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BRIEF REVIEWS

Hypoxia on the Pulmonary Circulation

How and Where It Acts

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THIRTY YEARS have elapsed since von Euler and Liljestrand advanced the proposition that acute hypoxia elicits pulmonary vasoconstriction. The idea was not new, but the report excited considerable interest because it was both propitious and prescient. Nineteen forty-six was a good year to perceive that the pulmonary vasoconstrictor response to hypoxia is part of a self-regulatory mechanism by which pulmonary capillary blood flow is automatically adjusted to alveolar ventilation: methods had been standardized for exploring the pulmonary circulation in a systematic and sophisticated way and the introduction of cardiac catheterization had brought the previously remote pulmonary circulation within reach.

Much has been learned since then about the pulmonary circulation and the pressor response to acute hypoxia. Particularly helpful in dispelling the original misgivings about the occurrence of a pressor response to acute hypoxia has been a succession of observations on cattle in which the pulmonary pressor response to hypoxia is much greater than in the conventional laboratory animal, particularly in the postnatal period. That pulmonary vasoconstriction underlies the rise in pulmonary arterial pressure no longer is in doubt. The biological significance of this mechanism has been sought both in human disease and in animals. And, the lessons from acute hypoxia have been extended to the chronic hypoxia of high altitude which also has proved to be associated with pulmonary vasoconstriction.

As uncertainty after uncertainty evaporated, two key questions came into sharp focus: (1) By what mechanism(s) does hypoxia elicit vasoconstriction? (2) What segment(s) of the pulmonary vascular tree constrict(s) during hypoxia? The purpose of this paper is to offer a personal view of the pulmonary circulation in a systematic and sophisticated way and the introduction of cardiac catheterization had brought the previously remote pulmonary circulation within reach.

The Role of the Autonomic Nervous System

It has taken about a century to complete the picture of the efferent neural control of the pulmonary circulation, from nerves to receptors. Despite considerable variation in the number, distribution, and concentration of nerve endings among species and from fetal to adult life, adrenergic and cholinergic components have been identified in the pulmonary vasomotor nerves of all species in which they have been sought. Both $\alpha$- and $\beta$-adrenergic receptors are present, but the $\alpha$-receptors clearly predominate, both numerically and functionally. In contrast to ample evidence for involvement of the adrenergic mechanism, a function for the cholinergic mechanism in the control of the pulmonary circulation has not been identified. What this potential for adrenergic motor control means with respect to the pulmonary pressor response to acute hypoxia will be considered subsequently.

Efferent Motor Control of the Large Pulmonary Arteries

That hypoxic stimulation of the carotid and aortic chemoreceptors might reflexly elicit pulmonary vasoconstriction was shown almost 20 years ago by two separate groups of investigators using exceedingly elegant preparations. But 10 years were to elapse before the operation of this reflex pathway was demonstrated under less artificial conditions: immature fetal lambs subjected to systemic asphyxia while the test lung continued to be normally aerated manifested pulmonary vasoconstriction.

Throughout the experiments mentioned above the focus was on the resistance vessels. A new turn was taken with the demonstration that hypoxic stimulation of the carotid and aortic chemoreceptors reflexly decreased the distensibility of the large pulmonary arteries. The entire pulmonary arterial tree seemed to tense, but the effect on resistance to blood flow through the small vessels was completely overshadowed by the decrease in compliance of the large ones. The reflex connections between the systemic chemoreceptors and the adrenergic nerves to the lung had central representation in the hypothalamic region of the brain, thereby completing a circuit by which the pulmonary circulation can participate quickly in the circulatory adjustments of sudden fear, rage, fight, or flight. Relevant to the "fight or flight" reaction is
the fact that catecholamines that reach the pulmonary vessels via the blood stream affect the vascular smooth muscle differently from those that are released at nerve endings in the vascular walls during stimulation of the adrenergic nerves.27,28

Much remains to be learned about the full functional implications of the generous adrenergic innervation of the blood vessels to the lungs. For example, whether it enhances alveolar-capillary gas exchange by redirecting pulmonary blood flow is entirely speculative.25,28 Much more likely is the prospect of hemodynamic gain by maintaining a proper balance between the resistance and compliance characteristics of the pulmonary circulation29 and ensuring a proper balance between the outputs of the two ventricles.30

Efferent Motor Control of the Small Pulmonary Arteries

From the days of Francois-Frank6-18 evidence has been accumulating that direct stimulation of the sympathetic nerves to the lungs heightens the tone of the resistance vessels. But, the sympathetic motor innervation does not appear to be necessary for the pulmonary pressor response of the adult lung to hypoxia. This conclusion is based on the ability to elicit the hypoxic pressor response in isolated preparations of lung which are devoid of sympathetic connections.5,6,14,15 in sympathectomized man and animals,6 and in animals after adrenergic depletion and the administration of adrenergic blocking agents.1,20,31-35 Unsettled is whether the hypoxic pressor response uses the α-adrenergic mechanism in the process of eliciting vasoconstriction9,20,32 even though catecholamines, per se, are not involved.

Interest in the adrenergic contribution was rekindled by the demonstration that the pulmonary pressor response to asphyxia in the fetal lamb studied near term depended heavily on the adrenergic nervous system and that this nervous component attenuated gradually during the neonatal period.24 Observations on adult lungs of other species have since succeeded in identifying a role for the adrenergic nervous system in the hypoxic pressor response for the awake dog,37 the perfused lung lobe,20,31 and the sympathectomized dog exposed to unilateral hypoxia.29

These observations leave the distinct impression that the extent to which adrenergic vasomotor innervation affects the pulmonary resistance vessels during hypoxia depends on the experimental circumstance, species, and level of maturity. In the fetus29 the nervous contribution is more apt to be marked than in the adult. Conversely, the nervous contribution to the hypoxic pressor response in the adult lung is so modest that its existence easily may be overlooked if observations are confined to the isolated, denervated lung.

The Role of Intrinsic Pulmonary Mechanisms

Acute hypoxia has been shown over and over again to elicit pulmonary vasoconstriction in preparations that are devoid of autonomic nerves.6-8,18,20 This ability to elicit pulmonary vasoconstriction in the denervated lung that is entirely free of external neurohumoral influences is persuasive evidence that at least a large component of the hypoxic pressor effect begins and ends within the lungs.

Mechanisms that have been invoked to account for the intrapulmonary effects of hypoxia may be sorted into four categories: reflexes confined to the lungs (venoarterial or alveolar-vascular); vasoactive substances (including hydrogen ions) in the perfusate; chemical mediators originating within the lungs; cellular events in the pulmonary vascular smooth muscle. Enthusiasm for the first of these, the intrapulmonary reflexes, has flagged because of a combination of improbability, lack of experimental support, and the inaccessibility of the small pulmonary vessels to test. But, each of the other three continues to excite interest and to attract proponents.

Vasoactive Constituents in the Pulmonary Perfusate

Any experimental deviation from the intact, unanesthetized state and natural conditions entails the risk of reducing the pulmonary vasoconstrictive response to hypoxia.9 In general, the more prolonged and elaborate the manipulations before hypoxic testing, the more apt is the pulmonary circulation to show a high threshold for stimulation and a blunted vasoconstrictor response. These concerns are perennial among investigators on the pulmonary circulation and attempts have been made to take them into account in many different ways. For example, it has been shown that after an hour or so, the hypoxic pressor response of the isolated perfused lobe of the dog may gradually lessen and then disappear at a time when vasoactive drugs can still elicit vasoconstriction.9,41,42 Substitution of platelet-free plasma for blood hastens the process;42 a switch in temperature from 38°C to 27.5°C also abolishes the response.44 Other causes for loss of reactivity to hypoxia include electrolyte imbalances, deep anesthesia, acid-base disturbances, and even glass connections in the perfusing system.44 In addition to these discernible causes, there may be other mysterious influences that still defy detection. Without some appreciation of the variability in responsiveness that may arise from the surgical and experimental manipulations, from the spectrum of ambient conditions, and from the progressive loss of viability with time, the discordant results obtained by different investigators who have applied the same hypoxic stimulus to seemingly identical preparations may be utterly incomprehensible.

Of the various ingredients in the perfusate that can modify the pulmonary pressor response to hypoxia, probably none has been as well studied as the hydrogen ion. That acidosis, per se, can evoke pulmonary vasoconstriction now is generally accepted. Moreover, whether the acidosis is produced by hypercapnia or by mineral acids is immaterial since it is the concentration of hydrogen ions—not of anions or molecular CO2—that counts. Conversely, alkalemia generally causes pulmonary vasodilation.45,46

Not only does the acid-base balance of the perfusate contribute to the tone of the pulmonary vessels, but acidosis also acts, in some unknown way, to potentiate the hypoxic pressor response.9,45,46 Indeed, hypoxia and acidosis seem to interact, each facilitating the effect of the other.16,48 The effect of alkalosis in depressing the hypoxic pressor response has not been as consistent.9 This interplay is of considerable importance in lung disease in which the supervision of local acidosis in a region of alveolar hypoventilation with respect to blood flow can enhance the effect of the local hypoxia in
diverting blood flow to better ventilated parts of the lungs. The interaction between these two stimuli has important implications for defining the site at which this interaction can occur. This aspect will be considered subsequently (see Metabolic Effect on Contractility).

By the sort of reasoning outlined above, the choice has narrowed to one of two likely mechanisms (Fig. 1): an indirect effect of hypoxia operating via intrapulmonary chemical mediators, or a direct effect on pulmonary vascular smooth muscle. As will be seen below, the choice remains difficult.

### Intrinsic Chemical Mediators

Three kinds of experimental observations have promoted dissatisfaction with the idea that the hypoxic pressor effect results from a direct action on pulmonary vascular smooth muscle and have prompted the search for a unique chemical intermediate that is released or generated within the lungs during hypoxia and that reaches the vascular smooth muscle by diffusion: (1) the diametrically opposite responses of the in situ pulmonary and systemic circulations to hypoxia, i.e., vasodilation and vasoconstriction, respectively; (2) the ability of a strip of pulmonary artery to constrict during hypoxia only if it retains a collar of parenchyma; and (3) the abolition of the hypoxic pressor response in the isolated, perfused lung by antihistamines. Exceptions can be raised to each of these separately: (1) in comparing systemic and pulmonary vasomotor responses, the systemic vascular responses to hypoxia provide a poor standard of reference because they are nonuniform and inadequately understood; (2) stripping the pulmonary artery of the rabbit entails the risk of deranging electrolyte composition and reactivity of the vascular wall in a species that is poorly responsive to the pressor effects of acute hypoxia; and (3) the abolition of the pressor response by antihistamines may be nonspecific. But, taken together, the evidence has prompted a vigorous search for a chemical intermediate that originates within the lung.

The criteria for a unique chemical mediator seem to correspond closely to those which generally are held to characterize transmitters that are released by vasomotor nerves during stimulation: (1) the mediator or its precursors must exist in the lungs; (2) the source of mediator must be strategically disposed with respect to the resistance vessels so as to gain ready access to their media during acute hypoxia; (3) the effect of the mediator must be mimicked by the application of the proposed mediator to the pulmonary blood vessels; (4) a mechanism must be present to turn on, and to inactivate, the mediator; (5) agents which modify the pressor response elicited by the mediator should have similar effects on responses to the exogenously administered mediator; (6) inhibition or depletion of the mediator, as by pharmacological agents, should depress the hypoxic response.

For the prospector in search of chemical mediators, the cells of the lung offer quite a trove of biologically active substances. In most species, mast cells in the lung contain histamine, serotonin, ATP, and slow-reacting substance; in some a great deal of dopamine is present. Other parenchymal cells also contain serotonin, histamine, and ATP. The autonomic nerve endings constitute a ready source of neurotransmitter substances. And, the endothelium constitutes a metabolic machine that is deeply involved in processing blood constituents that are brought to it from elsewhere in the body. But, from this abundance, only four continue to be explored as potential chemical mediators: catecholamines, histamine, prostaglandins, and angiotensin.

#### Catecholamines

Local release of catecholamines has been invoked repeatedly to account for pulmonary vasoconstriction during hypoxia. This is an attractive notion because of the many ways by which hypoxia might interfere with local synthesis, storage, or release of catecholamines. The main evidence for this proposition has been the blunting or abolition of the pressor response by dibenamine and phenoxybenzamine. Unfortunately, results with these agents have been neither consistent nor conclusive: not only have similar preparations failed on occasion to show a blunted pulmonary pressor response to hypoxia after successful a-adrenergic blockade, but more intact animals have consistently failed to do so. Many reasons have been invoked to account for the discrepancies: the different preparations, the nonspecific effects of blocking agents, excessive dosages and species differences, or even the uncertain effects of denervation. Nonetheless, the inconsistencies have shaken confidence in the catecholamines as the unique chemical mediators in the hypoxic pressor response. A particularly telling bit of evidence against an important role for the catecholamines is the persistence of a large pressor response to hypoxia in intact animals which have received sufficient quantities of the a-adrenergic blocking agent, phenoxybenzamine, to block the systemic vasconstrictor response to norepinephrine, or in which reserpine has depleted adrenergic nerve endings in the pulmonary vascular walls of

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**Figure 1** Alternate hypotheses to explain pulmonary vasoconstriction during hypoxia. Left: Indirect mechanism: mediator released by non-muscle cells of the lungs diffuses to vascular smooth muscle, where it engages cellular receptors and mechanisms to activate the contractile process. Right: Direct mechanism: the effects of hypoxia are exerted directly on vascular smooth muscle by affecting one or more stages in the contractile process: excitation, contraction, or the coupling of the two.
norepinephrine. On the other hand, the possibility remains that the catecholamines help to set the background tone that is necessary for the pulmonary vascular smooth muscle to respond to the vasoconstricting effects of hypoxia. This prospect will be raised again subsequently.

**Histamine**

Of all the humoral agents that have been proposed as intrinsic mediators of the pulmonary pressor response to hypoxia, histamine seems to fit the bill best. Thus, in the isolated perfused rat lung, large doses of antihistamines and histamine-depleters diminish the pulmonary pressor response to hypoxia, whereas a histaminase inhibitor (semicarbazide) potentiates it. During hypoxia, the concentration of histamine in the effluent from the lungs increases. In addition, according to the criteria for a mediator outlined above, deposits of histamine, in the form of mast cells, appear to be strategically dispersed along the course of the pulmonary resistance vessels, presumably in a fashion that allows prompt vasomotor responses to hypoxia. The periartrial mast cells in the lungs degranulate in the rat and guinea pig during hypoxia, and histidine which has been taken up by mast cells is released during hypoxia presumably in the form of histamine. Finally, it has been possible to draw interesting analogies between the overall circulatory effects exerted by hypoxia and those of histamine.

But not all investigators share this enthusiasm for histamine as the chemical mediator. Some have had difficulty in reproducing the blunting and blocking effects of antihistamines and histamine depleters on the pulmonary pressor response. Others have wondered about in vitro and in vivo discrepancies: Why has the administration of the histamine depleter, Compound 48/80, or of a histidine carboxylase inhibitor been more effective in blocking the pressor response in vitro than in vivo? Also, question has been raised about generalizing from the rat, a species that has a poor pulmonary pressor response to hypoxia. Most disturbing is the observation that histamine in the calf causes vasodilation and prevents the pulmonary pressor response to hypoxia.

These uncertainties are fortified by other misgivings about histamine. How specific for histamine are the antihistamines and histamine-releasers? Is histamine a reliable pulmonary vasoconstrictor in animals other than the calf wherein it clearly is a vasodilator? Why is the increase in histamine content of blood leaving the lungs during hypoxia unaccompanied by a decrease in the histamine content of the lungs? Are results from the lungs of the fetus, the newborn, and the adult different? Have the bronchoconstrictor and permeability effects of histamine been taken into proper account with respect to interpreting the level of pulmonary vascular tone?

How does the wide diversity of bioactive materials in mast cells, and the variations in concentration and disposition of mast cells from species to species, and the failure of mast cells to degranulate early (within the 1st hour) rather than later (after 1 hour) relate to their proposed role as histamine-providers during acute hypoxia?

From this tangle of contradictory evidence and uncertainty, it is not possible to conclude that histamine is the unique mediator of the pulmonary pressor response to hypoxia.

**Prostaglandins**

Interest in the possible role of the ubiquitous prostaglandins was stimulated by the observation that ventilation of the isolated perfused cat lung with hypoxic mixtures caused the elaboration of prostaglandin-like compounds into the perfusate. Furthermore, in anesthetized cats, infusions of large quantities of aspirin reduced the pulmonary vasoconstrictor (as well as bronchoconstrictor) response to hypoxia. Currently this hypothesis is in limbo. Unless new supporting evidence is adduced, it seems unlikely that any of the prostaglandins will emerge as the unique chemical mediator.

**Angiotensin**

The octapeptide, angiotensin II, generated in the lung from angiotensin I, is generally held to be a potent pulmonary vasoconstrictor even though there are reports to the contrary. It did not receive serious attention as a potential chemical mediator of the pulmonary pressor response to hypoxia until the recent demonstration that the addition of subpressor quantities of angiotensin I to the perfusate of a lung that was unresponsive to hypoxia would restore the pressor response for another 30-60 minutes.

Not excluded was the alternate possibility that restoration of responsiveness by angiotensin may have been a nonspecific effect in an artificial circumstance. This alternative bears serious consideration since the experiments demonstrating restoration of responsiveness to hypoxia involved the use of a synthetic medium as the perfusate, a situation that favors the loss of myotropic activity of angiotensin.

At present, the observations relating angiotensin to the pulmonary pressor response to hypoxia are too fresh for interpretation. As in the case of the catecholamines, it remains to be seen whether angiotensin does more than contribute to initial tone, a property which different vasoactive substances may share to different degrees, depending on the species and experimental conditions.

**OTHER POTENTIAL MEDIATORS**

Serotonin has been eliminated as the chemical mediator. No other candidates currently are under serious consideration. This exclusion, coupled with inconclusive evidence for histamine, catecholamines, or angiotensin as the unique mediator, automatically reopens the question of a direct effect of hypoxia on pulmonary vascular smooth muscle as the mechanism responsible for the pressor response.

**Initial Tone**

Even though neither histamine, the catecholamines, angiotensin, serotonin, nor any of the other substances that have been tested satisfy the criteria for the unique mediator, can they play subsidiary roles in promoting the pulmonary pressor response to hypoxia? Or do they contribute to the pulmonary pressor response to hypoxia as "multiple factors
Differing in combination in different species. Or do these various bioactive substances provide the background tone that is prerequisite for hypoxic vasoconstriction? Variability from species to species and from preparation to preparation is a regular feature of studies on the effects of hypoxia on the pulmonary circulation. Often in isolated lung preparations anoxia has been required to duplicate the response elicited by moderate hypoxia in more viable preparations. Sometimes enhancing agents have been added. Attention was called above to the modifying influences of acidity, temperature, and electrolyte composition of the perfusate on the threshold for and intensity of response.

Daly and Hebb wondered if the vasoconstrictor effect of hypoxia depended on the pre-existing state of tonus in the same (responding) vessels, or in the vessels belonging to some other part of the circuit. This query has been echoed by others. A variety of factors might contribute to this initial tone. In some circumstances, catecholamines might predominate; in others, angiotensin or serotonin or mysterious plasma factors. When this initial tone is high, as during combined hypoxia and acidosis, stimulators of the beta-receptor adrenergic mechanism and the infusion of acetylcholine elicit an impressive vasoconstriction, whereas either does little to the normal pulmonary circulation. The autonomic nervous system might contribute more importantly in the fetus than in the adult.

Clearly there is more to the concept of initial tone than the physical setting in which the experiments are performed, the nature of the perfusate, and the autonomic innervation. The fetal pulmonary circulation responds vigorously to vasoactive substances that the adult pulmonary circulation virtually ignores, e.g., bradykinin. Also, the fetal pulmonary circulation shows reactive hyperemia whereas the adult does not. A larger muscle mass and extent, as in the pulmonary circulation of high altitude dwellers, enhances the pressor response to hypoxia. There are species differences and genetic predispositions within species. Nonetheless, it may well be that a critical element in determining the pulmonary pressor response to hypoxia is a component of initial tone that is contributed by bioactive substances that do not qualify as the chemical mediators for the pulmonary pressor response to hypoxia.

Site(s) of Pulmonary Vasoconstriction

Fifteen years ago it seemed reasonable to conclude that vascular smooth muscle everywhere in the lungs constricted in response to acute hypoxia, that the pulmonary veins bore the brunt of the exposure to a decrease in the O2 content of the inspired air and contributed more to the total pressor response than the arteries, and that the normal hypoxemia of mixed venous blood returning to the heart was largely responsible for the continuing tone of the pulmonary precapillary vessels. Except for current doubt about the preponderant role of the pulmonary veins, these conclusions still hold. Confidence in their preponderant role was undermined by the demonstration that a change in alveolar O2 content promptly affects the oxygenation of blood in the terminal pulmonary arteries (as well as in the pulmonary veins). Coupled with the fact that the small pulmonary arteries are better built for effective constriction than are pulmonary veins of the same size, evidence that the pulmonary arterial blood volume decreases during hypoxia, and the prospect that pulmonary venous constriction might derange water exchange in the pulmonary capillaries by upsetting the balance of Starling forces, the current consensus is that the small pulmonary arteries ("pulmonary arterioles") are the main sites of increased vascular resistance during hypoxia.

The swing to the small pulmonary arteries has not excluded the possibility of a subsidiary role for the small pulmonary veins: the pulmonary veins certainly are affected as promptly as the arteries by any change in inspired gas composition. Also, in concept, pulmonary venous constriction could operate nicely to adjust alveolar perfusion to ventilation. Moreover, the pulmonary veins do constrict in response to a variety of stimuli, including hypoxia. Therefore, pulmonary venoconstriction may contribute to, even though it does not dominate, the hypoxic pressor response.

Over the years serious attention also has been given to the question of whether hypoxia by airway ("alveolar hypoxia") is the only way to elicit pulmonary vasoconstriction. The current consensus favors this traditional view and ignores the fact that, because of the shape of the oxyhemoglobin dissociation curve, the experiments underlying this notion have rarely entailed more than an exceedingly modest drop in the Po2 of mixed venous blood. Even though the usual experiments have succeeded in proving that a large drop in alveolar Po2 does elicit pulmonary vasoconstriction, they have not excluded the possibility that a sufficient drop in mixed venous Po2 may have the same consequence. This conclusion is based on the following types of evidence: (1) in cross-circulated fetal lambs, asphyxia of the donor caused pulmonary vasoconstriction in the unasphyxiated recipient; (2) in the isolated perfused lung, decreasing the mixed venous Po2 during ventilator arrest elicited pulmonary vasoconstriction; (3) the increase in pulmonary artery pressure during hypoxia was lessened by perfusing the pulmonary artery with well oxygenated blood; and (4) the synergistic effect of acidosis on the pulmonary pressor response to hypoxia suggests that pulmonary arterial smooth muscle may be the site of vasoconstriction. Less convincing, per se, but in keeping with these observations are the effects of carbon monoxide and of 2,3-dinitrophenol which concomitantly decrease the O2 tension of mixed venous blood and elicit the pulmonary pressor response.

Obviously, the mechanisms used above to drop mixed venous Po2 are quite drastic. Unfortunately more physiological devices, such as exercise or heart failure, are accompanied by changes in ventilation and cardiodynamics that preclude meaningful interpretation in terms of cause and effect. Nonetheless, the point seems to have been made experimentally that exaggeration of normal precapillary hypoxemia elicits pulmonary arterial and arteriolar constriction.

The two routes, alveolar and blood, by which the smooth muscle of the small pulmonary arteries (and venules) may be affected by hypoxia are shown schematically in Figure 2.
Fl 02 = determinant (cross-hatched). Upper frame: Air breathing: the gas decreases Po2, and O2 delivery by the airways, much through the airways, the alveolar aspect of the smooth hypoxia of pulmonary vascular smooth muscle has been to the same extent. But, because of the O2 transport proximal pulmonary vascular segments; the high alveolar about the same order of magnitude and the O2 contents of blood) since cardiac output and alveolar ventilation increase slightly and the same. During alveolar hypoxia (bottom half of Fig. 2), both alveolar gas and mixed venous blood are also about the same. These considerations challenge the idea of “alveolar hypoxia” as the sine qua non for the hypoxic pressor response.96–97, 100–103 Instead, “alveolar hypoxia” may be generated by compromising O2 delivery (flow times O2 content) from either the air side or the blood side. During air breathing at sea level (upper half of Fig. 2), O2 delivery to the media of the small pulmonary vessels is roughly the same from the two sides (alveolar air and venous blood) since cardiac output and alveolar ventilation are about the same order of magnitude and the O2 contents of alveolar gas and mixed venous blood are also about the same. During alveolar hypoxia (bottom half of Fig. 2), both alveolar ventilation and cardiac output increase slightly and to the same extent. But, because of the O2 transport properties of the blood, a decrease in O2 content of inspired gas decreases Po2, and O2 delivery by the airways, much more than by blood. Accordingly, because the O2 tension of mixed venous blood changes little during hypoxia induced through the airways, the alveolar aspect of the smooth muscle is exposed to a more dramatic change in O2 delivery than is the blood aspect. These considerations challenge the idea of “alveolar hypoxia” as the sine qua non for the hypoxic pressor response.96–97, 100–103 Instead, “alveolar hypoxia” emerges only as a practical expedient by which hypoxia of pulmonary vascular smooth muscle has been induced under conventional experimental conditions.

Where in the pulmonary vascular smooth muscle is vasoconstriction initiated? Although there have been several attempts to identify this site,104 the assumptions have been tenuous because of the unavailability of critical information. For example, it was not appreciated a few years ago that a change in alveolar Po2 promptly affects the oxygenation of blood in the small pulmonary arteries presumably because of the short diffusion distances between the blood and gas phases of the lungs, and the modest O2 consumption by vascular smooth muscle. Figure 2 takes this information into account by distinguishing between consecutive segments of the small pulmonary arteries (A and B). These small arteries are distal to the segments that are supplied by the bronchial arteries and are, therefore, oxygenated directly by the blood and gas phases with which they are in contact. The same mechanism for oxygenation is true for the small pulmonary veins. In this figure, the precapillary (and postcapillary) segment is subdivided into a proximal thick-walled portion and a distal thin-walled portion. Presumably, the proximal portion, which is chronically hypoxemic, is much less affected by a rapid change in alveolar Po2 than is the distal portion.

Ideas about the location of O2 sensors (or critical enzymatic pathways) within the smooth muscle are inextricably linked to preconceptions about the nature of these sensors. Is smooth muscle, per se, both receptor and effector? Or are "special O2 receptors" involved? Do the sensors, like Janus, face both sides equally, or do they favor one aspect of the muscle over the other? Moreover, if they do exist, how are they distributed with respect to proximal vs. distal precapillary (and postcapillary) segments?

Despite these and other questions, the schematic representations in Figure 2 are consistent with the idea that, during ambient air breathing, the tone of the proximal pulmonary arterial segments (A in Fig. 2) is predominantly influenced by the Po2 of the mixed venous blood, whereas the alveolar Po2 controls the tone of the terminal segments (B in Fig. 2). They also raise the possibility that during extreme experimental conditions in which O2 delivery is compromised by drastically reducing inflow of blood—as may obtain in an inadequately perfused isolated lung—the predominant hypoxic influence may shift from the alveolar phase to the blood phase.

Direct Effect on Vascular Smooth Muscle

Failure to adduce conclusive evidence for a particular chemical mediator has prompted reexamination of the alternative that a direct effect of hypoxia on the smooth muscle of the pulmonary arteries is responsible for the vasoconstriction. Consistent with this possibility is the synergistic effect of acidosis on the pulmonary pressor response to hypoxia. But, the direct effect is troublesome to explore on many accounts: (1) the difficulty in isolating and handling smooth muscle without modifying its reactivity or extinguishing its viability;102 (2) the sparseness of muscle in the small pulmonary vessels, which forces recourse to larger vessels which may differ in behavior;105 (3) the fact that muscle in arteries proximal to the sites of gas exchange is chronically "adapted" to hypoxic blood,106 whereas muscle
in the distal pulmonary arterial segments always is well oxygenated.

A priori, acute hypoxia could directly increase the tension of pulmonary arterial smooth muscle by affecting mechanisms that control membrane excitation, excitation-contraction coupling, or the chemomechanical transducer itself.105, 106 Dissection of the vasoconstrictive response in these terms has been attempted for the ductus arteriosus109 and the aorta.107 No evidence has been adduced that hypoxia acts directly on the contractile process. But, important beginnings have been made toward unraveling the respective roles played by the two universal requirements for contraction: the energy source [ATP] and the regulator ion [calcium]. This line of research presupposes that contraction may be rate-limited by constraints on either the fuel [ATP] or the activator [calcium ion].116 Since hypoxia is apt to affect ATP production, the possibility exists that the direct effects of hypoxia on pulmonary vascular smooth muscle may be rate-limited by the concentration of ATP. Serious consideration of this prospect has been encouraged by the demonstration that, in contrast to systemic vascular smooth muscle, in which hypoxia depresses oxidative production of ATP, hypoxia accelerates ATP production in pulmonary vascular smooth muscle by accelerating the glycolytic pathway.108 Another possibility involving ATP is its critical role in making activator calcium available to the contractile machinery. At the present time, these suggestions only can be regarded as intriguing hypotheses with respect to pulmonary pressor effects of acute hypoxia. But, aside from indicating directions for future research, they do have at least two important implications: (1) The divergent responses to hypoxia of systemic and pulmonary vascular smooth muscle may entail different biochemical mechanisms involving either ATP or calcium ion or an interplay of the two.106, 111 (2) The disparate contractile behavior of vascular smooth muscle from different sources suggests that the requirements for contraction may differ from site to site: rate limitation by ATP may be more critical in pulmonary vascular smooth muscle whereas rate limitation by calcium ion may be more critical in systemic vascular smooth muscle.107 To what extent these generalizations, based largely on experiments with large vessels, apply to resistance vessels in the pulmonary circulation is enigmatic. But, they do serve to underscore the biochemical credibility of a direct effect of hypoxia on pulmonary vascular smooth muscle.

Metabolic Effect on Contractility

Duke and Killick89 were able to block or blunt the pressor response to acute hypoxia by prior administration of the metabolic inhibitors, iodoacetate, carbon monoxide, or azide. From these experiments, Liljestrand was drawn to the hypothesis that hypoxia exerts its pulmonary pressor effect by liberating lactic acid in pulmonary vascular smooth muscle.92 The subsequent observations by others on the pressor effects of acidemia, per se,112 and the potentiating effects of acidemia on hypoxia97 were supportive of this idea. But convincing evidence to support this hypothesis has not materialized and the notion now has no staunch advocates.

That the smooth muscle cell in the pulmonary artery was organized so as to constrict when its aerobic energy sources were compromised was supported by the ability of hypoxic media to constrict strips of pulmonary arteries.108 Attracted by this notion, and prompted by the idea that in the lungs, as in the heart, local tissue PO2 might regulate local blood flow, Mentzer et al.113 examined the effects of adenosine and of AMP. They favored adenosine because hypoxia causes its release at myocardial cell margins by the action of 5'-nucleotidase; the adenosine, in turn, is degraded by nucleoside phosphorylase in endothelium.114 However, instead of eliciting vasoconstriction, adenosine (and AMP) proved to be modest vasodilators. The lasting implication of these experiments is that a strategically placed enzyme—possibly at the margins of the vascular smooth muscle—can form a vasoconstrictor substance that enters the interstitial fluid to constrict the pulmonary resistance vessels.

Electrical and Electrical-Mechanical Coupling

Until the observations by Lloyd115 on the naked pulmonary artery of the rabbit, pulmonary arterial smooth muscle was generally believed to constrict during hypoxia because of some unknown but definable intrinsic characteristics. In order to gain insight into electrical events at the membrane of the smooth muscle cell during hypoxia, Bergofsky and Holtzman116 compared the electrolyte behavior of strips of large pulmonary artery, vein, and systemic arteries. Of these, only the pulmonary arterial strip lost potassium and gained sodium during hypoxia; these changes in electrolyte content reversed when normal oxygenation was restored.105 Without excluding an effect on the contractile process or on excitation-contraction coupling, they surmised that hypoxia partially depolarized the membrane of vascular smooth muscle cells and brought them closer to the threshold for excitation. It is a far cry from these observations to electrical events in pulmonary vascular smooth muscle.112 The more pertinent observations on electrical activity, obtained by applying microelectrodes or the sucrose gap technique to pulmonary vascular smooth muscle during hypoxia, remain to be made.

More recently, attention has shifted to the calcium ion. There is little doubt that this regulator ion could be importantly involved in the pressor response to acute hypoxia. It could play its role in several different ways. In a previous section of this review the possibilities were suggested for interplay between the calcium and the supply of ATP in controlling contraction.118 Recently, by using calcium antagonists in an isolated, blood-perfused, rat lung preparation, evidence has been adduced that hypoxia can act directly to depolarize pulmonary vascular smooth muscle and to initiate the transmembrane flow of calcium into the cell where it can activate the contractile machinery.119 Although this preliminary report is quite plausible in terms of smooth muscle physiology, it is still too brief and too fresh to settle the question of if and how the calcium ion is involved. For example, it does not address the disposition of calcium within the myoplasm with respect to the contractile proteins. Nor does this type of experiment exclude the possibility that the calcium ion is affecting either the behavior of chemical mediators or the release of transmitter.
substances from the parenchyma around the vessels. Do the observations using calcium antagonists imply that the pharmacological blocking or releasing agents—that have been the mainstay of the search for chemical mediators—are exerting nonspecific effects on calcium transport across membranes in addition to their specific pharmacological actions? How does the hypoxic induction of calcium inflow and its modification of the behavior of the plasma membrane relate to other influences, such as temperature, which modulate thepressor response to hypoxia? Although these questions may be unanswerable at present, they are raised for two reasons: (1) to highlight the recent rekindling of interest in the direct effects of acute hypoxia on pulmonary vascular smooth muscle, and (2) to underscore the need that experiments along this line be incorporated into the total conceptual framework of smooth muscle physiology.

**Chronic Hypoxia**

For more than 20 years, it has been known that life at high altitude is associated with pulmonary hypertension. This is true for newcomers, for the acclimatized, and for native residents. The degree of pulmonary hypertension ordinarily is modest at tolerable altitudes but may approach systemic levels when alveolar hypoventilation and systemic arterial hypoxemia are severe, as in chronic mountain sickness. On microscopic examination, the vascular smooth muscle of the pulmonary arteries, both in man and animals, is hypertrophied, presumably a consequence of sustained pulmonary vasoconstriction. Striking species differences characterize the reactivity of the pulmonary circulation of animals and man exposed to high altitude, and genetic predisposition appears to be importantly involved in the hypertrophy of the more responsive reactive species, such as the cow.

What purpose is served by the pulmonary hypertension of high altitude? With respect to gas exchange, pulmonary hypertension could ensure better blood flow to the apices of the lungs, thereby improving oxygenation. More subtle benefits for gas exchange or for hemodynamics have not been tested.

It has been tacitly assumed that the vasomotor mechanisms underlying the sustained increase in pulmonary vascular tone during chronic hypoxia are directly related to, if not the same as, those that operate during acute hypoxia. This may not be so. Although the circumstance of lifelong hypoxia is difficult to reproduce in the laboratory, recent evidence suggests that, as in the case of systemic vascular smooth muscle, chronic hypoxia may introduce major detours in the metabolic pathways of pulmonary vascular smooth muscle. To what extent the changes in energetics modify pulmonary vascular tone and reactivity is unexplored.

With respect to unique chemical mediators, it is easier to picture histamine and catecholamine in this role during acute hypoxia than during chronic hypoxia because sustained contraction would be expected to require some mechanism for replenishing stores of precursors and of the mediator. Indeed, those who favor histamine as the mediator during chronic hypoxia have been encouraged in this idea by the concomitant proliferation of mast cells. A completely different tack has been taken by others who favor the renin-angiotensin system because of anatomical changes in the pulmonary arteries and hearts of rats exposed to hypobaric atmospheres. Here, again, the observations are too sparse and circumscribed to establish a role for the renin-angiotensin system and particularly of the angiotensin I-converting enzyme.

Much simpler to conceptualize as the basis for sustained pulmonary hypertension at high altitude than the continued operation of a chemical mediator is a direct effect of chronic hypoxia on vascular smooth muscle. For example, the adaptation to oxygen lack might favor anaerobic over aerobic metabolism in the vascular smooth muscle, or reset the flow of ions across the smooth muscle membrane, or readjust electromechanical coupling. Indeed, the same alternatives can be confronted as in the case of acute hypoxia. But, the choice will be easier to make in the case of chronic hypoxia because the hypertrophied muscle in the pulmonary resistance vessels may be easier to deal with experimentally.

**Concluding Remarks**

This review was undertaken on the assumption that hypoxic pulmonary hypertension is a distinct and reproducible biological entity, elicitable, albeit with some degree of variability, in all species. There is still no reason to cavil about this assumption. Indeed, over the last 30 years hypoxia has emerged as the most effective, uncomplicated, and consistent stimulus to pulmonary hypertension that has yet been discovered.

The phenomenon has been characterized in many ways, ranging from interplay with hydrogen ions to genetic variability. In the process, it has become clear that in addition to the intrinsic response that has preempted attention for the last 30 years, there is an important adrenergic element of control that varies in importance from fetus to adult and probably from species to species and state to state. One important contribution of this adrenergic mechanism may be in setting the level of initial tone that is required for hypoxia to act. But, the adrenergic contribution appears to be only one of many factors that interplay to set both the threshold for and sensitivity of the hypoxic pressor response.

Most of the experiments considered have required technical feats because of the inaccessibility of the pulmonary circulation. As such, they generally have paid the penalty of creating artificial conditions that depress responsiveness of pulmonary vascular smooth muscle. But, despite this compromise, two alternatives have evolved that currently defy resolution: Does hypoxia exert its effects indirectly, via a mediator released within the lung, or does it act directly on pulmonary vascular smooth muscle? One way to interpret the failure of the recent research effort to uncover a unique chemical mediator is that one will not be found. Instead, the inability to identify a unique chemical mediator seems destined to rekindle interest in direct mechanisms by which hypoxia can affect pulmonary vascular smooth muscle to elicit vasoconstriction.

In the search for mechanisms and sites of action of
hypoxia on the pulmonary circulation, much has been learned. A major distraction has been an overemphasis on "alveolar hypoxia" as the necessary route for inducing the pressor response. If this is a misconception, as proposed above, an important pillar for the belief in an intrinsic chemical mediator has been shaken. Another fundamental notion is the need for pulmonary parenchyma in order to elicit the pulmonary pressor response to hypoxia. Perhaps this hypothesis should be reexamined, preferably in a species in which the pulmonary pressor response is more vigorous than in the rabbit and under conditions which require less manipulation of the vessels under study. Finally, for those who have been prompted to search for a unique chemical mediator because the pulmonary circulation does not respond to hypoxia in the same way as the systemic circulation, it must be discouraging that the duc tus arteriosus, a link between the two circulations, has a peculiar response of its own to changes in ambient Po2, one that operates via a direct effect of oxygen on the smooth muscle in its walls, without a unique chemical intermediate.

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