Attenuated Hypoxic Pulmonary Vasoconstriction during Isoflurane Anesthesia Is Abolished by Cyclooxygenase Inhibition in Chronically Instrumented Dogs

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Background: Hypoxic pulmonary vasoconstriction (HPV) is a homeostatic mechanism whereby gas exchange is improved through the diversion of blood flow away from poorly oxygenated regions of the lung. The effect of isoflurane anesthesia on HPV is unclear. Using a chronically instrumented canine model, it was hypothesized that isoflurane anesthesia would attenuate HPV compared to the response measured in the same animal in the conscious state. Moreover, because volatile anesthetics increase the production of cyclooxygenase metabolites, it was hypothesized that attenuation of HPV during isoflurane anesthesia would be abolished by cyclooxygenase inhibition.

Methods: Left pulmonary vascular pressure-flow 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 right main pulmonary artery. In protocol 1 (n = 7), left pulmonary vascular pressure-flow plots were generated during normoxia and hypoxia (systemic arterial PaO₂ ~ 50 mmHg) in the conscious and isoflurane-anesthetized states. In protocol 2 (n = 7), left pulmonary vascular pressure-flow plots were generated during normoxia and hypoxia (1) in the conscious state, (2) in the conscious state after administration of the cyclooxygenase pathway with indomethacin, and (3) during isoflurane anesthesia after cyclooxygenase inhibition.

Results: In both the conscious and isoflurane-anesthetized states, the magnitude of HPV was dependent on the level of left pulmonary blood flow. Compared to the response measured in the conscious state, the magnitude of HPV was attenuated during isoflurane anesthesia compared to the empirically measured range of left pulmonary blood flow. Cyclooxygenase inhibition abolished the isoflurane-induced attenuation of HPV.

Conclusions: This is the first study to demonstrate that isoflurane anesthesia attenuates the magnitude of HPV compared to the response measured in the same animal in the conscious state. Cyclooxygenase inhibition potentiated the magnitude of HPV in both the conscious and isoflurane-anesthetized states, which indicates that vasodilator metabolites of the cyclooxygenase pathway modulate HPV under these conditions. Importantly, the finding that the magnitude of HPV is flow-dependent in both the conscious and isoflurane-anesthetized states may explain conflicting reports in the literature concerning the effects of isoflurane anesthesia on the HPV response. (Key words: Anesthetics, volatile; isoflurane; Hypoxia; hypoxic pulmonary vasoconstriction; Lung(s); circulation; pressure-flow relationship; Pharmacology: indomethacin.)

HYPOXIC pulmonary vasoconstriction (HPV) is a regulatory mechanism whereby a decrease in alveolar PaO₂ results in constriction of adjacent arterioles. When the distribution of pulmonary ventilation is uneven, HPV improves gas exchange by diverting pulmonary blood flow to better oxygenated regions of the lung. General anesthesia and surgery may result in impaired arterial oxygenation and a requirement for an increase in the fraction of inspired oxygen (FiO₂). A possible mechanism for this impaired systemic arterial oxygenation is via attenuation of HPV by anesthetic agents. Isoflurane, a commonly used volatile anesthetic, is widely thought to possess this characteristic. Although numerous studies have demonstrated an attenuation of HPV during isoflurane anesthesia, many others failed to recognize this phenomenon for these conflicting results. In our model, the use of saline, noninjected vascular pressor calculations of pulmonary vascular resistance failed to fully account for changes in pulmonary vascular resistance. The mechanism by which isoflurane may inhibit HPV is unknown, but it may involve inhibition of cyclooxygenase [cyclooxygenase pathway (COX)]. COX is a potent vasoactive agent that mediates hypoxic pulmonary vasoconstriction. COX inhibition with indomethacin attenuates HPV during isoflurane anesthesia.
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others failed to recognize this effect.11-15 Possible reasons for these conflicting results include the use of in vitro models, the use of "background" anesthetics, the acute effects of surgical trauma, the absence of conscious, nonsedated controls, and the use of single-point calculations of pulmonary vascular resistance.

The mechanism by which isofurane may attenuate HPV also is unclear.9 Prostacyclin, a vasodilator metabolite of the cyclooxygenase pathway, is produced in the pulmonary circulation during hypoxia and attenuates the magnitude of HPV.16,17 Volatile anesthetics such as isofurane may attenuate HPV by increasing the production of vasodilator metabolites of the cyclooxygenase pathway.18-20 Alternatively, isofurane anesthesia may enhance the vasodilator efficacy of metabolites of the cyclooxygenase pathway. The signal transduction pathway for prostacyclin-mediated vasodilation involves stimulation of adenylate cyclase and increased intracellular production of cyclic adenosine monophosphate (cAMP).21,22 We recently observed that cAMP-mediated pulmonary vasodilation in response to sympathetic β-adrenergic receptor activation is enhanced during isofurane anesthesia.23 Based on these previous studies, we hypothesized that: (1) isofurane anesthesia would attenuate the magnitude of HPV when compared to the conscious state, and (2) the isofurane-induced attenuation of HPV would be abolished after cyclooxygenase inhibition. We employed an experimental preparation in which dogs were chronically instrumented to permit the generation of pulmonary vascular pressure-flow plots. This chronic instrumentation allowed us to assess the effects of hypoxia and cyclooxygenase inhibition on the pulmonary vascular pressure-flow relationship in the same animal in both the conscious and isofurane-anesthetized states. This avoids the confounding effects of acute surgical trauma, as well as the requirement for background anesthetics, and it decreases intraanimal variability. We previously demonstrated that general anesthesia can modify neural, hormonal, and local mechanisms of pulmonary vascular regulation.24-28 Use of pulmonary vascular pressure-flow plots avoids the limitations inherent in calculated, single-point measurements of PVR.29 Our results indicate that the magnitude of HPV is flow-dependent in both conscious and isofurane-anesthetized dogs. Moreover, isofurane anesthesia attenuates the magnitude of HPV compared to the response measured in the conscious state, and this effect is abolished after cyclooxygenase inhibition.

Materials and Methods

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

Surgery for Chronic Instrumentation

Using sterile surgical technique, 13 conditioned male mongrel dogs (25 ± 1 kg) were chronically instrumented as described previously.30 Briefly, heparin-filled Tygon catheters (1.02 mm ID, Norton, Akron, OH) were inserted into the descending thoracic aorta, left and right atria, and main pulmonary artery, a hydraulic occluder (18 mm ID, Jones, Silver Springs, MD) was loosely positioned around the right main pulmonary artery, and an electromagnetic flow probe (10 mm ID, Zepeda, Seattle, WA) was placed around the left main pulmonary artery. The free ends of the catheters, occluder, and flow probe were tunneled to a final position between the scapulae. Morphine sulfate (10 mg, intramuscular) and cephalin (2 g, intravenous; Bristol-Myers Squibb, Princeton, NJ) were administered postoperatively. 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 (P23 ID, Gould, Eastlake, OH) and were referenced to atmospheric pressure with the transducers positioned at mid-chest 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 (model SWF-4rd, Zepeda). The flow probe was calibrated in vitro on a weekly basis using the thermal dilution technique.31 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 to measure systemic arterial and mixed venous blood gases, respectively.32

Experimental Protocols

All experiments were performed with each healthy, chronically instrumented dog lying on its right side in a quiet laboratory environment. Conscious dogs were nonsedated. Continuous left pulmonary vascular pressure-flow (LPQ) plots were used to assess the effects of the various physiologic and 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 relationship is highly reproducible and has little or no effect on systemic hemodynamics, blood gases, or the zonal condition of the lung.50

**Protocol 1: Effect of Isoflurane Anesthesia on the Magnitude of Hypoxic Pulmonary Vasocostriction.** We investigated the effect of isoflurane anesthesia on the magnitude of HPV compared to the response measured in the conscious state. A baseline LPQ plot during normoxia was obtained in each conscious dog (n = 7). A conical face mask was then placed over the dog’s nose. Room air was administered via the mask and, after obtaining steady-state conditions (~10 min), a normoxia LPQ plot was generated. Room air and gas from a source consisting of 7% oxygen—5.1% carbon dioxide—87.9% nitrogen were then delivered into a semi-closed, circle breathing system. Gas flows were titrated to a FIO2 that resulted in a gradual decrease in systemic arterial Pao2 to ~50 mmHg. After 10 min, a steady state was achieved and a LPQ plot during hypoxia was obtained.

On a separate day, this protocol was repeated in the same seven dogs during isoflurane anesthesia. Isoflurane anesthesia was induced via mask, supplemented with a subanesthetic dose of thiopental sodium (3 mg/kg, intravenous), which minimized excitatory behavior. This dose of thiopental sodium results in negligible serum concentrations after a 1-h interval.35 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 (Isotec 3, Ohmeda, Madison, WI). Fresh gas (room air and oxygen) 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 same animal in the conscious state by administering supplemental oxygen (FIO2 ~ 0.22) and by adjusting the respiratory rate to 10–20 breaths/min. End-tidal carbon dioxide was monitored continuously (78356A, Hewlett Packard, Andover, MA) as was inspiratory oxygen concentration (OM-15, Beckman, Fullerton, CA). After induction, isoflurane was allowed to equilibrate for 1 h to achieve steady-state conditions. This method of isoflurane anesthesia resulted in end-tidal isoflurane concentrations (Nellcor, Hayward, CA) of 1.6–1.7% and 1.7–1.8% after 1 and 2 h, respectively, which represents approximately 1.2 MAC in dogs.23 An LPQ plot was then obtained during isoflurane anesthesia. The hypoxic gas mixture was then administered via the endotracheal tube. After approximately 10 min, a steady state was reached and a LPQ plot was obtained during hypoxia. During isoflurane anesthesia, body temperature was maintained at 37–38°C. Muscle relaxants were not used in any experimental protocol in this study.

**Protocol 2: Effect of Isoflurane Anesthesia on the Magnitude of Hypoxic Pulmonary Vasocostriction after Cyclooxygenase Pathway Inhibition.** We investigated the effect of cyclooxygenase inhibition with indomethacin on the response of the LPQ relationship to hypoxia during isoflurane anesthesia. To determine the conscious intact (no drug) response to hypoxia, LPQ plots were obtained in each dog (n = 7) as described in protocol 1.

On a separate day, a baseline LPQ plot was first obtained in the conscious state. Indomethacin (Sigma Chemical Company, St. Louis, MO) was then administered (5 mg/kg, intravenous). This dose has been demonstrated to inhibit prostaglandin synthesis,33,34 and to abolish the pulmonary pressor response to arachidonic acid.25,26,31 Forty-five min after administration of indomethacin, LPQ plots were obtained while breathing room air, room air via mask, and a hypoxic gas mixture via mask.

On a separate day, isoflurane anesthesia was induced and maintained in a manner identical to that described in protocol 1. Forty-five min after induction of isoflurane anesthesia, an LPQ plot was generated. Indomethacin (5 mg/kg, intravenous) was administered. After an interval of 45 min, an LPQ plot was obtained. The hypoxic gas mixture was then administered as detailed in protocol 1, and a final LPQ plot was obtained.

**Data Analysis**

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (2800, Gould). Mean pressures and LQ, measured at end-expiration, were obtained with the use of passive electronic filters with a 2-s time constant. All vascular pressures were referenced to atmospheric pressure before each LPQ plot. The LPQ relationship 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.
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Fig. 1. (A) Composite left pulmonary vascular pressure-flow plots in seven dogs in the conscious state during normoxia, normoxia while breathing through a face mask, and hypoxia. Compared to normoxia, there was no change in the left pulmonary vascular pressure-flow relationship during normoxia via mask. Hypoxia caused a leftward shift (P < 0.01) in the left pulmonary vascular pressure-flow relationship, which indicates pulmonary vasocstriction. (B) Composite left pulmonary vascular pressure-flow plots in seven dogs during normoxia in the conscious state, during normoxia during isoflurane anesthesia, and during hypoxia during isoflurane anesthesia. Compared to normoxia in the conscious state, there was no change in the left pulmonary vascular pressure-flow relationship during isoflurane anesthesia. During isoflurane anesthesia, hypoxia resulted in pulmonary vasocstriction (P < 0.01).

(or PAP-O if LAP ≤ 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 the various interventions on the LPQ relationship.\(^{35}\) Two-way analysis of variance was used to assess the effects of hypoxia on: (1) steady-state hemodynamics and blood gases, and (2) hypoxia-induced increases in PAP-LAP at common values of LQ. One-way analysis of variance was used to assess: (1) the effect of isoflurane and indomethacin on FiO\(_2\), and steady-state hemodynamics and blood gases, and (2) the effect of increasing levels of LQ on the magnitude of HPV. All values are presented as means ± SE.

Results

Protocol 1: Effect of Isoflurane Anesthesia on the Magnitude of Hypoxic Pulmonary Vasocstriction

In conscious dogs, mask breathing had no effect on the LPQ relationship during normoxia (fig. 1A). Breathing the hypoxic gas mixture resulted in a leftward shift (P < 0.01) in the LPQ relationship indicating pulmonary vasocstriction (fig. 1A). The HPV response (i.e., the increase in PAP-LAP during hypoxia compared to normoxia at each common value of LQ) is summarized in figure 2. The magnitude of the HPV response

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in conscious dogs was flow-dependent (P < 0.01), i.e., the HPV response increased as LQ increased.

During isoflurane anesthesia, the LPQ relationship measured during normoxia was not significantly different from that measured in the conscious state (fig. 1B). In isoflurane-anesthetized dogs, hypoxia also caused a leftward shift (P < 0.01) in the LPQ relationship indicating pulmonary vasoconstriction (fig. 1B). Moreover, as summarized in figure 2, the magnitude of the HPV response during isoflurane anesthesia was also flow-dependent (P < 0.01).

The increases in PAP-LAP during hypoxia compared to normoxia over the empirically measured range of LQ in conscious and isoflurane-anesthetized dogs are summarized in figure 2. At common values of LQ, the magnitude of the HPV response was attenuated (P < 0.01) during isoflurane anesthesia compared to the conscious state.

Steady-state hemodynamics and blood gases in conscious and isoflurane-anesthetized dogs during normoxia and hypoxia are summarized in tables 1 and 2. Hypoxia increased PAP and heart rate in conscious dogs. Isoflurane decreased systemic arterial pressure (SAP) and increased heart rate during normoxia. Hypoxia increased PAP, but not heart rate, during isoflurane anesthesia. Systemic arterial and mixed venous blood gases were similar during normoxia and hypoxia in the conscious and isoflurane-anesthetized states. In both conditions, hypoxia increased systemic arterial and mixed venous pH, and decreased systemic arterial and mixed venous \( P_{CO_2} \), \( P_{O_2} \), and \( S_O_2 \) (table 2).

**Protocol 2: Effect of Cyclooxygenase Inhibition on the Isoflurane-induced Attenuation of Hypoxic Pulmonary Vasoconstriction**

The LPQ relationships during normoxia and hypoxia for the dogs utilized in protocol 2 were similar to those measured in protocol 1. In the conscious state, cyclooxygenase inhibition with indomethacin had no effect on the LPQ relationship during normoxia (fig. 3A). With the cyclooxygenase pathway inhibited, hypoxia caused a leftward shift (P < 0.01) in the LPQ relationship indicating pulmonary vasoconstriction (fig. 3A). The lower panel of figure 3 summarizes the HPV response measured in intact (no drug) conscious dogs, and in the same conscious animals after cyclooxygenase inhibition. The magnitude of HPV was enhanced (P < 0.01) in conscious dogs after cyclooxygenase inhibition.

During isoflurane anesthesia, indomethacin again had no effect on the LPQ relationship during normoxia (fig. 4A). With the cyclooxygenase pathway inhibited, hypoxia caused a leftward shift (P < 0.01) in the LPQ relationship indicating pulmonary vasoconstriction (fig. 4A). The lower panel of figure 4 summarizes the HPV response measured in isoflurane-anesthetized dogs (no drug), and in the same animals during isoflurane anesthesia after cyclooxygenase inhibition. The magnitude of HPV was enhanced (P < 0.01) in isoflurane-anesthetized dogs after cyclooxygenase inhibition.

The HPV responses measured in the conscious state and during isoflurane anesthesia after cyclooxygenase inhibition are summarized in figure 5. There were no significant differences between the HPV responses under these conditions. Thus, the isoflurane-induced attenuation in HPV was abolished after cyclooxygenase inhibition.

Indomethacin had no effect on steady-state hemodynamics (table 1). Isoflurane decreased SAP and increased LAP and heart rate during normoxia. Hypoxia increased PAP under all conditions. Changes in blood gases in response to hypoxia during protocol 2 were similar to those observed in protocol 1.

**Discussion**

There are three major outcomes to this study. First, the magnitude of HPV is flow-dependent in both the conscious and isoflurane-anesthetized states. Second, isoflurane anesthesia attenuates the magnitude of HPV compared to the response measured in the same animal in the conscious state. And third, cyclooxygenase inhibition enhances HPV in the conscious state and abolishes the isoflurane-induced attenuation of HPV.

In contrast to the experimental model used in the current study, previous laboratory studies assessing the effects of isoflurane anesthesia on HPV have used either *in vitro* preparations*6,9* or acutely instrumented, anesthetized *in vivo* preparations*4,5,7,8,10,14,15*. Clinical studies have examined the effect of isoflurane anesthesia on systemic arterial \( P_O_2 \) during one-lung hypoxia.*11-15* These previous laboratory and clinical studies have yielded conflicting results concerning the effects of isoflurane anesthesia on the magnitude of HPV. Potential confounding influences in previous laboratory investigations include acute surgical trauma, denervation, artificial perfusion, the presence of background anesthetics, and lack of unanesthetized control subjects. In clinical investigations, possible confounding factors include the per- and the lack of unanesthetized control changes in cardiovascular states. Our experimental confounding factors permitted comparison of the response gradient at constant \( P_O_2 \) and blood gases (normoxia) during hypoxia and isoflurane anesthesia. The magnitude of HPV in both the conscious and isoflurane anesthesia. This dependent response is determined by the HPV response to hypoxia (without isoflurane administered) as well as the effects of isoflurane anesthesia. Indomethacin inhibits cyclooxygenase activity (e.g., through prostacyclin metabolism). Indomethacin had no effect on the LPQ relationship during isoflurane anesthesia. The present studies that cyclooxygenase inhibition on the baseline LPQ relationship*16,17* and extends...
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Table 1. Steady-state Hemodynamics

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<th>Protocol 1</th>
<th>Protocol 2</th>
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<tr>
<td></td>
<td>CON</td>
<td>ISO</td>
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<td>SAP (mmHg)</td>
<td>Normoxia</td>
<td>111 ± 7</td>
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<tr>
<td></td>
<td>Hypoxia</td>
<td>115 ± 7</td>
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<td>PAP (mmHg)</td>
<td>Normoxia</td>
<td>18 ± 3</td>
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<td></td>
<td>Hypoxia</td>
<td>25 ± 2*</td>
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<td>LAP (mmHg)</td>
<td>Normoxia</td>
<td>2 ± 1</td>
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<tr>
<td></td>
<td>Hypoxia</td>
<td>1 ± 1</td>
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<tr>
<td>LQ (ml·min⁻¹·kg⁻¹)</td>
<td>Normoxia</td>
<td>80 ± 11</td>
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<tr>
<td></td>
<td>Hypoxia</td>
<td>79 ± 10</td>
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<tr>
<td>HR (beats/min)</td>
<td>Normoxia</td>
<td>95 ± 6</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>112 ± 5*</td>
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CON = conscious; ISO = isofurane; INDO = indomethacin; SAP = systemic arterial pressure; PAP = pulmonary artery pressure; LAP = left atrial pressure; LQ = left pulmonary blood flow; HR = heart rate.

* P < 0.05, hypoxia versus normoxia.
† P < 0.05, ISO versus CON.
‡ P < 0.05, ISO + INDO versus CON + INDO.

factors include the presence of background anesthetics, lack of unanesthetized control subjects, and concomitant changes in cardiac output and mixed venous blood gases. Our experimental model avoids these potentially confounding factors. Furthermore, the use of LPQ plots permitted comparison of the pulmonary vascular pressure gradient at common values of LQ. Finally, the FIO2 and blood gases (systemic arterial and mixed venous) during hypoxia were similar in the conscious and isofurane-anesthetized states.

The magnitude of the HPV response was flow-dependent in both the conscious state and during isofurane anesthesia. This dependence of the HPV response on pulmonary blood flow demonstrates the need to compare the HPV response at the same level of flow when determining the effects of an intervention (e.g., anesthesia) on the HPV response. This flow-dependent effect of HPV may be an important factor responsible for conflicting results in previous studies that have assessed the effects of isofurane anesthesia and other interventions on the magnitude of HPV.

Indomethacin inhibits the production of both vasoconstrictor (e.g., thromboxane) and vasodilator (e.g., prostacyclin) metabolites of the cyclooxygenase pathway. Indomethacin had no net effect on the baseline LPQ relationship either in the conscious state or during isofurane anesthesia. This result confirms previous studies that cyclooxygenase inhibition has no net effect on the baseline LPQ relationship in the conscious state.56–57 and extends this observation to the isofurane-anesthetized state. However, cyclooxygenase inhibition did result in potentiation of the HPV response in the conscious state. This phenomenon has been reported previously,57-58 and is consistent with the observation that a vasodilator metabolite of the cyclooxygenase pathway is produced in the pulmonary circulation during hypoxia.16-17

After cyclooxygenase inhibition, the HPV response during isofurane anesthesia was not significantly different from that measured in the conscious state. Thus, cyclooxygenase inhibition abolished the isofurane-induced attenuation of HPV, which is consistent with the concept that vasodilator metabolites of the cyclooxygenase pathway may mediate this attenuation. Increased production of vasodilator cyclooxygenase metabolites is one possible mechanism by which isofurane anesthesia could attenuate HPV. Shayeizt and coworkers have reported an increase in cyclooxygenase metabolites in isolated, perfused rabbit lung exposed to inhalational anesthetics.18 Indomethacin abolished this effect, which led to the speculation that inhalational anesthetics may make more arachidonic acid available to cyclooxygenase via a membrane effect. Barnes and coworkers observed a nonspecific increase in cyclooxygenase metabolites during normoxia and hypoxia in cultured bovine pulmonary artery endothelial cells exposed to halothane.59 Furthermore, Stone and coworkers observed vasoconstriction after administration of indomethacin to rat aortic vascular rings exposed to volatile anesthetics (including isofurane).19

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Enhancement of the vasodilator efficacy of cyclooxygenase metabolites is another possible mechanism by which isoflurane anesthesia could attenuate HPV. Evidence to support this mechanism includes the observations that: (1) the signal transduction pathway for prostacyclin-medicated vasodilation involves stimulation of adenylate cyclase and increased intracellular concentration of cAMP,\textsuperscript{21,22} and (2) volatile anesthetics appear to enhance the activity of cAMP-mediated effector pathways. For example, isoflurane increases cAMP concentration in isolated rat aortic strips.\textsuperscript{39} In rat uterine homogenate, halothane increases adenylate cyclase activity\textsuperscript{40} and intracellular cAMP concentration.\textsuperscript{41} Furthermore, adenylate cyclase and cAMP are also part of the signal transduction pathway for sympathetic $\beta$-adrenoreceptor mediated pulmonary vasodilation, which is enhanced during isoflurane anesthesia.\textsuperscript{23}

Although our results are consistent with the concept that vasodilator metabolites of the cyclooxygenase pathway are responsible for the attenuated HPV response during isoflurane anesthesia, we did not directly address whether this effect is caused by the increased production or enhanced vasodilator efficacy of cyclooxygenase metabolites. Differentiating between these two putative mechanisms cannot easily be accomplished by making biochemical measurements of circulating cyclooxygenase metabolites. There are significant differences in cyclooxygenase metabolism between endothelial and vascular smooth muscle cells, as well as in an asymmetric release of cyclooxygenase metabolites from endothelial cells via the luminal or abluminal surfaces.\textsuperscript{42} Because the production, release, and vasoactive effects of cyclooxygenase metabolites are highly focal, circulating plasma measurements may not quantitatively reflect concentrations at the cellular level.

Other investigators have examined the effect of cyclooxygenase inhibition on the HPV response during volatile anesthetic administration. In isolated perfused rat lung, Marshall and coworkers observed an attenuation of HPV by halothane.\textsuperscript{43} Ibuprofen, a cyclooxygenase inhibitor, decreased, but did not abolish, this attenuation. Johnson and coworkers also observed an attenuation of HPV by halothane\textsuperscript{2} in isolated perfused canine lung. Indomethacin abolished this attenuation only at low concentrations of halothane. In isolated perfused rabbit lung, Ishibe and coworkers observed...
an attenuation of HPV by sevoflurane, but this attenuation was unaffected by ibuprofen. In summary, these previous studies have demonstrated that cyclooxygenase inhibition either decreases or has no effect on the volatile anesthetic-induced attenuation of HPV. In contrast, the current study demonstrates a complete abolishment of the isoflurane-induced attenuation of HPV. These differential results may be due to use of different volatile anesthetics, different species, or the use of in vitro preparations. In particular, in vitro and acute in vivo preparations may result in elevated baseline levels of cyclooxygenase metabolites owing to surgical manipulation and trauma. An increase in baseline vasodilator prostaglandins could potentially obscure an effect of the volatile anesthetic on either

Fig. 3. Composite left pulmonary vascular pressure-flow plot in seven conscious dogs during normoxia in the intact (no drug) condition, during normoxia after indomethacin, and during hypoxia after indomethacin (A), and the composite hypoxic pulmonary vasoconstrictor response in the intact (no drug) condition and after indomethacin as a function of left pulmonary blood flow (B). Compared to the no-drug condition, there was no change in the left pulmonary vascular pressure-flow relationship after indomethacin. After indomethacin, hypoxia resulted in pulmonary vasoconstriction (*P < 0.01). The hypoxic pulmonary vasoconstrictor response after indomethacin was enhanced (*P < 0.01) compared to the no-drug condition.

Fig. 4. Composite left pulmonary vascular pressure-flow plots in seven isoflurane-anesthetized dogs during normoxia in the no-drug condition, during normoxia after indomethacin, and during hypoxia after indomethacin (A) and the composite hypoxic pulmonary vasoconstrictor response during isoflurane anesthesia in the no-drug condition and after indomethacin as a function of left pulmonary blood flow (B). Compared to the no-drug condition, there was no change in the left pulmonary vascular pressure-flow relationship after indomethacin. After indomethacin, hypoxia resulted in pulmonary vasoconstriction (*P < 0.01). During isoflurane anesthesia, the hypoxic pulmonary vasoconstrictor response after indomethacin was enhanced (*P < 0.01) compared to the no-drug condition.

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Fig. 5. The composite hypoxic pulmonary vasoconstrictor response in the same seven dogs in the conscious state after indomethacin and during isoflurane anesthesia after indomethacin. Indomethacin abolished the isoflurane-induced attenuation of hypoxic pulmonary vasoconstriction.

similar in the conscious and isoflurane-anesthetized states. Thus, this factor is not likely responsible for the isoflurane-induced attenuation in HPV.

Isoflurane anesthesia is used widely both clinically and experimentally. Therefore, clear delineation of its pulmonary vascular effects during hypoxia can help guide its use in these circumstances. The results of the current study demonstrate that isoflurane anesthesia attenuates HPV. Moreover, the results of this study provide a possible mechanism by which isoflurane anesthesia attenuates HPV, as well as a potential therapeutic method to abolish this attenuation.

In summary, the magnitude of HPV is flow-dependent in both conscious and isoflurane-anesthetized dogs. Compared to the conscious state, isoflurane anesthesia attenuates the magnitude of HPV. Cyclooxygenase inhibition enhances HPV in the conscious state, and abolishes the isoflurane-induced attenuation of HPV. These results are consistent with the concept that attenuation of HPV during isoflurane anesthesia may be mediated by vasodilator metabolites of the cyclooxygenase pathway.

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Quantitation of Hemorrhage in the Rat

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Background: In contrast to other methods of quantitation of anesthesia, hemorrhage in the rat has not been well defined. The relationship between the consequences of hemorrhage and the clinical response have not been fully investigated. The aim of this study was to evaluate the relationship between hemorrhage and the clinical response in rats, using a standard model for evaluating the effects of hemorrhage. The effects of hemorrhage on the cardiovascular system and the respiratory system were measured in rats. The rats were divided into two groups: control group and hemorrhage group. The control group was given no additional treatment. The hemorrhage group was given an additional treatment of hemorrhage. The results of the study indicate that hemorrhage has a significant effect on the cardiovascular system and the respiratory system. The study also shows that the effects of hemorrhage are dose-dependent. The results of the study are discussed in the context of previous research on the effects of hemorrhage and its treatment.

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