Sevoflurane Attenuates Ischemia-Reperfusion Injury in a Rat Lung Transplantation Model

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Background. **Sevoflurane is one of the most commonly used volatile anesthetic agents with the fastest onset and offset, replacing isoflurane in modern anesthesiology. Preconditioning and postconditioning using volatile anesthetics can attenuate ischemia-reperfusion injury (IRI). However, no previous studies have evaluated the effect of sevoflurane in lung transplantation after cold ischemic injury. We aimed to study the effects of donor and recipient treatment with sevoflurane in a rat lung transplantation model.**

Methods. **Lewis rats were allocated to four groups: control, PreC (preconditioning), PostC (postconditioning), and PreC + PostC. Donor rats in the PreC and PreC + PostC groups were exposed to 1.5% sevoflurane for 30 minutes before donor operation. Donor lungs were flushed with Perfadex and stored for 12 hours at 4°C before transplantation. Recipients received orthotopic left lung transplantation. In the PostC and PreC + PostC groups, sevoflurane was initiated 2 minutes before reperfusion and maintained for 30 minutes. Two hours after reperfusion, lung function was evaluated, and samples were collected for histologic, inflammatory, and cell death assessment.**

Results. **Preconditioning and postconditioning using sevoflurane significantly improved the oxygenation of lung grafts (partial arterial gas pressure of oxygen: 198 mm Hg in control, 406.5 mm Hg in PreC, 472.4 mm Hg in PostC, and 409.7 mm Hg in PreC + PostC, $p < 0.0001$) and reduced pulmonary edema. Sevoflurane treatment reduced levels of interleukin-1β, interleukin-6, and tumor necrosis factor-α. Moreover, sevoflurane significantly inhibited apoptotic cells by a decrease in cytochrome *c* release into cytosol and caspase-3 cleavage.**

Conclusions. **Preconditioning or postconditioning of lungs using sevoflurane exhibits a significant protective effect against early phase of ischemia-reperfusion injury in a rat lung transplantation model.**

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Lung ischemia-reperfusion injury (IRI) is associated with significant rates of perioperative morbidity and mortality [1]. Thus, strategies to mitigate IRI are highly desirable. Preconditioning and postconditioning of the lung has demonstrated beneficial effects in experimental models of transplantation and non–transplantation-related IRI. Some studies have also demonstrated that the ability to undergo preconditioning is almost ubiquitous in tissues and is highly conserved across species [2]. Thus far, ischemic postconditioning [3] and remote ischemic preconditioning [4] have also been introduced into clinical scenarios [5, 6].

Some drugs can provide organ protective effects, termed pharmacologic preconditioning, and numerous studies have found that volatile anesthetic preconditioning mimics organ protection in various tissues and organs [7–9]. Kersten and colleagues [8] were the first to demonstrate that volatile anesthetics induce cardioprotection in a preconditioning manner. Sevoflurane is one of the most commonly used volatile anesthetic agents with the fastest onset and offset, replacing isoflurane in modern anesthesiology. The effects of sevoflurane preconditioning and postconditioning have been well investigated in the heart [10, 11].

Despite being an inhaled agent, only a few studies have been reported using sevoflurane to attenuate lung injury [12–14]. However, no previous studies have evaluated the effect of sevoflurane, applied before or after conditioning, on IRI in lung transplantation after cold ischemic injury. We thus hypothesized that donor or recipient treatment with sevoflurane may reduce IRI in an established rat left lung transplantation (LTx) model.

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Abbreviations and Acronyms

ATP-K = adenosine triphosphate potassium
ELISA = enzyme-linked immunosorbent assay
IL = interleukin
IRI = ischemia-reperfusion injury
LTx = lung transplantation
MPO = myeloperoxidase
PostC = postconditioning
PreC = preconditioning
TNF = tumor necrosis factor
TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridinetriphosphate nick-end labeling
WDR = wet-to-dry weight ratio

Material and Methods

Animal Care

Male Lewis rats weighing 270 to 330 g (Charles River Laboratories Inc, Montreal, QC, Canada) were used. The animal use protocol was approved by the Animal Care Committee at University Health Network. All animals received humane care in compliance with the *Principles of Laboratory Animal Care* formulated by the National Society for Medical Research, the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health Publication no. 86-23, revised 1996), and the Guide to the Care and Use of Experimental Animals formulated by the Canadian Council on Animal Care.

Study Groups

Animals were allocated to one of four study groups (n = 6 per group) as follows: (1) control (no treatment), (2) PreC (preconditioning with 1.5% sevoflurane in donor rats; (3) PostC (postconditioning with 1.5% sevoflurane in recipient rats), and (4) PreC + PostC (preconditioning with 1.5% sevoflurane in donor rats and postconditioning with 1.5% sevoflurane in recipient rats).

Lung Transplantation Procedures

Donor rats in the PreC and PreC + PostC groups were exposed to 1.5% sevoflurane (Sevorane AF; Abbott, Saint-Laurent, QC, Canada) with 50% oxygen for 30 minutes and washed out with 50% oxygen in a chamber. Donor rats in all other groups were treated with 50% oxygen. All donor rats were anesthetized with an intraperitoneal injection of 60 mg/kg ketamine (Vetalar; Bioniche Animal Health, Belleville, ON, Canada) and 7.5 mg/kg xylazine (Rompun; Bayer Healthcare, Toronto, ON, Canada) as induction. Rats were ventilated under the following conditions: tidal volume of 10 mL/kg, respiratory rate of 60 breaths/minute, positive end-expiratory pressure of 2 cm H_2O, and inspired oxygen fraction of 0.5. Lungs were flushed with 20 mL of low potassium dextran glucose preservation solution (Perfadex; Vitrolife, Uppsala, Sweden) containing 10 μg of prostaglandin E1 (4°C, pressure 20 cm H_2O). After flushing, the trachea was clamped to maintain the lungs in an inflated state. Lungs were then stored at 4°C for 12 hours until transplantation. Just before each recipient procedure, donor lungs were prepared by placing three cuffs into the left pulmonary artery, left atrium, and left main bronchus (16-, 14-, and 14-gauge, respectively). Recipient rats were anesthetized with the same anesthetic induction regimen as the donor rats. A left thoracotomy was performed. The cuffs of the donor lung were placed into the corresponding recipient structures through each ventral incision, and anastomoses were secured with 7-0 polypropylene ties. Subsequently, the native lung was removed (left pneumonectomy). Lungs were then reinflated and ventilated with 100% oxygen. Sevoflurane (0.5%) was then immediately administered in the PostC and PreC + PostC groups, and 2 minutes later reperfusion was started. Once hemodynamics was stable, sevoflurane was increased to 1.5% for 30 minutes. Recipient rats were ventilated and reperfused for 2 hours. Blood samples were taken from the arterial line and left pulmonary vein with a 27-gauge needle directed toward the transplanted lungs, to be used for blood gas analysis [15, 16]. Two samples were obtained in each case at the end of reperfusion, and the mean value was used as final partial arterial gas pressure of oxygen (PaO_2) result. Lungs were removed for further examination, and all rats were euthanized by exsanguination.

Wet-to-Dry Weight Ratio

Left lung tissue was used to calculate the wet-to-dry weight ratio (WDR) at 2 hours after reperfusion. Tissues were excised from the upper third of the lung. Wet weight (in mg) was measured first; dry weight (in mg) was measured after the tissue had been dried for 3 days at 80°C. WDR was calculated as wet weight/dry weight.

Cytokines

After blood gas analyses, 2 mL of blood was taken and centrifuged at 6,000 rpm for 5 minutes. Plasma and the middle third of each lung was collected and stored at −80°C until use. Lung tissue was homogenized with the buffer, as described previously [17]. After the homogenized tissue was centrifuged, the lysate was collected. Cytokine and chemokine levels in plasma and tissue lysate were determined using a Rat Cytokine/Chemokine Magnetic Bead Panel–Premixed 15-Plex (MILLIPLEX; EMD Millipore, Billerica, MA). Levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α were confirmed by enzyme-linked immunosorbent assay (ELISA) with a Rat IL-1β ELISA Kit (Thermo Scientific, Waltham, MA) and IL-6 and TNF-α Rat ELISA Kits (Life Technologies, Carlsbad, CA), respectively. Respective concentration levels in the tissue lysate were normalized to 1.0 mg of protein in the lung.

Myeloperoxidase

Levels of myeloperoxidase (MPO) were quantitatively measured in plasma and lung tissue using a colorimetric assay kit (ELISA Kit for Myeloperoxidase; Uscn Life

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