

Influence of Isoflurane on Hypoxic Pulmonary Vasoconstriction in Dogs

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The authors studied the influence of locally administered isoflurane anesthesia on the pulmonary vascular response to regional alveolar hypoxia (hypoxic pulmonary vasoconstriction [HPV]) over a range of cardiac outputs (COs) in seven mechanically ventilated, closed-chest dogs. The right lung was ventilated with 100% O₂ throughout the study. The left lung was ventilated with either 100% O₂ (normoxia) or an hypoxic gas mixture (hypoxia). Different alveolar concentrations of isoflurane (0, 1, and 2.5 MAC) were administered to the left lung in a randomized sequence. The CO was altered by opening and closing surgically produced arteriovenous fistulae, at all isoflurane concentrations, and by hemorrhage at 0 MAC isoflurane. The magnitude of the HPV response was measured by differential CO₂ elimination in the absence of isoflurane and by venous admixtures in all phases. During normoxia, the left lung effective flow (\dot{Q}_L) measured from differential CO₂ excretion was $39.9 \pm 1.2\%$ of the total blood flow and decreased to $18.8 \pm 2.6\%$ when ventilated with the hypoxic gas mixture. Venous admixture (\dot{Q}_{VA}/\dot{Q}_T) was significantly correlated with \dot{Q}_L during hypoxic ventilation in the absence of isoflurane. \dot{Q}_{VA}/\dot{Q}_T was $22.3 \pm 2.7\%$ during hypoxia with normal CO, and it increased significantly to $27.7 \pm 1.1\%$ when the CO was increased 43%. It was not significantly altered ($23.6 \pm 3.6\%$) when the CO was decreased by 54%. Isoflurane 2.5 MAC significantly increased \dot{Q}_{VA}/\dot{Q}_T during hypoxic ventilation of the left lung to $33.9 \pm 2.6\%$ with low CO and $35.4 \pm 1.7\%$ with normal CO. Isoflurane 1 MAC increased \dot{Q}_{VA}/\dot{Q}_T to $27.2 \pm 2.7\%$ with normal CO and $28.1 \pm 2.6\%$ with high CO. Comparing the effects of the different concentrations of isoflurane on \dot{Q}_{VA}/\dot{Q}_T during left lung hypoxia under the same conditions of CO, mixed venous and alveolar oxygen tension, and pulmonary artery and pulmonary artery occlusion pressures revealed a significant direct effect of isoflurane dose such that: (% depression of HPV) = [22.8(% alveolar isoflurane) - 5.3]. The ED₅₀ for this response was 2.4% alveolar isoflurane. The authors conclude that isoflurane directly depresses HPV and that secondary influences of the anesthetic action

should be considered in the interpretation of the action of inhalational agents on this response *in vivo*. (Key words: Anesthetics, volatile: isoflurane. Heart: cardiac output. Hypoxia: pulmonary vascular response. Lung: blood flow; hypoxic pulmonary vasoconstriction; shunting. Oxygen: blood levels.)

GENERAL ANESTHESIA is associated with impairment of pulmonary oxygen exchange, and one of the suggested mechanisms is inhibition of hypoxic pulmonary vasoconstriction (HPV).¹ While isoflurane has been shown to reduce the pulmonary vasoconstrictor response to alveolar hypoxia in isolated perfused lungs,² studies in intact animals and humans have demonstrated less consistent effects.³⁻⁷ The HPV response of a particular lung segment is influenced by multiple variables, including: alveolar P_{O₂},⁸ mixed venous blood oxygen (P \bar{v} O₂),⁸ cardiac output,⁹ pulmonary artery and pulmonary venous pressures,¹⁰ as well as the direct and indirect effects of anesthetic agents on the normoxic and hypoxic lung regions. *In vitro* studies examine only the direct anesthetic effect on the pulmonary vasculature in the hypoxic lung. However, *in vivo* experiments are complicated by the effects of the anesthetic on the cardiovascular system and simultaneously may alter some or all of the variables that influence HPV. For example, isoflurane produces a dose-related depression of cardiac function in dogs¹¹ that may potentiate HPV and reduce pulmonary shunt while simultaneously creating a direct inhibitory effect on HPV, which increases shunt. The purpose of the present study was to compare the HPV response over a range of cardiac outputs in the presence and absence of isoflurane so that a direct inhibitory effect of the anesthetic on HPV could be identified with more certainty. The isoflurane was administered only to the hypoxic lung to minimize general hemodynamic changes.

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Materials and Methods

ANESTHETIC AND SURGICAL PREPARATION

Seven female mongrel dogs (mean weight 24.0 ± 1.2 kg) were anesthetized with pentobarbital (30 mg/kg iv, supplemented with 25-50 mg as required). The trachea was intubated, and the lungs were ventilated with 100% O₂. Muscle paralysis was secured with pancuronium (0.05 mg/kg iv, supplemented with 0.2-0.5 mg iv every 30 min). A Kottmier® double-lumen endobronchial tube was

inserted through a subcricoid tracheostomy, and complete lung isolation was verified by auscultation and the demonstration that cross-contamination of the left lung did not occur when it was ventilated with an hypoxic gas mixture. Both lungs were then ventilated synchronously with humidified 100% O₂ by a Harvard® dual-piston ventilator, and 5 cmH₂O PEEP was applied by water seal. Tidal volumes were selected to produce equal peak airway pressures (15–20 cmH₂O), and inspired CO₂ was added as necessary to maintain equal right and left lung end-tidal P_{CO₂} of 32–35 mmHg. Each piston of the Harvard® ventilator was part of a separate gas circuit, with its gas composition determined by separate flow meters. An isoflurane vaporizer (Dräger®) was connected into the left lung circuit. For each breathing circuit, end-tidal, inspired, and mixed expired carbon dioxide tensions (P_{CO₂}) (Godart® capnograph) and inspired and mixed expired oxygen tensions (P_{O₂}) (IL® #407 oxygen analyzer) were measured. Left lung inspired and mixed expired anesthetic percentage, P_{CO₂}, and P_{O₂} were measured by a mass spectrometer (Perkin-Elmer® 1100). The analyzers and mass spectrometer were calibrated daily with gases of known composition and corrected for barometric pressure, temperature, and water vapor.

A peripheral vein was cannulated for intravenous fluid administration to maintain euolemia (100–250 ml/h Normosol®). Urine was collected from a Foley catheter. Femoral arterial, central venous (*via* an external jugular vein), pulmonary arterial, and pulmonary occlusion (*via* Swan-Ganz® catheter inserted through a femoral vein) pressures were measured. The transducers were zeroed at the midcardiac level and calibrated to mmHg or cmH₂O as appropriate. Thermodilution (Edwards®) cardiac outputs (COs) were obtained in duplicate using an injection of 5 ml of ice-cold 5% dextrose in water. For the manipulation of CO, two arteriovenous (AV) fistulae (4 mm ID arterial end, 6 mm ID venous end) were constructed, one between a femoral artery and vein and the other between an internal carotid artery and external jugular vein. The CO was also reduced to the desired level by hemorrhage of 300–500 ml by connecting the arterial end of one of the AV fistulae to a bottle set to the appropriate height above the dog. The blood was retransfused at the end of the hemorrhage phase. Body temperature, measured by an esophageal temperature probe, was maintained at 37 ± 1° C with heating lamps, pads, and heated humidifier. NaHCO₃ was given when necessary to correct metabolic acidosis. The dog was anticoagulated with 300 U/kg of heparin iv, followed by 50 U/kg every 30 min.

EXPERIMENTAL DESIGN

Prior to the experimental sequence, three 15-min trials of hypoxic (4% O₂, 3% CO₂, 93% N₂) ventilation to the

left lung were alternated with 100% O₂ ventilation to insure stable, reproducible pulmonary blood flow and pressure responses to hypoxia.¹² The right lung was ventilated with 100% O₂ throughout the experiment. The left lung was ventilated with either 100% O₂ or the hypoxic gas mixture. Different alveolar concentrations of isoflurane (0, 1, or 2.5 MAC) were administered to the left lung. CO was altered by opening or closing the AV fistulae at all isoflurane concentrations and by hemorrhage only at 0 MAC isoflurane. Isoflurane was administered locally to the left lung to minimize cardiovascular depression and to reduce the influence of the anesthetic on the normoxic lung. After 5 min, the oxygen was changed to the hypoxic gas mixture, and isoflurane was continued until constant left lung mixed expired isoflurane levels were noted for 10 min. The experimental sequence began and ended with a control phase of 100% O₂ ventilation to both lungs (normoxia) and left lung hypoxic ventilation without isoflurane (0 MAC hypoxia) when the CO was normal (AV fistulae closed). The middle of the experimental sequence consisted of a randomized series of phases in which isoflurane concentration and CO were manipulated. The HPV response to left lung hypoxia was then tested. These phases were: 1) 0 MAC isoflurane, fistulae open; 2) 0 MAC isoflurane, hemorrhage; 3) 1 MAC isoflurane, fistulae closed; 4) 1 MAC isoflurane, fistulae open; 5) 2.5 MAC isoflurane, fistulae closed; and 6) 2.5 MAC isoflurane, fistulae open.

Each phase occupied approximately 30–50 min. After measurements were obtained, the lungs were hyperinflated to prevent microatelectasis and then were ventilated with 100% O₂ until left lung mixed expired isoflurane concentration was 0% and hemodynamic reequilibration occurred.

MEASUREMENTS

At each phase, right and left airway pressures, central venous pressures, pulmonary and systemic arterial pressures, pulmonary arterial occlusion pressures, and O₂ and CO₂ tensions of the right and left lungs were recorded on a Grass® Polygraph. Esophageal temperature and duplicate thermodilution COs were measured. Values were obtained at the end-expiration phase of the respiratory cycle. Arterial and mixed venous blood samples were collected simultaneously for pH, P_{CO₂}, and P_{O₂} analysis (Corning® Model 168 pH/Blood Gas Analyzer). Hemoglobin content was measured spectrophotometrically. The percentage of blood flow to each lung was determined by a differential CO₂ elimination technique^{13,14} during the normoxic and hypoxic phases of the study in the absence of isoflurane. It was not used during the isoflurane phases because this agent absorbs infrared radiation at the same wave length as CO₂ in the capnometer. The CO₂ excretion

was calculated by an on-line computer from the outputs of a capnometer (Hewlett-Packard®) and a pediatric spirometer (Boehringer®) connected to the expiratory limbs of each lung circuit. Corrections for measurement delays and the Haldane effect have been included in the program for calculation of CO₂ excretion.^{13,14} During the isoflurane phases, inspired and mixed expired isoflurane concentrations from the left lung were measured by mass spectrometer (Perkin-Elmer® 1100), and the mixed venous blood isoflurane levels were analyzed by gas chromatograph (Varian® Aerograph Model 940).

CALCULATIONS

During the 0 MAC isoflurane phases, the percentage of the CO perfusing the left ($\dot{Q}_L\%$) or the right lung was calculated as the ratio of CO₂ excretion from the left or right side to total CO₂ excretion. Absolute lung blood flow was calculated as the product of the fraction of blood flow to each lung and CO. Pulmonary perfusion pressure (PP) was calculated at end expiration as mean pulmonary artery pressure (PAP) minus mean pulmonary artery occlusion pressure (PAOP) in mmHg. Left, right, and total pulmonary vascular resistances (PVRs) in dyn · cm⁻⁵ · s were calculated by (PP × 80) divided by the respective lung blood flow in l/min during the 0 MAC isoflurane phases. Alveolar oxygen tension (PA_{O₂}) was calculated as the barometric pressure minus the saturated water vapor pressure and the Pa_{CO₂} when the lung was ventilated with 100% oxygen. During hypoxic ventilation, left lung alveolar oxygen tension was calculated as the mean of the measured left lung mixed expired P_{O₂} and the mixed venous P_{O₂}. Blood O₂ contents (Cb_{O₂}) were calculated from the measured O₂ tension and hemoglobin concentration using the equation:

$$Cb_{O_2} = (1.34 \times Hb \times \% \text{ sat}) + (Pb_{O_2} \times 0.0031)$$

where Cb_{O₂} = blood oxygen content in ml O₂/dl blood; 1.34 = O₂ capacity of hemoglobin in ml O₂/g Hb; Hb = hemoglobin in g/dl blood; % sat = per cent saturation; Pb_{O₂} = blood oxygen tension in mmHg; and 0.0031 = dissolved O₂ in ml O₂ · mmHg⁻¹ · dl⁻¹ blood. Per cent saturation, corrected for pH and temperature, was calculated from a nomogram for canine Hb.¹⁵ Calculated PA_{O₂} was used for end-capillary oxygen tension (Pc'_{O₂}). The venous admixture (\dot{Q}_{VA}/\dot{Q}_T) during the normoxic phases was calculated by the following equation:

$$\dot{Q}_{VA}/\dot{Q}_T = (Cc'_{O_2} - Ca_{O_2}) / (Cc'_{O_2} - C\bar{v}_{O_2})$$

where Cc'_{O₂} = end-capillary O₂ content; Ca_{O₂} = arterial O₂ content; and C \bar{v} _{O₂} = mixed venous O₂ content. For the hypoxic period (Phase II), a variation of this shunt equation was used to allow for the difference between the PA_{O₂} of the hypoxic lung and that of the normoxic lung.¹⁶

$\dot{Q}_{VA}/\dot{Q}_T\%$ includes total flow through the left lung during hypoxia as well as other sources.

The left alveolar isoflurane concentration (FA_{ISO}) was calculated by the alveolar gas mixing equation:

$$FA_{ISO} = [FI_{ISO}] - \left[\frac{[(FA_{CO_2} - FI_{CO_2}) / (F\bar{E}_{CO_2} - FI_{CO_2})]}{\times [FI_{ISO} - F\bar{E}_{ISO}]} \right]$$

where FI_{ISO} = inspired isoflurane concentration in per cent; F \bar{E} _{ISO} = mixed inspired isoflurane concentration; FA_{CO₂} = alveolar CO₂ concentration (estimated by Pa_{CO₂}); FI_{CO₂} = inspired CO₂ concentration; and F \bar{E} _{CO₂} = mixed expired CO₂ concentration.

STATISTICS

The data were analyzed by a within-subjects analysis of variance (ANOVA) for repeated measurements, and the Neuman-Keuls test was used for comparison of specific differences between means. Other statistical tests are identified in the "Results" section. *P* < 0.05 was deemed significant. Results are expressed as means ± SE.

Results

The initial general conditions (mean ± SE) of the animals, including temperature (37.6 ± 0.3° C), Pa_{CO₂} (37.6 ± 1.1 mmHg), pH (7.40 ± 0.01), base excess (-2.54 ± 0.4 mEq/l), and mean right and left airway pressures (9.6 ± 0.1 cmH₂O and 9.3 ± 0.1 cmH₂O, respectively) were maintained essentially constant throughout the experiment. Arterial Hb concentration decreased from 12.4 ± 0.8 g/dl at the start to 10.1 ± 0.6 g/dl at the final phase.

Because the hemodynamic and derived data from the normoxic and hypoxic phases (0 MAC isoflurane, fistulae closed) at the beginning and end of the protocol did not differ statistically, the values before and after the randomized sequence were averaged for the subsequent analysis.

When both lungs were ventilated with 100% O₂ (normoxia), $\dot{Q}_L\%$ = 39.9 ± 1.2%; $\dot{Q}_{VA}/\dot{Q}_T\%$ = 6.3 ± 1.5%; PAP = 17.3 ± 0.6 mmHg; PP = 9.1 ± 0.7 mmHg; PVR_L = 600 ± 50 dyn · cm⁻⁵ · s; Pa_{O₂} = 591 ± 22 mmHg; and P \bar{v} _{O₂} = 58 ± 3 mmHg. Hypoxic ventilation of the left lung (0 MAC, fistulae closed) resulted in a significant decrease in $\dot{Q}_L\%$ (18.8 ± 2.6%); Pa_{O₂} (264 ± 49 mmHg); and P \bar{v} _{O₂} (51 ± 1 mmHg) and significant increases of $\dot{Q}_{VA}/\dot{Q}_T\%$ (22.3 ± 2.7%); PAP (20.8 ± 0.7 mmHg); PP (12.8 ± 0.8 mmHg); and PVR_L (2800 ± 620 dyn · cm⁻⁵ · s (see table 1). CO (3.5 ± 0.3 l/min), mean arterial pressure (MAP), and systemic vascular resistance (SVR) did not change compared with normoxia.

TABLE 1. Effects of Changing Cardiac Output on Left Lung Blood Flow, Systemic and Pulmonary Hemodynamic, and Blood Gas Parameters during Left Lung Hypoxia

	0 MAC Hemorrhage	0 MAC Fistulae Closed	0 MAC Fistulae Open
$\dot{Q}_L\%$	25.4 ± 4.2*	18.8 ± 2.6	25.4 ± 3.1*
CO l/min	1.6 ± 0.1*	3.5 ± 0.3	5.0 ± 0.4*
$\dot{Q}_{VA}/\dot{Q}_T\%$	23.6 ± 3.7	22.3 ± 2.7	27.7 ± 2.2*
MAP mmHg	65 ± 4*	126 ± 4	126 ± 4
SVR dyn · cm ⁻⁵ · s	2880 ± 270	2910 ± 250	2140 ± 220*
PAP mmHg	13.3 ± 1.0*	20.8 ± 0.7	24.6 ± 0.9*
PAOP mmHg	5.0 ± 0.8*	7.7 ± 0.5	10.2 ± 1.1*
PP mmHg	8.3 ± 1.0*	12.8 ± 0.8	14.4 ± 1.5*
PVR _L dyn · cm ⁻⁵ · s	2340 ± 800	2800 ± 620	1340 ± 290*
PVR _R dyn · cm ⁻⁵ · s	502 ± 48*	369 ± 25	316 ± 47
HR beats/min	137 ± 8	152 ± 5	158 ± 7
Pa _{O₂} mmHg	176 ± 62*	264 ± 49	230 ± 29
P \bar{v} _{O₂} mmHg	31 ± 2*	51 ± 1	58 ± 2*
Left lung PA _{O₂} mmHg	30 ± 1*	40 ± 1	45 ± 1*

Abbreviations: CO = cardiac output; $\dot{Q}_{VA}/\dot{Q}_T\%$ = left lung flow as venous admixture per cent; $\dot{Q}_L\%$ = left lung blood flow as per cent of total lung flow; MAP = mean systemic arterial pressure; SVR = systemic vascular resistance; PAP = mean pulmonary artery pressure; PAOP = pulmonary arterial occlusion pressure; PP = pulmonary perfusion pressure; HR = heart rate; PVR_L = left lung pulmonary vascular re-

sistance; PVR_R = right lung pulmonary vascular resistance; Pa_{O₂} = arterial oxygen tension; P \bar{v} _{O₂} = mixed venous oxygen tension; PA_{O₂} = alveolar oxygen tension of left lung.

* Means significantly different from 0 MAC fistulae closed ($P < 0.05$).

EFFECTS OF CHANGING CARDIAC OUTPUT ON HPV

When CO was reduced to 1.6 ± 0.1 l/min by hemorrhage, $\dot{Q}_L\%$ (25.4 ± 4.2%) and PVR_R (502 ± 48 dyn · cm⁻⁵ · s) increased significantly; MAP, PAP, PAOP, PP, Pa_{O₂}, P \bar{v} _{O₂}, and left lung PA_{O₂} were significantly reduced; and $\dot{Q}_{VA}/\dot{Q}_T\%$, SVR, PVR_L and heart rate (HR) were not changed (see table 1). Increasing the CO to 5.0 ± 0.4 l/min by opening the AV fistulae significantly increased $\dot{Q}_L\%$ (25.4 ± 3.1%) and $\dot{Q}_{VA}/\dot{Q}_T\%$ (27.7 ± 2.2%). PAP, PAOP, PP, P \bar{v} _{O₂}, and left lung PA_{O₂} were also significantly increased; SVR and PVR_L were decreased significantly, and MAP, Pa_{O₂}, and PVR_R were unchanged (see table 1).

The estimates of left lung blood flow obtained during hypoxia by $\dot{Q}_L\%$ and $\dot{Q}_{VA}/\dot{Q}_T\%$ were compared by regression analysis. The linear expression, $\dot{Q}_L\% = [0.94 (\dot{Q}_{VA}/\dot{Q}_T\%) + 0.01]$, demonstrated a significant correlation ($r = 0.8$), and the slope was not significantly different from unity. This result confirms that $\dot{Q}_{VA}/\dot{Q}_T\%$ is an effective measure of left lung flow during left lung hypoxia.

EFFECTS OF ISOFLURANE ON HPV

The effects of ventilating the left lung with approximately 1 or 2.5 MAC isoflurane are summarized in table 2. $\dot{Q}_{VA}/\dot{Q}_T\%$ was significantly increased (33.9 ± 2.6%) when the left lung was ventilated with 2.5 MAC isoflurane (left FA_{ISO} = 3.4 ± 0.2%), with the fistulae closed (see fig. 1). The CO, PAP, P \bar{v} _{O₂}, left lung PA_{O₂}, Pa_{O₂}, MAP, HR, and SVR were all significantly reduced, and PAOP was significantly increased compared with the 0 MAC hy-

poxia, fistulae-closed phase. The concentration of isoflurane in the mixed venous blood corresponded to a gas concentration of 0.9 ± 0.1%. When the fistulae were opened, while the left lung continued to be ventilated with approximately 2.5 MAC isoflurane, the CO, PAP, PP, P \bar{v} _{O₂}, left lung PA_{O₂}, and mixed venous isoflurane % increased significantly; SVR decreased significantly; and $\dot{Q}_{VA}/\dot{Q}_T\%$, MAP, PAOP, HR, and Pa_{O₂} did not change. The changes associated with opening the fistulae were generally reduced in the presence of isoflurane.

Ventilating the left lung with 1 MAC isoflurane resulted in changes that were similar to but of lesser magnitude and significance than when ventilating with 2.5 MAC isoflurane. $\dot{Q}_{VA}/\dot{Q}_T\%$ was significantly increased to 27.2 ± 2.7% when the left lung was ventilated with 1 MAC isoflurane (left lung FA_{ISO} = 1.4 ± 0.1%), with the fistulae closed (see fig. 1). CO, MAP, and Pa_{O₂} were significantly reduced, and SVR, PAP, PAOP, PP, HR, P \bar{v} _{O₂}, and left lung PA_{O₂} were unchanged compared with the 0 MAC hypoxia, fistulae closed. The mixed venous isoflurane concentration corresponded to 0.5 ± 0.1%. When the fistulae were opened while the left lung continued to be ventilated with 1 MAC isoflurane, CO, PAP, PAOP, PP, Pa_{O₂}, and P \bar{v} _{O₂} increased significantly; SVR decreased significantly; while $\dot{Q}_{VA}/\dot{Q}_T\%$, MAP, HR, mixed venous isoflurane, and left lung PA_{O₂} did not change.

Discussion

This work was stimulated by contradictory reports concerning the action of isoflurane on HPV³⁻⁷ *in vivo*. We hypothesized that the specific effect of isoflurane would

TABLE 2. Effects of Isoflurane and Cardiac Output on Various Hemodynamic and Blood Gas Parameters during Left Lung Hypoxia

	1 MAC—Fistulae Closed	1 MAC—Fistulae Open	2.5 MAC—Fistulae Closed	2.5 MAC—Fistulae Open
CO l/min	3.0 ± 0.1*	4.5 ± 0.3*†	2.2 ± 0.3*	2.8 ± 0.2*†
$\dot{Q}_{VA}/\dot{Q}_T\%$	27.2 ± 2.7*	28.1 ± 2.6*	33.9 ± 2.6*	35.4 ± 1.7*
MAP mmHg	107 ± 8*	105 ± 6*	58 ± 10*	50 ± 7*
SVR dyn · cm ⁻⁵ · s	2750 ± 300	1780 ± 190*†	2350 ± 190*	1310 ± 130*†
PAP mmHg	20.1 ± 0.7	24.3 ± 1.2*†	16.8 ± 0.9*	19.1 ± 0.8†
PAOP mmHg	8.5 ± 1.1	9.7 ± 1.0*†	9.3 ± 0.9*	10.7 ± 0.6*
PP mmHg	11.6 ± 0.8	14.6 ± 1.3†	7.5 ± 1.0*	8.4 ± 0.7*†
HR beats/min	144 ± 6	148 ± 8*	121 ± 7*	125 ± 6*
PaO ₂ mmHg	164 ± 22*	214 ± 26†	91 ± 15*	99 ± 11*
P \bar{v} O ₂ mmHg	47 ± 1	56 ± 2*†	35 ± 2*	43 ± 1*†
Mixed venous isoflurane %	0.5 ± 0.1	0.5 ± 0.1	0.9 ± 0.1	1.0 ± 0.1†
Left lung alveolar isoflurane %	1.4 ± 0.1	1.4 ± 0.1	3.4 ± 0.2	3.0 ± 0.1
Left lung PA _{O₂} mmHg	37 ± 1	42 ± 1	31 ± 1*	37 ± 2†

See table 1 for abbreviations.

* Means significantly different from 0 MAC hypoxia, fistulae closed ($P < 0.05$).

† Means significantly different from fistulae-closed condition with same isoflurane concentration.

be demonstrated convincingly only when the variables known to influence HPV^{17,18} are included in the experimental design. The present study has demonstrated that isoflurane inhibits HPV in a dose-related manner.

When a segment of the lung becomes hypoxic, stimulation of HPV results in a reduction of blood flow to that segment. Species, sex, age, pH, P_{CO₂}, temperature, surgical trauma, CO, pulmonary arterial and venous pressures, size of the hypoxic segment, and intensity of the hypoxic stimulus are the principal nonpharmacologic variables that influence HPV. Adult female dogs were used because they, like humans, have a vigorous HPV response.¹⁹ The pH, P_{CO₂}, temperature, and size of the hypoxic segment (*i.e.*, the left lung) were maintained constant throughout the study, and surgical trauma was minimized by avoiding thoracotomy. The intensity of the hypoxic stimulus for HPV is a function of both the alveolar gas and the mixed venous blood oxygen tensions.⁸ The alveolar influence normally predominates, but the mixed venous oxygen effect becomes important as the alveolar P_{O₂} declines. Therefore, during hypoxia, the dependence of P \bar{v} O₂ on CO is a major variable.

Isoflurane causes changes in CO, pulmonary hemodynamics, and mixed venous and alveolar oxygen tensions.¹¹ The effects of these secondary changes were examined in order to reveal the direct action of the anesthetic on the HPV response. Isoflurane was administered only to the left lung to minimize generalized action of the anesthetic.

The three phases without isoflurane, therefore, examined the influence of CO change on the HPV response (fig. 1) in the hypoxic left lung. The blood flow to the left lung measured by CO₂ excretion during normoxia was 39.9 ± 1.2% of the total flow. During left lung hypoxia, the left lung flow represented by differential CO₂ excre-

tion was reduced by HPV to 18.8 ± 2.6%, and \dot{Q}_{VA}/\dot{Q}_T was 22.3 ± 2.7%. Increasing the CO increased left lung flow and \dot{Q}_{VA}/\dot{Q}_T . Decreasing the CO resulted in a significant increase in $\dot{Q}_L\%$ measured by differential CO₂ excretion and no change in \dot{Q}_{VA}/\dot{Q}_T .

The PVR of the normoxic right lung increased during the low CO phase to approximately twice the value expected by the normal passive pressure/flow relation of the normoxic lung.¹⁷ Low flow conditions, regional ex-

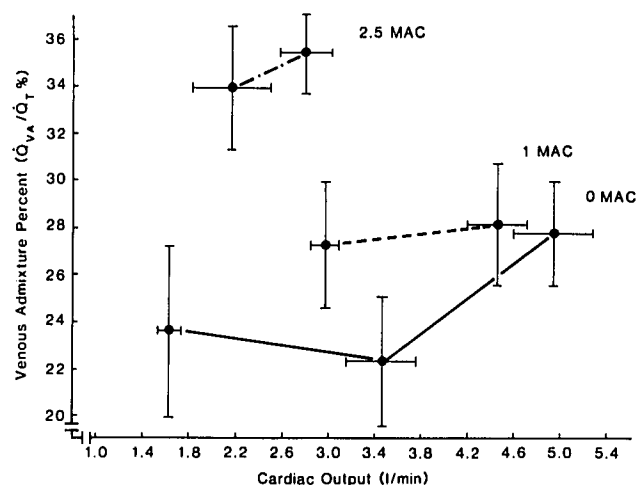


FIG. 1. Effects of cardiac output and isoflurane anesthesia on venous admixture during left lung hypoxia. Cardiac output (l/min) is on the abscissa and venous admixture in per cent ($\dot{Q}_{VA}/\dot{Q}_T\%$) is on the ordinate. Means ± SE are shown. 0 MAC left alveolar isoflurane data are represented by the solid line, 1 MAC by the dashed line, and 2.5 MAC by the dotted line. $\dot{Q}_{VA}/\dot{Q}_T\%$ is significantly greater than the 0 MAC, normal cardiac output (fistulae closed) condition when cardiac output is high (fistulae open phase) in the absence of isoflurane, and with 1 and 2.5 MAC isoflurane at all cardiac outputs. See text for full discussion.

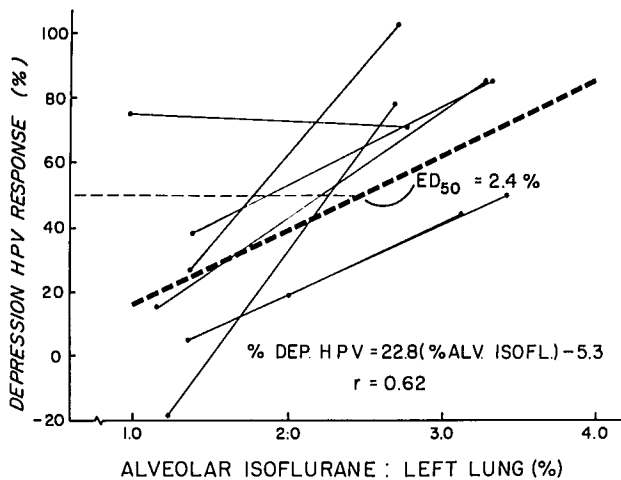


FIG. 2. Influence of isoflurane dose on depression of HPV response. For each animal, the maximal HPV response was identified as the difference in the venous admixture (\dot{Q}_{VA}/\dot{Q}_T) estimated by normoxic left lung blood flow and the actual \dot{Q}_{VA}/\dot{Q}_T during left lung hypoxia, where $\dot{Q}_{VA}/\dot{Q}_T\%$ represented predominantly left lung venous admixture and correlated well with $\dot{Q}_L\%$. The reduction of HPV response when isoflurane was administered was calculated as a per cent of this maximum and is the ordinate of this figure. The left lung alveolar isoflurane concentration in per cent is the abscissa. The linear regression line equation and ED_{50} are indicated.

cretion of nitrogen with the normoxic lung, and the markedly reduced mixed venous oxygen tension ($P\bar{v}O_2 = 31 \pm 2$ mmHg) probably induced an HPV response in the right lung, which then reduced the blood flow diversion from the hypoxic left lung. While the present study was not designed to confirm this hypothesis, the observations are consistent.

Reports from other investigators using undamaged lungs have shown a linear relationship between \dot{Q}_{VA}/\dot{Q}_T and $CO^{9,20,21}$ but, in those studies, the \dot{Q}_{VA}/\dot{Q}_T was generally small. Because of the importance of $P\bar{v}O_2$ in determining the HPV response, it is probable that the precise relationship changes with the size of the hypoxic segment. Thus, the linear relationship becomes modified when the hypoxic segment is large enough to reduce $P\bar{v}O_2$ sufficiently to induce HPV in the "normoxic" lung.

The changes in \dot{Q}_{VA}/\dot{Q}_T with CO were small for both 1 and 2.5 MAC isoflurane, but the purpose of the study design was to provide comparisons with the observations when isoflurane was absent under otherwise similar conditions. Examination of the data reveals that the CO , alveolar and mixed venous oxygen tensions, and pulmonary arterial and arterial occlusion pressures were essentially the same for the 0 MAC hypoxia, fistulae closed; 1 MAC isoflurane, fistulae closed; and 2.5 MAC isoflurane, fistulae open phases. Thus, all of the variables affecting HPV were constant except the concentration of isoflurane. The \dot{Q}_{VA}/\dot{Q}_T increased significantly from $22.2 \pm 2.7\%$ at 0 MAC to $27.2 \pm 2.7\%$ at 1 MAC and to $35.4 \pm 1.7\%$ at

2.5 MAC in these conditions (see fig. 1). Thus, isoflurane caused a dose-dependent increase in $\dot{Q}_{VA}/\dot{Q}_T\%$. These data may be analyzed further as shown in fig. 2 to provide the dose-response relationship for the action of isoflurane. The significant linear regression (% depression of HPV) = $[22.8 (\% \text{ alveolar isoflurane}) - 5.3]$ reveals that 50% depression of HPV response occurs on the average with an alveolar isoflurane concentration of 2.4%. Figure 2 also illustrates the individual variation in sensitivity of HPV to isoflurane, a factor that may be of particular relevance in clinical situations.

The results demonstrate that isoflurane directly inhibits HPV in a dose-related fashion and, therefore, confirm some previous reports.^{3,4} The dose-response curve suggests that low concentrations of isoflurane (0.5 MAC) have little adverse effect on HPV. However, this interpretation should be translated into practice with some caution, because the same alveolar concentration of isoflurane will be associated with greater inhibition when administered to both lungs. The reason for this is that the active site for HPV appears to be at, or in, the vascular smooth muscle of the precapillary arterioles, and the concentration of anesthetic at that site is determined by both the alveolar and the mixed venous gas tensions. This study was deliberately designed to reduce the systemic effects of anesthetics, and the mixed venous blood isoflurane tension was always less than 30% of the left lung alveolar isoflurane tension.

The results also reemphasize the importance of considering the indirect effects of inhalational anesthetics and suggest that, in some circumstances, the anesthetic effect on HPV may be subtle. For example, if an experiment compared a control condition with an elevated CO in the absence of isoflurane to an experimental condition with 1.0 MAC isoflurane, the blood flow to the hypoxic region would be unchanged (see fig. 1). It might then be concluded that isoflurane had no effect on HPV. However, the correct interpretation would be that, while the introduction of isoflurane had inhibited HPV, the reduction of CO and, therefore, of mixed venous oxygen tension provided a greater HPV stimulus and, hence, the response only appeared to be the same. Such interpretations may provide the explanation for some of the apparent contradictions in previous reports.⁵⁻⁷

In summary, this study has demonstrated that isoflurane directly inhibits the pulmonary vascular response to alveolar hypoxia. The secondary actions of the anesthetic, e.g., in producing changes in CO , pulmonary vascular pressures, and mixed venous and alveolar oxygen tensions, should be considered in the interpretation of the effects of inhalational anesthetics on the HPV response *in vivo*.

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