The pulmonary circulation responds to acute hypoxia with increases in pulmonary artery pressure and vascular resistance. This acute hypoxic pressor response (AHPR) is a unique physiologic feature distinguishing the pulmonary from the systemic circulation which dilates in response to hypoxia. Since Von Euler and Liljestrand described the phenomenon of acute hypoxic pulmonary vasoconstriction within the feline pulmonary circulation, it has fascinated vascular physiologists and stimulated a substantial number of studies aimed at defining the mechanism of this response.

Airway hypoxia is a consequence of many lung diseases. In addition, abnormalities of the pulmonary vasculature are prominent features of the pathophysiology of acute and chronic respiratory failure. In this context, the AHPR occupies a unique position at the interface between the normal and abnormal pulmonary circulation in transition from health to disease.

We will review the major features of the AHPR, and summarize the important aspects of investigations aimed at defining the mechanism of this response. In addition, we will discuss the known factors which modify the response in the clinical setting. We will place special emphasis on information obtained within the last five years, especially recent findings concerning the vascular endothelium.

**Physiologic Characteristics of the Response**

The AHPR has a long evolutionary history. It is present in fish, amphibia, reptiles, birds, and mammals. Figure 1 illustrates the major features of the response shared by all species in which it has been studied. The response begins within seconds of ventilation with hypoxic gas, reaches a maximum within minutes, and can be sustained for hours. Graded decreases in PAO2 produce similar increases in pulmonary vascular resistance with a threshold for vasoconstriction at PAO2 of 60 mm Hg. In both human subjects and animal preparations, alveolar hypoxia increases pulmonary artery pressure, does not consistently change left atrial pressure and heart rate, but has a variable effect on cardiac output. Although alveolar, or airway, hypoxia alone is sufficient to stimulate hypoxic vasoconstriction, an additional contribution to the initiation of the response comes from the PO2 of mixed venous blood.

**Physiologic Significance**

The AHPR is an important adaptive mechanism that diverts blood flow away from hypoxic alveoli. This shift in blood flow from poorly ventilated to better ventilated alveoli diverts flow away from areas of alveolar atelectasis to areas of normal ventilation.

**Alveolar Hypoxia Causes Pulmonary Vasoconstriction**

Figure 1. Characteristics of acute hypoxic pulmonary vasoconstriction. Lungs were isolated from rats, ventilated with 21 percent O2, 5 percent CO2, balance N2, and perfused with whole blood. When the lungs were ventilated with 10 percent O2, 5 percent CO2, balance N2, mean pulmonary arterial pressure (Ppa) promptly increased, returning to baseline upon ventilation with air.
ventilated areas improves the matching of ventilation and perfusion which minimizes arterial hypoxemia.\textsuperscript{11} The degree of flow diversion away from the hypoxic site with a localized pathologic process depends on the size of the hypoxic segment; the smaller the hypoxic region, the greater the percentage diversion of blood flow away from that segment.\textsuperscript{12}

Flow diversion becomes less effective with widespread hypoxia,\textsuperscript{13} but still serves the purpose of increasing perfusion of the apices of the lungs via an increase in pulmonary arterial pressure. The apices of the lungs are less well perfused than the bases with a lower pulmonary artery pressure due to the effect of gravity. Increased apical perfusion enhances recruitment of alveolar capillaries which can participate in effective gas exchange,\textsuperscript{13,14} thus improving arterial oxygenation. This effect is seen in residents at high altitude who are subject to global alveolar hypoxia and show a more uniform distribution of perfusion compared to residents at sea level.\textsuperscript{15} This may convey an advantage in living in such a rarified environment by providing a larger effective area for gas exchange.

Does the AHPR function as an adaptive mechanism in the normal lung? Maldistribution of ventilation/perfusion is usually considered an important indicator of lung disease, but subtle abnormalities of the distribution of ventilation to perfusion with each breath occur in the normal lung.\textsuperscript{16} Under these circumstances, the AHPR could play an important role in the maintenance of an optimal balance of ventilation to perfusion on a breath-by-breath basis. Evidence supporting this idea emerges from studies of vasodilator drugs which blunt the response. In normal subjects, as well as in patients with lung disease and in animal models of alveolar hypoxia, vasodilator drugs inhibit hypoxic vasoconstriction, produce a widening of the A-a gradient, and a fall of PaO\textsubscript{2},\textsuperscript{17,20} suggesting that this adaptive mechanism is present in the normal, as well as the abnormal lung.

The physiologic significance of the AHPR is further illustrated by a comparison of the response in animals with differences in collateral ventilation. Species with the least collateral ventilation, such as the cow and pig, are more likely to have the largest AHPR compared to species with well developed collateral ventilation, such as the dog and the sheep.\textsuperscript{21} Thus, it appears that a mechanism has evolved for the preservation of ventilation and perfusion matching in species which are susceptible to the development of alveolar hypoxia.

In the fetus, hypoxic pulmonary vasoconstriction serves to divert blood flow away from the unventilated alveoli, bypassing the lungs through the ductus arteriosus and foramen ovale. At birth, ventilation of alveoli with air leads to a substantial decrease in hypoxic vasoconstriction as normal gas exchange begins.\textsuperscript{22} The factors responsible for fetal hypoxic pulmonary vasoconstriction, and the alleviation of vasoconstriction at birth are an equally active field of investigation which is beyond the scope of this review.

**Anatomic Site**

It was initially assumed that the major locus of hypoxic vasoconstriction is located at the primary site of gas exchange, the alveoli. Angiographic visualization of the pulmonary vasculature during acute hypoxia demonstrates a decrease in caliber of small pulmonary arteries, but an increase in diameter of the larger proximal vessels, suggesting the small arteries as the major site for the AHPR and that the site of oxygen sensing is not exclusively located in the alveolar capillaries.\textsuperscript{23}

Kato and Staub\textsuperscript{24} provided histologic confirmation that the major site of hypoxic vasoconstriction is in the small muscular pulmonary arteries at the level of the terminal respiratory bronchioles using the technique of rapid freezing of hypoxic lung segments. Additional studies using this technique show that these same vessels are essentially surrounded by air-filled lung with oxygenated blood in the arterioles.\textsuperscript{25}

Thus, as illustrated in Figure 2, small pulmonary arteries are appropriately positioned to respond to changes in alveolar oxygen concentration.

In an elegant series of experiments employing the technique of micropuncture of subpleural vessels, Nagasaka et al\textsuperscript{26} determined the microvascular pressure profile in the feline lung during normoxia and hypoxia. These experiments confirm that the predominant site of hypoxic vasoconstriction lies in the small pulmonary arteries (30-50 μm), with the remaining increase in vascular resistance arising from the capillary bed and the venous system.

Although pulmonary veins constrict in response to

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{Location of small pulmonary arterioles in relation to alveoli. This section of rat lung demonstrates the close proximity of small pulmonary arterioles (A) to alveoli (ALV), alveolar ducts (AD), and terminal bronchioles (TB). Elastic tissue–von Gieson stain, original magnification ×420, bar = 50 μm. (From J Appl Physiol 1984, 56:398-96, with permission of the publisher.)}
\end{figure}

Aging is associated with a decrease in the magnitude of the AHPR in animal studies,\textsuperscript{30} along with a decrease in vasoconstriction in response to other pharmacologic stimuli.\textsuperscript{40} It is not known whether such findings extend to human subjects.

The degree and temporal pattern of exposure to hypoxia may also affect hypoxic vasoconstriction. Graded reductions of blood $P_{O_2}$ are associated with corresponding graded increases in pulmonary artery pressure in the isolated perfused lung down to $P_{O_2}$ values of 25-30 mm Hg. Below this point, vasodilator responses commence as $P_{O_2}$ is lowered further.\textsuperscript{44} Potentiation of the response after repeated intermittent hypoxic exposures has been observed by some investigators.\textsuperscript{42}

Female gender and sex steroid hormones are additional factors associated with an alteration in the magnitude of hypoxic vasoconstriction,\textsuperscript{45-47} which may be the result of hormonal alteration of components of the vascular wall.\textsuperscript{46} Sylvester et al\textsuperscript{41} reported that estrogen treatment attenuated the AHPR in juvenile female sheep. Prostacyclin (PGI$_2$) was implicated as the mediator of this altered reactivity since indomethacin administration abolished this effect and simultaneously inhibited the outflow of the stable metabolite of PGI$_2$, 6-keto PGF$_{1\alpha}$ from lungs of estrogen-treated animals. Data concerning alteration of the AHPR during pregnancy are conflicting; the response is diminished in the pregnant cat, rat, and dog,\textsuperscript{43,44,46} but increased in pregnant cattle susceptible to high-altitude disease.\textsuperscript{47} The recent demonstration of potentiation of the AHPR in the isolated perfused rat lung by treatment with a glucocorticoid\textsuperscript{40} lends support to speculation that hormonal modulation of the response may represent another important type of regulatory mechanism of pulmonary vascular reactivity. Neural influences also modify the APHR (see below).

**Mechanism**

Two main hypotheses underlie most investigations of the mechanism of the AHPR. The first is that the response is dependent on the release of a vasoactive mediator from some site within the lung. The opposing view states that acute hypoxia elicits vasoconstriction via a direct effect on pulmonary vascular smooth muscle without the involvement of a mediator.

**Mediator Hypothesis**

The mediator hypothesis is derived from work with isolated pulmonary artery segments in which the AHPR appeared to be dependent upon the presence of parenchyma attached to the vessels, since the response could not be elicited with isolated vessels alone.\textsuperscript{40} Data gathered in pursuit of this question occupied a central position in research involving the pulmonary circulation for many years.

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**Table 1—Factors Which Modify the Acute Hypoxic Pressor Response**

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<tr>
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<tbody>
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<td>Species</td>
<td>variable</td>
<td>29-31</td>
</tr>
<tr>
<td>Inter-individual</td>
<td>variable</td>
<td>32-33</td>
</tr>
<tr>
<td>Genetic</td>
<td>variable</td>
<td>34,35</td>
</tr>
<tr>
<td>pH</td>
<td>acidosis ↑; alkalosis ↓; or →</td>
<td>37,38</td>
</tr>
<tr>
<td>Age</td>
<td>↓</td>
<td>39</td>
</tr>
<tr>
<td>Severe hypoxia</td>
<td>↓</td>
<td>41</td>
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<td>(PaO$_2$&lt;25 mm Hg)</td>
<td></td>
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<td>↑</td>
<td>42</td>
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<td>↓ or ↑</td>
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<tr>
<td>Neural</td>
<td>↓</td>
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$\uparrow$, potentiation of the response; $\downarrow$, attenuation of the response; $\rightarrow$, no change in the response by factors listed.

It is not yet entirely clear whether these factors are independent or interrelated as to their mechanism of action. Although there is evidence that these factors influence the AHPR, it is still not clear how they mediate their influence. Some of these factors may influence the AHPR by modifying the sensitivity of the pulmonary vascular smooth muscle to the hypoxic stimulus, while others may modify the mechanism of vasoconstriction. For example, the presence of estrogen appears to alter the sensitivity of the pulmonary vascular smooth muscle to hypoxia, while the presence of dietary restriction may modify the mechanism of vasoconstriction.

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Table 2—Agents Investigated as Potential Mediators of the AHPR

<table>
<thead>
<tr>
<th>Agents no longer active candidates</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines</td>
<td>4, 11, 51, 53</td>
</tr>
<tr>
<td>Histamine</td>
<td>4, 11, 51</td>
</tr>
<tr>
<td>Serotonin</td>
<td>4, 11, 51</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>4, 11, 51</td>
</tr>
<tr>
<td>Neurotransmitters</td>
<td>53-59</td>
</tr>
<tr>
<td>Arachidonic acid metabolites</td>
<td>61-66</td>
</tr>
<tr>
<td>New candidates</td>
<td></td>
</tr>
<tr>
<td>Endothelial derived relaxing factor (EDRF)</td>
<td>69-72</td>
</tr>
<tr>
<td>Endothelin (EDCF)</td>
<td>73-75</td>
</tr>
</tbody>
</table>

The status of this field can be summarized very succinctly. Despite a lengthy list of candidates (Table 2), no single agent satisfies all the necessary requirements of a mediator. Fishman summarized the essential criteria for an ideal mediator as follows: 1) the agent or its precursors must exist within the lung; 2) the agent must be shown to be present in close proximity to its anatomic site of action; 3) an activation mechanism for release of the agent must be present within the lung; 4) the agent must simulate the AHPR when applied to the pulmonary vasculature under the appropriate conditions; and 5) inhibition or depletion of the agent should appropriately modify the AHPR in the intact lung or animal.

The candidates for mediator of acute hypoxic vasoconstriction included the catecholamines, histamine, serotonin, and the peptide, angiotensin II. Although none of these agents now qualifies as a mediator of the AHPR, we have learned a great deal about the pharmacologic regulation of pulmonary vascular reactivity from investigations involving these agents, notably, that the pulmonary vasculature, like its systemic counterpart, is responsive to a wide array of physical and chemical stimuli, and contains many different types of vascular receptor systems. Many questions still remain about the role of these agents in the regulation of pulmonary vascular reactivity in the normal and diseased lung.

The pulmonary vessels of many species are well endowed with autonomic nervous connections. The pulmonary vasculature has important links with the stellate ganglia, hypothalamus, and efferent connections with systemic chemoreceptors. Therefore, it was a logical step to speculate that neural input might mediate the AHPR. In support of this concept are studies demonstrating that alpha adrenergic antagonists and beta adrenergic agonists blunt the AHPR, while beta receptor antagonists augment the response. Nevertheless, the current view is that neural input does not have a primary role in the mechanism of the AHPR. Proof that sympathetic innervation is not essential for the AHPR is demonstrated by the following findings: 1) the response has been elicited in isolated perfused lungs in numerous studies; and 2) the response can still be observed in sympathectomized animals and after adrenergic transmitter depletion, although this has not been a universal finding.

The sympathetic nervous system does exert a modifying influence in the adult animal. The mediator released from sympathetic nerve endings, norepinephrine, has a biphasic tone-dependent effect. When pulmonary vascular resistance is low, the catecholamine has a vasoconstrictor effect, but when tone is elevated, norepinephrine produces a vasodilator response. In addition, systemic hypoxia, but not alveolar hypoxia alone, elicits a chemoreflexive stiffening or decrease in distensibility of the large pulmonary arteries with no change in pulmonary vascular resistance which is abolished by sympathectomy or vagotomy.

Prostaglandins attracted attention as potential mediators because of the appeal of the concept that a mediator might originate from the release of a substrate from the cell membrane. Arachidonic acid (AA), an essential fatty acid and a normal constituent of many cell membranes, is the endogenous source of all prostaglandins. Its release from the cell membrane is an early step in the formation of a number of vasoconstrictor and vasodilator compounds. The lung has a large capacity for prostaglandin production which led to the hypothesis that during acute hypoxia there might be a shift in metabolic pathways with increased production of vasoconstrictor metabolites. Thus, one or more prostanoid compounds could qualify as mediator(s) of the AHPR.

There are two major AA metabolic pathways: the cyclooxygenase and the lipoxygenase pathways. Inhibition of the cyclooxygenase pathway potentiates the AHPR in the isolated perfused lung, suggesting that products of this pathway modulate, but do not mediate, the AHPR. The vasodilator prostaglandin, PGI₂, is continuously produced under basal conditions in the isolated perfused rat lung. During acute hypoxia, PGI₂ output is significantly increased. Recent emphasis has shifted to the leukotrienes, the products of the other major AA metabolic pathway. Morganroth et al demonstrated that blockade of leukotriene synthesis inhibited hypoxic vasoconstriction in isolated perfused lungs, suggesting that leukotrienes mediate the AHPR. However, initial enthusiasm has been tem-
Hypoxic Pulmonary Vasoconstriction (Gutsie, Rounds)

Hypoxic pulses of leukotriene synthesis and action. By example, Lonigro et al\textsuperscript{66} demonstrated that blockade of leukotriene synthesis inhibited the increase of vasconstrictor leukotriene C\textsubscript{4}, D\textsubscript{4} in bronchoalveolar lavage during alveolar hypoxia, but did not abolish the AHPR. These data suggest that arachidonic acid metabolites are not the primary mediators of the response.

The most recent addition to the mediator controversy derives from the discovery that the vascular endothelium is an important regulator of vascular reactivity.\textsuperscript{67}\textsuperscript{68} For example, the uptake of serotonin by the pulmonary vasculature is regulated by proteins produced by endothelial cells.\textsuperscript{69} Pulmonary vessels, along with many systemic vessels, release a labile endothelial-derived relaxing factor (EDRF) which modifies vasopressor activity to different pharmacologic stimuli and acute hypoxia.\textsuperscript{69,70} Inhibitors of EDRF potentiate hypoxic vasoconstriction in isolated perfused lungs.\textsuperscript{71} Recent evidence suggests that this factor is nitric oxide.\textsuperscript{72} Systemic and pulmonary endothelial cells also release another peptide, endothelin, which is an endothelial cell-derived constricting factor.\textsuperscript{73-75} Since the endothelium is necessary for hypoxia-induced contractions of isolated pulmonary arteries,\textsuperscript{76,77} but not cerebral vessels,\textsuperscript{78} a similar factor could play a role in mediation of the AHPR.\textsuperscript{79} This area of research promises to contribute significantly to our understanding of the regulation of pulmonary vascular response in the normal or injured lung.

**Direct Effects on the Vasculature**

Direct effects of hypoxia on the vasculature are often discussed using a three-part model: sensor, transducer, and effector.\textsuperscript{80} The key questions for the oxygen sensor are its location and what specific cell or cell organelle plays this role. The likely site for the sensor is the precapillary arteriole, but the specific identity of the sensor cell(s) is still an open question. The location of the endothelial cell, the evidence that a normally functioning endothelium may be required for hypoxic vasoconstriction and endothelial production of relaxing and constricting factors strengthens the case that this cell may act as an oxygen sensor. Biochemical candidates for the sensor include: the mitochondrial oxidative phosphorylation system and cytochrome P\textsubscript{450}.\textsuperscript{81}

The pulmonary vascular smooth muscle cell is the effector cell. If the vascular smooth muscle cell is not also the sensor cell, a key unresolved issue is the form of communication, or signal transduction, between the sensor and effector cells. Undefined signals from other lung cells to the effector cell may be important in the cascade of events leading to contraction.

One approach to defining the nature of the sensor-transducer was to postulate that it must be part of the basic metabolic machinery of the cell, and that a hypoxia-induced decrease in oxidative phosphorylation is an important intermediary step in the vascular response to hypoxia.\textsuperscript{82} Several problems with this hypothesis have not been adequately resolved. First, how could a decrease in cellular fuel (ATP) production trigger pulmonary vascular smooth muscle contraction, an energy dependent process? Second, how can lowering oxygen tension result in vasodilation in coronary vasculature, but vasoconstriction within the lung? Additional evidence against this hypothesis is the finding that vasoconstriction produced by potassium chloride in the isolated perfused lung is not affected by a decrease in PaO\textsubscript{2} as low as 10 mm Hg, suggesting that during severe hypoxia, the ATP supply is not limited.\textsuperscript{83}

Alternatively, the sensor might be a non-mitochondrial oxygen-dependent component of the cell such as cytochrome P\textsubscript{450}.\textsuperscript{84} However, cytochrome P\textsubscript{450} metabolism is not affected by decreases in arterial oxygen tension to PaO\textsubscript{2} 55-60 mm Hg, the point at which hypoxic vasoconstriction begins.\textsuperscript{85} In addition, although inhibitors of cytochrome P\textsubscript{450} inhibit the AHPR, these agents are nonspecific and the evidence that cytochrome P\textsubscript{450} inhibition interferes with the AHPR is conflicting.\textsuperscript{86}

An increase in cytoplasmic calcium ion concentration is a necessary step in vascular smooth muscle contraction. A hypoxia-induced effect on vascular calcium ion movement would provide a potential mechanism for the AHPR. The AHPR is calcium dependent since verapamil, a calcium channel entry blocker, inhibits the response.\textsuperscript{87,88} and agents which facilitate calcium entry potentiate the response.\textsuperscript{89} These results suggest that hypoxia increases membrane permeability to calcium, allowing an influx of extracellular calcium ions, and a rise of intracellular calcium ion concentration.

This can be contrasted with calcium ion movements in systemic vascular smooth muscle and cardiac muscle during hypoxia. In several systemic vascular tissues in the rat, the relaxant effect of acute hypoxia on vessel tone in the active state is mimicked by removal of extracellular calcium.\textsuperscript{90} In the rabbit aorta, the normal increase in intracellular calcium content during KCl stimulation does not occur after acute hypoxic exposure.\textsuperscript{90} In cardiac muscle from several different species, hypoxia is associated with a fall in tension development,\textsuperscript{90,91} but no change in the intracellular calcium concentration measured with fluorescent dye techniques.\textsuperscript{86} These differences between pulmonary vs systemic vascular smooth muscle and cardiac muscle are difficult to explain, but suggest that pulmonary vessels may sequester or release calcium during hypoxia in a different manner which may contribute to the divergent responses. Less is known about calcium...
ion movements in other specific cellular components of the vascular wall such as the endothelium. An interesting, unexplored possibility is the relationship between oxygen tension and the redox status of the calcium ion channel involved in the AHPR. One hypothesis is that oxygen or one of several reduced oxygen species may act directly or indirectly on the calcium channel producing a conformational change in structure and function of this channel. 

Recent work on the effects of acute hypoxia on membrane electrophysiologic events in pulmonary vessels provides the first simultaneous demonstration of contraction, membrane depolarization, and action potential generation in small pulmonary arteries (<300 μm), in vitro in response to acute hypoxia. These results are the most convincing data obtained to support the hypothesis that hypoxia acts directly on the vessel wall. In this same study, it was also noted that large pulmonary arteries (>500 μm) exhibited electrical quiescence, which is compatible with the findings discussed earlier demonstrating that the small pulmonary arteries are the major site of the AHPR.

These electrophysiologic findings in pulmonary vessels are in sharp contrast with the effects of hypoxia on systemic vessels. Hypoxia does not alter resting membrane potential and inhibits spontaneous electrical activity of the rat portal vein. Collectively, these findings corroborate earlier demonstrations that pulmonary artery segments, in vitro, exhibit hypoxia-induced contraction and oxygen-induced relaxation, in contrast to hypoxia-induced relaxation of systemic vessels exposed to identical conditions. Therefore, the oxygen sensor/transducer system may be primarily related to normal membrane electrophysiologic events. A relevant unanswered question is how hypoxia-induced electrophysiologic changes relate to calcium ion movement in pulmonary vessels.

At first glance, these findings appear to have dealt the mediator hypothesis a fatal blow. On the contrary, the recent "discovery" of the endothelium and the release of endothelial-derived factors suggests that the endothelium is more than a passive interface between the vessel lumen and the contractile machinery of the vascular wall, and has kept the mediator hypothesis alive.

**Pathophysiologic Relevance of Alteration of AHPR**

The clinical implications of alterations of the AHPR are not widely appreciated. Our discussion of modification of the normal response will be arbitrarily divided into three areas: loss of the response in lung injury states; alteration of the response after chronic hypoxic exposure; and the alteration of the response in a diverse set of clinical conditions. Clinical conditions associated with alterations of the AHPR are summarized in Table 3.

### Loss of the Response in Lung Injury States

Pulmonary hypertension frequently accompanies the increase in vascular permeability in the adult respiratory distress syndrome. The pulmonary hypertension is the result of a combination of factors: vascular obstruction, obliteration, and vasoconstriction. The vasoconstrictive element in ARDS may represent a basic alteration of pulmonary vasoreactivity. In the presence of acute lung injury, even in the absence of pulmonary hypertension, blunting of hypoxic pulmonary vasoconstriction may produce a mal-distribution of ventilation relative to perfusion, an increase in shunting, and an exacerbation of arterial hypoxemia.

Alteration of the AHPR occurs in several models of acute lung injury. A diminished AHPR is found in lungs treated with hypoxia, endotoxin, hydrogen peroxide, oleic acid and platelet activating factor, while lung injuries secondary to alpha-naphthylthiourea (ANTU) or monocrotaline potentiate the response. In the endotoxin model, loss of the AHPR is nonspecific and includes the responses to other pharmacologic stimuli as well. The loss of reactivity is related to the production of vasodilator prostanooids, since attenuation of the response is abolished by pretreatment with a prostaglandin synthetase inhibitor in lung injury due to hypoxia or endotoxin, although this has not been a universal finding. On the other hand, lung edema and alterations of reactivity secondary to hydrogen peroxide are independent of cyclooxygenase products.

Platelet activating factor (PAF) is one of the newest proposed mediators of lung injury. This phospholipid is a product of the inflammatory cell response during acute lung injury, and has a broad spectrum of effects including endothelial cell damage, pulmonary edema, leukotriene-dependent vasoconstriction, and increased airway resistance. PAF blunts the vasocon-
strictor responses to angiotensin II and acute hypoxia in the isolated perfused rat lung.\footnote{106}

In contrast, acute lung injury from ANTU and monocrotaline is associated with a general increase in vascular responsiveness. ANTU potentiates the pressor response to acute hypoxia and angiotensin II, despite the fact that it does not cause acute pulmonary hypertension.\footnote{109} Monocrotaline, a pyrrolizidine alkaloid, increases endothelial cell permeability and enhances vasoconstrictor responses to KCl, angiotensin II, and norepinephrine.\footnote{110}

The different features of these models of acute lung injury may be due to differences in the extent or site of injury. At the present time, the different features are difficult to tie together in a unified model of vascular injury, but all models share the feature of endothelial cell injury and increased vascular permeability. Thus, these models focus attention on the role of the endothelium in the regulation of pulmonary vascular reactivity.

Loss or Attenuation of the Response after Chronic Hypoxia

The pathophysiologic role of the AHPR in patients with acute or pulmonary presenting with right ventricular failure, increased right ventricular afterload, and an elevated pulmonary vascular resistance is well known.\footnote{12} A more controversial subject is whether hypoxic vasoconstriction is a stimulus for the vascular changes that occur during chronic hypoxic exposure. Chronic hypoxia is associated with well-documented morphologic changes of the pulmonary vasculature consisting of an increased muscularization of the pulmonary arteries, most prominently the small arteries.\footnote{113} Most of the evidence to date suggests that elevation in pulmonary artery pressure and vascular resistance alone are not the initiating events in the morphologic changes seen in the pulmonary circulation after chronic hypoxic exposure,\footnote{114} although this remains a controversial point.\footnote{115}

Alteration of the AHPR in disease states associated with chronic hypoxia is of clinical interest because of the potential for a worsening of existing hypoxemia with loss of the response. Unfortunately, there are very few data available on this question in human subjects (see next section).

Several groups of investigators have attempted to answer this question in animal studies, with conflicting results. McMurtry et al\footnote{116} and Hill et al\footnote{117} found an attenuation of the AHPR in lungs isolated from rats exposed to chronic hypoxia for varying time periods ranging from one to two days to several weeks. Vasoactive responses to histamine and norepinephrine in the rat lung following chronic hypoxic exposure also undergo a change,\footnote{118} suggesting that the pulmonary vasculature undergoes an alteration of response to both pharmacologic and physical stimuli. In contrast, other investigators have found a significant increase in reactivity to acute hypoxia and several pharmacologic stimuli including serotonin, angiotensin II, PGE\textsubscript{2} and ATP, in the rat lung after chronic hypoxic exposure.\footnote{119,120} The conflicting results may be secondary to the confounding variables of age, strain of animal, or severity of hypoxia.

Taken collectively, these data suggest that the pulmonary vasculature undergoes a significant functional, as well as anatomic, remodeling after chronic hypoxic exposure. This remodeling extends down to the electrical events of the cell membrane, exemplified by the finding of a change in the resting membrane potential of isolated pulmonary vessels after chronic hypoxic exposure.\footnote{121} At the present time, the contribution of such alterations of pulmonary vascular reactivity to the morbidity and mortality of patients exposed to chronic hypoxemia is unknown.

**Alteration of the Response in Other Clinical States**

There are a group of diverse, unrelated clinical states where alteration of the normal AHPR is observed, but the mechanisms remain unclear. The influence of lung inflation on the response is controversial. An increase in lung inflation is associated with a decrease in the magnitude of the response.\footnote{122} Pulmonary hypertension and elevations of left atrial pressure blunt the AHPR,\footnote{123} which may help, in part, to explain the V/Q abnormalities and hypoxemia associated with congestive heart failure, mitral stenosis, and volume overload.

Alteration of the response occurs in some patients with pulmonary disease.\footnote{8,124,125} A recent report of variability of the response in patients with COPD illustrates this point.\footnote{9} Approximately 50 percent of the patients were nonresponders or poor responders in this series. An attenuation of hypoxic vasoconstriction in COPD is also suspected based upon the findings of maintained perfusion of nonventilated areas of lung in cases of suspected pulmonary embolism.\footnote{124} Reports of the presence of marked ventilation/perfusion abnormalities in the lungs of some, but not all, asthmatic patients with equivalent degrees of airway obstruction suggest variability of the AHPR in this patient population as well.\footnote{125} These scattered observations do not answer the question of whether the alteration of the response preceded the onset of symptoms, or is an integral part of the disease in some patients.

Unexplained hypoxemia has been reported in some patients with hepatic cirrhosis. A diminished or absent AHPR was suggested as a major contributing factor to this hypoxemia,\footnote{126} although these findings were not confirmed in more recent reports.\footnote{127,128}

Several studies have documented the presence of ineffective diversion of blood flow in animal models...
of pneumonia suggesting an attenuation of the AHPR. In a dog model of Pseudomonas aeruginosa pneumonia, perfusion of consolidated lung is significantly reduced after indomethacin treatment, suggesting restoration of hypoxic vasoconstriction. Indomethacin treatment also significantly improved arterial oxygen tension while decreasing serum levels of 6-keto PGF$_\text{1\alpha}$, the stable metabolite of PG$_I$. These results suggest that attenuation of the AHPR in pneumonia is related to the increased production of vasodilator prostaglandins.

Atelectasis is a common clinical problem associated with the development of arterial hypoxemia secondary to the maintenance of perfusion to the nonventilated lung segments creating a ventilation/perfusion imbalance. Mechanical factors may contribute to the maintenance of perfusion to a collapsed segment, but the strength of the AHPR is a more important factor which determines the degree of perfusion. The magnitude of the AHPR in an atelectatic segment varies inversely with the production of vasodilator prostaglandins in the atelectatic lung.

Pharmacologic modification of the AHPR is an under-appreciated clinical phenomenon. Table 4 summarizes the drugs which alter the AHPR. Changes in lung mechanics with a resultant decrease in functional residual capacity leading to atelectasis are usually considered the leading cause of postoperative arterial hypoxemia, but attenuation of the AHPR with several inhalation anesthetic agents may also contribute. This effect has been demonstrated with halothane, trichlo-roethylene, ether, methoxyflurane, and nitrous oxide in both animal preparations and in man.

Attenuation of hypoxic pulmonary vasoconstriction with vasodilator drugs is a form of pharmacologic modification of the AHPR which is being reported with increasing frequency. Several different types of vasodilator agents including calcium channel blockers, antihypertensive agents, anti-anginal agents, and beta adrenergic agonists can inhibit the AHPR with resultant hypoxemia. For example, hypoxemia in normal subjects after the administration of sublingual nitroglycerin is the result of attenuation of the AHPR.

This same phenomenon occurs in patients with coronary artery disease, and COPD.

Nitroprusside is frequently employed to lower blood pressure in a variety of situations where precise control over systemic hemodynamics is imperative. In the normal lung, this vasodilator does not produce any significant change in gas exchange. In contrast, a significant deterioration in gas exchange is produced when the drug is infused during pulmonary edema in experimental animals. Pulmonary edema is associated with an increase in lung segments with low V/Q ratios using the inert gas technique. After vasodilator therapy, a further increase in perfusion of lung segments with low V/Q ratios in association with a decrease in arterial PaO$_2$ and no change in cardiac output suggests inhibition of hypoxic vasoconstriction.

Inhibition of the AHPR with calcium antagonists was first reported by McMurry et al. These agents are utilized therapeutically as pulmonary vasodilators with variable results. The ideal pulmonary vasodilator should lower pulmonary artery pressure and vascular resistance with minimal adverse effects on systemic vascular resistance and cardiac output. Of the calcium channel blockers in clinical use, nifedipine appears to hold the most promise as a pulmonary vasodilator based upon reports from animal studies that it effectively antagonizes the AHPR with minimal decrease in systemic blood pressure and an increase in cardiac output. In addition, the worsening of arterial hypoxemia described with other pulmonary vasodilators either does not occur or is negligible with nifedipine. This is probably due to the increased cardiac output which raises mixed venous oxygen tension, and thus, may compensate for any ventilation/perfusion abnormality induced by the drug via attenuation of the AHPR.

Another practical example of a pharmacologic alteration of hypoxic vasoconstriction is the asthmatic or COPD patient treated with intravenous aminophylline and/or beta agonists without administration of supplemental oxygen. Such a patient is at risk of experiencing a deleterious fall in PaO$_2$ related to antagonism of the AHPR with these drugs. Although the fall in PaO$_2$ is usually modest, is can be unpredictably severe in some patients.

Some drugs, including cyclooxygenase inhibitors and propranolol, potentiate the AHPR in normal and abnormal lungs. In some instances, the effect is also correlated with an improvement in gas exchange. In the case of propranolol, intravenous infusion in acutely hypoxic patients produces a modest increase in PaO$_2$ presumably related to a decrease in shunt fraction within the lung. Nevertheless, agents which potentiate the AHPR cannot be recommended for routine clinical use at this time.

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**Table 4—Pharmacologic Modification of the AHPR**

<table>
<thead>
<tr>
<th>Agents which blunt response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalational anesthetics</td>
<td>134-136</td>
</tr>
<tr>
<td>Nitrogenates</td>
<td>17,20,140,141</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>142,143</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>138,146</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>18,19,147</td>
</tr>
<tr>
<td>Agents which potentiate response</td>
<td></td>
</tr>
<tr>
<td>Cyclooxygenase inhibitors</td>
<td>148</td>
</tr>
<tr>
<td>Propranolol</td>
<td>149,150</td>
</tr>
<tr>
<td>Almitrine</td>
<td>151-155</td>
</tr>
</tbody>
</table>

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Almitrine is a controversial new agent because of conflicting reports of its mechanism of action on the pulmonary vasculature and effects on gas exchange. A beneficial effect on gas exchange measured as an improvement in PaO₂ is observed in some patients with chronic obstructive pulmonary disease and in ARDS. The proposed mechanism is potentiation of the AHPR, although inhibition of the response with almitrine was noted in other studies. Although the drug produced a vasoconstrictor effect in a canine model of ARDS, gas exchange actually deteriorated. One explanation for these conflicting findings may be that the drug has a biphasic effect with low dose potentiation and high dose inhibition of the AHPR.

Collectively, the findings with vasoactive agents emphasize the diversity of drug-induced effects. Even agents such as the calcium antagonists with similar mechanisms of action may produce different hemodynamic responses when studied in vivo. Furthermore, an increase in pulmonary vascular resistance without potentiation of the AHPR may not improve gas exchange. In additions, agents with more than one effect, such as propranolol, may offset any advantage from potentiation of the AHPR. These findings emphasize that appropriate use of a pulmonary vasoactive agent must include an assessment of gas exchange as well as hemodynamic outcome. The important point is that there is a growing list of pharmacologic agents which have the potential to modify the AHPR with serious clinical consequences. The clinician’s role is more complicated because at the present time alteration of AHPR is not subject to a practical quantitative measurement at the bedside.

CONCLUSION

Despite decades of research, a definitive understanding of the mechanism of the AHPR has not yet emerged. Instead, we have a large, complex series of observations, or pieces of the puzzle. Substantial information has been gained regarding the site, modulation, and physiologic significance of the response. The two broad possibilities of viewing this response as either a direct effect on the vessel wall, or the result of mediation by a local agent are not mutually exclusive. The AHPR appears to be the synthesis of a complex series of events beginning with the sensing by a cellular component of the change in the partial pressure of oxygen, and subsequently involving both direct and mediator-related events acting in a synchronized pattern in the whole animal. In particular, the recent discovery of the active role of the endothelium in regulating vascular reactivity highlights how the two major mechanistic hypotheses may converge. Acute hypoxia may act directly on the cellular components of the vessel wall with the subsequent release of one or more locally acting mediators.

We have witnessed an explosion of physiologic and clinically relevant information which has deepened our understanding of the regulation and control of pulmonary vascular reactivity. Progress in this area will undoubtedly involve the use of newer techniques from other disciplines, and a new set of modified hypotheses which encompass the enlarging data base.

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