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

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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 ± 0.4 mmol·l⁻¹ vs 2.5 ± 0.3 mmol·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 lactate 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
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·kg⁻¹·h⁻¹ and pancuronium 0.4 mg·kg⁻¹·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 PaCO₂ and PaO₂ 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·kg⁻¹·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, aspartateaminotransferase (AST), alanineaminotransferase (ALT), and lactate 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 µg 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