Anesthesiology
1997; 86:923-35

Halothane and Enflurane Attenuate Pulmonary Vasodilation Mediated by Adenosine Triphosphate-sensitive Potassium Channels Compared to the Conscious State

Sumihiko Seki, M.D.,* Kosei Sato, M.D.,* Masayasu Nakayama, M.D.,* and Paul A. Murray, Ph.D.†

Background: **Adenosine triphosphate (ATP)-sensitive potassium (K^+_{ATP}) channels play an important role in pulmonary vasoregulation. However, the effects of volatile anesthetics on K^+_{ATP} channel-mediated pulmonary vasoregulation have not been elucidated. The purpose of the present study was to investigate the effects of halothane and enflurane anesthesia on the pulmonary vasodilator response to the selective K^+_{ATP} channel agonist lemakalim (BRL38227) compared with that measured in the conscious state. The authors also investigated the extent to which endogenous neurohumoral vasoconstrictor mechanisms modulate the vasodilator response to K^+_{ATP} channel activation.**

Method: **Nineteen conditioned, male mongrel dogs were chronically instrumented to measure the left pulmonary vascular pressure–flow (LPQ) relationship. LPQ plots were generated by continuously measuring the pulmonary vascular pressure gradient (pulmonary arterial pressure–left atrial pressure) and left pulmonary blood flow during gradual (~ 1 min) inflation of a hydraulic occluder implanted around the right main pulmonary artery. After preconstriction with the thromboxane analog, U46619 (9,11-dideoxy-11$_\alpha$,9$_\alpha$-epoxymethano-prostaglandin F$_{2\alpha}$), the pulmonary vascular dose–response relationship for the K^+_{ATP} agonist lemakalim was assessed in the conscious and halothane-anesthetized states and also in the conscious and enflurane-anesthetized states. This protocol was repeated in conscious and halothane-anesthetized dogs after combined neurohumoral block with antagonists of sympathetic α_1 adrenoreceptors, arginine vasopressin V_1-receptors, and angiotensin II receptors. The effect of the K^+_{ATP} antagonist glybenclamide on the baseline LPQ relationship and on the lemakalim dose–response relationship also was assessed in conscious dogs.**

Results: **Compared with the conscious state, halothane, enflurane and glybenclamide had no net effect on the baseline LPQ relationship. In contrast, halothane and enflurane attenuated ($P < 0.05$) the pulmonary vasodilator response to lemakalim compared with the conscious state. Glybenclamide also caused a rightward shift ($P < 0.05$) in the lemakalim dose–response relationship. Combined neurohumoral block did not modulate the vasodilator response to lemakalim in the conscious state. The halothane-induced attenuation of the vasodilator response to lemakalim was apparent after combined neurohumoral block.**

Conclusion: **These results indicate that halothane and enflurane act to reduce the magnitude of K^+_{ATP} channel-mediated pulmonary vasodilation. Reflex pulmonary vasoconstriction resulting from K^+_{ATP}-mediated systematic hypotension does not alter the magnitude of the pulmonary vasodilator response to lemakalim nor is it responsible for the attenuated response to K^+_{ATP} channel activation during halothane anesthesia. (Key words: Anesthetics, volatile: halothane; enflurane. Lung(s): circulation; pressure-flow relationship. Pharmacology: glybenclamide; lemakalim; prazosin; d(CH$_2$)$_5$AVP; saralasin. Ions: potassium; K^+ channel.)**

ADENOSINE triphosphate (ATP)-sensitive potassium (K^+_{ATP}) channels play an important role in the regulation of vascular smooth muscle tone.[1] Activation of K^+_{ATP} channels causes membrane hyperpolarization, reducing Ca^{2+} influx through voltage-dependent Ca^{2+} channels, resulting in vasorelaxation. K^+_{ATP} channel activation mediates a portion of the vasodilator effects of many endogenous mediators, such as calcitonin gene-related peptide,[2-4] adenosine,[5] prostacyclin,[6,7] and nitric oxide.[8,9] Further, recent reports indicate that cyclic adenosine monophosphate (cAMP)-[4,10] and cyclic guanine monophosphate (cGMP)-mediated[8,11] vasodilator pathways can involve activation of K^+_{ATP} channels.

K^+_{ATP} channels have been identified in pulmonary arterial smooth muscle cells.[12] Although K^+_{ATP} channels do not appear to be important in maintaining low pulmonary vasomotor tone,[13] there is evidence of a func-

* Research Fellow.

† Carl E. Wasmuth Endowed Chair and Director, Center for Anesthesiology Research.

Received from the Center for Anesthesiology Research, The Cleveland Clinic Foundation, Cleveland, Ohio. Submitted for publication May 22, 1996. Accepted for publication January 2, 1997. Supported by National Heart, Lung and Blood Institute (NHLBI) Grants HL-38291 and HL-40361. Drs. Seki and Nakayama were also supported by Professor Akiyoshi Namiki, M.D., Department of Anesthesiology, Sapporo Medical University School of Medicine, Sapporo, Japan. Dr. Sato was also supported by Professor Toshuhiro Shimada, M.D., Department of Anesthesiology, Nagoya University School of Medicine. Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 22-25, 1995.

Address correspondence to Dr. Murray: Center for Anesthesiology Research—FF-40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195. Address electronic mail to: murrayp@cesmtp.ccf.org

tional role for K^+_{ATP} channels in pulmonary vasoregulation. For example, K^+_{ATP} channel activation plays a role in anoxic pulmonary vasodilation.[14,15] Similarly, systemic hypotension causes pulmonary vasoconstriction,[16] and this response is enhanced by glybenclamide,[17] a K^+_{ATP} channel antagonist.[18]

Volatile anesthetics are known to have effects on K^+ channel activity. Halothane and isoflurane suppress the Ca^{2+}-dependent and -independent K^+ channel current in canine cerebral arteries.[19,20] In contrast, halothane and isoflurane induce coronary vasodilation via the activation of K^+_{ATP} channels.[21,22] The effects of halothane and enflurane on K^+_{ATP} channel-mediated pulmonary vasodilation are unknown.

The goal of the present study was to investigate the effects of halothane and enflurane anesthesia on the pulmonary vasodilator response to K^+_{ATP} channel activation compared with the response measured in the conscious state. We used lemakalim (BRL38227, SmithKline Beecham, Herts, UK), an active enantiomer of cromakalim,[23] to induce pulmonary vasodilation via activation of K^+_{ATP} channels.[24] We hypothesized that either halothane or enflurane would attenuate the magnitude of the pulmonary vasodilator response to lemakalim compared with the conscious state. Because K^+_{ATP} channel activation and these inhalational anesthetics cause systemic hypotension, which could result in reflex pulmonary vasoconstriction,[16] we also investigated the extent to which endogenous neurohumoral vasoconstrictor mechanisms modulate the pulmonary vasodilator response to lemakalim. We used an experimental preparation in which dogs were chronically instrumented to measure the left pulmonary vascular pressure-flow (LPQ) relationship.[25] This chronic instrumentation allowed us to assess the pulmonary vascular effects of K^+_{ATP} activation in the same dog in the conscious and anesthetized states. The chronic instrumentation also allowed us to avoid the confounding effects of acute surgical trauma and the requirement for background anesthetics. We have previously demonstrated that inhalational anesthetics can modify neural,[26,27] humoral,[28,29] and local[17,30] mechanisms of pulmonary vascular regulation. The use of pressure-flow plots avoids the limitations inherent in the interpretation of single-point calculations of pulmonary vascular resistance.[31]

Materials and Methods

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

Surgery for Chronic Instrumentation

Nineteen conditioned, male mongrel dogs (26 ± 1 kg) were used in this study. All dogs were premedicated with morphine sulfate (10 mg, intramuscular) and were anesthetized with intravenous pentobarbital sodium (20 mg/kg) and fentanyl citrate (15 μg/kg). After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with halothane (~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 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 1 day after surgery. Morphine sulfate (10 mg, intramuscular) was administered after surgery for pain as required. Intravenous ampicillin (1 g), cefazolin (1 g), and gentamicin (80 mg) were administered during surgery and on a daily basis for 10 days after surgery. 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 (Isotec™, 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 systemic arterial pressure (SAP) trace. Left pulmonary blood flow (LQ) was measured by connecting the flow probe to an electromagnetic flowmeter (SWF-5RD, Zepeda). The flow probe was calibrated *in vivo* on a weekly basis via the thermal dilution technique. Calibration was achieved by acutely inserting a 7-French balloon-tipped thermal dilution catheter into the pulmonary artery through a percutaneous jugular puncture after topical anesthesia (lidocaine spray). The catheter was positioned 2-3 cm beyond the pulmonic valve. The implanted perivascular hydraulic occluder then was inflated to occlude the

right main pulmonary artery completely, which directed total pulmonary blood flow through the left pulmonary artery (and flow probe). LQ then was measured by thermal dilution ($HEMOPRO_2$, Spectramed, Oxnard, CA) with multiple 10-ml sterile injectates of 5% dextrose in water. 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 pH, carbon dioxide tension (P_{CO2}), and oxygen tension (P_{O2}) were measured with an ABL-600 (Radiometer, Copenhagen, Denmark). Oxyhemoglobin saturation (S_{O2}) was measured with a Hemoximeter OSM-3 (Radiometer).

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 pharmacologic interventions on the pulmonary circulation. LPQ plots were constructed by continuously measuring the pulmonary vascular pressure gradient [pulmonary arterial pressure (PAP) − left atrial pressure (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.[25]

Protocol 1: Effect of Halothane Anesthesia on the Pulmonary Vascular Response to Lemakalim. We investigated the effect of halothane anesthesia on the pulmonary vascular response to cumulative doses of the K^+_{ATP} channel agonist lemakalim after preconstriction with the thromboxane analogue U46619 (9,11-dideoxy-11$_\alpha$,9$_\alpha$-epoxymethano-prostaglandin $F_{2\alpha}$, Sigma Chemical, St. Louis, MO). A baseline LPQ plot was first obtained in each dog (n = 7). U46619 then was administered (0.14 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) to preconstrict the pulmonary circulation before the administration of lemakalim. LPQ plots were obtained during U46619 preconstriction alone and then again with each dose of lemakalim (0.1, 0.5, 1.0, and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) during its cumulative administration (~ 15 min at each dose) while the infusion of U46619 was continued. We have previously verified that pulmonary vasoconstriction induced by U46619 is stable during the time course of this protocol.[28] 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 thiopental sodium (3 mg/kg, intravenous) to minimize excitatory behavior. The trachea was intubated (9 mm ID), and ventilation was controlled with a respirator 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 inspired oxygen tension [$F_{I_{O2}}$], 0.26) and by adjusting the respiratory rate to between 10–20 breaths/min. End-tidal carbon dioxide and halothane concentration were measured at the adapter end of the endotracheal tube (Solar 7000: Marquette Electronics, Milwaukee, WI). After induction, halothane was allowed to equilibrate for at least 1 hr to achieve steady-state conditions. At this time, end-tidal halothane concentration was 1.2–1.4% (1.4–1.6 minimum alveolar concentration [MAC]). During halothane anesthesia, the dose of U46619 (0.09 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) was titrated to achieve the same degree of preconstriction induced in the conscious state. The titration procedure involved administering incremental doses of U46619 and generating LPQ plots until a dosage was found that caused the same increase in PAP − LAP (at LQ = 75 $ml \cdot min^{-1} \cdot kg^{-1}$) from baseline that was achieved in the conscious state. This technique allowed us to assess the pulmonary vasodilator response to lemakalim at the same level of vasomotor tone in the conscious and halothane-anesthetized states.

Protocol 2: Effect of Enflurane Anesthesia on the Pulmonary Vascular Response to Lemakalim. We investigated the effect of enflurane anesthesia on the pulmonary vascular response to cumulative doses of lemakalim in the presence of U46619 preconstriction. For each conscious dog (n = 6), LPQ plots were obtained in the baseline condition, during U46619 preconstriction (0.16 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous), and during the cumulative administration of lemakalim 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% (1.4–1.5 MAC: Solar 7000). During enflurane anesthesia, the dosage of U46619 (0.06 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) was titrated to achieve the same degree of preconstriction induced in the conscious state.

Protocol 3: Effect of Combined Neurohumoral

Block on the Pulmonary Vascular Response to Lemakalim in Conscious and Halothane-anesthetized Dogs. We investigated the effect of combined sympathetic α_1 adrenoreceptor block, arginine vasopressin (AVP) V_1-receptor block, and angiotensin II receptor block on the magnitude of lemakalim-induced pulmonary vasodilation. This protocol tested the hypothesis that systemic hypotension during administration of lemakalim would result in reflex pulmonary vasoconstriction[16] and thereby attenuate the magnitude of lemakalim-induced pulmonary vasodilation. Sympathetic α_1 adrenoreceptor block, AVP V_1-receptor block, and angiotensin II receptor block were achieved via the intravenous administration of prazosin (1 mg/kg), $d(CH_2)_5$AVP ([1-(β-mercapto-β,β-cyclopentamethylenepropionic acid] AVP, Sigma Chemical; 10 μg/kg), and saralasin (Sigma Chemical; 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), respectively. These antagonists abolished the pressor responses to the bolus intravenous administration of phenylephrine (5 μg/kg),[27] AVP (10 ng/kg),[32,33] and angiotensin II (60 ng/kg),[16] respectively. The dose-response relationship for lemakalim was first obtained in three intact conscious dogs as described in protocol 1. On a separate day, LPQ plots were obtained in the same conscious dogs at baseline, after combined administration of the neurohumoral antagonists, during preconstriction with U46619, and during the cumulative intravenous administration of lemakalim (0.1, 0.5, and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The highest dosage of lemakalim (5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was not administered during combined neurohumoral block because it resulted in circulatory collapse. On a separate day, this protocol was repeated in the same dogs during halothane anesthesia. Anesthesia with halothane was induced and maintained as described in protocol 1. The dosages of U46619 after the administration of the neurohumoral antagonists in the conscious state (0.10 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and in the halothane-anesthetized state (0.08 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were titrated to achieve the same level of preconstriction induced in the conscious intact state (0.15 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Protocol 4: Effect of Glybenclamide on the Pulmonary Vascular Response to Lemakalim in Conscious Dogs. We investigated the effect of the K^+_{ATP} channel antagonist glybenclamide on the baseline LPQ relationship and on the pulmonary vascular response to cumulative doses of lemakalim in the presence of U46619 preconstriction. The dose-response relationship for lemakalim was obtained in seven intact conscious dogs as described in protocol 1. On a separate day, the protocol was repeated in the same dogs after the intravenous administration of glybenclamide (3 mg/kg).

Drug Preparation

All solutions were prepared on the day of the experiment. The thromboxane analogue U46619 was diluted in 0.9% saline. Lemakalim was dissolved in 95% ethanol and then diluted in sterile water. Prazosin HCl (Pfizer, Groton, CT), $d(CH_2)_5$AVP, and saralasin were diluted in sterile water. Glybenclamide (Sigma Chemical) was dissolved in 0.1 N NaOH and diluted in 5% dextrose.

Data Analysis

Phasic and mean vascular pressures and LQ were displayed continuously on an eight-channel strip-chart recorder (2800, 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 pressure were referenced to atmospheric pressure before and after each LPQ plot. The analogue 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.

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 $\leq$ 0 mmHg) as a function of LQ in each individual experiment. PAP-LAP intercept values were calculated at the midrange of empirically measured LQ in each protocol. This approach minimized the variance in the PAP-LAP intercept and avoided the use of intercept values outside the range of our empirical measurements; *i.e.*, PAP-LAP was not measured at LQ = 0 $ml \cdot min^{-1} \cdot kg^{-1}$. The correlation coefficient for the LPQ relationship in 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 halothane, enflurane, glybenclamide, U46619, and lemakalim on the regression parameters obtained in each experiment within each specific protocol.

The pulmonary vasodilator response to lemakalim (LQ = 75 $ml \cdot min^{-1} \cdot kg^{-1}$) was expressed as the percentage decrease in U46619 preconstriction[25,26] and was calculated with the following formula:

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

Thus, a lemakalim-induced decrease in PAP-LAP of 100%

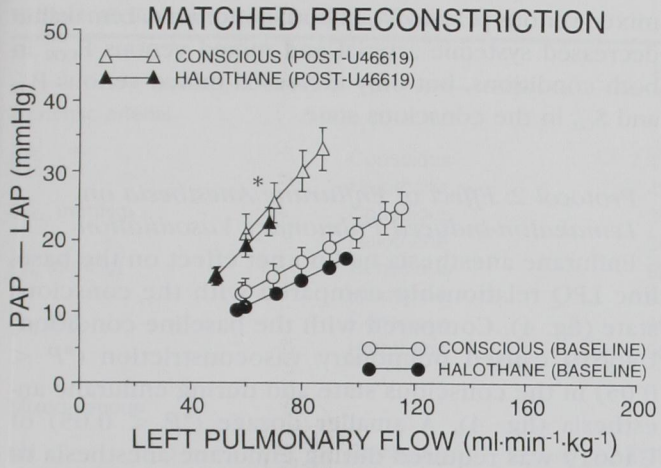

Fig. 1. Composite left pulmonary vascular pressure–flow (LPQ) plots in seven dogs at baseline and after U46619 preconstriction (*$P < 0.01$) in the conscious state and during halothane anesthesia. Compared with the conscious state, halothane had no net effect on the baseline LPQ relationship. The dosage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

represents a complete reversal of U46619 preconstriction and a full return to the baseline LPQ relationship. One-way analysis of variance (ANOVA) followed by Student's *t* test for paired comparisons was used to assess the pulmonary vascular effects of lemakalim within each group. Two-way ANOVA followed by Student's *t* test for paired comparisons was used to assess the effects of the volatile anesthetics on the magnitude of lemakalim-induced pulmonary vasodilation. Student's *t* test for paired comparisons also was used to assess changes in steady-state hemodynamics and blood gases. All values are presented as means ± SEM.

Results

Protocol 1: Effect of Halothane Anesthesia on Lemakalim-induced Pulmonary Vasodilation

Halothane anesthesia had no net effect on the baseline LPQ relationship compared with the conscious state (fig. 1). Compared with the baseline condition, U46619 caused pulmonary vasoconstriction (*$P < 0.05$) in the conscious state and during halothane anesthesia (fig. 1). A smaller dosage ($P < 0.05$) of U46619 was required during halothane anesthesia to match the same degree of preconstriction achieved in the conscious state. In the presence of U46619 preconstriction, lemakalim (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) resulted in pulmonary vasodilation (*$P < 0.05$) in the conscious state and during halothane anesthesia (fig. 2). The pulmonary vascular dose–response relationship for lemakalim in the conscious and halothane-anesthetized states is summarized in figure 3. In the presence of U46619 preconstriction, lemakalim resulted in dose-dependent pulmonary vasodilation (*$P < 0.05$) in conscious and halothane-anesthetized dogs. However, the magnitude of the pulmonary vasodilator response to lemakalim (1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was attenuated (†$P < 0.05$) during halothane anesthesia compared with the conscious state.

Steady-state hemodynamics and blood gases are sum-

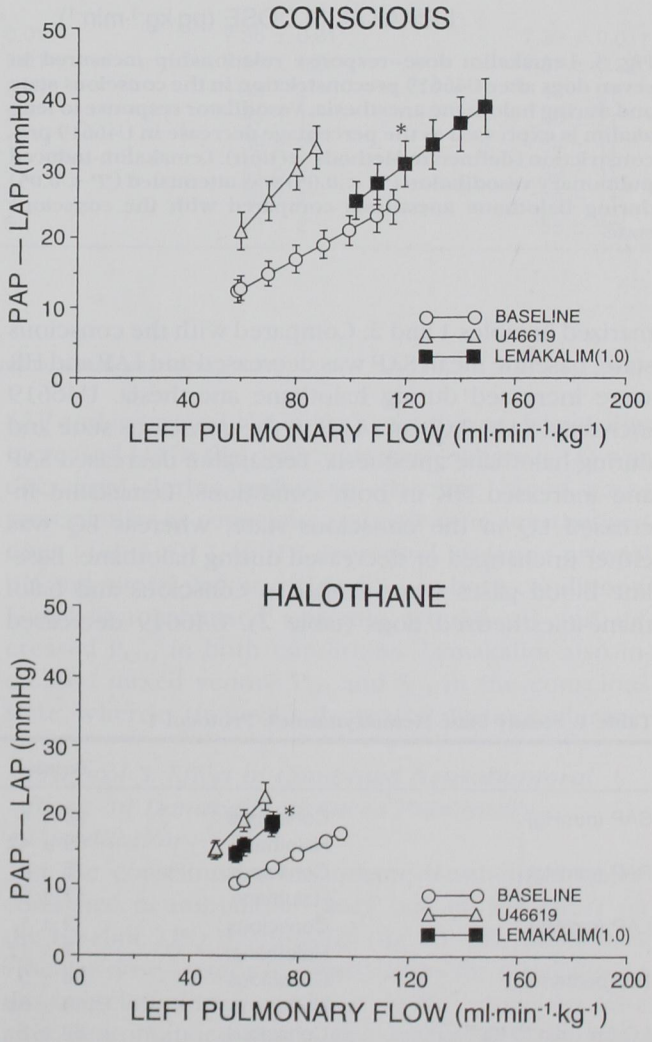

Fig. 2. Composite left pulmonary vascular pressure–flow (LPQ) plots in seven dogs at baseline, after preconstriction with U46619, and during administration of lemakalim (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) in the conscious state (top) and during halothane anesthesia (bottom). In the conscious state and during halothane anesthesia, this dosage of lemakalim caused a rightward shift in the LPQ relationship, indicating pulmonary vasodilation (*$P < 0.05$).

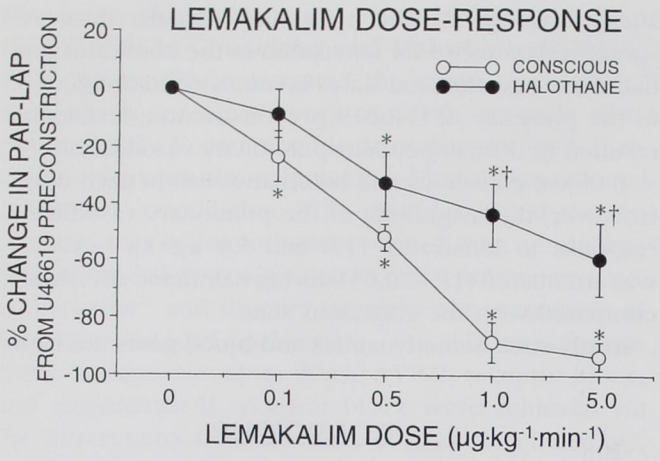

Fig. 3. Lemakalim dose–response relationship measured in seven dogs after U46619 preconstriction in the conscious state and during halothane anesthesia. Vasodilator response to lemakalim is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Lemakalim-induced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

marized in tables 1 and 2. Compared with the conscious state, baseline mean SAP was decreased and LAP and HR were increased during halothane anesthesia. U46619 increased SAP, PAP, and LAP in the conscious state and during halothane anesthesia. Lemakalim decreased SAP and increased HR in both conditions. Lemakalim increased LQ in the conscious state, whereas LQ was either unchanged or decreased during halothane. Baseline blood gases were similar in conscious and halothane-anesthetized dogs (table 2). U46619 decreased mixed venous pH and S_{O2} in both conditions. Lemakalim decreased systemic arterial and mixed venous P_{CO2} in both conditions, but only increased mixed venous P_{O2} and S_{O2} in the conscious state.

Protocol 2: Effect of Enflurane Anesthesia on Lemakalim-induced Pulmonary Vasodilation

Enflurane anesthesia had no net effect on the baseline LPQ relationship compared with the conscious state (fig. 4). Compared with the baseline condition, U46619 caused pulmonary vasoconstriction (*$P < 0.05$) in the conscious state and during enflurane anesthesia (fig. 4). A smaller dosage (*$P < 0.05$) of U46619 was required during enflurane anesthesia to match the same degree of preconstriction achieved in the conscious state. In the presence of U46619 preconstriction, lemakalim (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) resulted in pulmonary vasodilation (*$P < 0.05$) in the conscious state but not during enflurane anesthesia (fig. 5). The pulmonary vascular dose-response relationship for lemakalim in the conscious and enflurane-anesthetized states is summarized in figure 6. After U46619 preconstriction, lemakalim resulted in pulmonary vasodilation (*$P < 0.05$) in conscious and enflurane-anesthetized dogs. However, the magnitude of the pulmonary vasodilator response to lemakalim (1.0 and 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was attenuated (†$P < 0.05$) during enflurane anesthesia compared with the conscious state.

Steady-state hemodynamics and blood gases are summarized in tables 3 and 4. Compared with the conscious state, baseline SAP was decreased and LAP

Table 1. Steady State Hemodynamics: Protocol 1

		Baseline	U46619	Lem 1.0	Lem 5.0
SAP (mmHg)	Conscious	95 ± 4	109 ± 3*	90 ± 5†	73 ± 6†
	Halothane	69 ± 4‡	78 ± 3*‡	53 ± 1†‡	38 ± 4†‡
PAP (mmHg)	Conscious	15 ± 1	25 ± 2*	26 ± 1	25 ± 1
	Halothane	17 ± 2	21 ± 1*	20 ± 1†‡	16 ± 1†‡
LAP (mmHg)	Conscious	2 ± 1	5 ± 1*	3 ± 1	1 ± 1†
	Halothane	7 ± 1‡	8 ± 1*‡	7 ± 1‡	8 ± 1‡
HR (beats/min)	Conscious	94 ± 5	75 ± 5*	151 ± 5†	171 ± 5†
	Halothane	119 ± 5‡	119 ± 6‡	137 ± 4†	137 ± 4†‡
LQ ($ml \cdot min^{-1} \cdot kg^{-1}$)	Conscious	59 ± 5	60 ± 8	102 ± 9†	96 ± 7†
	Halothane	57 ± 7	50 ± 4	57 ± 4‡	33 ± 3†‡

* $P < 0.05$ U46619 *vs.* Baseline.

† $P < 0.05$ Lemakalim *vs.* U46619.

‡ $P < 0.05$ Halothane *vs.* Conscious.

Lemakalim (Lem) data for dosages of 1 and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. SAP = mean systemic arterial pressure; PAP = mean pulmonary arterial pressure; LAP = mean left atrial pressure; HR = heart rate; LQ = mean left pulmonary blood flow. Values are means ± SEM.

Table 2. Steady State Blood Gases: Protocol 1

		Baseline	U46619	Lem 5.0
Systemic arterial				
pH	Conscious	7.41 ± 0.01	7.39 ± 0.01	7.41 ± 0.01†
	Halothane	7.42 ± 0.01	7.39 ± 0.01*	7.44 ± 0.03
P_{CO_2} (mmHg)	Conscious	39 ± 1	39 ± 2	35 ± 1†
	Halothane	36 ± 1	37 ± 1	30 ± 2†
P_{O_2} (mmHg)	Conscious	92 ± 1	80 ± 6	83 ± 3
	Halothane	92 ± 5	89 ± 3	99 ± 7‡
S_{O_2} (%)	Conscious	96 ± 1	92 ± 2	94 ± 1
	Halothane	95 ± 1	95 ± 1	96 ± 1
Mixed venous				
pH	Conscious	7.38 ± 0.01	7.35 ± 0.01*	7.39 ± 0.01†
	Halothane	7.39 ± 0.01	7.36 ± 0.01*	7.37 ± 0.02
P_{CO_2} (mmHg)	Conscious	44 ± 2	48 ± 2*	40 ± 2†
	Halothane	40 ± 2	43 ± 1	40 ± 2†
P_{O_2} (mmHg)	Conscious	44 ± 1	39 ± 2*	54 ± 1†
	Halothane	47 ± 6	41 ± 2	39 ± 4‡
S_{O_2} (%)	Conscious	67 ± 3	56 ± 4*	79 ± 1†
	Halothane	68 ± 5	58 ± 2*	55 ± 6‡

* $P < 0.05$ U46619 *vs.* Baseline.

† $P < 0.05$ Lemakalim *vs.* U46619.

‡ $P < 0.05$ Halothane *vs.* Conscious.

P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension; S_{O_2} = oxyhemoglobin saturation. Values are means ± SEM.

and HR were increased during enflurane anesthesia. U46619 increased SAP and LAP in the conscious state, increased PAP in both conditions, and decreased LQ during enflurane anesthesia. Lemakalim decreased SAP and increased HR in both conditions. Lemakalim increased LQ in the conscious state, whereas LQ was decreased during enflurane. Baseline blood gases were similar in conscious and enflurane-anesthetized dogs (Table 4). U46619 decreased systemic arterial pH and mixed venous pH and S_{O2} in both conditions. Lemakalim increased systemic arterial pH and decreased P_{CO2} in both conditions. Lemakalim also increased mixed venous P_{O2} and S_{O2} in the conscious state, whereas they were decreased during enflurane.

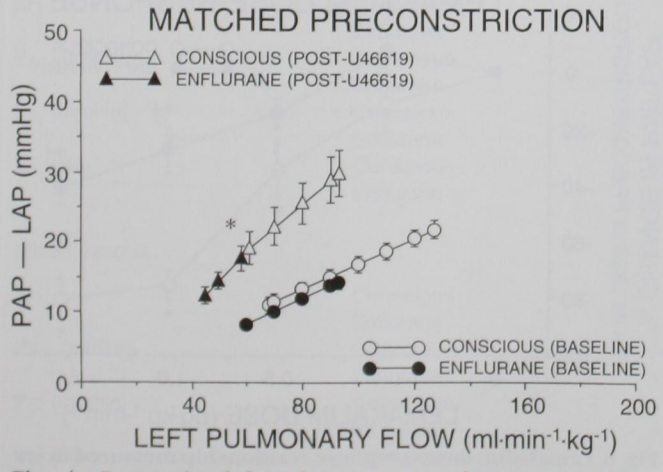

Fig. 4. Composite left pulmonary vascular pressure–flow (LPQ) plots in six dogs at baseline and after U46619 preconstriction (*$P < 0.01$) in the conscious state and during enflurane anesthesia. Compared with the conscious state, enflurane had no net effect on the baseline LPQ relationship. The dosage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

Protocol 3: Effect of Combined Neurohumoral Block on Lemakalim-induced Pulmonary Vasodilation

In the conscious and halothane-anesthetized states, combined neurohumoral block had no net effect on the baseline LPQ relationship (fig. 7). The pulmonary vascular dose-response relationships for lemakalim in the conscious intact condition, in the conscious state after neurohumoral block, and during halothane after neurohumoral block are summarized in figure 8. After U46619 preconstriction, lemakalim resulted in dose-dependent pulmonary vasodilation (*$P < 0.05$) in the conscious intact condition. Combined neurohumoral block did not alter the magnitude of the pulmonary vasodilator response to lemakalim in the conscious state. The

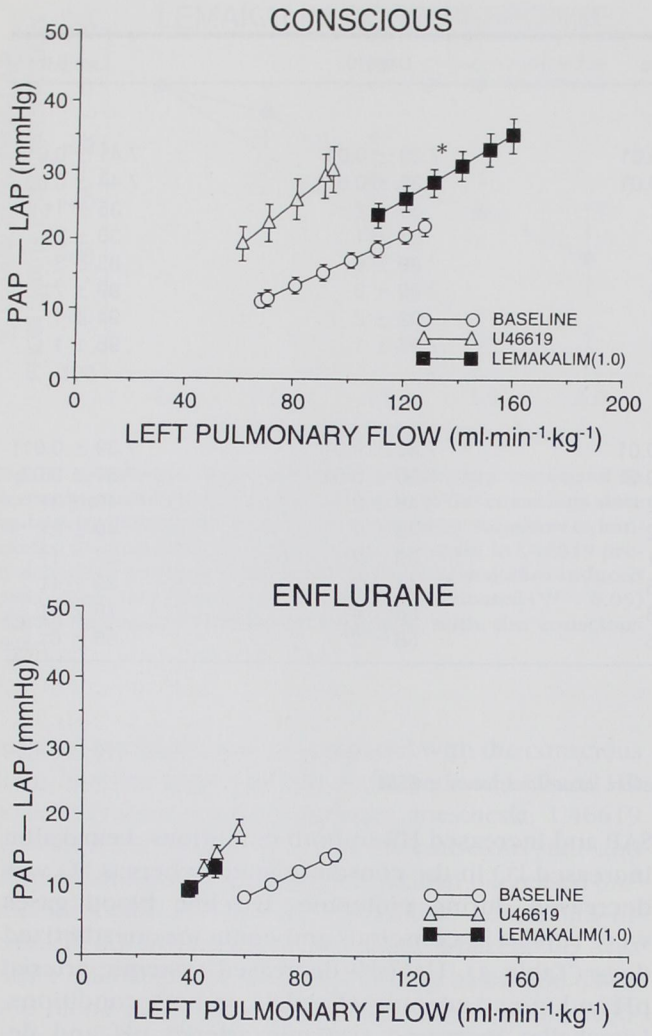

Fig. 5. Composite left pulmonary vascular pressure–flow (LPQ) plots in six dogs at baseline, after preconstriction with U46619, and during administration of lemakalim (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenous) in the conscious state (top) and during enflurane anesthesia (bottom). In the conscious state, but not during enflurane anesthesia, this dosage of lemakalim caused a rightward shift in the LPQ relationship, indicating pulmonary vasodilation (*$P < 0.05$).

attenuated (†$P < 0.05$) pulmonary vasodilator response to lemakalim during halothane was still apparent after combined neurohumoral block. Combined neurohumoral block did not alter baseline steady-state hemodynamics or blood gases. Changes in hemodynamics and blood gases in response to lemakalim during protocol 3 were similar to those observed in protocol 1.

Protocol 4: Effect of Glybenclamide on Lemakalim-induced Pulmonary Vasodilation

In conscious dogs, the K^+_{ATP} channel antagonist glybenclamide had no net effect on the baseline LPQ relationship (fig. 9, top panel). The pulmonary vascular dose-response relationships for lemakalim in the conscious intact condition and in the conscious state after pretreatment with glybenclamide are summarized in figure 9 (bottom panel). In conscious dogs preconstricted to the same level of vasomotor tone with U46619, the pulmonary vasodilator response (*$P < 0.05$) to lemakalim was attenuated (†$P < 0.05$) by glybenclamide.

Discussion

This study demonstrated that the pulmonary vasodilator response to the K^+_{ATP} channel agonist lemakalim was attenuated during halothane and enflurane anesthesia compared with the conscious state. Combined neurohumoral block did not modulate the pulmonary vasodilator response to lemakalim in the conscious state. Moreover, the attenuated pulmonary vasodilator response to lemakalim during halothane anesthesia was observed after combined neurohumoral block.

K^+_{ATP} channel activation, cAMP-mediated pathways and cGMP-mediated pathways are the three major mechanisms of vasodilation. We used lemakalim to activate K^+_{ATP} channels. Lemakalim is the (−)-enantiomer of cromakalim and has 100-200 times greater pharmacologic potency compared with the (+)-enantiomer.[18,23] Lemakalim also is more selective than croma-

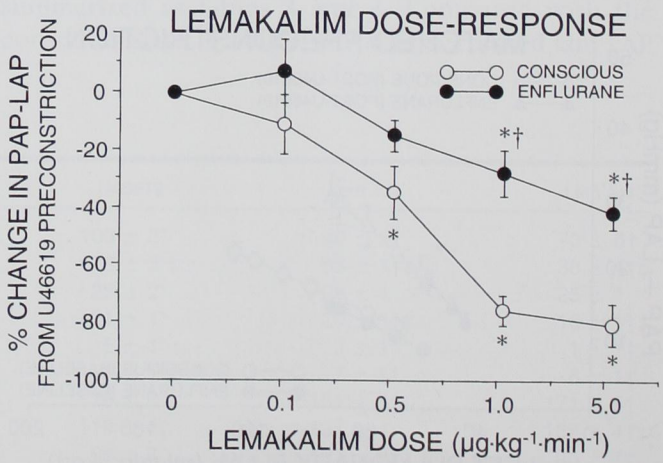

Fig. 6. Lemakalim dose–response relationship measured in six dogs after U46619 preconstriction in the conscious state and during enflurane anesthesia. Vasodilator response to lemakalim is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Lemakalim-induced pulmonary vasodilation (*$P < 0.05$) was attenuated (†$P < 0.05$) during enflurane anesthesia compared with the conscious state.

Table 3. Steady State Hemodynamics: Protocol 2

		Baseline	U46619	Lem 1.0	Lem 5.0
SAP (mmHg)	Conscious	98 ± 5	114 ± 4*	85 ± 3†	68 ± 3†
	Enflurane	60 ± 2‡	64 ± 4‡	43 ± 2†‡	32 ± 2†‡
PAP (mmHg)	Conscious	14 ± 1	23 ± 2*	23 ± 1	23 ± 1
	Enflurane	15 ± 1	20 ± 1*	17 ± 1‡	14 ± 1†‡
LAP (mmHg)	Conscious	3 ± 1	5 ± 1*	1 ± 1†	1 ± 1†
	Enflurane	7 ± 1‡	8 ± 1‡	8 ± 1‡	9 ± 1‡
HR (beats/min)	Conscious	92 ± 6	82 ± 7	149 ± 3†	172 ± 6†
	Enflurane	111 ± 4‡	112 ± 4‡	120 ± 5‡	124 ± 6†‡
LQ ($ml \cdot min^{-1} \cdot kg^{-1}$)	Conscious	68 ± 6	61 ± 8	110 ± 10†	104 ± 7†
	Enflurane	60 ± 3	45 ± 4*	39 ± 5†‡	26 ± 4†‡

* $P < 0.05$ U46619 *vs.* Baseline.

† $P < 0.05$ Lemakalim *vs.* U46619.

‡ $P < 0.05$ Enflurane *vs.* Conscious.

SAP = mean systemic arterial pressure; PAP = mean pulmonary arterial pressure; LAP = mean left atrial pressure; HR = heart rate; LQ = mean left pulmonary blood flow. Values are means ± SEM.

kalim, which inhibits calcium channels and activates K^+_{ATP} channels.[34] Using the patch-clamp technique, Clapp *et al.*[12] observed that lemakalim mimicked the membrane hyperpolarizing effect of intracellular ATP depletion in isolated rabbit pulmonary artery cells. These hyperpolarizing effects of lemakalim and ATP depletion were reversed by the selective K^+_{ATP} channel antagonist glybenclamide but not by the Ca^{2+}-activated K^+ channel (K^+_{Ca}) antagonist tetraethylammonium (TEA).[12] These investigators also have demonstrated that the pulmonary vasorelaxant response to lemakalim in precontracted rabbit pulmonary arterial rings was

Table 4. Steady State Blood Gases: Protocol 2

		Baseline	U46619	Lem 5.0
Systemic arterial				
pH	Conscious	7.40 ± 0.01	7.37 ± 0.01*	7.40 ± 0.01†
	Enflurane	7.39 ± 0.01	7.35 ± 0.01*	7.45 ± 0.03†
P_{CO_2} (mmHg)	Conscious	39 ± 1	40 ± 1	35 ± 2†
	Enflurane	38 ± 1	42 ± 1	29 ± 3†‡
P_{O_2} (mmHg)	Conscious	93 ± 4	84 ± 6	83 ± 6
	Enflurane	87 ± 5	85 ± 4	95 ± 12
S_{O_2} (%)	Conscious	96 ± 1	92 ± 3	93 ± 2
	Enflurane	94 ± 1	93 ± 1	94 ± 3
Mixed venous				
pH	Conscious	7.37 ± 0.01	7.34 ± 0.01*	7.38 ± 0.01†
	Enflurane	7.36 ± 0.01	7.30 ± 0.01*	7.31 ± 0.01‡
P_{CO_2} (mmHg)	Conscious	44 ± 1	46 ± 1	39 ± 2†
	Enflurane	43 ± 1	51 ± 2*‡	48 ± 2‡
P_{O_2} (mmHg)	Conscious	47 ± 2	42 ± 2*	55 ± 3†
	Enflurane	50 ± 6	37 ± 3	28 ± 2†‡
S_{O_2} (%)	Conscious	70 ± 2	61 ± 4*	80 ± 3†
	Enflurane	67 ± 3	47 ± 6*	31 ± 3†‡

* $P < 0.05$ U46619 *vs.* Baseline.

† $P < 0.05$ Lemakalim *vs.* U46619.

‡ $P < 0.05$ Enflurane *vs.* Conscious.

P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension; S_{O_2} = oxyhemoglobin saturation. Values are means ± SEM.

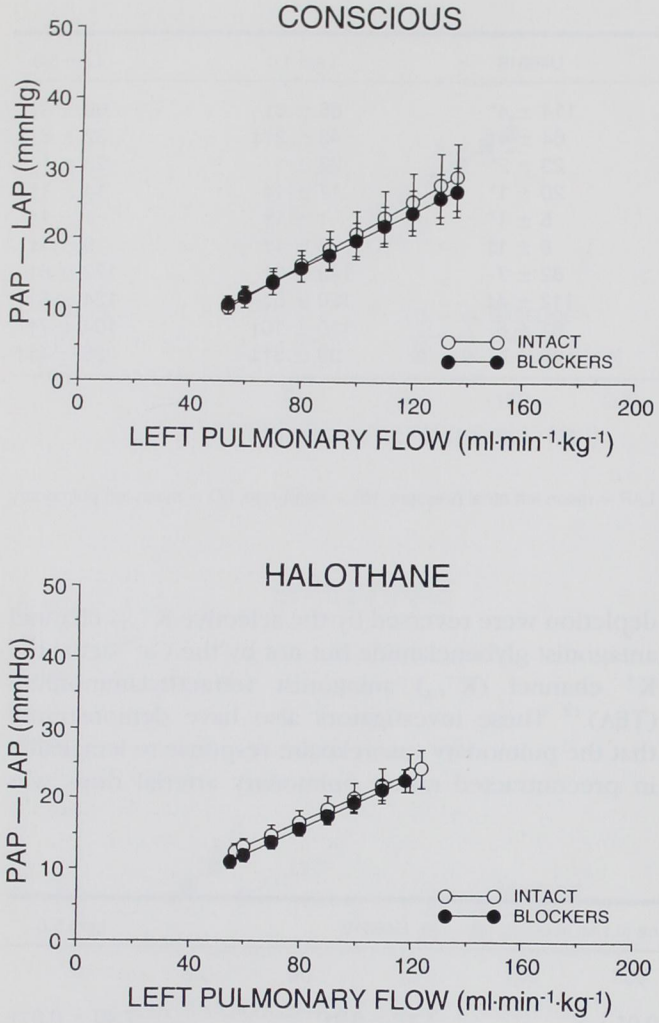

Fig. 7. Composite left pulmonary vascular pressure–flow (LPQ) plots in three dogs at baseline and after combined neurohumoral block in the conscious state (top) and during halothane anesthesia (bottom). Combined neurohumoral block had no net effect on the baseline LPQ relationship in either conscious or halothane-anesthetized dogs.

inhibited by glybenclamide but not by TEA.[24] We also observed that lemakalim-induced pulmonary vasodilation was inhibited by glybenclamide. Taken together, these results indicate that lemakalim is a potent and selective activator of K^+_{ATP} channels in the pulmonary artery.

Lemakalim administration resulted in systemic hypotension in the conscious state, and this effect was even more pronounced during halothane and enflurane anesthesia. Because systemic hypotension can cause reflex pulmonary vasoconstriction,[16] we tested the hypothesis that neurohumoral vasoconstrictor mechanisms activated during hypotension could modulate the vasodilator response to lemakalim. However, combined administration of sympathetic α_1 adrenoreceptor, AVP V_1 receptor, and angiotensin II receptor antagonists had no effect on the magnitude of lemakalim-induced pulmonary vasodilation in the conscious state. The attenuated vasodilator response to lemakalim was still apparent in halothane-anesthetized dogs after combined neurohumoral block. Thus, these results do not support the concept that reflex mechanisms attenuated the vasodilator response to K^+_{ATP} channel activation in either the conscious or halothane-anesthetized state. Further, in preliminary studies, we have observed that halothane attenuates lemakalim-induced pulmonary vasorelaxation in isolated canine pulmonary artery.[35] Thus, the inhibitory effect of halothane on K^+_{ATP} channel vasodilation appears to be a direct effect rather than a secondary effect caused by activation of vasoconstrictor mechanisms.

Larach and Schuler[21] observed that halothane attenuated cromakalim-induced coronary vasodilation, which is consistent with our results in the present study. Several recent studies have demonstrated that halothane-induced coronary vasodilation is mediated by the activation of K^+_{ATP} channels.[21,36,37] Based on these results, it has been postulated that halothane attenuated cromakalim-induced vasodilation because halothane had already opened the cromakalim-responsive K^+_{ATP} channels.[21] In the present study, K^+_{ATP} channel inhibition

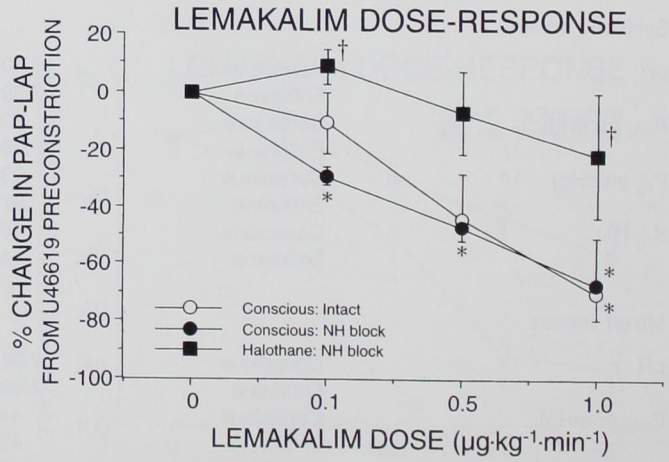

Fig. 8. Lemakalim dose–response relationship measured in three dogs after U46619 preconstriction in the conscious state and during halothane anesthesia. Vasodilator response to lemakalim is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). In the conscious state, combined neurohumoral block did not alter the magnitude of the pulmonary vasodilator response to lemakalim. The attenuated (†$P < 0.05$) pulmonary vasodilator response to lemakalim during halothane anesthesia was still apparent after combined neurohumoral block.

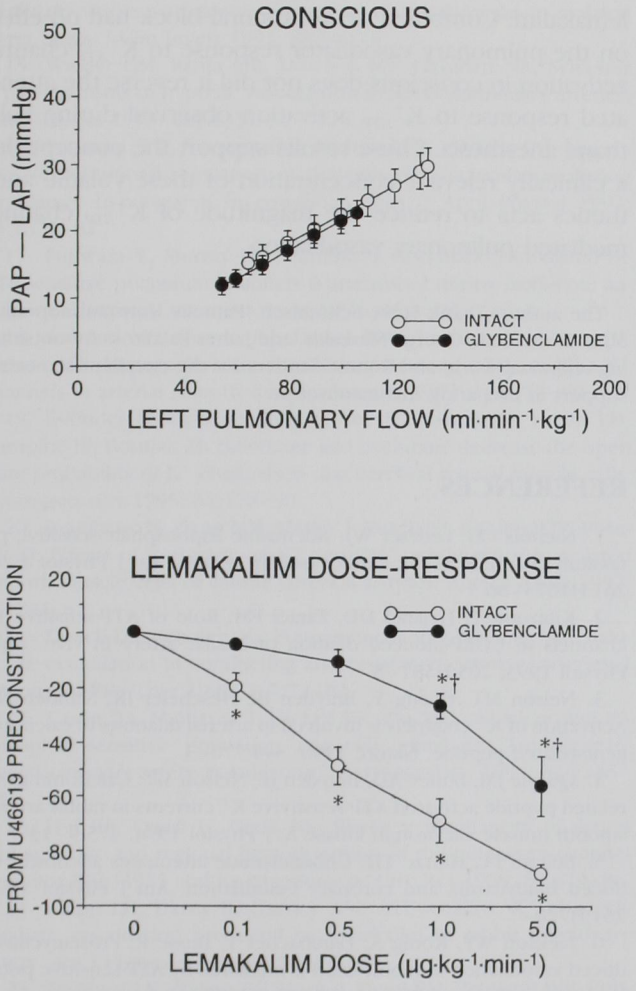

Fig. 9. Composite left pulmonary vascular pressure–flow (LPQ) plots in seven conscious dogs in the intact condition and after K^+_{ATP} channel inhibition with glybenclamide (top). Glybenclamide had no net effect on the baseline LPQ relationship. Lemakalim dose–response relationship measured in seven conscious dogs in the intact condition and after pretreatment with glybenclamide (bottom). Vasodilator response to lemakalim is expressed as the percentage decrease in U46619 preconstriction (defined in Methods section). Glybenclamide attenuated (†$P < 0.05$) the pulmonary vasodilator response (*$P < 0.05$) to lemakalim.

with glybenclamide did not alter the baseline LPQ relationship, indicating that K^+_{ATP} channels are not tonically active in the pulmonary circulation of conscious dogs. In contrast to the coronary circulation, neither halothane nor enflurane had a vasodilator influence on the baseline LPQ relationship in the present study. These differences may reflect regional vascular heterogeneity in terms of baseline K^+_{ATP} channel activity and halothane's effect on K^+_{ATP} channels.

The mechanism responsible for the attenuating effect of halothane and enflurane on K^+_{ATP} channel-mediated pulmonary vasodilation has yet to be determined. Recent evidence indicates that vascular smooth muscle cells and endothelial cells express K^+_{ATP} channels.[38–40] The K^+_{ATP} channel agonist pinacidil induced ATP-sensitive K^+ currents in rat aorta and brain microvascular endothelial cells.[38] In endothelial cells from rabbit thoracic aorta and pulmonary artery, lemakalim activated ATP-sensitive K^+ conductance, and this effect was inhibited by glybenclamide.[39] In endothelial cells, unlike smooth muscle cells, membrane hyperpolarization via K^+ channel activation augments Ca^{2+} influx,[40] which stimulates nitric oxide synthase and the production and release of nitric oxide, an endothelium-derived relaxing factor. Because volatile anesthetics are known to attenuate endothelium-dependent vasorelaxation,[41] it seems reasonable to speculate that volatile anesthetics may attenuate an endothelium-dependent component of K^+_{ATP}-mediated pulmonary vasodilation. Consistent with this possibility, we have preliminary results in isolated, canine pulmonary arterial rings that removal of the endothelium attenuates the pulmonary vasorelaxant response to lemakalim.[35] Halothane exerted an attenuating influence on lemakalim-induced pulmonary vasorelaxation in endothelium-intact, but not endothelium-denuded, vascular rings.[35] Thus, in the present *in vivo* studies, the attenuated response to K^+_{ATP} channel activation during halothane and enflurane anesthesia may involve an endothelial defect. An attenuation in endothelium-dependent pulmonary vasodilation also may be responsible for the lower dosages of U46619 that were required to achieve the same degree of preconstriction during halothane and enflurane anesthesia compared with the conscious state.

Mechanical ventilation was used to match systemic arterial blood gases in the conscious and anesthetized states. We attempted to minimize the effects of mechanical ventilation on the LPQ relationship by making all of our empirical measurements at end-expiration. Mixed venous P_{O2} and S_{O2} during lemakalim administration were lower during inhalational anesthesia compared with the conscious state. The stimulus for hypoxic pulmonary vasoconstriction is primarily determined by the local alveolar P_{O2}, whereas the P_{O2} of mixed venous blood has an important, although lesser, influence. It could be argued that hypoxic pulmonary vasoconstriction is responsible for the attenuated pulmonary vasodilator response to lemakalim during halothane and enflurane anesthesia. However, this seems unlikely because mixed venous P_{O2} and S_{O2} during lemakalim administration were not different from values mea-

sured during U46619 preconstriction in halothane-anesthetized dogs.

We have previously reported that halothane caused a small, but statistically significant, downward shift in the baseline LPQ relationship compared with the conscious state.[28] Although we saw a similar trend in the present study, it did not achieve statistical significance. It is unlikely that there is any important functional significance to these very small effects of halothane on the baseline LPQ relationship.

Combined neurohumoral block had no effect on the baseline LPQ relationship in either the conscious or halothane-anesthetized states. Because halothane attenuates the pulmonary vascular responses to sympathetic α adrenoreceptor,[27] AVP V_1 receptor,[28] and angiotensin II receptor[29] activation, we expected that combined neurohumoral block would have little or no effect on the baseline LPQ relationship during halothane anesthesia. In contrast, we have previously reported that combined neurohumoral block results in pulmonary vasodilation in conscious dogs and that this effect is mediated by vasodilator metabolites of the cyclooxygenase pathway.[42] However, there is a major difference between our previous study and the present study in terms of the techniques that were used to generate pressure-flow plots. In contrast to our previous technique that resulted in systemic hypotension and reflex neurohumoral activation,[42] our current technique for generating LPQ plots has no effect on systemic hemodynamics and does not result in neurohumoral activation. Thus, we did not anticipate that combined neurohumoral block would alter the baseline LPQ relationship in conscious dogs in this study.

It was not possible to assess the dose-response relationships for halothane and enflurane. It is difficult to assess lower dosages of the inhalational anesthetics because we do not use background anesthetics or muscle relaxants. Either of these agents could confound our results. It is important to have a level of anesthesia that is sufficient to prevent spontaneous ventilation and allow mechanical ventilation to control blood gases. Higher dosages of the inhalational anesthetics would cause even more profound changes in systemic hemodynamics. However, it is important to note that clinically relevant concentrations of halothane and enflurane were used in this study.

In summary, compared with the conscious state, neither halothane nor enflurane anesthesia had a net effect on the baseline canine pulmonary circulation. In contrast, halothane and enflurane anesthesia attenuated the pulmonary vasodilator response to the K^+_{ATP} channel agonist lemakalim. Combined neurohumoral block had no effect on the pulmonary vasodilator response to K^+_{ATP} channel activation in conscious dogs nor did it reverse the attenuated response to K^+_{ATP} activation observed during halothane anesthesia. These results support the concept that a clinically relevant concentration of these volatile anesthetics acts to reduce the magnitude of K^+_{ATP} channel-mediated pulmonary vasodilation.

The authors thank Steve Schomisch, Pantelis Konstantinopoulos, Mike Trentanelli, George Markakis, and James Palazzolo for outstanding technical work, and Ronnie Sanders for the excellent secretarial support in preparing this manuscript.

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