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## 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  $P_{O_2} \sim 50$  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 inhibition 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 over 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.)

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HYPOXIC pulmonary vasoconstriction (HPV) is a regulatory mechanism whereby a decrease in alveolar  $P_{O_2}$  results in constriction of adjacent arterioles.<sup>1</sup> 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 ( $FI_{O_2}$ ). 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.<sup>2,3</sup> Although numerous studies have demonstrated an attenuation of HPV during isoflurane anesthesia,<sup>4-10</sup> many

others failed to recognize these conflicting *in vitro* models, the use of acute effects of surgery on conscious, nonsedated dogs. Calculations of pulmonary blood flow during HPV also is unclear. The mechanism by which a metabolite of the cyclooxygenase pathway in the pulmonary circulation attenuates the magnitude of HPV, such as isoflurane, may involve stimulation of the cyclooxygenase pathway. Isoflurane may enhance the production of vasodilator metabolites of the cyclooxygenase pathway for intracellular production of cyclic adenosine monophosphate (cAMP). cAMP-mediated pulmonary sympathetic β-adrenergic stimulation during isoflurane anesthesia. Based on these previous reports, that: (1) isoflurane attenuates the magnitude of HPV in the conscious state, and (2) the isoflurane-induced HPV would be abolished by cyclooxygenase inhibition. We employed chronically instrumented dogs to examine the generation of pressure-flow plots. This chronic model allows us to assess the effects of isoflurane anesthesia on the pulmonary pressure-flow relationship in the same animal and isoflurane anesthesia without the confounding effects of surgery as the requirement for an increase in  $FI_{O_2}$  it decreases intra-arterial pressure. We demonstrated that isoflurane anesthesia attenuates the pressure-flow plots and that this effect is calculated, single-point results indicate that HPV is flow-dependent in both conscious and anesthetized dogs. Moreover, the magnitude of HPV was attenuated during isoflurane anesthesia and abolished after cyclooxygenase inhibition.

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others failed to recognize this effect.<sup>11-15</sup> 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 isoflurane may attenuate HPV also is unclear.<sup>9</sup> Prostacyclin, a vasodilator metabolite of the cyclooxygenase pathway, is produced in the pulmonary circulation during hypoxia and attenuates the magnitude of HPV.<sup>16,17</sup> Volatile anesthetics such as isoflurane may attenuate HPV by increasing the production of vasodilator metabolites of the cyclooxygenase pathway.<sup>18-20</sup> Alternatively, isoflurane 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).<sup>21,22</sup> We recently observed that cAMP-mediated pulmonary vasodilation in response to sympathetic  $\beta$ -adrenoreceptor activation is enhanced during isoflurane anesthesia.<sup>23</sup>

Based on these previous studies, we hypothesized that: (1) isoflurane anesthesia would attenuate the magnitude of HPV when compared to the conscious state, and (2) the isoflurane-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 isoflurane-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, humoral, and local mechanisms of pulmonary vascular regulation.<sup>24-28</sup> Use of pulmonary vascular pressure-flow plots avoids the limitations inherent in calculated, single-point measurements of PVR.<sup>29</sup> Our results indicate that the magnitude of HPV is flow-dependent in both conscious and isoflurane-anesthetized dogs. Moreover, isoflurane 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 ( $25 \pm 1$  kg) were chronically instrumented as described previously.<sup>23</sup> 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 cephazolin (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 vivo* on a weekly basis using the thermal dilution technique.<sup>23</sup> Values for LQ were referenced to body weight ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ). The aortic and pulmonary artery catheters were used to obtain blood samples to measure systemic arterial and mixed venous blood gases, respectively.<sup>23</sup>

### 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 ( $\sim 1$  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.<sup>30</sup>

**Protocol 1: Effect of Isoflurane Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction.** 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 snout. Room air was administered *via* the mask and, after obtaining steady-state conditions ( $\sim 10$  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  $F_{I_{O_2}}$  that resulted in a gradual decrease in systemic arterial  $P_{O_2}$  to  $\sim 50$  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.<sup>31</sup> 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) flow was set at  $100 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ . 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 ( $F_{I_{O_2}} \sim 0.22$ ) 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

in dogs results 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.<sup>23,32</sup> 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  $37\text{--}38^\circ\text{C}$ . Muscle relaxants were not used in any experimental protocol in this study.

**Protocol 2: Effect of Isoflurane Anesthesia on the Magnitude of Hypoxic Pulmonary Vasoconstriction 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,<sup>33,34</sup> and to abolish the pulmonary pressor response to arachidonic acid.<sup>25,26,31</sup> 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 detailed 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

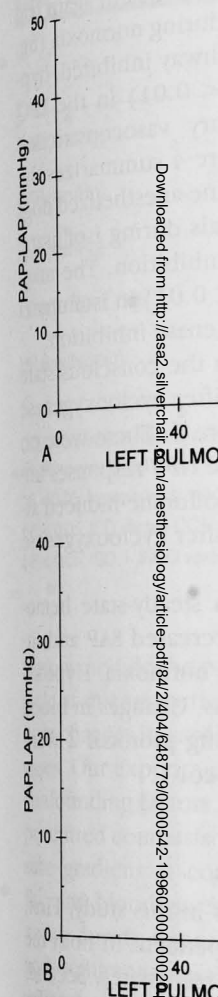


Fig. 1. (A) Composite LPQ plots in seven dogs in normoxia while breathing room air *via* mask. Compared to normoxia, hypoxia caused pulmonary vascular pressure to rise. (B) Composite LPQ plots in seven dogs in normoxia while breathing room air *via* mask, after administration of indomethacin. Compared to normoxia, hypoxia caused pulmonary vascular pressure to rise. (P < 0.01).

(or PAP-O if LAP  $\leq$  0) for each individual experiment. For each protocol average values were used in the analysis of variance to assess the effect of isoflurane anesthesia on the LPQ relationship.

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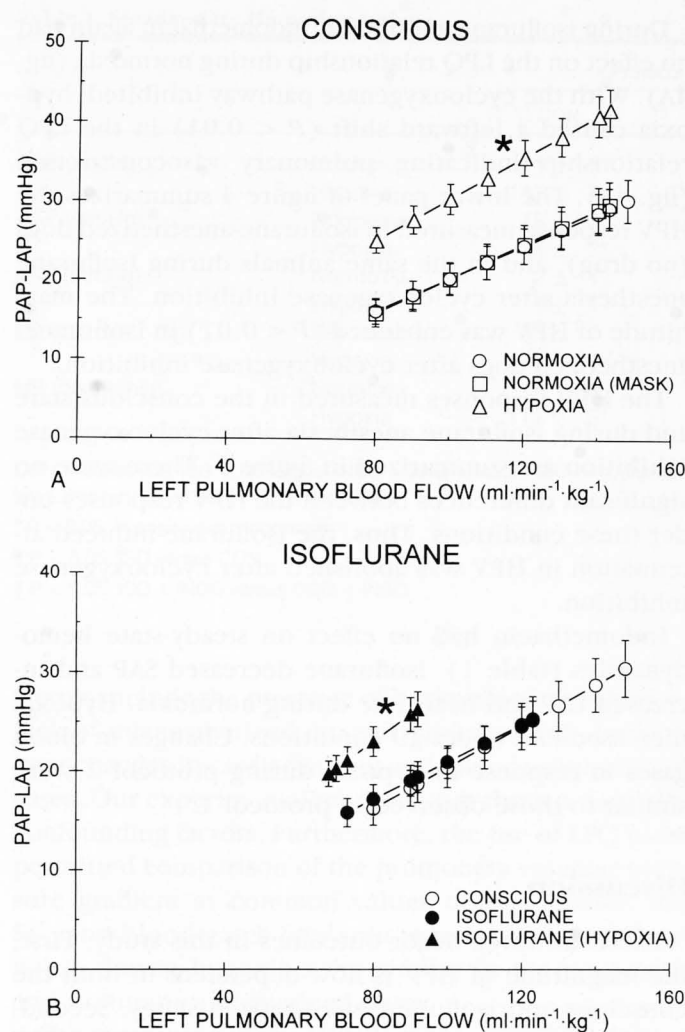


Fig. 1. (A) Composite left pulmonary vascular pressure-flow plots in seven dogs in the conscious state during normoxia, normoxia while breathing through a face mask, and hypoxia. Compared to normoxia, there was no change in the left pulmonary vascular pressure-flow relationship during normoxia *via* mask. Hypoxia caused a leftward shift ( $*P < 0.01$ ) in the left pulmonary vascular pressure-flow relationship, which indicates pulmonary vasoconstriction. (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 vasoconstriction ( $*P < 0.01$ ).

(or PAP-O if LAP  $\leq 0$  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.<sup>35</sup> 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  $FI_{O_2}$  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  $\pm$  SE.

## Results

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

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 vasoconstriction (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

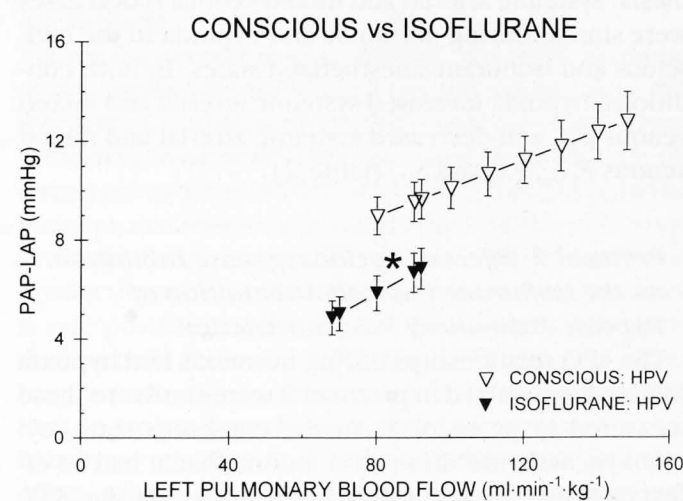


Fig. 2. The composite hypoxic pulmonary vasoconstrictor response (increase in pulmonary arterial pressure-left atrial pressure during hypoxia compared to normoxic values) as a function of left pulmonary blood flow in the same seven chronically instrumented dogs in the conscious state and during isoflurane anesthesia. In both the conscious and isoflurane-anesthetized states, the magnitude of the hypoxic pulmonary vasoconstrictor response was flow-dependent ( $P < 0.01$ ). During isoflurane anesthesia, the hypoxic pulmonary vasoconstrictor response was attenuated ( $*P < 0.01$ ) compared to the hypoxic pulmonary vasoconstrictor response measured in the conscious state.



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 in 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<sup>6,9</sup> or acutely instrumented, anesthetized *in vivo* preparations.<sup>4,5,7,8,10,14,15</sup> Clinical studies have examined the effect of isoflurane anesthesia on systemic arterial  $P_{O_2}$  during one-lung hypoxia.<sup>11-13</sup> 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

Table 1. Steady-state He

SAP (mmHg)
PAP (mmHg)
LAP (mmHg)
LQ (ml · min <sup>-1</sup> · kg <sup>-1</sup> )
HR (beats/min)

CON = conscious; ISO = isoflurane; LAP = left pulmonary blood flow; HR = heart rate.  
<sup>\*</sup>  $P < 0.05$ , hypoxia versus normoxia.  
<sup>†</sup>  $P < 0.05$ , ISO versus CON.  
<sup>‡</sup>  $P < 0.05$ , ISO + INDO versus ISO.

factors include the presence of anesthesia, lack of unanesthetized control subjects, and changes in cardiac output. Our experimental design minimized these confounding factors. The present study permitted comparison of the magnitude of HPV in the conscious state and during isoflurane anesthesia. This dependence of HPV on flow is consistent with the concept that HPV is a flow-dependent phenomenon. The magnitude of HPV may be an important factor in determining the effects of anesthesia on the HPV response. The effects of isoflurane anesthesia on the magnitude of HPV may be an important factor in determining the effects of isoflurane anesthesia on the magnitude of HPV. Indomethacin inhibition of cyclooxygenase (e.g., through prostacyclin) metabolism may alter the LPQ relationship either during isoflurane anesthesia or during normoxia. Studies that cyclooxygenase inhibition on the baseline LPQ relationship<sup>36,37</sup> and extends

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Table 1. Steady-state Hemodynamics

		Protocol 1		Protocol 2		
		CON	ISO	CON	CON + INDO	ISO + INDO
SAP (mmHg)	Normoxia	111 ± 7	81 ± 5†	108 ± 4	100 ± 4	75 ± 7‡
	Hypoxia	115 ± 7	74 ± 4†	115 ± 5	106 ± 6	79 ± 9‡
PAP (mmHg)	Normoxia	18 ± 3	17 ± 1	14 ± 1	13 ± 1	14 ± 1
	Hypoxia	25 ± 2*	22 ± 1*	23 ± 1*	24 ± 2*	24 ± 2*
LAP (mmHg)	Normoxia	2 ± 1	2 ± 1	2 ± 1	1 ± 1	3 ± 1‡
	Hypoxia	1 ± 1	1 ± 1	1 ± 1	1 ± 2	3 ± 1
LQ (ml · min <sup>-1</sup> · kg <sup>-1</sup> )	Normoxia	80 ± 11	74 ± 6	66 ± 6	58 ± 5	62 ± 6
	Hypoxia	79 ± 10	69 ± 5	66 ± 5	57 ± 4	58 ± 5
HR (beats/min)	Normoxia	95 ± 6	124 ± 5†	99 ± 5	93 ± 8	113 ± 6‡
	Hypoxia	112 ± 5*	119 ± 4	108 ± 6	105 ± 7	121 ± 7

CON = conscious; ISO = isoflurane; 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  $\text{FIO}_2$  and blood gases (systemic arterial and mixed venous) during hypoxia were similar in the conscious and isoflurane-anesthetized states.

The magnitude of the HPV response was flow-dependent in both the conscious state and during isoflurane 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 isoflurane 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 isoflurane anesthesia. This result confirms previous studies that cyclooxygenase inhibition has no net effect on the baseline LPQ relationship in the conscious state,<sup>36,37</sup> and extends this observation to the isoflurane-

anesthetized state. However, cyclooxygenase inhibition did result in potentiation of the HPV response in the conscious state. This phenomenon has been reported previously,<sup>37,38</sup> and is consistent with the observation that a vasodilator metabolite of the cyclooxygenase pathway is produced in the pulmonary circulation during hypoxia.<sup>16,17</sup>

After cyclooxygenase inhibition, the HPV response during isoflurane anesthesia was not significantly different from that measured in the conscious state. Thus, cyclooxygenase inhibition abolished the isoflurane-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 isoflurane anesthesia could attenuate HPV. Shayevitz and coworkers have reported an increase in cyclooxygenase metabolites in isolated, perfused rabbit lung exposed to inhalational anesthetics.<sup>18</sup> 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.<sup>20</sup> Furthermore, Stone and coworkers observed vasoconstriction after administration of indomethacin to rat aortic vascular rings exposed to volatile anesthetics (including isoflurane).<sup>19</sup>





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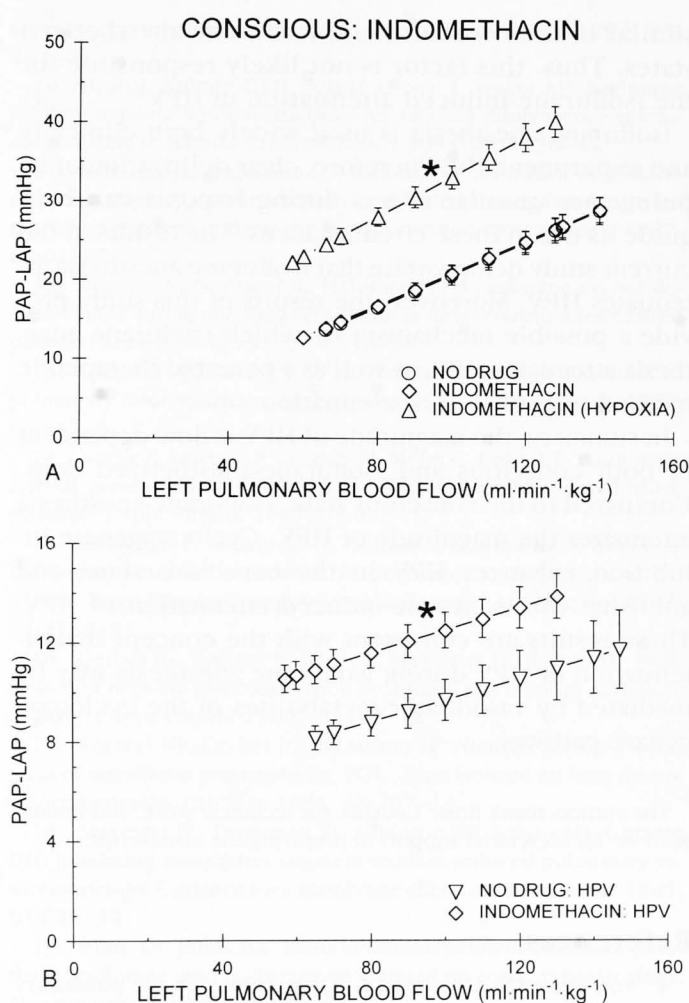


Fig. 3. Composite left pulmonary vascular pressure-flow plot: in seven conscious dogs during normoxia in the intact (no drug) condition, during normoxia after indomethacin, and during hypoxia after indomethacin (A), and the composite hypoxic pulmonary vasoconstrictor response in the intact (no drug) 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.

an attenuation of HPV by sevoflurane,<sup>45</sup> 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.<sup>46</sup> An increase in baseline vasodilator prostaglandins could potentially obscure an effect of the volatile anesthetic on either

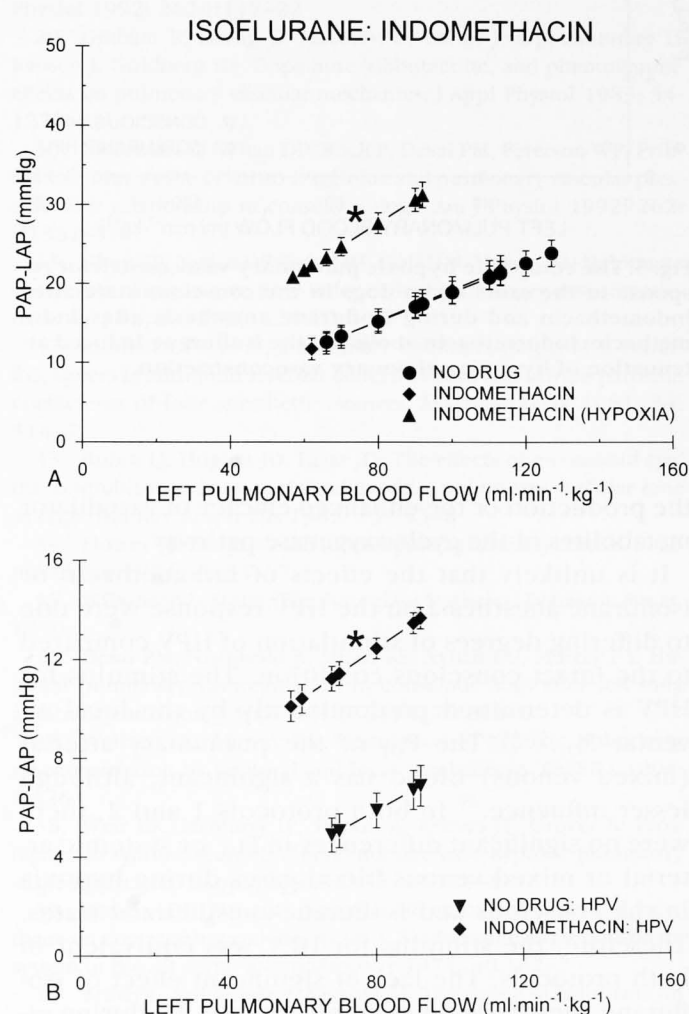


Fig. 4. Composite left pulmonary vascular pressure-flow plots in seven isoflurane-anesthetized dogs during normoxia in the no-drug condition, during normoxia after indomethacin, and during hypoxia after indomethacin (A) and the composite hypoxic pulmonary vasoconstrictor response during isoflurane anesthesia 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.



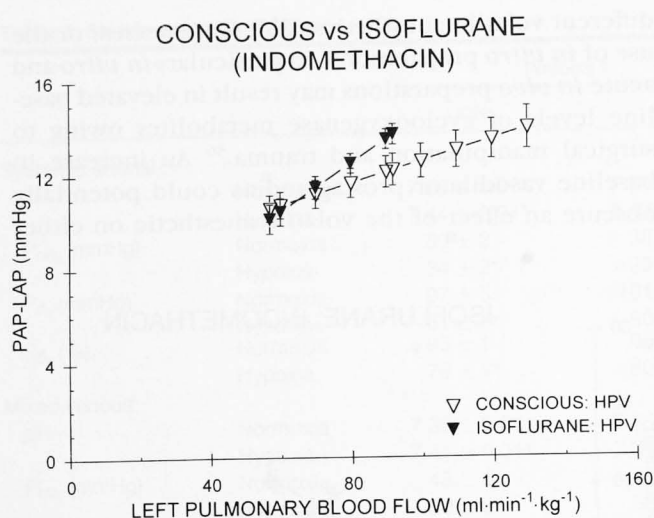


Fig. 5. The composite hypoxic pulmonary vasoconstrictor response in the same seven dogs in the conscious state after indomethacin and during isoflurane anesthesia after indomethacin. Indomethacin abolished the isoflurane-induced attenuation of hypoxic pulmonary vasoconstriction.

the production or the enhanced efficacy of vasodilator metabolites of the cyclooxygenase pathway.

It is unlikely that the effects of indomethacin or isoflurane anesthesia on the HPV response were due to differing degrees of stimulation of HPV compared to the intact conscious condition. The stimulus for HPV is determined predominantly by the local alveolar  $P_{O_2}$ .<sup>47,48</sup> The  $P_{O_2}$  of the pulmonary arterial (mixed venous) blood has a significant, although lesser influence.<sup>49</sup> In both protocols 1 and 2, there were no significant differences in  $F_{I_{O_2}}$  or systemic arterial or mixed venous blood gases during hypoxia in the conscious and isoflurane-anesthetized states. Therefore, the stimulus for HPV was equivalent in both protocols. The lack of significant effect of isoflurane anesthesia on systemic arterial  $P_{O_2}$  during either normoxia or hypoxia was not surprising. Although isoflurane anesthesia attenuates HPV, hypoxia was bilateral and global. In addition, previous studies have failed to show an effect of isoflurane anesthesia on systemic arterial  $P_{O_2}$  under similar conditions.<sup>8,14,15</sup> We did observe respiratory alkalosis during hypoxia, which can act to attenuate the HPV response.<sup>50,51</sup> However, the modest degree of alkalosis that we observed has been demonstrated to have only a small effect on the magnitude of HPV.<sup>50,51</sup> Moreover, the degree of respiratory alkalosis during hypoxia was

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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