Hypocapnic Bronchoconstriction and Inhalation Anesthetics

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The effects of halothane, enflurane, and methoxyflurane on hypocapnic bronchoconstriction (increased airway resistance and decreased compliance of the lung) were studied *in vivo* in the isolated left lower lobe of the canine lung. Hypocapnic bronchoconstriction, induced by altering the concentration of CO_2 in gas ventilating the lobe, was repeated in the presence and absence of various concentrations of anesthetic gases (halothane: 0.5, 1.0, and 3.0 per cent; enflurane: 1.0, 3.0, and 5.0 per cent; methoxyflurane: 0.25, 0.50, and 1.0 per cent). In the higher concentrations, all three drugs blocked the bronchoconstrictor effect produced when the inspired CO_2 was decreased from 5 to 0 per cent. In lower concentrations, halothane was the most effective blocking drug. Propranolol did not affect the ability of the three anesthetics to block hypocapnic bronchoconstriction, nor did the beta-receptor blocking drug sotalol affect the blocking effects of halothane. The ability of these anesthetics to block hypocapnic bronchoconstriction probably is mediated not through an adrenergic mechanism but by one that is nonspecific. (Key words: Lung, bronchoconstriction; Carbon dioxide, hypocarbia; Anesthetics, volatile, halothane; Anesthetics, volatile, enflurane; Anesthetics, volatile, methoxyflurane.)

HALOTHANE has been shown to dilate airways constricted by hypocapnia,[1-3] whereas methoxyflurane was ineffective.[3] The effect of enflurane on hypocapnic bronchoconstriction has not been studied.

The mechanism by which these anesthetics act on airway smooth muscle is unknown, but Klide and Aviado[4] have suggested that the bronchodilator effect of halothane is produced through a beta-adrenergic stimulatory mechanism.

The purpose of this study was, first, to compare the effects of halothane, enflurane, and methoxyflurane on hypocapnic bronchoconstriction in the isolated left lower lobe of the canine lung and, second, to determine the effects of beta-receptor blockade on the effects of these anesthetics on hypocapnic bronchoconstriction.

Methods

Figure 1 shows the animal preparation used for this study. Dogs, 18–28 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv). The left lower lobe (LLL) was exposed through a thoracotomy at the level of the seventh intercostal space. A Mariotte bottle placed in a water bath (35 to 38 C) was filled with 300 ml of blood from a catheter in a femoral vein. The lobar pulmonary artery and vein were cannulated. Blood was pumped by a Sarns nonocclusion roller pump from the reservoir into the lobar artery. To avoid a siphon effect on the lobar venous outflow, a second small reservoir was placed at the level of the lobe. Lobar venous blood flowed from the lobe into the bottom of this reservoir and returned to the first reservoir through an overflow tube. The perfusion rate was 244 ml/min. Ventilation of the LLL was separated from the ventilation of the rest of the lobes of the animal by a tube-within-a-tube system.

The LLL was partially denervated by cutting the vagosympathetic nerve tract. The remaining innervation was interrupted by sectioning the lobar artery prior to cannulation, by the tie around the cannula in the lobar vein, and by the tie around the tube in the lobar bronchus.

Lobar perfusion pressure, lobar airway pressure, and systemic arterial pressure were
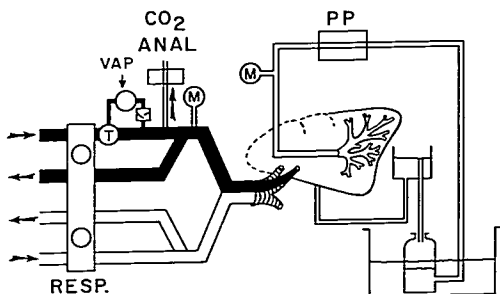
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FIG. 1. Preparation for isolation of the left lower lobe. RESP = respirator; VAP = vaporizer; CO_2 ANAL = CO_2 analyzer; PP = perfusion pump; M = Statham pressure transducer.

monitored by Statham transducers and recorded on a Grass polygraph. Lobar perfusion pressure was monitored from a T in the perfusion line and lobar airway pressure was monitored through a catheter placed with the catheter tip beyond the end of the cannula in the LLL bronchus. End-expired CO_2 was monitored using a Beckman IR CO_2 analyzer and recorded on the polygraph. Systemic arterial and lobar venous blood gases and pH were measured using a Radiometer blood-gas analyzer. Sodium bicarbonate was added when required to produce a zero base excess as calculated from a Siggaard-Andersen nomogram.

The ventilator used to ventilate the LLL and remaining lobes of the animal was a modification of a ventilator originally designed to ventilate the right and left lungs simultaneously with square-flow wave inflations during bronchospirometry.[5] The ventilator was modified so that during the apneic period of the remaining lobes the LLL underwent a high flow rate–square-flow pulse of short duration. This pulse was approximately 0.2 l in volume and 0.2 sec in duration. The volume of the pulse was measured with a spirometer at the end of the experiment. The high flow rate yielded a measurable resistance component, whereas the short duration produced ventilatory volumes that resulted in a lobar airway pressure of less than 15 cm H_2O. Airway resistance (measured from the practically instantaneous drop in pressure when flow was interrupted), kinetic compliance (measured after flow had been

interrupted), and static compliance (measured after expiration was delayed 1 second)[6-8] were determined from this square-flow pulse.

A calibrated vaporizer, specific for the anesthetic used, was placed between the ventilator and the lobe. A three-way valve was used to bypass the vaporizer when measurements of airway resistance and pulmonary compliance were made. A one-way valve was placed between the lobe and the vaporizer to eliminate the damping effect on the airway pressure tracing caused by having the vaporizer in the system.

A Veriflo mixing valve, connected to a tank of 10 per cent CO_2 in oxygen and to a tank of 100 per cent O_2, was used to produce the desired CO_2 mixtures used to ventilate the LLL. The remaining lobes were ventilated with 100 per cent O_2.

In the first series of experiments, moderate and severe hypocapnic bronchoconstriction were produced by reducing inspired CO_2 from 5 to 1.3 (moderate bronchoconstriction) and to 0 per cent (severe bronchoconstriction). Because of the possibility that the hypocapnic bronchoconstrictor response would decrease with time, inspired CO_2 was reduced from 5 to 1.3 per cent, returned to 5 per cent, and then reduced directly from 5 to 0 per cent. Resistance and compliance were measured immediately before and 1 to 2 minutes after the inspired CO_2 had been reduced. When pulmonary mechanics were measured, a lobar blood sample was also drawn and blood gases and pH determinations were made. This sequence

was first carried out without any anesthetic gas in the inspired gas mixture. Pulmonary mechanics were then measured in the presence of 5 per cent inspired CO_2, the vaporizer was adjusted to produce the desired concentration of anesthetic gas, and the sequence was repeated. Halothane and enflurane were administered for 5 to 8 minutes and methoxyflurane for 10 to 15 minutes before the first measurements were made. Similar intervals were allowed for the system to be cleared of the preceding anesthetic gas before another set of determinations, in the absence and presence of a different anesthetic gas or anesthetic gas concentration, was initiated. Inspired CO_2 was altered in this manner in the presence of inspired concentrations of 0.5, 1.0, and 3.0 per cent halothane (Fluothane: Ayerst Laboratories); 1.0, 3.0, and 5.0 per cent enflurane (Éthrane: Ohio Medical Products); 0.25, 0.50, and 1.0 per cent methoxyflurane (Penthrane: Abbott Laboratories). Comparisons of the effectiveness of these anesthetics in blocking hypocapnic bronchoconstriction were made at approximately equivalent multiples of the respective minimum alveolar concentrations required for preventing a response to a painful stimulus in 50 per cent of the subjects (MAC), namely, halothane 0.77 per cent, methoxyflurane 0.16 per cent,[9] and enflurane 1.68 per cent.[10] The concentrations administered in this series, expressed in multiples of these values of MAC, were approximately 0.64, 1.30, and 3.90 MAC for halothane, 0.60,

1.78, and 2.98 MAC for enflurane, and 1.56, 3.13, and 6.25 MAC for methoxyflurane. Nine animals were used in this series.

In the second series of experiments, the effect of propranolol on the blocking effect of halothane, enflurane, and methoxyflurane was evaluated. Infusions of isoproterenol were used to test the continued effectiveness of the beta-receptor block by propranolol. Inspired CO_2 was reduced from 5 to 0 per cent in the presence of these drugs in the following sequence: 1) control, 2) isoproterenol infusion, 3) isoproterenol infusion following administration of propranolol (3 mg), 4) inhalational anesthetic, 5) control, 6) isoproterenol infusion, 7) second inhalational anesthetic, 8) control, and 9) isoproterenol infusion. Pulmonary mechanics were also measured during ventilation of the lobe with 5 per cent inspired CO_2 prior to the administration of a drug. Steps 4 and 7 were repeated for each concentration of the anesthetic gas used: 1.0 and 3.0 per cent halothane, 5.0 per cent enflurane, and 0.5 and 1.0 per cent methoxyflurane. Isoproterenol was infused at a rate of 4 μg/min for 5 minutes. Inspired CO_2 was reduced from 5 to 0 per cent after 3 minutes of infusion; 1 minute was allowed for the CO_2 to be reduced and the response to occur; resistance and compliance were measured during the fifth minute of infusion. Fifteen minutes were allowed, after the isoproterenol infusion, before the inspired CO_2 was again reduced. Nine animals were used in this series.

FIG. 2. Effects on resistance and kinetic compliance of altering inspired CO_2. Vertical bars represent ± 1 SEM, n = 25. Lobar venous pH is also shown.
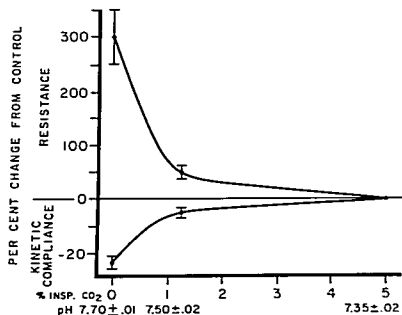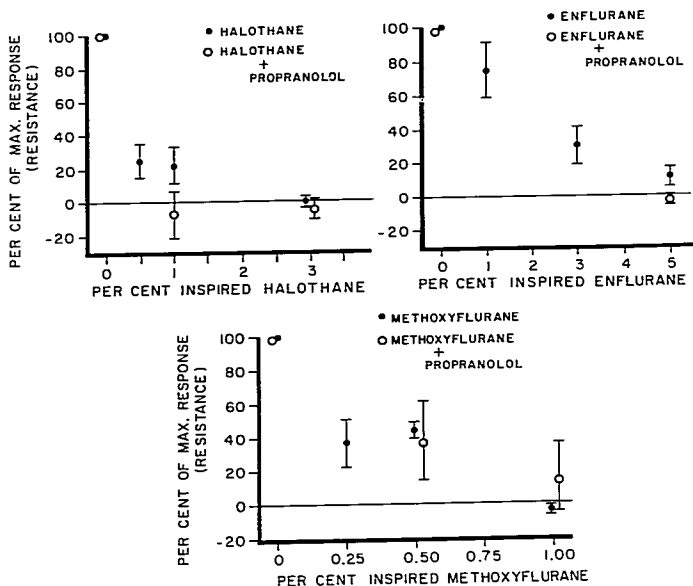
FIG. 3. Effects of various concentrations of halothane, enflurane, and methoxyflurane on the increase in resistance that occurred when inspired CO_2 was reduced from 5 to 0 per cent in the absence and presence of propranolol. Vertical bars represent ±1 SEM, n = 4–7.

In addition to the two series of animals, the effect of the beta-blocking drug sotalol (MJ 1999) on the blocking effect of halothane was evaluated in two animals. Again, inspired CO_2 was reduced from 5 to 0 per cent and lobar venous blood samples taken. This sequence was repeated during 1) 0.0, 0.5, 1.0, 2.0, 4.0, and 0.0 per cent halothane; 2) isoproterenol infusion; 3) isoproterenol infusion after the addition of 30 mg sotalol; 4) 0.0, 0.5, 1.0, 2.0, 4.0, and 0.0 per cent halothane; 5) isoproterenol infusion.

Data were analyzed for significance (P < 0.05) using Student's non-paired t test.

Results

Figure 2 shows the responses of airway resistance and lung compliance to a step-wise reduction of inspired CO_2. The mean

lobar venous pH for each set of determinations is also shown on the graph. Lobar venous P_{CO_2}'s were 34.5, 16.8, and less than 10.0 mm Hg at pH 7.35, pH 7.50, and pH 7.70, respectively. A major portion of the bronchoconstriction occurred between pH 7.50 and pH 7.70.

The effects of halothane, enflurane, and methoxyflurane on the increase in airway resistance that occurred when inspired CO_2 was reduced from 5 to 0 per cent are shown in figure 3. The response that occurred in the presence of the anesthetics is expressed as the percentage of maximum increase in resistance that occurred with no anesthetic in the inspired gas mixture when inspired CO_2 was decreased from 5 to 0 per cent. Three per cent halothane, 5 per cent enflurane, and 1 per cent methoxyflurane totally or nearly

totally blocked the hypocapnic bronchoconstrictor response. Five per cent enflurane was less effective than 1.0 per cent methoxyflurane ($P < 0.05$). At the two lower anesthetic concentrations hypocapnic bronchoconstriction, produced by reducing inspired CO_2 from 5 to 0 per cent, was more effectively blocked by 0.5 per cent halothane than by 1.0 per cent enflurane ($P < 0.05$) and was more effectively blocked by 1.0 per cent halothane than by 0.5 per cent methoxyflurane ($P < 0.05$). When compared at approximately equivalent multiples of MAC: 1) halothane, 0.6 MAC, was significantly more effective than enflurane, 0.6 MAC; 2) halothane, 1.3 MAC, on the average, was a more effective blocking drug than methoxyflurane, 1.6 MAC, or enflurane, 1.8 MAC, but this difference was not significant; 3) halothane, 3.9 MAC, and enflurane, 3.0 MAC, were significantly more effective than methoxyflurane, 3.1 MAC. The increase in resistance produced by a decrease in inspired CO_2 from 5 to 1.3 per cent was blocked by all concentrations of the anesthetics used. The effects of these anesthetics on pulmonary compliance and airway resistance were similar when inspired CO_2 concentration was reduced from 5.0 to 1.3 per cent and from 5 to 0 per cent.

Figure 3 also shows the effects of propranolol on the abilities of 1.0 and 3.0 per cent halothane, 5.0 per cent enflurane, and 0.5 and 1.0 per cent methoxyflurane to block hypocapnic bronchoconstriction. Propranolol did not significantly reduce the blocking ef-
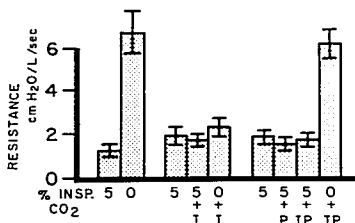

Fig. 4. Effectiveness of beta-receptor blockade by propranolol. I = isoproterenol infusion, 4 μg/min; P = propranolol, 3 mg; IP = isoproterenol infusion in the presence of propranolol. Vertical bars represent ±1 SEM, n = 7–8.

fects of these anesthetics in the concentrations used.

Verification of the effectiveness of the beta-receptor blockade by the dose of propranolol used is shown in figure 4 (combined results from the animals in the second series of experiments). Isoproterenol blocked the increase in airway resistance produced by decreasing inspired CO_2 from 5 to 0 per cent. Propranolol, in turn, blocked the beta stimulatory effects of isoproterenol infusion. Neither isoproterenol nor propranolol alone or in combination significantly affected lobar airway resistance during ventilation of the lobe with an inspired CO_2 of 5 per cent.

Figure 5 shows the effect of sotalol on the bronchoconstrictor blocking effect of halo-

FIG. 5. Effects of various concentrations of halothane on the increase in peak airway pressure that occurred when inspired CO_2 was reduced from 5 to 0 per cent, both in the absence and in the presence of sotalol. Inset shows the effectiveness of beta-receptor blockade by sotalol. I = isoproterenol infusion, 4 μg/min.
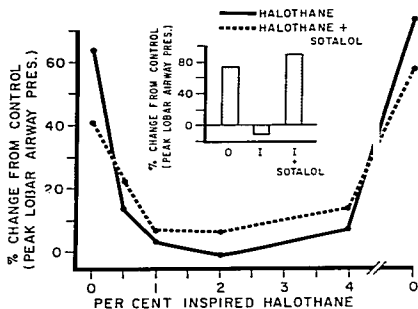
thane. Changes in pulmonary mechanics are represented by percentage changes in peak airway pressure. The inset shows the effectiveness of isoproterenol in blocking hypocapnic bronchoconstriction, and the reversal of this blocking effect by the beta blocking agent. Again, halothane blocked hypocapnic bronchoconstriction in the presence of this beta-receptor blocking agent.

Discussion

In the isolated denervated LLL of the canine lung ventilated with 5.0 per cent CO_2, there appears to be little bronchial muscle tone, since neither isoproterenol infusion nor ventilation of lobe with gas containing even the highest concentrations of the anesthetics decreased airway resistance or increased compliance of the lung.

Inspired concentrations of 3.0 per cent halothane, 5.0 per cent enflurane, and 1.0 per cent methoxyflurane blocked the bronchoconstrictor effect of severe hypocapnia. At lower concentrations halothane was more effective than enflurane or methoxyflurane in blocking hypocapnic bronchoconstriction produced by reducing inspired CO_2 from 5 to 0 per cent. These results are consistent with findings of others[1-3] that halothane is also an effective bronchodilator of hypocapnic airway constriction in human lungs during heart–lung bypass. The concentrations at which halothane blocked the constrictor effects of hypocapnia were also similar to the concentrations of halothane that dilate airways constricted by histamine or vagal stimulation.[11] The present results are inconsistent with the observation that methoxyflurane is ineffective in reducing the effects of hypocapnic bronchoconstriction in man during cardiopulmonary bypass.[3] In the study of McAslan et al.,[3] methoxyflurane was administered after constriction was produced, whereas in the present study methoxyflurane was administered before inspired CO_2 was reduced. Also, pulmonary blood flow was reduced during cardiopulmonary bypass, whereas lobar arterial blood flow was maintained constant and the lobar airway smooth muscle was equilibrated with methoxyflurane both from the inspired gas and from the

pulmonary circulation. This may have produced a more effective distribution of methoxyflurane to the airways in the present study than in the study of McAslan et al.[3] The effect of enflurane on hypocapnic bronchoconstriction has not previously been studied.

The anesthetics tested may be acting through either beta-adrenergic or nonspecific musculotropic receptors.[12] The failure of beta blocking agents (propranolol and sotalol) to affect the ability of halothane to inhibit hypocapnic bronchoconstriction is in conflict with the findings of Klide and Aviado.[4] In the study of Klide and Aviado,[4] the bronchodilator effect of halothane was effective against bronchomotor tone of an unspecified etiology, whereas in the present study beta blocking agents were administered in an attempt to block the ability of halothane to reverse hypocapnic bronchoconstriction. Furthermore, the beta blocking agent used by Klide and Aviado[4] was sotalol (in one experiment pronethalol was used, and the result was the same as with sotalol). In the present study, the primary blocking agent was propranolol, though a limited number of experiments were also carried out using sotalol. Halothane reversal of histamine constriction of the guinea pig tracheal preparation reportedly does not depend on halothane stimulation of beta receptors.[13] The ability of enflurane and methoxyflurane to reverse hypocapnic bronchoconstriction also was not blocked by propranolol.

The effectiveness of the beta-adrenergic block produced by propranolol and sotalol was verified by the infusion of isoproterenol sufficient to block the bronchoconstrictor effect of severe hypocapnia, and this amount of propranolol was ineffective in blocking the ability of halothane, enflurane and methoxyflurane to reverse hypocapnic bronchoconstriction. The doses of propranolol and sotalol, even though corrected for use in the isolated lobe, were slightly greater than the doses used in the intact animal. Large doses of propranolol have been shown to have anesthetic properties.[14] However, hypocapnic bronchoconstriction was unaffected by the concentrations of these drugs used.

The ability of the anesthetics studied to

block hypocapnic bronchoconstriction probably is mediated not through an adrenergic mechanism, but by one that is nonspecific.

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Propranolol

DANGERS OF PROPRANOLOL WITHDRAWAL Because of the potential dangers of anesthesia in the presence of *beta*-adrenergic blockade, some clinicians have advocated that propranolol be discontinued prior to anesthesia and operation. The authors call attention to the possible adverse effects of such an endeavor. Six patients with severe angina had been treated with 240 mg/day of propranolol. In all patients, the frequency of anginal pain had decreased substantially since therapy had been instituted. Propranolol therapy was abruptly discontinued in four patients because of research protocols, in one patient because of lack of availability, and in one patient because of scheduled angiography. In all six patients frequent, prolonged chest pain occurred at rest immediately after propranolol was discontinued. The pattern of pain was distinctly different from that experienced either before or during propranolol therapy. After 2–21 days of continuing unstable angina, three patients had acute myocardial infarction, while a fourth suddenly died. That angina at rest and nocturnal angina appeared in patients never previously experiencing such symptoms, as well as the increase in frequency and severity of pain, suggests that this represented a true rebound phenomenon rather than symptom reappearance. The authors point out that these findings should be considered when abrupt withdrawal of propranolol therapy is contemplated. *(Alderman EW, Coltart DJ, Wettach GE, et al.: Coronary Artery Syndromes after Sudden Propranolol Withdrawal. Ann Intern Med 81: 625–627, 1974.)*