Isoflurane pre-treatment before cardiopulmonary bypass alleviates neutrophil accumulation in dog lungs

GUI-ZHI DU, HONG GAO, JIN LIU, GUAN-SHENG WU, XIANG HE, XIANG-GANG ZENG, XUAN-YI HU, XIN-HUA LI

Abstract

Objective: This study investigated the effect of isoflurane pre-treatment on cardiopulmonary bypass (CPB)-related lung injury.

Methods: Twelve dogs were randomly divided into two groups of six each. In one group, 1.0 minimum alveolar concentration (MAC) of isoflurane was administered for 30 min before CPB, while the control group received no anaesthetic. Both groups then underwent 100 min of mild hypothermic CPB with 60-min aortic cross clamping. Haemodynamic parameters, respiratory mechanics and alveolar arterial oxygen difference ($AaDO_2$) were measured during the experiment. One hundred and fifty minutes after CPB, lung tissue samples from the non-dependent and dependent portions of the left and right lungs were harvested for polymorphonulear leukocyte (PMNs) counts.

Results: Following CPB, within the control group, pulmonary vascular resistance (PVR) was significantly increased at 60, 120 and 180 min after declamping, $AaDO_2$ deteriorated at 180 min post-declamping, and dynamic lung compliance (DLC) was reduced dramatically after declamping. Isoflurane pre-treatment before CPB significantly reduced PVR compared to the controls. $AaDO_2$ was impaired at 180 min after declamping and DLC was decreased after declamping within the isoflurane group. No differences in $AaDO_2$ and DLC were found between the isoflurane and control groups. At 180 min after declamping, the PMN count in both the non-dependent and dependent regions of the isoflurane pre-treated lungs was significantly lower than that of the controls.

Conclusions: Our results suggest that 30-min pre-treatment with 1.0 MAC isoflurane before CPB caused a reduction in

Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China
GUI-ZHI DU, MM
JIN LIU, MD, scujinliu@gmail.com

Department of Anesthesiology, the Affiliated Hospital of Guiyang Medical College, Guiyang 550004, Guizhou, China
HONG GAO, MM, anesth@21cn.com
XIANG-GANG ZENG, MB

Department of Anesthesiology, Guizhou Provincial Hospital, Guiyang 550002, Guizhou, China
XIANG HE

Department of Cardiac Surgery, the Affiliated Hospital of Guiyang Medical College, Guiyang 550004, Guizhou, China
GUAN-SHENG WU, MM
XUAN-YI HU, MM

Division of Public Health, Guiyang Medical College, Guiyang 550004, Guizhou, China
XIN-HUA LI, MB

PMN accumulation in the dog lungs, inhibition of increases in PVR, and it did not affect $AaDO_2$ in the early post-CPB stage.

The lungs are one of the most susceptible organs to ischaemia/reperfusion (IR) injury and systemic inflammatory response syndrome (SIRS) initiated during cardiopulmonary bypass (CPB).[1] Laboratory and clinical investigations have demonstrated that accumulation of polymorphonuclear leukocytes (PMNs) in the lungs plays a key role in the pathogenesis of CPB-related lung injury, which leads to impairment of gas exchange, increase in pulmonary vascular resistance (PVR) and decrease in pulmonary compliance.[1-5]

Volatile anaesthetics are commonly used during cardiac surgery. Nevertheless the effects of inhaled anaesthetic agents on lung injury remain controversial. Some studies showed that volatile anaesthetics can enhance the sensitivity of pulmonary artery endothelial cells to oxidation-mediated injury,[6] heighten pulmonary alveolar capillary membrane permeability in rabbits after aortic occlusion-perfusion,[7] and augment acute inflammatory response and leukocytic infiltration in acid-impaired rat lungs,[8] indicating that volatile anaesthetics may potentially exacerbate lung injury.

By contrast, in a mouse model of multiple organ dysfunction syndrome, it was shown that halothane and isoflurane attenuated lung inflammation and injury.[9] Liu and colleagues[10, 11] reported the administration of isoflurane before ischaemia and during reperfusion inhibited IR-induced isolated rabbit lung injury and demonstrated that not only isoflurane but also sevoflurane administered before ischaemia attenuated IR-induced injury in isolated rat lungs. More recently, Reutershan[12] and Li[13] documented the protective pre-treatment effects by isoflurane against endotoxin-induced lung injury in mouse and rat models.

In addition, the protective effects against IR injury by volatile anaesthetics have been shown in the myocardium,[14] brain,[15] liver[16] and kidney.[17] These data suggest that inhaled anaesthetics may not necessarily exacerbate lung injury after CPB. We therefore used an adult mongrel dog model of CPB to verify the hypothesis that pre-treatment of 30-min 1.0 minimum alveolar concentration (MAC) isoflurane before CPB would not aggravate lung injury related to CPB during the early post-CPB stage.

Methods

All experimental procedures used in this investigation were reviewed and approved by the Animal Care and Experimental

Committees of Guiyang Medical College and Huaxi Medical School of Sichuan University.

Surgical preparation and cardiopulmonary bypass

The studies were performed in 12 adult mongrel dogs weighing 10–18 kg. The animals were anaesthetised with intravenous pentobarbital sodium (25 mg/kg as an initial bolus and then 4 mg/kg/h), paralysed with intravenous vecuronium (0.1 mg/kg as an initial bolus and then 50 µg/kg every 30–40 min during the experiment). They were endotracheally intubated and ventilated on a volume-controlled mode with a tidal volume (TV) of 12 ml/kg, an inspiratory:expiratory ratio (I:E) of 1:2, extrinsic positive end-expiratory pressure ($PEEP_e$) of 0 cm H_2O, and an inspired O_2 fraction (FiO_2) of 1.0. Respiratory rate (RR) was adjusted to maintain normocapnia as guided by end-tidal CO_2 monitoring and intermittent arterial blood gas analyses. Peak inspiratory pressure (PIP), intrinsic positive end-expiratory pressure ($PEEP_i$) and mean airway pressure (MPaw) were continually measured by the airway monitor system of the anaesthesia machine (Narkomed GS; Dräger Medical Inc, Telford, PA).

The femoral vein and artery were cannulated to administer drugs and fluids, monitor arterial pressure and collect blood samples. A 7-French Swan–Ganz catheter (CritiCath™ SP107H-14 TD Catheter; Becton Dickinson Critical Care Systems, Singapore) was inserted through the right external jugular vein and placed in the main pulmonary artery to record central venous pressure (CVP), pulmonary artery pressure (PAP), and cardiac output (CO) by thermodilution technique (Spacelabs Monitor model 90369; Spacelabs Medical Inc, Redmond, WA). Nasopharyngeal temperature was continuously recorded.

For CPB, the bypass circuit consisted of a heat exchanger, cardiotomy reservoir, roller pump, bubble oxygenator, and microfilter primed with Ringer lactate solution (30 ml/kg), 6% HAES-steril (HES 200/0.5; 20 ml/kg), 30 ml 5% sodium bicarbonate, and heparin (150 U/kg). Gas flow to the oxygenator was 100% oxygen at 1 l/min. After median sternotomy and heparinisation (300 U/kg, IV), the ascending aorta and the right atrium were cannulated for initiation of bypass, and the left atrium for left atrial pressure (LAP) monitoring. The time between commencement of CPB and cardiac plegia arrest was standardised at 10 min. The aorta was clamped in combination with the pulmonary artery for 60 min to prevent any antegrade flow to the lungs and therefore make the ischaemic degree of the lungs comparable.

Ventilation was terminated during the period from cross clamping to declamping. The heart was arrested via the aortic root with cold (4°C) crystalloid St Thomas' solution (20 ml/kg) at a pressure of 70 mmHg immediately and 30 min after cross clamping. During total CPB, the pump flow was maintained between 80 and 100 ml/kg/min at a mean perfusion pressure of 40–80 mmHg and each animal was cooled to a nasopharyngeal temperature of 28–30°C. Alpha-stat pH management was observed during CPB. Twenty minutes before declamping, rewarming was initiated until the nasopharyngeal temperature of each animal was rewarmed to 38°C before termination of CPB. The heart was defibrillated with 20 J if necessary after cross clamp removal.

At the end of total CPB, the lungs were inflated manually for 15 s to 40 cm H_2O, according to a technique by Magnusson, *et al*.[18] Thirty minutes after declamping, all animals were weaned

from CPB using dopamine, starting at 3 µg/kg/min and up to 8 µg/kg/min. Following cessation of CPB, the blood in the oxygenator was transfused back into the circulation and all the dogs without heart decannulation and chest closure were closely observed for 150 min. Then lung tissue samples were taken after administration of an overdose of pentobarbital sodium (50 mg/kg, IV). Twelve lung tissue samples of approximately 1 cm × 1 cm × 1 cm were harvested from the non-dependent and dependent portions of the upper, middle and lower lobes of each animal's left and right lungs, with the excised lungs were inflated to a constant pressure of 20 cm H_2O. Harvested lung tissue samples were used for PMN counts.

Experimental protocol

Twelve adult mongrel dogs were randomly divided into two groups (*n* = 6 each). Measurable variables recorded after 15-min stabilisation following heart cannulation served as baseline. During the 40-min period from recording the baseline to initiating CPB, the animals in the control group received no treatment, while the other six dogs received 30 min 1.0 MAC isoflurane (Abbott Laboratories, North Chicago, IL; 1.39% for 1.0 MAC in dogs;[19] Spacelabs). The pre-treatment time of the clinically frequent applied concentration (1.0 MAC) of isoflurane was based on previous *in vivo* studies concerning myocardial protective preconditioning in dogs.[20]

Dynamic lung compliance (DLC), measured at baseline and 5, 31, 60, 120 and 180 min after declamping, was calculated using the following formula:

$$DLC \ (ml/cm \ H_2O) = \frac{TV \ (ml)}{PIP \ (cm \ H_2O) - PEEP \ (cm \ H_2O)}$$

Pulmonary vascular resistance, measured at baseline and 31, 60, 120 and 180 min after declamping, was calculated using the following formula:

$$PVR \ (dynes/s/cm^5) = [mean \ PAP \ (mm \ Hg) - mean \ LAP \ (mm \ Hg)] \times 79.92/CO \ (l/min)$$

Arterial blood samples, taken at baseline and 5, 31 and 180 min after declamping, were examined in a blood gas analyser (i-Stat; Abbott Laboratories Inc., East Windsor, NJ). Alveolar arterial oxygen difference ($AaDO_2$) was calculated using the following formula:

$$AaDO_2 \ (mmHg) = \frac{PiO_2 - PaCO_2}{R - PaO_2}$$

$$PiO_2 = (P_B - P_{H2O}) \times FiO_2$$

Where PiO_2 is inspired oxygen pressure, R is respiratory quotient with an assumed value of 0.8, P_B is barometric pressure with an assumed value of 760, P_{H2O} is the pressure of the water vapour at body temperature with an assumed value of 47, and PaO_2 is arterial oxygen tension.

The excised lung tissue samples were immediately fixed in 10% formol, then dehydrated, embedded in paraffin, cut into 4-µm slices along a coronal plane from apex to base and stained with haematoxylin and eosin. The slices were coded and examined in a blinded manner by a single examiner. Interstitial and intra-alveolar PMNs were identified and counted in 10 different fields, excluding airways and pulmonary vessels, under 400 × magnification (Model CH30RF200, Olympus, Tokyo, Japan). The data were expressed as number of PMNs per high-power lung field.[21]

TABLE 1. HAEMODYNAMIC VARIABLES						
		Time after aortic declamping (min)				
Parameter	*Baseline*	*5*	*31*	*60*	*120*	*180*
Mean arterial pressure (mmHg)						
Control	82.5 ± 5.5	66.2 ± 6.6	75.5 ± 5.8	60.7 ± 4.9*	59.2 ± 2.8*	57.0 ± 3.8**
Isoflurane	85.8 ± 6.9	57.0 ± 4.5**	61.0 ± 3.1**	64.3 ± 7.6	63.8 ± 6.8	60.2 ± 6.1*
Heart rate (beats/min)						
Control	161.0 ± 9.8		135.7 ± 11.3	119.8 ± 10.2**	98.5 ± 5.9***	91.5 ± 5.1***
Isoflurane	168.5 ± 8.1		140.7 ± 13.0	137.3 ± 9.5	118.5 ± 5.7**	101.3 ± 5.5***
Central venous pressure (mmHg)						
Control	5.7 ± 0.7	4.5 ± 0.9	6.7 ± 1.0	6.6 ± 0.7	7.5 ± 1.3	6.7 ± 0.6
Isoflurane	7.1 ± 0.6	6.6 ± 0.7	6.5 ± 0.7	7.0 ± 0.5	6.7 ± 0.4	7.9 ± 0.4
Mean pulmonary artery pressure (mmHg)						
Control	10.2 ± 1.2	12.2 ± 1.2	15.7 ± 2.6	15.8 ± 2.0	15.0 ± 1.6	14.7 ± 0.6
Isoflurane	10.7 ± 1.7	7.8 ± 1.9	13.8 ± 2.0	13.3 ± 1.1	14.7 ± 0.9	12.8 ± 1.5
Mean left atrial pressure (mmHg)						
Control	5.3 ± 1.2	4.7 ± 0.8	6.5 ± 1.2	5.7 ± 1.4	7.7 ± 1.9	6.3 ± 1.5
Isoflurane	6.2 ± 1.9	4.2 ± 1.5	6.0 ± 1.2	5.3 ± 0.5	8.0 ± 1.2	7.2 ± 1.3
Cardiac output (l/min)						
Control	3.7 ± 0.4		4.0 ± 0.5	3.8 ± 0.5	2.6 ± 0.5	3.0 ± 0.6
Isoflurane	3.3 ± 0.5		3.6 ± 0.6	3.4 ± 0.5	3.0 ± 0.5	2.6 ± 0.4
Data shown are mean ± SEM. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ compared with baseline.						

Statistical analysis

Data in the text, tables and figures are expressed as mean ± SEM. Lung tissue PMN counts were evaluated by independent samples *t*-test. Changes in haemodynamic parameters, respiratory mechanics, PVR and $AaDO_2$ over time between groups were determined by repeated-measures analysis of variance (ANOVA). Intra-group data at any given time point for a given continuous variable were compared with a respective baseline using the Dunnett *post hoc* test when univariate ANOVA for repeated measures was significant. Additionally, independent samples *t*-tests were used to compare the parameters at each time point between the two groups. Statistical analysis was performed with SPSS software package, version 11.5 (SPSS Inc., Chicago, IL). Significance was assumed at $p < 0.05$.

Results

Changes in haemodynamic variables are shown in Table 1. MAP, HR, CVP, MPAP, mean LAP and CO values did not change significantly between the groups during the experiment. HR and CO measured at 5 min after declamping were not analysed because of comparatively lower cardiac function at the time. CVP and mean LAP in both groups were within the physiological range at the end of the experiment.

At baseline, PIP, MPaw, $PEEP_i$ and DLC values in the group treated with isoflurane were comparable to those in the control group. Following declamping, PIP and MPaw were significantly increased, and DLC decreased in both the isoflurane and control groups. Isoflurane pre-treatment did not affect PIP, MPaw, $PEEP_i$ and DLC significantly, compared to the controls (Table 2).

| TABLE 2. RESPIRATORY MECHANICS						
		Time after aortic declamping (min)				
Parameter	*Baseline*	*5*	*31*	*60*	*120*	*180*
Peak inspiratory pressure (cm H_2O)						
Control	10.8 ± 1.1	16.3 ± 1.5	17.5 ± 1.8*	17.8 ± 1.9*	19.2 ± 2.0**	19.3 ± 1.9**
Isoflurane	9.5 ± 0.4	13.8 ± 1.1	15.2 ± 1.5**	16.2 ± 1.4**	17.5 ± 1.2***	18.3 ± 1.1***
Mean airway pressure (cm H_2O)						
Control	4.7 ± 0.3	7.0 ± 0.5	7.5 ± 0.7*	7.5 ± 0.7*	7.8 ± 0.7**	7.7 ± 0.7**
Isoflurane	4.0 ± 0.3	5.3 ± 0.2*#	5.8 ± 0.3**	6.2 ± 0.4***	6.7 ± 0.2***	6.7 ± 0.4***
Intrinsic positive end expiratory pressure (cm H_2O)						
Control	1.3 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.8 ± 0.2	1.8 ± 0.2
Isoflurane	1.3 ± 0.2	1.0 ± 0.3	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.7 ± 0.5
Dynamic lung compliance (ml/cm H_2O)						
Control	27.7 ± 4.0	16.8 ± 1.7*	14.6 ± 2.8**	14.3 ± 2.1**	13.3 ± 1.9**	12.4 ± 2.1**
Isoflurane	25.5 ± 1.6	16.4 ± 2.1**	14.1 ± 1.8***	13.6 ± 1.5***	11.6 ± 1.3***	11.2 ± 1.1***
Data shown are mean ± SEM. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ compared with baseline. #$p < 0.05$ compared with control at a given time point.						
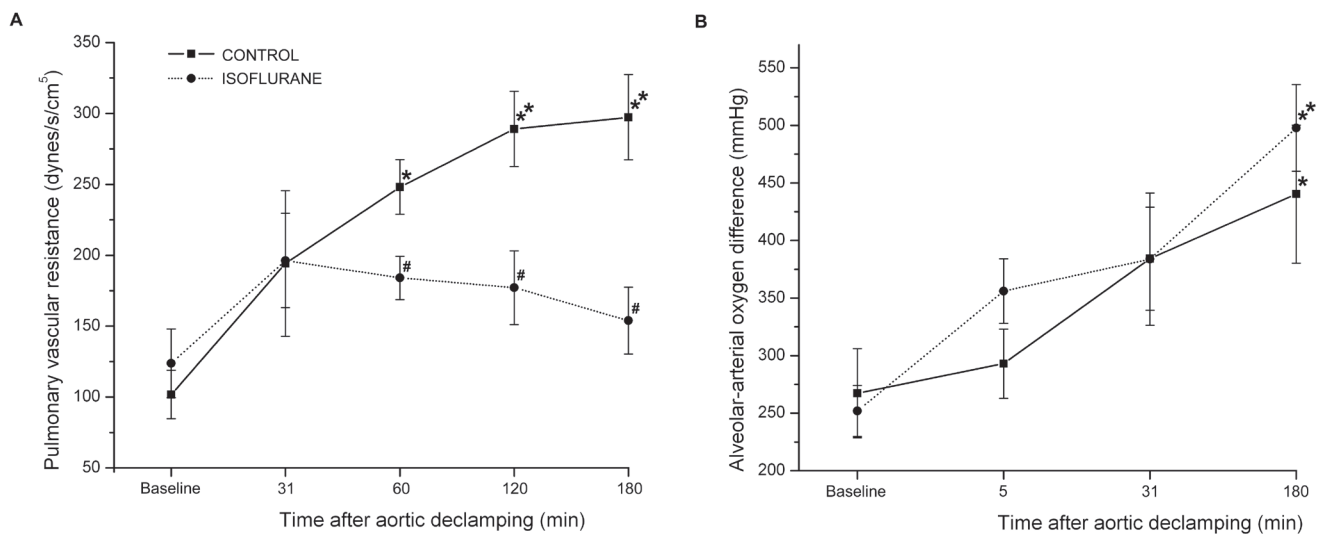
Fig. 1. Changes in pulmonary vascular resistance (PVR) at baseline and 31, 60, 120 and 180 min after aortic declamping (A), and alveolar arterial oxygen difference ($AaDO_2$) at baseline and 5, 31 and 180 min after aortic declamping (B), of the control and isoflurane groups. Data shown are mean $\pm$ SEM. *$p < 0.05$ vs baseline and **$p < 0.01$ vs baseline; #$p < 0.05$ compared with control at a given time point.

Fig. 1A reflects the pattern of PVR changes in each group during the study. At baseline, PVR in the isoflurane group was comparable to that in the control. Following CPB, in the control group, PVR was significantly increased at 60 ($p < 0.05$ vs baseline), 120 ($p < 0.01$ vs baseline) and 180 min ($p < 0.01$ vs baseline) after declamping. No differences in PVR were found within the isoflurane group ($p > 0.05$ vs baseline). There were significant differences in PVR between the isoflurane and control groups ($p < 0.05$). At 60, 120 and 180 min after declamping, PVR values were lower in the isoflurane group compared to those in the control group ($p < 0.05$).

Fig. 1B shows the changes in $AaDO_2$ in the isoflurane and control groups over the experimental time. At baseline, $AaDO_2$ did not differ between the isoflurane and control groups ($p = 0.429$). Within both the isoflurane and the control group, $AaDO_2$ at 180 min after declamping was markedly higher than that at baseline ($p < 0.01$ and $p < 0.05$, respectively). Pre-treatment of isoflurane did not affect $AaDO_2$ significantly over the experiment, compared to the control group ($p > 0.05$).

PMNs infiltrations in both the non-dependent and dependent lung regions were significantly lower in the isoflurane group compared to those in the controls (both $p < 0.001$). No differences in PMN counts were detected between the non-dependent and dependent lung regions or between left and right lungs in each group ($p > 0.05$) (Figs 2 and 3).

Discussion

Mechanisms of lung injury and respiratory complications following CPB are multi-factorial, including aspects due to CPB.[22] During CPB, blood contact with the artificial surface of the bypass circuit, coupled with IR injury contribute to the initiation of SIRS which is partially attributed to activation of PMNs with up-regulation of adhesion molecules. This process may ultimately result in adhesion of PMNs to the endothelium of the lung vessels, and endothelial damage due to protease release.[1] Researchers in multi-disciplinary fields have been attempting to find better lung protective and therapeutic strategies against CPB-associated lung injury. Few currently developed strategies, however, have been demonstrated to be clinically beneficial.[22]

Recently, some literature reports that volatile anaesthetics showed protective effects against lung injury.[9-13] In a male mouse model of endotoxin-induced lung injury, isoflurane pre-treatment significantly attenuated PMN recruitment into the injured lung.[12] The clinical dilemma of lung injury during CPB and this encouraging *in vitro* and *in vivo* evidence gave us insight into conducting the experiment. The primary findings of the current experiment were that isoflurane pre-treatment before CPB alleviated PMN accumulation in the lungs, reduced PVR, and did not affect $AaDO_2$ during the early post-CPB stage, compared to the controls.

Reduced static and dynamic compliance is one of the characteristics of pulmonary function in patients after exposure to CPB.[23,24] Postulated causes include atelectasis, pulmonary oedema, inflammation, increased capillary permeability, and pleural
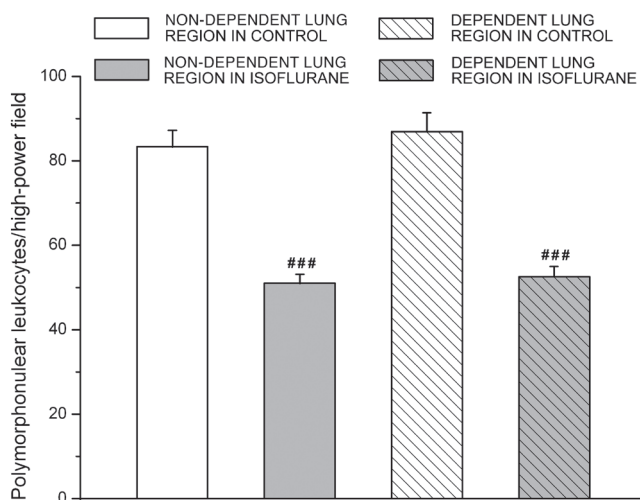

Fig. 2. Lung tissue polymorphonuclear leukocyte (PMN) counts (expressed as PMNs/field) in 10 different fields, excluding airways and pulmonary vessels under 400 × magnification in non-dependent and dependent lung regions of the control and isoflurane groups. Data shown are mean $\pm$ SEM. ###$p < 0.001$ vs control.
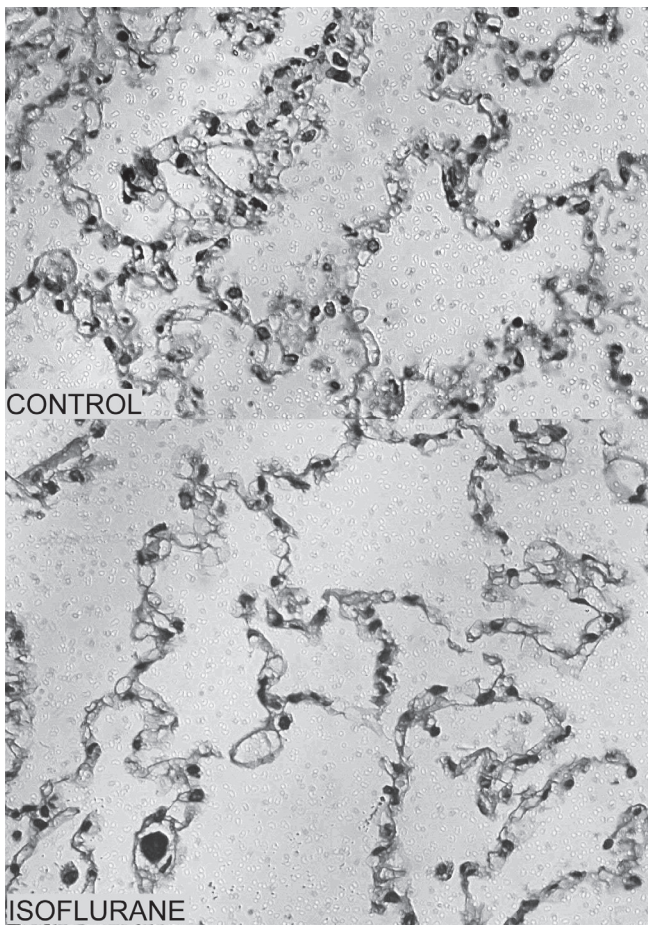
Fig. 3. Microscopic findings of polymorphonuclear leuko-cyte (PMN) filtration in the dependent portion of the lower lobe of the left lung three hours after aortic declamping in the control and isoflurane groups (haematoxylin-eosin; magnification × 400).

effusions.[25] Dogs pre-treated with isoflurane in our experiment showed significantly reduced DLC values after CPB, as did the control group. However, no difference in DLC was found between the two groups. Consistent with our DLC results, in an oleic acid-induced lung injury model, it was also documented that lung compliance of the injured canine lungs was not affected by inhalation of isoflurane.[26]

In the present study we found 30-min pre-treatment with 1.0 MAC isoflurane before CPB significantly decreased PVR in the early post-CPB stage. The effect of isoflurane on PVR shown in our study may potentially be ascribable to the demonstrated phenomenon that isoflurane attenuates hypoxic pulmonary vasoconstriction (HPV).[27-30] It has been shown that metabolites of the cyclooxygenase pathway,[28] endogenous vasodilator,[29] calcium-activated potassium (K_{Ca}) channels and voltage-dependent potassium (K_V) channels[30] may be involved in the modulation of isoflurane-induced attenuation of HPV. More recently, it has been reported that TASK-1 channels play a role in HPV and contribute to volatile anaesthetic-induced pulmonary vasodilation.[31]

In our experiment, although it was striking that gas exchange in the isoflurane group, assessed by $AaDO_2$ changes, deteriorated steadily following the diminution of PVR after aortic declamping, no difference in $AaDO_2$ was found between the isoflurane-treated and control groups. The reason might be that the inhibition of HPV by isoflurane caused only minor effects on

gas exchange in our study setting. In an oleic acid-induced lung injury model, it has been demonstrated that low concentrations of isoflurane resulted in an increase in ventilation and perfusion mismatch, as evaluated by multiple inert gas analysis.[26] However, $AaDO_2$ in the injured lungs was not significantly changed by inhalation of the low concentrations of isoflurane.[26]

By contrast, in a porcine model with gas-exchange defect by air pneumoperitoneum, it was shown that sevoflurane but not isoflurane caused significant ventilation and perfusion mismatch using the multiple inert gas elimination technique.[32] The differences between the experimental model (oleic acid-induced vs air pneumoperitoneum-induced gas-exchange defect) and the controls (sodium pentobarbital-anaesthetised animals with definite lung injury vs propofol-anaesthetised animals with gas-exchange defect) may account for the inconsistence shown in the abovementioned two experiments regarding the effect of isoflurane on gas-exchange disturbance.

It is well known that PMNs play a key role in the development of post-CPB lung injury.[1-5,22] Previous studies showed that volatile anaesthetics reduced PMN adhesion in the reperfused coronary system.[33,34] Recently it was demonstrated that isoflurane pre-treatment attenuated PMN accumulation in the lung interstitium and alveolar space in a male mouse model of lipopolysaccharide-induced lung injury.[12] Our results of PMN counts showed that isoflurane remarkably alleviated PMN filtration into the non-dependent and dependent lung regions three hours after declamping, indicating that isoflurane could be beneficial for inhibition of inflammation in lungs during CPB.

Some limitations of our experiment should be noted. First, pentobarbital showed an inhibitary effect on HPV.[35] Consequently, the effects of isoflurane on CPB-related lung injury may be altered with the pentobarbital anaesthesia. However, the results should be reliable since a continuous quantitative infusion (25 mg/kg as an initial bolus and then 4 mg/kg/h) of pentobarbital was performed in the current study. In addition, to prevent any antegrade flow to the lungs and therefore make any lung injury in each animal as similar as possible, our animals were subject to pulmonary artery as well as aortic clamping during CPB. This may have aggravated the degree of lung injury, in that exposure to CPB alone is enough to cause pulmonary injury, and cessation of pulmonary arterial flow during CPB contributes significantly to pulmonary dysfunction.[24]

Conclusion

The present study showed that 30-min pre-treatment with 1.0 MAC isoflurane before CPB alleviated PMN accumulation in canine lungs, inhibited the increase in PVR, and did not significantly affect $AaDO_2$ in the early post-CPB stage, suggesting isoflurane could be beneficial in preventing CPB-related lung injury.

References

1.   Asimakopoulos G, Smith PL, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. *Ann Thorac Surg* 1999; **68**: 1107–1115.
2.   Dreyer WJ, Michael LH, Millman EE, Berens KL, Geske RS.

Neutrophil sequestration and pulmonary dysfunction in a canine model of open-heart surgery with cardiopulmonary bypass. Evidence for a CD18-dependent mechanism. *Circulation* 1995; **92**: 2276–2283.

3. Friedman M, Wang SY, Sellke FW, Cohn WE, Weintraub RM, Johnson RG. Neutrophil adhesion blockade with NPC 15669 decreases pulmonary injury after total cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1996; **111**: 460–468.

4. Tönz M, Mihaljevic T, von Segesser LK, Fehr J, Schmid ER, Turina MI. Acute lung injury during cardiopulmonary bypass. Are the neutrophils responsible? *Chest* 1995; **108**: 1551–1556.

5. Redmond JM, Gillinov AM, Stuart RS, Zehr KJ, Winkelstein JA, Herskowitz A, *et al*. Heparin-coated bypass circuits reduce pulmonary injury. *Ann Thorac Surg* 1993; **56**: 474–479.

6. Shayevitz JR, Varani J, Ward PA, Knight PR. Halothane and isoflurane increase pulmonary artery endothelial cell sensitivity to oxidant-mediated injury. *Anesthesiology* 1991; **74**: 1067–1177.

7. Nielsen VG, Baird MS, McAdams ML, Freeman BA. Desflurane increases pulmonary alveolar-capillary membrane permeability after aortic occlusion-reperfusion in rabbits: evidence of oxidant-mediated lung injury. *Anesthesiology* 1998; **88**: 1524–1534.

8. Nader-Djalal N, Knight PR, Bacon MF, Tait AR, Kennedy TP, Johnson KJ. Alterations in the course of acid-induced lung injury in rats after general anesthesia: volatile anesthetics versus ketamine. *Anesth Analg* 1998; **86**: 141–146.

9. Shayevitz JR, Rodriguez JL, Gilligan L, Johnson KJ, Tait AR. Volatile anesthetic modulation of lung injury and outcome in a murine model of multiple organ dysfunction syndrome. *Shock* 1995; **4**: 61–67.

10. Liu R, Ishibe Y, Ueda M, Hang Y. Isoflurane administration before ischemia and during reperfusion attenuates ischemia/reperfusion-induced injury of isolated rabbit lungs. *Anesth Analg* 1999; **89**: 561–565.

11. Liu R, Ishibe Y, Ueda M. Isoflurane-sevoflurane adminstration before ischemia attenuates ischemia-reperfusion-induced injury in isolated rat lungs. *Anesthesiology* 2000; **92**: 833–840.

12. Reutershan J, Chang D, Hayes JK, Ley K. Protective effects of isoflurane pretreatment in endotoxin-induced lung injury. *Anesthesiology* 2006; **104**: 511–517.

13. Li QF, Zhu YS, Jiang H, Xu H, Sun Y. Isoflurane preconditioning ameliorates endotoxin-induced acute lung injury and mortality in rats. *Anesth Analg* 2009; **109**: 1591–1597.

14. Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Warltier DC. Mechanism of myocardial protection by isoflurane. Role of adenosine triphosphate-regulated potassium (KATP) channels. *Anesthesiology* 1996; **85**: 794–807.

15. Kurth CD, Priestley M, Watzman HM, McCann J, Golden J. Desflurane confers neurologic protection for deep hypothermic circulatory arrest in newborn pigs. *Anesthesiology* 2001; **95**: 959–964.

16. Kon S, Imai M, Inaba H. Isoflurane attenuates early neutrophil-independent hypoxia-reoxygenation injuries in the reperfused liver in fasted rats. *Anesthesiology* 1997; **86**: 128–136.

17. Lee HT, Ota-Setlik A, Fu Y, Nasr SH, Emala CW. Differential protective effects of volatile anesthetics against renal ischemia-reperfusion injury in vivo. *Anesthesiology* 2004; **101**: 1313–1324.

18. Magnusson L, Zemgulis V, Tenling A, Wernlund J, Tydén H, Thelin S, *et al*. Use of a vital capacity maneuver to prevent atelectasis after cardiopulmonary bypass: an experimental study. *Anesthesiology* 1998; **88**: 134–142.

19. Kazama T, Ikeda K. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. *Anesthesiology* 1988; **68**: 435–437.

20. Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Warltier DC. Isoflurane mimics ischemic preconditioning via activation of K(ATP) channels: reduction of myocardial infarct size with an acute memory phase. *Anesthesiology* 1997; **87**: 361–370.

21. Reickert CA, Rich PB, Crotti S, Mahler SA, Awad SS, Lynch WR, *et al*. Partial liquid ventilation and positive end-expiratory pressure reduce ventilator-induced lung injury in an ovine model of acute respiratory failure. *Crit Care Med* 2002; **30**: 182–189.

22. Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. *Chest* 2002; **21**: 1269–1277.

23. Kochamba GS, Yun KL, Pfeffer TA, Sintek CF, Khonsari S. Pulmonary abnormalities after coronary arterial bypass grafting operation: cardiopulmonary bypass versus mechanical stabilization. *Ann Thorac Surg* 2000; **69**: 1466–1470.

24. Chaney MA, Nikolov MP, Blakeman B, Bakhos M, Slogoff S. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. *Anesth Analg* 1998; **87**: 27–33.

25. Barnas GM, Watson RJ, Green MD, Sequeira AJ, Gilbert TB, Kent J, et al. Lung and chest wall mechanical properties before and after cardiac surgery with cardiopulmonary bypass. *J Appl Physiol* 1994; **76**: 166–175.

26. Putensen C, Räsänen J, Putensen-Himmer G, Downs JB. Effect of low isoflurane concentrations on the ventilation-perfusion distribution in injured canine lungs. *Anesthesiology* 2002; **97**: 652–659.

27. Groh J, Kuhnle GE, Sckell A, Ney L, Goetz AE. Isoflurane inhibits hypoxic pulmonary vasoconstriction. An *in vivo* fluorescence microscopic study in rabbits. *Anesthesiology* 1994; **81**: 1436–1444.

28. Lennon PF, Murray PA. Attenuated hypoxic pulmonary vasoconstriction during isoflurane anesthesia is abolished by cyclooxygenase inhibition in chronically instrumented dogs. *Anesthesiology* 1996; **84**: 404–414.

29. Tschaikowsky K, Ritter J, Schröppel K, Kühn M. Volatile anesthetics differentially affect immunostimulated expression of inducible nitric oxide synthase: role of intracellular calcium. *Anesthesiology* 2000; **92**: 1093–1102.

30. Liu R, Ueda M, Okazaki N, Ishibe Y. Role of potassium channels in isoflurane- and sevoflurane-induced attenuation of hypoxic pulmonary vasoconstriction in isolated perfused rabbit lungs. *Anesthesiology* 2001; **95**: 939–946.

31. Olschewski A. Targeting TASK-1 Channels as a Therapeutic Approach. *Adv Exp Med Biol* 2010; **661**: 459–473.

32. Kleinsasser A, Lindner KH, Hoermann C, Schaefer A, Keller C, Loeckinger A. Isoflurane and sevoflurane anesthesia in pigs with a preexistent gas exchange defect. *Anesthesiology* 2001; **95**: 1422–1426.

33. Kowalski C, Zahler S, Becker BF, Flaucher A, Conzen PF, *et al*. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. *Anesthesiology* 1997; **86**: 188–195.

34. Heindl B, Reichle FM, Zahler S, Conzen PF, Becker BF. Sevoflurane and isoflurane protect the reperfused guinea pig heart by reducing postischemic adhesion of polymorphonuclear neutrophils. *Anesthesiology* 1999; **91**: 521–530.

35. Wetzel RC, Martin LD. Pentobarbital attenuates pulmonary vasoconstriction in isolated sheep lungs. *Am J Physiol* 1989; **257**: H898–H903.