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General Anesthetics and Regional Hypoxic Pulmonary Vasoconstriction

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Administration of N_2O, fluroxene and isoflurane to the left lower lobe (LLL) of dogs anesthetized with pentobarbital was previously shown to inhibit LLL hypoxic pulmonary vasoconstriction (HPV). Using the same experimental model, the present study examined the effect of whole-lung administration of N_2O, fluroxene, isoflurane, halothane, and enflurane on left-lower-lobe HPV. Selective ventilation of the LLL with N_2 alone caused blood flow to the lobe to decrease 53.3 ± 3.0 per cent. Responses to LLL hypoxia were remeasured during administration of inhalation anesthetics at 1 and 2 MAC to both the LLL and the rest of the lung. Isoflurane and fluroxene progressively inhibited and at 2 MAC halved lobar HPV. N_2O (one third MAC) caused slight but significant inhibition, while halothane and enflurane caused slight and nonsignificant changes in lobar HPV. These effects of whole-lung administration of anesthetics on HPV were almost identical to those obtained when the administration was confined to the test lobe alone. It is concluded that N_2O, isoflurane, and fluroxene locally inhibit regional HPV and via this mechanism increase total venous admixture, while halothane and enflurane do not have this effect. (Key words: Lung, hypoxic pulmonary vasoconstriction; Hypoxia, pulmonary vascular response; Anesthetics, volatile.)

PREVIOUSLY, we demonstrated that N_2O, fluroxene and isoflurane inhibit lobar hypoxic pulmonary vasoconstriction (HPV) when administered locally to a hypoxic test lobe of lung.[1] Since the administration of anesthetics was confined to the test lobe, only the direct effects of anesthetics on HPV were determined. The experimental design, therefore, precluded assessment of the net effect of anesthesia on the distribution of perfusion in abnormal lungs. It is possible that in the clinical circumstance, where the entire organism is anesthetized, changes in cardiac output, metabolic rate, and pulmonary vascular pressures and resistances might alter the impact of anesthetics on HPV. Accordingly, we have examined the effect of whole-lung administration of halothane, fluroxene, isoflurane, enflurane, and N_2O on regional test lobe HPV.

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Methods

Our experimental preparation has been described[1,2] and is only summarized here. Twenty mongrel dogs, anesthetized with 25 mg/kg pentobarbital, were endotracheally intubated and ventilated by one side of a dual-piston pump with 100% O_2. Through a left fifth–sixth intercostal thoracotomy, electromagnetic flow proves (Statham SP7515) were placed on the main and left-lower-lobe (LLL) pulmonary arteries. Both flow probes had been calibrated *in vitro* with known blood flows in excised vessels. The flow probe on the main pulmonary artery was further calibrated by simultaneous thermal dilution curves obtained *in vivo*; the maximum deviation was less than 6 per cent. Pulmonary arterial and left atrial pressures were measured directly.

The left-lower-lobe bronchus was incised distal to a ligature and ventilated independently but synchronously with the remainder of the lung with 100 per cent O_2 by a second respirator pump. External deadspace and tidal volume were manipulated to produce airway pressures and end-tidal CO_2 concentrations (Beckman LB-2) that were the same in both ventilated compartments. The respiratory rate was adjusted to achieve a Pa_{CO_2} of 40 mm Hg. LLL end-tidal P_{O_2} was monitored continuously with a rapidly responding Clark electrode. Arterial and mixed venous blood oxygen contents were measured in duplicate by the Klingenmeier method.[3] Oxygen consumption was calculated by use of the Fick equation.

In all dogs, after baseline measurements were made, while the animals were ventilated with 100 per cent O_2, the control LLL hypoxic response was obtained by selectively ventilating the LLL with N_2 alone. During LLL N_2 ventilation CO_2 was added to the inspired gases to keep LLL end-tidal CO_2 concentration reasonably constant.[4] The rest of the lung was ventilated with 100 per cent O_2 at all times and minute ventilation was kept constant in both compartments. Since changes in cardiac output alter LLL blood flow, the control vasoconstriction response to LLL hypoxia was calculated as the maximum percentage decrease in the fraction of the cardiac output perfusing the LLL (per cent decrease Q_{LLL}/Q_t).

The experimental sequence was as follows: a) measure control LLL hypoxic response; b) return to 100 per cent O_2 ventilation of the LLL and administer one anesthetic drug until a random stable

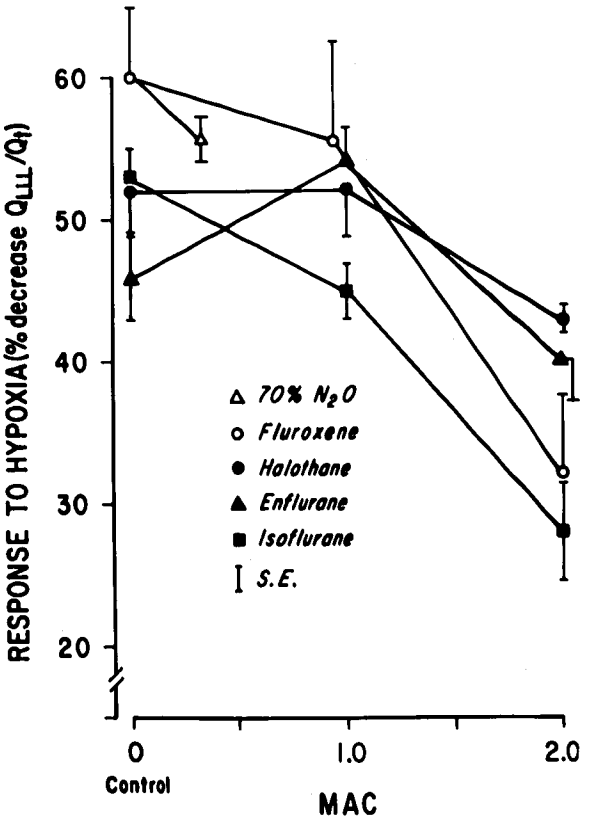

FIG. 1. The vasoconstriction response of the left lower lobe to hypoxia as a function of anesthetic concentration (MAC multiple). The response to hypoxia was defined by the percentage decrease in the fraction of the cardiac output perfusing the left lower lobe (per cent decrease Q_{LLL}/Q_t).

end-tidal (Beckman LB-2) MAC multiple was achieved in both the LLL and the rest of the lung; c) measure test LLL hypoxic response; d) return LLL to 100 per cent O_2 ventilation and change anesthetic concentration in both the LLL and the rest of the lung to a different MAC multiple; e) retest LLL hypoxic response. Five dogs were used to study each anesthetic drug; the dogs used to study halothane were also used to study N_2O. The end-tidal concentrations that were assumed to equal 1 MAC have been described.[1] Statistical significance of results was analyzed by Student's paired t analysis.

Results

Effects of Anesthetics on Pulmonary Circulation and Metabolism

Table 1 summarizes changes in hemodynamic and metabolic variables as a function of anesthetic depth before LLL hypoxia was induced. Compared with control conditions (0 MAC), halothane, isoflurane and enflurane at the greatest dose level significantly decreased pulmonary arterial pressure (P_{pa}), cardiac output (Q_t), and metabolic rate ($\dot{V}_{O_2}$). Since Q_t decreased more than $\dot{V}_{O_2}$ with these three drugs, the arteriovenous oxygen content difference $C(a-\bar{v})_{O_2}$ was significantly increased at the greastest dose level. Pulmonary vascular resistance (PVR) was slightly but statistically significantly decreased at the highest dose level with halothane, isoflurane and enflurane, but was insignificantly affected by fluroxene. Except for fluroxene, changes in left atrial pressure (P_{la}) were variable and inconsistent. Fluroxene, on the other hand, significantly elevated P_{pa} and P_{la} but was without significant effect on Q_t, PVR, $C(a-\bar{v})_{O_2}$ and $\dot{V}_{O_2}$. Administration of N_2O produced no significant change in any of the variables.

Effect of Anesthetics on Hypoxic Pulmonary Vasoconstriction

Figure 1 shows the LLL hypoxic response (per cent decrease Q_{LLL}/Q_t) as a function of anesthetic

TABLE 1. Hemodynamic and Metabolic Effects of Anesthetics

	MAC	Pulmonary Arterial Pressure (P_{pa}) (mm Hg ± SE)	Left Atrial Pressure (P_{la}) (mm Hg ± SE)	Cardiac Output Q_t (ml/min ± SE)	Pulmonary Vascular Resistance (PVR) (dynes·sec·cm^{-5} ± SE)	Arteriovenous Oxygen Content Difference $C(a-\bar{v})_{O_2}$ (Vol %)	Oxygen Consumption ($\dot{V}_{O_2}$) (ml/min)
Halothane	0	14.0 ± 0.9	4.4 ± 0.8	1896 ± 244	407 ± 36	5.3 ± 0.3	93 ± 8
	1.0	11.9 ± 1.6*	6.0 ± 1.2	1480 ± 117*	391 ± 60	5.5 ± 0.4	83 ± 4
	2.0	10.2 ± 1.4*	5.7 ± 0.4	1136 ± 156*	359 ± 79*	7.4 ± 0.7*	70 ± 4*
Isoflurane	0	15.2 ± 0.3	7.3 ± 0.7	2032 ± 464	330 ± 59	6.1 ± 0.8	104 ± 10
	1.0	13.8 ± 0.6*	7.0 ± 1.1	1306 ± 429*	316 ± 44	6.8 ± 1.2	71 ± 9*
	2.0	12.0 ± 0.6*	8.4 ± 2.4	1000 ± 336*	264 ± 41*	8.7 ± 1.9*	62 ± 15*
Enflurane	0	15.3 ± 1.3	4.9 ± 0.9	2082 ± 266	353 ± 38	4.6 ± 0.3	103 ± 10
	1.0	10.0 ± 0.4*	4.4 ± 0.4	1370 ± 75*	328 ± 18	5.3 ± 0.4	76 ± 10*
	2.0	10.7 ± 1.0*	5.7 ± 0.7	1370 ± 265*	321 ± 36*	6.7 ± 0.3*	69 ± 12*
Fluroxene	0	12.6 ± 0.8	4.4 ± 1.2	1894 ± 122	431 ± 54	6.2 ± 0.4	99 ± 9
	1.0	16.6 ± 1.4*	7.3 ± 1.0*	1800 ± 89	432 ± 40	6.0 ± 0.4	108 ± 9
	2.0	16.4 ± 2.0*	8.2 ± 1.4*	1781 ± 97	396 ± 68	5.3 ± 0.3	95 ± 8

* $P < 0.05$ compared with control conditions (0 MAC).

depth. Isoflurane progressively inhibited the hypoxic response at each anesthetic level ($P < 0.02$). Inhibition of HPV by isoflurane was maximal when $C(a - \bar{v})_{O_2}$ was also maximal (table 1). Fluroxene progressively decreased LLL HPV, but the effect was statistically significant only at the 2 MAC level ($P < 0.01$). Enflurane and halothane had no significant effect on LLL HPV. N_2O caused a small but significant ($P < 0.02$) inhibition of the LLL hypoxic response.

Figure 2 shows the changes in Pa_{O_2} during LLL hypoxia caused by the anesthetic drugs. The changes in Pa_{O_2} paralleled the effects of the drugs on HPV and had the same statistical significances as the HPV changes. During the LLL hypoxic responses the regression equation relating Pa_{O_2} to the hypoxic response was $Pa_{O_2} = 5.6$(hypoxic response) $- 4.0$ with a correlation coefficient $r = 0.73$, which was significant ($P < 0.01$).

Discussion

The principal findings of this study were that 1) halothane, isoflurane and enflurane decreased PVR; 2) fluroxene and isoflurane progressively inhibited HPV in a dose-dependent manner; 3) the inhibition of HPV by isoflurane was maximal when the $C(a - \bar{v})_{O_2}$ was maximal; 4) the magnitude of the hypoxic response correlated well, but not precisely, with Pa_{O_2}. Consideration should be given to the mechanism and importance of these findings. Sources of variability and errors related to our methods and experimental model have been described.[1,2,4]

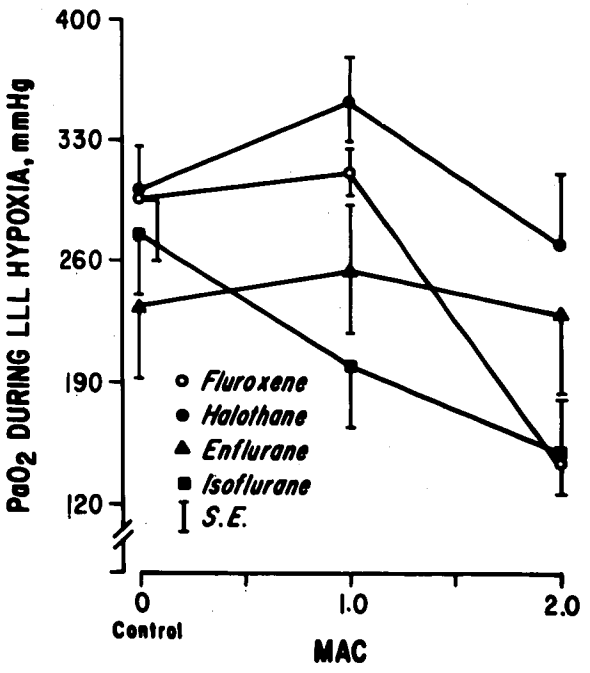

FIG. 2. The arterial partial pressure of oxygen (Pa_{O_2}) during left-lower-lobe hypoxia as a function of anesthetic concentration (MAC multiple).

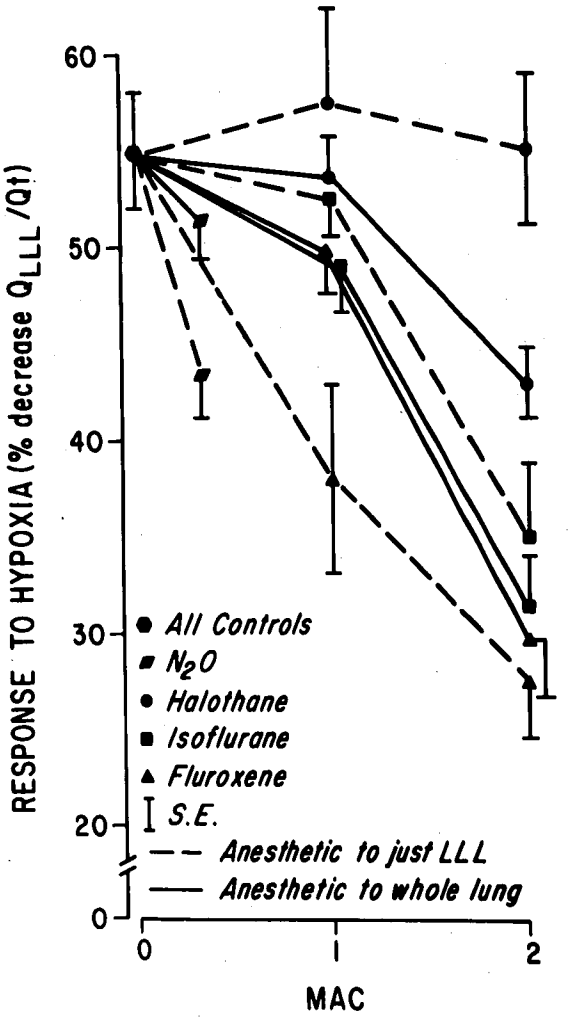

FIG. 3. Left-lower-lobe (LLL) responses to hypoxia during selective LLL administration of anesthetic (*dashed lines*)[1] compared with whole-lung administration of anesthetic (*solid lines*) (MAC multiple). Response to hypoxia was defined as in figure 1. All control responses were grouped to facilitate comparison.

Decreased PVR

Halothane, isoflurane and enflurane all caused between 30–40 per cent decreases in Q_t. Decreases in Q_t are normally accompanied by passive increases in PVR because Q_t decreases more than P_{pa}. In our study, anesthetic depth caused a decreased Q_t accompanied by a slightly decreased PVR. Thus, the observed decrease in P_{pa} was slightly out of proportion to the decrease in Q_t. This may represent anesthetically induced relaxation of normally present tone in the pulmonary circulation.

Anesthetics and HPV

N_2O, fluroxene and isoflurane inhibited HPV. Previous studies from our laboratory,[1] in which the administration of anesthetics was confined to the LLL, had similar results. Figure 3 compares the LLL repsonse to hypoxia during LLL (*dotted line*)

versus whole-lung administration (*solid line*) of anesthetic. Although enflurane was not previously studied, all control responses in the single-lobe anesthetic experiments (per cent decrease Q_{LLL}/Q_t = 55.5 ± 2.0) were close to all control responses in this experiment (per cent decrease Q_{LLL}/Q_t = 55.0 ± 3.0, enflurane excluded), and in order to facilitate the comparison we have grouped them together. The effects of the anesthetics on HPV are remarkably similar in the two circumstances. This suggests that the mechanism of inhibition is a local pharmacological one and may be the result of interference with any of the metabolic processes responsible for the production, activation, inactivation, or release of the mediator of HPV, or direct alteration of the contractile mechanism of smooth muscle.

Inhibition of HPV and Metabolism

Inhibition of HPV by isoflurane occurred at an anesthetic concentration that increased the $C(a - \bar{v})_{O_2}$ (V_{O_2}/Q_t increased). This is important because it magnifies the deleterious effects on oxygenation of the blood resulting from anesthetic inhibition of HPV. Thus, the blood shunted through the LLL contained less oxygen.

Inhibition of HPV and Pa_{O_2}

The determinants of Pa_{O_2} during LLL hypoxia are the magnitude of HPV, the initial Pa_{O_2} before LLL hypoxia, and $P\bar{v}_{O_2}$ during LLL hypoxia. The correlation between the response to hypoxia and Pa_{O_2} was good, but because the initial Pa_{O_2} and $P\bar{v}_{O_2}$ during LLL hypoxia varied among individual dogs and from one anesthetic level to another and from one anesthetic group to another, the correlation coefficient was not closer to 1.

These findings are important for several reasons. First, inhibition of HPV by fluroxene and isoflurane can be expected to aggravate ventilation–perfusion inequalities in anesthetized patients who have preexisting pulmonary disease, as well as patients in whom ventilation–perfusion inequalities develop during or as a consequence of anesthesia and surgery. Second, inhibition of HPV by isoflurane and inhibition by N_2O are additive,[1] and coupled with isoflurane limitations on $C\bar{v}_{O_2}$ and N_2O limitations on FI_{O_2}, this combination might result in serious arterial hypoxemia. Third, these findings indicate that the anesthetics studied have only slight effects on PVR. Last, these findings also emphasize the importance of considering the effect of anesthetics on HPV in studies of total venous admixture during anesthesia.

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