Pulmonary Vascular Effects of Isoflurane Anesthesia after Left Lung Autotransplantation in Chronically Instrumented Dogs

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Background: Single lung transplantation has become a viable therapy for treatment of end-stage pulmonary disease. We previously observed that left lung autotransplantation (LTA) results in a chronic increase in pulmonary vascular resistance and enhanced pulmonary vascular reactivity to sympathetic α adrenergic receptor activation. The effects of inhalational anesthetics on the pulmonary circulation after lung transplantation have not been investigated. In the current study, the authors tested the hypothesis that isoflurane anesthesia, known to cause systemic vasodilatation, would exert a vasodilator influence on the baseline pulmonary circulation after LTA. In addition, they tested the hypothesis that isoflurane anesthesia, known to attenuate the systemic vasoconstrictor response to sympathetic α adrenergic agonists, would reduce the magnitude of the pulmonary vasoconstrictor response to sympathetic α adrenergic receptor activation after LTA.

Methods: Left pulmonary vascular pressure–flow (LPQ) plots were generated in chronically instrumented dogs by measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure–left atrial pressure) and left pulmonary blood flow during inflation of a hydraulic occluder implanted around the main pulmonary artery. Left pulmonary vascular pressure–flow plots were generated in 8 dogs 2–5 weeks after LTA in the conscious and isoflurane-anesthetized states at baseline, after β adrenergic receptor block with propranolol, and during the cumulative administration of the α agonist, phenylephrine. Left pulmonary vascular pressure–flow plots also were generated in eight conscious, sham-operated control dogs at baseline, after β block, and during phenylephrine administration.

Results: Compared with conscious control dogs, LTA resulted in a leftward shift (P < 0.01) in the baseline left pulmonary vascular pressure–flow relation, indicating chronic pulmonary vasoconstriction. Despite the enhanced level of pulmonary vasoconstrictor tone after LTA, isoflurane did not exert a vasodilator influence on the baseline left pulmonary vascular pressure–flow relation. The pulmonary vasoconstrictor response to phenylephrine was enhanced (P < 0.01) after LTA compared with the response measured in conscious control dogs. The magnitude of the pulmonary vasoconstrictor response to phenylephrine after LTA was not attenuated during isoflurane anesthesia.

Conclusions: Isoflurane anesthesia does not exert a vasodilator influence on the pulmonary circulation in the setting of increased pulmonary vascular resistance after LTA. In addition, in contrast to previous studies of the systemic circulation, isoflurane does not attenuate the enhanced pulmonary vasoconstrictor response to sympathetic α adrenergic receptor activation after LTA. (Key words: Anesthetics, volatile; isoflurane; Lung(s): circulation; pressure–flow relation; autotransplantation; chronic instrumentation. Pharmacology: phenylephrine; propranolol.)

SINGLE lung transplantation has become a viable therapy for treatment of end-stage pulmonary disease. Despite recent improvements in outcome, surgical procedure continues to result in significant morbidity and mortality.1,2 We observed that both an acute and a chronic increase in pulmonary vascular resistance occurs after left lung autotransplantation (LTA) in chronically instrumented dogs.3–7 This increase in pulmonary vascular resistance after LTA is partially mediated by sympathetic α adrenergic receptor activation,8 and may reflect "denervation supersensitivity."8,9 Isoflurane also exhibits an enhanced endogenous adrenergic α adrenergic receptor agonist activity.

In the systemic vascular beds in baseline vasomotor tone and vasoconstrictor response to sympathetic stimulation. These systemic vascular effects may be beneficial if they ameliorate the pulmonary vasodilator response to chronic isoflurane anesthesia and thereby reduce pulmonary vascular resistance.3,10,11 Further, isoflurane may produce direct pulmonary vasodilatation and increase pulmonary blood flow. However, these effects have not been investigated in vivo under conditions of chronic isoflurane anesthesia after LTA.

We used an experimental model of chronic isoflurane anesthesia to determine whether isoflurane anesthesia produced changes in pulmonary vascular resistance after LTA. Our goal was to investigate whether isoflurane anesthesia decreases the effects of background pulmonary vasodilator response to sympathetic α adrenergic receptor activation after LTA. (Key words: Anesthetics, volatile; isoflurane; Lung(s): circulation; pressure–flow relation; autotransplantation; chronic instrumentation. Pharmacology: phenylephrine; propranolol.)

Materials and Methods

All surgical procedures were approved by the National Heart, Lung and Blood Institute (NHLBI) and Videosurgery and Endoscopy Use Committee. Surgery for Chronic Ischemia

Sixteen conditioned canine autotransplantation models were used in this study.

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supersensitivity. The pulmonary circulation after LLA also exhibits an enhanced vasoconstrictor response to the exogenous administration of phenylephrine, a sympathetic α-adrenoreceptor agonist.

In the systemic circulation, isoflurane anesthesia results in baseline vasodilation and an attenuation of the vasoconstrictor response to the exogenous administration of sympathetic α-adrenoreceptor agonists. These systemic vascular effects of isoflurane could be beneficial if they also were to occur in the pulmonary circulation after LLA. However, the effects of isoflurane on the pulmonary circulation after lung transplantation have not been investigated. Patients, after lung transplantation, are undergoing general anesthesia and surgery with increasing frequency. In these patients, anesthetic agents may result in abrupt and severe cardiovascular deterioration. Therefore, due to its extensive clinical use and potential benefits, we chose to investigate the effects of isoflurane anesthesia on the pulmonary circulation after LLA.

We used an experimental preparation in which dogs were chronically instrumented, to permit the generation of pulmonary vascular pressure–flow plots. This allowed us to assess the pulmonary vascular pressure–flow relation in the conscious state and during isoflurane anesthesia, thereby avoiding the confounding effects of background anesthetics and acute surgical trauma. We previously demonstrated that general anesthesia modifies neural, humoral, and local mechanisms of pulmonary vascular regulation. The use of pulmonary vascular pressure–flow plots to assess the effects of physiologic and pharmacologic interventions on the pulmonary circulation also avoids the limitations inherent in single-point calculations of pulmonary vascular resistance. In addition, the autotransplantation model used in this investigation permitted us to investigate pulmonary vasoregulation after LLA without the important but confounding effects of tissue rejection, immunosuppression, lung preservation techniques, and prolonged ischemia.

Materials and Methods

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee.

Surgery for Chronic Instrumentation

Sixteen conditioned male mongrel dogs (27 ± 1 kg) were used in this study. All dogs were premedicated intramuscularly with 10 mg morphine sulfate and anesthetized intravenously with 20 mg/kg pentobarbital sodium and 15 μg/kg fentanyl citrate. Tracheal intubation was performed, and the lungs were mechanically ventilated. Anesthesia was maintained with ~1.2% endtidal halothane. A left thoracotomy was performed via the fifth intercostal space, using sterile surgical technique. The pericardium was incised ventrally to the phrenic nerve. Heparin-filled Tygon catheters (1.02 mm internal diameter [ID], Norton, Akron, OH) were inserted into the descending thoracic aorta, left and right atrium, and main pulmonary artery. The catheters were secured with purse-string sutures. After careful dissection and isolation, a hydraulic occluder (16–18 mm ID, Jones, Silver Springs, MD) was loosely positioned around the right main pulmonary artery, and an electromagnetic flow probe (10–12 mm ID, Zepeda, Seattle, WA) was placed around the left main pulmonary artery.

Eight dogs underwent LLA as described previously. The remaining eight dogs served as sham-operated, healthy control dogs. Left lung autotransplantation was achieved by sequential division and anastomosis of the left pulmonary veins, left main bronchus, and left main pulmonary artery. A wide, circumferential pericardial incision mobilized the left lung. After 3,000 U heparinization intravenously, the left pulmonary veins (inferior, middle, and superior) were individually dissected to their point of confluence with the left atrium. These veins were then cross-clamped, divided, and Anastomosed with a continuous stitch of 7-0 Prolene suture. The left main bronchus was clamped distal to the carina, divided, and anastomosed using a continuous stitch of 4-0 Prolene suture. The left main pulmonary artery was isolated, cross-clamped, divided, and anastomosed with a continuous stitch of 4-0 Prolene suture. These anastomoses required approximately 10–20 min of left pulmonary artery cross-clamp time. Care was taken to avoid air emboli after release of the vascular clamps, to avoid luminal narrowing, and to ensure good intimal apposition at the anastomotic sites.

In all 16 dogs, the pericardial edges were loosely apposed, and the free ends of the catheters, occluder, and flow probe were threaded through the chest wall and tunneled subcutaneously to a final position between the scapulae. A chest tube was placed in the left thorax before closure and was removed on the first postoperative day. Ten milligrams intramuscular morphine sulfate was administered postoperatively for pain, as required. Two grams intravenous Cephazolin

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(Bristol-Myers Squibb, Princeton, NJ) was administered intraoperatively and for 10 days postoperatively (cephalexin, 2 g daily, by mouth). The dogs were allowed to recover for at least 2 weeks before experimentation.

**Experimental Measurements**

Vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Gould Statham P23 ID, Eastlake, OH) and were referenced to atmospheric pressure with the transducers positioned at midchest at the level of the spine. Heart rate was calculated from the phasic aortic pressure trace. Left pulmonary blood flow (LQ) was measured by connecting the flow probe to an electromagnetic flowmeter (Zepeda model SWF-3rd, Seattle, WA). The flow probe was calibrated in vivo on a weekly basis using the thermal dilution technique. Calibration was achieved by temporarily inserting a balloon-tipped catheter (7-Fr) into the pulmonary artery through a percutaneous jugular puncture after topical anesthesia (lidocaine spray). The catheter was positioned 2–3 cm beyond the pulmonary valve. The hydraulic occluder that encircled the right main pulmonary artery was then inflated, to direct pulmonary blood flow entirely through the left pulmonary artery (and flow probe). Left pulmonary blood flow was then measured by thermal dilution (American Edwards model 9520A, Irvine, CA) with multiple 5-ml, sterile, iced injections of 5% dextrose in water. Values for LQ were referenced to body weight (ml·min⁻¹·kg⁻¹). The aortic and pulmonary artery catheters were used to obtain blood samples for measurement of systemic arterial and mixed venous blood gases, respectively. Systemic arterial and mixed venous pH, carbon dioxide tension, and oxygen tension were measured with a Radiometer ABI-3 (Copenhagen, Denmark). Oxyhemoglobin saturation (SO₂) was measured with a Radiometer Hemoximeter model OSM-5.

**Experimental Protocols**

All experiments were performed with each healthy, chronically instrumented dog lying on its right side in a quiet laboratory environment. The 8 LLA dogs were studied 22 ± 3 days after the surgical procedure. The 8 sham-operated, healthy control dogs were studied 34 ± 10 days after surgery for chronic instrumentation. Conscious dogs were unsedated. Continuous left pulmonary vascular pressure - flow (LPPQ) plots were used to assess the effectiveness of the various pharmacologic interventions on the pulmonary circulation. Left pulmonary vascular pressure - flow plots were constructed by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure - left atrial pressure: PAP - LAP) and LQ during gradual (~1 min) inflation of the hydraulic occluder implanted around the right main pulmonary artery. This technique to measure the LPQ relation is highly reproducible and has little or no effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.¹³

**Protocol 1: Effect of Isoflurane Anesthesia on the Baseline Left Pulmonary Vascular Pressure - Flow Relation.** We investigated the effect of isoflurane anesthesia on the baseline LPQ relation after LLA. Baseline LPQ plots also were generated in the eight conscious, sham-operated control dogs. For each LLA dog (n = 8), a LPQ plot was first generated in the conscious state. Then, isoflurane anesthesia was then induced via mask, supplemented with a subanesthetic dose of 3 mg/kg intravenous thiopental sodium, to minimize excitatory behavior. This dose of thiopental sodium results in negligible serum levels after a 1-h interval.¹⁴ An endotracheal tube (8-mm ID) was placed, and ventilation was controlled (Harvard respirator, Natick, MA) with zero end-expiratory pressure. Immediately after intubation, 2.0% isoflurane (Anaquest, Madison, WI) was delivered via a vaporizer (Ohmeda Isotec 3, Madison, WI). Fresh gas (room air and oxygen) flow was set at 100 ml·min⁻¹·kg⁻¹. Tidal volume was fixed at 15 ml/kg. Systemic arterial blood gas values were matched to values measured in the conscious state by administering supplemental oxygen (FiO₂ ~ 0.22) and by adjusting the respiratory rate to between 10 and 20 breaths per minute. End-tidal carbon dioxide was monitored continuously (Hewlett Packard model 78356A, Andover, MA), as was inspiratory oxygen concentration (Beckman model OM-15, Fullerton, CA). After induction, isoflurane anesthesia was allowed to equilibrate for 1 h, to achieve steady-state conditions. This method of isoflurane anesthesia in dogs results in end-tidal isoflurane concentrations (Nellcor, Hayward, CA) of 1.6 – 1.7% and 1.7 – 1.8% after 1 h and 2 h, respectively, which represents approximately 1.2 minimum alveolar concentration in dogs.¹⁵ An LPQ plot was then obtained. During isoflurane anesthesia, body temperature was maintained at 37 – 38°C by increasing ambient temperature and by using heating lights.

**Protocol 2: Effect of Isoflurane Anesthesia on the Pulmonary Vascular Response to Sympathetic α Adrenoreceptor Activation.** We investigated the effect of isoflurane anesthesia on the pulmonary vascular response to curare and sympathetic β adrenergic stimulation. A baseline LPQ plot (after 2 days of LLA) dog (unconsciously) was then paralyzed with pancuronium (0.1 mg/kg intravenously) and phenylephrine (0.01 mg/kg intravenously) was infused at 0.15 μg-kg⁻¹·min⁻¹ for 15 min at each dose level. The experiment was repeated (0.3 and 1.0 μg-kg⁻¹·min⁻¹) at increased phenylephrine doses as repeated in the same dog. Anesthesia was maintained in a totally relaxed state with isoflurane and additional control after each experiment was performed.

**Data Analysis**

Phasic and mean pressures were displayed continuously on a chart recorder (Gould model 334, Cleveland, OH), and were maintained with passing and high-pass filters. All vascular pressure was measured with a Statham P23ID pressure transducer (Statham P23ID, Oxnard, CA) using a Gould ATL 7200 data acquisition system. The systolic and diastolic pressures were recorded for the entire experiment. The phenylephrine responses were calculated (or generated) digitally for each individual dog, and the data were analyzed using a computer spreadsheet program. The data were used to assess the effects of isoflurane anesthesia on phenylephrine-induced LPQ changes. The data were then used to assess the effect of isoflurane anesthesia on the LPQ response to phenylephrine, with phenylephrine-induced changes in LPQ expressed as a percentage of the initial (isoflurane-free) LPQ values.
effect of isoflurane anesthesia on the pulmonary vascular response to cumulative doses of phenylephrine after sympathetic \( \beta \) adrenoceptor block with propranolol. A baseline LPQ plot was first obtained in each conscious LLA dog (n = 8). Propranolol (1 mg/kg intravenously) was then administered to block the \( \beta \) agonist effect of phenylephrine. This dose of propranolol completely inhibits the tachycardic and systemic hypotensive response to isoproterenol. An LPQ plot was obtained after \( \beta \) block and again after each dose of phenylephrine (0.01, 0.1, 0.5, and 1.0 \( \mu \)g \( \cdot \) kg\(^{-1} \cdot \) min\(^{-1} \) intravenously) during its cumulative administration (\( \sim \)15 min at each dose). Propranolol administration was repeated (0.5 mg/kg intravenously) 30 min after the initial dose. On a separate day, this protocol was repeated in the same LLA dogs during isoflurane anesthesia. Anesthesia with isoflurane was induced and maintained in a manner identical to the methods detailed in protocol 1. A phenylephrine dose–response relation also was obtained in the eight conscious sham-operated control dogs after \( \beta \) adrenoceptor block.

**Data Analysis**

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (Gould model 2800, Eastlake, OH). Mean pressures and LQ, measured at end-expiration, were obtained with passive electronic filters with a 2-s time constant. All vascular pressures were referenced to atmospheric pressure before and after each LPQ plot. The analog pressure and LQ signals were digitally converted and multiplexed (Medical Systems, PCM-8, Greenvile, NY) and stored on videotape (Panasonic videocassette recorder model AG-1260, Secaucus, NJ) for later playback and analysis. The LPQ relation was linear, by inspection, over the empirically measured range of LQ. Therefore, linear regression analysis was used to calculate the slope and intercept for PAP–LAP (or PAP–O if LAP \( \equiv \) 0 mmHg) as a function of LQ in each individual experiment. The correlation coefficient for each protocol averaged 0.98 or higher. Multivariate analysis of variance in the form of Hotelling’s \( T^2 \) was used to assess the effects of isoflurane, propranolol, phenylephrine, and LLA on the regression parameters obtained in each individual experiment, compared with values measured at baseline. PAP–LAP intercept values were calculated at the midrange of empirically measured LQ in each protocol. This minimizes the variance in the PAP–LAP intercept and avoids the use of intercept values outside the range of our empirical measurements (i.e., PAP–LAP was not measured at LQ = 0 \( \cdot \) \( \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \)). One-way and two-way analyses of variance were used to assess the effects of isoflurane, propranolol, phenylephrine, and LLA on (1) steady-state hemodynamics and blood gases and (2) the effects of cumulative doses of phenylephrine on PAP–LAP at a common value of LQ (70 \( \cdot \) \( \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \)). Student’s \( t \) test for group comparisons was used to compare responses to phenylephrine in control versus LLA dogs. All values are presented as means ± SE.

**Results**

**Protocol 1: Effect of Isoflurane Anesthesia on the Baseline Left Pulmonary Vascular Pressure–flow Relation After Left Lung Autotransplantation**

Compared with healthy conscious dogs, LLA was associated with a leftward shift in the baseline LPQ relation, which indicated pulmonary vasoconstriction (fig. 1). Despite the elevated level of pulmonary vasmotor tone after LLA, isoflurane had no effect on the baseline LPQ relation (i.e., isoflurane did not cause pulmonary vasoconstriction).
isoflurane decreased systemic arterial pressure and increased heart rate (table 1). Isoflurane had no effect on systemic arterial or mixed venous blood gases after LLA (table 2).

**Protocol 2: Effect of Isoflurane Anesthesia on the Pulmonary Vasoconstrictor Response to Sympathetic α Adrenoceptor Activation After Left Lung Autotransplantation**

Pretreatment with propranolol had no effect on the baseline LQ relation in either the conscious or isoflurane-anesthetized states after LLA (fig. 2). Phenylephrine (1.0 μg·kg⁻¹·min⁻¹ intravenously) caused a leftward shift in the LQ relation, which indicated pulmonary vasoconstriction in both the conscious and isoflurane-anesthetized states after LLA (fig. 2). The pulmonary vascular dose-response relation for phenylephrine is summarized in figure 3. Increases in PAP-LAP in response to phenylephrine at a midrange value of LQ (70 ml·min⁻¹·kg⁻¹) are presented for healthy conscious dogs, conscious dogs after LLA, and isoflurane-anesthetized dogs after LLA. Compared with healthy conscious dogs, the magnitude of phenylephrine-induced pulmonary vasoconstriction was enhanced in conscious dogs after LLA. Isoflurane had no effect on the magnitude of phenylephrine-induced pulmonary vasoconstriction after LLA.

Compared with baseline, propranolol decreased heart rate in both the conscious and isoflurane-anesthe-

tized states after LLA (table 1). In both conditions, phenylephrine increased systemic arterial pressure, PAP, and LAP, and decreased LQ and heart rate (table 1). Neither propranolol nor phenylephrine had an effect on systemic arterial blood gases after LLA (table 2). Both propranolol and phenylephrine decreased mixed venous oxyhemoglobin saturation in conscious and isoflurane-anesthetized dogs (table 2).

**Discussion**

Three conclusions can be reached based on the results of this study. First, LLA results in chronic pulmonary vasoconstriction and enhanced reactivity to sympathetic α adrenoceptor activation in conscious dogs. Second, despite the chronic increase in pulmonary vasomotor tone after LLA, isoflurane did not exert a vasodilator influence on the baseline LQ relation. And third, the enhanced pulmonary vasoconstrictor response to sympathetic α adrenoceptor activation measured in conscious dogs after LLA was not attenuated during isoflurane anesthesia.

This is the first study to systematically investigate the pulmonary vascular effects of isoflurane after lung transplantation. This study supports the notion that isoflurane may be a useful anesthetic agent for pulmonary transplantation.
transplantation. There were several isolated case reports that suggested that isoflurane may cause pulmonary vasodilation in patients with primary pulmonary hypertension. However, it is difficult to discern the specific effects of isoflurane on the pulmonary circulation in those reports because (1) anesthetic agents in addition to isoflurane were used; (2) measurements of cardiac output by thermal dilution may not have been accurate because of tricuspid regurgitation; and (3) changes in pulmonary vasomotor tone were assessed via changes in single-point calculations of pulmonary vascular resistance.

Isoflurane has been reported to cause vasodilation in the systemic circulation. In contrast, we previously reported that isoflurane has no net effect on baseline pulmonary vasomotor tone as assessed by measuring the LPQ relation in healthy conscious dogs. This latter result is not surprising, because the normal pulmonary circulation is close to being maximally vasodilated at baseline. Isoflurane does cause pulmonary vasodilation when pulmonary vasomotor tone is elevated in the setting of acute hypoxia. However, in the current study, isoflurane had no effect on the baseline LPQ relation after LLA, despite a chronic increase in pulmonary vasomotor tone.

Compared with conscious, sham-operated control dogs, the pulmonary vasoconstrictor response to sympathetic α adrenoreceptor activation was potentiated after LLA. We previously observed this abnormality in pulmonary vascular regulation after LLA both in in vivo

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**Fig. 2.** Composite left pulmonary vascular pressure–flow (LPQ) plots in eight dogs after left lung autotransplantation at baseline (no drug), after β adrenoreceptor block with propranolol, and during administration of 1.0 μg·kg⁻¹·min⁻¹ phenylephrine in the conscious state (top) and during isoflurane anesthesia (bottom). Propranolol had no effect on the baseline LPQ relation in either the conscious or isoflurane-anesthetized states. In both the conscious and isoflurane-anesthetized states, phenylephrine caused a leftward shift in the LPQ relation, which indicated pulmonary vasoconstriction (*P < 0.01*).

**Fig. 3.** Phenylephrine dose–response relation measured in eight healthy conscious dogs and in eight dogs in the conscious state and during isoflurane anesthesia after left lung autotransplantation (LLA). The pulmonary vascular response to phenylephrine was assessed in the presence of β adrenoreceptor block with propranolol (PROP). Changes in the pulmonary vascular pressure gradient (pulmonary arterial pressure [PAP]–left atrial pressure [LAP]) at left pulmonary blood flow >70 ml·min⁻¹·kg⁻¹ in response to the cumulative administration of phenylephrine are summarized. The magnitude of phenylephrine-induced pulmonary vasoconstriction was potentiated (*P < 0.05*) in conscious dogs after LLA compared with healthy conscious dogs. Compared with the conscious state, isoflurane had no effect on the magnitude of the pulmonary vasoconstrictor response to phenylephrine after LLA.
studies of conscious dogs and in *in vitro* studies of isolated pulmonary arterial rings. Because inhalational anesthetics were shown to attenuate the systemic vasoconstrictor response to $\alpha$ adrenergic receptor activation,\textsuperscript{11,12} we hypothesized that the enhanced response to this stimulus observed in conscious dogs after LLA would be attenuated during isoflurane anesthesia. However, isoflurane had no effect on the magnitude of the pulmonary vasoconstrictor response to phenylephrine after LLA. Isoflurane also has no effect on the magnitude of the pulmonary vasoconstrictor response to phenylephrine in healthy dogs.\textsuperscript{22} In contrast, other inhalational anesthetics (e.g., enflurane, and, to a lesser extent, halothane) potentiated the pulmonary vasoconstrictor response to phenylephrine.\textsuperscript{32}

The lack of effect of isoflurane on the baseline pulmonary circulation and the vasoconstrictor response to phenylephrine represents the net effect of the anesthetic on pulmonary vasoregulation. It is possible that isoflurane exerts opposing effects on several pulmonary vasoregulatory mechanisms that are offsetting, which could mask an overall effect of isoflurane. For example, isoflurane attenuates pulmonary vasodilatation mediated by ATP-sensitive $K^+$ channel activation\textsuperscript{13} and by endothelin-dependent agonists,\textsuperscript{24} whereas isoflurane potentiates the pulmonary vasodilator response to sympathetic $\beta$ adrenergic receptor activation.\textsuperscript{29} This latter effect underscores the importance of performing the phenylephrine dose-response curves in the presence of $\beta$ adrenergic blocker in both the conscious and isoflurane-anesthetized states.

As we observed previously,\textsuperscript{28,33} systemic arterial pressure was decreased and heart rate was increased during isoflurane anesthesia, whereas blood gases were unchanged compared with the conscious state. Heart rate decreased after propranolol administration, consistent with its effect as a $\beta$ adrenergic receptor antagonist. Propranolol had no effect on the baseline LQ relation in either the conscious or isoflurane-anesthetized states. This confirms our previous observation that the chronic increase in pulmonary vasomotor tone after LLA in conscious dogs is not modulated by circulating catecholamines,\textsuperscript{7} and extends this finding to the isoflurane-anesthetized state.

General anesthesia is being administered to a growing number of patients who have been lung transplant recipients.\textsuperscript{13} It is somewhat surprising that there has not been a systematic study to determine whether chronic pulmonary vasocostriction occurs in the transplanted human lung. As with all laboratory studies, care must be taken when attempting to extrapolate the results obtained in our canine LLA model to human lung transplantation. In this and previous studies, we observed that the chronic increase in pulmonary vasomotor tone after LLA is not readily responsive to vasodilator therapy. For example, the $\alpha$ adrenergic antagonist, prazosin, only partially reverses pulmonary vasomotor tone to normal baseline conditions.\textsuperscript{34} Similar results were observed with the phosphodiesterase inhibitor amrinone, the $\beta$ adrenergic antagonist isoproterenol, and the nitric oxide donor sodium nitroprusside.\textsuperscript{35} Paradoxically, the endothelium-dependent vasodilators, acetylcholine and bradykinin, actually cause pulmonary vasocostriction at higher doses in dogs after LLA.\textsuperscript{4} In the current study, isoflurane had no effect on baseline vasomotor tone, which further suggests that the pulmonary circulation after LLA is refractory to conventional pharmacological therapy. In addition, the fact that isoflurane did not attenuate the pulmonary vasoconstrictor response to $\alpha$ adrenergic receptor activation, taken together with its known attenuating effect on the systemic vaspressor response to $\alpha$ agonists, suggests that $\alpha$ agonists may preferentially constrict the pulmonary circulation during isoflurane anesthesia. This effect could exacerbate any preexisting right ventricular dysfunction.

In summary, LLA results in a chronic increase in baseline vasomotor tone and an enhanced pulmonary vasoconstrictor response to sympathetic $\alpha$ adrenergic receptor activation. A clinical concentration of isoflurane ($\sim$1.2 minimum alveolar concentration) did not exert a vasodilator influence on the baseline pulmonary circulation nor did it attenuate the pulmonary vasoconstrictor response to $\alpha$ adrenergic receptor activation after LLA. These results could influence the intraoperative anesthetic care of patients with similar abnormalities in pulmonary vasoregulation.

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