Inhalation Anesthetics Augment Oxidant-induced Pulmonary Vasocostriction: Evidence for a Membrane Effect

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Inhalational anesthetics "fluidize" biologic membranes. Since arachidonate metabolism also occurs in cell membranes, anesthetic agents may modify arachidonic acid mediator production. The authors used the isolated perfused rabbit lung preparation to examine the effects of inhalational anesthetics on the production of arachidonate mediators. The oxidant tert-butyl-hydroperoxide (t-bu-OOH) is known to cause pulmonary vasocostriction by causing increased production of thromboxane A2 (TxA2). The authors administered three anesthetics (halothane, cyclopropane, and nitrous oxide) of widely different potencies, at different dosages, to each of three different groups of preparations and challenged the lungs at each anesthetic dose with t-bu-OOH. They found a dose-related augmentation of the pulmonary vasopressor response to t-bu-OOH. Preparations given t-bu-OOH alone showed no change in response over time. Lungs perfused with indomethacin (5 μg · ml⁻¹ in Krebs-Henseleit buffer), ventilated with cyclopropane (2 MAC), and challenged with t-bu-OOH showed almost complete inhibition of the response to t-bu-OOH. Indomethacin at this concentration is a specific inhibitor of cyclooxygenase. The authors also have demonstrated significantly increased perfusate levels of thromboxane B2 (TxB2), the inactive metabolite of TxA2, after oxidant challenge during exposure to 2% halothane compared with TxB2 levels before halothane exposure. The authors believe that the augmented pressor response and mediator production occur because of increased substrate (arachidonic acid) availability induced by anesthetic agent. (Key words: Anesthetics, gases: cyclopropane; nitrous oxide. Anesthetics, volatile: halothane. Hormones: prostaglandins. Lung: vascular resistance. Membrane: cell.)

INHALATIONAL anesthetic agents are highly lipid-soluble drugs. Ernst and Lowe¹ have hypothesized that a critical molar concentration of all volatile anesthetic agents is present in brain lipids when the anesthetics are administered in equipotent doses. This concentration, approximately 20 mM at 1.3 MAC, is remarkably constant throughout the range of anesthetic potency. Additionally, anesthetic potency is highly correlated with lipid solubility, suggesting that the site of action of volatile anesthetics is at the lipid region of the cell membrane.

The high degree of lipid solubility of volatile anesthetic agents allows their accumulation within the plasma membrane. Arachidonic acid is chemically bound within cell membranes in phospholipids and released by microsomally bound enzymes. It seems possible that inhalational anesthetics may affect arachidonate metabolism in proportion to their lipid solubility, and this effect could be related to anesthetic potency.

We find that arachidonate mediator production can be reproducibly and repeatedly stimulated by administration of an oxidant, tert-butyl-hydroperoxide (t-bu-OOH). The predominant physiologic effect of this stimulation in the isolated perfused rabbit lung is pulmonary hypertension, which is related to the production of thromboxane.²,³ We have used the reproducibility of this phenomenon to study the mechanism of thromboxane action on the pulmonary vasculature by using drugs that affect mediator production or vascular reactivity.⁴ In the present study we use a similar protocol to assess the effects of inhalation anesthetic agents on the same processes. In order to test the hypothesis that thromboxane-mediated pulmonary vasocostriction is related to anesthetic potency, we measured changes in the pulmonary vasopressor response to t-bu-OOH before and after administration of various doses of three different anesthetic agents of widely differing potencies: halothane (MAC = 0.76%), cyclopropane (MAC = 9.2%), and nitrous oxide (MAC = 105%). We believe that the major source of arachidonic acid metabolites in our preparation is the pulmonary vascular endothelium, which has been shown to produce a significant quantity of these substances.⁵,⁶ We also measured effluent perfusate concentration of thromboxane B2, the stable metabolite of thromboxane A2, and of 6-keto-PGF1α, the stable metabolite of PGF2α, after administration of t-bu-OOH with and without 2% inspired halothane. In addition, we examined the effect of indomethacin, a cyclooxygenase inhibitor, on t-bu-OOH-induced pulmonary vasocostriction before and after concurrent administration of cyclopropane at a dose of 2 MAC.

Methods

THE PREPARATION

We carried out our experiments using the isolated, perfused rabbit lung preparation that has been described
We used male New Zealand white rabbits weighing approximately 2 kg, which were fed with commercially available chow (Southern States) and allowed water ad libitum. On the day of the experiment, the animals were first given heparin, 1,000 U · kg⁻¹ by marginal ear vein, and then anesthetized with pentobarbital sodium (25 mg · kg⁻¹). A small incision was made in the left lateral chest wall, and the rabbits then were killed by rapid withdrawal of blood through a needle placed in the left ventricle. The sternum was split and the chest opened widely. A tracheostomy was performed, and the main pulmonary artery and left atrium were cannulated and secured with umbilical tapes. The ligature around the pulmonary artery cannula also included the aorta, preventing loss of perfusate into the systemic circulation and effectively isolating the pulmonary circulation. The opened chest was covered with moist gauze and plastic wrap to conserve heat. The lungs then were ventilated with a commercially prepared compressed gas mixture (Puritan-Bennett Corporation, Lenexa, Kansas) of 21% O₂/5% CO₂/balance N₂ (which will be referred to as air/CO₂) with a tidal volume of 10 ml · kg⁻¹ at 20 breaths/min using a Harvard small animal ventilator and were perfused with Krebs-Henseleit buffer at a rate of 60 ml · min⁻¹ using a Sarns roller pump without recirculation. The temperature of the perfusate was maintained between 36 and 38°C by a heat exchanger (Precision Scientific) and water bath. Ten to 15 min were allowed for the preparation to stabilize with respect to pulmonary artery pressure (Ppa), airway pressure (Paw), and perfusate temperature. T-bu-OOH (Sigma Chemical Company, St. Louis, Missouri) was introduced into the inflowing tube by a Sage infusion pump over 1 min at a rate calculated to give a final perfusate concentration of 200 µM. Ppa and Paw were measured with Gould–Statham P23Db transducers and recorded by a Grass® model 5 polygraph.

**Dose–Response Curves with Anesthetic Agents**

After the preparation had stabilized, t-bu-OOH was infused as described above once and, after the Ppa had returned to baseline (approximately 10–15 min), a second time. We have found that the first administration of t-bu-OOH causes a submaximal pressor response that is associated with the washout of sequestered blood from the lung. After the first dose of t-bu-OOH, the magnitude of the pressor response was reproducible (see below). After the second t-bu-OOH administration, the lungs were ventilated with inhalation anesthetic agents at various multiples or fractions of MAC while maintaining 1.05 and 1.20 for all experiments, except those using the highest dose of nitrous oxide, in which the F₁O₂ was 0.10. Mixtures of cyclopropane (C₃H₆) and nitrous oxide (N₂O) were prepared by passing appropriate flows of anesthetic gas, oxygen, and carbon dioxide through calibrated rotameters into a 10-l reservoir bag. The outlet of the reservoir bag was attached to the inspiratory port of the ventilator. The halothane (H) mixtures were prepared by placing a Fluotec Mark II vaporizer in the inspiratory limb of the ventilator circuit, so that halothane vapor was mixed with the air/CO₂ gas mixture. Since the MAC values of these agents for rabbits are not well defined,⁶,¹⁰ we used the MAC values for humans to compare the effects of each agent. Because the relationship between the MAC values for different agents is essentially constant,¹¹ the use of human MAC values seemed reasonable. T-bu-OOH was infused for 1 min at each dose of anesthetic while Ppa was recorded. For H (N = 5) we used doses of 0.25, 0.5, 1, and 2 MAC; for C₃H₆ (N = 5), 0.5, 1, 2, and 3 MAC; and for N₂O (N = 5), 0.25, 0.5, and 0.9 MAC.

Data were normalized by dividing peak Ppa–baseline Ppa (ΔPpa) at each dose by dPpa at 1 MAC. Because we were unable to use 1 MAC of N₂O, we normalized these data to 0.9 MAC. We elected to analyze normalized data because the variability of absolute dPpa from preparation to preparation could thereby be eliminated.

In order to rule out time-dependent changes incurred by t-bu-OOH itself, additional experiments (n = 5) were performed in which t-bu-OOH was infused five consec-
utive times over approximately 45 min without concurrent administration of anesthetic agent. This length of time was similar to the duration of each anesthetic experiment. The goal of this group of experiments was to determine if successive infusions of oxidant produced incremental increases in the vasopressor response.

The normalized ΔPpa's at each MAC level were compared using one-way ANOVA. If the F-ratio was significant (P < 0.05), the mean normalized ΔPpa's were compared with each other using the Bonferroni t procedure (also known as Dunn's multiple comparison test). P ≤ 0.01 was considered significant. Linear-regression analysis was used to describe both the relationship between normalized dPpa and dose of anesthetic and the relationship between dPpa and t-bu-OOH infusion number in preparations not exposed to anesthetic agent.

**Experiments with Measurements of Mediators (n = 5)**

These experiments were performed in the same manner as the dose-response experiments described above, except that only 2% halothane was used. Duplicate perfusate samples were withdrawn from the left atrium before administration of t-bu-OOH and at 30, 60, and 90 s after administration had begun. Additional samples were taken after the pressor response had subsided. After anesthetic was administered, samples were withdrawn before and after administration of t-bu-OOH as before.

Samples of effluent perfusate were buffered with 50 μl of 4-(2-hydroxyethyl)-1-piperazine)-ethane sulfonic acid (HEPES) and stored at −20° C. TbxB2 and 6-keto-PGF1α were measured by specific radioimmunoassay (RIA) using previously described methods and antisera. This RIA is sensitive to 20 pg·ml⁻¹ and employs dextran-coated charcoal as the separation technique. No organic extraction is required. Cross-reactivity of all rabbit antisera was evaluated with the following heterologous ligands: TbxB2, PGF2α, PGE2, and PGD1α. Antiserum cross-reactivity was less than 1% with all heterologous ligands, except for the 6-keto-PGF1α antisera, which showed 4.5% cross-reactivity with PGE1 and 2.3% with PGE2.

The values for ΔPpa, TbxB2, and the ratio TbxB2/6-keto-PGF1α before and during anesthetic administration were compared before and during anesthetic administration using the paired t test. Regression analysis was used to determine the relationship between dPpa and the ratio TbxB2/6-keto-PGF1α.

**Inhibitor Experiments (n = 5)**

The isolated lung was prepared as described above. After perfusing the lungs for approximately 10–15 min to allow for stabilization, t-bu-OOH was infused for 1 min at a concentration of 200 μM while the lungs were ventilated with the air/CO2 gas mixture. Following the initial t-bu-OOH infusion, the lungs were ventilated with a mixture of O2, CO2, and C2H6 at a concentration of 2 MAC. As in the dose–response experiments, FCO2 was maintained at 0.05 at all times. After 3–5 min of ventilation with anesthetic agent, t-bu-OOH again was administered.

The perfusate then was changed to Krebs–Henseleit buffer containing indomethacin (Sigma Chemical Company, St. Louis, Missouri) at a concentration of 5 μg·ml⁻¹ while continuing ventilation with anesthetic agent. T-bu-OOH was again administered. When Ppa returned to baseline, the anesthetic agent was washed out with the air/CO2 gas mixture for 3–5 min while continuing perfusion with the indomethacin-containing perfusate. T-bu-OOH then was infused a fourth time.

Absolute values for peak Ppa response to t-bu-OOH before and during administration of anesthetic agent and before and during perfusion with indomethacin were compared using ANOVA. If the F-ratio was significant (P < 0.05), we found the honestly significant difference (HSD)¹² to determine if the differences among the mean pressor responses were statistically significant. P < 0.025 was considered significant.

**Results**

**Effect of Anesthetic Agents on the Vasopressor Response to t-bu-OOH**

The pulmonary vascular response to t-bu-OOH in the presence of anesthetic agent is shown in figure 2, which is a reproduction of the record of a single experiment using N2O as the anesthetic agent. Ppa is incrementally increased with increasing inspired concentration of anesthetic agent. Paw does not change with t-bu-OOH administration. In the N2O experiments, there was no effect of FCO2 on baseline Ppa, even when FCO2 = 0.10. Figure 3A is a plot of log (MAC) versus mean normalized ΔPpa at each dose of anesthetic for all experimental conditions. Using one-way ANOVA we found that inspired concentration of anesthetic agent had a significant effect on the pressor response for all three agents (for H and C2H4, P < 0.001; and for N2O, P = 0.002). The Bonferroni t procedure also reveals a significant difference (P ≤ 0.01) between the normalized ΔPpa at 0.9 MAC (100%) and the control normalized ΔPpa (99 ± 35%) for N2O, between the normalized ΔPpa at 3 MAC (190 ± 65%) and the normalized ΔPpa’s at 1 MAC (100%), 0.5 MAC (89 ± 38%), and control (66 ± 61%) for C2H4, and, for halothane, between the normalized ΔPpa at 2 MAC (120 ± 21%) and the normalized ΔPpa’s at 0.5 MAC (93 ± 17%), 0.25 MAC (73 ± 16%), and control (44 ± 8%).
between 1 MAC (100%) and 0.25 MAC and control, and between 0.25 MAC and control (all values expressed as mean ± SD). The correlation coefficient for the N₂O group is significant at \( P = 0.001 \); for the C₃H₆ group, at \( P = 0.002 \); and for the H group, at \( P < 0.001 \).

Figure 3B is the plot of t-bu-OOH infusion number \( \Delta \text{Ppa} \) for the experiments in which the lungs were challenged repeatedly with t-bu-OOH but not exposed to anesthetic agent. We were unable to demonstrate a statistically significant effect of infusion number (time) on \( \Delta \text{Ppa} \) after t-bu-OOH administration. Linear regression analysis of the relationship between infusion number and \( \Delta \text{Ppa} \) gave a correlation coefficient of 0.18 (\( P = 0.45 \)), which was also not statistically significant.

**Mediator Production Before and After 2% Halothane**

Pulmonary artery pressure, concentration of TxB₂, the ratio, and the sum of TxB₂ and 6-keto-PGF₁α before, during, and after administration of t-bu-OOH with and without 2% H are shown in figure 4. The pressor response, the concentration of TxB₂, and the ratio of TxB₂ to 6-keto-PGF₁α were markedly increased after t-bu-OOH challenge during air ventilation. In the presence of halothane, Ppa, TxB₂ concentration, and the ratio of TxB₂ to 6-keto-PGF₁α increased further, and the sum of the concentrations of the two mediators also was increased. Differences in \( \Delta \text{Ppa} \), TxB₂, and TxB₂/6keto-PGF₁α between ventilation with air and ventilation with 2% halothane were all statistically significant (\( P < 0.001 \)). The linear relationship between pulmonary artery pressure and the ratio TxB₂/6keto-PGF₁α during administration of halothane is shown in figure 5. There is a highly significant correlation between Ppa and the ratio.

**The Effect of Cyclooxygenase Inhibition on the Pulmonary Vasopressor Response to t-bu-OOH, With and Without Anesthetic Agent**

Figure 6 is the tracing obtained during an experiment using indomethacin-containing perfusate and C₃H₆ at 2

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**Fig. 2.** Representative tracing of anesthetic experiment, this one using N₂O. Time and pressure scales as shown. Note that small changes in airway pressure do not affect Ppa. Also note the incremental rise in \( \Delta \text{Ppa} \) with increasing dose of N₂O.

**Fig. 3A.** Dose–response curve, log (MAC) versus \( \Delta \text{Ppa} / \Delta \text{Ppa}_1 \text{M} \). Regression equations are as follows: for N₂O, \( Y = 98 + 80x \); for C₃H₆, \( Y = 115 + 126x \); and for halothane, \( Y = 104 + 44x \). A. Plot of t-bu-OOH infusion number versus \( \Delta \text{Ppa} \) for the group of animals that received no anesthetic agent. There is no significant correlation between t-bu-OOH infusion number and pulmonary vasopressor response. We interpret this to mean that the pressor response to t-bu-OOH is fairly constant over time in our model. Thus, the increased pressor response over time with anesthetic agent, seen in figure 3A, can be interpreted as the effect of anesthetic agent and not the effect of t-bu-OOH.

**Fig. 3B.**
Discussion

Although the mechanisms of action of the volatile anesthetic agents remain controversial, it has been hypothesized that these drugs produce general anesthesia by effects on the plasma membrane.\textsuperscript{11,13} Various inhalational anesthetics have been shown to protect erythrocytes from lysis in hypotonic solutions,\textsuperscript{14} to expand erythrocyte membranes\textsuperscript{15} and nerve lipid monolayers,\textsuperscript{11} and to inhibit depolarization of electrically excitable membranes without altering resting membrane potential.\textsuperscript{11}

Arachidonic acid is a ubiquitous component of cell membranes throughout the body. Arachidonic acid metabolites play an important role in the regulation of platelet adhesiveness, in the generation of the local inflammatory response to injury, and in the regulation of peripheral and pulmonary vasomotor tone and vascular permeability. Figure 8 depicts a simplified schema of arachidonic acid metabolism. Arachidonic acid is a C-20 polyunsaturated essential fatty acid that is found primarily in esterified form in the phospholipid fraction of plasma membranes.\textsuperscript{16} It is deesterified by the action of phospholipase A\textsubscript{2}, a Ca\textsuperscript{2+}-dependent microsomal bound enzyme.\textsuperscript{16} This initial step has been found to require stimulation to produce free arachidonic acid.\textsuperscript{17} This stimulation can be mechanical (e.g., vibration)\textsuperscript{16} or chemical, in the form of certain vasoactive substances, such as bradykinin\textsuperscript{16,18} or oxidants such as t-bu-OOH.\textsuperscript{19} Free arachidonic acid is rapidly converted to the endoperoxide

FIG. 4. In this figure we have plotted the pulmonary artery presssure, TxB\textsubscript{2} concentration in the effluent perfusate, the ratio TxB\textsubscript{2}/6-Keto-PGF\textsubscript{1α} in the effluent perfusate, and the sum of the concentration of these two mediators. Measurements were made under control conditions, during infusion of t-bu-OOH alone and during infusion of the peroxide in the presence of 2% halothane. Note the marked accentuation of vasoconstriction and thromboxane production in the presence of 2% halothane. There is also increased production of both mediators during administration of t-bu-OOH during halothane exposure.

MAC. The vasoconstrictor response to t-bu-OOH both with and without anesthetic agent is almost completely eliminated after perfusion of the lungs with indomethacin.

The response of the five preparations are shown in figure 7. Absolute baseline and peak Ppa's are shown. Two-way ANOVA reveals a statistically significant effect of either indomethacin or anesthetic agent on the vasopressor response to t-bu-OOH ($P = 0.002$). For multiple comparisons, we have calculated the Honestly Significant Difference at $P = 0.025$, which is depicted in the figure by a bar. The figure shows that the peak Ppa after t-bu-OOH is not different from the baseline Ppa before C\textsubscript{3}H\textsubscript{6}. Administration of 2 MAC C\textsubscript{3}H\textsubscript{6} causes the peak Ppa after t-bu-OOH challenge to be significantly greater than both the baseline Ppa and the peak Ppa without anesthetic. After the lungs are perfused with indomethacin, there is no statistically significant difference in either peak or baseline Ppa's before or after administration of C\textsubscript{3}H\textsubscript{6}.

FIG. 5. In this figure, pulmonary artery pressure is plotted against TxB\textsubscript{2}/6-Keto-PGF\textsubscript{1α} x 10\textsuperscript{3}. The slope and intercept of the relationship for the halothane experiments are statistically significantly different from the previous reported experiments that were carried out without halothane.\textsuperscript{2} This may represent an attenuation of the contractile response caused by halothane or attainment of maximum contractile response with high mediator levels.
PGG₂ by cyclooxygenase or to 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE) by the action of lipooxygenase.¹⁷ PGG₂ is converted to the more stable endoperoxide PGGH₂ by prostaglandin peroxidase.²⁰ PGGH₂ is, in turn, converted to thromboxane A₂ by the action of thromboxane synthetase or to prostacyclin by the action of prostacyclin synthetase.¹⁷ 5-HPETE is converted into a series of substances called leukotrienes, which, apparently as a group, have recently been shown to be slow-reacting substances of anaphylaxis.¹⁷,²⁰⁻²² Cyclooxygenase activity is increased in the presence of endoperoxides, thus forming a positive feedback loop.²³ Cyclooxygenase activity also has been shown to be increased in the presence of lipid peroxides and in the presence of oxygen-derived free radicals, which react with polyunsaturated lipids to form lipid peroxides.²³

In the rabbit pulmonary circulation PGI₂ and PGE₂ have been shown to be vasodilators.²⁴,²⁵ and thromboxane A₂, PGF₂α, and leukotrienes C₄ and D₄, vasocostricators.²,³,²⁴,²⁶ We² have demonstrated that the pulmonary vasoconstriction that occurs after t-bu-OH infusion into isolated rabbit lungs is mediated by markedly increased production of thromboxane A₂. Vasodilator metabolites are also produced in response to t-bu-OH infusion, but the relative production of the vasoconstrictor metabolites is greater, probably because thromboxane synthetase has a higher level of maximal activity than prostacyclin synthetase.³,²⁷⁻³⁰ The thromboxane-induced pulmonary vascular contractile response also has been shown to be calcium dependent in that it is inhibited by verapamil and by trifluoperazine, a phenothiazine inhibitor of calmodulin, and it does not occur in Ca²⁺-free perfusate.³ The results of our experiments suggest that inhalational anesthetic agents augment the contractile response to t-bu-OH in the rabbit pulmonary circulation and that this augmentation of contractile response is produced by augmented of release of thromboxane A₂ into the pulmonary circulation.

We demonstrated first that anesthetic agents of widely different potencies administered at equipotent doses have similar effects on the pulmonary vascular contractile response to t-bu-OH. These findings suggest that the increased pulmonary vasoactivity in response to t-bu-OH is dependent on the volume of anesthetic present.
crementally increased pulmonary vasoactivity seen with anesthetic agents. Theoretically, equipotent doses of anesthetic agent should, at equilibrium, deliver equal volumes of anesthetic to the cell membrane. It is thus reasonable to expect similarity of effect over the range of anesthetic potency if anesthetic agents are administered in equipotent doses.

We next demonstrated that ventilation of the lungs with 2% halothane caused a significant augmentation of release of thromboxane B_2 into the pulmonary circulation, above those levels obtained with ventilation with air/CO_2 alone. Although levels of 6-keto-PGF_1 alpha also were found to be increased after halothane exposure over those obtained before halothane exposure, the ratio of TXB_2 to 6-keto-PGF_1 alpha was found to be increased significantly after halothane exposure. These two sets of results suggest in turn that the mechanism by which inhalational anesthetic agents augment the rabbit pulmonary vasopressor response to t-bu-OOH is to cause increased release of thromboxane A_2 into the pulmonary circulation and that, as seen in earlier experiments without anesthetic agents, the pulmonary vasopressor response is related to thromboxane A_2 concentration.

In the final series of experiments, in which indomethacin, a cyclooxygenase inhibitor, was infused through the lungs during ventilation with both air/CO_2 and cyclopropane, we gave further support to the hypothesis that the augmented pressor response is due to thromboxane production. We demonstrated that indomethacin attenuates the pulmonary vascular contractile response to t-

![Diagram of the metabolic pathways involving arachidonic acid metabolism.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931408/)

**Fig. 8.** Schema of arachidonic acid metabolism. Protacyn synthetase has slightly higher affinity for PGH_2 than thromboxane synthetase, but thromboxane synthetase has a higher maximal activity. In our model, PGH_2 is produced in greater quantities with low t-bu-OOH doses; but with high t-bu-OOH doses, the ratio is reversed. All steps occur within the cell membrane. Unless the cell membrane system is perturbed in some way (disruption, alteration of membrane conformation), there is very little cyclooxygenase activity, suggesting strict compartmentalization of the system. Oxidants and lipid peroxides stimulate both phospholipase A_2 and cyclooxygenase activities.
bu-OOH with and without cyclopropane. The ΔPpa during indomethacin perfusion was slightly greater with anesthetic agent than without, but the difference was not statistically significant, nor was the response to t-bu-OOH significantly greater than baseline Ppa. The attenuation of the vasopressor response during indomethacin perfusion both with and without anesthetic agents suggests that the pulmonary hypertension caused by t-bu-OOH is produced by the same mechanism with air or with anesthetic agent ventilation.

The augmentation of the pulmonary vasopressor response to t-bu-OOH by anesthetic agents is thus apparently due not to a separate mechanism, but rather to further augmentation of thromboxane A2 production, likely induced by the anesthetic agents themselves. The ratio TxB2/6-keto-PGF1α shows good correlation with Ppa in the presence of anesthetic agent; inhibition of thromboxane production attenuates the pressor response. Thus, the effect of anesthetic agents seems directly related to the appearance of larger quantities of thromboxane in the pulmonary circulation than are present without anesthetic agent. The inhalational anesthetic agents may act specifically by making more arachidonic acid available to cyclooxygenase. This mechanism may occur because of the ability of anesthetic agents to alter membrane conformation by displacing phospholipids from more hydrophobic regions to less hydrophobic regions, making the phospholipids more available for hydrolysis. We have ruled out the possibility that anesthetic agents themselves directly increase either phospholipase A2 or cyclooxygenase activity because the anesthetic agents alone do not cause an increase in Ppa.

What are the possible clinical implications of this series of experiments? Anesthetic agents augment production of thromboxane when arachidonic acid metabolism is stimulated by oxidant challenge. Oxidant-induced lung injury may occur in the adult respiratory distress syndrome or with pulmonary oxygen toxicity with concomitantly increased production of vasoactive arachidonate-derived mediators. Anesthetic agents may potentiate production of arachidonate mediators in the face of ongoing injury, may cause increased pulmonary hypertension, and may enhance edema formation.

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