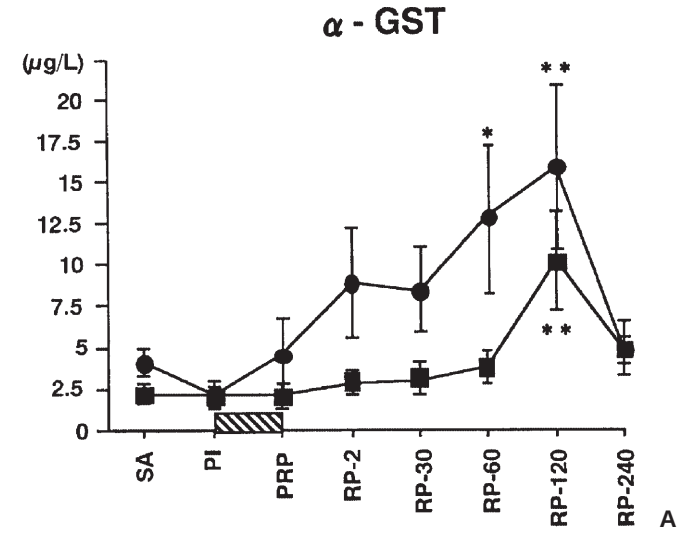
No significant difference in body weight was observed between the two groups (sevoflurane, 23.3 ± 1.0 kg; isoflurane, 23.5 ± 0.7 kg). Throughout the experiment, the blood concentration of each anesthetic was maintained at a level not significantly different from that measured at 30 min after the start of the period of anesthesia (Table 1).

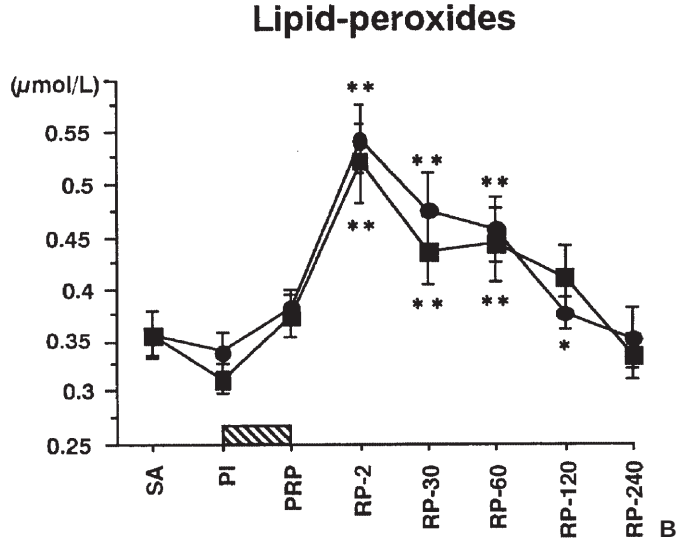
The α-GST concentration reached a maximum in both groups at 120 min after reperfusion (sevoflurane, 15.9 ± 5.4 μg·l^{-1}; isoflurane, 10.2 ± 3.3 μg·l^{-1}). Despite the tendency for a greater α-GST level in the sevoflurane group than in the isoflurane group from the start of reperfusion to 120 min after its start, no significant difference was observed between the two groups over the entire experimental period (Fig. 1).

The lipid peroxide level rose to a maximum at 2 min after reperfusion and remained significantly higher than the preischemia level until 60 min of reperfusion in both groups. No significant differences were observed between the two groups in terms of lipid peroxide levels (Fig. 1).

In both groups, the plasma lactate level reached a maximum at 2 min after reperfusion and remained significantly higher than the preischemia level until 60 min into the period of reperfusion. The lactate level was significantly higher in the isoflurane group than in the sevoflurane group at only one sampling point: at 120 min into the reperfusion (Fig. 1).

No significant differences were observed between the two groups in terms of AST, ALT, or LDH levels (Fig. 2). The AST level rose after reperfusion, and it showed





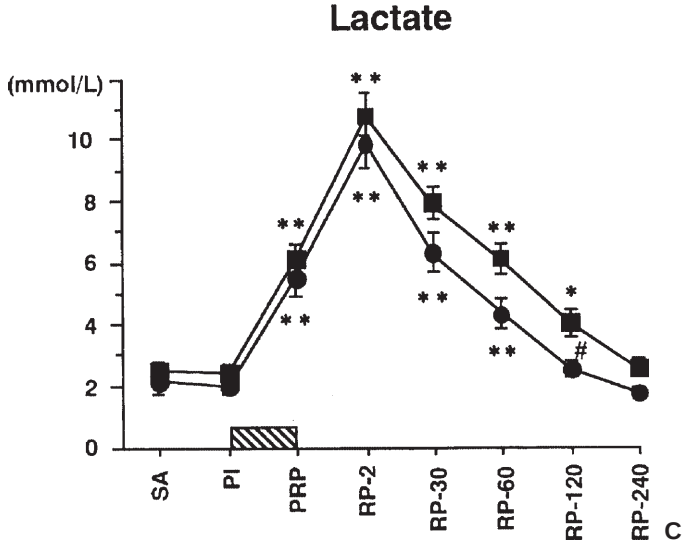


Fig. 1A–C. Changes in plasma alpha glutathione-S-transferase (α-GST), lipid peroxide, and lactate concentrations in sevoflurane (*closed circles*) and isoflurane (*closed squares*) groups before, during, and after hepatic warm ischemia (*striped areas*). Values are means ± SE. **A** Changes in plasma α-GST in the sevoflurane ($n = 6$) and isoflurane ($n = 8$) groups. Note that, in **A**, the sevoflurane and isoflurane groups contain 6 and 8 pigs, respectively. These numbers differ from those in **B** and **C** because data could not be obtained from 5 pigs for technical reasons (measuring machine problems). **B** Changes in plasma lipid peroxides in the sevoflurane ($n = 9$) and isoflurane ($n = 10$) groups. **C** Changes in the plasma lactate level in the sevoflurane ($n = 9$) and isoflurane ($n = 10$) groups. $^{\#}P < 0.05$ sevoflurane group versus isoflurane group. $^{*}P < 0.05$; $^{**}P < 0.01$ versus corresponding PI value. *SA*, Start of anesthesia; *PI*, preischemia; *PRP*, prereperfusion; *RP-2*, *RP-3*, *RP-60*, *RP-120*, and *RP-240*, 2 min, 30 min, 60 min, 120 min, and 240 min after reperfusion, respectively

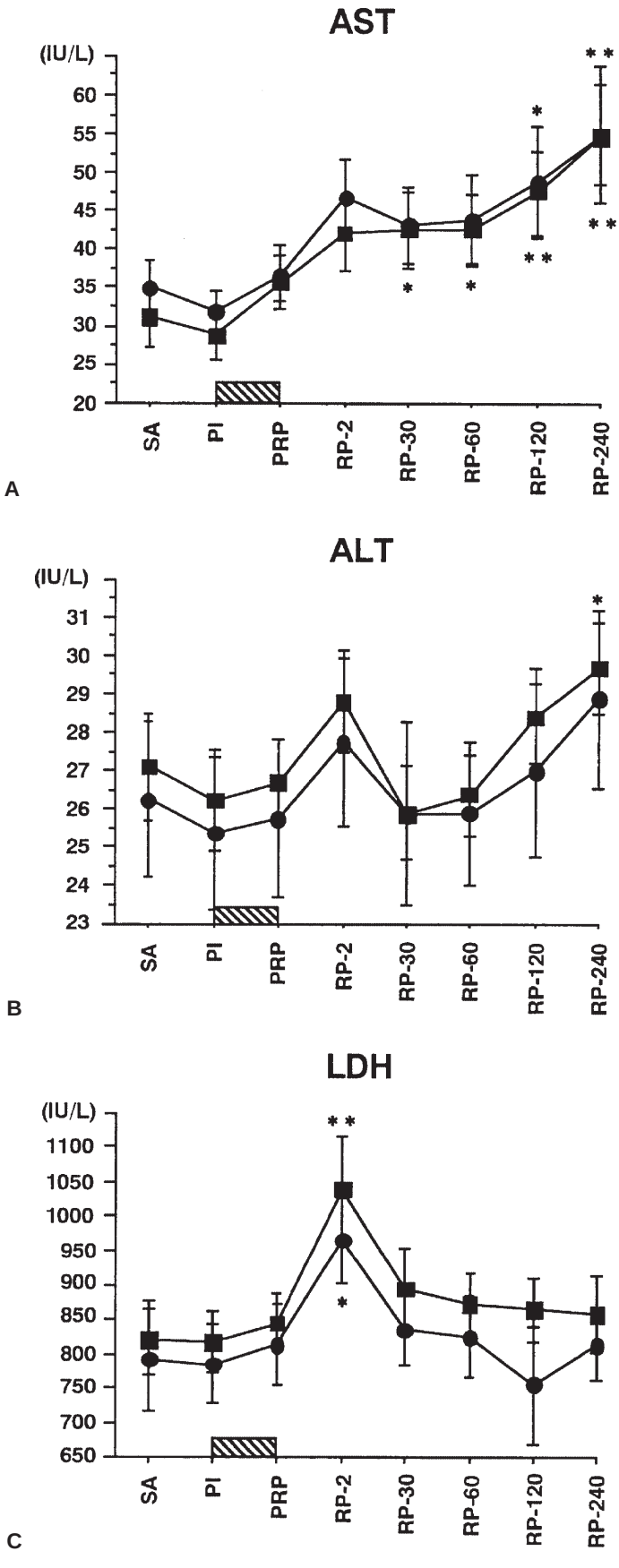
Table 1. Anesthetic concentrations, hemodynamic data, and blood gas values for each group

	Sampling time (min)													
	0 (SA)	30	60	90 (PI)	100	110	120 (PRP)	122 (RP-2)	135 (RP-15)	150 (RP-30)	165 (RP-45)	180 (RP-60)	240 (RP-120)	360 (RP-240)
Sevoflurane concentration ($\mu mole \cdot l^{-1}$)	0	180 ± 9	173 ± 11	198 ± 15	175 ± 15	196 ± 16	191 ± 11	204 ± 17	176 ± 14	205 ± 13	179 ± 18	181 ± 10	169 ± 9*	171 ± 9
Isoflurane concentration ($\mu mole \cdot l^{-1}$)	0	204 ± 12	191 ± 10	219 ± 7	220 ± 13	211 ± 6	225 ± 13	225 ± 13	203 ± 9	238 ± 19	193 ± 7	214 ± 9	215 ± 10	208 ± 15
MAP (mmHg)														
Sevoflurane group	102 ± 8	77 ± 9	74 ± 8	71 ± 6	33 ± 4**	29 ± 4**	26 ± 3**	51 ± 8**	63 ± 6**	63 ± 5**	64 ± 5*	67 ± 5*	74 ± 7	71 ± 6
Isoflurane group	122 ± 6	71 ± 3	74 ± 3	74 ± 3	36 ± 1**	33 ± 1**	30 ± 1**	53 ± 4*	59 ± 4	60 ± 3	62 ± 3	62 ± 3	65 ± 4	66 ± 6
HR (bpm)														
Sevoflurane group	173 ± 8	144 ± 10	142 ± 10	136 ± 10	189 ± 16**	195 ± 13**	191 ± 13**	189 ± 9**	164 ± 7**	170 ± 9**	172 ± 10**	174 ± 12**	166 ± 15**	168 ± 16*
Isoflurane group	182 ± 8	135 ± 11	130 ± 13	128 ± 13	214 ± 8**	222 ± 6**	215 ± 7**	203 ± 4**	171 ± 8	177 ± 8*	183 ± 8	184 ± 8	165 ± 11	159 ± 7
PaO_2 (mmHg)														
Sevoflurane group	254 ± 16			246 ± 20			213 ± 31	191 ± 26		232 ± 22**		240 ± 17	233 ± 17	222 ± 21
Isoflurane group	250 ± 12			235 ± 9			197 ± 23	158 ± 16**		217 ± 22		231 ± 12	220 ± 9	204 ± 14
$PaCO_2$ (mmHg)														
Sevoflurane group	39 ± 2			36 ± 2			22 ± 2**	55 ± 3**		44 ± 3*		42 ± 2*	40 ± 1	41 ± 1
Isoflurane group	35 ± 2			38 ± 1			25 ± 1**	60 ± 3**		46 ± 2**		44 ± 2*	40 ± 2	41 ± 3
BE ($mmol \cdot l^{-1}$)														
Sevoflurane group	2.5 ± 1.2			2.7 ± 0.9			−5.0 ± 0.5**	−11.1 ± 1.5**		−4.2 ± 1.3**		−1.9 ± 1.1**	1.1 ± 0.8	3.4 ± 1.0
Isoflurane group	3.4 ± 0.5			3.5 ± 0.4			−3.5 ± 1.0**	−11.3 ± 0.9**		−4.2 ± 0.7**		−1.1 ± 0.6**	1.4 ± 0.4**	3.3 ± 0.8

*$P < 0.05$; **$P < 0.01$ *vs* corresponding PI value

Values are means ± SE

SA, Start of anesthesia; PI, preischemia; PRP, prereperfusion; RP-2, RP-15, RP-30, RP-45, RP-60, RP-120, and RP-240, 2 min, 15 min, 30 min, 45 min, 60 min, 120 min, and 240 min after reperfusion, respectively; MAP, mean arterial pressure; HR, heart rate; BE, base excess



a significant elevation above the preischemia level at both 120 min and 240 min after the reperfusion in both groups. ALT increased significantly in the isoflurane group, but not in the sevoflurane group at 240 min after the reperfusion. In each group, the LDH level was raised significantly only at the sampling point at 2 min after reperfusion. There were no significant differences between the two groups in terms of arterial blood gas analysis or hemodynamic changes after the start of inhalation anesthesia (Table 1).

Discussion

In the present study, we compared the degree of liver IRI between sevoflurane and isoflurane anesthesia using the following variables. (1) The plasma levels of the liver enzymes AST, ALT, LDH, and α-GST were measured. α-GST is primarily located in the centrilobular hepatocytes [10], which are considered to receive blood that is poorer in both oxygen and nutrients than the periportal hepatocytes, in which AST and ALT are mainly distributed. The half-life of α-GST in plasma is less than 90 min, which is considerably shorter than the half-lives of AST and ALT [10]. Therefore, α-GST is considered to be a more sensitive marker of acute hepatic damage and its recovery than either AST or ALT [10,11]. (2) Plasma lipid peroxides were measured both to evaluate oxidative stress, which is one of the underlying mechanisms for IRI, and to enable the inhibitory effect of anesthetics on this stress to be evaluated [12,13]. Oxygen radicals, which cause cell damage via lipid peroxidation, are considered to be generated during liver ischemia-reperfusion [18,19]. (3) Plasma lactate was measured because this indicates not only the degree of IRI (regional and systemic) but also the metabolic activity of the liver [20].

From the present experiments, the following conclusions can be drawn. (1) Liver damage in the periportal and centrilobular regions did not differ significantly between the two anesthetics over the time course of the experiment. Based on the α-GST level, the damage in the centrilobular region was recovered at 240 min after reperfusion in both groups, and the degree of recovery

Fig. 2A–C. Changes in conventionally used liver damage markers **A** aspartate aminotransferase [AST]; **B** alanine aminotransferase [ALT]; **C** lactate dehydrogenase [LDH] in sevoflurane ($n = 9$; *closed circles*) and isoflurane ($n = 10$; *closed squares*) groups before, during, and after hepatic warm ischemia (*striped areas*). Values are means ± SE. $^{*}P < 0.05$; $^{**}P < 0.01$ versus corresponding PI value. *SA*, Start of anesthesia; *PI*, preischemia; *PRP*, prereperfusion; *RP-2*, *RP-30*, *RP-60*, *RP-120*, and *RP-240*, 2 min, 30 min, 60 min, 120 min, and 240 min after reperfusion, respectively

in the sevoflurane group was the same as that in the isoflurane group. (2) The degree of systemic lipid peroxidation after liver ischemia-reperfusion did not differ between the two groups. (3) The regional and systemic damage during and after liver ischemia-reperfusion, as shown by the peak plasma lactate concentration, did not differ between the two groups. The recovery in lactate metabolism after liver ischemia-reperfusion was somewhat faster in the sevoflurane group than in the isoflurane group. However, after 240 min of reperfusion, this difference between the two groups had disappeared, suggesting that the recovery in liver metabolic activity is not different between the two anesthetics over a 240-min period of reperfusion.

The above results showed that the liver IRI after a 240-min reperfusion was not significantly different between the two groups, suggesting that whether sevoflurane or isoflurane is chosen for surgery that involves a temporary interruption of the hepatic blood supply may not make a significant difference in the early phase (240 min) of reperfusion.

Inhalation anesthetics have been shown to exert protective effects against IRI in various organs, including the heart [5,6,9], brain [7], lung [8], and liver [1–4]. Possible explanations for these protective effects of inhalation anesthetics [21] and the preservation of ATP levels during ischemia, reduced adhesion of polymorphonuclear neutrophils, increased nitric oxide production, inhibition of free radical production, or a reduction in calcium overloading. Both isoflurane [22] and sevoflurane [23] have been reported to mimic ischemia preconditioning effects in the heart, suggesting that the preischemic administration of these anesthetics may be protective against IRI. Imai et al. [3] showed that the reduction in IRI, assessed by measuring LDH release, was greater when isoflurane was administered during the reperfusion than when it was administered during the ischemia. This suggests that inhaled anesthetic administration is more important during the reperfusion phase than during the ischemic phase in terms of providing a protective effect against such injury. In the present experiment, we administered both agents before, during, and after the ischemic phase. Hence, our data suggest that the effects of sevoflurane on liver IRI throughout these three phases may be almost the same as the effects of isoflurane.

Although many in vivo and in vitro studies have suggested that inhalation anesthetics exert protective effects against IRI in various organs [1–9], few studies have compared the protective effects of isoflurane and sevoflurane. Imai et al. [3] reported that isoflurane and sevoflurane exerted protective effects of similar magnitude against IRI in a perfused rat liver model. Heindl et al. [9] showed that both sevoflurane and isoflurane reduced the adhesion of polymorphonuclear neutrophils in the reperfused coronary system, and thereby helped to preserve cardiac function; the effects of these two agents were not significantly different from each other. However, Preckel et al. [5] and Schlack et al. [6] both suggested that sevoflurane had more prominent protective effects than isoflurane on myocardial reperfusion injury (in vivo and in vitro investigations, respectively). In our in vivo experiment, the absence of a significant difference between sevoflurane and isoflurane in terms of liver IRI at 240 min after reperfusion indicates that the two agents may have similar effects on this injury. This conclusion is consistent with that obtained with a perfused rat liver in vitro [3].

Our experimental model has the following experimental limitations. (1) We assessed the extent of liver IRI by measuring various parameters in the 240 min after reperfusion. Hence, we cannot comment on the influence of the two anesthetics against IRI in the longer term. (2) Our main aim was to compare the effect of sevoflurane anesthesia on liver IRI with that of isoflurane anesthesia. For this reason, we did not create a control or reference group, such as an intravenous anesthetic group. Further detailed study will be necessary to clarify the full extent of the protective effect of the two inhalation anesthetics against liver IRI. (3) Our study revealed specifically that the effects of 1.0 MAC sevoflurane anesthesia against liver IRI did not differ from those of 1.0 MAC isoflurane anesthesia in a 30-min hepatic ischemia model. However, for an understanding of the effects of the two anesthetics on liver IRI, we need to perform additional experiments using not only different concentrations of these anesthetics but different degrees of IRI. (4) To judge from the changes in α-GST level, the liver damage in the centrilobular regions after reperfusion was not significantly different between the two anesthetics. However, we did observe a tendency for a higher α-GST level in the sevoflurane group than in the isoflurane group from 2 min after reperfusion to 120 min after its start. Because the sample size for the α-GST measurements was relatively small compared with those for the other parameters, we checked for a type II error (β) in the α-GST measurements. The β values calculated for the time points from 2 min after reperfusion to 120 min after its start were between 0.44 and 0.53, indicating that our sample size for the α-GST measurements was too small to allow definite conclusions to be reached in regard to liver damage in the centrilobular region. Consequently, we will need to do further experiments to clarify whether the damage in the centrilobular regions after reperfusion differs between the two anesthetics. (5) In this experiment, we did not actively treat conditions such as hypotension, hyperkalemia, and severe acidosis, which are observed during and after liver ischemia-reperfusion, all of which may have exacerbated the injury. Treatment of these

conditions with appropriate fluid and drug therapy may have reduced the hepatic IRI in our experiment. For this reason, the extent of the injury in the present experiment may differ from that experienced clinically.

In conclusion, the extent of hepatic IRI seen under sevoflurane anesthesia in pigs did not differ significantly from that seen under isoflurane, when judged from a number of parameters over a 240-min reperfusion period in vivo. Further study will be necessary to assess more fully the influence of these two anesthetics on such injury.

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