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Effects of Halothane and Enflurane Anesthesia on Sympathetic β-adrenoreceptor–mediated Pulmonary Vasodilation in Chronically Instrumented Dogs

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Background: **The authors previously reported that the pulmonary vasodilator response to the sympathetic β-adrenoreceptor agonist isoproterenol is potentiated during isoflurane anesthesia compared with the conscious state. In the present *in vivo* study, the authors tested the hypothesis that halothane and enflurane anesthesia also enhance sympathetic β adrenoreceptor-mediated pulmonary vasodilation. The authors also used the membrane-permeable analog of cyclic adenosine monophosphate (cAMP), dibutyryl cAMP, to help delineate the site in the signaling pathway for an anesthesia-induced effect on β adrenoreceptor-mediated pulmonary vasodilation.**

Methods: **Mongrel dogs were chronically instrumented to measure the left pulmonary vascular pressure–flow (LPQ) relationship. LPQ plots were measured on separate days in the conscious, halothane-, and enflurane-anesthetized states at baseline, after preconstriction with the thromboxane analog U46619, and during the cumulative intravenous administration of isoproterenol. LPQ plots were also measured in conscious, halothane-, and isoflurane-anesthetized dogs after U46619 preconstriction and during the cumulative intravenous administration of dibutyryl cAMP.**

Results: **Compared with the conscious state, neither halothane nor enflurane had an effect on the baseline LPQ relationship. The magnitude of the pulmonary vasodilator response to isoproterenol was potentiated during halothane anesthesia but unchanged during enflurane anesthesia. The pulmonary vasodilator response to dibutyryl cAMP was not altered during either halothane or isoflurane anesthesia compared with the conscious state.**

Conclusions: **These results indicate that inhalational anesthetic agents can exert differential effects on the pulmonary vasodilator response to sympathetic β-adrenoreceptor activation. The potentiated vasodilator response observed during halothane and isoflurane anesthesia is the result of effects proximal to cAMP accumulation in the β-adrenoreceptor signaling pathway.**

THE current investigation is part of an ongoing series of studies designed to elucidate the effects of general anesthesia on mechanisms of pulmonary vascular regulation. The pulmonary circulation is the afterload against which the right ventricle must eject blood. Because the contractile reserve of the right ventricle is relatively limited, it is important to evaluate the effects of anesthetic agents and cardiovascular drugs on pulmonary vasoregulation. We have previously reported that inhalational anesthetic agents have diverse effects on the three primary mechanisms of pulmonary vasodilation. For example, pulmonary vasodilation mediated by endothelium-derived relaxing factors is attenuated during halothane[1] and isoflurane[2,3] anesthesia. Similarly, pulmonary vasodilation mediated by adenosine triphosphate (ATP)-sensitive potassium channel (K^+_{ATP}) activation is attenuated during halothane, enflurane, and isoflurane anesthesia.[4,5] In contrast, isoflurane potentiates the pulmonary vasodilator response to sympathetic β-adrenoreceptor activation.[6] In the present *in vivo* study, we have investigated the effects of halothane and enflurane anesthesia on the pulmonary vasodilator response to the sympathetic β-adrenoreceptor agonist isoproterenol. We tested the hypothesis that these inhalational anesthetic agents would potentiate the pulmonary vasodilator response to isoproterenol compared with the response measured in the conscious state. We also used the membrane-permeable analog of cyclic adenosine monophosphate (cAMP), dibutyryl cAMP, to ascertain if the anesthesia-induced potentiation is the result of effects on the β-adrenoreceptor signaling pathway either proximal or distal to cAMP accumulation.

Materials and Methods

All surgical procedures and experimental protocols were approved by the Cleveland Clinic Foundation Institutional Animal Care and Use Committee, Cleveland, Ohio.

Surgery for Chronic Instrumentation

Eighteen conditioned mongrel dogs (weight, 28 ± 1 kg) were used in this study. The surgery for chronic instrumentation has been described in detail.[7] All dogs were premedicated with intramuscular morphine sulfate, 10 mg, and were anesthetized with intravenous pentobarbital sodium, 20 mg/kg, and intravenous fentanyl citrate, 15 μg/kg. After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with halothane (approximately 1.2% end-tidal). A left thoracotomy was performed *via* the fifth intercostal space using sterile surgical technique, and the pericardium was incised ventral to the phrenic nerve. Heparin-filled Tygon catheters (1.02 mm ID, Norton, Akron, OH) were inserted into the descending thoracic aorta, left and right atrium, and main pulmonary artery and were

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secured with purse-string sutures. After careful dissection and isolation, a hydraulic occluder (18 mm ID, In Vivo Metric, Healdsburg, CA) 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. After loose apposition of the pericardial edges, the free ends of the catheters, occluder, and flow probe were threaded through the chest wall and were tunneled subcutaneously to a final position between the scapulae. A chest tube placed in the left thorax before closure was removed on the first postoperative day. Intramuscular morphine sulfate, 10 mg, was administered postoperatively for pain as required. Ampicillin, 1 g, cefazolin, 1 g, and gentamicin, 80 mg, were administered intraoperatively and on a daily basis for 10 days postoperatively. The dogs were allowed to recover for at least 2 weeks before experimentation.

Experimental Measurements

As described previously,[7] vascular pressures were measured by attaching the fluid-filled catheters to strain-gauge manometers (Quest Medical, Allen, TX) and were referenced to atmospheric pressure with the transducers positioned at midchest at the level of the spine. Heart rate (HR) was calculated from the phasic aortic pressure trace. Left pulmonary blood flow (LQ) was measured by connecting the flow probe to an electromagnetic flowmeter (SWF-5RD, Zepeda, Seattle, WA). The flow probe was calibrated *in vivo* on a weekly basis by the thermal dilution technique.[7] Values for LQ were referenced to body weight ($ml \cdot min^{-1} \cdot kg^{-1}$). The aortic and pulmonary artery catheters were used to obtain blood samples to measure systemic arterial and mixed venous blood gases, respectively. Systemic arterial and mixed venous *p*H, carbon dioxide tension (P_{CO_2}), and oxygen tension (P_{O_2}) were measured with an ABL-600 (Radiometer, Copenhagen, Denmark). Oxyhemoglobin saturation (S_{O_2}) was measured with a Hemoximeter OSM-3 (Radiometer).

Drug Preparation

All solutions were prepared on the day of the experiment. Isoproterenol (Sanofi Winthrop Pharmaceuticals, New York, NY), dibutyryl cAMP (N^6,2'-O-dibutyryl adenosine 3',5'-cyclic monophosphate, Sigma Chemical, St. Louis, MO), and the thromboxane analog U46619 (9,11-dideoxy-11α,9α-epoxymethano-prostaglandin $F_{2\alpha}$, Sigma Chemical) were diluted in 0.9% saline.

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 not sedated. LPQ plots were used to assess the effects of the various interventions on the pulmonary circulation. LPQ plots were constructed by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure–left atrial pressure [PAP-LAP]) and LQ during gradual (approximately 1 min) inflation of the hydraulic occluder implanted around the right main pulmonary artery. Measuring the pulmonary vascular pressure gradient takes into account the possibility that an experimental intervention could alter the driving pressure (PAP) or the effective downstream pressure (LAP). 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.[7]

Protocol 1: Effect of Halothane on the Pulmonary Vasodilator Response to Sympathetic β-adrenoreceptor Activation. We investigated the effect of halothane anesthesia on the pulmonary vascular response to cumulative doses of the sympathetic β-adrenoreceptor agonist isoproterenol after preconstriction with the thromboxane analog U46619. Preconstriction is necessary because the normal pulmonary circulation is essentially maximally dilated at rest. A baseline LPQ plot was first obtained in each conscious dog (n = 8). U46619 was then administered (0.12 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) intravenously to preconstrict the pulmonary circulation before the administration of isoproterenol. LPQ plots were obtained during U46619 preconstriction alone and again with each dose of intravenous isoproterenol (0.01, 0.02, 0.05, and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during its incremental administration ($\approx$15 min at each dose) and while the infusion of U46619 was continued. We have verified that pulmonary vasoconstriction induced by U46619 is stable over the time course of this protocol.[8] On a separate day, this protocol was repeated in the same dogs during halothane anesthesia. Anesthesia with halothane was induced by mask and was supplemented with a subanesthetic dose of intravenous thiopental sodium, 3 mg/kg, to minimize excitatory behavior. The trachea was intubated (9 mm ID), and ventilation was controlled with a mechanical ventilator with zero end-expiratory pressure. Muscle relaxants were not used in this study. Immediately after intubation, halothane was delivered *via* a vaporizer (Fluotec MK III, Ohmeda, Austell, GA). 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 (fractional inspiratory oxygen = 0.22) and by adjusting the respiratory rate to 10–20 breaths/min. End-tidal carbon dioxide and halothane concentrations were continuously measured at the adapter end of the endotracheal tube throughout the experiment (Solar 7000, Random Access Mass Spec, Marquette Electronics, Milwaukee, WI). After induction, halothane was allowed to equilibrate for at least 1 h to achieve steady-state conditions. At this time, the end-tidal halothane concentration was 1.2–1.4%. During halothane anesthesia, the dose of in-

travenous U46619 (0.08 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was titrated to achieve the same degree of preconstriction induced in the conscious state (*i.e.*, an approximate doubling of PAP-LAP at any given value of LQ). This technique allowed us to assess the pulmonary vasodilator response to isoproterenol at the same level of vasomotor tone in the conscious and halothane-anesthetized states.

Protocol 2: Effect of Enflurane on the Pulmonary Vasodilator Response to Sympathetic β-adrenoreceptor Activation. We investigated the effect of enflurane anesthesia on the pulmonary vascular response to cumulative doses of isoproterenol in the presence of U46619 preconstriction. For each conscious dog (n = 8), LPQ plots were obtained in the baseline condition, during intravenous U46619 preconstriction (0.11 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and during the incremental administration of isoproterenol as described in protocol 1. On a separate day, this protocol was repeated in the same dogs during enflurane anesthesia. Anesthesia with enflurane was induced as described in protocol 1, and the end-tidal concentration was maintained at 3.0–3.3%. During enflurane anesthesia, the dose of intravenous U46619 (0.06 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was titrated to achieve the same degree of preconstriction induced in the conscious state.

Protocol 3: Effect of Halothane on the Pulmonary Vasodilator Response to Dibutyryl cAMP. We investigated the effect of halothane anesthesia on the pulmonary vascular response to cumulative doses of dibutyryl cAMP, the membrane-permeable cyclic AMP analog, after preconstriction with U46619. A baseline LPQ plot was first obtained in each conscious dog (n = 8). Intravenous U46619 was then administered (0.12 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to preconstrict the pulmonary circulation before the administration of dibutyryl cAMP. LPQ plots were obtained during U46619 preconstriction alone and then again with each intravenous dose of dibutyryl cAMP (150, 300, and 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during its incremental administration (approximately 15 min at each dose) while the infusion of U46619 was continued. On a separate day, this protocol was repeated in the same dogs during halothane anesthesia. Anesthesia with halothane was induced as described in protocol 1, and the end-tidal concentration was maintained at 1.2–1.4%. During halothane anesthesia, the dose of intravenous U46619 (0.08 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was titrated to achieve the same degree of preconstriction induced in the conscious state.

Protocol 4: Effect of Isoflurane on the Pulmonary Vasodilator Response to Dibutyryl cAMP. Because we have previously observed that isoflurane potentiates the pulmonary vasodilator response to isoproterenol,[6] we investigated the effect of isoflurane anesthesia on the pulmonary vascular response to cumulative doses of dibutyryl cAMP in the presence of U46619 preconstriction. For each conscious dog (n = 8), LPQ plots were obtained in the baseline condition, during intravenous U46619 preconstriction (0.12 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and during the incremental administration of dibutyryl cAMP as described in protocol 3. On a separate day, this protocol was repeated in the same dogs during isoflurane anesthesia. Anesthesia with isoflurane was induced as described in protocol 1, and the end-tidal concentration was maintained at 1.6–1.7%. During isoflurane anesthesia, the dose of intravenous U46619 (0.08 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was titrated to achieve the same degree of preconstriction induced in the conscious state.

Data Analysis

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (Gould, Eastlake, OH). 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 and after each LPQ plot. The analog pressure and LQ signals were digitally converted and multiplexed (Medical Systems, PCM-8, Greenvale, NY) and stored on videotape (Videocassette recorder AG-1260, Panasonic, Secaucus, NJ) for later playback and analysis. As reported in previous studies,[9,10] 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 (or PAP-0 if LAP was ≤ 0 mmHg) as a function of LQ in each experiment. The correlation coefficient for the LPQ relationship in each protocol averaged 0.98 or higher. The composite LPQ plots summarized in the figures were generated using the regression parameters from each continuously measured LPQ plot to calculate PAP-LAP at 10-$ml \cdot min^{-1} \cdot kg^{-1}$ intervals of LQ over the empirically measured range of LQ. The minimum and maximum values of LQ in each composite LPQ plot represent the average minimum and maximum values of LQ for the dogs studied in that protocol. One-way analysis of variance followed by Student *t* test for paired comparisons was used to assess the pulmonary vascular effects of isoproterenol and dibutyryl cAMP within each group. Two-way analysis of variance followed by Student *t* test for paired comparisons was used to assess the effects of the anesthetic agents on steady-state hemodynamics and blood gases. Two-way analysis of variance was also used to assess the effects of the anesthetics on the pulmonary vascular responses to isoproterenol and dibutyryl cAMP compared with responses measured in the conscious state. The pulmonary vasodilator response to isoproterenol (or dibutyryl cAMP) is expressed as the percentage

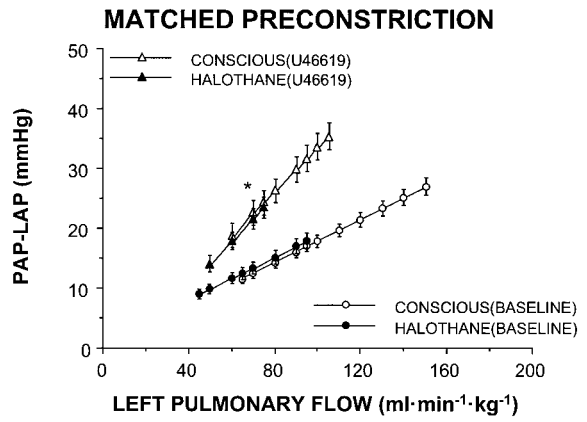

Fig. 1. Composite left pulmonary vascular pressure–flow (LPQ) plots in eight dogs at baseline and after U46619 preconstriction (*$P < 0.01$) in the conscious state and during halothane anesthesia. Compared with the conscious state, halothane had no net effect on the baseline LPQ relationship. The dose of U46619 was titrated to achieve the same degree of preconstriction in the conscious and halothane-anesthetized states.

decrease in U46619 preconstriction and was calculated with the following formula:[2,4,5,7,11]

$$\frac{(\text{PAP-LAP})_{\text{U46619}} - (\text{PAP-LAP})_{\text{isoproterenol}}}{(\text{PAP-LAP})_{\text{U46619}} - (\text{PAP-LAP})_{\text{baseline}}} \times 100\%$$

Thus, an isoproterenol-induced (or dibutyryl cAMP-induced) decrease in PAP-LAP of 100% represents a complete reversal of U46619 preconstriction and a full return to the baseline LPQ relationship. A "floating" value of LQ was used to calculate the percent reversal of U46619 preconstriction because isoproterenol and dibutyryl cAMP increased LQ in a dose-dependent manner. This allowed us to calculate the agonist-induced percent reversal of U46619 preconstriction at mid-range values of empirically measured LQ. For isoproterenol, LQ values of 80, 100, 120, and 140 ml · min^{-1} · kg^{-1} were used at concentrations of 0.01, 0.02, 0.05, and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, in the conscious and anesthetized states. For dibutyryl cAMP, LQ values of 80, 100, and 120 ml · min^{-1} · kg^{-1} were used at concentrations of 150, 300, and 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. All values are presented as mean ± SEM.

Results

Protocol 1: Effect of Halothane on Sympathetic β-adrenoreceptor–mediated Pulmonary Vasodilation

Halothane had no net effect on the baseline LPQ relationship compared with the conscious state (fig. 1). Matched preconstriction of the pulmonary circulation in conscious and halothane-anesthetized dogs was achieved with U46619 (fig. 1). A lower dose ($P < 0.05$) of U46619 was required during halothane to match the same degree of preconstriction achieved in the conscious state. Figure 2 summarizes the effects of one dose of isoproterenol on the LPQ relationship in conscious and halothane-anesthetized

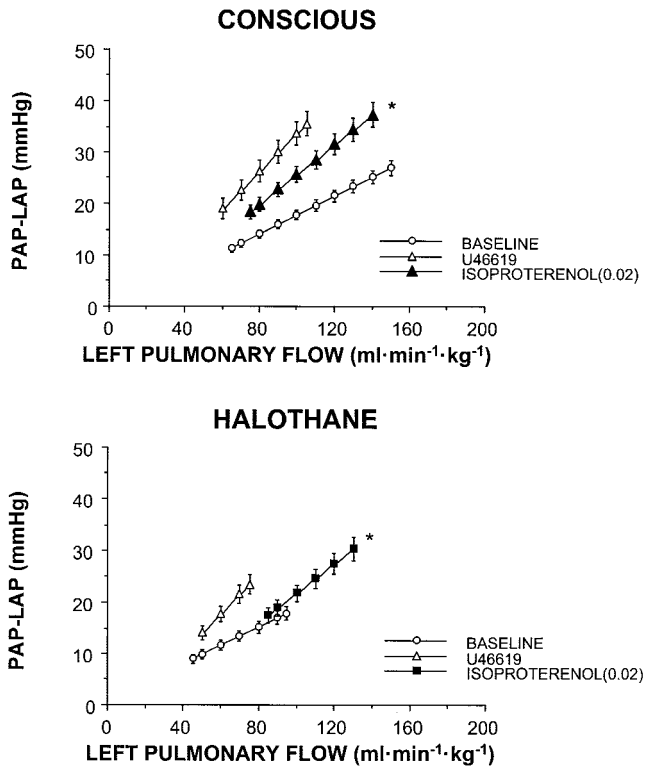

Fig. 2. Composite left pulmonary vascular pressure–flow (LPQ) plots in eight dogs at baseline, after preconstriction with U46619, and during administration of intravenous isoproterenol, 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in the conscious state (*top*) and during halothane anesthesia (*bottom*). In both the conscious state and during halothane anesthesia, this dose of isoproterenol caused a rightward shift in the LPQ relation, indicating pulmonary vasodilation (*$P < 0.05$).

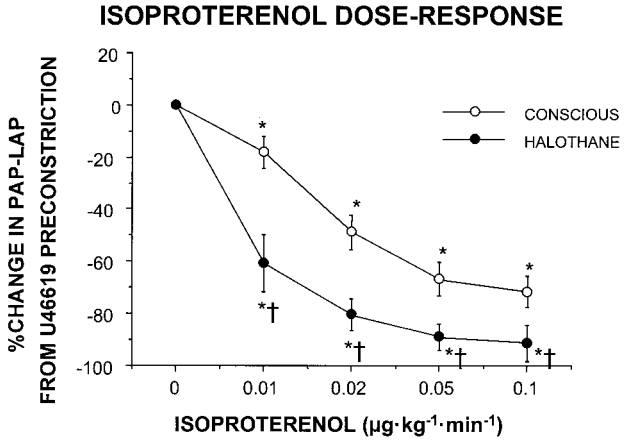

Fig. 3. Isoproterenol dose–response relationship measured in eight dogs after U46619 preconstriction in the conscious state and during halothane anesthesia is shown. Vasodilator response to isoproterenol is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Isoproterenol-induced pulmonary vasodilation (*$P < 0.05$) was potentiated (†$P < 0.05$) during halothane anesthesia compared with the conscious state.

Table 1. Steady State Hemodynamics: Protocol 1

		Baseline	U46619	Isop 0.01	Isop 0.10
SAP (mmHg)	Conscious	96 ± 4	105 ± 3*	102 ± 4	100 ± 5
	Halothane	64 ± 1‡	77 ± 3*‡	71 ± 4†‡	69 ± 3†‡
PAP (mmHg)	Conscious	16 ± 1	24 ± 2*	23 ± 1	27 ± 2
	Halothane	15 ± 1	22 ± 1*	23 ± 1†	28 ± 2†
LAP (mmHg)	Conscious	4 ± 1	4 ± 1	3 ± 1†	3 ± 1
	Halothane	6 ± 1‡	7 ± 1‡	6 ± 1‡	5 ± 1‡
LQ ($ml \cdot min^{-1} \cdot kg^{-1}$)	Conscious	67 ± 5	60 ± 5	67 ± 6	117 ± 13†
	Halothane	41 ± 5‡	46 ± 5	65 ± 6†	114 ± 6†
HR (beats/min)	Conscious	96 ± 7	82 ± 7*	87 ± 6	135 ± 5†
	Halothane	113 ± 4	117 ± 3‡	133 ± 5†‡	165 ± 4†‡

* $P < 0.05$ U46619 *versus* baseline; † $P < 0.05$ isoproterenol *versus* U46619; ‡ $P < 0.05$ halothane *versus* conscious. Isoproterenol (Isop) data for doses of 0.01 and 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All hemodynamics are mean values.

SAP = systemic arterial pressure; PAP = pulmonary arterial pressure. LAP = left atrial pressure; LQ = left pulmonary blood flow; HR = heart rate.

dogs. In the presence of U46619 preconstriction, the intravenous infusion of isoproterenol (0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced pulmonary vasodilation in the conscious state and during halothane anesthesia. The pulmonary vascular dose–response relationship for isoproterenol in the conscious and halothane-anesthetized states is summarized in figure 3. After U46619 preconstriction, isoproterenol induced pulmonary vasodilation at all doses in conscious and halothane-anesthetized dogs. However, the magnitude of the pulmonary vasodilator response to isoproterenol was markedly enhanced during halothane anesthesia.

Steady-state hemodynamics and blood gases for protocol 1 are summarized in tables 1 and 2. Compared with the conscious state, baseline mean systemic arterial pressure (SAP) and LQ were decreased and LAP was increased during halothane anesthesia. U46619 increased SAP and PAP in the conscious state and during halothane anesthesia and decreased HR in the conscious state. Isoproterenol decreased SAP and increased PAP during halothane anesthesia and increased LQ and HR in both conditions. Baseline systemic arterial P_{CO_2} and mixed venous P_{CO_2}, P_{O_2}, and S_{O_2} were slightly decreased during halothane compared with the conscious state. U46619 decreased systemic arterial S_{O_2}, and mixed venous *p*H, P_{O_2} and S_{O_2} in both conditions. Isoproterenol, 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, decreased systemic arterial and mixed venous *p*H during halothane and mixed venous P_{CO_2} in both conditions. Isoproterenol, 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, increased mixed venous P_{O_2} and S_{O_2} in both conditions.

Protocol 2: Effect of Enflurane on Sympathetic β-adrenoreceptor–mediated Pulmonary Vasodilation

Enflurane had no net effect on the baseline LPQ relationship compared with the conscious state (fig. 4). A lower dose ($P < 0.05$) of U46619 was required during enflurane anesthesia to match the same degree of preconstriction achieved in the conscious state (fig. 4). The pulmonary vascular dose–response relationship for isoproterenol in the conscious and enflurane-anesthetized states is summarized in figure 5. Although the magnitude

Table 2. Steady State Blood Gases: Protocol 1

		Baseline	U46619	Isop 0.01	Isop 0.10
Systemic arterial					
pH	Conscious	7.40 ± 0.01	7.38 ± 0.01	7.39 ± 0.01†	7.38 ± 0.01
	Halothane	7.41 ± 0.01	7.40 ± 0.01	7.40 ± 0.01	7.34 ± 0.01†‡
P_{CO_2} (mmHg)	Conscious	39 ± 1	40 ± 2	37 ± 1†	34 ± 1†
	Halothane	35 ± 1‡	37 ± 1	36 ± 2	34 ± 1
P_{O_2} (mmHg)	Conscious	93 ± 3	84 ± 4*	89 ± 4†	90 ± 6†
	Halothane	92 ± 3	88 ± 5	95 ± 4	96 ± 2
S_{O_2} (%)	Conscious	96 ± 1	93 ± 1*	95 ± 1†	94 ± 1
	Halothane	96 ± 1	94 ± 1*	95 ± 1	95 ± 1
Mixed venous					
pH	Conscious	7.36 ± 0.01	7.34 ± 0.01*	7.35 ± 0.01	7.36 ± 0.01†
	Halothane	7.38 ± 0.01	7.36 ± 0.01*	7.37 ± 0.01	7.32 ± 0.01†‡
P_{CO_2} (mmHg)	Conscious	45 ± 1	47 ± 2	45 ± 1†	38 ± 1†
	Halothane	41 ± 1‡	44 ± 1*	41 ± 2†‡	39 ± 1†
P_{O_2} (mmHg)	Conscious	45 ± 1	40 ± 1*	44 ± 1†	56 ± 2†
	Halothane	42 ± 1‡	39 ± 1*	46 ± 2†	62 ± 1†‡
S_{O_2} (%)	Conscious	68 ± 1	58 ± 2*	65 ± 2†	79 ± 2†
	Halothane	65 ± 1‡	58 ± 2*	70 ± 2†	83 ± 1†

* $P < 0.05$ U46619 *versus* baseline; † $P < 0.05$ isoproterenol *versus* U46619; ‡ $P < 0.05$ halothane *versus* conscious.

P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension; S_{O_2} = oxygen saturation.

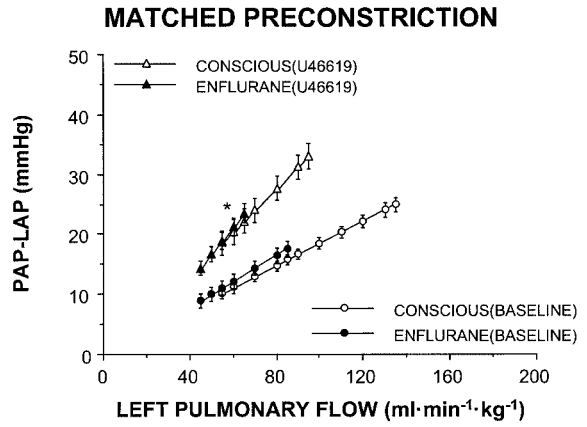

Fig. 4. Composite left pulmonary vascular pressure–flow (LPQ) plots in eight dogs at baseline and after U46619 preconstriction (*$P < 0.01$) in the conscious state and during enflurane anesthesia. Compared with the conscious state, enflurane had no net effect on the baseline LPQ relationship. The dose of U46619 was titrated to achieve the same degree of preconstriction in the conscious and enflurane-anesthetized states.

of the pulmonary vasodilator response to isoproterenol tended to be slightly greater during enflurane anesthesia compared with the conscious state, this effect did not achieve statistical significance.

Steady-state hemodynamics and blood gases for protocol 2 are summarized in tables 3 and 4. Compared with the conscious state, the effects of enflurane on steady-state hemodynamics were similar to changes observed during halothane anesthesia. Baseline blood gases were similar in conscious and enflurane-anesthetized dogs. Changes in systemic arterial and mixed venous blood gases in response to U46619 and isoproterenol were similar to responses observed in protocol 1.

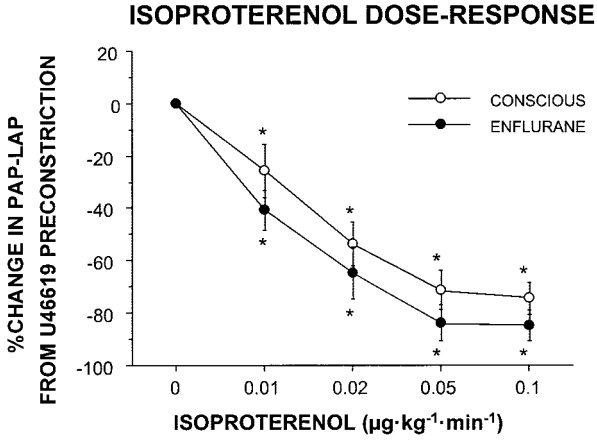

Fig. 5. Isoproterenol dose–response relationship measured in eight dogs after U46619 preconstriction in the conscious state and during enflurane anesthesia is shown. Vasodilator response to isoproterenol is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Isoproterenol-induced pulmonary vasodilation (*$P < 0.05$) was not altered during enflurane anesthesia compared with the conscious state.

Protocol 3: Effect of Halothane on Dibutyryl cAMP-mediated Pulmonary Vasodilation

A smaller dose ($P < 0.05$) of U46619 was required during halothane anesthesia to match the same degree of preconstriction achieved in the conscious state. The pulmonary vascular dose–response relationship for dibutyryl cAMP in the conscious and halothane-anesthetized states is summarized in figure 6. After U46619 preconstriction, the magnitude of dibutyryl cAMP-induced pulmonary vasodilation was similar in the conscious state and during halothane anesthesia.

Steady-state hemodynamics and blood gases for protocol 3 are summarized in tables 5 and 6. Dibutyryl cAMP, 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$, decreased SAP during halothane anesthesia and decreased LAP and increased LQ and HR in both conditions. Dibutyryl cAMP decreased systemic arterial and mixed venous P_{CO_2} and increased systemic arterial and mixed venous P_{O_2} and mixed venous S_{O_2} in both conditions.

Protocol 4: Effect of Isoflurane on Dibutyryl cAMP-mediated Pulmonary Vasodilation

Because we previously observed that the magnitude of isoproterenol-induced pulmonary vasodilation is potentiated during isoflurane anesthesia,[6] we assessed the effects of dibutyryl cAMP on the LPQ relationship in conscious and isoflurane-anesthetized dogs. A smaller dose ($P < 0.05$) of U46619 was required during isoflurane anesthesia to match the same degree of preconstriction achieved in the conscious state. The pulmonary vascular dose–response relationship for dibutyryl cAMP in the conscious and isoflurane-anesthetized states is summarized in figure 7. After U46619 preconstriction, the magnitude of dibutyryl cAMP-induced pulmonary vasodilation was similar in the conscious state and during isoflurane anesthesia.

Changes in steady-state hemodynamics and blood gases in response to dibutyryl cAMP during isoflurane anesthesia were similar to the changes observed during halothane anesthesia (tables 5 and 6).

Discussion

This *in vivo* study demonstrated that the magnitude of the pulmonary vasodilator response to the β-adrenoreceptor agonist isoproterenol was potentiated during halothane anesthesia compared with the conscious state but not during enflurane anesthesia. Moreover, the pulmonary vasodilator response to dibutyryl cAMP was similar in conscious, halothane-anesthetized, and isoflurane-anesthetized dogs.

These studies used dogs that were chronically instrumented to measure the LPQ relationship. There are several advantages to this experimental model. First, this model avoids the effects of background anesthetic

Table 3. Steady State Hemodynamics: Protocol 2

		Baseline	U46619	Isop 0.01	Isop 0.10
SAP (mmHg)	Conscious	99 ± 4	108 ± 4*	105 ± 5	102 ± 5
	Enflurane	66 ± 5‡	76 ± 7*‡	70 ± 8‡	70 ± 7†‡
PAP (mmHg)	Conscious	16 ± 1	23 ± 1*	22 ± 1	25 ± 2†
	Enflurane	15 ± 2	22 ± 2*	25 ± 2†	31 ± 2†‡
LAP (mmHg)	Conscious	4 ± 1	5 ± 1	4 ± 1†	3 ± 1†
	Enflurane	6 ± 1‡	7 ± 1*	7 ± 1‡	6 ± 1†‡
LQ (ml · min^{-1} · kg^{-1})	Conscious	60 ± 4	55 ± 4	63 ± 5†	108 ± 9†
	Enflurane	44 ± 5‡	45 ± 3	63 ± 7†	121 ± 8†
HR (beats/min)	Conscious	96 ± 4	80 ± 5*	88 ± 6	131 ± 4†
	Enflurane	107 ± 5	109 ± 6‡	124 ± 8†‡	156 ± 8†‡

* $P < 0.05$ U46619 *versus* baseline; † $P < 0.05$ isoproterenol *versus* U46619; ‡ $P < 0.05$ enflurane *versus* conscious.

SAP = systemic arterial pressure; PAP = pulmonary arterial pressure; LAP = left atrial pressure; LQ = left pulmonary blood flow; HR = heart rate.

agents and acute surgical trauma. Second, we were able to study the same dogs in the conscious and anesthetized states. And third, this model avoids the limitations that are inherent in the interpretation of single-point calculations of pulmonary vascular resistance.[12]

Neither halothane nor enflurane had an effect on the baseline LPQ relationship, which confirms a previous finding from our laboratory.[4] A lower concentration of U46619 was required during halothane, enflurane, and isoflurane anesthesia to match the same degree of pulmonary vasoconstriction observed in the conscious state. This effect is likely the result of an attenuating influence of inhalational anesthetics on endothelium-derived relaxing factors,[1–3] which normally modulate the pulmonary vascular response to a vasoconstrictor influence.[7] One may expect the anesthetic agents to shift the conscious baseline LPQ relationship because of this effect. However, we have previously reported that the endothelium-derived relaxing factor nitric oxide does not tonically regulate the baseline LPQ relationship in conscious dogs.[7]

Recent evidence suggests that there are at least three possible mechanisms by which β-adrenoreceptor activation can result in vasodilation. Classically, the signal transduction pathway for β-adrenoreceptor–mediated vasodilation involves stimulation of vascular smooth muscle adenylyl cyclase and an increase in the intracellular concentration of cAMP.[13] Consistent with this, isoproterenol-induced increases in cAMP have been observed in endothelium-denuded isolated canine pulmonary artery[14] and rat aorta.[15] A second mechanism for isoproterenol-induced vasodilation appears to be mediated by the endothelium-dependent release of nitric oxide, resulting in an increase in vascular smooth muscle cyclic guanosine monophosphate (cGMP). In rat aorta, removal of the endothelium or pretreatment with a nitric oxide synthase inhibitor markedly attenuated the vasorelaxant response to isoproterenol.[16,17] A direct role for nitric oxide in isoproterenol-induced vasorelaxation has also been reported in rat mesenteric resistance arteries[18] and canine coronary resistance vessels[19] but not in large canine coronary arteries.[20] We previously reported that isoproterenol caused an endothelium-dependent increase in cGMP in isolated canine pulmonary artery.[14] A

Table 4. Steady State Blood Gases: Protocol 2

		Baseline	U46619	Isop 0.01	Isop 0.10
Systemic arterial					
pH	Conscious	7.40 ± 0.01	7.38 ± 0.01	7.39 ± 0.01†	7.39 ± 0.01
	Enflurane	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01	7.31 ± 0.01†‡
P_{CO_2} (mmHg)	Conscious	38 ± 1	39 ± 2	36 ± 1†	33 ± 1†
	Enflurane	36 ± 1	36 ± 1	36 ± 1	36 ± 1‡
P_{O_2} (mmHg)	Conscious	94 ± 3	86 ± 4*	91 ± 4†	93 ± 6†
	Enflurane	94 ± 2	97 ± 3‡	98 ± 3‡	103 ± 3
S_{O_2} (%)	Conscious	96 ± 1	94 ± 1*	95 ± 1†	95 ± 1
	Enflurane	96 ± 1	96 ± 1	96 ± 1	95 ± 1
Mixed venous					
pH	Conscious	7.37 ± 0.01	7.35 ± 0.01*	7.35 ± 0.01	7.37 ± 0.01†
	Enflurane	7.36 ± 0.01	7.34 ± 0.01	7.34 ± 0.01	7.29 ± 0.01†‡
P_{CO_2} (mmHg)	Conscious	44 ± 1	46 ± 1	44 ± 1†	37 ± 1†
	Enflurane	42 ± 1	45 ± 1*	43 ± 2†	41 ± 1†‡
P_{O_2} (mmHg)	Conscious	45 ± 1	40 ± 1*	44 ± 1†	57 ± 2†
	Enflurane	43 ± 1	40 ± 2*	48 ± 2†	68 ± 2†‡
S_{O_2} (%)	Conscious	68 ± 1	58 ± 2*	65 ± 2†	81 ± 2†
	Enflurane	62 ± 2	56 ± 4*	67 ± 3†	84 ± 1†

* $P < 0.05$ U46619 *versus* baseline; † $P < 0.05$ isoproterenol *versus* U46619; ‡ $P < 0.05$ enflurane *versus* conscious.

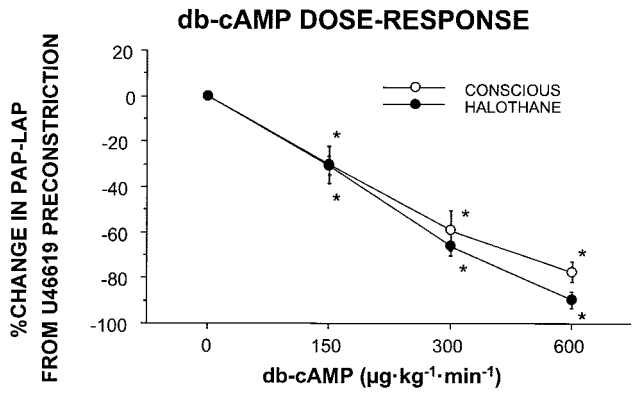

Fig. 6. Dibutyryl cyclic adenosine monophosphate (cAMP) dose–response relationship measured in eight dogs after U46619 preconstriction in the conscious state and during halothane anesthesia is shown. Vasodilator response to dibutyryl cAMP is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Dibutyryl cAMP-induced pulmonary vasodilation (*$P < 0.05$) was similar in the conscious state and during halothane anesthesia.

third mechanism for isoproterenol-induced vasodilation appears to involve activation of K^+_{ATP} channels.[21] Inhibition of K^+_{ATP} channels attenuated the vasorelaxant response to isoproterenol in isolated rat pulmonary artery rings, whereas activation of K^+_{ATP} channels potentiated isoproterenol-induced vasorelaxation.[21] These effects required activation of β adrenoreceptors and were not observed in response to direct activation of adenylyl cyclase with forskolin.[21] Thus, there are at least three vasodilator pathways that could mediate the enhanced pulmonary vasodilator response to isoproterenol during halothane anesthesia observed in the present study.

There is a surprising paucity of information in the literature concerning the effects of inhalational anesthetic agents on β-adrenoreceptor–mediated vasodilation. Halothane and isoflurane were found to inhibit the vasorelaxation response to isoproterenol in endothelium-denuded rat aortic strips.[15] Isoflurane also attenuated isoproterenol-induced relaxation in denuded rat coronary microvessels.[22] In contrast, halothane had no effect on the vasorelaxant response to isoproterenol in endothelium-intact rat aortic rings.[16] As noted earlier, we have previously reported that isoflurane anesthesia actually potentiated the pulmonary vasodilator response to isoproterenol.[6] In the present study, halothane, but not enflurane, also potentiated the pulmonary vasodilator response to isoproterenol.

What is the mechanism by which halothane (and isoflurane) potentiated the pulmonary vasodilator response to isoproterenol? It seems unlikely that this effect could be mediated by an enhanced nitric oxide-mediated component of isoproterenol-induced vasodilation. Halothane[1] and isoflurane[2] have been shown to attenuate the pulmonary vasodilator response to endothelium-dependent cGMP-mediated agonists. It also appears unlikely that the potentiated response could be the result of an enhanced K^+_{ATP}-mediated component of isoproterenol-induced vasodilation. Halothane[4] and isoflurane[5] have been shown to attenuate the pulmonary vasodilator response to K^+_{ATP} channel activation in chronically instrumented dogs. Thus, it appears most likely that the potentiated response is the result of an effect of the anesthetic agents on the β-adrenoreceptor–cAMP signaling pathway. Inhalational anesthetic agents have been shown to alter intracellular cAMP concentration. For example, isoflurane and halothane increased cAMP in rat aortic strips.[23] In rat uterine homogenate, halothane increased cAMP[24] and enhanced the stimulation of adenylyl cyclase by isoproterenol.[25] These effects of halothane and isoflurane on cAMP accumulation were not altered by β-adrenoreceptor inhibition.[23–25] Moreover, halothane had no effect on β-adrenoreceptor affinity for

Table 5. Steady State Hemodynamics: Protocol 3 and 4

		Baseline	U46619	db cAMP 150	db cAMP 600
SAP (mmHg)	Conscious	92 ± 4	102 ± 6	108 ± 5	105 ± 3
	Halothane	64 ± 2‡	86 ± 2*‡	84 ± 3‡	76 ± 3†‡
	Isoflurane	68 ± 4‡	90 ± 6*	84 ± 4‡	75 ± 3†‡
PAP (mmHg)	Conscious	14 ± 1	23 ± 2*	23 ± 1	22 ± 1
	Halothane	15 ± 1	23 ± 2*	22 ± 2	23 ± 1
	Isoflurane	17 ± 1‡	24 ± 2*	23 ± 2	23 ± 1‡
LAP (mmHg)	Conscious	3 ± 1	6 ± 1*	5 ± 1	3 ± 1†
	Halothane	6 ± 1‡	8 ± 1*	7 ± 1	6 ± 1†‡
	Isoflurane	6 ± 1‡	6 ± 1	6 ± 1	5 ± 1‡
LQ (ml · min^{-1} · kg^{-1})	Conscious	62 ± 6	59 ± 6	69 ± 6	91 ± 4†
	Halothane	55 ± 4	54 ± 4	62 ± 5†	93 ± 7†
	Isoflurane	61 ± 2	62 ± 4	67 ± 5	89 ± 5†
HR (beats/min)	Conscious	88 ± 10	72 ± 7*	75 ± 5	101 ± 7†
	Halothane	97 ± 8	100 ± 10‡	99 ± 7‡	130 ± 3†‡
	Isoflurane	115 ± 8‡	112 ± 9‡	117 ± 7‡	144 ± 5†‡

* $P < 0.05$ U46619 *versus* baseline; † $P < 0.05$ dibutyryl cAMP *versus* U46619; ‡ $P < 0.05$ halothane or isoflurane *versus* conscious.

dibutyryl cyclic AMP (db cAMP) data for doses of 150 and 600 μg · kg^{-1} · min^{-1}.

SAP = systemic arterial pressure; PAP = pulmonary arterial pressure; LAP = left atrial pressure; LQ = left pulmonary blood flow; HR = heart rate.

Table 6. Steady State Blood Gases: Protocol 3 and 4

		Baseline	U46619	db cAMP 150	db cAMP 600
Systemic arterial					
pH	Conscious	7.40 ± 0.01	7.37 ± 0.01*	7.37 ± 0.01	7.37 ± 0.02
	Halothane	7.42 ± 0.02	7.39 ± 0.01	7.39 ± 0.01	7.40 ± 0.02
	Isoflurane	7.39 ± 0.02	7.38 ± 0.02	7.36 ± 0.01	7.39 ± 0.01
P_{CO_2} (mmHg)	Conscious	42 ± 1	42 ± 1	40 ± 2	38 ± 2†
	Halothane	38 ± 1‡	40 ± 1	38 ± 1	36 ± 1†
	Isoflurane	41 ± 2	41 ± 2	40 ± 1	35 ± 1†
P_{O_2} (mmHg)	Conscious	95 ± 2	84 ± 5	87 ± 5	92 ± 5†
	Halothane	94 ± 3	84 ± 4*	85 ± 4	91 ± 4†
	Isoflurane	93 ± 2	83 ± 4*	84 ± 6	91 ± 5†
S_{O_2} (%)	Conscious	97 ± 1	93 ± 2	94 ± 1	95 ± 2†
	Halothane	96 ± 1	93 ± 1*	93 ± 1	94 ± 1
	Isoflurane	96 ± 1	93 ± 1*	92 ± 2	95 ± 1
Mixed venous					
pH	Conscious	7.37 ± 0.01	7.34 ± 0.01*	7.33 ± 0.01†	7.34 ± 0.01
	Halothane	7.39 ± 0.02	7.36 ± 0.01	7.34 ± 0.01	7.36 ± 0.02
	Isoflurane	7.36 ± 0.02	7.35 ± 0.02	7.32 ± 0.01	7.35 ± 0.01
P_{CO_2} (mmHg)	Conscious	48 ± 1	50 ± 2	48 ± 2	45 ± 2†
	Halothane	43 ± 1‡	47 ± 1*	46 ± 1	41 ± 1†
	Isoflurane	46 ± 1	48 ± 2*	47 ± 1	41 ± 1†
P_{O_2} (mmHg)	Conscious	45 ± 2	40 ± 2*	44 ± 2	49 ± 1†
	Halothane	44 ± 2	39 ± 2*	43 ± 1	51 ± 1†
	Isoflurane	49 ± 1	43 ± 1*	46 ± 3	52 ± 2†
S_{O_2} (%)	Conscious	70 ± 2	60 ± 4*	65 ± 3	72 ± 2†
	Halothane	69 ± 2	58 ± 2*	62 ± 1	74 ± 1†
	Isoflurane	74 ± 1‡	66 ± 2*	67 ± 4	76 ± 1†

* $P < 0.05$ U46619 *versus* baseline; † $P < 0.05$ dibutyryl cAMP *versus* U46619; ‡ $P < 0.05$ halothane or isoflurane *versus* conscious.

isoproterenol and may have even reduced β-adrenoreceptor density.[26,27] Taken together, these *in vitro* studies suggest that inhalational anesthetic agents may enhance the action of β-adrenoreceptor agonists by activating adenylyl cyclase in a receptor-independent manner to increase cAMP.

Not all *in vitro* studies support the aforementioned conclusion. Tanaka and Tsuchida reported an inhibitory effect of halothane and isoflurane on isoproterenol-induced vasorelaxation in endothelium-denuded rat aortic strips that was associated with a concomitant reduction in cAMP concentration.[15] Moreover, these investigators observed that the anesthetic agents had no effect on vasorelaxation or cAMP accumulation in response to direct activation of adenylyl cyclase with forskolin, nor did they observe an effect of the anesthetics on the binding characteristics of β adrenoreceptors. These investigators concluded that the anesthetic agents exerted their inhibitory effects at a point in the signaling pathway distal to β-receptor activation but proximal to adenylyl cyclase activation. However, Iranami *et al.*[16] did not observe an inhibitory effect of halothane on either isoproterenol-induced vasorelaxation or cAMP accumulation in endothelium-intact rat aortic rings. The differential findings in these *in vitro* studies remain unresolved.

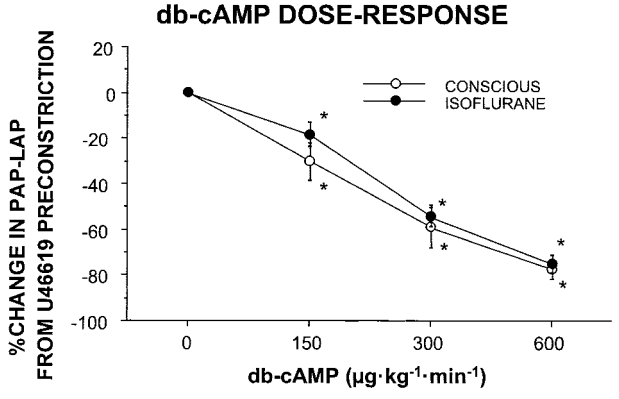

Fig. 7. Dibutyryl cyclic adenosine monophosphate (cAMP) dose–response relationship measured in eight dogs after U46619 preconstriction in the conscious state and during isoflurane anesthesia is shown. Vasodilator response to dibutyryl cAMP is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Dibutyryl cAMP-induced pulmonary vasodilation (*$P < 0.05$) was similar in the conscious state and during isoflurane anesthesia.

In vivo studies provide an opportunity to assess the integrative response of an intervention on the measurement of interest. Our results clearly indicate that halothane potentiates the pulmonary vasodilator response to isoproterenol compared with the response measured in the same animal in the conscious state. This effect could be beneficial in the clinical setting in instances where pulmonary vasodilation is desired, particularly because a lower concentration of the β agonist may be efficacious. A limitation of *in vivo* studies is that it is more difficult to identify the mechanism of action of inhalational anesthetic agents on isoproterenol-induced vasodilation. The potentiated pulmonary vasodilator response to isoproterenol is not likely the result of differential changes in

systemic hemodynamics or blood gases because these changes were similar in halothane- and enflurane-anesthetized dogs, and yet the potentiated vasodilator response was only observed during halothane. The fact that the pulmonary vasodilator response to dibutyryl cAMP was not altered during either halothane or isoflurane anesthesia would suggest that the effects of the anesthetic agents are not mediated at sites distal to adenylyl cyclase activation (*e.g.*, inhibitory effect on cAMP phosphodiesterase activity). Although dibutyryl cAMP is widely used to investigate the β-adrenoreceptor signaling pathway, a possible confounding variable is the associated release of butyrate, which has been shown to mediate some of the actions of dibutyryl cAMP in some cell systems.[28] This possibility aside, it seems reasonable to postulate that the anesthetic agents are likely to exert their effects on the β adrenoreceptors, the guanine nucleotide binding proteins (G-proteins), or the interactions between β adrenoreceptors and G-proteins.

Clinically relevant concentrations of the anesthetic agents were used in this study. Because muscle relaxants were not used, spontaneous respiration precluded a systematic study of subanesthetic concentrations of the inhalational anesthetic agents. Similarly, supraanesthetic concentrations would only have exacerbated anesthesia-induced systemic hypotension.

In summary, compared with the conscious state, the pulmonary vasodilator response to β-adrenoreceptor activation was potentiated during halothane, but not during enflurane, anesthesia. The normal pulmonary vasodilator response to dibutyrl cAMP in halothane- and isoflurane-anesthetized dogs indicates that the site in the signaling pathway for the anesthesia-induced potentiation is proximal to cAMP accumulation.

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