to improper equipment or inappropriate application in a patient with established respiratory failure are deleterious at the very least. The variation in performance of different CPAP systems that supposedly provide the same level of support is striking. A rose may always be a rose, but the same cannot be said for CPAP!

If CPAP, correctly used, has the benefits alleged, might it not also be useful in "prophylaxis" against ARDS? In this regard, decreased inspiratory work of breathing and maintenance of lung volume could reasonably be expected to ameliorate the severity of subsequent respiratory failure. Many articles have addressed this issue but no concensus view has emerged. The most recent study[4] reported no efficacy in this regard. However, only one level of expiratory pressure was employed (8 cmH_2O), and the patients were already intubated and mechanically ventilated. Its clinical relevance, thus, is open to question.

Katz and Marks are to be congratulated for a beautifully designed study with results that are both clearly defined and clinically useful.

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The Fascination of the Hypoxic Lung

IN THEIR CONTINUING ANALYSIS of hypoxic pulmonary vasoconstriction (HPV), Chen *et al.*, in this issue of ANESTHESIOLOGY[1] again ask the question whether the pulmonary vasoconstrictor response is maximal with the initial hypoxic stimulus, or whether repeated hypoxic challenges are required to elicit a maximal response. Put another way, do repeated bouts of hypoxia potentiate the vasoconstrictor response? This question has been asked repeatedly by various investigators, and, in fact, a progressive increase in HPV with repeated hypoxic stimuli has been reported.[2] Indeed, Chen *et al.*[3] found just such a potentiation only 2 years ago. However, in their latest investigation,[1] Chen *et al.* find that the initial pulmonary vasoconstrictor response to hypoxia is no less than the subsequent responses and therefore conclude that the initial response is in fact maximal, *i.e.*, that potentiation with repeated bouts of hypoxia is not the "usual physiological circumstance." They now attribute previous reports of potentiation in open chest preparations to some influence of surgical trauma.

Why is all this important? To begin with, ever since von Euler and Liljestrand reported[4] nearly 40 years ago that the pulmonary arterial pressure of the cat was raised by airway hypoxia, a succession of investigators have been trying to elucidate the physiologic mechanisms involved. Fundamental to an understanding of HPV is an accurate description of the phenomenon. This includes knowledge of whether each hypoxic pressor response is an independent event or whether in a series of responses, initial ones modify subsequent ones. The latter does not seem to be the case, according to this latest report by Chen *et al.*[1]

Our understanding of HPV also benefits from knowledge of factors that modify the basic vasoconstrictor response. Immediately, the products of arachidonic acid metabolism[5] come to mind, although this would not have been our first thought 15 years ago. Today we know that metabolism of arachidonic acid by way of the cyclooxygenase pathway generates prostacyclin, a potent pulmonary vasodilator, and thromboxane, a potent pulmonary vasoconstrictor. Alternatively, metabolism by way of the lipoxygenase pathway generates leukotriene C_4, which is another pulmonary vasoconstrictor. Arachidonic acid is derived from normal cell membrane lipids, and its metabolism is triggered by a wide variety of stimuli. In fact, HPV appears to be one such stimulus, leading to the production of a vasodilator, probably prostacyclin, since in-

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hibition of cyclooxygenase, *e.g.*, with indomethacin, augments the pulmonary pressor response to hypoxia.[6]

Tissue trauma also stimulates endogenous arachidonic acid metabolism,[7] leading to the production of significant quantities of vasodilator metabolites. This phenomenon is well known to those investigators studying pulmonary vascular reactivity in the isolated perfused (rat) lung. A similar situation is created by surgical manipulation of the lung following thoracotomy. This is the "surgical trauma" alluded to by Chen *et al.*,[1] and which results in hyporeactivity of the pulmonary vascular bed initially, with return toward more normal reactivity with time.[8] This gradual recovery of reactivity would resemble potentiation of an initially poor response to hypoxia, either in the lung lobe preparation or in the isolated perfused lung.

The surgical trauma invoked by Chen *et al.* cannot explain the apparent potentiation of HPV reported in the intact, closed chest dog subjected only to catheterization.[2] Some other stimulus to arachidonic acid metabolism must be sought. This alternative stimulus could be endotoxin. It has been demonstrated[9] that minute amounts of endotoxin will abolish HPV and that the effect of endotoxin can be prevented by the inhibition of cyclooxygenase with meclofenamate. This implies that endotoxin stimulates the production of dilator prostaglandins that then oppose HPV. Small amounts of endotoxin could be introduced into the experimental animal during nonsterile catheterization. This would be a random occurrence and probably explains why in some animals HPV is initially weak with subsequent recovery, *i.e.*, "potentiation," while in other animals HPV is strong from the outset and remains stable, *i.e.*, shows no potentiation.[10]

This iatrogenic phenomenon should be distinguished from true individual variability in HPV. As with most biologic phenomena, so with HPV there are hyperresponders and hyporesponders.[11] Such variability correlates with the degree of muscularization of the pulmonary arterial bed[12] and appears to be determined genetically.[11] This individual variability is evident in the data of Chen *et al.*,[1] where, in the per cent diversion of blood flow away from the hypoxic lung, the standard error is at least 10% of the mean.

In terms of human medicine, what is the significance of these observations? Teleologically, the purpose of HPV is to match local perfusion to local ventilation throughout the lung.[13] More specifically, HPV diverts blood flow away from hypoxic regions of the lung to more well-ventilated regions. As pointed out by the Marshalls,[14] as well as by Benumof *et al.*,[15] the completeness of this diversion is inversely proportional to the size of the hypoxic lung segment. The effect of this diversion is to reduce venous admixture and thereby help preserve arterial blood oxygenation.

It follows that any intervention that impairs HPV will increase the perfusion of hypoxic lung segments, and this would lead to a fall in arterial oxygen tension with hypoxemia. During thoracic surgery, to facilitate exposure, ventilation frequently is limited to one lung while the other lung is collapsed. Obviously the nonventilated lung will be hypoxic, and we would hope that HPV would minimize perfusion of that lung. However, manipulation of that lung could very well stimulate arachidonic acid metabolism[7] with the generation of dilator metabolites that would prevent HPV. Maintaining the desired level of oxygenation of the patient then would be more difficult.

We may anticipate that the excellent group of investigators at the University of Pennsylvania headed by the Marshalls will continue their valuable and provocative studies of the pulmonary circulation.

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Cardiac Alpha Receptors and Arrhythmias

THERE IS NO LONGER any doubt that there are alpha-adrenergic receptors in the heart, but we are far from certain about their function. A number of recent findings point to a connection with cardiac arrhythmias developing under a variety of conditions. The report by Maze, *et al.*[1] in this issue concludes that the alpha-adrenergic receptor is to blame for halothane–epinephrine arrhythmias. It is based on the antiarrhythmic effects of droperidol, a rather nonspecific drug acting at many receptors including the alpha-1 receptor, and of doxazosin, a relatively specific alpha-1 receptor blocker, and adds to a previous report by the same group, which used prazosin as a specific blocker. Others have demonstrated a role for this receptor, for example, in arrhythmias seen in the infarction–reperfusion model.[2] These results are exciting, but our enthusiasm at having found an "arrhythmogenic receptor" must be tempered by our knowledge that many types of drugs, among which we can count the antihistaminics, the beta-receptor blockers, and of course the antiarrhythmics, are also highly effective in preventing epinephrine arrhythmias in sensitized hearts.

Data on the antiarrhythmic effects of alpha-blockers first were obtained in 1948 by Moe *et al.*, who showed dibenamine and some of its derivatives to be effective in sensitized dogs[3] and who first showed that blood pressure played a role. Much work has been done since, especially as concerns the role of heart rate and the blood pressure in causing the arrhythmias, their mechanism, and the localization of their origin. Too little attention has been paid to the fact that epinephrine-induced arrhythmias differ in detail not only between sensitized *versus* nonsensitized preparations (in which vagotomy blocks arrhythmias and fibrillation never occurs), but also as a function of the manner in which sensitization is studied. The early work from my own laboratory used cyclopropane as the anesthetic agent primarily because it caused "pure" sensitization with no chance of cardiac depression associated with chloroform, its close congeners, or halothane.[4] The animals were routinely induced with thiopental—several years passed before we found the difference this made. The data were clear: cyclopropane–epinephrine arrhythmias due to low doses of epinephrine were due to reentry rather than increased automaticity and were completely dependent on blood pressure. Mechanical changes in blood pressure changed the "minimal arrhythmia," defined by us as a constantly coupled bigeminy, to either sinus rhythm or multifocal tachycardia but never to fibrillation. The nonfatal arrhythmias could be abolished by stimulation of the vagus nerve. Several series of experiments were required to show that this effect of the vagus was not totally due to its effect on sinus rate.[5,6] Our study with halothane[6] was an attempt to summarize the observations of many years, as well as to confirm that halothane sensitization did not materially differ from that caused by cyclopropane. Further, we were able to confirm by direct recordings that the site of origin of the abnormal beat of the typical bigeminal rhythm was the intraventricular septum, a conclusion reached less directly in cyclopropane-anesthetized dogs.[7]

The properties of the arrhythmia change considerably when thiopental induction is omitted from the protocol. Larger doses of epinephrine are now required to cause any given severity of ventricular arrhythmia.[8,9] Particularly noteworthy is the observation by Atlee and Malkinson[9] that atrial arrhythmias, regularly observed to precede ventricular arrhythmias as graded doses of epinephrine are administered, are not potentiated by thiopental and therefore can no longer be observed with regularity. Bigeminal rhythm may not occur at all[8] or occurs less regularly.[9] The exquisite sensitivity to the level of systolic blood pressure can no longer be observed.[1] In short, the halothane-anesthetized animal behaves quite differently from the thiopental-induced preparation.

Nothing is known about the mechanism of this action of thiopental. The site of action corresponds to the site implicated in the origin of the bigeminy. As little as 200 ng to 200 μg injected into the circumflex coronary artery

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