Physiol Rev 92: 367–520, 2012
doi:10.1152/physrev.00041.2010

HYPOXIC PULMONARY VASOCONSTRICTION

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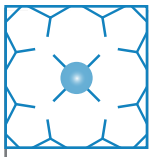


Sylvester JT, Shimoda LA, Aaronson PI, Ward JPT. Hypoxic Pulmonary Vasoconstriction. Physiol Rev 92: 367–520, 2012; doi:10.1152/physrev.00041.2010.—It has been known for more than 60 years, and suspected for over 100, that alveolar hypoxia causes pulmonary vasoconstriction by means of mechanisms local to the lung. For the last 20 years, it has been clear that the essential sensor, transduction, and effector mechanisms responsible for hypoxic pulmonary vasoconstriction (HPV) reside in the pulmonary arterial smooth muscle cell. The main focus of this review is the cellular and molecular work performed to clarify these intrinsic mechanisms and to determine how they are facilitated and inhibited by the extrinsic influences of other cells. Because the interaction of intrinsic and extrinsic mechanisms is likely to shape expression of HPV in vivo, we relate results obtained in cells to HPV in more intact preparations, such as intact and isolated lungs and isolated pulmonary vessels. Finally, we evaluate evidence regarding the contribution of HPV to the physiological and pathophysiological processes involved in the transition from fetal to neonatal life, pulmonary gas exchange, high-altitude pulmonary edema, and pulmonary hypertension. Although understanding of HPV has advanced significantly, major areas of ignorance and uncertainty await resolution.

I. INTRODUCTION

A. Historical Perspective

By the middle of the 19th century, development of techniques to measure and record intravascular pressures in living animals by physiologists such as Ludwig (1142), Poiseuille (1536), and Chaveau and Marey (290) had stimulated widespread interest in circulatory function. In 1852, Beutner (164), working under Ludwig in Zurich, reported the first measurements of pulmonary arterial pressure (P_{PA}), which he found to average 29.6 mmHg in the dog, 17.6 mmHg in the cat, and 12.1 mmHg in the rabbit. Beutner also observed fluctuations in P_{PA}, which he attributed to cardiac activity and ventilation, and discovered that interruption of ventilation "for a longer time" caused an increase in P_{PA} that reversed upon resumption of ventilation **(FIGURE 1*A*)**. Since his animals had been subjected to bilateral vagotomy, he concluded that "no possible explanation (for the increase in P_{PA}) remains than this, that venous blood is a significant stimulant for the cardiac nerves," which he believed would signal a prolonged increase in the force of cardiac contraction, and thus cardiac output.

Subsequently, other laboratories investigated the effects of respiration on circulation; in particular, the changes in P_{PA} and systemic arterial pressure (P_a) caused by asphyxia. In animals anesthetized with chloroform or morphine and paralyzed with curare, cessation of artificial ventilation caused asynchronous increases in P_{PA} and P_a to ~200 and 200–400% of baseline, respectively, followed by a fall in P_a in association with progressive bradycardia and a further rise in P_{PA} to ~200–500% of baseline (212, 1092, 1434, 2115). If ventilation were not reinstituted, P_{PA} reversed its rise to fall in concert with P_a, and the animal soon died. A consensus gradually developed that the cause of the final rise and fall in P_{PA} was, as expressed by Openchowski in 1882 (1434), "paralysis of the left ventricle…induced by interaction of high pressure and oxygen impoverishment of the blood…(and)…obstruction of blood in the left atrium and lungs and later paralysis of the right heart." However, explanations for the early rise in P_{PA} were more controversial. As summarized by Wood in 1902 (2115), the possibilities were "first, that it is due to a damming back of the blood; second, that it results from a greater flow to the right heart; third, that it is due to direct contraction of the arteries of the pulmonary circulation."

The first explanation was thought unlikely because the early phase of asphyxia was sometimes found to increase P_{PA} without increasing either P_a or left atrial pressure (212, 1092, 1401, 1434, 2115) **(FIGURE 1*B*)**. The second was not really testable because adequate methods for measurement of cardiac output were not yet available; however, this did not deter development of complicated arguments that an

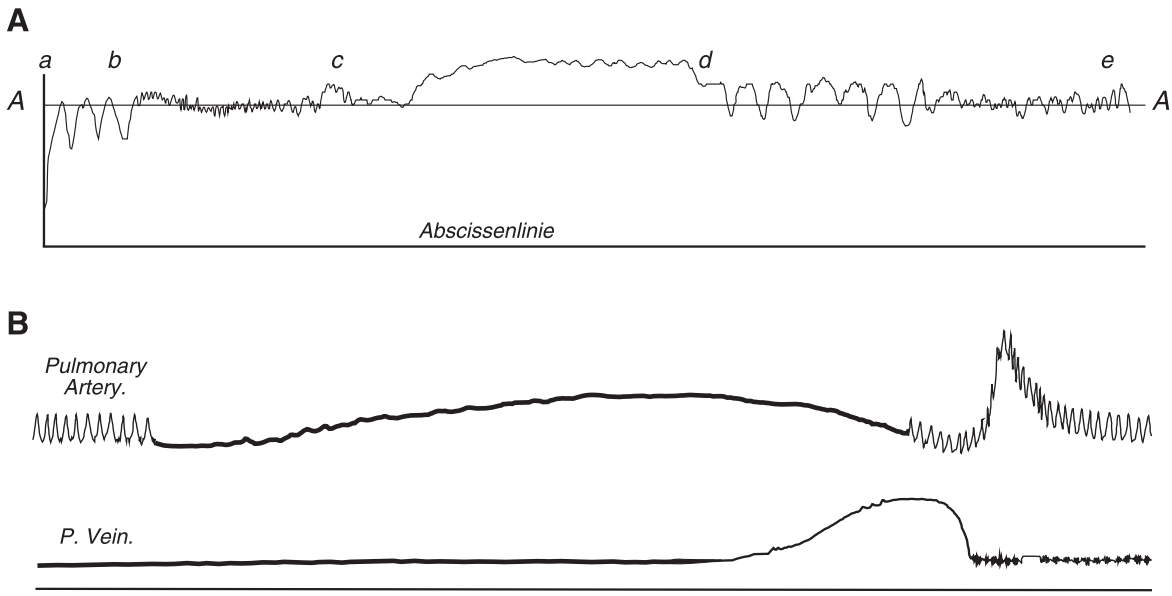


FIGURE 1 The time course of pulmonary arterial pressure in a cat recorded by Beutner in 1852 (164) (*A*) and pulmonary arterial and venous (P. Vein) pressures in a dog recorded by Bradford and Dean in 1894 (212) (*B*). In *A*, as described by Beutner (164), "*AA'* (is) mean pressure level; *a-b* movement of the bellows (used to ventilate the animal), *b-c* heart beats after cessation of bellows movement, *d-e* heart beats with very slow bellows movement." Note the rise in pulmonary arterial pressure from *b* to *d*, when ventilation was stopped, and fall in pressure from *d* to *e*, when ventilation was resumed. As described by Bradford and Dean (212), *B* shows the "effects of asphyxia on the blood pressure in the pulmonary artery and … in the central end of the pulmonary vein. Mercurial manometers were used in both cases. The rise of pressure in the left auricle at the end of asphyxia is well seen, also the temporary rise in the pulmonary artery following the re-establishment of artificial respiration." Both *A* and *B* were digitally traced from the published recordings, resized, and relabeled for clarity of presentation. Neither recording included scales for pressure (ordinate) or time (abscissa).

increase in cardiac output either did (1434) or did not (212, 2115) occur. The third explanation, constriction of pulmonary arteries, was thought possible by most investigators, and of course probable by those who had excluded the first two. Because pulmonary vessels were thought to be supplied by sympathetic nerves (227) and electrical stimulation of cervical sympathetics (80) or the vasomotor center (212) increased P_{PA}, it was generally assumed that pulmonary vasoconstriction resulted from reflex activation of sympathetic nerves; however, the increase in P_{PA} during early asphyxia proved resistant to spinal cord transection at or above the level of the seventh dorsal spinal nerves, whereas the increase in P_a was markedly reduced by these procedures (212, 2115). Indeed, because the P_{PA} response to asphyxia persisted after transection of the spinal cord at the medulla, Bradford and Dean (212) suggested in 1894 that it was caused in part by "a direct action of the venous blood on the walls of the pulmonary arterioles."

In 1904, Plumier (1530) reported that ventilation with hydrogen **(FIGURE 2*A*)**, prepared "as pure as possible," or occlusion of the trachea caused changes in P_{PA} and P_a in spontaneously breathing dogs similar to those induced by cessation of artificial ventilation in paralyzed dogs. He concluded that "asphyxia always causes an increase in pulmonary arterial pressure, whether produced by suspending artificial respiration in open-chest dogs or obtained by breathing hydrogen or obstructing the trachea of a closed-chest animal." Furthermore, he stated that "…we must admit with Bradford and Dean that under the influence of asphyxia pulmonary vessels constrict, which causes a rise in pressure in the pulmonary artery." Implicit in Plumier's statements and experimental design is the notion that pulmonary vasoconstriction during asphyxia was caused by hypoxia.

Over the next 42 years, however, only a few studies addressed this possibility. In 1924, Löhr (1122) used the ex vivo isolated lung preparation developed 20 years earlier by Brodie and Dixon (222) to determine, among other things, the effect of ventilation with O_2 or N_2 on pulmonary vessels in the absence of neural input from outside the lungs. This preparation avoided uncertainties associated with inferring alteration of pulmonary vasomotor tone from changes in P_{PA} when cardiac output was unknown, since the lungs were perfused with defibrinated blood at constant pressure, and pulmonary vascular constriction or dilation was measured directly as decreases or increases in perfusate flow. In isolated cat lungs, Löhr found that O_2 ventilation had "only a small effect, if any, on pulmonary vessels, which expresses itself as a small decrease in tone." With respect to N_2 ventilation, "no specific effect on the pulmonary vessels was determined with certainty. Sometimes there is a temporary vascular relaxation that soon converts to an increase in

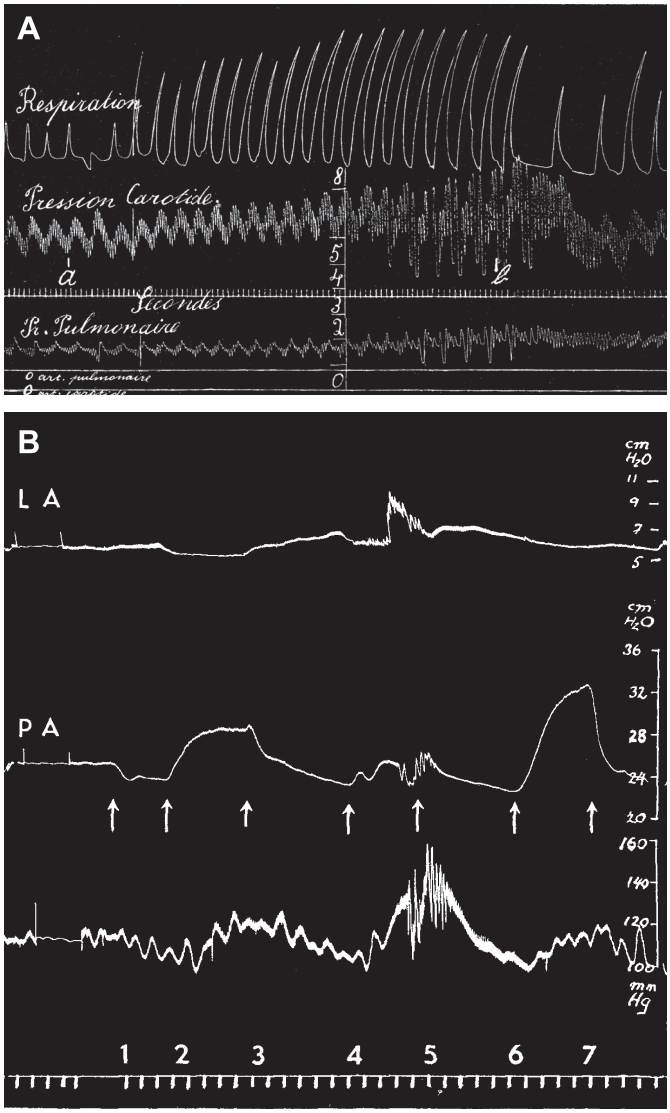


FIGURE 2 Time course of respiration, carotid arterial pressure ("Pression Carotide"), and pulmonary arterial pressure ("Pr. Pulmonaire") recorded in a closed-chest spontaneously breathing dog by Plumier in 1904 (1530) (*A*) and pressures in the left atrium (LA), pulmonary artery (PA), and carotid artery (third tracing from the top, unlabeled) recorded in an open-chest artificially ventilated cat by von Euler and Liljestrand in 1946 (1987) (*B*). In *A*, time marks at 1-s intervals are shown in the third tracing from the top; zero pressure baselines are shown at the bottom; and the interval "from *a* to *b* (indicates) hydrogen breathing. Asphyxiation by hydrogen produced an increase in pressure in the pulmonary artery and the carotid artery (1530)." In *B*, changes in inspired gas concentrations are indicated at arrows by numbers [*1* = 100% O_2 (from air), *2* = 6.6% CO_2 in O_2, *3* = 100% O_2, *4* = 18.7% CO_2 in O_2, *5* = 100% O_2, *6* = 10.5% O_2 in N_2, *7* = 100% O_2], pressure scales are shown at the *right*, and time marks at 30-s intervals are shown at the *bottom*.

tone, but often the opposite reaction is observed." In a brief communication to the Société de Physiologie in 1942, Beyne (165) reported that ventilation of chloralosed dogs with inspired O_2 tensions (P_IO_2) <70 mmHg increased P_{PA} from 30 mmHg at baseline to a high of 45 mmHg at a "fictitious altitude" of 8,000 m, which most likely corresponded to a fractional inspired O_2 concentration (F_IO_2) of ~8% and a P_IO_2 of ~54 mmHg. In additional experiments, Beyne found that decreased P_IO_2 had no affect on the pressure required to maintain a constant flow of heparinized blood through the circulation of the left lower lobe, which he isolated in vivo; therefore, he concluded that the hypoxia-induced increases in P_{PA} observed previously were due to increases in cardiac output rather than constriction of pulmonary vessels.

The study that launched the current era of investigation of hypoxic pulmonary vasoconstriction (HPV) was published in 1946 by von Euler and Liljestrand (1987). To determine "in what way the lung vessels react to variations in the blood gases," they ventilated anesthetized open-chest cats with various concentrations of O_2 and CO_2. 100% O_2 caused a small decrease in P_{PA}, whereas 10.5% O_2 caused a large increase **(FIGURE 2*B*)**. Ventilation with 6.5–20% CO_2 in O_2 also increased P_{PA}, but to a lesser extent. As subsequently stated by Liljestrand (1094), these results were "somewhat unexpected," suggesting that the authors may not have been aware of the previous work on asphyxia (164, 212, 1092, 1401, 1434, 2115) and ventilation with hypoxic gas mixtures (165, 1122, 1530). Since the increase in P_{PA} induced by hypoxia occurred with little or no change in left atrial pressure, exceeded the increase in P_{PA} caused by moderate exercise (which they assumed to cause a 2- to 3-fold increase in cardiac output), and was not prevented by vagotomy or removal of the stellate ganglia, they concluded that it was due in part to a direct constrictive action of hypoxia on the pulmonary vessels, as suggested by Bradford and Dean in 1894 (212).

Just as significant, however, was von Euler and Liljestrand's insight that HPV could lead to "an adequate distribution of the blood through the various parts of the lungs according to the efficiency of aeration (1987)," i.e., they proposed that HPV was the mechanism that optimized oxygenation of blood in the lung by matching local perfusion to local ventilation. That such a mechanism should exist had been hypothesized 24 years earlier by Haldane, who stated, "It is evident that in any particular air-sac system the mean composition of the contained air will depend on the ratio between the supply of fresh air and the flow of blood. If the supply of fresh air is unusually small in relation to the supply of venous blood, there will be a lower percentage of oxygen and higher percentage of carbon dioxide in the air of the air sac, and vice versa. It seems probable that by some means at present unknown to us a fair adjustment is maintained normally between air supply and blood supply. For instance, the muscular walls of bronchioles may be concerned in adjusting the air supply, or the arterioles or capillaries may contract or dilate so as to adjust the blood supply (715)."

These ideas found fertile ground as the quantitative understanding of pulmonary gas exchange developed in the years

following World War II. HPV was quickly confirmed in humans by Motley (1328), Westcott (2080), Doyle (431) and their respective coinvestigators; in intact animals by Dirken and Heemstra (414, 415), Atwell et al. (73), Peters and Roos (1509), Hall (723), Rahn and Bahnson (1579), Stroud and Rahn (1849) and Duke (447); and in isolated lungs by Nisell (1395), Duke (445, 446), and Duke and Killick (448). Most of the intact animal studies demonstrated that regional ventilation of the lung with hypoxic gas mixtures caused diversion of cardiac output away from the hypoxic region (73, 414, 415, 1509, 1579). The isolated lung studies confirmed not only that the pulmonary pressor response to hypoxia was caused by vasoconstriction, since the lungs were perfused at constant flow and outflow pressure, but also that HPV did not depend on neural or humoral influences from outside the lung. These studies validated the insight of von Euler and Liljestrand that hypoxia could act through local mechanisms to cause pulmonary vasoconstriction and thereby regulate local ventilation-perfusion relationships.

Since publication of von Euler and Liljestrand's paper (1987), many investigators have worked hard to identify the mechanisms of HPV. Two general hypotheses have been considered, both of which remain viable: *1*) hypoxia causes pulmonary vasoconstriction indirectly by activating a vasoconstrictor and/or inactivating a vasodilator produced somewhere in the lung, which then secondarily causes contraction of pulmonary vascular smooth muscle; and *2*) hypoxia causes pulmonary vasoconstriction through a direct contractile effect on pulmonary vascular smooth muscle. With respect to the first possibility, early work in intact animals and isolated lungs demonstrated that a wide variety of endogenous substances could increase pulmonary vasomotor tone, but none emerged as a unique mediator of HPV (533, 1248, 1982, 2043). Nevertheless, as discussed below, more recent experiments in isolated pulmonary arteries suggest that HPV may depend in part on substances released from endothelial cells. The nature of this dependence is an area of active investigation.

With respect to the second possibility, Bergofsky and Holtzman (150) reported in 1967 that hypoxia reversibly decreased intracellular [K^+] and increased intracellular [Na^+] in pulmonary arterial segments stripped of adventitia and intima, but not in similarly treated segments of pulmonary veins or systemic arteries. Calculations using the Nernst equation indicated that these changes were associated with depolarization of pulmonary arterial smooth muscle, which had to result from a direct effect of hypoxia on these cells. Additional support for this conclusion appeared in 1976, when McMurtry et al. (1242) demonstrated that antagonists of the L-type voltage-operated Ca^{2+} channels found in vascular smooth muscle strongly inhibited pressor responses to hypoxia in isolated lungs; and in 1985, when Madden et al. (740, 1157) reported that hypoxia caused both depolarization and constriction in small pulmonary arteries of the cat. However, definitive confirmation of the central role played by the pulmonary arterial smooth muscle cell (PASMC) in HPV did not occur until the early 1990s, when it was reported by Murray (1341, 1342), Post (1545), and Madden (1160) and their associates that hypoxia caused both depolarization and contraction of isolated PASMC. One obvious and important conclusion to be drawn from these data is that the essential sensor, transducer, and effector mechanisms of HPV are contained in the pulmonary arterial myocyte.

B. About This Review

Over the last 20 years, a large amount of work using the powerful techniques of cellular and molecular biology has been performed to clarify the effects of hypoxia in PASMC. This work is a major focus of our review. For purposes of discussion, we distinguish between mechanisms that mediate and modulate HPV. Mediation includes mechanisms that are both intrinsic to PASMC and required for HPV. Modulation includes mechanisms intrinsic to PASMC that alter but are not required for HPV, as well as mechanisms extrinsic to PASMC that alter HPV. We emphasize that these distinctions are intended to provide a framework for discussion, and not to indicate the relative importance of a particular mechanism. Indeed, as we shall see, full expression of HPV is likely to require interaction of intrinsic and extrinsic mechanisms.

Another major focus is the relation of results obtained in reduced preparations, such as isolated vessels and cells, to results obtained in more intact preparations, such as isolated lungs and intact animals. Although reduced preparations allow more exact testing of hypotheses, they are vulnerable to experimental conditions and other factors that can render results inapplicable to the real world. Conversely, intact preparations generally yield results that are relevant to reality, but their complexity can preclude precise testing of hypotheses. In this context, comparisons of reduced and intact preparations are essential, particularly for stimuli like hypoxia that affect many biological processes. Thus we discuss the response characteristics and mechanistic investigations in both types of preparations in some detail, and compare results whenever useful. Finally, because they give HPV its importance, we review results relevant to the roles played by HPV in physiological and pathophysiological situations, including the fetal-neonatal transition, pulmonary gas exchange, high-altitude pulmonary edema, and pulmonary hypertension.

From its beginning, HPV research has been characterized by controversy. In this review, we try to present all sides of current disagreements fairly and objectively, make sound conclusions on the basis of the best available data, and present these data in enough detail so that readers can make

up their own minds. To emphasize results rather than reputations, we do not name investigators in the text, except for authors of a few historically significant studies. This approach does not always provide pat answers; however, in our view, lingering uncertainty is preferable to premature explanations that may be more concise than correct.

II. CHARACTERISTICS

A. Intact and Isolated Lungs

1. Measurement of stimulus and response

Since HPV is initiated locally, and the lung consumes a negligible amount of the O_2 delivered to it via ventilation and blood flow, it has been assumed that the P_{O_2} stimulus for HPV (P_sO_2) is determined by O_2 tensions in alveolar gas (P_AO_2) and mixed venous blood ($P_{mv}O_2$). Indeed, changing one independently of the other in ventilated lungs (142, 753, 826, 841, 1197, 1199, 1487) or changing $P_{mv}O_2$ in atelectatic lungs (424) altered pulmonary vasomotor tone. Quantification of these effects allowed estimation of P_sO_2 as a weighted average of alveolar and mixed venous P_{O_2}; e.g., for the dog, $P_sO_2 = P_AO_2^{0.62} + P_{mv}O_2^{0.38}$ (1190, 1197). Given such weighting and the fact that steady-state P_AO_2 exceeds $P_{mv}O_2$ in the intact animal, P_sO_2 is dominated by P_AO_2. Thus, to quantify the HPV stimulus in intact lungs, most investigators either calculated P_AO_2 or estimated it by measuring O_2 tension in pulmonary venous or systemic arterial blood (P_aO_2).

These considerations ignore a possible contribution to P_sO_2 by P_aO_2, which is the O_2 tension in blood supplied to the vasa vasorum of larger pulmonary arteries by the bronchial circulation. Most investigators believe this omission is reasonable, since bronchial blood flow is so much smaller than pulmonary blood flow. Nevertheless, when the bronchial circulation of sheep was perfused at a pressure 40 mmHg higher than mean systemic arterial pressure (and thus at higher bronchial blood flow), decreases in bronchial arterial P_{O_2} caused modest HPV during ventilation with air, but not during ventilation with 100% O_2 (1194). Whether P_aO_2 is a significant determinant of P_sO_2 in intact animals remains unclear.

The situation is simpler in isolated lungs, where hypoxia is typically generated by ventilation with hypoxic gas mixures, pulmonary perfusate is recirculated, and the bronchial circulation is unperfused. If the perfusion circuit is impermeable to gas, the HPV stimulus can be measured simply as P_{O_2} in inspired gas, expired gas, or perfusate at equilibrium. However, when hypoxia was generated by decreasing P_{O_2} in inflowing perfusate during normoxic ventilation, effects on pulmonary vasomotor tone varied with the type of perfusate. In blood-perfused lungs ventilated with air, decreases in perfusate P_{O_2} caused HPV (1197, 1199). In lungs perfused with physiological salt solution, decreases in perfusate P_{O_2} did not alter pulmonary vasomotor tone, even after erythrocytes were added to achieve a perfusate Hct of 5% (2057). In the latter experiments, because of the low solubility of O_2 in water and low Hct, only a small amount of O_2 would need to diffuse from alveolar gas to perfusate to raise perfusate P_{O_2} above levels required to stimulate HPV. Moreover, departure of this amount of O_2 from alveolar gas would cause only a small decrease in alveolar P_{O_2}. As a result, perfusate and gas would equilibrate at a P_{O_2} much closer to the normoxic O_2 tension in the inspired gas than the hypoxic O_2 tension in the inflowing perfusate.

The most accurate way to evaluate the HPV response is to measure the relationship between the rate of pulmonary perfusion ($\dot{Q}$) and driving pressure. The latter is usually assumed to equal the difference between mean pulmonary arterial and left atrial pressures ($P_{PA} - P_{LA}$), where P_{LA} can be measured directly or estimated as pulmonary arterial wedge pressure (P_w). Vasoconstriction due to hypoxia or other stimuli shifts the pressure-flow relation to higher pressures (818, 1190, 1483, 1867, 2081). This approach has been used most often in isolated lungs, where pressures and flows can be conveniently controlled and measured. A derivative approach is to measure pressure at constant flow, or flow at constant pressure; however, HPV in isolated lungs perfused at constant flow was less than in lungs perfused at constant pressure, probably due to progressive closure of pulmonary vessels during constant pressure perfusion (179, 319). This vascular derecruitment could be reversed by increasing perfusion pressure, but not by resuming normoxic ventilation at constant perfusion pressure (179, 319). Nevertheless, both approaches have been used to measure HPV stimulus-response relations in isolated lungs (1852).

Measurements of the relation between P_{PA}-P_w and $\dot{Q}$, or P_{PA}-P_w at constant $\dot{Q}$, have also been used to assess HPV in intact animals, where cardiac output was controlled by obstruction of the inferior vena cava and/or opening of systemic arterial-venous fistulas (218, 423, 1065, 1119). Although these approaches allow more accurate assessment of pulmonary vascular constriction and dilation, care must be taken to avoid undesired effects, such as changes in mixed venous and arterial blood gases and pH, and activation of sympathoadrenal responses. More often, HPV has been quantified in intact animals by measuring pulmonary vascular resistance (PVR), defined as $(P_{PA} - P_w)/\dot{Q}$. At constant $\dot{Q}$, PVR would increase if HPV shifted the pulmonary vascular pressure-flow relation to higher pressures; however, PVR would also increase if $\dot{Q}$ decreased without a change in the pressure-flow relation. This occurs because the pressure-flow relation is curvilinear; i.e., $d[P_{PA} - P_w]/d\dot{Q}$ decreases with increasing pressure and flow because of recruitment and distention of pulmonary vessels. Thus it could be erroneous to interpret changes in PVR to indicate

changes in pulmonary vasomotor tone when increases in PVR are associated with decreases in $\dot{Q}$, or vice versa.

Another strategy used in intact animals is to ventilate a region of lung, such as the left lower lobe or left lung, with an hypoxic gas mixture while ventilating the remaining lung with 100% O_2 to avoid systemic hypoxemia and secondary changes in cardiac output. HPV is then quantified by diversion of blood flow away from the hypoxic region, calculated as the decrease in regional flow divided by its hyperoxic baseline value. However, if larger and larger regions of lung are made hypoxic, $P_{PA} - P_{LA}$ will progressively increase because more and more of the vasculature becomes constricted (1192). Although this increase will be the same throughout the lung, pressure-induced inhibition of HPV in the hypoxic region and/or pressure-induced vasodilation in remaining lung could cause flow diversion to be different from the value it would have if $P_{PA} - P_{LA}$ were constant. Indeed, as the size of the hypoxic region approaches that of the total lung, diversion of regional flow will approach 0 and $P_{PA} - P_{LA}$ will approach a maximum. In dogs, for example, diversion of regional flow fell from 67 to 22% and the increase in $P_{PA} - P_{LA}$ rose from 14 to 85% of baseline as the size of the hypoxic region was increased from a single lobe to one lung plus a contralateral lobe (1192). Thus measurement of HPV as flow diversion during regional hypoxia should be limited to lung regions small enough to preclude changes in P_{PA}.

2. Temporal characteristics

For mechanisms of HPV to be fully understood, the relationships among time, P_{O_2}, and the magnitude of pulmonary vasoconstriction must be known. The time course of HPV during 20–210 min of mild to moderate global lung hypoxia (P_{O_2} 30–50 mmHg) has been evaluated by serial assessment of PVR in awake humans (428, 1885) and intact anesthetized dogs (1946) and pigs (1022); and P_{PA} at constant $\dot{Q}$ in isolated lungs of pigs (1867) and ferrets (2091). In general, these studies indicate that HPV increased to a maximum within 15 min, and was then maintained at or near this level for an additional 15–45 min. Beyond this time, HPV either remained constant in anesthetized pigs for 3 h (1022) or increased further in awake humans to achieve a new higher plateau at ~2 h that was maintained for the remainder of an 8-h exposure (428, 1885). One exception was the intact dog (1946), in which PVR increased to a maximum within 5 min and then fell during the remainder of a 20-min hypoxic exposure. In all of these studies, efforts were made to maintain P_ACO_2 constant.

Similar time courses were reported for mild to moderate regional hypoxia when HPV was quantified as diversion of blood flow from the atelectatic left lung of dogs (613) or right-to-left shunt in rabbits with an unventilated N_2-filled left lung (1969). Mixed venous P_{O_2}, the main determinant of P_sO_2 under these conditions, ranged between 45 and 55 mmHg. In the dogs (613), regional HPV increased gradually over 1 h and then remained constant for 3 more hours. In the rabbits (1969), shunt measurements suggested that regional HPV increased to a plateau within 5 min that was maintained until 2 h, when an additional gradual increase in HPV finally returned shunt to its control value at 6 h.

The time course of HPV during severe global lung hypoxia (P_{O_2} <30 mmHg) has been examined over 20–180 min in intact lungs (1170, 1946), lungs isolated in vivo by means of biventricular cardiac bypass (2072, 2073), and lungs isolated ex vivo (319, 477, 1643, 1867, 2053, 2057, 2091). In these investigations, HPV was quantified as the increase in driving pressure or PVR, and flow was constant except for one study in intact lungs (1170). Species included dog (1170, 1946), pig (1867), ferret (2091), rabbit (319, 2057), rat (477, 1643), and mouse (2053, 2066). Although the magnitude of HPV varied widely among species and preparations, the time courses of the relative responses were remarkably consistent. Severe global hypoxia caused an initial increase in pulmonary vasomotor tone to a maximum within 10–15 min, followed by a 20–100% decline at 15–50 min and a gradual increase to near maximal levels at 30–180 min.

During severe regional hypoxia, however, the time course was different. Regional HPV was quantified as diversion of blood flow from the hypoxic left lung or left lower lobe of dogs (141, 421) and right apical lobe of sheep (1764). In these studies, there was little or no change in cardiac output or P_{PA}, confirming that diversion of regional flow was a reasonable index of regional vasomotor tone. The results indicated that severe regional hypoxia caused vasoconstriction that achieved a maximum within 15–30 min and then did not change or increased slightly over the ensuing 30–225 min. Why the time course of HPV during severe regional hypoxia differed from that during severe global hypoxia is not known. Possibly, the decrease in HPV after its initial increase during global hypoxia was caused by very low O_2 tensions not achieved during regional hypoxia. For example, during severe regional hypoxia, P_sO_2 may have been higher than expected on the basis of inspired or alveolar P_{O_2} because mixed venous and bronchial arterial O_2 tensions were normal and unchanged, whereas both were decreased during severe global hypoxia. Alternatively, as observed during severe global hypoxia in isolated lungs perfused at constant pressure (179, 319), pulmonary arteries closed by HPV during severe regional hypoxia may not have reopened when regional vasomotor tone fell because there was little or no change in P_{PA}.

From a purely descriptive viewpoint, these data suggest that HPV in intact and isolated lungs occurs in three phases **(FIGURE 3*A*)**: *1*) rapidly developing vasoconstriction at 0–30 min that is not sustained when P_{O_2} is less than ~30 mmHg; *2*) more gradually developing sustained vasocon-

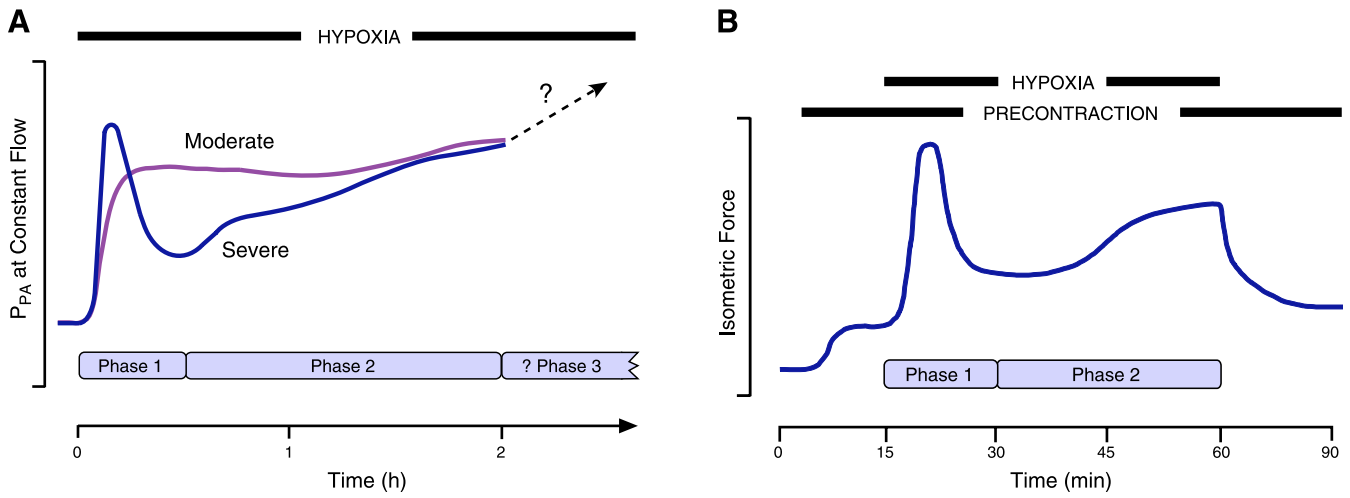


FIGURE 3 Representative time courses of pressor responses of isolated lungs or lung lobes to moderate and severe hypoxia (*A*) and contractile responses of precontracted isolated pulmonary arteries to severe hypoxia (*B*). In each case, phases of HPV are indicated, as discussed in the text.

striction at 30–120 min; and possibly, *3*) augmentation of sustained vasoconstriction at times >120 min. With respect to underlying mechanisms, phases 1 and 2 have received the most investigative attention; however, the relationship of these phases to the biphasic contractile response caused by severe hypoxia in isolated pulmonary arteries, discussed below (**FIGURE 3*B***; see sect. II*B1*), remains unclear. There have been no mechanistic studies of phase 3 HPV, which needs to be confirmed in other preparations.

3. Stimulus-response relation

Characteristics of HPV stimulus-response relations measured in intact and isolated lungs are shown in **TABLE 1**. The O_2 tensions used to quantify stimulus are indicated. Responses are expressed as percentage changes in perfusion pressure or regional flow from baseline, depending on the preparation. To allow quantitative comparisons between these different types of response, changes in regional flow are also expressed as percentage changes in resistance when perfusion pressure did not change significantly. These values are shown in parentheses next to the maximum flow responses induced by HPV. With a few exceptions, shown in italics, all studies attempted to maintain P_ACO_2 constant during hypoxic exposures. Some data were extracted from published figures, and thus are subject to errors associated with such estimations.

Many studies of the relation between HPV and P_{O_2} in intact and isolated lungs used hypoxic exposures ≤10 min in duration **(TABLE 1)**. At these durations, HPV began to occur at an average threshold stimulus P_{O_2} of 83 ± 5 mmHg, was 50% of maximum at a P_{O_2} of 55 ± 4 mmHg, and was maximum at a P_{O_2} of 19 ± 3 mmHg. At longer durations (15–50 min), these O_2 tensions increased to 95 ± 9 ($P >$ 0.2), 73 ± 6 ($P < 0.02$), and 37 ± 4 ($P < 0.0002$) mmHg, respectively. Maximum HPV expressed as percentage change in resistance from baseline averaged 198 ± 52% during short exposures and 267 ± 116% during long exposures ($P > 0.6$). These results suggest that longer hypoxic exposures shifted the stimulus-response relation to higher O_2 tensions, but did not change maximum HPV. This conclusion is supported by a direct comparison of short (10 min) and long (20–50 min) hypoxic exposures in isolated pig lungs (1867).

Stimulus-response studies in intact dogs (103, 142, 218, 1899), ferrets (1852), and pigs (373, 790, 1828) as well as isolated lungs of cats (1483), ferrets (1483, 1852), pigs (1867), rabbits (1483), rats (1247), and sheep (2081) demonstrated that HPV could fall below its maximum at very low P_{O_2}. From **TABLE 1**, exposure to an average O_2 tension <27 ± 2 mmHg was required to decrease HPV. The maximum decrease averaged 29 ± 8% of peak HPV and occurred at a P_{O_2} of 12 ± 3 mmHg. This effect on the stimulus-response relation most likely represents the vasodilation component of Phase 1 HPV seen during severe global hypoxia **(FIGURE 3*A*)**, as discussed above.

4. Site of HPV

HPV has been localized functionally with respect to vascular sites of gas exchange, fluid filtration, blood volume, and compliance, as well as vascular surrounding pressure; and anatomically by histological methods and measurements of pressures and/or diameters in anatomically defined vessels.

A) FUNCTIONAL LOCALIZATION. *I) Gas exchange.* Perfusion of isolated cat lungs with a constant flow of partially deoxygenated blood during ventilation with air did not alter P_{PA}, but ventilation with hypoxic gas mixtures increased inflow pressure during both forward and reverse perfusion, suggesting that HPV occurred in vessels that exchanged O_2 (447). Such vessels obviously included capillaries, but pul-

Table 1 HPV stimulus-response relationships

Species	Prep	Test Lung	Time, min	Stim Index	Resp Index	Constriction: P_{O_2} Stimulus (mmHg) Threshold	Constriction: P_{O_2} Stimulus (mmHg) Half-Max	Constriction: P_{O_2} Stimulus (mmHg) Max	Constriction: Max Response (% Baseline)	Dilation: P_{O_2} Stimulus (mmHg) Threshold	Dilation: P_{O_2} Stimulus (mmHg) Max	Dilation: Max Response (% Max Constriction)	Reference
Calf	Intact	Whole	"min"	P_aO_2	PVR	50	30	20	80		Not observed		1674
Cat	Intact	LLL	~5	$P_{pv}O_2$	$\dot{Q}_{LLL}$	*100*	*~60*	*25*	*68 (213)*		*Not observed*		*103*
	IPL	Whole	20–50	P_AO_2	$P_{PA}(\dot{Q})$	75	55	25	46	<10	0	100	1483
Dog	Intact	Whole	4	P_aO_2	PVR			28	86		Not observed		1946
			20	P_aO_2	PVR			44	30		28	67	1946
			5–10	P_AO_2	P_{PA}-P_{LA}	80–110	69	25	122		Not observed		1192
			20–30	P_IO_2	PVR	*130*	*130–150*	*70*	*63*	*<70*	*67*	*55*	*1899*
			10–30	P_IO_2	P_{PA}-$P_w(\dot{Q})$	150	110	71	133	<71	29	47	218
					P_aO_2				32	<32			
		Whole LLL	15	P_AO_2	PVR	165	123	66	143	34	15	50	142
		LL	20	P_AO_2	$\dot{Q}_{LL}$	>84	~75	38	50 (100)		Not observed		473
		LLL or RLL	5–10	P_AO_2	$\dot{Q}_{LLL}$ or $\dot{Q}_{RLL}$	80–110	81	17	67 (203)		Not observed		1192
			~5	$P_{pv}O_2$	$\dot{Q}_{LLL}$	*100*	*~65*	*20*	*53 (113)*	*33 (ln 2/7)*	*14 (ln 2/7)*	*17 (ln 2/7)*	*103*
			2–3	P_AO_2	$\dot{Q}_{LLL}$	100	70	22	50 (100)		Not observed		143
	IPL	Whole	20–50	P_AO_2	$P_{PA}(\dot{Q})$		Not observed				Not observed		1483
Ferret	Intact	LLL	5–10	$P_{ET}O_2$	$\dot{Q}_{LLL}(P_{PA})$	*90*	*~55*	*18*	*63 (170)*	*18*	*7*	*47*	*1852*
					$P_{PA}(\dot{Q})$	*76*	*~50*	*12*	*93*	*19 (ln 3/9)*	*10 (ln 3/9)*	*22 (ln 3/9)*	
	IPL	Whole	5–10	$P_{ET}O_2$	$\dot{Q}(P_{PA})$	45	~35	13	90 (900)		Not observed		1852
					$P_{PA}(\dot{Q})$	58	~30	7	215	11 (ln 4/9)	1 (ln 4/9)	50 (ln 4/9)	
			20–50	P_AO_2	$P_{PA}(\dot{Q})$	50	38	25	185	<25	0	96	1483
Human	Intact	LL	25	P_IO_2	$\dot{Q}_{LL}$	>86	57	36	40 (67)		Not observed		727
Pig	Intact	Whole	8	P_aO_2	P_{PA}-$P_w(\dot{Q})$	80	~65	38	121	<38	34	53	373
			20	P_aO_2	PVR	86	65	47	143	32	26	42	1828
			20	P_aO_2	PVR	88	62	40	77	40	31	48	790
		LL	20	P_AO_2	$\dot{Q}_{LL}$	>84	>84	38	95 (1900)		Not observed		473
	IPL	Whole	20–50	P_AO_2	$P_{PA}(\dot{Q})$	100–200	89	60–30	240	<30	0	100	1867
			10	P_AO_2	$P_{PA}(\dot{Q})$	~100	65	0	227		Not observed		1867
Pony	Intact	LL	20	P_AO_2	$\dot{Q}_{LL}$	>83	~73	33	76 (317)		Not observed		473
Rabbit	IPL	Whole	10	P_AO_2	$P_{PA}(\dot{Q})$	~90	43	0	80		Not observed		2057
			20–50	P_AO_2	$P_{PA}(\dot{Q})$	50–100	64	25	82	<25	0	57	1483
Rat	IPL	Whole	6	P_AO_2	$P_{PA}(\dot{Q})$	40–80	32	20	120		Not observed		1198
			10	$P_{pv}O_2$	$P_{PA}(\dot{Q})$	75	~55	33	200	<33	17	19	1247
Sheep	Intact	RAL	≥40	$P_{ET}O_2$	$\dot{Q}_{RAL}$	≤100	70	25	87 (669)		Not observed		1761
	IPL	Whole	20–50	P_AO_2	$P_{PA}(\dot{Q})$	100	80	25	70	<25	0	139	2081

Preparation (Prep), isolated perfused lung (IPL) or intact animal (Intact); time, duration of hypoxic exposure; stimulus (Stim), P_{O_2} at maximum (Max), half-maximum, and threshold responses (Resp). Numbers in parentheses under maximum constriction response are flow responses expressed as % change in resistance, assuming constant pressure. $\dot{Q}$, perfusate flow; P_{PA}, pulmonary arterial pressure; P_w, pulmonary arterial wedge pressure; P_{LA}, left atrial pressure; PVR, pulmonary vascular resistance; LL, left lung; LLL, left lower lobe; RAL, right apical lobe; A, alveolar; a, arterial; pv, pulmonary venous; I, inspired; ET, end-tidal. $\dot{Q}$ or P_{PA} in parentheses indicate that these variables were constant. *Italics* means alveolar P_{CO_2} not controlled.

monary arteries can also exchange gas (331, 881, 1811). Other studies revealed that changes in perfusate P_{O_2} could alter the pressor response to ventilatory hypoxia during forward perfusion, but had little or no effect during reverse perfusion (149, 841, 1199). These results suggested that HPV occurred on the arterial side of vessels participating in gas exchange. In support of this possibility, inhibition of HPV in isolated rat lungs by equimolar perfusate concentrations of the anesthetic halothane was most effective when halothane was administered in inspired gas, less effective when administered in pulmonary arterial blood during forward perfusion, and least effective when administered in pulmonary venous blood during reverse perfusion (180).

II) Fluid filtration. In isolated rat lungs perfused at constant flow, ventilatory hypoxia increased inflow pressure but had no consistent effect on lung weight during forward perfusion: however, both inflow pressure and lung weight gain were increased by hypoxia during reverse perfusion, suggesting that HPV occurred in vessels on the arterial side of the permeable region of the pulmonary vasculature (3). In isolated lung lobes of dogs, estimates of capillary pressure as intravascular pressure at the site of filtration determined by the isogravimetric technique (576, 1457) suggested that 68% of total pulmonary vascular resistance was on the arterial side of capillaries and 32% on the venous side, and that hypoxia increased only arterial resistance (1468). Consistent with these results, ventilation of awake sheep with 10% O_2 increased P_{PA} and cardiac output but did not change lung lymph flow, the lymph-to-plasma protein concentration ratio, or extravascular lung water (183). In contrast, hypoxia increased lung lymph flow and decreased the lymph-to-plasma protein concentration ratio in newborn lambs (215) and P_{PA} and filtration rate in isolated pig lungs perfused at constant flow (1295). These results suggested that the site of HPV was within or downstream from the permeable region of the vasculature and might vary with age or species.

These conclusions assume that changes in filtration were caused by HPV-induced changes in intravascular hydrostatic pressure and not by changes in intravascular or interstitial osmotic pressure, interstitial hydrostatic pressure, or the area and permeability of the vasculature. However, hypoxia can cause capillary recruitment (254) and derecruitment (370, 614) and may also change vascular permeability (2086). Furthermore, pulmonary arteries and veins may be more permeable per unit surface area than capillaries (25, 1466, 1467). Thus determining the effects of hypoxia on lung fluid filtration is an imprecise way to identify the vessels responsible for HPV.

III) Vascular volume. In the ether bolus technique, the mean transit time of a saline solution of ether from its site of injection (usually, the pulmonary artery) to the pulmonary capillaries is determined from the time course of the change in tracheal pressure or lung gas volume caused by diffusion of ether from blood into alveolar gas (369, 505). Vascular volume between the injection site and capillaries can then be calculated as the product of mean transit time and perfusate flow. In isolated cat lungs, hypoxia decreased arterial and venous blood volumes, determined by the ether bolus method during forward and reverse perfusion, respectively, but did not alter capillary blood volume, determined by subtracting arterial and venous volumes from total pulmonary blood volume, calculated as the product of perfusate flow and the mean transit time of indocyanine green dye across the entire pulmonary vasculature (369). These results suggested that both pulmonary arteries and veins constricted in response to hypoxia.

The low-viscosity bolus method (223) was used to estimate the site of HPV relative to pulmonary vascular volume in isolated dog lungs (370, 661, 662). In this approach, a bolus of saline is injected into the pulmonary artery during perfusion with a constant flow of blood as pressure and perfusate viscosity are measured continuously at entry and exit of the vasculature. Typically, pulmonary artery pressure declines and then returns to baseline in a manner thought to depend on the position and shape of the bolus within the vasculature and the resistance encountered as the bolus traverses the lung. The analysis suggested that HPV occurred in small pulmonary arteries, causing an increase in upstream volume that was exceeded by a decrease in downstream volume due to vascular derecruitment. The strength of these conclusions depends on assumptions concerning bolus dispersion, vascular geometry, and longitudinal distribution of vascular resistance (662). The validity of these assumptions is unknown.

IV) Vascular compliance. In the pulmonary inflow/outflow occlusion technique, perfusate inflow or outflow is suddenly occluded as pulmonary arterial or left atrial pressure are monitored. The sudden decrease in pulmonary arterial pressure caused by inflow occlusion (ΔPa) is interpreted to result from cessation of flow across relatively noncompliant arterial vessels extending from the pulmonary artery to a compliant middle region of the vasculature. The sudden increase in left atrial pressure caused by outflow occlusion (ΔPv) is interpreted to result from cessation of flow across relatively noncompliant venous vessels extending from the left atrium to the compliant middle region. In normoxic dog lung lobes (709, 713), the sum of ΔPa and ΔPv was less than the total gradient across the vasculature ($\Delta Pt = P_{PA} - P_{LA}$), indicating a pressure gradient across the middle compliant region ($\Delta Pm = \Delta Pt - \Delta Pa - \Delta Pv$). Hypoxia increased all three gradients, but 75% of the total increase occurred in the middle region (714). Qualitatively similar results were obtained in isolated lungs of pigs (1648), cats (712), and lambs (637, 1914).

In the double occlusion technique (371), inflow and outflow are occluded simultaneously, causing P_{PA} and P_{LA} to equilibrate at a static double occlusion pressure (P_{do}), which is theoretically equal to the average of pressures in all vascular regions during flow, each weighted by regional vascular compliance expressed as a fraction of total vascular compliance (225). P_{PA}-P_{do} and P_{do}-P_{LA} can be interpreted as pressure gradients driving flow through arterial and venous regions, respectively, that have resistance but no compliance and are separated by a middle region that has compliance but no resistance. In isolated ferret lungs perfused at different flows and constant P_{LA}, hypoxia increased P_{PA}-P_{do} markedly and P_{do}-P_{LA} slightly, and did not alter vascular compliance, indicating that HPV occurred mainly in the arterial region (225). Similar results were obtained in lungs of neonatal pigs (1369). These results are not necessarily inconsistent with inflow/outflow occlusion data discussed above, which suggested that HPV occurred predominantly in the middle compliant region (637, 712, 714, 1648, 1914). Upon inflow occlusion P_{PA} will fall to the pressure in the first compliant region in the pulmonary vasculature, while upon outflow occlusion P_{LA} will rise to the pressure in the last compliant region. In contrast, P_{do} is determined by all compliant regions.

Although it is generally accepted that the arterial region contains arteries, the venous region veins, and the middle region capillaries, several laboratories attempted to define the anatomic boundaries of these regions more precisely. In isolated canine lung lobes, comparison of pressures measured by inflow/outflow occlusion to those measured by small catheters in pulmonary arteries and veins suggested that the middle region contained vessels with diameters as large as 1,200 μm (1277). Subsequent studies in the same preparation using vascular micropuncture and the retrograde catheter technique indicated that diameters of vessels composing the arterial and venous regions were 50–900 μm, implying that the middle region was composed of vessels with diameters $<$50 μm (710). In isolated lamb lungs, however, comparison of micropuncture and occlusion pressures suggested that the middle region included arteries as large as 80 μm and veins as large as 150 μm (516). In isolated pig lungs, measurements of ΔPa, ΔPm, and ΔPv after lobar arterial ligation or pulmonary arterial embolization with beads of known diameters suggested that the arteries forming the boundary between the arterial and middle regions had diameters $>$2–3 mm (1913). Collectively, these results indicate that the middle region defined by vascular occlusion contains muscularized arteries and veins, as well as capillaries. Thus occurrence of HPV in the middle region is not surprising.

V) Vascular surrounding pressure. Alveolar vessels are defined functionally as pulmonary vessels that are surrounded by alveolar pressure (P_A) and therefore compressed by lung inflation (1130). In contrast, extra-alveolar vessels are pulmonary vessels surrounded by the difference between P_A and the pressure generated by the outward-acting pull exerted on the vessel by its parenchymal attachments. Because the decompressive effects of this outward-acting pull equal or exceed the compressive effects of P_A, extra-alveolar vessels are unaffected or decompressed by lung inflation. Thus lung inflation would increase HPV if HPV occurred in alveolar vessels, but have no effect or decrease HPV if HPV occurred in extra-alveolar vessels.

In intact dogs (423, 1067) and isolated lungs of dogs (1565), ferrets (224, 1852), and rats (106), increases in P_{PA} caused by hypoxia were decreased or not changed by lung inflation, suggesting that HPV occurred in extra-alveolar vessels. In contrast, inflation increased hypoxic pressor responses in isolated lungs of normoxic pigs (1869) and rats with pulmonary hypertension due to chronic hypoxia (106). Such augmentation of HPV by inflation would be expected if intra-acinar arteries, which exhibited enhanced muscularity in pigs and chronically hypoxic rats (759, 1268, 1272, 1570, 1609, 1610, 1944), constricted more vigorously to hypoxia and were surrounded by alveolar pressure.

B) ANATOMIC LOCALIZATION. *I) Histology*. In rat, average diameters of muscular, partially muscular, and nonmuscular pulmonary arteries were $>$150, 150–50, and $<$50 μm, respectively (789). Additionally, muscular or partially muscular arteries made up 100, 65, and 20%, respectively, of arteries accompanying terminal bronchioli, respiratory bronchioli, and alveolar ducts. These distributions were similar in humans, except that partially muscular arteries were as small as 30 μm and fully muscular arteries were more numerous in the acinus (789). In canine pulmonary vessels, 29% of arteries and 5% of veins $<$50 μm in diameter and 100% of vessels $>$100 μm in diameter were muscular or partially muscular (1275). In the pig, 55% of arteries 30 μm in diameter and all arteries $>$40 μm in diameter were muscular or partially muscular (1610). In addition, all intra-acinar arteries had a muscular coat, and small muscularized arteries were found in association with alveolar walls (1610). Thus, on the basis of smooth muscle content, HPV could occur in pulmonary vessels as small as 30–50 μm in diameter.

In intact cats, ventilating the right lower lobe with 100% N_2 and the remaining lung with 100% O_2 caused decreases in both right lower lobe blood flow, estimated as right-to-left shunt, and diameters of small pulmonary arteries associated with terminal and respiratory bronchioles, measured in rapidly frozen right lower lobe tissue sections (939). Other vessel types were not examined. Similar rapid freezing techniques were used in isolated dog lungs to demonstrate that hypoxia decreased capillary erythrocyte concentration during forward perfusion but had no effect during reverse perfusion or at zero flow (614). With the assumption that

erythrocyte concentration was determined by capillary pressure and that under these experimental conditions capillary pressure during flow was not affected by changes in downstream vascular resistance, it was concluded that HPV occurred in pulmonary arteries, but not veins or capillaries. In rapid freezing studies, it must also be assumed that vascular structure was not altered by freezing and that vessels near the pleural surface, which were chosen for examination because they were the most rapidly frozen, were representative of vessels at major sites of HPV.

Immunofluorescence studies in lungs of several species demonstrated interstitial cells in alveolar septa that contained fibrils composed in part of actin different from the α-actin isoform found in smooth muscle (928, 930). Because hypoxia contracted strips of peripheral lung parenchyma, had no effect on pulmonary arterial strips, and relaxed bronchial strips, it was proposed that the parenchymal contraction induced by hypoxia was due to activation of these "contractile interstitial cells," also known as alveolar myofibroblasts (928). It was further speculated that hypoxic contraction of these cells could compress pulmonary capillaries through folding of alveolar basement membranes and thereby match perfusion to ventilation at the alveolar level (929). Alveolar myofibroblasts were thought to be distinct from the potentially contractile intermediate cells and pericytes that take the place of smooth muscle in the most distal pulmonary arterioles (365, 930). Cultured alveolar myofibroblasts, identified on the basis of morphology, positive staining for prostaglandin F synthase, and negative staining for smooth muscle α-actin, contracted in response to endothelin-1 and hypoxia (568); however, these results remain unconfirmed. The effects of acute hypoxia on pulmonary vascular intermediate cells or pericytes in culture have not been determined, but lung pericytes cultured on a collagen lattice were found to contract in response to bradykinin, 5-hydroxytryptamine (5-HT), and H_2O_2 (950, 1820).

II) Measurements of pressure and/or diameter in anatomically defined vessels. Vascular transmural pressures and diameters were measured in extrapulmonary lobar arteries and veins of sedated or lightly anesthetized dogs by means of instrumentation placed surgically several weeks before experiments (1316). Hypoxia increased transmural pressure of both lobar arteries and veins. These increases were associated with decreased lobar venous diameter in 13 of 18 experiments, but lobar arterial diameter either increased (6/9 experiments) or did not change (3/9 experiments). Thus unequivocal constriction occurred in veins more often than arteries. Although vasoconstriction could occur with both transmural pressure and diameter increasing, confirmation would require the entire pressure-diameter relationship, which was not measured.

In intact anesthetized dogs subjected to pulmonary angiography, ventilation with 10% O_2 increased P_{PA} and caused constriction and tortuosity of pulmonary arteries 0.5 to 2 mm in diameter (784). Although P_{PA} decreased rapidly upon ventilation with 100% O_2, these angiographic alterations persisted for 10–15 min. Since systemic hypoxia occurred, changes in cardiac output and neural or humoral influences from outside the lung may have influenced the findings.

In angiographic studies of isolated lung lobes perfused and ventilated in situ in intact greyhounds, lobar hypoxia caused reversible constriction of pulmonary arteries $\leq$678 μm in diameter (36). Constriction was maximum (19% reduction in diameter) in arteries ~300 μm in diameter, the smallest vessels studied. Similarly, in isolated left lower lung lobes of intact cats, HPV occurred in arteries and veins 100–600 μm in diameter, but was greatest (21–26% reduction in diameter) in 200–300 μm pulmonary arteries (1781). More recently, synchrotron radiation microangiography in intact anesthetized rats demonstrated HPV in pulmonary arteries 100–500 μm in diameter, with the greatest constriction (~25% reduction in diameter) occurring in 200- to 300-μm vessels (1740). Since hypoxia was limited to a single lobe in greyhounds (36) and cats (1781), systemic hypoxia did not occur, and P_{PA} changed slightly, if at all; therefore, changes in diameter probably reflected changes in vasomotor tone more accurately than measurements in rats (1740), where global lung hypoxia changed both intravascular pressure and P_aO_2.

In isolated dog lung lobes perfused at constant $\dot{Q}$ and outflow pressure, angiography demonstrated that ventilatory hypoxia dilated pulmonary arteries >800 μm in diameter but caused a large constriction in 150–800 μm arteries and a small constriction in 200–1000 μm veins (23). Hypoxic vasodilation of the larger arteries was less than half of the vasodilation achieved by elevating P_{PA} to its hypoxic level during normoxia, suggesting that HPV also occurred in these vessels. A subsequent study in the same preparation demonstrated that hypoxia decreased the volume of pulmonary vessels <50 μm in diameter (320). Since pulmonary capillaries were thought to be more compliant than small pulmonary arteries or veins, it was suggested that HPV occurred in capillaries.

High-resolution computed tomography was used in intact pigs to measure diameters of pulmonary vessels $\geq$300 μm (771). In addition, parenchymal background attenuation was measured as an index of vascular volume relative to gas volume in vessels with diameters <300 μm. Ventilatory hypoxia increased P_{PA}, had no consistent effect on diameters in larger arteries or veins, and decreased parenchymal background attenuation. Because similar increases in P_{PA} caused by intravascular volume loading were associated with increases in vascular diameters and background attenuation, it was concluded that HPV occurred in vessels with diameters both larger and smaller than

300 μm; however, systemic hypoxemia, possible changes in lung compliance and volume secondary to vascular congestion and/or edema, and uncertainty about vascular transmural pressures suggest that the results be interpreted with caution.

Pressures in subpleural arterioles and venules 20–80 μm in diameter were measured using micropuncture techniques in isolated lungs of adult cats (1354, 1917), ferrets (1584), and rabbits (519) perfused with blood at constant $\dot{Q}$ and P_{LA}. In cats during normoxia, pulmonary arteries, microvessels <20–80 μm in diameter, and veins each contributed about one-third of the total pressure gradient (P_{PA}-P_{LA}). In ferrets and rabbits, this distribution was weighted toward arteries (43 and 69% of total, respectively) at the expense of the venous gradient in ferrets (21% of total) and both the microvascular and venous gradients in rabbits (10 and 21% of total, respectively). Hypoxia (perfusate P_{O_2} = 25–38 mmHg for 60–120 min) increased all gradients in cats (1354, 1917), the arterial and venous gradients in ferrets (1584), but only the arterial gradient in rabbits (519). In 3- to 5-wk-old ferrets (1584) and 7- to 23-day-old rabbits (521), hypoxia had effects similar to those in the adult animals. In newborn lambs, hypoxia increased the arterial and venous gradients (1582). Thus micropuncture data from four species suggest that HPV occurred consistently in arteries, but inconsistently in veins and microvessels.

This conclusion assumes that flow in the examined region was constant, as was apparently the case in isolated lungs of lambs (1582), adult and newborn rabbits (519), and dogs (779), where hypoxia did not alter the regional distribution of flow measured with radiolabeled microspheres. However, hypoxia did alter regional flow distribution in isolated rabbit lungs (1444) and intact pigs (790, 811) and sheep (1375), indicating that this assumption is not always valid. Other potential problems associated with the micropuncture technique include the time required for measurements, alteration of flow and pressure in the punctured vessel by the pipette, exchange of O_2 and CO_2 across the pleural surface at the site of puncture, possible differences between subpleural vessels and vessels elsewhere in the lung, and lung injury associated with lung isolation and extracorporeal perfusion.

In intact anesthetized rabbits (668), diameters of subpleural vessels were measured by fluorescence videomicroscopy through a sealed window in the right chest wall. Right lung hypoxia, produced by inflation with N_2 to a constant airway pressure after right bronchial occlusion, caused a 10% constriction of pulmonary arterioles and venules 20–50 μm in diameter and a 50% reduction in erythrocyte velocity, suggesting reduced flow. When the same techniques were used in intact mice (1876), ventilating both lungs with 11% O_2 caused a 15% constriction of 30–50 μm arterioles that was sustained for an hour; however, hypoxia did not constrict 20- to 30-μm arterioles or 20- to 50-μm venules. In isolated rat lungs perfused at constant $\dot{Q}$ and outflow pressure, diameters of subpleural vessels were measured with confocal laser-scanning fluorescence microscopy (1859, 2138). Ventilation with 2% O_2 caused a 10% constriction of subpleural pulmonary arterioles 20–30 μm in diameter, but had no effect on venules of similar size or 6- to 7-μm capillaries. Similar studies in isolated lungs of Tie2-GFP mice, in which vessels were defined by endothelial fluorescence, showed that inflation with 1.5% O_2 for 10 min decreased diameters of small (≤40 μm) intra-acinar arteries by 9% (153). However, without knowledge of transmural pressures, it is not possible to conclude that these decreases in diameter were due to active microvascular constriction. For example, a decrease in regional flow caused by vasoconstriction of the lobar artery feeding the examined subpleural region or vasodilation in another region could decrease microvascular transmural pressure and diameter passively, and these decreases could be greater in arterioles than capillaries or venules.

To date, the only study to deal with these uncertainties experimentally was performed in isolated blood-perfused canine lung lobes, where intravascular pressures were maintained constant within 1.5 mmHg by decreasing flow and adjusting outflow pressure during intermittent measurement of subpleural microvascular diameters with a computer-linked videomicroscopy system (779). In addition, ventilatory hypoxia was shown not to alter intralobar flow distribution. In this preparation, hypoxia (P_{O_2} = 38 mmHg) reduced diameters of 30- to 70-μm arterioles and venules by an average of 25%. This constriction was reversed when nitric oxide (NO) was added to the hypoxic gas mixture. These results indicate that hypoxic caused active vasoconstriction in these vessels. Furthermore, since many vessels in this size range lack smooth muscle (1275), the data also suggest that constriction was due to other cell types, including the alveolar myofibroblasts, pericytes, and intermediate cells discussed above, or even endothelial cells (see sect. IV*B1*).

C) SUMMARY. The available functional and anatomical evidence indicates that HPV occurs throughout the pulmonary vascular bed, including the microvascular region containing nonmuscular arterioles, capillaries, and venules; however, the largest and most consistent HPV responses occur in small pulmonary arteries.

5. Sources of variation

A) SPECIES. HPV varies greatly among species. Direct comparisons in isolated lungs indicated that the magnitude of HPV was high in ferrets (1483, 1851) and pigs (712, 1012, 1483); intermediate in cats (712, 1483, 1851), rats (712, 1851, 1995), and rabbits (1483); and low in dogs (1012, 1483) and hamsters (1995). Direct comparisons in intact animals indicated that HPV magnitude was again high in

pigs (473, 2031), intermediate in cats (103), and low in dogs (103, 2031), and also intermediate in ponies (473) and goats (2031). Single-species studies suggest that HPV magnitude was high in cattle (1787, 2094, 2226) and coatimundi (737), intermediate in sheep (183, 838, 2081) and humans (261, 428, 561, 727, 2080), and low in guinea pigs (699, 1904) and mice (2053). The magnitude of HPV was also low in several species indigenous to high altitude, such as yak (455), pika (594), and blue sheep (1690), as well as humans native to Tibet (674).

Among cattle, pigs, dogs, and sheep, the magnitude of HPV and medial thickness of pulmonary arteries varied directly with resistance to collateral ventilation, suggesting that HPV was greater in species that were more dependent on redistribution of pulmonary blood flow for optimization of ventilation-perfusion relationships (1012, 1013) (see sect. V*B*). Furthermore, the relative magnitudes of acute HPV and medial hypertrophy of pulmonary arteries among species were similar to that of right ventricular pressure and hypertrophy caused by exposure to chronic hypoxia (1944), suggesting that magnitude of acute HPV contributed to the pathogenesis of high-altitude pulmonary hypertension (1622) (see sect. V*D1*). Against this possibility is the coatimundi, which has vigorous acute HPV, thick pulmonary arteries, and no collateral ventilation, but does not develop significant pulmonary hypertension during chronic hypoxia (737, 738); and the Madison Sprague-Dawley rat, which has more vigorous acute HPV than the Hilltop Sprague-Dawley rat, but develops less severe pulmonary hypertension during chronic hypoxia (1028, 1440).

Direct comparisons of HPV stimulus-response relations demonstrated that the maximum slope of the relation was greater in cats than dogs (103), and that HPV began to occur and was maximum at higher O_2 tensions in pigs than ferrets (1483). These results suggest that sensitivity to the hypoxic stimulus, as well as the magnitude of the response, differs among species.

The mechanisms underlying species variability in HPV are unknown; however, the ubiquity of the response and observations that differences are quantitative rather than qualitative argue against variability in the fundamental mechanisms of HPV. More likely, species differences result from variability in mechanisms that modulate HPV (see sect. IV). The same is probably true of intraspecies differences, such as those in different rat strains (762, 1691).

B) AGE. At birth, PVR decreases dramatically upon initiation of ventilation, due in part to relief of HPV as a consequence of increased P_AO_2 and decreased P_ACO_2 (265, 1673, 1914) (see sect. V*A*). Postnatally, pressor responses to hypoxia continued to decrease between 2 h and 8 mo of age in intact calves (1603); however, HPV increased between 2–4 and 9–12 wk of age in intact pigs (1609), 3–8 and 10–14 days in isolated lungs of rabbits (517), and 0–4 days and 1 mo in isolated lungs of sheep (637, 1914, 1916). The mechanisms underlying these developmental effects remain unclear. Current proposals include postnatal structural changes in pulmonary vessels, such as diminution of medial thickness in muscular pulmonary arteries and extension of smooth muscle into previously nonmuscular intra-acinar pulmonary arteries (759, 1270, 1276, 1609, 1610); release of endogenous modulators, such as prostaglandins (637, 641, 1595, 1673, 1916, 1952) and NO (305, 640, 984, 1547); and alteration of membrane potential and K^+ channel activity in pulmonary arterial smooth muscle (190, 490).

Less is known about the effects of age on HPV in adults. HPV and pressor responses to angiotensin II and 5-HT were smaller in lungs isolated from middle-aged (12–14 mo) than young (3–5 mo) adult rats (1942). Similar diminution of pressor responses to hypoxia and angiotensin II was observed in lungs of hamsters between 3 and 10 mo of age (1939). These results suggest that aging causes a generalized hyporeactivity of the pulmonary vasculature; however, pulmonary pressor responses to KCl and 5-HT were not different in isolated lungs of rats 7, 14, and 28 wk of age (1135).

C) GENDER AND PREGNANCY. HPV was greater in the isolated lungs of male than female adult sheep (2081) and cats (350, 1483), but not different in lungs of adult male sheep and male sheep of similar age that were castrated during the first week of life (2081). Moreover, HPV in isolated lungs of prepubertal male and female sheep was the same as that of adult males (2082). These findings suggested that attenuation of HPV in adult female sheep was due to the presence of female sex hormones rather than the absence of male sex hormones. Consistent with this possibility, treatment with 17β-estradiol for 2–5 days depressed HPV in lungs from both prepubertal females and adult castrated males (2082). This attenuation could be due to enhanced release of vasodilator prostaglandins (643) or NO (631, 1029, 1469).

In intact awake rats, increases in P_{PA} induced by acute hypoxia were not different in males and females; however, contributions by cardiac output and left atrial pressure to these responses were not evaluated (1441). In isolated rat pulmonary arterial rings precontracted with phenylephrine, HPV was greater in males than females during proestrus, when estrogen levels are high (1019), and attenuated by high concentrations of 17β-estradiol (1018). In addition, the attenuation of HPV by diarylpropiolnitrile, an estrogen receptor agonist, was reversed by N^{ω}-nitro-L-arginine methyl ester (L-NAME), an antagonist of NO synthase (1017). These data are consistent with the results in sheep (643, 2081, 2082).

Chronic hypoxic pulmonary hypertension (see sect. V*D1*) was also greater in male than female rats (1441, 1571,

1804), pigs (1243), and chickens (242). In rats, this gender difference was eliminated by ovarectomy but not orchiectomy (1441). Furthermore, enhancement of pulmonary hypertension in ovarectomized females was reversed by estradiol (1618). As with acute HPV, these results suggest that the gender difference was due to estradiol-induced depression of chronic hypoxic pulmonary hypertension in adult females; however, estradiol had no effect and testosterone enhanced right ventricular hypertrophy caused by chronic hypoxia in orchiectomized male rats (1310). Thus the mechanisms responsible for gender differences during chronic hypoxia in rats may differ from those during acute hypoxia in sheep (643, 2081, 2082).

Pregnancy depressed HPV in dogs (1311), rats (565), and cats (350). In dogs, pulmonary vasoconstrictor responses to $PGF_{2\alpha}$ were also reduced. Treatment of pregnant females with the cyclooxygenase inhibitor meclofenamate did not alter HPV, and treatment of nonpregnant females with estrogen or progesterone for 2 wk did not alter pulmonary vascular responses to either hypoxia or $PGF_{2\alpha}$ (1311). Observations that HPV was blunted in nonpregnant rat lungs perfused with pregnant blood, but not in pregnant lungs perfused with nonpregnant blood, suggested that the effect of pregnancy on HPV was due to a blood-borne mediator (565); however, neither estrogen nor progesterone inhibited HPV in isolated lungs of nonpregnant female rats. In isolated cat lungs, pregnancy inhibited HPV, as well as pulmonary vasoconstrictor responses to angiotensin II, 5-HT, and epinephrine. In contrast, pregnancy enhanced HPV in cows genetically predisposed to develop severe pulmonary hypertension at high altitude, but had no significant effect in normal cows (1312). Collectively, these results suggest that pregnancy usually inhibits HPV nonspecifically by mechanisms independent of estrogen, progesterone, and cyclooxygenase, but that this effect can vary within and among species.

D) EXTRACELLULAR PH AND P_{CO_2}. During normoxia, both hypercapnic acidosis (88, 102, 103, 107, 143, 151, 219, 839, 1052, 1344, 1395, 1781, 1788, 1973, 1979, 2141) and isocapnic acidosis (102, 105, 107, 151, 219, 639, 652, 1064, 1674, 1788, 1898, 1973, 1974, 2139) caused pulmonary vasoconstriction, suggesting that hypercapnia caused vasoconstriction via its effect on extracellular H^+ concentration ($[H^+]_e$). Occasionally, hypercapnic acidosis had no effect (842, 953, 1856) or caused vasoconstriction less than that caused by isocapnic acidosis at the same pH (1973), suggesting that the pulmonary vasomotor response to hypercapnic acidosis was the net effect of vasoconstriction due to increased $[H^+]_e$ and vasodilation due to increased P_{CO_2}, with the former usually predominating. Consistent with this possibility, hypocapnic alkalosis during normoxia decreased pulmonary vascular resistance (88, 143, 219, 518, 2139) or had no effect (1148, 1733). The same was true of isocapnic alkalosis (102, 105, 151, 219, 518, 639, 1148, 1898).

With respect to HPV, the most consistent effect has been attenuation by alkalosis, whether hypocapnic (143, 219, 518, 1114, 1148, 1195, 1733, 1764, 1974, 2140) or isocapnic (105, 107, 219, 518, 639, 1114, 1148, 1169, 1195, 1733, 1898, 1974, 2140). A few studies reported that alkalosis did not alter HPV (151, 518, 639, 1788); however, two of these studies, both performed in newborn animals, found that alkalosis would also attenuate HPV if it were acute (20 min) rather than sustained (60–80 min) (639) or imposed during rather than before hypoxia (518).

The effects of acidosis on HPV were less consistent. Both hypercapnic acidosis (143, 476, 953, 1052, 1645, 1788, 1974, 2141) and isocapnic acidosis (105, 219, 639, 1064, 1674, 1788, 1974) potentiated HPV; however, other investigators found that HPV was unaltered by hypercapnic (219) or isocapnic acidosis (151, 639, 652, 1898, 1974), and a few studies concluded that acidosis attenuated HPV (107, 476, 1169, 1195). These inconsistencies remain unexplained, but could be related to differences in baseline pulmonary vasomotor tone, duration or magnitude of the acidosis (151, 638, 639), level of P_{CO_2} (652), severity of hypoxia (107, 1195), and species (107, 476).

As might be expected from such variability, the mechanisms underlying the effects of extracellular pH and P_{CO_2} remain unclear. Tested possibilities include release of arachidonic acid products (498, 636, 1754, 1965, 2138, 2140) and NO (525, 636, 642, 953, 1965, 2138, 2139, 2141), activation of the sympathetic nervous system (1344), and alteration of K^+ channel activity in pulmonary arterial smooth muscle (21, 636, 1965).

E) MISCELLANEOUS FACTORS. In anesthetized dogs, the magnitude of HPV varied directly with temperature between 30 and 42°C (144). Perfusate temperatures <27.5°C abolished HPV in isolated rat and dog lungs (700, 1116).

HPV was more vigorous and persistent in isolated rat lungs if blood, plasma plus erythrocytes, or physiological salt solution plus erythrocytes were used as perfusate rather than physiological salt solution or plasma (1244, 1245). Salutory effects of erythrocytes on HPV were also seen in intact dogs (949) and isolated lungs of rats, cats, rabbits, and ferrets, but not pigs (379, 712, 1120, 2057, 2091, 2137). Enhancement of HPV occurred at Hct as low as 1–7% (2057, 2137) but not with increases in Hct above ~40% (1120). Proposed mechanisms include inactivation of NO by erythrocyte Hb (377–379), decreased erythrocyte deformability during hypoxia (711), and scavenging of injurious reactive oxygen species by erythrocyte antioxidant enzymes (949, 2137).

There is little evidence that blood cells other than erythrocytes enhance HPV. Rat lungs perfused with platelet-rich plasma were more responsive to hypoxia than lungs perfused with platelet-poor plasma (754); however, this was not confirmed in isolated rat lungs (1245) or intact dogs (2051). Perfusion of isolated dog lung lobes with blood depleted of granulocytes and platelets did not alter HPV (1216). HPV was vigorous in anesthetized dogs made leukopenic or leukopenic/thrombocytopenic with leukocyte and platelet antiserum (1298).

Reversal of the decrease in perfusate glucose concentration that usually occurs in isolated blood-perfused lungs accelerated the decline in HPV elicited by repeated 4- to 10-min exposures to hypoxia in isolated rat lungs (1245, 1667). These results were not confirmed during 30-min exposures to hypoxia in ferret lungs, where normal and high glucose concentrations had no effect on HPV induced by an inspired P_{O_2} of 30 mmHg and potentiated HPV caused by a P_{O_2} of 10 or 0 mmHg (2091).

B. Isolated Pulmonary Vessels and Other Lung Tissue Preparations

1. Pulmonary arteries

Isolated pulmonary artery preparations eliminate potentially confounding effects of extravascular influences on HPV, such as circulating mediators and neural activity, and allow evaluation of influences localized to the vessel wall, such as endothelium-derived relaxing and contracting factors. Vasoconstriction has been measured in vascular rings or strips as an increase in isometric force or, less commonly, in cannulated vessel segments as a decrease in vascular diameter at constant transmural pressure. Easier dissection and mounting probably explains why most investigators have chosen to study proximal (orders 1–5) rather than distal (orders 6 and greater) pulmonary arteries, where main, right or left, lobar, segmental, and subsegmental arteries represent orders 1, 2, 3, 4, and 5, respectively.

A) PROXIMAL PULMONARY ARTERIES. Hypoxic responses of proximal pulmonary arteries have been studied in a wide variety of species, including cat (1157), dog (375, 429, 814, 876), ferret (2089), guinea pig (4, 1818), human (394, 815, 1715), pig (506, 578, 799, 991, 1045, 1282, 1976), rabbit (197, 198, 399, 413, 903, 1417), rat (60, 126, 139, 412, 436, 656, 896, 899, 900, 908, 909, 934, 935, 1018, 1038, 1041, 1043, 1056, 1131, 1207, 1208, 1413, 1474, 1638–1642, 1651, 1652, 1691, 1715, 1767, 1894, 1896, 1905, 1934, 2018, 2175, 2185, 2190, 2206–2208), and sheep (392, 393, 1959–1961). While some investigators were able to elicit contractile responses to hypoxia under basal conditions (4, 392–394, 412, 413, 799, 1417, 1652, 1715, 1818, 2175), most found that exposure to a contractile stimulus before and during hypoxia was required to obtain measurable, reproducible responses in this preparation. Development of hypoxic responses varied with the increase in isometric force caused by prestimulation ("pretone") (1445, 1652), but not the agonist, which included acetylcholine (399), angiotensin II (1652), electrical field stimulation (1818), epinephrine (399), endothelin-1 (394, 1131, 2018), histamine (506, 815, 1282), KCl (139, 197, 393, 399, 815, 899, 900, 1043, 1652, 1976, 2206–2208), norepinephrine (139, 197, 198, 375, 429, 814, 1043, 1056, 1652, 2018, 2206), $PGF_{2\alpha}$.(126, 413, 908, 909, 1038, 1041, 1043, 1638–1642, 1894, 1896, 1905), phenylephrine (60, 436, 578, 656, 876, 896, 903, 934, 935, 991, 1018, 1045, 1131, 1151, 1207, 1208, 1413, 1474, 1651, 1652, 1691, 1767, 1934, 2089, 2185, 2207, 2208), phorbol 12,13-dibutyrate (1715), 5-HT (139, 393, 900, 1151, 1430, 1959–1961), and the thromboxane mimetic U46619 (506, 1652, 2018).

The requirement for prestimulation does not necessarily mean that hypoxic responses in these preparations have no relevance to HPV in intact or isolated lungs. In vivo, pulmonary arteries are constantly exposed to vasoactive agents, both blood-borne and local, which may be lost during dissection and isolation of the vessel, along with the hypoxic response. Indeed, loss of HPV occurs in isolated lungs perfused with physiological salt solutions, and can be prevented or restored by administration of vasoconstrictors (152, 1240). Furthermore, it is well recognized that basal tone can influence pulmonary vasomotor responses to a variety of stimuli, including hypoxia (814, 876, 1046, 1445). Thus precontraction may restore an initial level of intrinsic tone necessary for expression of HPV. In some studies where prestimulation was not required, hypoxic responsiveness may have been promoted by particular experimental conditions, such as absence of glucose (1417, 1818) or bicarbonate and CO_2 (2175) in the bathing media, and "adaptation" of vessels by continuous exposure to hypoxia for 4–6 h before hypoxic challenges (799). In others, hypoxic responses were present but much smaller and more variable than responses in precontracted vessels (393, 413, 1652). Why hypoxic responsiveness varies among isolated vessel preparations is not clear.

As illustrated in **FIGURE 3*B***, measurements of isometric force in proximal pulmonary arteries from rat, the species most studied, indicated that exposure to severe hypoxia (0–2% O_2) for ≥30 min caused a biphasic response consisting of transient vasoconstriction (phase 1) followed by sustained vasoconstriction (phase 2) (126, 139, 412, 436, 896, 899, 900, 934, 935, 1038, 1041, 1043, 1131, 1638–1642, 1896, 2190, 2206–2208). In some studies, phase 1 was preceded by a small vasodilation (908, 909, 1018, 1474, 1894, 1905, 1934, 2018). Similar results were obtained from prestimulated proximal pulmonary arteries in rabbit (413) and first- and third-order pulmonary arteries in pig (578, 991, 1045). On the other hand, phase 2 HPV did

not occur in proximal pulmonary arteries of orders 3–5 in ferret (2089) or orders 4–5 in pig (991). The reasons for these differences are unknown.

At durations ≤20 min in rats (1413, 1651, 1652, 1691, 1715, 1767, 2185) and ≤30 min in other species, including cow (1430), dog (375, 429), ferret (2089), guinea pig (1818), human (394, 815), pig (1282, 1976), rabbit (399, 903, 1417), and sheep (392, 393, 1959–1961), severe hypoxia caused either vasoconstriction or vasoconstriction followed by vasodilation, perhaps representing partial or complete phase 1 responses, respectively. As with phase 1 during prolonged hypoxia, these responses were occasionally preceded by a brief vasodilation (506, 656, 876, 1151, 1207, 1208). In addition, one study in dogs (814) reported that 10 min of severe hypoxia caused a small transient constriction superimposed on a larger constriction.

In general, phase 1 HPV begins within seconds and peaks within 5 min **(FIGURE 3*B*)**. Relationships between the level of hypoxia and magnitude of phase 1 vasoconstriction in prestimulated rat proximal pulmonary arteries suggested that the response began to occur at ~8% O_2, and was half-maximum at ~3% O_2 and maximum at 0% O_2 (1651, 1652, 1691). These O_2 concentrations were shifted to higher values when the intensity of prestimulation was increased (1652) or when measurements were made in a rat strain more responsive to hypoxia (1691). The maximum magnitude of phase 1 was quite variable, ranging from 10 to 300% of pretone (375, 394, 991, 1282, 1652, 1691) or 35–100% of the maximum vasoconstrictor response to KCl (413, 1038, 1639, 1652, 1715).

There is debate concerning the contribution of endothelium to phase 1. Most investigators found that endothelium was necessary to fully elicit the response (139, 375, 392, 394, 429, 506, 578, 656, 799, 814, 900, 903, 935, 991, 1043, 1045, 1131, 1151, 1413, 1430, 1651, 1652, 1691, 1896, 1961, 1976, 2018, 2089, 2185). Moreover, substantial data suggested that the endothelium dependence of phase 1 was caused by an hypoxia-induced decrease in endothelial NO production, leading to smooth muscle contraction (506, 656, 814, 903, 934, 935, 991, 1151, 1413, 1430, 1691, 1896, 1976, 2018). In contrast, other studies reported that removal of endothelium did not eliminate or even enhanced phase 1 HPV (412, 413, 876, 1038, 1043, 1151, 1207, 1208, 1638, 2190). In this case, phase 1 was proposed to result from a direct action of hypoxia on pulmonary arterial smooth muscle, such as release of Ca^{2+} from internal stores (413) or downregulation of NO-independent cGMP-mediated relaxation (1208).

In contrast to phase 1, phase 2 HPV developed gradually, achieving and sustaining a maximum at 30–60 min **(FIGURE 3*B*)**. In many studies of proximal pulmonary arteries, phase 2 HPV was smaller than phase 1 (412, 413, 896, 909, 1038, 1041, 1043, 1044, 1639–1642, 1894, 2018); however, others demonstrated that the magnitude of phase 2 could equal or exceed that of phase 1 (139, 436, 578, 899, 900, 934, 935, 991, 1045, 1131, 1896, 2208). There is virtually no information regarding the stimulus-response relation between level of hypoxia and magnitude of phase 2. In pig proximal pulmonary arteries, phase 2 HPV was present at 0% O_2, but absent at 10 and 4% O_2 (991). In rat (412), the magnitude of phase 2 HPV elicited by 6% O_2 was half of that elicited by 2% O_2. With few exceptions (54, 139), phase 2 HPV was found to be endothelium-dependent (392, 394, 413, 506, 578, 799, 814, 815, 991, 1038, 1043, 1044, 1131, 1639, 1652, 1896, 2024). As discussed in section IV*B2*B, it is widely held that phase 2 HPV requires a diffusible contracting factor released by endothelium, which may act by increasing Ca^{2+} sensitivity in pulmonary arterial smooth muscle.

During prolonged severe hypoxia, the time course of HPV measured as isometric force in proximal pulmonary arteries was similar to the time course of HPV measured as P_{PA} at constant flow in lungs **(FIGURE 3)**. Although it is tempting to assume that similar mechanisms are operating in these preparations, severe hypoxia also caused early constriction in isolated systemic arteries (139, 375, 429, 1041, 1043, 1045, 1638, 1652, 1818, 1976, 2185), raising questions about the relevance of phase 1 vasoconstriction to in vivo HPV. Because phase 2 vasoconstriction in precontracted pulmonary arteries is sustained, not observed in systemic arteries (139, 991, 1041, 1043, 1045, 1638), and often attenuated by removal of extracellular Ca^{2+} (413, 900, 1641, 2190) and antagonists of L-type Ca^{2+} channels (900, 1043), some investigators believe that phase 2 is the proximal pulmonary artery response most relevant to in vivo HPV. On the other hand, phase 2 seems to occur primarily at very low P_{O_2}, is slow to develop, and has been associated with increased vascular expression of inflammatory cytokines, such as TNF-α and interleukin-1 (1934), which can enhance pulmonary vasomotor responses (1838). Thus its relevance to in vivo HPV needs to be confirmed.

B) DISTAL PULMONARY ARTERIES. Pulmonary arteries of orders 6 and greater, where HPV may occur most vigorously (see sect. II*A4*), have been studied in cat (198, 740, 1157), cow (240, 1151, 1430), horse (1151), human (394, 1418, 1490), pig (991, 1102, 1104, 1411), rabbit (198) and sheep (1762), where vasomotor responses were measured as changes in isometric force. Half of these studies reported sustained or transient contraction in response to 3–30 min of severe hypoxia in the absence of prestimulation (198, 394, 740, 1157, 1411, 1418). Except for studies in rabbit (198) and sheep (1762), the others observed HPV after prestimulation (240, 991, 1151, 1430, 1490), and two of these confirmed that prestimulation was necessary for the response (991, 1151). Although the duration of hypoxia may have been insufficient to determine if HPV was bipha-

sic, 30-min exposures gave no hint of it (198, 991, 1151). In cat distal pulmonary arteries, HPV began to occur at P_{O_2} ≤250 mmHg and was half-maximum and maximum at 100–80 and 50–30 mmHg, respectively, where maximum HPV was about the same as maximum vasoconstriction induced by KCl (1157). These results indicate an hypoxic sensitivity similar to HPV in lungs (see sect. II*A3*, **TABLE 1**). On the other hand, human distal pulmonary arteries contracted at a P_{O_2} of 5 but not 38 mmHg, whether prestimulated or not (394). As in proximal pulmonary arteries, the response appeared to be endothelium dependent in some studies (991, 1151, 1430) and independent in others (240, 1411, 1418).

In vivo, vasoconstriction is neither isometric nor isotonic. Moreover, HPV may occur locally, causing vasoconstriction without a change in P_{PA}. Consequently, a more physiological and relevant in vitro measurement of HPV may be the decrease in vascular internal diameter (ID) induced by hypoxia at a constant vascular transmural pressure (P_{tm}) (725). Such measurements require cannulation of a vessel segment at each end to control P_{tm} while ID is measured microscopically, and have been used only rarely in pulmonary arteries (644, 645, 1102, 1104, 1105, 1376). In seventh-order pig pulmonary arteries held at a P_{tm} of 20 mmHg, exposure to O_2 tensions <60 mmHg for 30–60 min caused monophasic constriction that was complete within 30–40 min, half-maximum at P_{O_2} = 40 mmHg, and maximum at P_{O_2} = 2 mmHg, where maximum was ~40% of the maximum vasoconstrictor response to KCl (1102, 1104). Similarly treated bronchial arteries of comparable size did not respond to hypoxia. HPV in these distal pulmonary arteries did not require prestimulation and was dependent on endothelium, enhanced by inhibition of NOS, and blocked by Ca^{2+}-free perfusate, nifedipine, ryanodine, BQ123 (an endothelin A receptor [ET_A] antagonist), or superoxide dismutase (1102, 1104).

2. Pulmonary veins

Experiments in isolated pulmonary veins confirm the functional and anatomical evidence in lungs that HPV occurs in these vessels (see sect. II*A4*). Proximal pulmonary veins from dog (375), guinea pig (1926–1928), pig (506, 1282, 1976), and rat (2206, 2207) exhibited an increased isometric force in response to hypoxia. In most of these studies, the veins were prestimulated with histamine (506), KCl (1976, 2206, 2207) or norepinephrine (375, 2206). Human and sheep pulmonary veins contracted minimally or did not respond to 0% O_2; however, these vessels were not prestimulated and P_{O_2} fell to only 40–55 mmHg during 5-min exposures (1715, 1762). In proximal pulmonary veins from guinea pig (1926–1928) and pig (506, 1282), HPV occurred without prestimulation.

Direct comparisons of proximal pulmonary veins and arteries suggested that HPV was more vigorous and/or sustained in veins. Unlike the biphasic response frequently seen in arteries, hypoxic constrictions were monophasic in rat prestimulated proximal pulmonary veins. At O_2 tensions of 30 and 55–75 mmHg, peak constrictions equal to 472% and 70% of the maximum KCl response, respectively, were achieved within 20 min, and followed by a slow decline to lower but still elevated levels of constriction during the remainder of the 60-min exposure (2206, 2207). At P_{O_2} = 30 mmHg, the magnitude of HPV in veins was 2- to 20-fold greater than phase 2 HPV in arteries. Whether these remarkably vigorous venous responses are related to the presence of sphincters or cardiac muscle in rat pulmonary veins is unknown (17, 749, 1732). In pig proximal pulmonary veins with or without prestimulation, transient constriction induced by a 5-min exposure to a P_{O_2} of 30 mmHg was twofold greater than that measured in prestimulated proximal pulmonary arteries (506). Consistent with these differences, exposure of unstimulated proximal pulmonary veins from guinea pig to a P_{O_2} of 0 mmHg caused a monophasic increase in isometric force to a plateau, which was achieved within 10 min, sustained for up to 4.5 h, and rapidly reversed by restoration of normoxia (1928). Constriction induced by a P_{O_2} of 25 mmHg was also monophasic, but smaller. Similar to phase 1 HPV in pulmonary arteries, the effects of endothelial inactivation on HPV in pulmonary veins were variable, with no effect (2206), partial or complete inhibition (375, 506), and enhancement (1927) being reported.

It remains unclear whether differences in HPV between isolated proximal pulmonary veins and arteries reflect differences in mediation or modulation of the response. Nor is it clear whether HPV in proximal pulmonary veins is similar to HPV in distal pulmonary veins, which have not been studied in isolated preparations and where, on the basis of indirect evidence (see sect. II*A4*), HPV may be more vigorous than in proximal pulmonary veins but less vigorous than in distal pulmonary arteries.

3. Pulmonary parenchymal strips

While the term *hypoxic pulmonary vasoconstriction* appears to limit consideration of the effects of hypoxia to muscular pulmonary vessels, the possibility that other structures contribute to the increase in pulmonary arterial pressure induced by hypoxia should not be ruled out. Early experiments demonstrated that rabbit pulmonary parenchymal strips without grossly visible vascular structures contracted in response to hypoxia, whereas pulmonary arterial strips dilated (1113). It was suggested that hypoxic parenchymal contraction was caused by contraction of small vessels or extravascular smooth muscle. Subsequent studies confirmed that rat, human, and bovine pulmonary parenchymal strips without visible vessels or airways exhibited reproducible and reversible contraction when oxygen levels fell below 80 mmHg (928). These responses were attributed to contractile interstitial cells (subsequently

termed alveolar myofibroblasts) in the alveolar septum, which were thought to surround pre- and postcapillary alveolar vessels and contribute to vasomotion during hypoxia (928) (see sect. II*A4*B); however, this possibility has yet to be convincingly demonstrated.

4. Lung slices

Originally developed to evaluate airway constriction using videomorphometric analysis (1201), lung slices are prepared by inflating the lung with warmed agarose, which gels as it cools, allowing sectioning of the tissue into slices ~200-μm thick. The slice is then placed in warmed salt solution to melt the agarose, which is washed away, leaving in a thin section of tissue with intact microanatomy and functional responses. This preparation was recently used to study lung vascular responses to various stimuli, including hypoxia (1446, 1447). Its major advantages include direct measurement of vasoconstriction and fluorescent indicators in small intra-acinar arterioles 20–30 μm in diameter independent of extrapulmonary neural or humoral influences and intravascular pressure changes (398, 1446, 1447); however, it is possible that absence of normal mechanical stresses could alter vasomotor responses. In murine lung slices superfused with physiological solutions equilibrated with 1–1.5% O_2, vascular luminal area decreased monophasically over the first 20–30 min of hypoxia by 20–40%, roughly half of the decrease induced by U46619, and then slowly increased, returning to normoxic values after ~80 min of hypoxia (1446, 1447). This preparation shows promise, but its hypoxic responses remain relatively uncharacterized.

C. Pulmonary Arterial Smooth Muscle Cells

Observations that hypoxia caused contraction of isolated PASMC confirmed that sensor, transduction, and effector mechanisms of HPV are present these cells. Two methods have been used to assess PASMC contraction. The first requires growing cells on a flexible polymerized polydimethyl siloxane membrane. After the cells are attached to the membrane, contractions are indicated by membrane wrinkling and/or distortion. Fetal calf myocytes isolated from main or second branch pulmonary arteries were found to induce minor wrinkling under normoxic conditions (P_{O_2} = 145 mmHg), indicating a degree of basal contractility (1341). When P_{O_2} was reduced to 20–30 mmHg, the number of wrinkles increased. Occasionally, these changes were reversed by reoxygenation. Hypoxic contraction of PASMC measured in this manner was maintained after multiple passages of the cultured cells. An obvious disadvantage of this approach is that wrinkling is a qualitative rather than quantitative index; however, parallel experiments in the same cells confirmed that hypoxia also caused phosphorylation of myosin light chains, as would be expected with active contraction (see sect. III*C*).

The second method is measurement of cell length using a reticule in the microscope eyepiece or images of the microscopic field. This approach was used in PASMC of cat (1160), pig (1752), rabbit (199), and rat (2188). Hypoxia decreased cell length in myocytes from distal pulmonary arteries (1160, 1752), but had variable effects in proximal PASMC, where cell length either decreased (1752, 2188) or remained unaltered (199, 1160). Hypoxic contraction of distal PASMC was associated with myosin phosphorylation (1160). Hypoxia did not alter cell length or myosin phosphorylation in myocytes from systemic arteries (1160, 1752).

The maximum decreases in PASMC length caused by hypoxia were achieved within 5–30 min and varied between 9 and 24% of initial cell length (1160, 1752, 2188), comparable to decreases caused by KCl, norepinephrine, phenylephrine, $PGF_{2\alpha}$, and 5-HT (1160, 1752, 2188). In pig distal PASMC, hypoxic contraction was maximal and half-maximal at O_2 tensions of 0 and ~10 mmHg, respectively (1752). It is not clear why the latter value is so much lower than half-maximal P_{O_2} for HPV in lungs and pulmonary arteries (see sect. II, *A* and *B*). Possible explanations include elimination of sensitizing inputs from other cells and the additional load imposed by the attachments of cultured PASMC to substrate, which must be broken for the cells to shorten.

More recently, sophisticated cellular imaging techniques have been used to quantify constriction and the changes in mechanical properties and cell-matrix interaction induced by hypoxia in cultured endothelial cells (42, 153); however, these methods have not yet been applied to PASMC.

III. MEDIATION

Mediation of HPV includes mechanisms of O_2 sensing, signal transduction, and smooth muscle contraction that are both intrinsic to PASMC and required for the response.

A. Sensor Mechanisms

1. Overview of O_2 sensing

Identification of the O_2 sensor that triggers HPV has proven difficult and fraught with controversy, in part because there are many potential candidates. A variety of O_2-sensitive mechanisms responding over different ranges of P_{O_2} are now recognized, each probably serving different functions, and more than one of these may be present in a particular tissue (8, 1126, 2020, 2047).

In broad terms, interactions between proteins and O_2 involve either reversible binding of molecular O_2 leading to allosteric alterations of protein structure that initiate a sig-

naling pathway, as exemplified by heme-ligand interactions; or biochemical reactions in which O_2 is a substrate with or without an initial heme-binding step **(FIGURE 4)**. The latter category can be further subdivided into bioenergetic hypoxia, which occurs when P_{O_2} is insufficient to maintain normal function of cytochrome *aa3* and, consequently, a normal concentration of high-energy phosphates and redox state of pyridine nucleotides; and metabolic hypoxia, which occurs when P_{O_2} is insufficient to maintain normal function of O_2-dependent enzymes other than cytochrome *aa3*.

A) GENERAL CLASSIFICATION OF O_2-SENSITIVE SYSTEMS. *I) Direct modification of protein residues*. O_2 and redox state can directly and reversibly modify sulfur-containing protein residues, as in oxidation of thiol groups on cysteine to form disulfide bonds, or oxidation of methionine to form methionine sulfoxide. Consequent allosteric alteration of protein conformation can then modify function. In terms of O_2 sensing in PASMC, the most studied of such interactions is O_2-dependent modulation of K^+ channel function, where demonstrations of O_2 sensitivity in channels studied in excised membrane patches or recombinant expression systems imply direct effects of P_{O_2} on channel proteins (585, 1074, 1075, 1439, 1471, 1473). Such effects could include alteration of cysteine thiols, methionine, or oxidoreductase domains in channel proteins (1126, 1471); however, indirect effects via membrane-delimited O_2 sensors like heme oxygenase or NADPH oxidase (1057, 2099) remain possible. Overall, there is little hard evidence that direct effects of O_2 on channel proteins play a role in O_2 sensing. In contrast, the evidence for indirect effects mediated via modulation of redox state is significant (see sect. III*A*2C).

II) Heme. The archetypical O_2 binding molecule is heme, a member of the porphyrin family composed of four pyrrole rings bound to a central iron atom, which can be converted from ferrous (Fe[II]) to ferric (Fe[III]) by binding of molecular O_2 (682) **(FIGURE 4)**. Heme synthesis from glycine and succinyl-CoA begins and ends in the mitochondrion, although intermediate steps are cytosolic. Heme is not recycled, but degraded by heme oxygenase to produce CO, biliverdin, and ultimately bilirubin. Among several forms,

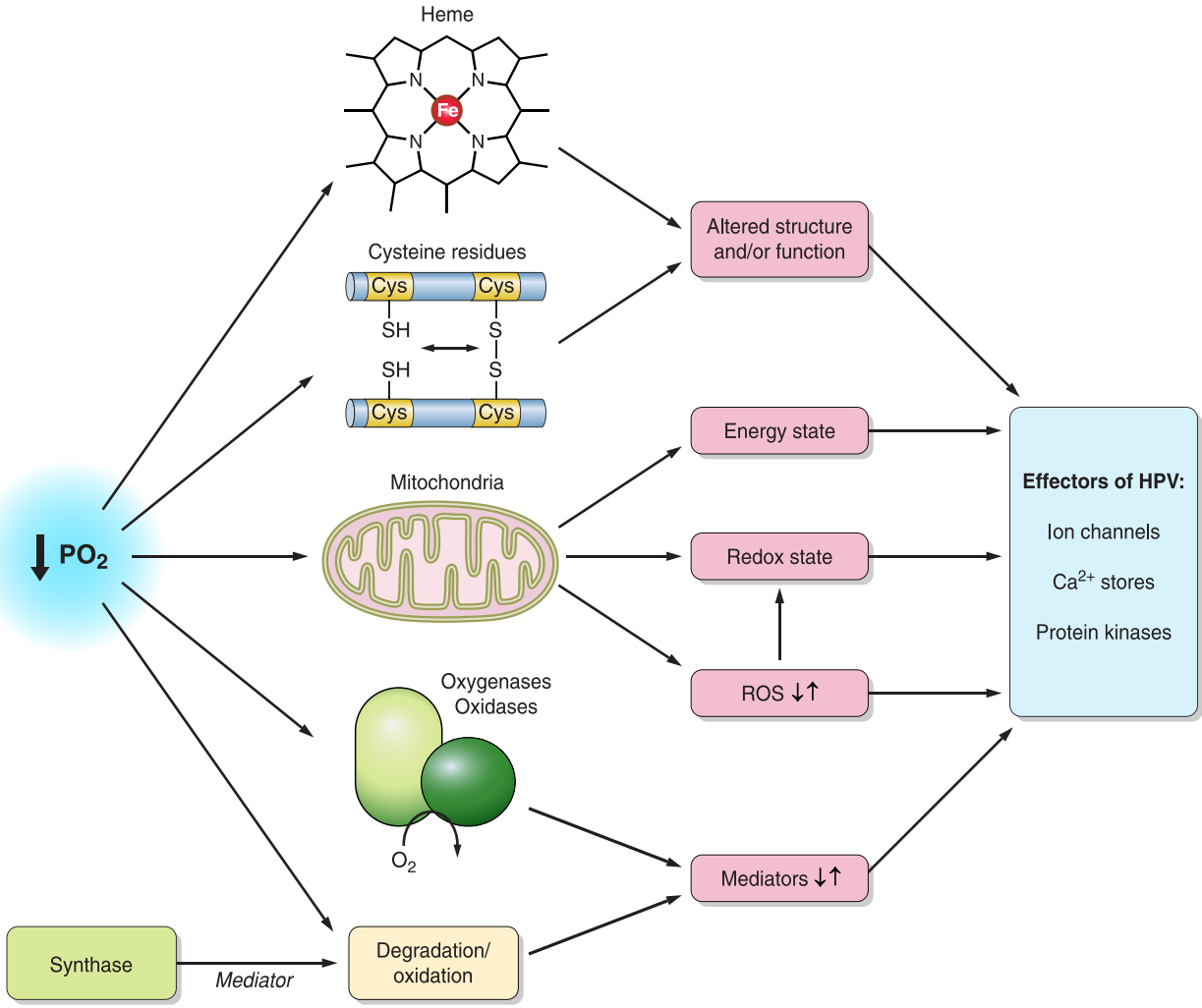
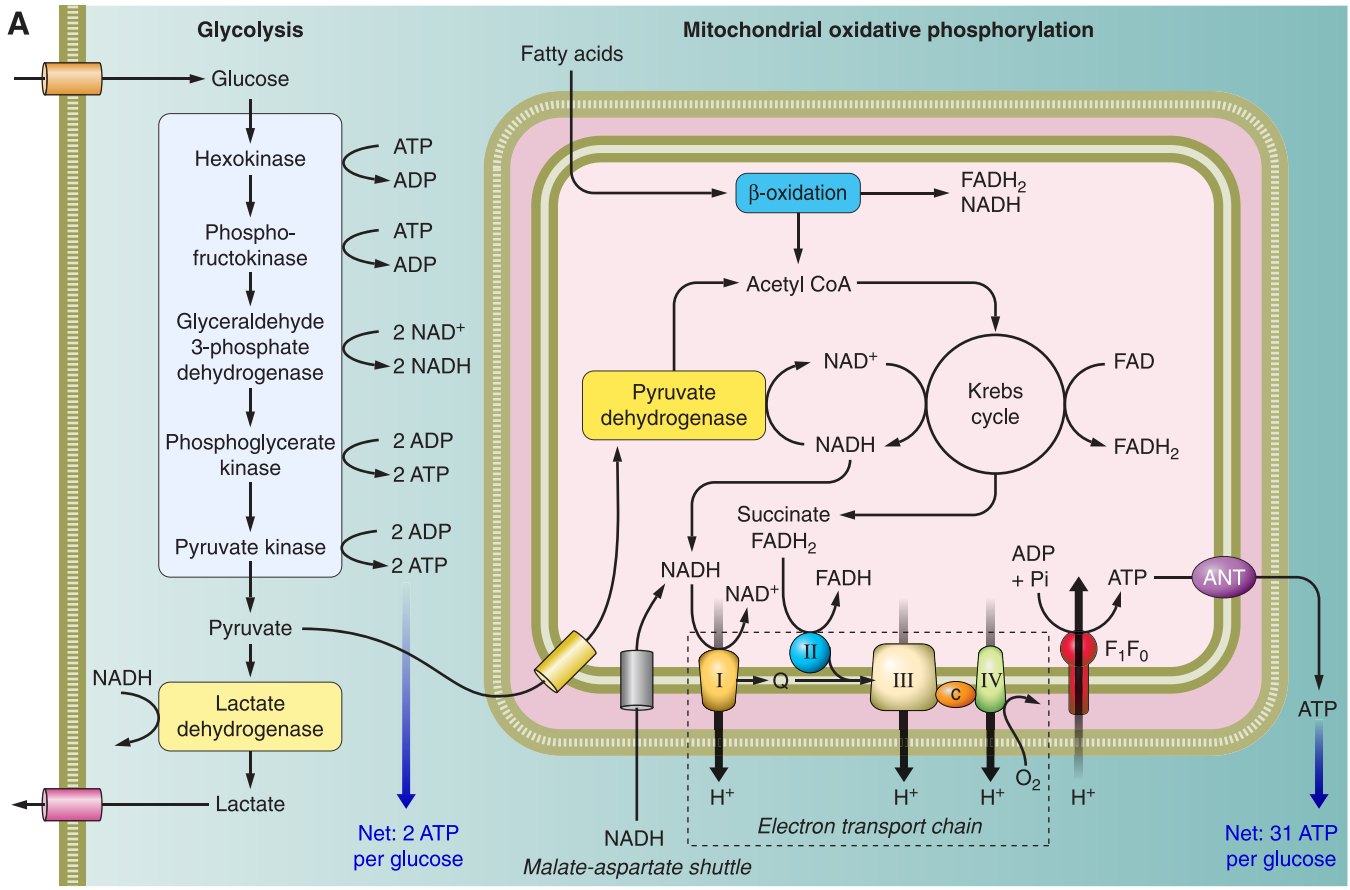


FIGURE 4 Possible O_2 sensing pathways. ROS, reactive oxygen species.



heme B found in Hb is the most common. Heme A is found in cytochrome *aa3*, and heme C in cytochrome *c* (271). Heme usually forms coordination bonds to its associated protein via the iron moiety, but heme C is also covalently bound.

The ability of heme to bind O_2 reversibly has long been of interest in terms of O_2 sensing (8, 283, 682, 1125). A large number of enzymes and signaling proteins have prosthetic heme groups, and mediate oxidation-reduction reactions and electron transport. These include oxidoreductases and cytochromes, although some of the latter are purely concerned with electron transport (e.g., heme B of cytochrome bc_1 and heme C of cytochrome *c*) and do not involve O_2 binding. Heme proteins implicated in O_2 sensing include mitochondrial cytochromes, NADPH oxidase, cytochrome *P*-450, NO synthase, guanylate cyclase, catalase, cystathionine β-synthase, and heme oxygenase, as discussed below. Heme itself is a pro-oxidant (1682).

III) Oxygenases. Oxidoreductase enzymes catalyze reversible oxidation-reduction (redox) reactions, where one substrate acts as an electron or H^+ donor and is oxidized, and the other acts as acceptor and becomes reduced. Oxygenases (or oxidases) are oxidoreductases where O_2 is the acceptor substrate, and are of two main classes. Monooxygenases (or mixed function oxidases) catalyze incorporation of one atom of O_2 into a substrate as an hydroxyl group, and reduction of the other atom into water, using sequential transfer of two electrons from NADH or NADPH. Examples of relevance to O_2 sensing include cytochrome *P*-450 monooxygenases (see sect. III*A4*C) and heme oxygenase (see sect. III*A3*B). Dioxygenases catalyze incorporation of both atoms of molecular O_2 into a reduced substrate. Important examples include prolyl and asparaginyl hydroxylases (see sect. III*A4*B), cyclooxygenase, lipoxygenases, and NO synthase (see sect. III*A4*, D and E). Cytochrome *aa3* (also known as cytochrome *c* oxidase) in complex IV of the mitochondrial electron transport chain sequentially reduces the two atoms of molecular O_2 to two molecules of water (see sect. III*A2*A), while NADPH oxidase transfers a singlet electron to O_2 to produce superoxide (see sect. III*A3*A).

B) GENERAL REQUIREMENTS FOR O_2 SENSING IN HPV. Isolated PASMC and endothelium-denuded pulmonary arteries respond to hypoxia by increasing intracellular [Ca^{2+}], a prerequisite for HPV. While endothelium may provide an important component of the response, it is nevertheless clear that the key O_2 sensor must reside in PASMC. This sensor must be sensitive over an appropriate range of P_{O_2}, a seemingly simple point that is complicated by lack of direct knowledge of normal cytosolic P_{O_2} in PASMC. In other cell types, however, cytosolic P_{O_2} is believed to be 5–15 mmHg, depending on *1*) the rate and sites of O_2 consumption in the cell, the most important of which are mitochondria; and *2*) barriers to the diffusion of O_2 to those sites (2020). As HPV is rapid and reversible, changes in distal signaling pathways of any putative O_2 sensor must precede or coincide with the effector response. Finally, there should be a definable mechanism linking the sensor to contraction.

2. Mitochondria

Mitochondria consume most of the O_2 within the cell and are generally thought to function as signaling organelles as well as producers of energy (438, 1568). Low P_{O_2} can alter mitochondria-dependent variables, such as [ATP], energy state, redox state, and generation of reactive oxygen species (ROS), which could theoretically signal HPV. In vascular smooth muscle, mitochondria can modulate Ca^{2+} content in sarcoplasmic reticulum (SR) (434, 635, 1533, 1871) and are often closely associated with SR and sarcolemma and thus well situated for localized signaling (see sect. III*B2*). Indeed, many studies have shown that inhibition of oxidative phosphorylation has strong and selective effects on HPV (51, 61, 62, 1041, 1115, 1278, 1666, 1667, 1814, 2032, 2033, 2035, 2055, 2066, 2207). Moreover, PASMC that are depleted of mitochondrial DNA (ρ^0) by incubation with ethidium bromide, and thus lack a functional mitochondrial electron transport chain (METC), do not respond to hypoxia (282, 2032). Inhibition of mitochondrial electron transport may be a crucial prerequisite for O_2 sensing not only in PASMC but also in carotid body type 1 and neonatal chromaffin cells (1126, 1330, 2020, 2025, 2036, 2129). Thus mitochondria are obvious candidates for the role of O_2 sensor in HPV.

A) SYNOPSIS OF MITOCHONDRIAL FUNCTION. Discussion of mitochondrial O_2 sensing requires an understanding of mitochondrial function **(FIGURE 5)**. Mitochondrial ATP production depends on metabolic fuels including glucose, amino acids, and fatty acids. Glucose and fatty acids are metabolized, respectively, by glycolysis in the cytosol and β-oxidation in the mitochondria. Glycolysis involves a series of membrane-associated enzymatic reactions that ultimately produce pyruvate and two molecules of ATP and reduce two molecules of nicotinamide adenosine dinucleotide (NAD^+) to NADH. Pyruvate is carried into the mitochondria and converted by pyruvate dehydrogenase to acetyl

FIGURE 5 Pathways of ATP production via glycolysis and mitochondrial oxidative phosphorylation (*A*) and details of electron transport, proton movement, and production of ATP and reactive O_2 species in mitochondria (*B*). ANT, adenine nucleotide translocator; I, II, III, and IV indicate mitochondrial electron transport protein complexes; Q, QH_2, and $QH^{\cdot}$, ubiquinone, ubiquinol, and ubisemiquinone, respectively. Cytochromes *c, c1, b_L. b_H*, and *aa3* are indicated by their letters. FeS, Rieske Fe-S protein; F_1F_O, F_1F_O ATP synthetase; SOD, superoxide dismutase; GPX, glutathione peroxidase. Sites of action of commonly used mitochondrial inhibitors (rotenone, myxothiazole, antimycin A, and cyanide) are shown in *B*.

coenzyme A (acetyl CoA), the key substrate of the tricarboxylic acid (TCA) cycle, whereas NADH equivalents enter primarily via the malate-aspartate shuttle. β-Oxidation of fatty acids in the mitochondrion generates acetyl CoA, NADH, and $FADH_2$. In the TCA cycle, substrate molecules are progressively dehydrogenated causing the reduction of NAD^+ and flavin adenine dinucleotide (FADH) to NADH and $FADH_2$. These are reoxidized by the METC, which ultimately reduces molecular O_2 to water **(FIGURE 5)**. The oxidation of NADH can be summarized as follows: $NADH + H^+ + 3ADP + 3P_i + 1/2O_2 \rightarrow NAD^+ + 3ATP + H_2O$.

The METC is composed of four multiprotein complexes (I–IV) in the mitochondrial inner membrane. NADH and $FADH_2$ are oxidized by oxidoreductases in complex I and II, respectively. These electrons are then transferred down a redox gradient via the ubiquinone (Q) cycle, involving a two-electron reduction of ubiquinone to ubiquinol (QH_2), which binds to the outer intermembrane (Qo) site of complex III (cytochromes *b* and c_1). Here, one electron is removed from QH_2 by the Rieske Fe-S protein, leaving ubisemiquinone ($QH^{\cdot}$). The electron is transferred via cytochrome c_1 to the mobile carrier cytochrome *c*. $QH^{\cdot}$ passes its remaining electron to cytochrome b_L, which transfers it to cytochrome b_H at the inner matrix site (Qi) of complex III. This first reduces ubiquinone to $QH^{\cdot}$ and then, with the next electron, to QH_2, which reenters the cycle at Qo **(FIGURE 5*B*)**. Three operations of complex III are therefore required for a complete cycle: oxidation of two QH_2; sequential transfer of two electrons to two molecules of cytochrome *c*; and rereduction of one ubiquinone to QH_2. Cytochrome *c* is oxidized by cytochrome *aa3* (complex IV), where O_2 acts as the final electron acceptor and is reduced to H_2O. The transfer of electrons through the METC is accompanied by extrusion of protons towards the cytosol at complex I (4 H^+), III (4 H^+), and IV (2 H^+), generating the mitochondrial membrane potential ($\Delta\Psi_M$) and proton gradient (ΔpH) which drive production of ATP in the mitochondrial matrix by F_1F_0 ATP synthetase. ATP in the matrix is subsequently exchanged for cytosolic ADP by the adenine nucleotide translocator (ANT), and thereby made available to the cell (1625). Commonly used inhibitors of the METC and their sites of action are also shown in **FIGURE 5*B***.

B) O_2 SENSITIVITY. The concept that a mitochondrial O_2 sensor triggers responses to physiological hypoxia has been questioned because the P_{O_2} that decreases cytochrome *aa3* activity by 50% of maximum (P_{50}) was generally reported to be <0.5 mmHg (620, 1951), suggesting that mitochondrial electron transport should be unaffected by reductions in P_{O_2} that elicit HPV (see sect. II*A3*). In contrast, O_2 tensions of 20–50 mmHg reduced mitochondrial flavoproteins and $\Delta\Psi_M$ and increased NAD(P)H autofluorescence in carotid body glomus cells (8, 441, 442) and altered energy state (1045) and increased mitochondrial NAD(P)H autofluorescence (1041) in pulmonary arteries. Indeed, the effects of P_{O_2} on pulmonary arterial NAD(P)H autofluorescence provided a P_{50} of 21 mmHg (2020), similar to that for HPV in an equivalent preparation (1104).

A number of factors may account for this apparent dichotomy. First, P_{O_2} at the mitochondria will depend on the rate of O_2 diffusion to mitochondria relative to the rate of mitochondrial O_2 consumption. This P_{O_2} has been estimated to equal 5–15 mmHg during normoxia, or about 10- to 30-fold greater than generally accepted values of P_{50} for cytochrome *aa3* (620, 2020). Thus, when alveolar P_{O_2} falls to levels sufficient to elicit HPV, barriers to O_2 diffusion might cause perimitochondrial P_{O_2} to fall to levels sufficient to reduce mitochondrial function.

Second, the apparent P_{50} of cytochrome *aa3* will vary inversely with its level of expression relative to proximal components of the METC; i.e., low relative expression of cytochrome *aa3* not only increases its apparent P_{50}, but also makes the proximal METC more reduced and, importantly perhaps, promotes formation of ROS (619, 620). Effectively, the same outcome can be caused by mediators that interact with cytochrome *aa3*; e.g., NO may increase P_{50} by competing with O_2 for binding (464, 2133), although it should be noted that inhibition of NO synthase potentiates HPV (see sect. IV*B2*A). Interestingly, H_2S also competes with O_2 for cytochrome *aa3* and has recently been implicated in HPV (see sect. III*A4*F).

Third, the apparent P_{50} of the overall response (e.g., vascular constriction) could be increased without a change in threshold P_{O_2} if the pathways that coupled O_2 sensing to PASMC contraction amplified the response in a manner proportional to the change in P_{O_2}, such as would occur if contraction were a power function of the fall in P_{O_2} below threshold (2020). In this case, even a small change in sensor signal caused by a reduction in P_{O_2} well above its actual P_{50} could be translated into a large effector response.

A fourth possibility is provided by the "near-equilibrium" hypothesis (479, 2100). Briefly, this hypothesis states that the reactions at the first two sites of oxidative phosphorylation (Complex I and III; **FIGURE 5**) are at near-equilibrium. As a consequence, the rate of mitochondrial electron flux and O_2 consumption is set by the rate of the irreversible reaction of reduced cytochrome *c* with O_2, which is catalyzed by cytochrome *aa3* at complex IV. The rate of this reaction is determined by its rate constant and the concentrations of both O_2 and reduced cytochrome *c*. The latter depends in turn on mitochondrial [NAD^+]/[NADH] and the cytosolic phosphorylation potential ([ATP]/[ADP][P_i] where P_i = inorganic phosphate). When O_2 concentration falls and limits the rate of reaction at complex IV, continued ATP utilization decreases the phosphorylation potential, which then induces an increase in the reduction of cyto-

chrome *c* through the near-equilibrium reactions at complexes I and III. As a result, the rate of the reaction of O_2 with reduced cytochrome *c* at complex IV is restored to its previous level, along with the rates of mitochondrial electron flux, O_2 consumption, and ATP production via oxidative phosphorylation. Maintenance of mitochondrial respiration in this manner leads to a low apparent P_{50} when the actual P_{50} is high. This innate regulation and reduction of the METC proximal to cytochrome *c* may depend on enhanced glycolysis to provide additional NADH to the METC, which could be important for ROS-mediated signaling (698) and explain the catastrophic effects of combined hypoxia and lack of glucose on energy state in pulmonary arteries (1041, 1045). In support of the near-equilibrium hypothesis, progressive hypoxia within the physiological range has been found to increase reduction of cytochrome *c* in several cell types (2100), including PASMC (1814).

Finally, mitochondrial function and O_2 sensitivity could be different in O_2-sensitive cells such as PASMC and carotid body glomus cells (441, 442, 1278). A cytochrome *aa3* with low O_2 sensitivity was implicated in carotid body (1284, 1285, 1847), and pulmonary artery mitochondria were reported to have a lower respiratory rate, higher ROS production, and a more depolarized $\Delta\Psi_M$ under normoxic conditions than renal artery mitochondria (1278). More recently, P_{50} values for mitochondrial O_2 consumption in PASMC, as well as aortic and renal arterial smooth muscle cells, were reported to be <1 mmHg (1814), suggesting that PASMC do not contain a unique cytochrome *aa3* of low O_2 affinity; however, if the near-equilibrium hypothesis is correct, the apparent P_{50} of cytochrome *aa3* could be lower than its actual P_{50} in these cells.

This study also reported that physiological levels of hypoxia caused small but significant reductions in mitochondrial respiration and cytochromes in association with small but significant responses in cultured rabbit PASMC (1814). For example, O_2 tensions of 38, 23, and 8 mmHg, respectively, decreased mitochondrial O_2 consumption by 2.1, 3.3, and 9.7% of maximum, as measured by high-resolution respirometry; and increased concentrations of reduced cytochrome *aa3* to 0, 7.1, and 17.5% of total, cytochrome *b* to 0, 0, and 10.9% of total, and cytochrome *c* to 4.8, 7.1, and 18.1% of total, as measured by deconvolution of remission absorbtion spectra. Since these same O_2 tensions hyperpolarized $\Delta\Psi_M$ (JC-1 fluorescence) by 0, 3.6, and 15.2%, increased ROS production (MitoSox fluorescence) by 0, 2.4, and 4.0%, and increased $[Ca^{2+}]_i$ (fura 2 fluorescence) by 0, 6.7, and 11.3%, it was concluded that inhibition of cytochrome *aa3* in PASMC was an essential step in the O_2 sensing that leads to HPV (1814).

It has also been hypothesized that mitochondrial O_2 sensing is divorced from changes in mitochondrial electron flux and ATP generation altogether. In this case, hypoxia-induced changes in the lipid-protein structure of the mitochondrial inner membrane might *1*) move ROS generation from the Qi (matrix) to the Qo (intermembrane) site in complex III; *2*) increase electron transfer to O_2 by increasing $QH^{\cdot}$ lifetime; or *3*) increase the availability of O_2 for reaction with $QH^{\cdot}$ (1739, 2037). Consistent with *option 1*, recent measurements of intracellular redox state in PASMC using targeted molecular redox sensors demonstrated that hypoxia reduced the mitochondrial matrix but oxidized the cytosol and mitochondrial intermembrane space (2034). In addition, it was recently reported that terpestacin, a small molecule produced by the fungus *Embellisia chlamydospora*, inhibited hypoxia-induced ROS production and HIF-1α stabilization in HT1080 cells but did not alter oxygen consumption in isolated mouse liver mitochondria (916). These effects appeared to result from binding of terpestacin to a 13.4-kDa subunit of complex III known as ubiquinol-cytochrome *c* reductase binding protein (UQCRB). On the basis of these and other data, it was proposed that under hypoxic conditions the interaction of UQCRB with cytochrome *b* could prolong $QH^{\cdot}$ lifetime at the Qo site of complex III, thereby enhancing generation and release of ROS into the intermembrane space and cytosol **(FIGURE 5*B*)**. Since terpestacin also caused mitochondrial depolarization (916) and ROS production by complex III was increased by hyperpolarization (1665), it was further speculated that hypoxic prolongation of $QH^{\cdot}$ lifetime at Qo was due to decreased electron transfer from cytochrome b_L to b_H, perhaps as a result of mitochondrial hyperpolarization (916) **(FIGURE 5*B*)**. Consistent with this possibility, two laboratories have reported that hypoxia caused mitochondrial hyperpolarization in PASMC (1278, 1814); however, another found that hypoxia had no effect on $\Delta\Psi_M$ (2032). The mechanisms by which hypoxia and terpestacin might cause mitochondrial hyperpolarization and depolarization, respectively, remain unclear. Further work is necessary to determine if and how UQCRB contributes to O_2 sensing in PASMC.

C) REDOX STATE. Cellular redox state reflects the balance between cytosolic oxidizing and reducing equivalents, including the important redox couples, reduced/oxidized glutathione (GSH/GSSG) and NADH/NAD^+, and the balance between production and degradation of ROS. The latter could be compartmentalized, and therefore not reflect cell redox state as a whole. The mitochondrial TCA cycle is the major source, and the METC the major sink, for reducing equivalents in the form of NADH. Hypoxia has been reported to shift lung, PASMC, and carotid body glomus cells to a more reduced state, as indicated by increased GSH/GSSG and NADH/NAD^+ ratios (62, 284, 347, 1041, 2084).

Early reports suggested that inhibition of oxidative phosphorylation might mimic the effects of hypoxia on pulmonary vessels (1666) and that HPV could be reversed by

oxidants (2042). Such studies led to formulation of the Redox Hypothesis of HPV (51, 62, 2045, 2046), which proposes that suppression of mitochondrial oxidative phosphorylation by hypoxia leads to a more reduced cytosolic redox state and decreased [ROS], causing inhibition of a K^+ current (I_K), and subsequent PASMC depolarization, Ca^{2+} influx via voltage-gated Ca^{2+} channels, and vasoconstriction (**FIGURE 6*A***). A central tenet of this hypothesis is that oxidation of K^+ channel proteins during normoxia, possibly at cysteine thiols, methionine residues, or oxidoreductase domains (680, 1225, 1471, 1503, 1911), maintains channel opening and thus I_K and membrane potential, while reduction of these proteins during hypoxia causes closure of K^+ channels, decreased I_K, and depolarization. In support of this possibility, oxidizing agents such as diamide, dithio-bis 5-nitropyridine (DTNB), GSSG, and NAD^+ were shown to increase I_K in PASMC, while reducing agents including GSH, dithiothreitol, and NADH, reduced I_K (1424, 1461–1463, 1600, 1718, 2045). The effects of such agents were largely attributable to voltage-gated K^+ (K_V) channels, which are thought to contribute to resting membrane potential in PASMC (see sect. III*B1*A); however, other effects remain possible. For example, a recent report suggests that diamide can also inhibit store-operated Ca^{2+} entry (1718), thought to be a key component of HPV (see sect. III*B2*D). Furthermore, the relatively profound alterations elicited by some oxidants and reductants may not reflect effects of moderate hypoxia, perhaps explaining why such agents affected K_V channel activity in pulmonary and systemic arteries in the same way (1461, 1600). In many cells (611, 1719), including PASMC (2033), the cytosol is usually in a highly reduced state during normoxia, potentially leaving little room for further reduction by hypoxia. Moreover, recent studies have shown a paradoxical cytosolic oxidation in PASMC during hypoxia (2033, 2034).

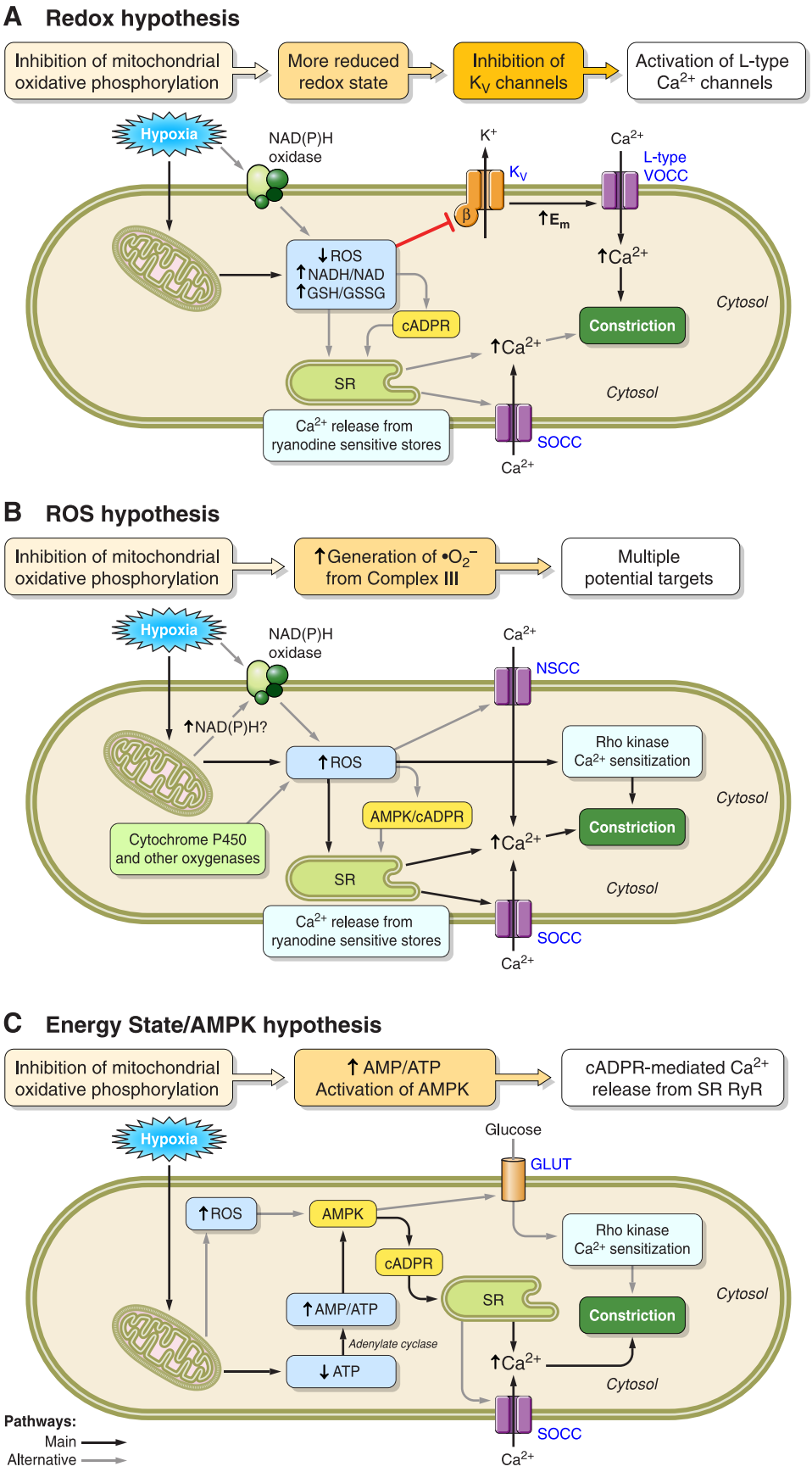
As originally proposed, the executive arm of the Redox Hypothesis was limited to inhibition of K^+ channels, depolarization, and Ca^{2+} entry via L-type Ca^{2+} channels (51, 62, 2045); however, the preeminent role of this pathway has been challenged, as other reports have shown that HPV is not affected by inhibition of K_V channels (751, 1752), can be elicited following depolarization with high [K^+] and blockade of L-type channels (1641), and is critically dependent on Ca^{2+} release from ryanodine-sensitive intracellular Ca^{2+} stores in sarcoplasmic reticulum (412, 876, 1104, 1963, 2101) (see sect. III*B2*C). Interestingly, hyperreactive thiol groups, glutathione redox state, NADH, and ROS-mediated dissociation of FK506-binding protein have all been implicated as regulators of ryanodine-sensitive Ca^{2+} release channels in sarcoplasmic reticulum (302, 510, 511, 1091, 1860). It has also been suggested that the hypoxia-induced increase in [NADH] inhibits breakdown of cyclic ADP ribose (cADPR) by ADP-ribosyl hydrolase, thereby increasing cADPR concentration and cADPR-induced Ca^{2+} release from ryanodine-sensitive stores (412, 413, 2101) (**FIGURE 6*A***).

D) ROS. ROS include superoxide ($O_2^{\cdot -}$), hydroxyl ($^{\cdot}OH$) and peroxyl ($RO_2^{\cdot}$) oxygen radicals, and oxidizing agents such as peroxide (H_2O_2) and hypochlorous acid (HOCl). The most common ROS are $O_2^{\cdot -}$, $RO_2^{\cdot}$, and $^{\cdot}OH$ (724). Although originally viewed as toxic byproducts of metabolism, ROS are now recognized as signaling moieties with roles in a wide range of regulatory mechanisms in vascular smooth muscle and endothelium (127, 433, 1133, 1145, 1862). ROS are appropriate to consider as hypoxic signals in PASMC because they can trigger many of the pathways that may be involved in HPV, including Ca^{2+} release from ryanodine-sensitive stores (1096, 1546, 1860), increased synthesis of cADPR (1006, 1421), activation of AMP kinase (307, 1701), increased Ca^{2+} entry via nonselective cation and TRP channels (91, 541, 772), and activation of Rho kinase-mediated Ca^{2+} sensitization (898), src kinase (978, 2023), and other signaling pathways (433, 1145).

Over the last few years, a significant body of evidence has emerged suggesting that ROS, specifically superoxide and peroxide, may be key mediators in HPV; however, there is considerable controversy concerning their source and target mechanisms, and whether they are increased, decreased, or involved at all (488, 633, 1330, 2021, 2036, 2044). Since O_2 is the major substrate for ROS formation, the concept that ROS might fall in hypoxia, as proposed by the Redox Hypothesis (51, 62, 1330, 2045, 2046), is easy to understand; however, it has also been proposed that an apparently paradoxical increase in mitochondrial ROS generation underlies responses to hypoxia in many cell types (**FIGURE 6*B***), including PASMC (283, 1041, 1102, 1591, 2010, 2032, 2033, 2035).

I) Generation and fate of ROS. In mitochondria, ~3% of electron flux through the METC is constitutively lost to formation of superoxide. As shown in **FIGURE 5*B***, this occurs primarily in complex I, where superoxide formed by auto-oxidation of flavins enters the mitochondrial matrix; and in complex III, where superoxide formed by donation of an electron from $QH^{\cdot}$ at the Qi site enters the matrix, while that formed by $QH^{\cdot}$ at the Qo site enters the intermembrane space (210, 1950, 1951). Alternatively, it has been suggested that superoxide formation at Qo could involve a reverse reaction in complex III, whereby oxidized Q promotes electron transfer to O_2 from reduced cytochrome

FIGURE 6 Diagrams of possible mechanisms that explain how hypoxia causes constriction in pulmonary arterial smooth muscle, as proposed by the Redox (*A*), ROS (*B*), and energy state/AMP kinase (*C*) hypotheses. Main and alternative pathways are indicated by black and gray arrows, respectively. K_V, VOCC, SOCC, and NSCC, voltage-dependent K^+, voltage-operated Ca^{2+}, store-operated Ca^{2+}, and nonselective cation channels, respectively; E_m, membrane potential; cADPR, cyclic ADP ribose; AMPK, AMP kinase; SR, sarcoplasmic reticulum.



b_L (435). In the mitochondrial matrix, superoxide is converted by manganese SOD (MnSOD; SOD 2) to H_2O_2, which is degraded by gluthathione peroxidase (GPX) to water. In the intermembrane space, superoxide is degraded by CuZnSOD (SOD 1), scavenged and recycled by cytochrome *c*, or transported to cytosol *via* voltage-dependent anion channels (VDAC) in the outer mitochondrial membrane (732, 2032).

The cytosol contains a number of antioxidant defense mechanisms, including CuZnSOD, catalase, GSH, and GPX, as well as scavengers like heme and sulfur-containing protein residues (724, 1070). Superoxide is highly reactive and largely membrane impermeable, although it passes through anion channels, and is rapidly dismuted by SOD to the more stable peroxide. Superoxide is the precursor of other ROS and radicals, such as peroxynitrite formed by interaction with NO, and can deplete reducing equivalents, as in oxidation of GSH to GSSG. Consequently, superoxide and SOD are important determinants of cellular oxidant stress and redox state (2109). Although often regarded purely as an oxidant, superoxide can also reduce disulfide bonds and cytochrome *c* (1511). Peroxide is degraded by catalase or GPX in the presence of GSH to O_2 and water. Transition metals such as Fe(II) promote decomposition of peroxide to the highly reactive $^{\cdot}OH$ in the Fenton reaction. Since peroxide is more stable, mobile, and membrane permeable than superoxide, it is generally regarded as the most likely species to mediate HPV; however, recent evidence suggests that superoxide may play a direct role in the activation of Rho kinase (977).

II) Modulation of mitochondrial ROS generation. As superoxide production depends on electron donation from reduced components of the METC (flavin in Complex I, $QH^{\cdot}$ in Complex III), anything that shifts these components to a more reduced state would be predicted to enhance superoxide generation (1291). Thus ROS generation is potentiated by inhibition of cytochrome b_H with antimycin A, which prolongs $QH^{\cdot}$ lifetime, or when electron transport by complex IV becomes rate limiting (1338, 1950), as in the presence of complex IV modulators like cyanide, NO, or H_2S (283, 466, 1449, 2032). Whether this also occurs in hypoxia, or whether ROS generation falls because there is less O_2 as substrate for superoxide production is controversial (698, 1330, 2021, 2044). For example, hyperoxia increases mitochondrial ROS generation by providing more O_2 as substrate (228, 280, 555), and hypoxia might be expected to do the opposite.

Superoxide formation is constrained by the law of mass action, and will therefore be proportional to $[O_2] \times$ [electron donor] (1950). If $[O_2]$ were raised above normoxic values, [electron donor] would not change because cytochrome *aa3* would not be rate-limited by O_2 availability, and superoxide formation would increase. If $[O_2]$ were lowered during hypoxia to levels sufficient to limit electron transport, then the proximal METC would become reduced, [electron donor] would rise as $[O_2]$ fell, and superoxide production could increase or decrease depending on the relative magnitude of these offsetting effects. It has been shown that mitochondrial electron transport is maintained during hypoxia as proximal elements of the METC become more reduced, perhaps due to regulated increases in glucose uptake, glycolysis, and NADH/NAD^+ (479, 1041, 1045, 2100). Thus it is possible that the increase in [electron donor] could exceed the fall in $[O_2]$ during hypoxia, and that both hyperoxia and hypoxia could increase mitochondrial ROS generation. The question is whether this happens.

III) Measurement of ROS. Measurements of ROS during HPV have not provided an unequivocal answer to this question. The issue has been confounded by use of different preparations and probes with various limitations and differential sensitivity to peroxide, superoxide, and other ROS and lack of differentiation between extracellular and intracellular sources of ROS. The last is of particular importance, as the major source of ROS in the vasculature is NADPH oxidase, the phagocytic form of which (NOX2) expels superoxide to the extracellular space and is expressed in numerous cell types, including endothelium, alveolar macrophages, and airway epithelium (657). Lungs from mice lacking the $gp91^{phox}$ subunit of NADPH oxidase have levels of ROS that are almost undetectable by chemiluminescence (58); therefore, studies on multicellular preparations and in particular perfused lungs may be compromised by differential effects of hypoxia on intracellular and extracellular ROS.

TABLE 2 summarizes reports where the effects of hypoxia on ROS generation have been estimated using different probes and preparations. Notably, most of the studies reporting a reduction in ROS during hypoxia were performed in perfused lungs or pulmonary arterial rings using luminol or lucigenin-enhanced chemiluminescence or the peroxide indicator Amplex Red. In contrast, most of the studies reporting an elevation of ROS were performed in isolated PASMC using the intracellular indicator dichlorofluorescein (DCF).

There are known limitations of most ROS-sensitive probes (409, 2027). Chemiluminescence measurements with lucigenin and luminol, which primarily (but not solely) detect superoxide, suffer from ROS generation and redox cycling. Although these problems can be limited by using low concentrations or newer probes (409), these indicators, like Amplex red and electron spin resonance (ESR), are more likely to detect extracellular than intracellular ROS. For example, an SOD-inhibitable ESR signal was increased by hypoxia in lungs from $p47^{phox}$ knockout mice, but decreased in lungs from wild-type mice, suggesting that a large hypoxic decrease in extracellular ROS derived from NADPH oxidase masked an hypoxic increase in intracellu-

Table 2 Effect of acute hypoxia on reactive oxygen species in isolated lungs, pulmonary arteries, and pulmonary arterial smooth muscle cells

Preparation	Probe	ROS	Reference Nos.
IPL	Chemiluminescence	↓	51, 56, 203, 1301, 1302, 1448, 1597
	EPR	↓	2058, 2066
		↑ (+PMA)	2058
	DCF	0	2062
PA	Amplex Red	↓	203, 1278
	Chemiluminescence	↓	18, 58, 64, 1278
		↑	1102
	DCF	↓	1278
	EPR	↑	1102
PASMC	Amplex Red	↓	1253
	Chemiluminescence	↑	1196, 2010
	DCF	↓	1253
		↑	960, 1102, 1591, 1592, 2010, 2032
	Dihydroethidium	↓	1253, 2127
	FRET	↑	2033, 2037
	MitoSox	↑	1814
	Cyto-RoGFP	↑	2034
	IMS-RoGFP	↑	2034
	M-RoGFP	↓	2034

Chemiluminescence was enhanced by lucigenin or luminol. ROS, reactive oxygen species; IPL, isolated perfused lungs; PA, pulmonary arteries; PASMC, pulmonary arterial smooth muscle cells; DCF, 2′,7′-dichlorofluorescin diacetate; EPR, electron paramagnetic resonance; PMA, phorbol-12-myristate-13-acetate; FRET, fluorescence resonance energy transfer; RoGFP, a green fluorescent protein ROS probe targeted to cytosol (Cyto), mitochondrial intermembrane space (IMS), or mitochondrial matrix (M).

lar ROS derived from mitochondria (2066). DCF has attracted particularly stern criticism because it can itself generate ROS and its detection of peroxide is indirect, requiring peroxidase activity or the Fenton reaction (283, 409, 2027); however, observations that catalase, antioxidants, and pharmacological inhibition of the potential source of ROS reduced or prevented DCF oxidation and the elevation in intracellular [Ca^{2+}] during hypoxia lends some credence to the data it provides (960, 1103, 2010, 2032, 2035).

Recently developed intracellular probes may clarify the confusion. The redox-sensitive fluorescence resonance energy transfer probe HSP-FRET, which can be transfected into cultured PASMC, also indicated an hypoxia-induced increase in [ROS] that was inhibited by catalase and antioxidants (2033, 2037). Importantly, when ROS and [Ca^{2+}] were measured in the same cell using these techniques, the initial increases in these two signals occurred simultaneously (2033). A more recent development is RoGFP, an intracellular redox sensor based on green fluorescent protein, which is ratiometric (thereby overcoming differences in expression) and can be calibrated by exogenous oxidants and reducing agents (398, 2034). In mouse lung slices, RoGFP indicated that hypoxia caused oxidation, arguing that increases in ROS observed previously in hypoxic PASMC were not artifacts of cell culture (398). In PASMC, RoGFP probes targeted to cytosol, mitochondrial intermembrane space, and mitochondrial matrix revealed that hypoxia caused oxidation of cytosol and intermembrane space, but reduction of the matrix (2034). These important findings may explain the disparity among other studies, where the intracellular distribution of probes was not well defined.

In the light of the above, it seems increasingly likely that ROS signaling, like that for Ca^{2+}, is compartmentalized within the cell. It is also possible that cytosolic ROS signaling is confined to microdomains where mitochondria, SR, and/or sarcolemma are in close proximity, analogous to the situation with Ca^{2+}. In this case, it would be naive to expect any but targeted probes to distinguish localized changes in [ROS] from global alterations, especially as some classical probes may partially distribute to the mitochondria.

IV) Inhibition of mitochondrial electron transport. Evaluations of the role played by the METC in HPV have made frequent use of pharmacological inhibitors, often of dubious selectivity. The most commonly used agent has been rotenone **(TABLE 3)**, which blocks the METC proximally at complex I **(FIGURE 5B)**. While some studies suggest that rotenone mimicked hypoxia by inducing vasoconstriction during normoxia (51, 58, 203, 1278, 1597, 1666), others report that rotenone or myxothiazol, another proximal METC antagonist, did not have this effect (1041, 2010,

Table 3 Rotenone-induced vasoconstriction in isolated perfused lungs and pulmonary arteries during normoxia

Preparation	[Rotenone], μM	Vasoconstrictor Response		Reference Nos.
		Maximum, %HPV	Duration, min	
IPL	0.04	<10	Transient (2)	2066
	0.08	<10	Transient (5)	2055
	0.125	45	Transient (<10)	2032
	0.35	75	Transient (~10?)	2055
	0.5	100	Transient (<10)	1666
	1	93	Transient (<5)	51
	5	30	Transient (<15)	1278
	10	60	Transient (?)	1597
	50	80	*No trace shown*	58
	50	70	*No trace shown*	203
PA	0.1	No response		2207
	0.1	No response		1041
	5	50	*No trace shown*	1278

IPL, isolated perfused lungs; PA, pulmonary arteries.

2032, 2035, 2055, 2066, 2207). This distinction is crucial, since the former result would support both the Redox and Energy State Hypotheses **(FIGURE 6, *A* AND *C*)**, while the latter would not.

Rotenone has high affinity for the complex I NADH oxidoreductase, with a K_i of ~1 nM in isolated mitochondria (667). At 100 nM, rotenone increased mitochondrial NADH autofluorescence maximally in pulmonary arteries (1041) and decreased O_2 consumption by ~80% in PASMC (2032). However, at concentrations between 40 and 125 nM, rotenone either did not cause pulmonary vasoconstriction during normoxia or caused vasoconstriction that was only transient and much smaller than HPV **(TABLE 3)**. Furthermore, most reports show that rotenone inhibited HPV, even at concentrations as low as 40 nM (51, 58, 203, 1041, 1278, 1597, 1666, 2032, 2055, 2066, 2207). These findings indicate that the larger pulmonary vasoconstrictor responses to higher rotenone concentrations (350 nM to 50 μM; **TABLE 3**) were due to nonselective effects. Consistent with this possibility, rotenone inhibited K_V channels in neuroepithelial body cells independently of mitochondrial function, with 30% of current blocked at 1 μM and 70% at 10 μM (1745). Nonselective effects could also explain why 1–10 μM rotenone inhibited K_V channels in PASMC, an action that was attributed instead to changes in redox state (51, 1278, 1597). Arguing against nonselectivity are findings that the vasoconstrictive effects of rotenone in lung were opposite to those in the renal circulation, renal artery, and ductus arteriosus, where hypoxia caused vasodilation (1278, 1280).

Nevertheless, there is a developing consensus that inhibitors of the proximal METC, such as rotenone, myxothiazol, 1-methyl-4-phenylpyridinium iodide, and diphenylene iodonium, reduce ROS generation by blocking mitochondrial electron transport, and suppress or abolish HPV in lungs and pulmonary arteries and hypoxia-induced elevation of $[Ca^{2+}]_i$ in PASMC (1, 1330, 1814, 2010, 2025, 2036, 2047, 2060). Overall, evidence suggesting that rotenone's effects in pulmonary arteries mimic those of hypoxia is weak. In support of this conclusion, myxothiazol blocked the effects of hypoxia without eliciting vasoconstriction in pulmonary arteries or a rise in intracellular $[Ca^{2+}]$ during normoxia in PASMC (1041, 2010, 2032, 2033, 2035).

Inhibitors of the distal METC cause reduction of more proximal components, potentially facilitating ROS production. Antimycin A, which inhibits cytochrome b_H in complex III **(FIGURE 5B)**, is generally reported to cause transient constriction during normoxia, and either to inhibit or not affect HPV in lungs and pulmonary arteries or $[Ca^{2+}]_i$ responses to hypoxia in PASMC (18, 51, 1278, 1666, 2010, 2032, 2035, 2066); however, this agent is difficult to use due to its highly lipophilic nature and variable potency and, like rotenone, may have nonspecific effects on K_V channels at concentrations >0.4 μM (1745).

There is also disagreement concerning cyanide, an inhibitor of complex IV. At concentrations of 10–150 μM, cyanide tended to increase ROS generation but did not inhibit and even augmented HPV (51, 1041, 1278, 2032, 2035). In some studies, these cyanide concentrations increased $[Ca^{2+}]_i$ in PASMC (2035) or caused concentration-dependent constriction during normoxia (51, 233, 1666, 1814, 2032). In isolated rabbit lungs, however, cyanide concentrations ≤5 μM caused dose-dependent suppression of HPV with complete abolition occurring at concentrations ≥10 μM (1814, 2066). Furthermore, these effects correlated with reduction of mitochondrial cytochromes in lungs

but not mitochondrial respiration in PASMC. At much higher concentrations (≥1 mM), cyanide caused deterioration of energy state in association with vasodilation in precontracted pig pulmonary arteries (1045) and reversal of vasoconstriction elicited at lower cyanide concentrations in isolated pig lungs (233); and caused complete reduction of mitochondrial NAD(P)H and abolition of HPV in rat pulmonary arteries (2022). In theory, cyanide should completely inhibit cytochrome *aa3* at concentrations <10 μM; however, it is highly labile in solution, making the actual concentrations seen by different preparations uncertain (2129) and comparisons of results difficult. Nevertheless, some of these studies suggest that complete ablation of electron transport with cyanide inhibited HPV, possibly through effects on O_2 sensing. Consistent with this possibility, O_2 sensing was lost in cells lacking cytochrome *c* (1177) or following siRNA suppression of Rieske Fe-S protein (697).

Observations that proximal METC inhibitors decreased ROS, HPV, and $[Ca^{2+}]_i$ responses to hypoxia in PASMC while distal METC inhibitors increased ROS and did not inhibit HPV or $[Ca^{2+}]_i$ responses to hypoxia led to the proposal that the signal responsible for coupling the mitochondrial O_2 sensor to its effectors is derived from complex III distal to the point of inhibition by myxothiazol, most likely ubisemiquinone ($QH^{\cdot}$), the electron donor for superoxide generation (283, 1041, 2032, 2035) **(FIGURE 5*B*)**. Further evidence of the key role played by complex III is provided by observations that succinate, the substrate for complex II that provides reducing equivalents to complex III, completely reversed inhibition of HPV by rotenone but not myxothiazol (1041); that hypoxia caused reduction of the mitochondrial matrix but oxidation of the mitochondrial intermembrane space, which receives ROS from the Q_O site of complex III (2034); and that terpestacin, a small microbial molecule that binds to the UQCRB subunit of complex III, blocked hypoxia-induced increases in ROS (916). These results are consistent with the ROS Hypothesis, but do not appear to be consistent with the Redox or Energy State Hypotheses **(FIGURE 6)**.

V) Effects of antioxidants. If decreased superoxide generation were the initial event underlying HPV, antioxidants should cause pulmonary vasoconstriction during normoxia and possibly potentiate HPV. Conversely, if increased superoxide generation were the initial event, antioxidants should suppress HPV without mimicking hypoxia. Consistent with the former, early studies reported that SOD or SOD plus catalase increased P_{PA} in perfused rat lungs during normoxia, and enhanced both HPV and pressor responses to angiotensin II (56, 57); however, since these enzymes may not enter cells easily, their main effects may have been extracellular. Indeed, it was proposed that the effects of SOD were due to relief of superoxide-dependent inhibition of NO-dependent relaxation (57). Similarly, the antioxidants coenzyme Q10 (ubiquinone) and its analog duroquinone also appeared to mimic hypoxia by causing dose-dependent constriction in pulmonary arteries and suppression of K^+ currents in PASMC (1600).

Most later studies, however, suggested that antioxidants suppressed HPV. For example, the superoxide scavenger nitro blue tetrazolium (NBT) or the SOD inhibitor triethylenetetramine (TETA) inhibited HPV in perfused rabbit lungs without affecting pressor responses to U46619 or angiotensin II, or causing vasoconstriction during normoxia (1301, 2056, 2061, 2065). Since NO synthase was inhibited in these studies, these effects occurred independently of NO scavenging by intravascular superoxide. Other studies demonstrated selective suppression of HPV or $[Ca^{2+}]_i$ responses to hypoxia following inhibition of SOD or application of the antioxidants pyrrolidinedithiocarbamate (thiol reductant), *N*-acetyl-L-cysteine, or ebselen (synthetic GPX), in perfused lungs (2032) or PASMC (2033); catalase and SOD in small pulmonary arteries (1102); the superoxide scavenger, Tempol, in perfused rat lungs (792); and EUK134, a synthetic SOD-catalase mimetic, in mouse lung slices (398). Moreover, hypoxic responses in PASMC were suppressed by overexpression of catalase and GPX and enhanced by GPX gene deletion (398, 1591, 2010, 2033–2035). Notably, none of these procedures produced effects during normoxia that mimicked responses to hypoxia. In addition, inhibition of catalase in perfused lungs potentiated HPV (1305) while overexpression of mitochondrial MnSOD in PASMC potentiated hypoxia-induced increases in $[Ca^{2+}]_i$ (2033). Both procedures would be expected to increase cytosolic peroxide. Overall, the effects of altered antioxidant status suggested that an increase, rather than a decrease, in ROS is a key signaling event in HPV.

VI) Effects of exogenous ROS. There have been few reports concerning the effects of exogenous ROS, and these have focused largely on peroxide. In systemic arteries, peroxide generally caused vasodilation, sometimes preceded by a transient constriction, although the response was highly dependent on vascular bed, arterial caliber, and peroxide concentration (65, 1145). In bovine pulmonary arterial strips, peroxide concentrations >100 μM caused cGMP-dependent vasorelaxation (238). Later studies in rat and rabbit main pulmonary arteries, however, demonstrated a slowly developing, sustained vasoconstriction that, unlike HPV, was independent of extra- and intracellular Ca^{2+}, myosin light-chain kinase, and phosphorylation of 20-kDa regulatory myosin light chains (901, 1491, 1763). These inconsistencies may be related to the use of extremely high peroxide concentrations (up to 1 mM). Indeed, peroxide concentrations >100 μM have been found to cause irreversible reduction of vasoreactivity (608).

More recently, lower peroxide concentrations (~50 μM), like hypoxia, were reported to increase DCF oxidation, $[Ca^{2+}]_i$, Ca^{2+} release from ryanodine- and IP_3-sensitive stores, and activation of PKC-ε in PASMC (1096, 1592, 2010). Peroxide also caused sustained vasoconstriction and elevation of $[Ca^{2+}]_i$ due to release from ryanodine-sensitive stores with an EC_{50} of ~12 μM in rat intrapulmonary arteries (1546); however, unlike hypoxia, peroxide did not appear to activate Rho kinase-mediated Ca^{2+} sensitization (1546) or Ca^{2+} influx through voltage- or store-dependent Ca^{2+} channels (1096). Interestingly, superoxide was shown to induce Rho kinase-dependent constriction in both aorta (898) and intrapulmonary arteries (977), suggesting that peroxide and superoxide may have independent functions in HPV.

VII) Other evidence of increased oxidant stress in hypoxia. It is generally believed that cytosolic redox state is reduced by hypoxia; however, it was recently reported that hypoxia decreased GSH/GSSG and oxidized a cytosol-targeted fluorescent protein redox sensor, Rho-GFP, in cultured PASMC, reflecting increased cytosolic oxidant stress (2033, 2034). Consistent with these findings, hypoxia caused formation of DNA base oxidation products in pulmonary arterial endothelial and smooth muscle cells (665, 2222), as well as membrane lipid peroxidation and accelerated degradation of membrane phospholipids in pulmonary arterial endothelial cells, presumably due to activation of phospholipase (PLA_2) (188). In addition, urinary levels of isoprostanes such as 8-epi-$PGF_{2\alpha}$, which are produced by ROS-generated lipid peroxidation and regarded as selective markers of oxidant stress (384), were increased in humans after acute and chronic exposure to high altitude (888). Interestingly, both hypoxia and ROS can stimulate cytosolic and Ca^{2+}-independent PLA_2 (1021), and 8-epi-$PGF_{2\alpha}$ can stimulate endothelin-1 production in endothelial cells (569) and PASMC via activation of Rho kinase (2154), as well as vasoconstriction via activation of Rho and tyrosine kinases (886), all of which have been implicated in HPV.

E) ENERGY STATE. *I) ATP, PCr, and adenylate kinase.* ATP is the immediate source of energy for cellular function. While mitochondrial oxidative phosphorylation is much more efficient than glycolysis at producing ATP **(FIGURE 5*A*)**, vascular smooth muscle is unusual in that ~30% of its ATP may be derived from glycolysis during normoxia (1480). During hypoxia, glycolysis is potentiated, in part via enhanced glucose uptake (1041). Under these conditions, as much as 65% of smooth muscle ATP production has been attributed to glycolysis (2075). The shift to glycolysis leads to cytosolic accumulation of pyruvate, which is converted to lactate by lactate dehydrogenase.

ATP and ADP are relatively immobile molecules, and probably highly compartmentalized to sites of production and utilization. Energy transfer between such sites involves the small diffusible molecule, phosphocreatine (PCr), which is present in smooth muscle at concentrations similar to those of ATP (859). Creatine kinase in the outer mitochondrial membrane uses ATP to phosphorylate creatine to PCr, which then diffuses to sites of utilization where the reaction is reversed (Lohman reaction) (318): ATP + Cr ↔ PCr + ADP + H^+.

This relationship implies that [ATP] is to some extent buffered, contributing to its resilience in the face of altered production or consumption. Notably, [PCr] is better maintained in pulmonary than in systemic arteries and has a stronger relationship to force production than [ATP] (1044, 1045, 1742). When PCr reserves are low, as during hypoxia or inhibition of oxidative phosphorylation, inhibition of creatine kinase due to phosphorylation by AMP kinase (850, 1538) could limit consumption of glycolytic [ATP] by the Lohman reaction. This effect may reflect interdependent regulation of compartmental energy production, since creatine kinase is localized with mitochondria and glycolysis is associated with plasma and SR membranes, where it could preferentially support membrane-associated processes such as ion channels and transporters, Ca^{2+} release, and activation of Rho kinase (859, 1041, 1479, 1581, 2132).

[ATP] is also maintained during ADP accumulation by the adenylate kinase reaction, in which high-energy phosphate is transferred from one ADP to another, creating one molecule of ATP and another of AMP: 2ADP ↔ ATP + AMP.

As long as glucose is present, the combined effects of glycolysis, PCr, and adenylate kinase contribute to maintenance of pulmonary vascular smooth muscle [ATP] during even relatively severe hypoxia (233, 1044, 1045) and preservation of maximal contractile activity in the absence of a functioning METC (51, 1041, 2032, 2035, 2055, 2066). Thus cytosolic [ATP] is a poor indicator of either energy state or O_2 availability.

It has been suggested that enhanced extracellular concentrations of ATP breakdown products, notably adenosine, could cause HPV by acting at adenosine receptors on PASMC (169, 221, 1903); however, adenosine caused vasodilation and suppressed HPV, whereas adenosine deaminase and adenosine receptor antagonists did not alter HPV in isolated lungs or pulmonary arteries (648, 761, 900, 1265, 2147).

II) Phosphorylation potential. Phosphorylation potential ($[ATP]/[ADP][P_i]$), a commonly used index of energy state, is proportional to mitochondrial redox state and may be an important factor for regulation of oxidative phosphorylation, membrane transport, actin-myosin crossbridge cycling, and thus vasoreactivity (226, 410, 479, 1036, 1385, 1480, 2100). Its effects on crossbridge cycling are partly related to the fact that dissociation of P_i from the actin-

myosin complex is the rate-limiting step in turnover of smooth muscle crossbridges (69), and a reduction in cytosolic [P_i] is associated with increased tension in systemic arteries (746). Like [PCr], phosphorylation potential declines less in pulmonary than systemic arteries during hypoxia, as long as glucose is available (1045, 1417), suggesting that energy state is better controlled in pulmonary arteries during hypoxia, due in part to enhanced glycolysis (1042, 1044, 1045).

III) AMP/ATP and AMP-activated kinase. Since adenylate kinase maintains the reaction, 2ADP ↔ ATP + AMP, close to equilibrium, the AMP/ATP ratio will vary approximately as the square of the ADP/ATP ratio; therefore, AMP/ATP is a sensitive index of energy state (745). Increases in AMP/ATP stimulate AMP-activated kinase (AMPK), a ubiquitous sensor of intracellular energy state, which promotes production and suppresses consumption of ATP such that the ADP/ATP ratio remains remarkably constant in the face of metabolic stresses such as glucose deprivation and hypoxia (742, 743). AMPK is a heterotrimer consisting of catalytic α and regulatory β and γ subunits. AMP, which competes with ATP for binding to the γ subunit, activates AMPK by promoting phosphorylation of the α subunit by a protein complex composed of the serine/threonine kinase, LKB1, and two accessory proteins known as STRAD and MO25; inhibiting dephosphorylation by protein phosphatases; and causing allosteric alterations of the phosphorylated enzyme (743, 744, 756, 2117). Since these mechanisms are mutually synergistic, they further increase the sensitivity of AMPK to changes in energy state.

As described in section III*B2*C, it has been proposed that hypoxia-induced release of Ca^{2+} from ryanodine receptors in sarcoplasmic reticulum of PASMC is mediated by an increased concentration of cADPR, an intracellular messenger synthesized by ADP-ribosyl cyclase and catabolized by ADP-ribosyl hydrolase (412, 413, 487, 2101). Originally thought to result from NADH-dependent inhibition of cADPR catabolism, more recent observations from the same group suggest that this increase in [cADPR] may be associated with hypoxic activation of AMPK, which acts as the O_2 sensor for HPV (485, 488). For example, AMPK activity during normoxia was higher in third-order pulmonary arteries than in main pulmonary or mesenteric arteries (488). One hour of severe hypoxia (P_{O_2} = 16–21 mmHg) doubled AMP/ATP and AMPK activity in PASMC (488). Activation of AMPK by 5-aminoimidazole-4-carboxamide riboside (AICAR), which is metabolized to the AMP analog ZMP (AICAR monophosphate), caused an increase in PASMC $[Ca^{2+}]_i$ that was antagonized by the cADPR antagonist 8-Br-cADPR (484, 488). Hypoxia and AICAR caused contractions of rat pulmonary arteries that were inhibited similarly by caffeine, ryanodine, and removal of extracellular Ca^{2+} or endothelium (488). Compound C, an AMPK inhibitor with nonselective effects (85), suppressed HPV in rat pulmonary arteries (1642) and $[Ca^{2+}]_i$ responses to hypoxia in human PASMC (1889). These observations support the hypothesis **(FIGURE 6*C*)** that hypoxia-induced increases in AMP/ATP activate AMPK, leading to increased [cADPR], Ca^{2+} release from sarcoplasmic reticulum, and constriction; however, it is not yet certain that AMPK directly increases [cADPR], and the mechanism of such an effect remains unclear.

The AMPK hypothesis also predicts that inhibition of oxidative phosphorylation, which activates AMPK, should mimic HPV. Phenformin, which is thought to stimulate AMPK by inhibiting the METC, was reported to have this effect (488). As discussed in section III*A2*D however, the effects of METC inhibitors on pulmonary vessels depend on their locus of action. In appropriate concentrations, inhibitors of the proximal METC, such as rotenone and myxothiazol, blocked HPV while inhibitors of the distal METC, such as cyanide, usually did not. Inhibition of HPV by METC inhibitors was not due to nonspecific actions, because vasoconstrictor responses to other stimuli were not blocked (51, 1041, 2032, 2035, 2055, 2066). Moreover, inhibition of HPV by rotenone was fully reversed by restoration of mitochondrial ATP production with succinate **(FIGURE 5)**, which provides electrons to complex III via complex II (1041, 2025).

Activation of AMPK increases glucose uptake by increasing synthesis and translocation of the glucose transporters, GLUT-1 and GLUT-4, to plasma membrane (1014, 1266, 1679). Since glycolysis in the lung is rate-limited by glucose entry (1502), this may explain the increased glucose uptake associated with HPV in isolated pulmonary arteries (1041, 1045). In this case, high [glucose] could increase and low [glucose] decrease glycolytic ATP production, leading to suppression and enhancement, respectively, of AMPK signaling. Consistent with this possibility, inhibition of glucose metabolism potentiated pressor responses to brief hypoxic exposures in isolated rat lungs (1667) and increased $[Ca^{2+}]_i$ in rat cultured PASMC, in part by causing Ca^{2+} release (216); however, just the opposite was suggested by results in isolated ferret lungs and rat pulmonary arteries, where sustained HPV was suppressed by low [glucose] or inhibitors of glycolysis and enhanced by high [glucose] (1041, 2091).

These apparent inconsistencies cannot be easily explained unless AMPK were also activated by signals other than AMP/ATP. In this regard, a large number of reports suggest that AMPK can be activated by ROS and peroxynitrite (307, 554, 1355, 1568, 1701, 1925, 2131, 2225). These observations provide a potential link between hypoxic elevation of ROS production by mitochondria (see sect. III*A2*D) and elevation of $[Ca^{2+}]_i$ by AMPK **(FIGURE 6*C*)**. Recently, however, the possibility that ROS directly activate AMPK has been thrown into doubt by findings that

peroxide increased ADP/ATP (an index of AMP/ATP) but did not activate AMPK in cells expressing an AMP-insensitive AMPK γ-subunit variant (757). The possibility that AMPK plays a role in HPV deserves further investigation.

F) INTRACELLULAR PH. As previously discussed, a shift from mitochondrial to glycolytic production of ATP will lead to accumulation of lactate and intracellular acidosis unless corrected by pH regulatory mechanisms. However, hypoxia activated Na^+-dependent Cl^--HCO_3^- transport and increased intracellular pH (pH_i) in PASMC from distal cat pulmonary arteries, which constricted in response to hypoxia, and decreased pH_i in PASMC from proximal cat pulmonary arteries, which did not exhibit HPV (1157, 1159, 1160). These findings led to the proposal that intracellular alkalinization could underlie HPV (1159). Intracellular alkalosis was indeed shown to inhibit K_V channels in canine PASMC (21). In addition, enhanced activity of Na^+-dependent Cl^--HCO_3^- transport and subsequent Cl^- efflux *via* Cl^-/anion channels was found to depolarize rat pulmonary arteries (1966). In contrast, hypoxia caused intracellular acidosis that was unrelated to vasoconstriction in rat pulmonary arteries (2024). Thus the evidence for hypoxia-induced changes in intracellular pH being the stimulus for HPV is inconclusive.

3. Plasma membrane

A) NADPH OXIDASE. NADPH oxidases (NOX) are multicomponent protein complexes specified by their catalytic subunits (NOX1–5, DUOX1–2), which form a family of transmembrane proteins with binding sites for NADPH, FAD, and heme that transport electrons across membranes and cause reduction of O_2 to superoxide in luminal or extracellular spaces (127). NADPH oxidase was first discovered in neutrophils, where its activated form has five subunits, including a cytochrome b_{558} moiety composed of membrane subunits known as NOX2 (also known as $gp91^{phox}$) and $p22^{phox}$. NOX2 is activated when an organizer subunit, $p47^{phox}$, translocates from cytoplasm to sarcolemma, carrying with it the activator subunit $p67^{phox}$ and the monomeric G protein Rac. The process is driven by phosphorylation of $p47^{phox}$, which facilitates binding of $p67^{phox}$ to $p22^{phox}$, and GTP-bound Rac, which may transfer electrons from NADPH to cytochrome b_{558} (127, 192). The K_m of NOX2 for O_2, expressed as P_{O_2}, is ~13 mmHg (347).

NOX1 and NOX4 seem to be the predominant isoforms in smooth muscle (127, 1145). NOX1 has a high degree of homology with NOX2, but is activated by NOXA1, a $p67^{phox}$ homolog, and organized by either $p47^{phox}$ or NOXO1, a $p47^{phox}$ homolog (127). NOX4 is dependent on $p22^{phox}$; however, it apparently does not require $p67^{phox}$ and $p47^{phox}$ or their homologs for activation and may be constitutively active, although in some cells there may be a dependency on Rac (127, 596).

NOX1, NOX2, and NOX4 were all detected in mouse lung (1294), but expression of these isoforms has been variable in pulmonary arteries and PASMC. NOX1 mRNA (1294) and protein (1591) were detected in mouse pulmonary arteries, but NOX1 transcripts were not expressed in either bovine pulmonary arteries (690) or human PASMC (797). NOX2 mRNA was expressed in mouse (1294) and bovine (690) pulmonary arteries and human PASMC (797), but NOX2 protein was either not detected (1591) or present only at low levels (58) in mouse pulmonary arteries. NOX2 protein was detected in bovine pulmonary arteries, but Western blots revealed multiple bands, suggesting poor antibody specificity (18, 690). NOX4 was the most consistently expressed isoform, with mRNA and/or protein detected in mouse, human, and bovine pulmonary arteries (18, 690, 1294, 1591), as well as human PASMC (405, 797, 1294).

Initial evidence for a role of NOX in O_2 sensing was obtained from carotid body, where enhancement of chemoreceptor discharge during normoxia by diphenyliodinium (DPI), a NOX antagonist, led to the proposal that the effects of hypoxia in this organ were due to decreased ROS production by NOX (347). There is also evidence that NOX may be the O_2 sensor in neuroepithelial bodies (564, 1745, 2162); however, the situation is less clear in the pulmonary vasculature.

DPI inhibited HPV in perfused rat lungs, with an IC_{50} similar to that for NOX (1901). If hypoxic inhibition of NOX were the trigger for HPV, then DPI and other NOX antagonists, such as apocynin and 4-[2-aminoethyl]benzene sulfonylfluoride (AEBSF), should mimic hypoxia and cause constriction, but this has not been observed. Indeed, these antagonists can suppress HPV (664, 1196, 1300, 2061), suggesting a role for increased NOX activity and ROS production during hypoxia. Consistent with this possibility, hypoxia increased superoxide production in cultured calf PASMC, and this increase was inhibited by DPI but not the METC antagonist myxothiazol (1196). On this basis, it was proposed that a NOX-mediated increase in ROS was central to HPV. The strength of this proposal obviously depends on the selectivity of the NOX antagonists, which is questionable. For example, DPI inhibits electron transport in many enzymes, including complex I of the METC, NO synthase, xanthine oxidase, and cytochrome *P*-450 oxidase (127). Apocynin, which must be metabolized by peroxidases for its product to inhibit translocation of cytosolic subunits (127), may even increase ROS production in nonphagocytic cells (1970). Moreover, it was recently suggested that apocynin does not inhibit vascular NADPH oxidases, but instead acts as an antioxidant (773).

More convincing data were obtained from preparations lacking the relevant proteins. Pressor responses to brief periods of hypoxia in perfused lungs of mice without

NOX2 (gp91^{phox}) were not different from responses in lungs of control animals (58, 2066), suggesting that NOX2 was not the O_2 sensor for phase 1 HPV. Consistent with these results, knockdown of NOX2 by RNA interference did not alter contractile responses to 20 min of severe hypoxia in precontracted bovine pulmonary arteries (18). In perfused lungs of p47^{phox} knockout mice exposed to hypoxia, the transient phase 1 pressor response was inhibited, but the sustained phase 2 response was not altered (2066). Since p47^{phox} is the organizer subunit used by NOX2 and pressor responses to brief hypoxia persisted in mice without NOX2, this result suggests that another NOX isoform using the p47^{phox} subunit contributed to phase 1 HPV.

Consistent with this possibility, AEBSF strongly inhibited phase 1 HPV in perfused rabbit lungs without affecting phase 2 (2066). Furthermore, hypoxia <15 min in duration increased NOX activity and p47^{phox} translocation in mouse PASMC; and hypoxia-induced cell shortening and elevations of intracellular ROS and Ca^{2+} were all suppressed by apocynin or p47^{phox} gene deletion (1591). Interestingly, the same study also showed that NOX was activated during hypoxia via PKC-ε-mediated phosphorylation of p47^{phox}, and that PKC-ε was itself activated by an hypoxia-induced increase in mitochondrial ROS (1591). Collectively, these results imply that a p47^{phox}-utilizing NOX, perhaps NOX1, acts in concert with mitochondria to generate an initial large elevation in ROS that mediates phase 1 HPV but is not required for phase 2, where mitochondrial ROS alone appear to be sufficient and Rho kinase-dependent Ca^{2+} sensitization may become important (2019). These possibilities do not conflict with previous studies using pharmacological inhibitors, since most also used relatively short periods of hypoxia to study HPV.

Since NOX4 does not require p47^{phox} or its homologs and would therefore be unaffected by p47^{phox} gene deletion, it remains possible that NOX4 could play a role in HPV. Indeed, attenuating expression of NOX4 protein by RNA interference caused decreased production of superoxide and inhibition of contractile responses to hypoxia in bovine pulmonary arteries (18). In this context, it is interesting that NOX4 was found to colocalize with and confer O_2 sensitivity to the twin pore K^+ channel, TASK-1, in a model cell system (1057). Like NOX4, TASK-1 is expressed in PASMC, where it contributes to the maintenance of resting membrane potential and is inhibited by hypoxia (see sect. III*B1*).

Superoxide production by NOX utilizes NADPH produced by the pentose phosphate pathway of glucose metabolism, where the rate-limiting enzyme is glucose 6-phosphate dehydrogenase (G6PD). Hypoxia increased G6PD activity and NADPH, and caused vasoconstriction in rat lungs and rat or bovine pulmonary arteries (689, 692). In addition, HPV was inhibited in lungs of G6PD-deficient mice, rat lungs and pulmonary arteries treated with G6PD antagonists, and bovine pulmonary arteries treated with small interfering RNA targeted to G6PD (689, 691, 692). Although these results are consistent with involvement of NOX-generated superoxide in HPV, they could also be due to inhibition of other NADPH-dependent effects.

B) HEME OXYGENASE. Heme oxygenase (HO) is a membrane-associated enzyme that degrades heme to CO, biliverdin, and Fe(II) in the presence of O_2 and NADPH (1895). Three O_2 molecules are consumed during degradation of one heme molecule, which acts as both substrate and cofactor for HO, with electrons provided by NADPH-cytochrome *P*-450 reductase (1681). Biliverdin is subsequently converted to bilirubin by biliverdin reductase, and both biliverdin and bilirubin play important antioxidant roles (1681). CO has numerous regulatory functions in a variety of tissues, including the cardiovascular system (454). At least two types of HO have been identified: HO-1 is inducible by stress factors, and HO-2 is constitutively expressed in a wide range of tissues (1681). Both HO-1 and HO-2 are inherently O_2 sensitive and associated with plasmalemmal caveolae (961). HO-1 expression is strongly regulated by stress factors, including oxidants and alterations in P_{O_2}, and is upregulated by hypoxia in pulmonary artery (990, 1324).

HO-mediated signaling is largely attributable to CO, which activates guanylate cyclase and increases cGMP. HO-2 and CO play important roles in regulation of vascular function (1323, 1324, 2182) and have been implicated in O_2 sensing in carotid body glomus cells (1217, 1550), where hypoxia is associated with inhibition of maxi-K^+ (BK_{Ca}) channels (1125). In these cells, HO-2 is thought to maintain BK_{Ca} channel activity during normoxia via the action of CO, whereas decreased CO production during hypoxia reduces BK_{Ca} channel opening, leading to depolarization, Ca^{2+} entry, and release of neuromediators (946, 2099). Consistent with this proposal, ventilatory responses to hypoxia were attenuated in HO-$2^{-/-}$ mice (9); however, a subsequent study found that carotid body sensitivity to hypoxia was similar in HO-$2^{-/-}$ mice and their control littermates, and that hypoxic responses of mouse and rat carotid body glomus cells were maintained after blockade of BK_{Ca} channels with iberiotoxin (1436).

There is little evidence that BK_{Ca} channels are involved in HPV (see sects. III*B1*B and IV*A2*). Furthermore, inhibition of HO with chromium mesoporphyrin or treatment with HO-2 antisense oligodeoxynucleotides facilitated HPV in rat pulmonary arteries and intact animals (2189). Because this facilitation was prevented by ET-1 receptor blockade or removal of endothelium, it was concluded that CO suppressed ET-1 production and/or sensitivity (2189). In another study, HPV was unaffected in mice lacking either HO-2 or the α subunit of BK_{Ca} (1663). Taken together,

these results suggest that HO is not an O_2 sensor for HPV. Rather, the CO produced by HO seems to suppress pulmonary vascular reactivity, in much the same way as NO produced by NO synthase.

4. Cytoplasm

A) CATALASE, SOLUBLE GUANYLATE CYCLASE, AND NADH. Catalases are ubiquitous antioxidant heme proteins that catalyze breakdown of two peroxide molecules to O_2 and water. Some also detoxify compounds through peroxidation. Catalysis of peroxide involves a two-step process, with the first peroxide binding to catalase to form the redox intermediate, Compound 1, which oxidizes peroxide directly to O_2 (278). An early study suggested that peroxide-induced activation of soluble guanylate cyclase (sGC), which produces cGMP and thus vasorelaxation, was mediated by catalase or Compound 1 in pulmonary artery (237). The same group later described a rotenone-insensitive (i.e., nonmitochondrial) oxidoreductase in calf PASMC microsomes that preferentially utilized NADH to produce superoxide (1301). DPI, which inhibited this NADH oxidoreductase, and nitro blue tetrazolium (NBT), a superoxide scavenger, both suppressed HPV with little effect on contractions induced by high K^+ or U46619 (1300). In addition, hypoxia reduced superoxide production in calf pulmonary arteries and PASMC microsomes (1300, 1301). It was therefore proposed that HPV was mediated by hypoxic inhibition of superoxide production by the putative NADH oxidoreductase, which reduced catalase/Compound 1 activation of sGC and thereby relieved a tonic vasodilator influence (239, 1305, 2111).

Subsequent observations have cast doubt on this hypothesis. First, the apparent preference of the oxidoreductase for NADH over NADPH (1301) was probably an artifact of the high concentrations (>10 μM) of lucigenin used to measure superoxide production (1080), and it is now accepted that the enzyme in question utilizes NADPH. Second, if inhibition of an NADH oxidoreductase (or NADPH oxidase) were responsible for HPV, then DPI should cause pulmonary vasoconstriction, but this was not observed (664, 1196, 1300, 2061). Third, inhibition of sGC with 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) augmented HPV (546, 692). Fourth, sGC activity was increased by hypoxia (692). Thus it seems unlikely that this mechanism plays a role in HPV.

B) PROLYL AND ASPARAGINYL HYDROXYLASES. Hypoxia-inducible factor (HIF) (2000) is a transcription factor instrumental to many of the alterations in gene expression that allow organisms to adapt to hypoxia. Over 70 genes are targets for HIF, including those involved in erythropoiesis, the first to be discovered (1747). HIF is a heterodimeric DNA-binding protein composed of an O_2-regulated α-subunit and a constitutively expressed β-subunit. Three HIF-α isoforms have been found (HIF-1α, -2α and -3α). HIF-1α is thought to be the primary mediator of hypoxia-induced gene expression. The functions of HIF-2α are not yet well understood, and HIF-3α may suppress hypoxic gene induction.

In normoxia, HIF-1α has a half-life of <5 min because of ubiquitination by a ubiquitin-ligase complex containing von Hippel-Lindau (vHL) protein, and subsequent rapid proteosomal degradation. In hypoxia, degradation is suppressed because vHL is no longer able to bind HIF-1α, so HIF-1α is stabilized, its concentration increases, and transcription occurs (157, 1215). vHL binding requires hydroxylation of proline residues on HIF-1α by prolyl hydroxylase domain proteins (PHD), members of the Fe(II) and 2-oxoglutarate-requiring dioxygenase family (867, 875). Three HIF-1α PHD have been identified. PHD have a relatively high K_m for O_2 of ~230 μM (782), and their activity is therefore regulated over a wide range of [O_2] (785, 2020).

HIF-1 activity is also regulated by O_2-dependent transactivation. HIF-1α contains two transactivation domains (TAD) that bind coactivators, and transactivation is prevented by hydroxylation of an asparagine residue in TAD-C by the asparaginyl hydroxylase, FIH-1 (factor inhibiting HIF-1) (775, 1025, 1026). FIH-1 is similar in structure to PHD, with a dependency on Fe(II) and a requirement for O_2 and 2-oxoglutarate as substrates. Its K_m for O_2 is somewhat lower at ~90 μM (782).

Although the effects of PHD and FIH-1 on HIF-1α clearly depend on O_2, factors other than hypoxia can potentially lead to HIF-1α stabilization, including NO and ROS (1567, 1746). Indeed, a number of reports suggest that functioning mitochondria and/or an increase in ROS production are essential (281, 650, 1177, 1736, 1790). It has been argued that prevention of HIF-1α stabilization during moderate hypoxia by inhibition of mitochondrial function may be due to increased cytosolic O_2 availability (157, 1568, 2077); however, this concept cannot explain why HIF-1α stabilization is apparently prevented by antioxidants and overexpression of glutathione peroxidase or catalase (133, 281).

There is no doubt that HIF-1 is an important regulator for the adaptation of the pulmonary circulation to chronic hypoxia (1771, 2006, 2164), affecting expression of gene products known to be involved in pulmonary vascular function and remodeling, including NO synthase (1451), heme oxygenase (1054), VEGF (125), and TRPC channels (2006). Moreover, unlike other cell types, pulmonary artery smooth muscle expresses HIF-1 under normoxic conditions (2163). The question arises whether HIF-1, PHD, and FIH-1 play any role in acute responses to hypoxia, such as HPV. As yet, there is no evidence to suggest that they do, but their speed and mode of action raise this possibility (2163).

C) CYTOCHROME *P*-450. The cytochrome *P*-450 monooxygenases (CYP) are a large group of homologous membrane-bound and O_2-sensitive heme proteins, which in the presence of the cofactors NADPH-cytochrome *P*-450 reductase and $CYPb_5$ oxidase, catalyze NADPH-dependent oxidation of a wide range of compounds (253, 1658). The CYP family is encoded by more than 500 genes, and as many as 50 different CYP isoforms may be present in a single species with considerable variability in expression among tissues (1658). In the pulmonary vasculature, CYP metabolism of arachidonic acid provides the majority of vasoactive compounds (877). CYP ω-hydroxylases produce ω-terminal hydroxyeicosatetraenoic acids (19- and 20-HETE), while epoxygenases produce *cis*-epoxyeicosatrienoic acids (EET). Several also catalyze mid-chain hydroxylation of arachidonic acid to form HETE, including 11-, 13-, and 15-HETE (1658, 1819). Commonly used inhibitors of CYP enzymes include the suicide substrates 1-aminobenzotriazole (1-ABT) and 17-octadecynoic acid (ODYA). Although designed to be selective blockers of CYP 4A ω-hydroxylases, these agents are equally effective against epoxygenases (975, 2224).

Numerous studies report physiological responses to changes in P_{O_2} that can be attributed to alterations in CYP activity (560, 741, 877, 1274, 1658, 2215). CYP ω-hydroxylase production of 20-HETE is extremely sensitive to changes in P_{O_2}, with an apparent P_{50} of 50–80 mmHg in vascular tissue, whereas epoxygenases are less sensitive (741). As CYP activity is depressed by hypoxia, it might be expected that distal signaling would be achieved by a decrease in reaction product; however, as CYP activity is limited by arachidonic acid availability, increased arachidonic acid liberation by phospholipase A_2 (PLA_2) would potentiate activity, and both hypoxia and ROS stimulate cytosolic and Ca^{2+}-independent PLA_2 (1021).

Early studies in pigs (1868) and dogs (1283) suggested that CYP might be involved in HPV as an O_2 sensor; however, this possibility was not supported by later studies in rats (285), guinea pigs (1926), rabbits (2059), and newborn pigs (1507). These disparities may be due to the nonselective nature of the CYP inhibitors used. In rabbit lungs, HPV was potentiated by inhibition of 20-HETE synthesis with ODYA, and 20-HETE synthesis itself was suppressed by hypoxia (2215). This led to the hypothesis that CYP 4A and/or its metabolite 20-HETE might play a modulatory role in HPV, since hypoxic inhibition of *P*-450-dependent production of vasodilatory eicosanoids like prostacyclin or hypoxia-induced decreases in 20-HETE, which causes vasodilation, could promote vasoconstriction (877).

More recently, it was proposed that a CYP 2C9 epoxygenase product plays a major role in HPV (1537). In this study, HPV in mice was inhibited by *N*-methylsulfonyl-6-(2-propargyloxyphenyl) hexanamide (MSPPOH), a novel CYP 2C9 antagonist, and potentiated by the soluble epoxide hydrolase inhibitor IK-950. Overexpression of CYP 2C9 also caused a rise in basal P_{PA}, which was blocked by the CYP 2C9 inhibitor sulfaphenazole (1537). These results suggested that hypoxia did not inhibit CYP 2C9 and that CYP 2C9-derived epoxyeicosatrienoic acids elicited pulmonary vasoconstriction. A subsequent study by the same group implicated the CYP product 11,12-EET, which elevated P_{PA} in mice, enhanced HPV in a Rho kinase-dependent manner and, like hypoxia, induced translocation of a TRPC6-TRPV5 fusion protein to plasma membrane (951). Moreover, neither 11,12-EET nor hypoxia caused vasoconstriction in $TRPC6^{-/-}$ mice. This interesting study suggests that CYP-derived EET could play a central role in HPV by promoting both TRPC6-mediated Ca^{2+} entry (see sect. III*B*2D) and activation of Rho kinase (see sect. III*C*2).

The duration of hypoxia in these perfused lung studies was only 10 min, and the associated pressor responses were transient (951). HPV is biphasic in mouse lungs, consisting of a transient phase 1 lasting <15 min followed by a slowly developing phase 2 that may last for hours (2053, 2054, 2066). Moreover, TRPC6 gene deletion abolished phase 1 HPV, but had no effect on phase 2 (2054). Thus CYP-derived EET may contribute to phase 1 HPV, but their role in phase 2 HPV remains unclear. It is also unclear whether CYP-derived EET merely facilitated HPV or instead formed part of a potential ROS/PLA_2/CYP signaling axis that directly linked the O_2 sensor to vasoconstriction. In this case, the O_2 sensor is unlikely to be CYP 2C9, which requires O_2 for synthesis of epoxyeicosatrienoic acids. This mechanism may not be critical in other species, since 5,6-, 8,9-, 11,12-, and 14,15-EET constricted pulmonary arteries in rabbit (2216), but not dog (1833). In addition, ODYA and 1-ABT, which should inhibit CYP 2C (975, 2224), did not selectively inhibit HPV in perfused lungs of rat and rabbit (285, 2059, 2215), and ODYA did not inhibit HPV in rat pulmonary arteries (Knock, Aaronson, and Ward, unpublished observations). Overall, the data indicate that a CYP-derived EET may contribute to phase 1 HPV in mice (2054), but further studies will be necessary to determine whether CYP enzymes play a role in the O_2 sensing and transduction pathways that mediate phase 2 HPV in mice or HPV in other species.

D) NO SYNTHASE. The dioxygenase NO synthase (NOS) requires heme to dimerize and provide electron transport between its NADPH reductase and oxygenase domains. When activated in the presence of the cofactor tetrahydrobiopterin (BH_4), NOS uses molecular O_2 and L-arginine as substrates to synthesize NO and L-citrulline (543). Uncoupling of NOS by reduced or defective BH_4 or low levels of L-arginine results in formation of superoxide (1967). In addition to neuronal (nNOS, NOS-1), inducible (iNOS, NOS-2), and endothelial NOS (eNOS, NOS-3), all of which are expressed in pulmonary arterial smooth muscle (382, 523,

1450, 1835, 1968, 2026, 2112, 2113, 2156), there is some evidence for a specific isoform associated with mitochondria (mtNOS). The subcellular localization of the other NOS isoforms in PASMC is uncertain. In endothelial cells, eNOS is both cytosolic and associated with plasmalemmal caveolae and intracellular membranes, and shuttles among these loci in response to stimulation, suggesting that location contributes to function (537).

Hypoxia usually decreased production of NO and/or cGMP in cells, pulmonary arteries, lungs, and the exhaled air of intact humans, consistent with substrate limitation of NOS activity by O_2 (1039). In purified preparations of eNOS, iNOS, and nNOS studied at 25°C, NO production was decreased by half at O_2 concentrations of 4, 130, and 350 μM, respectively (1850), corresponding to O_2 tensions of 2.5, 81, and 217 mmHg at 37°C. Roughly comparable values were obtained in whole animals, tissues, and cells, where conditions were more physiological, but the contributing NOS isoforms less certain and modification of NO production by factors such as NO-O_2 competition for heme binding sites more likely (470, 1039, 1611, 1612, 1850). Since expression of iNOS in cells other than airway epithelial cells (688) is thought to require exposure to inductive signals such as lipopolysaccharide or cytokines (765), nNOS may be the NOS isoform most likely to signal responses to physiological levels of hypoxia in normal vascular smooth muscle.

Hypoxic inhibition of NO production could cause HPV by uncovering basal tone (1413, 1651, 1896); however, the contribution of NO to the normally low basal pulmonary vascular vasomotor tone is not sufficient for this to account for more than a small proportion of hypoxia-induced vasoconstriction (60, 752, 1043). Moreover, studies on whole animals or perfused lungs almost universally demonstrate that inhibition of NO production potentiates HPV (60, 185, 752, 1039, 2064), as does inhibition of the NO target guanylate cyclase (546, 692) and eNOS knockdown (493, 1106). Conversely, gene transfer of eNOS to the lung suppresses HPV (277, 887). On this basis, it seems unlikely that NOS plays a critical role as an O_2 sensor for HPV, although it may provide a physiologically important braking mechanism (2, 185, 1039). Alternatively, an O_2-dependent decrease in NO production by PASMC may be the mechanism by which hypoxia increases myofilament sensitivity to $[Ca^{2+}]_i$ in PASMC, suggesting that NOS may be a sensor for this important component of HPV (see sect. III*C2*).

E) OTHER OXYGENASES. Cyclooxygenase and lipoxygenase are dioxygenases that utilize arachidonic acid and O_2 as substrates and are thus inherently O_2 sensitive. Their activity may also be indirectly affected by hypoxia via elevated intracellular $[Ca^{2+}]$, or increased availability of arachidonic acid secondary to hypoxic stimulation of PLA_2 (1021). As noted above in this section, cyclooxygenase and lipoxygenases can also metabolize CYP products to other vasoactive compounds.

The end product of arachidonic acid metabolism by cyclooxygenase is PGH_2, the precursor for a number of vasoactive prostanoids, including the vasoconstrictors thromboxane A_2 (TXA_2) and $PGF_{2\alpha}$, and the vasodilators prostacyclin (PGI_2) and PGD_2. The endothelium predominantly synthesizes PGI_2 upon stimulation by factors such as flow/shear stress and increased intracellular $[Ca^{2+}]$. Suggestions that decreased production of vasodilator prostanoids (393, 394) or increased production of vasoconstrictor prostanoids (814) may underlie HPV have been discounted, since inhibition of cyclooxygenase does not suppress HPV (799, 991, 1043, 1104, 1242, 1413, 1652, 1938, 2059, 2146). Indeed, cyclooxygenase inhibition can enhance HPV (590, 647, 1242, 1985), and hypoxia can increase PGI_2 in perfused lungs and pulmonary endothelial cells (845, 1202). Thus, while cyclooxygenase products may modulate HPV (see sect. IV*B2*), there is no evidence that they mediate HPV or that cyclooxygenase acts as an O_2 sensor.

Lipoxygenases that metabolize arachidonic acid include 5-lipoxygenase, which ultimately produces the leukotrienes; 8-lipoxygenase, which produces 8-hydroxyeicosatetraenoic acid (8-HETE); 12-lipoxygenase, which produces 12-HETE; and 15-lipoxygenase, which produces 15-HETE and the lipoxins. Most interest has focused on 5-lipoxygenase, as the leukotrienes are important inflammatory mediators and the cysteinyl leukotrienes LTC_4, LTD_4, and LTE_4 are powerful vasoconstrictors. Initial conclusions that 5-lipoxygenase and cysteinyl leukotrienes mediated HPV were based on the effects of nonselective inhibitors and receptor antagonists (1319, 1583, 1734), and later studies did not support this possibility (139, 647, 1221, 1232, 1727, 1938, 2059). It is unlikely that a lipoxygenase contributes to HPV as an O_2 sensor.

F) HYDROGEN SULFIDE. Hydrogen sulfide (H_2S) is a colorless, noxious gas that is both synthesized and consumed by tissues and is now known to act as a signaling moiety, joining the ranks of NO and CO as an endogenous "gasotransmitter" implicated in cardiovascular signaling (600, 1082, 1427, 2011, 2145). H_2S is synthesized primarily from L-cysteine by the multifunctional enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CGL) and has a half-life of minutes in vivo largely due to its oxidation in mitochondria (2011). CBS contains a redox-sensitive heme group in its regulatory domain and is activated by oxidizing environments and ROS (93). H_2S metabolism is therefore strongly redox- and O_2-dependent, with a P_{50} in the physiological range (92, 416, 1429).

Depending on species and vascular bed, H_2S causes vasorelaxation or vasoconstriction (420, 1427), and endogenous H_2S modulates vascular tone (301, 420, 983, 1428, 1891, 2192,

2203, 2204). Both H_2S and hypoxia elicited depolarization and contraction in pulmonary arteries (420, 1428, 1429) and hyperpolarization and relaxation in systemic arteries (301, 1428, 1429, 1891, 2205). In rat isolated pulmonary artery, inhibition and stimulation of H_2S synthesis, respectively, suppressed and enhanced HPV (1428). These results led to the proposal that H_2S could act as both a sensor and transducer of HPV (1428). In these studies, however, hypoxia was severe (P_{O_2} <5 mmHg) and the vasoconstriction induced by H_2S was not well characterized, limiting comparisons with HPV. A critical unanswered question is whether H_2S activates the same vasoconstrictor mechanisms as hypoxia.

H_2S binds to the mitochondrial O_2-binding cytochrome *aa3* with a K_D of <0.1 μM (1386), causes functional hypoxia in lung mitochondria (955), and reduces O_2 consumption in rat aorta (983); however, H_2S can also provide reducing equivalents to cytochrome *aa3* (116, 1387). In both cases, H_2S acts like hypoxia in that it causes reduction of the proximal METC and stimulates mitochondrial ROS production (466, 914). As inhibition of electron transport and modulation of ROS form the basis of key hypotheses of O_2 sensing in HPV **(FIGURE 6)**, it seems rational to suggest that the reason that hypoxia and H_2S have such similar effects is that H_2S merely mimics hypoxia (1428, 1429); however, this would not explain why inhibition of H_2S synthesis suppressed HPV, and vice versa (1428). An alternative hypothesis is that H_2S facilitates O_2 sensing. Because it competes with O_2 at cytochrome *aa3*, H_2S could effectively increase the apparent P_{50} of cytochrome *aa3* for O_2, as proposed for NO (464, 2133), and thus facilitate sensing of moderate hypoxia (see sect. III*A2*B). This possibility has not been tested. On balance, current data allow neither acceptance nor rejection of the hypothesis that H_2S is critically involved in mediation of HPV (1428, 1429); however, since both the metabolism and actions of H_2S are dependent on redox state and P_{O_2}, it could be at least a modulator of the response.

5. Summary: O_2 sensing in PASMC

Currently, the bulk of evidence suggests that the primary sensor for HPV is the PASMC mitochondrion, which increases production of ROS during hypoxia, most likely at complex III. It is possible that secondary sensor mechanisms, such as ROS production by sarcolemmal NADPH oxidase, also contribute. The particular ROS involved, the mechanisms by which they are produced, their intracellular sites of action, and the specific transduction pathways they activate remain unclear.

B. Transduction Mechanisms

1. Membrane potential

A) RESTING MEMBRANE POTENTIAL. *I) Overview*. Direct measurements of resting membrane potential (E_m) in isolated pulmonary arteries from a variety of species ranged from −46 to −60 mV (172, 201, 267, 589, 707, 740, 852, 1011, 1357, 1553, 1858). Similar variation (−38 to −58 mV) was found in isolated PASMC under current-clamp conditions (49, 53, 63, 527, 598, 807, 911, 1423, 1438, 1544, 1545, 1599, 1949, 2103, 2172). Discounting contributions by electrogenic ion pumps, resting E_m in PASMC will depend on the transmembrane concentration gradients of ions present in the cells and their membrane permeabilities, as determined by the number, conductance, and open probability of ion channels in the sarcolemma. In practice, only monovalent ions are taken into account, in which case resting E_m can be represented by the Goldman-Hodgkin-Katz equation:

$$E_m = \frac{RT}{F} \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

where RT/F = 26.7 mV and P_K, P_{Na}, and P_{Cl} represent membrane permeabilities of K^+, Na^+, and Cl^-. The contribution of each ion to E_m can be calculated by eliminating the terms contributed by other ions, in which case the equation simplifies to the Nernst equation for that ion and E_m becomes its equilibrium, or reversal, potential.

Precise quantitative information regarding the intracellular concentrations and permeabilities of these ions in PASMC is limited; however, intracellular concentrations of Na^+, K^+, and Cl^- in myocytes of rabbit main pulmonary artery were reported to equal 15, 134, and 51 mM, respectively (267). These measurements indicate that $[Cl^-]_i$ is much higher than would be expected purely on the basis of a passive Cl^- distribution, an observation also made for other types of smooth muscle (22, 2103). Based on these measurements and ion permeabilities estimated from fluxes of radioactive tracers, the calculated resting E_m was −31 mV, and reversal potentials for K^+, Na^+, and Cl^- were −83, +59, and −26 mV, respectively. This estimate of resting E_m is less negative than measured values, probably due to inaccurate estimates of ion permeabilities. The calculated reversal potentials are typical for smooth muscle (2103 4387) and indicate that measured levels of resting E_m must be achieved through adjustment of ion permeabilities such that the strongly negative K^+ reversal potential is offset by the more positive Na^+ and Cl^- reversal potentials. Nevertheless, almost all investigative attention has focused on K^+ channels.

II) Generation of resting membrane potential. A) K^+ channels and currents. Four major types of K^+ channels have been identified in pulmonary arterial smooth muscle: voltage-gated (K_V), twin-pore (K_{2P}), Ca^{2+}-activated (K_{Ca}), and ATP-sensitive (K_{ATP}), which is a subclass of inwardly rectifying (K_{IR}) channels. K_V and K_{2P} channels have received the most attention regarding regulation of E_m in PASMC. In contrast, as discussed below, there is a general consensus that K_{Ca} and K_{ATP} channels are not important determinants of resting E_m in PASMC of adult animals;

however, K_{Ca} channels may play this role in fetal or newborn animals (see sect. V*A*), and both K_{Ca} and K_{ATP} channels may modulate hypoxic depolarization in adult PASMC (see sect. IV*A*).

i) K_V channels. K_V channels, the largest class of K^+ channels, are composed of 4 α-subunits encoded by 12 families of K_V genes (K_V1-K_V12), each with multiple subtypes. The α-subunits of K_V1, K_V7, and K_V10 can form homo- or heterotetramers, in the last case incorporating different α-subunits within the same family. K_V2 subunits also form homotetramers, but can also associate with subunits encoded by K_V5, K_V6, K_V8, and K_V9 genes, which do not form functional homomultimers. Tetramers also interact with regulatory proteins, including β subunits, which affect properties such as inactivation kinetics and O_2 sensitivity. In the pulmonary circulation, mRNA for 25 K_V channel α-subunits was detected, as was protein for $K_V1.2$–1.7, $K_V2.1$–2.2, $K_V3.1$, and $K_V4.3$ β-subunits (1331). More recently, mRNA for $K_V7.1$, $K_V7.4$, and $K_V7.5$ was found in rat distal pulmonary arteries (911). Consistent with their structural complexity, the functional characteristics of K_V channels are enormously diverse (696).

When measured using the whole cell patch-clamp technique and a "physiological" K^+ gradient, activation of K_V channels by depolarization results in transient ("A-like") or sustained ("delayed rectifier") outward currents. For a K_V channel to contribute to resting E_m, it must be open at resting E_m. Because I_{KV} in this range of potentials is very small and difficult to distinguish from noninactivating K^+ or leak currents, inhibition of K_V channels with 4-aminopyridine (4-AP), a general K_V channel antagonist, has been used to demonstrate "difference currents" in PASMC, which indicate K_V channel activity (59, 1423, 1544, 1802). 4-AP also caused depolarization in current-clamped PASMC (1438, 1544, 1545, 1803, 2170). These results indicate that K_V channels contribute to resting E_m in PASMC.

Which types of K_V channels contribute to resting E_m has not been resolved. Heterologous expression studies demonstrated that $K_V2.1$ or $K_V2.1/9.3$ channels were less sensitive to 4-AP (IC_{50} >3 mM) than channels formed from $K_V1.2$, $K_V1.2/1.5$ or $K_V3.1\beta$ (IC_{50} <600 μM) (696, 1473), suggesting that the extent to which low concentrations of 4-AP block I_{KV} could reflect the relative contribution of K_V1 channels to resting E_m. Accordingly, 4-AP at concentrations ≤1 mM blocked most of the outward current recorded near resting E_m in PASMC from several species (1422, 1473, 1544, 1599, 1802, 1949). In addition, the K_V1-selective inhibitor correolide (63, 917) and cell dialysis with antibodies against $K_V1.5$ α-subunits (59, 63, 794), usually [but not always (59)] had a similar effect. Correolide and $K_V1.5$ antibodies also caused depolarization in current-clamped PASMC (63, 598). Collectively, these results suggest that K_V1 channels, possibly $K_V1.5$, contribute the bulk of I_{KV} in distal PASMC; that activation of this current occurs at or near resting E_m; and that inhibition of this current causes sustained depolarization.

In contrast, other studies showed that 1 mM 4-AP did not inhibit I_K in distal rat PASMC (1279) and elicited only minimal depolarization in proximal pulmonary arteries from young rats (1437), implying that K_V1 channels contributed little to resting I_K and E_m. Dexfenfluramine, the appetite suppressant associated with development of severe pulmonary hypertension, blocked I_{KV} in rat distal PASMC at concentrations that inhibited $K_V2.1/K_V9.3$ channels (1473) but had little effect on $K_V1.5$ channels (1501). Anti-$K_V2.1$ antibodies, but not anti-$K_V1.5$, inhibited I_{KV} by 50% and caused depolarization in dialyzed rat distal PASMC and increased P_{PA} in isolated rat lungs (59, 63). These results suggest that the contribution of $K_V2.1$ channels to resting E_m in PASMC was more important than that of $K_V1.5$.

K_V7 (KCNQ) channels are resistant to 4-AP and contribute to I_{KV} in vascular and other smooth muscle (1419, 2153). $K_V7.1$-$K_V7.5$ α-subunits combine to form homo- or heteromultimers, and may also form complexes with KCNE β subunits. Compared with other K_V classes, K_V7 channels have properties that lend themselves to regulation of resting E_m, namely, slow activation over a more negative range of potentials and, with the exception of $K_V7.1$, no inactivation (1635). The K_V7 inhibitors linopirdine and XE991 depolarized rat distal PASMC, while the K_V7 channel openers retigabine and flupirtine caused hyperpolarization (911). K_V7 inhibitors also increased P_{PA} in isolated rat lungs and tension in rat and mouse pulmonary arteries at concentrations less than or equal to those which block K_V7 channels, but had little effect in systemic arteries (910, 911). In pulmonary arteries, these vasoconstrictor responses were prevented by removal of extracellular Ca^{2+} or antagonists of voltage-operated Ca^{2+} channels (VOCC) but not by removal of endothelium or antagonists of α_1-adrenoceptors and P2X receptors, supporting the concept that contractions caused by the K_V7 antagonists were due to depolarization (910). These results indicate that K_V7 channels may also contribute to resting E_m in PASMC.

Little information is available regarding the role of K_V channels in regulation of E_m in human pulmonary arteries. Two studies (1499, 1526) report the presence of delayed rectifier currents that activated near −50 mV. In one (1499), the current had an unusual pharmacological profile in that it was abolished by 5 mM 4-AP, but was also completely inhibited by TEA with an IC_{50} of 1.5 mM. In the other (1526), four types of I_{KV} were reported, three of which were slowly inactivating or noninactivating and all of which were relatively insensitive to 4-AP.

ii) Noninactivating K^+ current. In rabbit PASMC treated with glibenclamide and TEA to block K_{ATP} and K_{Ca} channels and held at 0 mV for 10 min to inactivate I_{KV}, ramping E_m from +60 to −100 mV revealed a residual noninactivating K^+ current (I_{KN}) that, unlike I_{KV}, activated slowly with a threshold of −65 to −80 mV and was not inhibited by 10 μM quinine (489). On the basis of the amplitude of I_{KN} and the recorded linear "leak" current, I_{KN} was estimated to account for the entire K^+-selective conductance at resting E_m in these cells. Consistent with this possibility, inactivation of I_{KV} by prolonged depolarization or inhibition of K_V channels with 10 μM quinine did not alter resting E_m in rabbit PASMC, whereas higher quinine concentrations caused decreases in I_{KN} that were correlated with depolarizations (1438). Although the detailed characterization of I_{KN} was carried out in the main pulmonary artery, this current was found throughout the pulmonary arterial tree down to arteries <200 μm in diameter, albeit at a smaller I_{KN}/I_{KV} ratio (1228). Speculation that I_{KN} was mediated by $K_V2.1/K_V9.3$ heteromultimers was not confirmed, and in any case seems unlikely since the threshold voltage for expressed $K_V2.1/K_V9.3$ was noticeably more positive than that for I_{KN} (1473). More likely, I_{KN} is a composite current contributed by K_V7 (693) and TASK-1 (694), as discussed in the next section.

iii) K_{2P} channels. Twin-pore K^+ channels are dual-pore channels encoded by 15 *KCNK* genes. The channels are complexes of two subunits, each with four transmembrane spanning units and two pore domains. K_{2P} channels have been classified into five structural subfamilies (1472) and act as background or "leak" channels that are open at resting E_m. K_{2P} channels are regulated by multiple factors, including G protein-coupled receptors, polyunsaturated fatty acids, pH, membrane stretch, and temperature, but not E_m (624). Two of these channels, TASK-1 (TWIK-related acid sensitive channel-1; $K_{2P}3.1$; KCNK3) and TASK-2 ($K_{2P}5.1$; KCNK5), are of particular interest in PASMC.

Expression of TASK-1 was demonstrated by RT-PCR and immunohistochemistry in proximal rabbit (694) and distal human (1425) and rat (589) PASMC. I_{KN} in these cells demonstrated known properties of TASK-1 currents, including enhancement by halothane or alkalinization and inhibition by acidification, anadamide, bupivicaine, or Zn^{2+} (489, 589, 694, 1425). Resting E_m was altered by anadamide (694, 1425), bupivicaine (589), Zn^{2+} (694), halothane (694), and changes in pH (589, 694, 1425) in the manner expected if TASK-1 channels were regulating resting E_m. Furthermore, shifts in E_m evoked by these agents were unaffected by a cocktail of drugs designed to block K_V, K_{IR}, K_{ATP}, and K_{Ca} channels (589). These results suggest that TASK-1 channels are responsible for I_{KN} and contribute to regulation of resting E_m in PASMC; however, this conclusion cannot be made with certainty because *1)* I_{KV} was similarly affected by changes in pH and Zn^{2+} and found to activate at potentials less than resting E_m (about −40 mV); *2)* halothane had complex time- and concentration-dependent effects on I_{KN}; and *3)* the effect of anandamide on I_{KV} was not examined (694). Since I_{KN} was negligible at potentials below −80 mV in a symmetrical K^+ gradient and activated in a time- and voltage-dependent manner (489), it seems possible that a separate K_V current (perhaps K_V7) was also activated at very negative E_m and contributed to the I_{KN} previously reported in these cells.

In addition to TASK-1, rat distal pulmonary arteries also expressed TASK-2, and the other K_{2P} channels, TREK-2 and TWIK-2 (589). Immunostaining indicated that TASK-1 and TASK-2 were present in both endothelial and smooth muscle cells, whereas TWIK-2 was mainly localized to smooth muscle and TREK-2 appeared to have an intracellular distribution. Furthermore, partial knockdown of TASK-2 by RNA interference caused a 4-mV depolarization and attenuated the effects of changing pH on E_m (629). Thus K_{2P} channels other than TASK-1 may contribute to resting E_m in PASMC.

iv) K_{Ca} channels. K_{Ca} channels are independently activated by increased $[Ca^{2+}]_i$ and membrane depolarization and have been divided into two main groups: small- or intermediate-conductance K_{Ca} (SK_{Ca} and IK_{Ca}) channels and large-conductance K_{Ca} (Maxi-K or BK_{Ca}) channels. These channels are composed of four pore-forming α-subunits encoded by SK1–4 (SK_{Ca} and IK_{Ca}) or the *slo* gene (BK_{Ca}), which produces several variants via alternative splicing. While the α-subunits are similar to those of K_V channels, and likely to convey voltage sensitivity, they also have conserved COOH-terminal regions and extra membrane-spanning domains that allow interaction with β-subunits and may contribute to Ca^{2+} sensing (1921). K_{Ca} channels have been detected in a wide range of smooth muscle cells (1373), and identified functionally in pulmonary vascular smooth muscle (52, 83, 112, 501, 1463, 1500, 1526, 1775, 2170). In addition, expression of K_{Ca} channel proteins has been confirmed in human pulmonary arterial rings (1490) and PASMC from humans (1526), rats (202, 1614, 2179), and cows (1614).

K_{Ca} currents are blocked by inhibitors such as iberiotoxin, charybdotoxin, and (at low concentrations) TEA. Use of these inhibitors indicated that K_{Ca} channels contributed significantly to regulation of resting E_m in the systemic vasculature (626, 880, 979, 2074). A similar situation was described in fetal PASMC (see sect. V*A*), where K_{Ca} channels appeared to be the main K^+ channel regulating membrane potential (338, 339, 808, 1614, 1623). During development, however, E_m became increasingly regulated by K_V channels (1599), such that in the adult lung K_{Ca} channels were not activated under resting conditions, and contributed to overall K^+ conductance only at potentials much more positive than resting E_m (1499, 1775). K_{Ca} channel inhibition had no effect on resting E_m in PASMC from adult

animals (53, 1334, 1438, 1599, 1623, 1776, 1949, 2170, 2179). Moreover, K_{Ca} channel inhibitors did not alter tone in isolated pulmonary vessels (53, 1360, 2089) or P_{PA} in isolated lungs (751). Collectively, these results provide strong evidence that K_{Ca} channels do not contribute significantly to basal E_m in adult PASMC.

v) K_{ATP} channels. Characteristics of K_{ATP} currents include voltage-independent gating, weak inward rectification, inhibition by intracellular ATP and sulfonylurea drugs (e.g., glibenclamide), and activation by intracellular nucleotide diphosphates and a class of drugs termed K^+ channel openers (KCO; e.g., pinacidil)."Classical" K_{ATP} channels found in the pancreas, heart, and skeletal muscle are all potently inhibited by intracellular ATP and have conductances of 70–90 pS in a symmetrical K^+ gradient (567). K_{ATP} channels in vascular smooth muscle seem to form a separate and diverse group, and usually demonstrate lower conductances. Intracellular ATP may have stimulatory as well as inhibitory effects on these channels, and often their opening requires the presence of intracellular nucleotide diphosphates (131). K_{ATP} channels have been functionally identified in rabbit (314, 1464) and human (348) PASMC.

Molecular identification of K_{ATP} channels is ongoing. Most studies indicate that they are composed of four pore-forming subunits encoded by members of the $K_{IR}6.0$ subfamily, most likely $K_{IR}6.1$ and $K_{IR}6.2$, with four sulfonylurea receptor (SUR) subunits that are members of the ATP-binding cassette protein family. Two SUR subunits, SUR1 and SUR2, have been proposed, the second of which has variants generated by alternative splicing (SUR2A and SUR2B). K_{ATP} channels in pancreas and heart have been shown to consist of SUR1/$K_{IR}6.2$ and SUR2A/$K_{IR}6.2$, respectively (229, 567). In smooth muscle, SUR2B/$K_{IR}6.2$ and SUR2B/$K_{IR}6.1$ have been reported, with co-expression of SUR2B and either $K_{IR}6.1$ or $K_{IR}6.2$, producing channels with properties consistent with those of native K_{ATP} channels (864, 2136). Cultured human PASMC expressed only $K_{IR}6.1$ and SUR2B, whereas rat proximal pulmonary arteries also expressed SUR1 in addition to $K_{IR}6.1$ and SUR2B (252, 316, 348). Whether a similar molecular distribution occurs in smooth muscle cells from more distal pulmonary arteries is unknown.

Early work in smooth muscle cells from rabbit main (313, 314) and rat intralobar (1803) pulmonary arteries demonstrated both basal activation of K_{ATP} channels and glibenclamide-induced depolarization in cells dialyzed with a concentration of ATP thought to exist in situ (1–2 mM), implying that K_{ATP} channels contributed to resting E_m; however, subsequent studies using the permeabilized patch technique to preserve intracellular milieu showed that glibenclamide did not affect resting E_m in myocytes derived from distal pulmonary arteries of late-gestation fetal sheep or rabbits (808, 1599). Moreover, basal intracellular [ATP] was estimated to be 2.7 mM in endothelium-denuded pulmonary arteries (1044), and dialysis of PASMC with a pipette solution containing 3 mM ATP abolished the prominent glibenclamide-induced depolarization seen when the pipette solution was ATP free (312, 314). In addition, glibenclamide had no effect on resting E_m in PASMC (59, 1776, 2170), baseline tone in isolated pulmonary arteries (1767, 2018, 2089) or, with a few exceptions (109, 509), P_{PA} in isolated lungs (449, 622, 751, 1710, 2090) or intact animals (337, 450, 1290, 1710). On balance, the evidence indicates that K_{ATP} channels do not contribute significantly to resting E_m in PASMC.

B) Cl^- channels. Although agonist-induced Cl^- currents produce depolarization and secondary Ca^{2+} influx through VOCC in vascular smooth muscle (890, 891, 1032, 1519, 1606, 1693, 2169), the contribution of Cl^- channels to resting E_m in PASMC has received little attention. It appears that PASMC possess volume-sensitive and Ca^{2+}-activated Cl^- (Cl_{Ca}) channels, but the molecular identities of these channels remain unclear (891). Several studies suggest that the volume-sensitive Cl^- channel may be the ClC-3 channel (356, 1606). Both the ClC-3 gene (356, 2143) and volume-activated I_{Cl} (356, 1090, 2214) were expressed in canine and rat PASMC. Ample functional data demonstrate Ca^{2+}-activated Cl^- currents [$I_{Cl(Ca)}$] in PASMC from rat (87, 1695, 2169) and rabbit (45, 317, 1519, 1692, 2009). Initial evidence suggested that Cl_{Ca} channels may be encoded by the gene *rbCLCA*, which is expressed in rat lung (892); however, expression of rbCLCA in PASMC has not been explored. More recent reports indicate that Cl_{Ca} channels may be composed of proteins in the TMEM16/Anocotamin family (255, 1735, 2151). In particular, expression of TMEM16A/Anoctamin1 in HEK293 cells produced currents with characteristics consistent with $I_{Cl(Ca)}$ (255, 1176, 1735, 2151). These proteins have been found in rat PASMC and human pulmonary arteries, and depletion of TMEM16A with RNA interference virtually abolished $I_{Cl(Ca)}$ in PASMC (1176). TMEM16B was also expressed at low levels in rat PASMC (1176), but whether this protein, or other members of the TMEM16 family, contribute to $I_{Cl(Ca)}$ remains unknown.

Cl_{Ca} channels exhibit no activity in the absence of Ca^{2+} (1518, 1519); however, their affinity for Ca^{2+} is highly voltage dependent, with their K_d for Ca^{2+} decreasing from 250 to 8 nM at $E_m = -100$ and $+100$ mV, respectively (1519). Indeed, $I_{Cl(Ca)}$ was activated when $[Ca^{2+}]_i$ increased above ~185 nM in rat distal PASMC (87), and single-channel analysis suggested that half-maximal activation of $I_{Cl(Ca)}$ occurred at basal levels of $[Ca^{2+}]_i$ (~100 nM) and E_m (−50 to −60 mV) (1519). Substitution of Cl^- by the more permeant anion SCN^- elicited an outward current at −50 mV (1031). In rabbit distal PASMC, changes in extra- and intracellular [Cl^-] shifted the reversal potential of caffeine-induced currents in accordance with the change in Cl^-

equilibrium potential (82). Furthermore, under K^+-free conditions most of this current was blocked by niflumic acid. Similar findings were obtained in systemic arterial myocytes. In contrast, neither DIDS nor substitution of extracellular Cl^- with I^- induced membrane hyperpolarization in rat proximal PASMC (1090). In addition, photolytic release of intracellular caged Ca^{2+} induced $I_{Cl(Ca)}$ in 80% of rat proximal PASMC but only 43% of distal PASMC (317). The ability to alter expression of the proteins responsible for $I_{Cl(Ca)}$ and development of more specific pharmacological antagonists should allow the contribution of Cl_{Ca} channels to resting E_m in PASMC to be quantified.

C) Na^+ and nonselective cation channels. Tetrodotoxin-sensitive voltage-gated Na^+ currents (I_{Na}) were recorded in freshly isolated myocytes from rabbit main pulmonary artery (1422) and cultured human PASMC (1527). In addition, the latter cells expressed mRNA for seven Na^+ channel α and two β subunits (1527). In neither species, however, did tetrodotoxin cause hyperpolarization (970, 1527), indicating that these currents did not contribute significantly to resting E_m.

A Na^+ contribution to resting E_m could also be made by nonselective cation channels (1906). In rabbit distal PASMC, substitution of extracellular Na^+ with the membrane-impermeable cation *N*-methyl-D-glucamine caused a ~20 mV hyperpolarization in association with abolition of a time-independent nonselective cation current with a reversal potential of −14 mV (83), suggesting that a nonselective cation conductance was a regulator of resting E_m. This possibility is also supported by observations that influx of Mn^{2+}, which occurs through nonselective cation channels, was present in unstimulated PASMC from rat (1807) and dog (1382); however, Mn^{2+} influx did not occur in unstimulated distal rat PASMC (2005). Thus the contribution of Na^+-permeable nonselective cation channels to resting E_m in PASMC is unclear.

Inhibition of the sarcolemmal Na^+-K^+-ATPase pump with ouabain or K^+-free solution depolarized rabbit proximal pulmonary arteries by 6–7 mV; however, this depolarization was gradual, and may have been due to rundown of the Na^+ and K^+ gradients rather than direct inhibition of a pump-mediated hyperpolarizing current (267). Consistent with this possibility, measurements using whole cell patch-clamp in myocytes from the same artery showed that Na^+-K^+-ATPase inhibition did not alter E_m (1438).

B) EFFECTS OF HYPOXIA ON MEMBRANE POTENTIAL. *I) Overview.* Decreasing P_{O_2} from 300 to 50 mmHg caused contraction, depolarization, and action potentials in intact distal cat pulmonary arteries (740, 1157). Since the open probability of VOCC increases steeply with depolarization (1801), the observed depolarization (13 mV) would be expected to cause a substantial rise in Ca^{2+} current, especially if action potentials are also stimulated; however, it should be noted that basal conditions were hyperoxic in these studies (740, 1157) and that the tension generated when P_{O_2} was decreased to 100 mmHg was ~60% of the tension developed under hypoxic conditions (P_{O_2} ~50 mmHg) (1157). The depolarization that would occur if P_{O_2} was decreased from normoxic to hypoxic levels was not defined in these studies, and apparently has not been measured in other studies of intact pulmonary arteries.

Hypoxic depolarizations in single PASMC recorded using both conventional and perforated whole cell patch-clamp techniques have generally achieved stability after several minutes of hypoxia at levels ranging from 10 to 31 mV (49, 53, 63, 598, 1423, 1438, 1544, 1545, 1599, 1949, 2172). In rat PASMC, O_2 tensions of 35–44, 24–30, and 11–17 mmHg caused depolarizations of 5, 12, and 25 mV, respectively (1423). Hypoxic depolarization was not seen at a resting E_m of −47 mV in rat PASMC, but did occur at more positive E_m, suggesting that an initial "priming" depolarization was required to activate K_V channels, which could then be inhibited by hypoxia, leading to further depolarization (1949); however, other studies have reported hypoxic depolarization from resting $E_m \leq -47$ mV (598, 1423, 1544).

As indicated by the Goldman-Hodgkin-Katz equation, hypoxic depolarization could result from *1)* increased membrane permeability to Na^+ and Cl^- or *2)* decreased membrane permeability to K^+. Consistent with *possibility 1*, early studies reported that hypoxic depolarization of PASMC was associated with decreased $[K^+]_i$, increased $[Na^+]_i$, and increased membrane conductance (150, 740); however, virtually all subsequent investigation focused on *possibility 2*.

II) Generation of hypoxic depolarization. A) Inhibition of K^+ channels and currents. i) K_V channels. Hypoxia (P_{O_2} ~40 mmHg) inhibited I_K in canine proximal PASMC (1545). This effect was prevented by the VOCC blocker nisoldipine or dialysis of cells with the Ca^{2+} chelator BAPTA, leading to an initial conclusion that hypoxia inhibited K_{Ca} channels, presumably large-conductance (BK_{Ca}) channels. Consistent with this possibility, 500 μM TEA, which was thought to be selective for BK_{Ca} channels, also inhibited the current and caused depolarization. Soon afterwards, however, it was found that hypoxia reduced a voltage-dependent I_K in rat PASMC (2172). A significant component of this inhibition and all of the attendant depolarization persisted when both bath and pipette solutions were made Ca^{2+}-free with EGTA, suggesting that hypoxia inhibited K_V rather than K_{Ca} channels. A subsequent study in canine PASMC (1544) demonstrated that *1)* intracellular BAPTA prevented hypoxic inhibition of I_K; *2)* the inhibitory effect of hypoxia on I_K was lost in the presence of the K_V antagonist 4-AP; *3)* both

hypoxia and increased $[Ca^{2+}]$ on the cytoplasmic face of the membrane reduced the open probability of a small-conductance 4-AP-sensitive K^+ channel, and *4*) the hypoxia-sensitive current was activated at the resting E_m. These results indicated that hypoxic inhibition of I_K in canine PASMC was caused by inhibition of K_V channels due to an hypoxia-induced increase in $[Ca^{2+}]_i$ rather than inhibition of K_{Ca} channels, i.e., hypoxic depolarization was the result rather than the cause of an hypoxia-induced increase in $[Ca^{2+}]$. In agreement with this, the K_{Ca} antagonist charybdotoxin did not affect HPV in rat perfused lungs (622) or pulmonary arteries (934), and HPV was not altered in perfused lungs of mice deficient in BK_{Ca} channels (1663). Why hypoxic inhibition of I_{KV} was apparently Ca^{2+}-dependent in canine PASMC (1544) but Ca^{2+}-independent in rat PASMC (2172) remains unclear. Possibly, this difference was caused by use of EGTA rather than the stronger Ca^{2+} buffer BAPTA to remove intracellular Ca^{2+} in rat PASMC (2172).

Initial experiments implicating K_V channels as the target for hypoxia used the O_2 scavenger dithionite to achieve hypoxia (1544, 2172). Although this compound has other effects that could impact I_K (50), it seems unlikely that the observed inhibition of I_K was due to these effects, since dithionite had no effect on I_K if solutions were vigorously gassed with air to prevent hypoxia (2172), and hypoxia in the absence of dithionite strongly reduced the open probability of K_V channels (1544). Furthermore, authentic hypoxia in rat PASMC reversibly reduced activity of a small-conductance K^+ channel (53); 4-AP (1423) but not pharmacological blockers of BK_{Ca} and/or K_{ATP} channels (63, 1949) prevented attenuation of I_K induced by authentic hypoxia; and graded decreases in O_2 concentration from 21 to 10, 5, 3, and 0% caused graded decreases in I_K amplitude in association with graded increases in E_m and $[Ca^{2+}]_i$ (1423).

The evidence linking K_V channel inhibition to HPV is based predominantly on the effects of pharmacological antagonists, which would be expected to cause constriction during normoxia and inhibit HPV. At concentrations $\leq$1 mM, 4-AP blocked K_V currents in freshly isolated myocytes from distal pulmonary arteries (1802) and strongly constricted and/or depolarized isolated systemic arteries and veins (327, 861, 1407, 1523 4303, 1769). Nevertheless, these concentrations of 4-AP were seldom found to constrict or depolarize isolated pulmonary arteries **(TABLE 4)**. Although higher 4-AP concentrations did constrict pulmonary arteries during normoxia, this result is difficult to interpret since these 4-AP concentrations could block other types of K^+ channels and have been shown to cause a rise in $[Ca^{2+}]_i$ that was insensitive to VOCC blockade and may therefore be depolarization-independent (2170). These and other nonspecific actions may explain why 4-AP concentrations $\geq$1 mM inhibited, enhanced, or did not alter HPV **(TABLE 4)**. Thus the pharmacological evidence linking hypoxic depolarization and HPV to K_V channel inhibition is weak.

The effects of hypoxia on specific K_V channels have been studied in only a few of the many subtypes expressed in PASMC. Identifying the channel proteins responsible for specific K_V currents defined by kinetic and pharmacological properties is difficult due to the existence of K_V heteromultimers and accessory β-subunits. Nevertheless, alteration of a functionally defined I_{KV} by molecular techniques or specific antibodies is an important first step in this identification.

a) $K_V1.5$. Dialysis of rat PASMC with an antibody to $K_V1.5$ caused rapid depolarization and prevented hypoxia-induced depolarization (598). A subsequent study in rat PASMC reported that $K_V1.5$ antibody attenuated I_K, but did not alter resting E_m (59). In addition, perfusates containing high concentrations of $K_V1.5$ antibody and the detergent Tween 20 to enhance antibody uptake inhibited HPV but did not alter basal P_{PA} in isolated rat lungs (59). Hypoxic inhibition of I_{KV} in PASMC, as well as HPV in isolated lungs and pulmonary arteries, was reduced in knockout mice deficient for the $K_V1.5$ α-subunit (54). Adenoviral transfection of the human $K_V1.5$ gene restored O_2-sensitive I_{KV} in PASMC and normalized HPV in isolated lungs of chronically hypoxic rats, in which I_{KV}, HPV, and expression of $K_V1.5$ and other α-subunits would ordinarily be diminished (1549). Collectively, these results suggest that a K_V channel incorporating the $K_V1.5$ α-subunit may contribute to O_2-sensitive I_{KV} in PASMC.

Expression of human $K_V1.5$ in mouse L cells caused development of a current that was insensitive to hypoxia, whereas coexpression of $K_V1.2$ and $K_V1.5$ produced a current that was inhibited by hypoxia (827, 1439). Moreover, the hypoxia-sensitive I_K in rat PASMC was insensitive to 1 mM 4-AP (1279), which should block $K_V1.5$ (666), $K_V1.5$/$K_V1.2$ heteromultimers (1680), and all proposed O_2-sensitive K_V channels except $K_V2.1$ (696). These results appear to argue against a role for homomeric $K_V1.5$ in hypoxic depolarization; however, $K_V1.5$ was later shown to be O_2 sensitive when expressed in PASMC, but not in other cell types (1525), indicating that O_2 sensitivity may be determined by the host cell (333, 1126).

The contribution of $K_V1.5$ to O_2-sensitive I_{KV} may also depend on myocyte location within the pulmonary vascular tree. Expression of $K_V1.5$ mRNA and protein was greater in myocytes from small ($<$40 μm) than large (100–200 μm) distal pulmonary arteries (63). Small distal PASMC also exhibited a large O_2-sensitive I_{KV} that activated in the range of the resting E_m. These results seem inconsistent with an earlier study by the same group, in which hypoxia was found to inhibit I_K in proximal rat PASMC (51). Possibly, this discrepancy is explained by heterogeneity among isolated PASMC. For example, K_V α- and β-subunit expres-

Table 4 Effects of K_V channel antagonists and antibodies

Antagonist or Antibody	Species	Preparation	PA Diameter or Branch	[Antagonist]	Effects Under Basal Conditions	Effects on Hypoxic Responses	Reference Nos.
4-Aminopyridine	Dog	IPL		5 mM	↑ P_{PA}		1545
		PA	Branch 3	5 mM	Contraction		1545
	Human	PA	Main	1 mM	No effect on tension		1499
				10 mM	Contraction		1499
	Mouse	IPL		0.01–1 mM	No effect on P_{PA}	No effect on pressor response	1821
	Pig	PA	200–700 μm	10 mM	Contraction	No effect on contractile response	1752
	Rabbit	PA	Branch 3	1 mM	No effect on tension		1437
	Rabbit	PASMC	Branch 3	1–10 mM	Depolarization (4–10 mV)		1437
			Main	22 mM	Depolarization (22 mV)		1438
		PASMC (fetal)	Branch 4	5 mM	Depolarization (10 mV)		808
	Rat	IPL		1–10 mM	↑ P_{PA}	↑ Pressor response	751
		PA	~75 μm	1–10 mM	Contraction (graded, maximum =50% of KCl response)	↓ Contractile response	63
			<300 μm	10 mM	Contraction (transient)		53
			331 μm	1, 10 mM	Contraction (0, 10% of KCl response)		1553
			300–700 μm	1, 10 mM	Depolarization (4, 10 mV)		1803
			Branch 1–2	1, 5, 10 mM	Contraction (~35, 70, 120% of phenylephrine response)		59
			Branch 1	1 mM		↓ Contractile response	98
			Main	1 mM	No effect on tension, E_m, $[Ca^{2+}]_i$		201
				10 mM	Contraction (50% of KCl response)		201
		PASMC	<300 μm	10 mM	Depolarization (~20 mV)		53
			300-500 μm	1 mM	Depolarization (~15 mV)		59
			Branch 4	6 mM	↑ $[Ca^{2+}]_i$		59
			Branch 4–6	5 mM	↑ $[Ca^{2+}]_i$		1423
			Branch 1–2	0.3–10 mM	Depolarization (2-16 mV; action potentials at 5-10 mM)		2170
Correolide	Rat	PA	~75 μm	1–100 μM	Contraction		63
		PASMC	~75 μm	1–100 μM	Depolarization (graded, maximum ≈20 mV)	↓ Depolarization	63
Dexfenfluramine	Rat	IPL		1 mM	↑ P_{PA}		2050
				100 μM	↑ P_{PA}		1598
Fluoxetine	Rat	IPL		100 μM	↑ P_{PA}		1598
Linopirdine	Mouse	PA	100–200 μm	1 nM–100 μM	Contraction (maximum =54% of KCl response; EC_{50} = 0.6 μM)		910
	Rat	PA	300–400 μm	1 nM–100 μM	Contraction (maximum = 85% of KCl response; EC_{50} =1.3 μM)		910
Pergolide	Mouse	PASMC		10 μM	↑ $[Ca^{2+}]_i$ (380% of baseline)		807
	Rat	IPL		10 μM	↑ P_{PA}	↑ Pressor response	807
		PA	150-400 μm	10 μM	Contraction (58% phenylephrine response)		807
		PASMC	Branch 4	10 μM	Depolarization (7 mV) and ↑ $[Ca^{2+}]_i$ (38% of baseline)		807
Phentermine	Rat	IPL		100 μM	↑ P_{PA}		1598
XE 991	Mouse	PA	100-200 μm	1 nM–100 μM	Contraction (maximum ≈61% of KCl response; EC_{50} = 0.12 μM)		910
	Rat	PA	300-400 μm	1 nM–100 μM	Contraction (maximum = 79% of KCl response; EC_{50} = 0.3 μM)		910
Anti-K_V1.5	Rat	IPL			No effect on P_{PA}	↓ Pressor response	59
		PASMC	~75 μm		Depolarization (~20 mV)		63
			Branch 4			↓ $[Ca^{2+}]_i$ response	59
Anti-K_V2.1	Rat	IPL			↑ P_{PA}	No effect on pressor response	59
		PASMC	~75 μm		Depolarization (~14 mV)		63
			Branch 4			No effect on $[Ca^{2+}]_i$ response	59
Anti-K_V1.5 + Anti-K_V2.1	Rat	PASMC	~75 μm		Depolarization (~30 mV)	↓ Depolarization	63

Preparations include isolated perfused lungs (IPL), pulmonary arteries (PA), or pulmonary arterial smooth muscle cells (PASMC). P_{PA}, pulmonary arterial pressure; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; E_m, membrane potential; EC_{50}, effective concentration causing half-maximum response.

sion varied considerably among isolated rat PASMC, and hypoxia reduced whole cell I_{KV} only in cells with high levels of Kv1.5 (1529).

Taken together, the evidence suggests that $K_V1.5$ channels may contribute to O_2-sensitive I_{KV} and hypoxic depolarization in PASMC. Whether these channels are $K_V1.5$ homotetramers or $K_V1.5$-containing heterotetramers is unknown.

b) $K_V2.1$ and $K_V2.1/9.3$. In rat distal PASMC, I_K was strongly attenuated by hypoxia or dialysis with a $K_V2.1$ antibody (794). Similar inhibition of I_K was observed in cells exposed to both anti-$K_V2.1$ and hypoxia, implying that only currents inhibited by anti-$K_V2.1$ were sensitive to hypoxia. $K_V2.1$ antibodies also attenuated I_K and reduced hypoxic depolarization in rat proximal PASMC (59). Unlike anti-$K_V1.5$, perfusion of isolated rat lungs with anti-$K_V2.1$ in the presence of Tween 20 increased baseline P_{PA} during normoxia; however, effects on HPV could not be determined due to edema formation. Based on differences in the effects of anti-$K_V2.1$ and anti-$K_V1.5$, it was proposed that hypoxia caused PASMC depolarization by inhibiting $K_V2.1$, thus bringing E_m into the range where $K_V1.5$ was activated, such that its suppression by hypoxia would then cause further depolarization (59). However, it is difficult to understand how this could work, since activation of $K_V1.5$ channels by depolarization due to hypoxic inhibition of $K_V2.1$ channels would generate a hyperpolarizing current that would at best be only partially offset by hypoxic inhibition of the $K_V1.5$ channels. Alternatively, if the selective inhibition of either channel caused a depolarization that activated the other, it might be necessary for hypoxia to suppress both channels simultaneously to elicit depolarization sufficient to cause contraction.

As noted above, basal I_{KV} (201, 1528, 1803), expression of $K_V2.1$ (1279, 1528, 2001, 2007), and the inhibitory effect of acute hypoxia on I_{KV} (1279) were reduced in pulmonary arteries or PASMC from chronically hypoxic rats. In these preparations, the metabolic inhibitor dichloroacetate reversed the downregulated protein expression of $K_V2.1$ (but not $K_V1.5$) and partially restored HPV and the sensitivity of I_{KV} to acute hypoxia, suggesting that this sensitivity was associated mainly with $K_V2.1$ rather than $K_V1.5$ (1279).

$K_V2.1$ and a novel K_V α-subunit, $K_V9.3$, were found to coimmunoprecipitate in rat PASMC (1473). Expression of $K_V2.1$ in *Xenopus* oocytes and COS cells gave rise to a low-conductance current that was not activated at physiologically relevant E_m and sensitive to hypoxia in only a small subset of cells. Expression of $K_V9.3$ alone did not produce functional channels; however, coexpression of $K_V2.1$ and $K_V9.3$ produced a current with a single-channel conductance larger than $K_V2.1$ alone that was activated in the voltage range of resting E_m and reversibly inhibited by hypoxia. Based on these findings, a $K_V2.1/K_V9.3$ heteromultimer was proposed to play an important role in hypoxic depolarization of PASMC (827, 1473).

c) Other K_V subtypes. Expression of rat $K_V1.2$ protein in mouse L cells revealed that hypoxia (P_{O_2} ~30 mmHg) caused a 23% inhibition of the resulting current at +60 mV; however, hypoxia had no effect on the current at negative E_m (827). Rat $K_V1.2$ expressed in B82 cells was also O_2 insensitive (1439), and dendrotoxin, which blocks expressed $K_V1.2$ homomultimers, had no effect on I_{KV} in PASMC from proximal or distal rat pulmonary arteries (1802). Thus $K_V1.2$ homomultimers, while O_2 sensitive, are unlikely to contribute to hypoxic depolarization of PASMC.

Although $K_V3.1b$ was expressed in proximal pulmonary arteries of rabbit and immature rats (1439), it was not detected in proximal or distal arteries of young adult rats (1802). Heterologous expression of $K_V3.1b$ in L929 cells produced a current that was O_2 sensitive, even in excised patches (1439); however, this current activated at relatively positive E_m, suggesting that its sensitivity to hypoxia could be a factor in PASMC function only if the cells were already depolarized.

d) Mechanisms. There are two main models describing how hypoxia might inhibit K^+ channel activity in PASMC (333, 1126). In the first, hypoxia acts directly on the pore-forming subunit, where thiol-containing residues are reduced during hypoxia due to reduction of redox state and decreased ROS concentrations, leading to decreased channel opening (51, 2045). In the second, properties of the pore-forming subunit are altered by interactions with ancillary proteins that act as O_2 sensors. The reader is referred to section III*A2*, C and D, for discussion of how hypoxia affects redox state and ROS production in PASMC, which is directly relevant to both models.

In support of the first model, both reduced glutathione and inhibition of the mitochondrial electron transport chain mimicked hypoxic inhibition of I_K (51, 2176). Reduced glutathione also accelerated inactivation of $K_V1.4$ and $K_V3.4$, an effect that was abolished when the cysteine residue responsible for rapid inactivation in the NH_2-terminal "ball" region of the $K_V1.4$ channel was changed to a serine (1676). Conversely, the oxidizing agent tert-butylhydroperoxide inhibited inactivation of heterologously expressed $K_V1.4$ and $K_V3.4$ channels (453). In addition, photoactivation of the dye Rose Bengal, a classic generator of ROS, depressed currents mediated by these channels, as well as $K_V1.3$ and $K_V1.5$.

Interestingly, hypoxic inhibition of cloned K_V channel α-subunits depended on the cell type in which they were expressed, and often occurred in only a subset of the trans-

fected cells (333, 827, 1439, 1473). For example, $K_V1.5$ was O_2 sensitive when expressed in rat PASMC, but not when expressed in rat mesenteric artery smooth muscle, HEK-293, or COS-7 cells (1525). These results suggest that the unique effects of hypoxia in PASMC depend on some special aspect of cellular milieu rather than a unique property of K_V channel proteins.

With regard to the second model, K_V β-subunits are plausible candidates for O_2 sensors capable of regulating K^+ channel activity. For example, the $K_V4.3$ α-subunit, which is thought to underlie the hypoxia-sensitive I_K in type 1 carotid body cells (1127), was O_2 insensitive when expressed alone, but inhibited by hypoxia when coexpressed with $K_V\beta1.2$ (1503). K_V β-subunits form aldo-keto oxidoreductase enzymes, which utilize NAD(P)H/NAD(P)$^+$ as cofactors to reduce/oxidize a variety of substrates (679, 1225). It has been proposed that conformational changes induced by oxidation/reduction of NAD(P)H/NAD(P)$^+$ bound to the active sites of $K_V\beta$ subunits may affect gating of associated K_V α-subunits (679). Consistent with this concept, the inactivation rate of K^+ channels formed by coexpression of $K_V1.4$ and $K_V\beta2$ was diminished by substrates that oxidized $K_V\beta2$-bound NADPH (2076). This effect was reversed by exogenous NADPH, and did not occur in oocytes in which $K_V\alpha1.4$ was coexpressed with a mutant $K_V\beta2$ incapable of NADPH-mediated substrate reduction. Along similar lines, inactivation of I_K resulting from cotransfection of $K_V1.5$ and $K_V\beta1.3$ was strongly inhibited and activation shifted to more positive E_m, when the cells were dialyzed with $NADP^+$ or NAD^+, whereas dialysis with NADH or NADPH had no effect (168, 1911). In contrast, none of these pyridine nucleotides had any effect on I_K that developed when $K_V1.5$ was expressed alone. If $K_V1.5$/$K_V\beta1.3$ contributes a major component of I_{KV} in PASMC, these results predict that an increased NADPH/$NADP^+$ ratio due to hypoxia should cause I_{KV} activation at more negative E_m, and I_{KV} inhibition as inactivation becomes more prominent at increased E_m. This pattern was apparent in hypoxic PASMC of dog (1545) but not rat (1423), where hypoxia-induced inhibition of I_K was associated with a shift of activation threshold to more positive E_m. Expression of K_V β-subunits was much higher in distal compared with proximal bovine PA (334), as would be expected if these subunits were crucial for O_2 sensing and HPV.

Other mechanisms have been proposed, but whether they act directly on pore-forming channel proteins or indirectly on regulatory proteins is not known. One example is hypoxic inhibition of I_{KV} caused by a rise in $[Ca^{2+}]_i$. In canine PASMC, hypoxic inhibition of I_{KV} was abolished by the Ca^{2+} buffer BAPTA or pretreatment of cells with caffeine to deplete intracellular Ca^{2+} stores (1544, 1545). In cell-attached and inside-out patches, hypoxia reduced opening of a 4-AP-sensitive K^+ channel that was inhibitable by 1 μM $[Ca^{2+}]$ (1544). These results suggest that K_V channel inhibition was secondary to an hypoxia-induced rise in $[Ca^{2+}]$ and would therefore be more likely to amplify than to initiate hypoxic depolarization. In line with this possibility, agents that release Ca^{2+} from sarcoplasmic reticulum increased both $[Ca^{2+}]_i$ and E_m in isolated PASMC, and abolished these responses to subsequent hypoxic exposures (598).

High levels of $[Mg^{2+}]_i$ attenuated currents conducted by several K_V channel subtypes, including $K_V1.5$ and $K_V2.1$ (1888), and inhibited I_{KV} in several types of smooth muscle cells, including PASMC (599). In rat PASMC, increased $[Mg^{2+}]_i$ caused I_{KV} to activate at more negative E_m and decrease in amplitude, similar to the effects of the mitochondrial inhibitors antimycin A and CCCP, both of which also increased $[Mg^{2+}]_i$ (527). These results suggested that hypoxic inhibition of I_{KV} might be caused by the increased $[Mg^{2+}]_i$ associated with hypoxia-induced mitochondrial inhibition. This concept was further supported by the close proximity of mitochondria to plasma membrane in PASMC and attenuation of the inhibitory effects of mitochondrial inhibition on I_{KV} when this proximity was altered by the cytoskeletal disruptor cytochalasin B (526). Mitochondrial inhibitors had smaller effects on I_{KV} in mesenteric arterial myocytes, where similar mitochondrial-sarcolemmal proximity was not observed. Mitochondrial-sarcolemmal proximity in PASMC could also facilitate effects of mitochondrial signals other than Mg^{2+} on I_{KV} or other currents.

Finally, it was recently proposed that hypoxic inhibition of I_{KV} in PASMC is due to activation of PKC-ζ by ceramide generated by neutral sphingomyelinase (326). In support of this possibility, hypoxia increased ceramide content in rat PASMC, and these increases, as well as hypoxic inhibition of I_{KV} in PASMC and HPV in pulmonary arteries and lungs, were inhibited by antagonists of neutral sphingomyelinase or PKC-ζ (326). Interestingly, PKC-ζ was also found to mediate ROS-dependent inhibition of I_{KV} by U46619 (326); however, whether hypoxic inhibition of I_{KV} was also linked to ROS was not explored.

ii) Noninactivating K^+ current and K_{2P} channels. An enduring objection to K_V channel inhibition as the cause of hypoxic depolarization is that I_{KV} should be negligibly activated (and therefore negligibly inhibitable) at resting E_m because the apparent activation threshold of delayed rectifier current is more positive than resting E_m. This viewpoint recently received support from a mathematical analysis of E_m regulation in PASMC (276). As a result, investigators have sought to demonstrate in PASMC an hypoxia-sensitive I_K with an activation threshold that was either negative to that of "classical" delayed rectifiers or independent of voltage.

As described in section III*B1*A, one such current, noninactivating K^+ current (I_{KN}), was characterized in PASMC more than a decade ago (489), and is thought to be a composite current generated by K_V7 and TASK-1. Hypoxia decreased I_{KN} amplitude by 60% in rabbit proximal pulmonary arteries (1438) and almost abolished I_{KN} in human PASMC (1425). The effect of hypoxia on K_V7 has not yet been reported; however, involvement of TASK channels in O_2 sensing has been suspected for some time.

Carotid bodies of neonatal rats exhibited a voltage-insensitive K^+ current that was strongly inhibited by hypoxia (230). This current had properties resembling both I_{KN} in rabbit PASMC (489) and currents generated by TASK-1 and TASK-3, which formed functional heterodimers when coexpressed in *Xenopus* oocytes (352). Based on these similarities and observations that TASK-1 was inhibited by hypoxia, it was proposed that I_{KN} was generated, at least in part, by TASK-1 (694). In support of this possibility, subsequent studies confirmed hypoxic inhibition of TASK-1 (589, 1425) and demonstrated that downregulation of TASK-1 expression by RNA interference dramatically reduced I_{KN}, which was no longer sensitive to hypoxia, anandamide, or acidification (1425). These data provide strong evidence that TASK-1 channels are an important target for hypoxia in PASMC.

The mechanism by which hypoxia inhibits TASK channels remains unclear. In type 1 cells of the carotid body, effects of hypoxia on TASK were mimicked by metabolic inhibitors, suggesting regulation by cellular ATP levels (231). It seems unlikely that a similar regulation occurs during hypoxia in PASMC, since hypoxia did not change ATP levels in these cells (1044). TASK-1 and TASK-3 were insensitive to H_2O_2 when expressed in CHO cells (964); however, TASK-1 expressed in immortalized adrenomedullary chromaffin cells was also insensitive to O_2 (905), suggesting that regulation of heterologously expressed TASK-1 differs from that in native cells.

b) Activation of Cl^-, Na^+, and nonselective cation channels. As noted above, early studies concluded that hypoxic depolarization of PASMC was associated with increases in $[Na^+]_i$ and membrane conductance and a decrease in $[K^+]_i$ (150, 740). These results imply that hypoxic depolarization was caused by activation of ion channels with reversal potentials greater than resting E_m (such as Cl^-, Na^+, or nonselective cation channels) rather than inhibition of open ion channels with reversal potentials less than resting E_m (such as some K^+ channels). Cl_{Ca} channels are candidates for this role because $I_{Cl(Ca)}$ is prominent in pulmonary arteries of several species, may help set resting E_m (1031), contributes a depolarizing current during increases in $[Ca^{2+}]_i$ and, at least in some cell types, can be activated by ROS (895). In addition, the VOCC blocker verapamil caused a slight hyperpolarization during hypoxia in cat distal pulmonary arteries, which may have been due to inhibition of activated Cl_{Ca} channels caused by a decrease in $[Ca^{2+}]_i$ (740). Nonselective cation channels are candidates because of evidence indicating that they are required for Ca^{2+} signaling in PASMC during hypoxia (see sect. III*B2*D). For example, recent results in mouse PASMC suggested that hypoxia activated a nonselective cation channel containing canonical transient receptor potential 6 (TRPC6) protein, which is thought to be a key component of receptor-operated Ca^{2+} channels (2054). The possibility that hypoxic depolarization of PASMC is due to activation of Cl^-, Na^+, or nonselective cation channels needs to be thoroughly evaluated.

C) SUMMARY: HYPOXIC DEPOLARIZATION OF PASMC. Hypoxic depolarization may result from inhibition of K^+ efflux through several types of K^+ channels and activation of Na^+ influx through nonselective cation channels and/or Cl^- efflux through Cl_{Ca} channels **(FIGURE 7)**. The precise mix of channels involved may depend on species, location within the pulmonary vascular tree, and other factors. Observations that O_2 sensitivity differed among PASMC from the same vessel (1529) and that PASMC from proximal and distal pulmonary arteries exhibited different patterns of K_V currents (49, 1802) suggests that hypoxic responsiveness may exist as a mosaic both within and among pulmonary arteries. The O_2 sensitivity of at least some of these channels is dependent on the cell type in which they are expressed, e.g., $K_V1.5$ channels are O_2 sensitive in PASMC but not mesenteric arterial myocytes (1525). Such cell-specific functionality implies that O_2 sensitivity depends crucially on factors that exist only in O_2 sensitive cells, such as a particular trigger, regulatory protein, signaling complex, or organelle arrangement.

It is striking that so many types of PASMC K^+ channels, including $K_V1.2$, $K_V1.5$, $K_V1.5/K_V1.2$, K_V 2.1, $K_V2.1/K_V9.3$, $K_V3.1b$ and TASK-1, are susceptible to hypoxic inhibition. Since K_V channels are uniquely "designed" to oppose depolarization caused by other channels, hypoxic suppression of I_{KV} may permit rather than cause hypoxic depolarization, i.e., widespread inhibition of K_V channels by hypoxia may allow depolarization generated by effects of hypoxia on TASK-1, Cl_{Ca}, or nonselective cation channels. Along these lines, a recent mathematical analysis of E_m regulation in PASMC concluded that depolarizations observed experimentally during hypoxia would require not only inhibition of I_K but also a 250% increase in nonselective cation current (276). Although this conclusion obviously depends on the validity of the underlying assumptions and information used to describe the behavior of the involved channels, it is consistent with early reports that hypoxia caused depolarization of cat PASMC in association with decreases in $[K^+]_i$ and increases in $[Na^+]_i$ and membrane conductance (150, 740), as well as more recent findings indicating an important role for nonselective cation channels in HPV (see sect. III*B2*D).

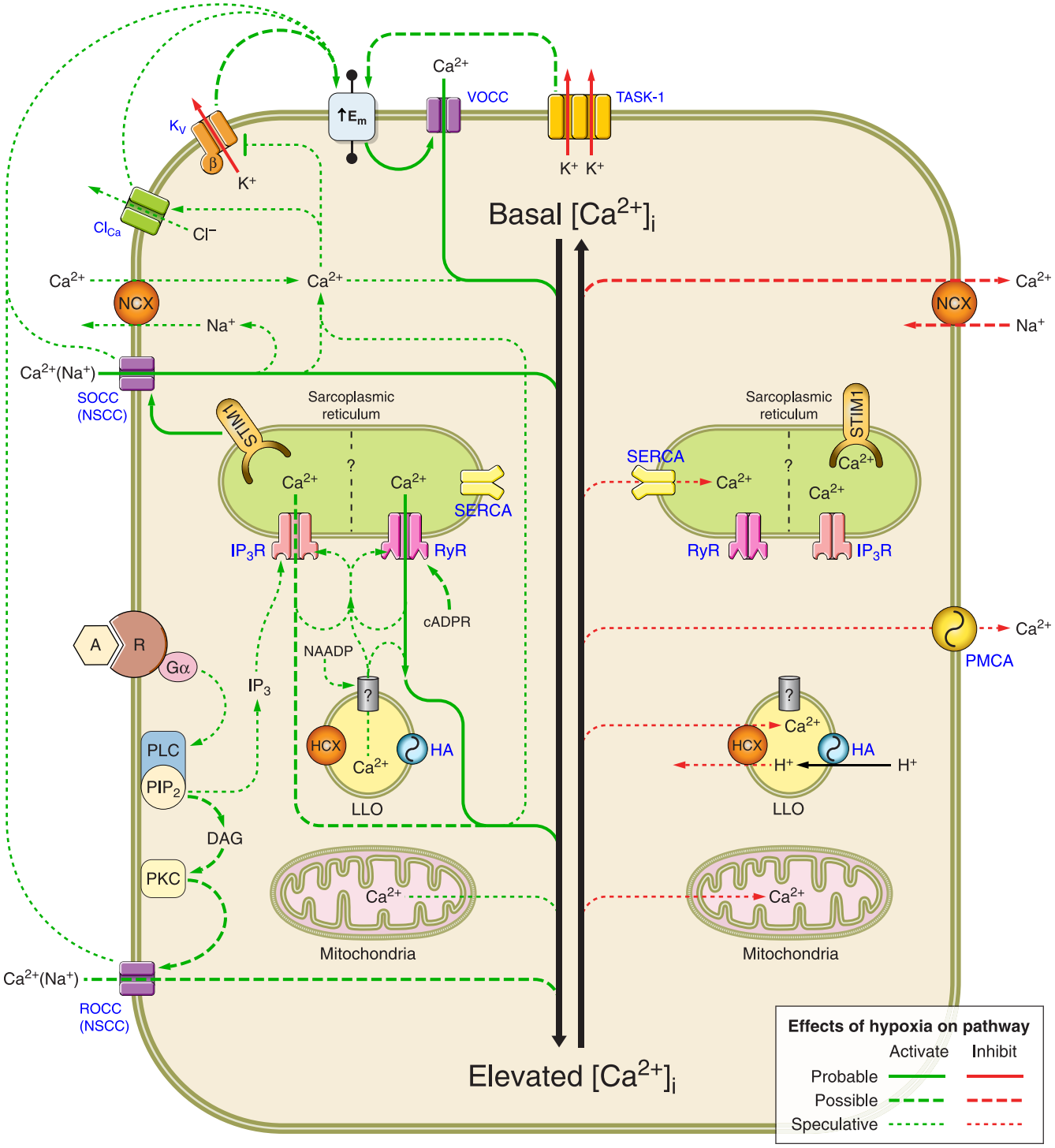


FIGURE 7 Effects of acute hypoxia on intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in pulmonary arterial smooth muscle. Pathways that increase $[Ca^{2+}]_i$ are shown on the *left*, while those that decrease $[Ca^{2+}]_i$ are on the *right*. Hypoxia can activate (green) or inhibit (red) these pathways. Whether these effects are probable, possible, or speculative is indicated by solid, dashed, and dotted lines, respectively, as shown in the key at the bottom. With respect to plasma membrane and associated cytosolic signals, TASK-1 is TWIK-related acid-sensitive channel-1; VOCC, K_V, Cl_{Ca}, SOCC, NSCC, and ROCC indicate voltage-operated Ca^{2+}, voltage-dependent K^+, calcium-dependent Cl^-, store-operated Ca^{2+}, nonselective cation, and receptor-operated Ca^{2+} channels, respectively. NCX, Na-Ca exchanger; A, agonist; R, receptor; PLC, phospholipase C; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; PMCA, plasma membrane Ca^{2+}-ATPase. With respect to sarcoplasmic reticulum (SR) and associated cytosolic signals, SERCA is sarcoplasmic-endoplasmic reticulum ATPase, IP_3R is IP_3 receptor, RyR is ryanodine receptor, STIM1 is stromal interaction molecule 1, and cADPR is cyclic ADP ribose. With respect to lysosome-like organelles (LLO) and associated cytosolic signals, NAADP is nicotinic acid adenine dinucleotide phosphate, HCX is H-Ca exchanger, and HA is H^+-ATPase. Mito, mitochondria.

Despite intense effort, the mechanisms by which hypoxia causes depolarization of PASMC remain largely unknown. The ion conductances that maintain resting E_m positive to K^+ equilibrium potential and could contribute to hypoxic depolarization have not been identified. The roles of Cl_{Ca} and nonselective cation channels, which seem suited to produce depolarization, have not been defined. How hypoxia inhibits K_V and TASK-1 channels has not been elucidated. Perhaps most importantly, the extent to which membrane depolarization contributes to HPV remains unclear, as discussed in section III*B*2D*I*.

2. Ca^{2+} signaling

There is general agreement that smooth muscle contraction is usually signaled by a global increase in intracellular Ca^{2+} concentration. Furthermore, accumulating evidence suggests that global increases in $[Ca^{2+}]_i$ are generated by local $[Ca^{2+}]_i$ transients known as "sparks" and "puffs," which regulate a wide variety of cellular processes (158, 194, 1700, 2118). Ca^{2+} sparks are generated by transient release of Ca^{2+} from local clusters of ryanodine receptors in sarcoplasmic reticulum and were first described in cardiac myocytes (300, 1129). Ca^{2+} puffs are caused by release of Ca^{2+} from local clusters of IP_3 receptors, and were observed first in *Xenopus* oocytes (1465) and later in PC12, HeLa, and endothelial cells (206, 837, 1594).

In PASMC, Ca^{2+} sparks were lower in amplitude and frequency but similar in size and duration to those in heart, located near sarcolemma and the nuclear membrane, blocked by ryanodine, and enhanced by caffeine, confirming origination from ryanodine receptors (882, 1608). In addition, sparks were associated with depolarization and spontaneous transient inward currents (STIC), possibly due to Ca^{2+}-dependent activation of Cl_{Ca} or inhibition of K_V channels in nearby sarcolemma (1608, 2014); however, hyperpolarization and spontaneous transient outward currents (STOC) due to activation of K_{Ca} channels, as found in systemic vascular smooth muscle (880), were also reported (83, 1542). Ca^{2+} puffs have not been reported in PASMC, suggesting that IP_3 receptors may not be clustered in these cells (882, 2201). On the other hand, endothelin-1 or intracellular photorelease of caged IP_3 induced local $[Ca^{2+}]_i$ transients that were abolished by antagonists of either ryanodine or IP_3 receptors (1608, 2201). These results suggest that Ca^{2+} released from IP_3 receptors promoted release from nearby clusters of ryanodine receptors, a phenonmenon known as Ca^{2+}-induced Ca^{2+} release (CICR). In the case of caged IP_3, these $[Ca^{2+}]_i$ transients triggered global increases in $[Ca^{2+}]_i$ (2201), implying that they could signal PASMC contraction.

Whether Ca^{2+} sparks and puffs play a role in HPV is an important but unanswered question. The current lack of data may be due in part to the difficulty of $[Ca^{2+}]_i$ measurements at body temperature, which is necessary for HPV (144, 359, 700) but causes PASMC to rapidly lose the nonratiometric fluorescent Ca^{2+} indicators now used in confocal microscopy. Until such data are available, discussion of Ca^{2+} signaling in HPV must be limited to global changes in $[Ca^{2+}]_i$.

A) EFFECTS OF HYPOXIA ON GLOBAL $[Ca^{2+}]_i$. Ca^{2+}-sensitive fluorescent indicators such as fura 2 and indo 1 have been used to measure the effects of acute hypoxia on $[Ca^{2+}]_i$ in isolated rat distal pulmonary arteries (1639, 1641) and cultured or freshly isolated PASMC of rat (59, 86, 598, 1139, 1423, 1697, 2005, 2014, 2035, 2188), mouse (2010, 2054, 2211, 2213), rabbit (413, 924, 1958), fetal lamb (340, 341), cat (1963), dog (1544), pig (1752), and human (1889). Baseline $[Ca^{2+}]_i$ values averaged 40–200 nM in these preparations, and exposure to physiological salt solutions equilibrated with 0–5% O_2 (P_{O_2} <4–44 mmHg) for 1–45 min increased $[Ca^{2+}]_i$ by 36–512 nM. When $[Ca^{2+}]_i$ responses to hypoxia were expressed as a percentage of baseline, they averaged 27.2–64.1% (413, 1544, 1639, 1641, 1963). Response magnitude was proportional to the decrease in P_{O_2} and half-maximal at O_2 tensions of 7–39 mmHg (1423, 1752, 2005). The response was usually rapid in onset and occasionally exhibited an overshoot followed by a gradual decline of $[Ca^{2+}]_i$ to a lower, stable plateau that was higher than its normoxic baseline value (59, 1639, 1641, 1697, 1963). The overshoot may depend on the speed and severity of the decrease in P_{O_2} (1697). Hypoxia-induced increases in $[Ca^{2+}]_i$ were generally greater or more readily observed in myocytes from distal than proximal pulmonary arteries (86, 341, 1139, 1752, 1958, 1963) and absent in cells from systemic arteries (341, 924, 1752, 1963, 2005, 2014). In some studies, maximal $[Ca^{2+}]_i$ responses to hypoxia were comparable to maximal responses induced by pharmacological agonists or depolarization (598, 1544, 1697, 2188), while in others they were smaller (59, 86, 1753, 1963, 2005). Repetitive spiking of $[Ca^{2+}]_i$ was observed in myocytes freshly isolated from rabbit distal pulmonary arteries (1958). Hypoxia increased basal $[Ca^{2+}]_i$ and decreased spike amplitude in 40% of these cells, but decreased basal $[Ca^{2+}]_i$ and increased spike amplitude in the remainder.

The physiological relevance of these observations remains somewhat uncertain. Isolation and culture could change cell phenotype (1443), particularly in PASMC exposed to growth media (340, 341, 924, 1697, 1963, 2035, 2188). To obtain reproducible $[Ca^{2+}]_i$ responses to hypoxia, some investigators pretreated their preparations with agents that increased resting membrane potential or tone (86, 1639, 1641). Perhaps to mitigate loss of intracellular fluorophore, many studies were performed at 30–35°C (59, 340, 341, 413, 924, 1423, 1697, 1752, 2014, 2035) or even room temperature (598, 1958), which can inhibit HPV (144, 359, 700). Occasionally, dithionite was used to generate severe hypoxia (413, 1544, 1697, 1752). The reaction of this ox-

ygen scavenger with O_2 produces reactive oxygen species (50), which can have complicated effects on Ca^{2+} signaling (1133). Although reactive oxygen species have been proposed to mediate HPV (see sect. III*A2*D), dithionite did not reproduce the effects of hypoxia in isolated lungs (50). Indeed, dithionite-induced contractions in smooth muscle were independent of extracellular [Ca^{2+}] and myosin light-chain phosphorylation, not mediated by hypoxia or PKC, and not specific for pulmonary arterial smooth muscle (2166). In some studies (413, 1697, 2188), hypoxic responses were measured in cells from proximal rather than distal pulmonary arteries, which are thought to be the major locus of HPV (see sect. II*A4*).

Another uncertainty is the accuracy of $[Ca^{2+}]_i$ measurements with fura 2 and indo 1 under hypoxic conditions. With both indicators, $[Ca^{2+}]_i$ is determined from ratios (R) of fluorescence intensities. In the case of fura 2, emission is measured at 510 nm after excitation at 340 and 380 nm ($R = F_{340}/F_{380}$). In the case of indo 1, emission is measured at 405 and 485 nm after excitation at 350 nm ($R = F_{405}/F_{485}$). The major advantage of ratiometric measurements is relative insensitivity to differences in indicator loading by cells and loss of indicator fluorescence due to defocusing, leakage from cells, or photobleaching; however, other potential sources of error remain (1878)], some of which are particularly relevant to studies of hypoxic responses. For example, intracellular concentrations of NADH and NADPH, which autofluoresce at 450–500 nm after excitation with ultraviolet light, increase during hypoxia (1041, 1878), and could cause overestimation of R in cells loaded with fura 2 or indo 1. In calibrating solutions containing fura 2, F_{340} decreased and F_{380} increased over time, causing a progressive decrease in R (F_{340}/F_{380}) at constant free Ca^{2+} concentration ($[Ca^{2+}]_f$) (124). These unexpected changes did not occur in solutions gassed with 95% N_2-5% CO_2, suggesting that photobleaching of fura 2 produced a fluorescent Ca^{2+}-insensitive product during normoxia that caused $[Ca^{2+}]_i$ to be underestimated.

To express R as $[Ca^{2+}]_i$ requires calibration, which is usually performed in vitro by measuring R in calibrating solutions of known $[Ca^{2+}]_f$ or in situ by measuring R in cells loaded with fluorophore and permeabilized with 4-bromo-A23187 or ionomycin to equalize [Ca^{2+}] between intracellular fluid and extracellular calibrating solutions of known $[Ca^{2+}]_f$. Calibrating solutions typically have $[Ca^{2+}]_f$ nominally equal to 0 (achieved by adding a Ca^{2+} chelator such as EGTA to a Ca^{2+}-free solution) and a value sufficiently high (0.04–10 mM) to saturate the fluorophore, yielding minimum and maximum fluorescence ratios (R_{min}, R_{max}), respectively. Intermediate $[Ca^{2+}]_f$ are usually achieved by adding known amounts of Ca^{2+} and EGTA to Ca^{2+}-free solutions. $[Ca^{2+}]_f$ is then calculated from the total concentration of Ca^{2+} and EGTA and the CaEGTA dissociation constant (K_{CaEGTA}). Calibration curves of $[Ca^{2+}]_f$ versus R generated in this manner can be used empirically to determine $[Ca^{2+}]_i$ from R values measured during experiments. Alternatively, $[Ca^{2+}]_i$ can be calculated as $K_{CaF}\beta(R - R_{min})/(R_{max} - R)$, where R_{min}, R_{max}, and β (ratio of fluorescence intensity in the denominator of R_{min} to that in the denominator of R_{max}) are measured directly, and K_{CaF} (dissociation constant of the Ca^{2+} fluorophore) is either assumed or determined from R measured at intermediate values of $[Ca^{2+}]_f$ during calibration (676). When assumed, K_{CaF} is commonly assigned values of 224 nM for fura 2 and 250 nM for indo 1, which were determined by Grynkiewicz et al. (676) in calibrating solutions that mimicked intracellular fluid and contained 115 mM KCl, 20 mM NaCl, 1 mM free Mg^{2+}, and 10 mM K-MOPS (pH 7. 05) at 37°C. These investigators found that decreasing pH to 6.75 had little effect on fura 2 fluorescence, whereas increasing ionic strength to 250 mM caused K_{CaF} to increase to 760 nM.

Because the fluorescent properties of fura 2 and indo 1 may change with ionic strength, temperature, pH, and other factors (586, 849, 1033, 1034, 1535, 1655, 1837, 1878), in situ calibrations performed under the specific conditions of the experiment are generally preferred to in vitro calibrations. In practice, however, in situ calibrations present some challenges. First, the dissociation constant of CaEGTA, the chelator most frequently used to control $[Ca^{2+}]_f$ in calibration solutions, also varies with temperature, pH, and ionic strength (163). As a result, the intermediate values of $[Ca^{2+}]_f$ that can be reliably achieved with EGTA under typical in situ extracellular conditions (pH 7.4, temperature 37°C, ionic strength 0.16 M) are low and narrow in range (≈18–180 nM) compared with the values (≈50–500 nM) possible under typical in vitro intracellular conditions (pH 7.2, temperature 22°C, ionic strength 0.1 M) (163, 1478). A narrow range of $[Ca^{2+}]_f$ may not permit adequate description of the calibration curve. Second, low levels of $[Ca^{2+}]_f$ may not produce Ca^{2+} fluxes large enough to defeat the cell's homeostatic mechanisms and cause equalization of intra- and extracellular [Ca^{2+}]. Third, contamination of chemicals and apparatus used to prepare calibration solutions may cause the presumed concentrations of Ca^{2+} and EGTA to be in error.

Several solutions to these problems have been proposed, including *1*) use of a chelator with a lower Ca^{2+} affinity; e.g., dibromoBAPTA, which has a dissociation constant of 1.35 μM under physiological extracellular conditions and should reliably produce $[Ca^{2+}]_f$ between 400 and 4000 nM; *2*) use of the latest data and state-of-the-art computer programs to calculate $[Ca^{2+}]_f$ in calibrating solutions at the pH, ionic strength, and temperature present in situ (1478); *3*) measurement of $[Ca^{2+}]_f$ in calibrating solutions with a Ca^{2+} electrode, which has been calibrated appropriately (162), and use of Scatchard and double reciprocal plot analysis to resolve total and bound chelator concentrations and

the apparent Ca-chelator dissociation constant to estimate $[Ca^{2+}]_f$ (1234); and *4*) measurement of unbound and total chelator concentration in calibrating solutions by titration with Ca^{2+} and Cd^{2+}, respectively (2097). In these titrations, the amount of Ca^{2+} required to completely displace H^+ from chelator (and thereby minimize pH) is assumed to equal the amount of unbound chelator, while the amount of Cd^{2+} (which displaces both Ca^{2+} and H^+) required to minimize pH is assumed to equal the amount of total chelator. These procedures and the problems they address have usually been ignored in studies of HPV.

To avoid the doubts and difficulties of calibration, many investigators have chosen to express results simply as R; however, this approach does not avoid errors due to autofluorescence, photobleaching, or changes in fluorophore properties. In addition, absolute values of R at the same $[Ca^{2+}]_i$ can vary widely due to differences in exposure times at each wavelength and the distribution of fluorophore within cells. This variability and the fact that R is a ratio that varies alinearly with true $[Ca^{2+}]_i$ could complicate statistical analysis and comparisons among the results of different studies.

There have been only a few attempts to determine whether hypoxia alters in situ calibration of Ca^{2+} fluorophores. In fura 2-loaded bovine pulmonary arterial endothelial cells exposed to calibrating solutions equilibrated with room air (P_{O_2} = 120–125 mmHg) or gassed with 0% O_2 (P_{O_2} <25–35 mmHg) at 32°C, hypoxia decreased K_{CaF} and increased R_{max} (1837). In cells loaded with indo 1, hypoxia increased R_{max}, but did not alter K_{CaF}. Thus R increased at any given $[Ca^{2+}]_i$. These effects of hypoxia remain unexplained; however, in the case of fura 2, they were probably not due to photobleaching, autofluorescence, or changes in intracellular pH, which were negligible, or to alterations in viscosity, energy production, or redox state (1837).

R_{max}, R_{min}, and a single intermediate value of R (R_{med}) were measured in fura 2-loaded myocytes from rat distal pulmonary arteries by perfusing the cells with normoxic or hypoxic (P_{O_2} = 112 or 34 mmHg, respectively) calibrating solutions (2005). These solutions were based on Krebs Ringer bicarbonate and contained cyclopiazonic acid, 4-bromo-A23187, and either *1)* 2.5 mM $[Ca^{2+}]$, *2)* no added Ca^{2+} and 5 mM EGTA, or *3)* the Ca^{2+} buffer dibromo-BAPTA and sufficient Ca^{2+} to yield a free $[Ca^{2+}]$ of 897 nM, as determined with a computer program (http://www.stanford.edu/~cpatton/maxc.html) that took pH, temperature, and ionic strength into account (1478). During normoxia, R_{max}, R_{min}, and R_{med} averaged 3.257, 0.535, and 1.988, respectively. These values were not changed by exposure to 4% O_2, suggesting that, unlike its effects in endothelial cells (1837), hypoxia did not alter behavior of fura 2 in PASMC. These results need to be confirmed in other laboratories and at other levels of hypoxia. As discussed below, hypoxia-induced increases in R in PASMC, as well as contractile responses in pulmonary arteries and pressor responses in isolated lungs, were inhibited by Ca^{2+}-free extracellular fluid or antagonists of Ca^{2+} influx and release. Furthermore, increases in R correlated with the degree of PASMC contraction (1753). Such observations suggest that measurements of $[Ca^{2+}]_i$ in hypoxic PASMC with fura 2 are at least qualitatively valid.

New Ca^{2+} indicators based on fluorescence resonance energy transfer are being developed. One of these (YC2.3) has been used to measure hypoxia-induced increases in $[Ca^{2+}]_i$ in PASMC (658, 2033). Although these probes offer potential advantages, such as targeting to specific intracellular sites, their utility in PASMC has not yet been established.

B) OVERVIEW OF Ca^{2+} HOMEOSTASIS. Changes in global $[Ca^{2+}]_i$ are determined by the rates at which Ca^{2+} enters and exits the cytosol; therefore, hypoxia could increase $[Ca^{2+}]_i$ in PASMC by *1)* increasing Ca^{2+} release from intracellular storage sites such as sarcoplasmic reticulum (SR) and mitochondria; *2)* increasing Ca^{2+} influx from extracellular fluid through sarcolemmal Ca^{2+} channels or Na^+-Ca^{2+} exchangers (NCX) acting in reverse mode; *3)* decreasing Ca^{2+} uptake by intracellular Ca^{2+} buffers or storage sites such as SR, which take up Ca^{2+} via sarcoplasmic-endothelial Ca^{2+}-ATPase (SERCA) pumps, and mitochondria, which take up Ca^{2+} via uniporters driven by the strong negative charge generated inside the organelle by extrusion of protons during electron transport; and *4)* decreasing Ca^{2+} efflux to extracellular fluid through plasma membrane Ca^{2+}-ATPase (PMCA) pumps or NCX acting in forward mode. The kinetic relationships among these processes are complex and inadequately characterized, making the determinants of time-dependent changes in $[Ca^{2+}]_i$ difficult to resolve (502).

Providing it is short enough to avoid depletion of intracellular Ca^{2+}, removal of extracellular Ca^{2+} can be a useful intervention in the initial analysis of $[Ca^{2+}]_i$ responses; however, only a few studies have reported the effects of hypoxia on $[Ca^{2+}]_i$ in PASMC exposed to Ca^{2+}-free conditions. In myocytes from rat main pulmonary artery, removal of extracellular Ca^{2+} did not affect a large initial increase in $[Ca^{2+}]_i$ generated by the oxygen scavenger sodium dithionite, but abolished a subsequent smaller sustained increase in $[Ca^{2+}]_i$ (1697). The effects of Ca^{2+}-free perfusate on $[Ca^{2+}]_i$ responses to authentic hypoxia in rat distal PASMC perfused at 37°C were similar, as shown in **FIGURE 8*A***. These results indicate that the early increase in $[Ca^{2+}]_i$ was due to Ca^{2+} release from intracellular storage sites, while the late increase in $[Ca^{2+}]_i$ was due to Ca^{2+} influx. Qualitatively similar results were obtained in myocytes from distal pulmonary arteries of rabbit (924), dog (1382, 1383), and human (1889) exposed to authentic hypoxia; however, severe hypoxia was administered in the absence of extracellular glucose in rabbit PASMC (924); a

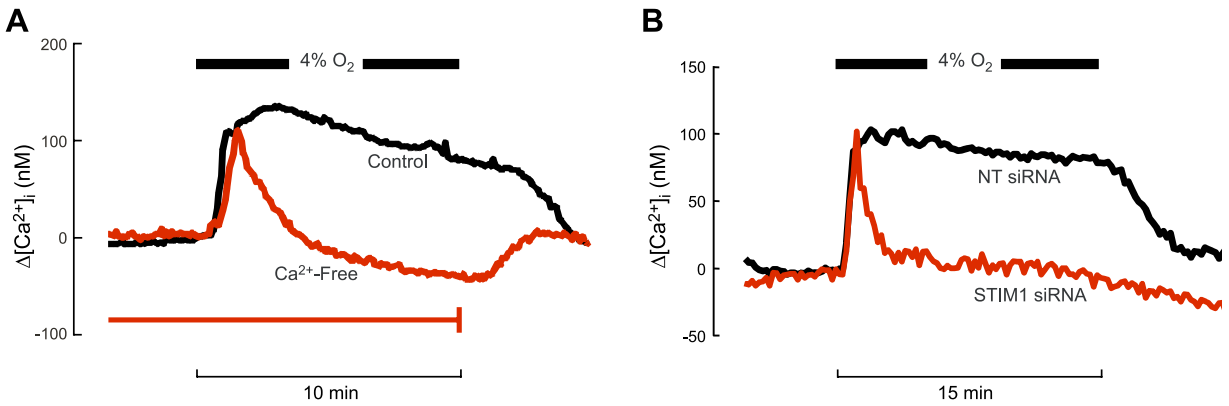


FIGURE 8 Effects of acute hypoxia (4% O_2) on intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in rat distal pulmonary arterial smooth muscle cells exposed to normal (Control) or Ca^{2+}-free perfusates (2002) (*A*) and normal perfusate after treatment with nontargeted small interfering RNA (NT siRNA) or siRNA targeted to stromal interaction molecule 1 (STIM1 siRNA) (1138) (*B*).

small initial increase in $[Ca^{2+}]_i$ was followed by a rapid fall to levels well below the normoxic baseline in canine PASMC (1382, 1383), suggesting that a high level of Ca^{2+} influx was required to maintain basal $[Ca^{2+}]_i$; and the duration of hypoxic exposure was only 4 min in human PASMC (1889). In distal PASMC from fetal lambs, decreasing extracellular $[Ca^{2+}]$ to 100 nM abolished the gradual increase in $[Ca^{2+}]_i$ caused by hypoxia (341).

In general, these results are consistent with vasoconstrictor responses measured in isolated pulmonary arteries (413, 598, 900, 1104, 1641) and lungs (500, 2039), where Ca^{2+}-free perfusate either abolished HPV or reduced it to a small transient constriction. Collectively, the data indicate that in PASMC hypoxia causes the sum of Ca^{2+} release and influx to exceed the sum of Ca^{2+} efflux and uptake. The effects of hypoxia on each of these processes, which are subserved by different organelles, is discussed below.

c) SARCOPLASMIC RETICULUM. *I) Ca^{2+} release channels*. In vascular smooth muscle, Ca^{2+} release is caused primarily by activation of channels in the SR membrane known as ryanodine receptors (RyR) and inositol 1,4,5-trisphosphate receptors (IP_3R) (932). Pharmacologically, RyR can be activated by caffeine and blocked by ryanodine, whereas IP_3R can be activated by agonists of G protein- or tyrosine kinase-linked receptors and blocked by xestospongin C (XeC) or 2-aminoethoxydiphenyl borate (2-APB) (160, 234, 268, 577, 1030, 1048, 1205, 1292, 1700). RyR and IP_3R each have three subtypes (RyR1–3; IP_3R1–3), all of which have been detected in PASMC (436, 2150, 2201, 2212, 2213). In myocytes from rat intralobar pulmonary arteries, immunostaining was positive for RyR1 and RyR2 in subsarcolemmal regions and RyR1 and RyR3 in perinuclear regions (2150). Moreover, RyR2 mRNA was 15–20 times more abundant than RyR1 or RyR3 mRNA (2150); however, this difference was not confirmed in cells from "resistance" pulmonary arteries of mice, where expression of RyR1, RyR2, and RyR3 mRNA was similar (2212). The functional significance of these differences is unknown.

The principal regulator of RyR and IP_3R is thought to be Ca^{2+} itself, which is stimulatory at low concentrations and inhibitory at high concentrations (161, 545). Activation of IP_3R by Ca^{2+} is facilitated by binding of IP_3, which is produced from phosphatidylinositol 4,5-bisphosphate (PIP_2) in a reaction catalyzed by phospholipase C (PLC) upon binding of an agonist to its G protein- or tyrosine kinase-linked receptor (176, 374, 1356, 1416, 1731). Local increases in $[Ca^{2+}]_i$ due to Ca^{2+} release from IP_3R or other sources cause Ca^{2+}-induced Ca^{2+} release (CICR) from RyR, which may be facilitated by binding of cADPR to the channel or an associated regulatory protein (580, 1049, 1051). cADPR is synthesized from nicotine adenine dinucleotide (NAD^+) by an ADP-ribosyl cyclase (perhaps CD38 or CD157) and activates RyR in many cells, including vascular smooth muscle (926, 1083–1086, 1293, 2142, 2180, 2187).

A) RyRs. The most common approach to evaluate the role played by RyR in HPV has been to determine the effects of ryanodine, a polycyclic polyhydroxylic diterpene found in the wood of *Ryania* trees. At nanomolar to low micromolar concentrations, this agent is thought to increase open probability and decrease conductance of RyR, thereby locking the channel in an open state of reduced conductance, eventually leading to depletion of its store; however, if SERCA are active and Ca^{2+} influx is possible, depletion may not be complete (522, 847, 932, 1030, 1857). At moderate micromolar concentrations, ryanodine is thought to cause irreversible closure of RyR.

At 5–300 μM, ryanodine inhibited hypoxia-induced increases in $[Ca^{2+}]_i$ in PASMC exposed to normal extracellular $[Ca^{2+}]$ (598, 1963, 2213), constriction in pulmonary arteries (436, 598, 1104, 2213), and pressor responses in isolated lungs (1322). Inhibition of hypoxic responses by

ryanodine was not always complete (1322, 2213), suggesting incomplete depletion of RyR-accessible stores, contributions by other sources of Ca^{2+}, or increased myofilament Ca^{2+} sensitivity.

To enhance depletion of SR stores accessed by RyR, ryanodine has been used with other agents. Ryanodine plus the RyR activator caffeine blocked hypoxia-induced increases in $[Ca^{2+}]_i$ in rabbit PASMC (413) and tension in rabbit, dog, and rat pulmonary arteries by ≥80% (412, 413, 876); however, some laboratories reported that ryanodine plus caffeine caused only slight inhibition of HPV in rat pulmonary arteries (1641). Adding ryanodine to Ca^{2+}-free perfusate did not alter a small transient hypoxic constriction in rat pulmonary arteries precontracted with 5-HT (900); however, vasomotor responses may have been limited by the marked reduction in 5-HT precontraction caused by Ca^{2+}-free perfusate. By itself, caffeine lowered $[Ca^{2+}]_i$ during normoxia and blocked the early transient increase in $[Ca^{2+}]_i$ caused by dithionite-induced hypoxia in rat PASMC, but only partially inhibited the steady-state increase in $[Ca^{2+}]_i$ (1697). Caffeine mimicked and prevented the inhibitory effects of dithionite-induced hypoxia on K_V currents in canine PASMC (1544) and blocked hypoxia-induced contractions in rat pulmonary arteries (1055). Overall, these results indicate Ca^{2+} release from RyR in PASMC contributes to HPV. Consistent with this conclusion, less specific inhibitors of RyR, such as ruthenium red, tetracaine, and dantrolene, also reduced $[Ca^{2+}]_i$ responses to hypoxia in PASMC (436, 2213) and hypoxic constriction in pulmonary arteries (2213).

The immunophilins, FK506 binding proteins 12 and 12.6 (FKBP12, FKB12.6), bind to RyR, thereby decreasing probability of channel opening as well as the number of openings to fractional levels of conductance (292, 1181, 1857). The resultant stabilization of the channels in a closed state and decrease in SR Ca^{2+} permeability can be reversed by the immunosuppressant drug FK506, which causes dissociation of FKBP from RyR (292, 1857). FKBP12 and FKBP12.6 mRNA have been detected in murine and equine PASMC, but only FKBP12.6 was expressed as a protein (2211). In equine PASMC, affinity chromatography indicated that FKBP12.6 protein associated with RyR2 but not RyR1 or RyR3, which were not detected. Moreover, FK506-induced increases in PASMC $[Ca^{2+}]_i$ were blocked by dialysis of patched PASMC with ryanodine or ruthenium red, and hypoxia-induced increases in $[Ca^{2+}]_i$ in PASMC and isometric force in pulmonary arteries were augmented in FKBP12.6$^{-/-}$ mice (2211). Concerns that FKBP12.6 might bind to IP_3R (234, 1181) were allayed by findings that FKBP12.6 did not associate with IP_3R on affinity chromatography and that heparin, an antagonist of IP_3R, did not alter the increased $[Ca^{2+}]_i$ induced by FK506 in patched PASMC (2211). These results suggested that RyR2 contributes to HPV.

Hypoxia-induced increases in $[Ca^{2+}]_i$ in PASMC and isometric tension in pulmonary arteries were reduced ~50% in RyR1$^{-/-}$ embryonic and RyR1$^{+/-}$ adult mice (1087) and ~30–50% in RyR3$^{-/-}$ adult mice (2213). The latter responses were further reduced by ruthenium red or tetracaine (2213). These results suggest that RyR1 and RyR3 also contribute to HPV.

Although most studies suggest that activation of RyR is required for HPV, only a few have investigated the mechanisms of this activation. As introduced in section III*A2*E, Ca^{2+} release from RyR may be activated by binding of cADPR (412, 2101) to the channel or an accessory protein, such as FKBP12.6 (1400, 1892, 2211). In support of this possibility, cADPR synthesis in distal pulmonary arteries was higher than in systemic arteries, and cADPR concentration was increased 10-fold by hypoxia (2101). In current-clamped rat PASMC, cADPR caused hyperpolarization, which was blocked by ryanodine and caffeine and therefore thought to result from activation of BK_{Ca} channels due to local release of Ca^{2+} from RyR (2101). The membrane-permeant cADPR antagonist 8-Br-cADPR did not alter the transient phase 1 HPV in pulmonary arteries or KCl-induced vasoconstriction in pulmonary arteries and isolated lungs, but abolished HPV in isolated lungs and phase 2 HPV in pulmonary arteries (412, 2101). Collectively, these results suggested that HPV required cADPR-induced release of Ca^{2+} from RyR in PASMC.

Another mechanism by which hypoxia could induce Ca^{2+} release from RyR in PASMC is alteration of channel structure through modification of sulfhydryl groups by increased ROS and/or a more oxidized redox state (see sect. III*A2*), leading to enhanced RyR activity and increased resistance to inhibition by calmodulin (CaM) and Mg^{2+} (728, 1096, 1546). Consistent with this possibility, recent results in murine PASMC suggest that hypoxia causes Ca^{2+} release through ROS-dependent dissociation of FKBP12.6 from RyR2 (1091). For example, exposure to 1% O_2 for 5 min caused dissociation of FKBP12.6 from RyR2. This dissociation was mimicked by H_2O_2 and blocked by myxothiazol in normal PASMC, and absent in PASMC overexpressing GPX but enhanced in GPX-deficient PASMC. Furthermore, the $[Ca^{2+}]_i$ response to hypoxia was increased by removal of FKBP12.6 with FK506 and decreased by RyR2 gene deletion. Whether similar results would be obtained in species other than mouse or with less severe hypoxia of longer duration is not known.

B) IP_3Rs. In contrast to RyR, there has been little direct evaluation of the role of IP_3R in HPV. In part, this may be due to the ability of hypoxia to increase PASMC $[Ca^{2+}]_i$ in the absence of exogenous agonists of G protein- or tyrosine kinase-linked receptors, suggesting that production of IP_3 was not required for the response; however, IP_3 production could occur in response to endogenous agonists. Similarly,

blockade of hypoxic responses by depletion of SR Ca^{2+} stores accessed by RyR has sometimes been interpreted to rule out a role for IP_3R; however, this conclusion would not be valid if IP_3R and RyR accessed the same SR Ca^{2+} store (see sect. III*B2*C) or hypoxia caused IP_3R-triggered CICR from RyR.

In rat proximal pulmonary arteries, norepinephrine caused monophasic increases in both isometric force and tissue IP_3 concentration, whereas hypoxia caused a biphasic contraction and did not alter IP_3 concentration (899). In canine pulmonary arteries, thapsigargin and cyclopiazonic acid, which were thought to deplete IP_3R- but not RyR-accessible SR Ca^{2+} stores, potentiated contractions to hypoxia (876). Similar observations were subsequently reported in isolated rat lungs (1322). Since this potentiation of HPV was completely blocked by removal of extracellular Ca^{2+} but only partially blocked by nisoldipine or ryanodine, it was proposed to result in part from hypoxia-induced influx of Ca^{2+} through a nisoldipine- and ryanodine-insensitive pathway (876). Such influx could result from IP_3R-dependent depletion of SR Ca^{2+} stores and hypoxic facilitation of secondary store-operated Ca^{2+} entry (SOCE; see sect. III*B2*D); however, subsequent studies suggested that cyclopiazonic acid did not potentiate hypoxic constriction in rat pulmonary arteries (412, 1641) and the IP_3R antagonist, xestospongin C, did not alter the increase in SOCE caused by hypoxia in canine distal PASMC (1383). In contrast, xestospongin C abolished Ca^{2+} release caused by norepinephrine or hypoxia, but not caffeine, in distal rat PASMC (2002). Since Ca^{2+} release to hypoxia was also blocked by ryanodine, the latter results suggested that both IP_3R and RyR were required for hypoxic release of Ca^{2+} from SR, perhaps due to RyR activation by CICR from IP_3R or vice versa. Additional work utilizing direct measurements of Ca^{2+} release is needed to confirm that IP_3R in PASMC contribute to HPV.

II) SR Ca^{2+} stores. In PASMC, RyR and IP_3R may access common or separate Ca^{2+} stores. In saponin-skinned guinea pig pulmonary artery, two SR stores (Sα, Sβ) were identified functionally, each containing about half of total SR Ca^{2+} (847, 848). On the basis of $[Ca^{2+}]_i$ responses to caffeine and IP_3, it was concluded that RyR accessed Sα while IP_3R accessed both Sα and Sβ. Ca^{2+} release experiments in SR vesicles from bovine pulmonary artery led to similar conclusions (1844).

In canine pulmonary arteries and PASMC, depletion of SR Ca^{2+} with thapsigargin or cyclopiazonic acid blocked contraction and increases in $[Ca^{2+}]_i$ caused by phenylephrine or angiotensin II, but not caffeine (876, 882). In addition, store depletion with ryanodine plus caffeine eliminated $[Ca^{2+}]_i$ responses to caffeine but not angiotensin II (882). These results suggested that the SR Ca^{2+} stores accessed by RyR and IP_3R were independent in canine PASMC. Subsequent investigations in the same preparation indicated that SOCE was blocked by inhibitors of IP_3R but not RyR, even though activation of SOCE required simultaneous depletion of both RyR- and IP_3R-sensitive stores (1383, 2105). These results suggested that activation of SOCE was coupled to IP_3R, but not RyR.

Other studies suggest that RyR and IP_3R access a common SR Ca^{2+} store. In rat pulmonary arteries skinned with β-escin and exposed to an extracellular free $[Ca^{2+}]$ of 300 nM, thapsigargin or cyclopiazonic acid (CPA) inhibited contractile responses to both norepinephrine and caffeine (634). In rat PASMC, caffeine prevented Ca^{2+} release to norepinephrine or IP_3 and, conversely, depletion of SR Ca^{2+} with norepinephrine or IP_3 prevented Ca^{2+} release to caffeine (2014, 2213). In addition, as noted above, caffeine prevented Ca^{2+} release to norepinephrine or hypoxia, norepinephrine prevented Ca^{2+} release to caffeine or hypoxia, ryanodine blocked Ca^{2+} release to caffeine or hypoxia but not norepinephrine, xestospongin C blocked Ca^{2+} release to norepinephrine or hypoxia but not caffeine, and CPA prevented Ca^{2+} release to norepinephrine, caffeine, or hypoxia (2002). On this basis, it seems likely that distal rat PASMC have a single SR Ca^{2+} store, which is accessed by both RyR and IP_3R, replenished by CPA-sensitive SERCA, and depleted by hypoxia.

Similar variability has been reported in other smooth muscles (932), suggesting that SR Ca^{2+} stores may be organized differently in different vessels or species. With respect to pulmonary vessels, depletion of RyR-sensitive stores abolished ATP-induced release of Ca^{2+} from IP_3R in freshly isolated myocytes from rabbit third- or fourth-order pulmonary arteries studied at 25°C, but not in myocytes from main pulmonary artery (1958). These results suggested that RyR and IP_3R accessed a common SR Ca^{2+} store in distal "resistance" PASMC, but independent stores in proximal "conduit" PASMC. In addition, evidence suggested that RyR and IP_3R accessed separate SR Ca^{2+} stores in freshly isolated PASMC, but a common store in cultured PASMC from lobar and sublobar canine pulmonary arteries (1378). Thus both vessel locus and cell culture may affect SR Ca^{2+} storage in PASMC, and these differences may impact $[Ca^{2+}]_i$ responses to hypoxia.

III) Sarco(endo)plasmic reticulum Ca^{2+}-ATPase. Ca^{2+} is pumped from cytosol into SR/ER storage sites by sarco(endo)plasmic Ca^{2+}-ATPases (SERCA) in the SR/ER membrane. SERCA are 110-kDa proteins that belong to the P-type ion pump family (540, 1030). Pumping is initiated by binding of Ca^{2+} to the protein's cytoplasmic domain, followed by binding of ATP, autophosphorylation, and conformational changes that cause release of Ca^{2+} into the SR/ER lumen (1030, 1304). Simultaneous countertransport of H^+ helps maintain electrical neutrality (1071). SERCA are encoded by three genes: SERCA1, expressed mainly in fast-twitch skeletal muscle; SERCA2,

expressed mainly in cardiac, slow-twitch skeletal, and smooth muscle; and SERCA3, which is expressed more ubiquitously (540, 1030, 2122). Two splice variants of SERCA2 (SERCA2a and SERCA2b) have been detected in vascular smooth muscle, including pulmonary artery (465). Affinities for Ca^{2+} and ATP, expressed as K_m, are ~0.5 and 700 μM, respectively (670). SERCA2 is thought to be regulated mainly by phospholamban, a 52-amino acid protein that forms homopentamers in SR membrane and increases SERCA2 activity upon phosphorylation (1030). For example, phosphorylation of phospholamban by protein kinase G may increase SERCA2 activity and thereby contribute to the decrease in $[Ca^{2+}]_i$ caused by NO (1576, 1577). Phospholamban expression in pulmonary artery appears to vary widely among species (465). The functional significance of this variation is unknown.

SERCA can be blocked with thapsigargin or CPA (1030). Thapsigargin is a sesquiterpene lactone obtained from plants of the genus *Thapsia*. At concentrations of 0.1–10 μM, thapsigargin locks SERCA in a Ca^{2+}-free state causing virtually irreversible inhibition (191, 418, 634, 843, 876, 1030, 1697, 1777, 1844, 1929, 2014). At micromolar concentrations, thapsigargin can also inhibit Ca^{2+} influx through store-operated Ca^{2+} channels (SOCC) (597) and VOCC (243, 1371, 1662). CPA is an indole tetramic acid metabolite produced by molds such as *Aspergillus* and *Penicillium*. At concentrations of 10–30 μM, CPA decreases the affinity of SERCA for ATP, leading to rapid and reversible inhibition (412, 634, 876, 882, 925, 1030, 1377, 2004, 2005, 2014). Like thapsigargin, high CPA concentrations may also inhibit store-operated Ca^{2+} entry (1206) but, unlike thapsigargin, CPA does not inhibit voltage-operated Ca^{2+} channels (1030).

When SERCA are blocked, the poorly understood but well documented leakage of Ca^{2+} from SR causes depletion of SR Ca^{2+} stores (248). Thus, in PASMC exposed to Ca^{2+}-free extracellular solutions, thapsigargin and CPA usually cause transient increases in $[Ca^{2+}]_i$ (1377, 2004, 2005), the magnitude and duration of which will depend on how much Ca^{2+} leakage from SR exceeds the sum of Ca^{2+} uptake by mitochondria, sequestration by intracellular buffers, and efflux by plasma membrane Ca^{2+}-ATPase and/or forward Na^+-Ca^{2+} exchange. In the presence of extracellular Ca^{2+}, increases in $[Ca^{2+}]_i$ induced by thapsigargin and CPA are sustained (1777), presumably due to Ca^{2+} influx through sarcolemmal store-operated Ca^{2+} channels and possibly other pathways, such as voltage-operated Ca^{2+} entry (VOCE) due to depolarization resulting from Ca^{2+}-dependent alteration of sarcolemmal ion channel activity.

Both thapsigargin and dithionite-induced hypoxia caused biphasic (early transient, late sustained) increases in $[Ca^{2+}]_i$ in myocytes from rat main pulmonary artery exposed to normal extracellular $[Ca^{2+}]$ (1697). Moreover, thapsigargin prevented the response to hypoxia. On the basis of this and other evidence, it was proposed that thapsigargin and hypoxia acted by common mechanisms and that the early transient increase in $[Ca^{2+}]_i$ was due to Ca^{2+} release from SR stores, while the late sustained increase was due to influx through store-operated Ca^{2+} channels. Similar results were obtained with authentic hypoxia (598). Like thapsigargin and CPA, authentic hypoxia increased $[Ca^{2+}]_i$ and membrane potential in rat PASMC and isometric force in deendothelialized rat pulmonary arteries. In addition, responses to authentic hypoxia were blocked by thapsigargin or CPA.

Similarities in the effects of hypoxia and SERCA antagonists on PASMC $[Ca^{2+}]_i$ suggest that hypoxia could act by inhibiting SERCA pumps. In rat pulmonary arteries, hypoxic inhibition of SERCA was proposed to trigger phase 1 hypoxic contraction because CPA, which inhibits SERCA, blocked phase 1 contraction; 8-bromo-cADPR, which inhibits cADPR-induced release of SR Ca^{2+} from RyR, blocked phase 2 contraction; and ryanodine plus caffeine blocked both phase 1 and phase 2 contraction (412). This proposal assumes that CPA did not deplete SR Ca^{2+} stores accessed by RyR, which is controversial (see sect. III*B2*c). Moreover, the same investigators found that 8-bromo-cADPR completely blocked HPV in isolated lungs, suggesting that phase 1 hypoxic contraction in isolated pulmonary arteries (and the hypoxic inhibition of SERCA proposed to cause it) may not be relevant to HPV in vivo. In addition, other indirect data question whether the effects of hypoxia and SERCA antagonists on PASMC $[Ca^{2+}]_i$ are indeed similar. Thapsigargin or CPA had little or no effect on normoxic tone and either did not alter or enhanced sustained HPV in pulmonary arteries (412, 876) or isolated lungs treated with inhibitors of cyclooxygenase and NOS (1322).

If it occurs, hypoxic inhibition of SERCA could be due to an hypoxia-induced increase in ROS, which were shown to inhibit SERCA in systemic vascular smooth muscle (671, 1861), or a decrease in mitochondrial ATP production sufficient to limit SERCA activity, as may occur during anoxia in rat sensory neurons (768). Neither possibility has been directly tested in PASMC; however, hypoxia did not alter [ATP] in resting or precontracted pulmonary arteries (1044, 1045). Furthermore, SERCA seemed to prefer ATP produced by glycolysis (402), which hypoxia enhanced (1041, 1044, 1045). Conversely, in isolated pulmonary arteries, the absence of extracellular glucose decreased [ATP] but had no effect on the $[Ca^{2+}]_i$ response to hypoxia while abolishing phase 2 without altering phase 1 HPV (1041, 1045). These results argue against the possibility that hypoxia triggered an increase in PASMC $[Ca^{2+}]_i$ by inhibiting SERCA through an effect on [ATP]. Nevertheless, since vasomotor tone and $[Ca^{2+}]_i$ are affected by multiple processes, direct assessments of SERCA activity will be necessary to determine if and how hypoxia alters Ca^{2+} uptake by

SERCA in PASMC, and the impact of these effects on the $[Ca^{2+}]_i$ response to hypoxia.

D) SARCOLEMMA. *I) Ca^{2+} influx channels. A) Voltage-operated Ca^{2+} channels*. Voltage-operated Ca^{2+} channels have been classified on the basis of molecular, electrophysiological, and pharmacological characteristics (270). In vascular smooth muscle, VOCC are either T type (transient) or L type (long lasting) and identified by specific pore-forming α_1 proteins containing the channel's voltage sensor, gating apparatus, and regulatory sites (270). All three subtypes of T-type channels, $Ca_V3.1$ (α_{1G}), $Ca_V3.2$ (α_{1H}), and $Ca_V3.3$ (α_{1I}), were detected in human PASMC by quantitative PCR (1649). Protein for $Ca_V3.1$, which was the most abundant in terms of mRNA, was detected by immunostaining in tunica media of pulmonary arteries and the perinuclear region of PASMC but only sparsely expressed in sarcolemma, perhaps explaining the infrequent occurrence of T-type currents in these cells (345, 1649). These currents are characterized by rapid activation at relatively negative membrane potentials, small unitary conductance, rapid inactivation, sensitivity to inhibition by the nonspecific Ca^{2+} channel antagonist mibefradil (Ro-40–5967), and insensitivity to agents that block L-type channels (269, 270, 345, 1504). Although the role of T-type VOCC in vascular smooth muscle remains unclear (345), mibefradil (but not the L-type VOCC antagonist, diltiazem) or siRNA knockdown of $Ca_V3.1$ blocked proliferation of human PASMC in culture, suggesting a requirement for $Ca_V3.1$ in cell cycling (1649). In addition, mibefradil but not L-type VOCC antagonists blocked NO-suppressible vasoconstriction in chronically hypoxic hypertensive rat lungs, suggesting that Ca^{2+} influx through T-type VOCC may have contributed to this vasomotor response (1336); however, such conclusions are compromised by the nonspecificity of mibefradil, which can also block Na^+, K^+, and Cl^- channels, in addition to nonselective cation channels such as SOCC (345). Indeed, lack of specific antagonists of T-type VOCC has been a major impediment to research in this area. Whether T-type VOCC play a role the $[Ca^{2+}]_i$ response to acute hypoxia in PASMC is not known.

Of four subtypes of L-type VOCC ($Ca_V1.1$-$Ca_V1.4$), $Ca_V1.2$ is predominantly expressed in vascular smooth muscle. $Ca_V1.2$ is composed of an α_{1C} protein and auxiliary $\alpha_2\delta$, β, and γ subunits, and characterized by relatively slow voltage-dependent inactivation, large single-channel conductance, and specific inhibition by dihydropyridines (nifedipine), phenylalkylamines (verapamil), and benzothiazepines (diltiazem) (269, 270, 2071). Although activation of L-type VOCC is generally thought to require relatively high membrane potentials, data in tracheal smooth muscle cells suggest that activation may occur at voltages very close to resting membrane potential (535). In this case, small depolarizations could activate the channel and enhance Ca^{2+} influx, while small hyperpolarizations could have the opposite effect (1372, 1670); however, nifedipine or removal of extracellular Ca^{2+} did not alter baseline $[Ca^{2+}]_i$ in rat PASMC, suggesting that the voltage required for activation in these cells exceeded resting membrane potential, which averaged −38 mV (1773).

L-type Ca^{2+} currents have been demonstrated in rabbit and rat PASMC (315, 549, 550, 2173). Current density was greater in cells from distal than proximal pulmonary arteries (549). Nifedipine blocked the increase in $[Ca^{2+}]_i$ caused by depolarization in distal PASMC (86, 2005). Expression of mRNA for α_{1C} or β subunits was detected in PASMC from fetal sheep (1615) and humans (628, 1649), respectively. Microscopic autoradiography demonstrated selective binding of dihydropyridine radioligands to tunica media of human (40) and rat (1624) pulmonary arteries. Immunostaining of lung slices revealed the presence of $Ca_V1.2$ protein in rat pulmonary arterial smooth muscle (376). These studies confirm that PASMC contain L-type VOCC.

As discussed above, hypoxia depolarized PASMC (see sect. III*B1*B), and removal of extracellular Ca^{2+} prevented sustained hypoxia-induced increases in PASMC $[Ca^{2+}]_i$ (see sect. III*B2*B). In addition, antagonists of L-type VOCC abolished or reduced $[Ca^{2+}]_i$ responses to hypoxia in PASMC (86, 340, 1958, 2005, 2054), whereas these responses were potentiated by the VOCC facilitator BAY K 8644 (340). These data were consistent with results in isolated pulmonary arteries, where hypoxia caused increases in $[Ca^{2+}]_i$ (1639), depolarization (739, 740, 816, 1157), and constriction that was inhibited by L-type VOCC antagonists or removal of extracellular Ca^{2+} (740, 900, 1043, 1104, 1715) and potentiated by BAY K 8644 (1418, 1652). Similarly, HPV was moderately to strongly inhibited by L-type VOCC antagonists in isolated lungs (1242, 1596, 1851, 2039) and intact animals (1826, 1943), including humans (1347), and potentiated by BAY K 8644 in intact and isolated lungs (1241, 1920, 2161). These results indicate that Ca^{2+} influx through L-type VOCC contributes significantly to HPV and the increase in $[Ca^{2+}]_i$ caused by hypoxia in PASMC.

In addition to depolarization, Ca^{2+} influx through L-type VOCC could result from a shift of the channel's voltage-current relation to more negative potentials. This was observed in rabbit distal PASMC patched-clamped at room temperature, where a P_{O_2} of ~20 mmHg caused a shift of −6 mV and potentiated currents between 0 and −30 mV (549). Such effects, which have not been reported by other laboratories, could facilitate voltage-operated Ca^{2+} influx at small or even absent depolarizations. Interestingly, hypoxia had the opposite effect in proximal PASMC and myocytes from systemic arteries, where shifts of +5 to +8 mV inhibited currents between 0 and −30 mV (549–551, 1798). Although it is well recognized that L-type VOCC are regulated by phosphorylation (269, 1231) and redox state

(304, 503, 824), the mechanisms of these hypoxic effects remain unknown.

Other data suggest that Ca^{2+} influx through L-type VOCC is not the whole story in HPV. Antagonists of L-type VOCC inhibited but did not completely block $[Ca^{2+}]_i$ responses to hypoxia in PASMC (340, 1697, 1889, 2005). During hypoxia in rat pulmonary arteries precontracted with $PGF_{2\alpha}$, L-type VOCC antagonists partially inhibited phase 1 increases in $[Ca^{2+}]_i$ and tension, but did not alter sustained phase 2 increases in these variables so long as the level of normoxic "pretone" was maintained by upward adjustment of $PGF_{2\alpha}$ concentration (1641), suggesting that inhibition of HPV by L-type VOCC antagonists reported by other laboratories could be a nonspecific effect of decreased basal tone (1445, 1652). Strikingly, phase 2 responses remained unaltered even after depolarization with 80 mM KCl in the presence of an L-type VOCC antagonist. These results have not been confirmed by other laboratories, but are consistent with earlier reports that L-type VOCC antagonists were not always effective at blocking HPV in pulmonary arteries (393, 394, 1418, 1652, 2116, 2190) or intact lungs (1258, 1347, 1596, 1943, 2161). On the other hand, these agents were reasonably effective at blocking HPV in isolated lungs (947, 1242, 1851, 2039), suggesting that the contribution of Ca^{2+} influx through VOCC may vary among preparations.

B) Store- and receptor-operated Ca^{2+} channels. Store-operated Ca^{2+} channels are activated by decreased $[Ca^{2+}]$ in the SR/ER lumen. This can result from inhibition of SERCA pumps, activation of IP_3R or RyR, or exposure to intracellular Ca^{2+} chelators. The resulting Ca^{2+} influx, known as store-operated or capacitative Ca^{2+} entry (SOCE, CCE), is thought to replete SR/ER stores and signal cellular responses (1459, 1460). Receptor-operated Ca^{2+} channels (ROCC) are activated by binding of an agonist directly to a receptor that is also a channel, such as binding of ATP to P2X receptors (954), or by second messengers produced in response to binding of an agonist to a receptor distinct from the channel, such as diacylglycerol produced in response to binding of norepinephrine to α_1-adrenoreceptors (1233, 1607). Agonists that activate ROCC in PASMC could originate either intrinsically or extrinsically, e.g., endothelin-1, a pulmonary vasoconstrictor usually assumed to originate in endothelial cells, can also be produced by PASMC (108, 1179, 1252, 1893, 2154, 2183). Inasmuch as some second messengers (e.g., IP_3) release Ca^{2+} from SR, SOCE may accompany receptor-operated Ca^{2+} entry (ROCE).

Because SOCC and ROCC can be permeable to Ca^{2+}, Na^+, and other cations and may be composed of similar proteins (1233), they have been collectively referred to as nonselective cation channels (NSCC). Depending on their number and unitary conductance, NSCC activation could cause depolarization and secondary Ca^{2+} entry through VOCC. Moreover, increases in $[Ca^{2+}]_i$ resulting from store- or receptor-operated Ca^{2+} influx could alter activity of K^+ or Cl^- channels, leading to depolarization and Ca^{2+} influx through VOCC. These possibilities emphasize the need for more rigorous definitions of SOCC and ROCC, which should be forthcoming when their molecular identities are known (884, 1233). In this section, we will discuss, first, the functional evidence concerning the role of SOCC and ROCC in HPV and, second, the structural protein components of these channels.

i) Functional assessment. SOCE can be assessed by removing Ca^{2+} from extracellular fluid, inhibiting SERCA pumps and L-type VOCC with antagonists such as CPA and nifedipine, and then measuring *1)* $[Ca^{2+}]_i$ as extracellular $[Ca^{2+}]$ is restored to normal or *2)* fura 2 fluorescence at 510 nm after excitation at 360 nm as extracellular $[Mn^{2+}]$ is increased from 0 to 100–200 μM. In the former, SOCE is evaluated from the immediate increase in $[Ca^{2+}]_i$ caused by restoration of extracellular $[Ca^{2+}]_i$, and in the latter, from the rate at which fura 2 fluorescence is quenched by Mn^{2+}, which enters the cell as a Ca^{2+} surrogate. Because Mn^{2+} decreases fura 2 fluorescence excited at 360 nm, which is isosbestic for Ca^{2+}, the decrease is assumed to result from Mn^{2+} alone and its rate to be proportional to the rate that Ca^{2+} would enter the cell if Ca^{2+} were present in extracellular fluid.

Neither method is foolproof. In the case of Ca^{2+} restoration, the increase in $[Ca^{2+}]_i$ could be influenced by alterations of SOCC activity (1134), PMCA pump activity (974, 1808), Na^+/Ca^{2+} exchange (184), and Ca^{2+} uptake by mitochondria and intracellular buffers (1460). In the case of Mn^{2+} quenching, the decrease in fura 2 fluorescence could be influenced by Mn^{2+}-dependent alteration of intracellular regulatory mechanisms (1459). Both approaches are susceptible to alteration of membrane potential and influx through channels other than SOCC (1459, 1460).

At present, the gold standard for assessment of SOCE is direct measurement of ion currents induced by depletion of SR/ER Ca^{2+} stores in patch-clamped cells under conditions that isolate Ca^{2+} currents and permit control of membrane potential and $[Ca^{2+}]_i$ (1459, 1460). Although this approach eliminates many of the problems associated with the other methods, it has problems of its own, including potential washout of important intracellular constituents, unphysiological composition of intracellular solutions, insensitivity to small currents, and the need to make measurements at room temperature to limit channel "rundown" (1459, 1460). Consequently, most investigators use a combination of methods to assess SOCE.

Similar approaches have been used to evaluate ROCE (1095, 1889, 2054). In this case, the second messenger di-

acylglycerol or an analog such as 1-oleoyl-2-acetyl-*sn*-glycerol (OAG) is substituted for the SERCA antagonist; however, Ca^{2+} entry stimulated in this manner presumably does not include receptor-operated influx stimulated by other second messengers, such as IP_3, or direct agonist-dependent activation of a receptor that is also a channel. To avoid these uncertainties, an alternative approach is to measure the effects of an appropriate receptor agonist on $[Ca^{2+}]_i$ in PASMC after VOCE is blocked and SOCE is stable (893).

Restoration of extracellular Ca^{2+} after depletion of SR Ca^{2+} stores in Ca^{2+}-free media increased $[Ca^{2+}]_i$ in distal pulmonary arteries of rat (677, 893, 1641, 1807) and PASMC of dog (418, 812, 1382, 1383, 1768, 2105), human (627, 628, 1863, 2195, 2196), rabbit (924, 925), rat (1009, 1095, 1230, 1377, 2004–2006, 2168), and fetal sheep (1616). Similarly, depletion of SR Ca^{2+} stores increased the rate of Mn^{2+} quenching in distal rat pulmonary arteries (893, 1641) and PASMC from dog (1382, 2105), human (627), rabbit (925), rat (1095, 1377, 1807, 2004–2006), and fetal sheep (1616). Measurements of store-operated currents have been made in patch-clamped PASMC from human (628, 1863, 2168), rat (1230, 1377, 1807), and dog (2104). Current-voltage relationships demonstrated reversal potentials close to 0 mV, consistent with NSCC. Whole cell store-operated current magnitude has varied considerably. Similarly, estimation of single-channel currents in repeatedly passaged human (628) and freshly isolated rat (1807) PASMC indicated unitary conductances of 5 and 30 pS, respectively, suggesting differences due to species or cell culture. In general, indices of SOCE were insensitive to antagonists of L-type VOCC, but inhibited by agents thought to block SOCC, such as La^{3+} (925, 1095, 1641, 1807, 2004), Ni^{2+} (628, 893, 1230, 1377, 1382, 2004, 2105), Gd^{3+} (1807), Cd^{2+} (1377), SKF-96365 (418, 1377, 1382, 1768, 2004, 2005, 2168), and 2-APB (1383, 1807). Collectively, these data indicate that SOCE is present in PASMC.

As discussed in section III*B*2c, hypoxia causes release of Ca^{2+} from SR, and therefore could elicit SOCE. Indeed, this possibility was proposed in 1993 to explain observations that caffeine or thapsigargin inhibited the increase in $[Ca^{2+}]_i$ caused by dithionite-induced hypoxia in rat PASMC (1697). More recently, hypoxia was shown to increase the rate of Mn^{2+} quenching in distal PASMC from rat (2005) and dog (1382) during perfusion with physiological salt solutions containing VOCC antagonists. In murine distal PASMC, hypoxia increased cation currents measured in the presence of Cs and nifedipine (2054). In rat and canine PASMC (1382, 2005), this influx was abolished by SKF-96365 and Ni^{2+} at concentrations that blocked CPA-induced SOCE but not KCl-induced VOCE in normoxic PASMC (2004). Moreover, the increase in $[Ca^{2+}]_i$ caused by hypoxia was also inhibited by SKF-96365, Ni^{2+}, or removal of extracellular Ca^{2+} (2005). These data indicate that Ca^{2+} entry through SOCC and/or store-independent Ca^{2+} channels sensitive to SKF-96365 or Ni^{2+} (1641) is an essential component of the PASMC response to hypoxia.

Hypoxia was also found to enhance SOCE induced by CPA (1139, 2005). This could occur if hypoxia plus CPA caused greater SR Ca^{2+} release and depletion than CPA alone; however, in rat distal PASMC exposed to Ca^{2+}-free perfusate, Ca^{2+} release induced by CPA prevented subsequent release of Ca^{2+} in response to caffeine, norepinephrine, or hypoxia, consistent with complete depletion of SR Ca^{2+} by CPA (2002). Alternatively, hypoxia could enhance CPA-induced SOCE via facilitating effects on the channels or the transduction pathways linking SR store depletion to channel activation. Against this possibility, hypoxia did not alter the increase in $[Ca^{2+}]_i$ caused by restoration of extracellular Ca^{2+} in freshly isolated canine PASMC after store depletion with a "cocktail" consisting of CPA, ryanodine, caffeine, and 5-HT (1382); however, removal of extracellular Ca^{2+} alone caused marked reduction in basal $[Ca^{2+}]_i$, suggesting that basal influx was already very high and perhaps could not be further increased in this preparation.

Several hypotheses have been proposed to explain transduction of SOCE. Depletion of SR/ER Ca^{2+} could *1)* release a small phosphorylated compound (Ca^{2+} influx factor) from SR, which diffuses to plasma membrane and induces SOCE (1588, 1931), perhaps by liberating membrane lysophospholipids through activation of phospholipase A_2 (1799, 1800); *2)* reduce $[Ca^{2+}]_i$ in a restricted space between SOCC and SR, leading to reversal of Ca^{2+}-dependent SOCC inactivation (115, 1558); *3)* trigger fusion of SOCC-containing intracellular vesicles with plasma membrane (30, 2152); and *4)* decrease binding of Ca^{2+} to the COOH-terminal domain of IP_3R within the depleted SR lumen, causing a conformational change in the receptor that promotes an activating interaction of the receptor's cytoplasmic head with SOCC (159, 855, 1477, 1560). The last hypothesis is based on the generally accepted notion of physical interaction between RyR and VOCC in skeletal muscle (522), and is known as conformational coupling. Conformational coupling has also been suggested to explain activation of SOCE by RyR (969).

Recently, a new type of conformational coupling has been proposed, in which stromal interaction molecule 1 (STIM1), a 90-kDa transmembrane protein found mainly in SR/ER, mediates activation of SOCC (774, 1077, 1288, 1559). According to this hypothesis, decreased $[Ca^{2+}]$ in the SR/ER lumen causes dissociation of Ca^{2+} from an EF-hand motif in the intraluminal NH_2-terminal region of STIM1, leading to aggregation of STIM1 proteins at "puncta" in close proximity to SOCC in plasma membrane, interaction of STIM1 with SOCC or its regulatory proteins, and channel activation (774, 2124, 2199). Although originally demonstrated in HeLa (1099) and *Drosophila* S2 cells

(1659), STIM1 is now known to be required for SOCE in many cell types, including smooth muscle (408, 1488, 1880). STIM1 is also expressed in PASMC (1138, 1139, 1379), and both STIM1 expression and $[Ca^{2+}]_i$ responses to acute hypoxia were greater in rat distal than proximal PASMC, whereas VOCE was the same (1139). Moreover, knockdown of STIM1 by RNA interference in rat distal PASMC markedly reduced SOCE (1138, 1379) and the sustained $[Ca^{2+}]_i$ response to hypoxia without altering the initial transient $[Ca^{2+}]_i$ response to hypoxia or VOCE (1138) **(FIGURE 8*B*)**. These results indicate that the sustained increase in $[Ca^{2+}]_i$ induced by hypoxia in these cells required SR Ca^{2+} release and STIM1-dependent activation of SOCC. A related protein, STIM2, was also expressed in PASMC, albeit in much smaller quantities than STIM1 at the mRNA level (1138, 1139). Furthermore, STIM2 knockdown had only a small effect on SOCE and did not alter the $[Ca^{2+}]_i$ response to hypoxia (1138). These results suggest that STIM2 plays a minor role in SOCE and apparently no role in the $[Ca^{2+}]_i$ response to hypoxia in PASMC.

In addition to the above hypotheses, numerous studies suggest that G proteins, PKC, tyrosine kinase, cGMP, and other factors may be involved in the transduction process (159, 1459). Moreover, electrophysiological studies in portal vein myocytes indicate that PKC and CaM may activate SOCC independently of Ca^{2+} store depletion (24). Whether these mechanisms contribute to the effects of hypoxia on SOCE in PASMC is not known.

In rat distal PASMC, SKF-96365 and $NiCl_2$ blocked $[Ca^{2+}]_i$ responses to hypoxia and SOCE but not VOCE, while nifedipine blocked $[Ca^{2+}]_i$ responses to hypoxia and VOCE but not SOCE (2005). In isolated rat lungs, SKF-96365 and $NiCl_2$ blocked HPV but not pressor responses to KCl, while nifedipine blocked responses to both hypoxia and KCl (2039). These results suggest that HPV requires influx of Ca^{2+} through both SOCC and VOCC.

One possible explanation for this dual requirement is that neither SOCE or VOCE on their own increased PASMC $[Ca^{2+}]_i$ sufficiently to trigger contraction. Alternatively, increases in $[Ca^{2+}]_i$ due to SOCE and/or SR Ca^{2+} release may have inhibited K_V channels and/or activated Cl_{Ca} channels (317, 542, 1544), causing depolarization and secondary activation of VOCC (see sect. III*B1*). Because SOCC have reversal potentials near 0 mV and may be permeable to Na^+ as well as Ca^{2+}, hypoxic activation of these channels may have depolarized PASMC directly, again leading to secondary VOCE. Moreover, if Na^+ entry through activated SOCC were significant, increased $[Na^+]_i$ and depolarization could promote Ca^{2+} influx via reverse-mode Na^+-Ca^{2+} exchange, as discussed below in this section. More investigation is needed to evaluate these possibilities.

ii) Structural assessment. In vascular smooth muscle, store-operated channels may be composed of mammalian homologs of the transient receptor potential (TRP) and TRP-like (TPRL) proteins that form plasmalemmal cation channels in photoreceptor cells of *Drosophila* eye (24, 407, 1306, 1460, 1515). Activation of these channels by light is mediated by rhodopsin and the PLC/phosphoinositide signaling cascade, and leads to Ca^{2+} influx and depolarization. Interestingly, TPR and TRPL channels can also be activated by hypoxia, uncoupled oxidative phosphorylation, or ATP depletion, suggesting that an ATP-dependent process is required to keep the channels closed (13).

Mammalian homologs of TRP and TRPL have been divided into six subfamilies (1393, 2123): "canonical (TRPC)," "melastatin (TRPM)," "vanilloid (TRPV)," "ankyrin (TRPA)," "polycystin (TRPP)," and "mucolipin (TRPML)." In vascular smooth muscle, the most studied of these is the TRPC subfamily, whose seven members (TRPC1–7) have been cloned and sequenced in human, mouse, rat, rabbit, and cow (1289). TRPC proteins have 25–45% homology with *Drosophila* TRP and TRPL and were linked to SOCE by appearance of SOCE after heterologous expression in cells normally without SOCE, and inhibition of SOCE after knockdown of TRPC by RNA interference in cells normally with SOCE (176, 1289, 1460). The composition of TRPC channels is still unknown, but a heterotetrameric assembly of subunits seems likely and could explain the observed diversity with respect to cation selectivity, conductance, and mechanism of activation. All TRPC have been implicated as components of SOCC; however, evidence is accumulating that TRPC1 and TRPC6 form mainly store- and receptor-operated channels, respectively (407, 851, 1460, 1977).

TRPC1, -4, and -6 were consistently detected at the mRNA and/or protein level in endothelium-denuded pulmonary arteries (1139, 2004, 2006) and PASMC (628, 1008, 1095, 1139, 1230, 1377, 1379, 1616, 1863, 1996, 2004, 2006, 2054, 2167, 2168, 2195), with two exceptions: TRPC1 mRNA was not detected in PASMC from canine main pulmonary artery (1996) and TRPC4 protein was not detected in PASMC from rat distal pulmonary artery (1095). Quantitative PCR analysis revealed that TRPC1 and -6 were expressed much more abundantly than other TRPC in myocytes from distal pulmonary arteries of mice (2054) and rats (1139, 2004). Furthermore, expression of TRPC1, -4, and -6, as well as $[Ca^{2+}]_i$ responses to hypoxia, were greater in distal than proximal rat PASMC, whereas $[Ca^{2+}]_i$ responses to KCl were the same (1139).

Results for TRPC2 (1230, 1996, 2004, 2054), TRPC3 (1095, 1139, 1230, 1377, 1616, 1996, 2004, 2054, 2167, 2195), TRPC5 (1095, 1139, 1230, 1377, 1616, 1996, 2004, 2054, 2167), and TRPC7 (1230, 1996, 2004, 2054, 2167) have been less consistent, with mRNA detected in

60–75% of studies and protein in 0–67%. This inconsistency could be due to variability in species, source of PASMC (proximal vs. distal pulmonary arteries), culture conditions (freshly isolated cells vs. prolonged culture in growth media), existence of TRPC splice variants, specificity of TRPC antibodies, and other factors.

Despite widespread documentation of TRPC expression in PASMC, relatively few studies provide direct evidence that TRPC proteins contribute to store- and/or receptor-operated Ca^{2+} entry in these cells. Ca^{2+} entry elicited by CPA was reduced in proliferating human PASMC treated with a TRPC1 antisense oligonucleotide (1863) and in growth-arrested mouse PASMC treated with an antibody against an extracellular epitope of TRPC1 (1379). In PASMC from rat (1095) and human (1889), knockdown of TRPC1 expression by RNA interference decreased Mn^{2+} quenching or $[Ca^{2+}]_i$ responses to restoration of extracellular Ca^{2+} after exposure to Ca^{2+}-free perfusate containing thapsigargin, but did not alter these responses after exposure to OAG. Conversely, TRPC6 knockdown decreased these responses in PASMC exposed to OAG, but not in cells exposed to thapsigargin. In proliferating rat PASMC cultured in the presence of ATP, knockdown of TRPC4 expression by RNA interference inhibited the $[Ca^{2+}]_i$ response to restoration of extracellular Ca^{2+} after exposure to Ca^{2+}-free perfusate containing CPA (2196). In proliferating rat PASMC cultured in the presence of platelet-derived growth factor, downregulation of TRPC6 expression by a TRPC6 antisense oligonucleotide decreased CPA-induced ion currents recorded under conditions that blocked currents through K^+ and Cl^- channels (2168). In rat distal PASMC, knockdown of TRPC1, -4, or -6 by RNA interference reduced Mn^{2+} quenching of fura 2 fluorescence after exposure to Ca^{2+}-free perfusate containing CPA (2003). Collectively, these results suggest that TRPC1, -4, and -6 contribute to SOCE and/or ROCE in PASMC.

Even fewer studies have examined the role of TRPC proteins in HPV. In isolated lungs from $TRPC6^{-/-}$ knockout mice, transient phase 1 HPV was absent, but sustained phase 2 HPV and pressor responses to U-46619 were unaltered (952, 2054). Hypoxia increased $[Ca^{2+}]_i$, Mn^{2+} quenching of fura 2 fluorescence, and cation currents through pathways other than K^+ channels or L-type VOCC in wild-type distal PASMC "primed" with endothelin-1 or angiotensin II, but had no effect in similarly treated PASMC from $TRPC6^{-/-}$ mice. Moreover, $[Ca^{2+}]_i$ responses to hypoxia were restored in $TRPC6^{-/-}$ PASMC infected with an adeno-associated virus coding for TRPC6. These findings indicate that TRPC6 was required for phase 1 HPV. Additional results suggested that TRPC6 fulfilled this requirement by forming ROCC that provided DAG-dependent Ca^{2+} influx during hypoxia. For example, both hypoxia and OAG increased cation currents in wild-type but not $TRPC6^{-/-}$ PASMC; and both hypoxia and an inhibitor of diacylglycerol kinase, which inactivates diacylglycerol, caused accumulation of diacylglycerol in wild-type and $TRPC6^{-/-}$ PASMC, but increased $[Ca^{2+}]_i$ only in wild-type PASMC (2054). The mechanisms by which hypoxia may have increased DAG and which, if any, receptors and agonists were involved remain unknown. In PASMC, it is possible that TRPC6 knockout eliminated receptor-dependent facilitation of hypoxic responses by endothelin-1 or angiotensin II, which were given to "prime" the cells. TRPC6 knockout may have had similar effects in isolated lungs, which can make "primers" of their own (1710). Nevertheless, the complete elimination of phase 1 HPV in lungs of $TRPC6^{-/-}$ mice suggests that TRPC6 contributes to HPV. Consistent with this possibility, a more recent study in multiply-passaged human PASMC reported that knockdown of TRPC6 by RNA interference had no effect on SOCE but markedly attenuated both the transient increase in $[Ca^{2+}]_i$ caused by exposure to 0% O_2 for 2.5–7.5 min and ROCE, measured as the increase in $[Ca^{2+}]_i$ caused by restoration of extracellular Ca^{2+} after exposure to Ca^{2+}-free perfusate containing OAG (1889).

The latter study also reported that knockdown of TRPC1 blocked SOCE without altering ROCE or the peak $[Ca^{2+}]_i$ response to brief severe hypoxia (1889). In contrast, knockdown of TRPC1, -4, or -6 all blocked SOCE in primary cultures of rat distal PASMC (2003). Moreover, the increase in $[Ca^{2+}]_i$ caused by exposure of these cells to 4% O_2 for 20 min was only partly inhibited by knockdown of TRPC4 or -6 but abolished by knockdown of TRPC1. Treatment of mouse PASMC with an antibody raised against TRPC1 had similar effects (1380). Taken together, these results suggest that the early transient increase in $[Ca^{2+}]_i$ caused by hypoxia could be due to TRPC6-dependent ROCE while the late sustained increase could be due to TRPC1-dependent SOCE. Additional investigation is needed to test this possibility and to determine why effects of TRPC knockdown on SOCE were inconsistent in these studies.

The prototypical SOCC is the "Ca^{2+} release activated Ca^{2+} (CRAC)" channel, which plays a major role in cells of the immune system (514, 1459, 1460). Characterized by extremely high Ca^{2+} selectivity and low unitary conductance (1460), CRAC channels are composed of the recently discovered Orai1 protein (515, 1972, 2198). Related Orai2 and Orai3 proteins may also contribute, either as channel components or regulatory components (1077, 1559). All three Orai proteins are expressed in PASMC (542, 1137, 1381). In mouse PASMC, knockdown of Orai1 expression by RNA interference reduced Mn^{2+} quenching induced by CPA and the $[Ca^{2+}]_i$ response to hypoxia (1380, 1381). It was recently proposed that a ternary complex of Orai, TRPC1, and STIM1 is required for SOCE (963, 1431). Consistent with this possibility, TRPC1 and Orai1 coimmunoprecipitated with STIM1 in mouse PASMC, and pre-

cipitation was increased in cells subjected to SR Ca^{2+} store depletion (1379, 1381). In addition, knockdown of both Orai1 and STIM1 by RNA interference decreased Mn^{2+} quenching of fura 2 fluorescence more than knockdown of Orai1 alone (1381). These results suggest that Orai proteins and/or possible complexes of Orai with TRPC and STIM proteins contribute to SOCE and $[Ca^{2+}]_i$ responses to hypoxia in PASMC.

II) Na^+/Ca^{2+} exchange and Na^+-K^+-ATPase. In mammals, plasmalemmal Na^+/Ca^{2+} exchangers belong to three branches of the Ca^{2+}/cation antiporter superfamily: *1)* the Na^+/Ca^{2+} exchanger (NCX) family, which has three members (NCX1–3) that exchange 3 Na^+ for 1 Ca^{2+}; *2)* the $Na^+/(Ca^{2+}+K^+)$ exchanger (NCKX) family, which has five members (NCKX1–5) that exchange 4 Na^+ for 1 Ca^{2+} + 1 K^+; and *3)* the Ca^{2+}/cation exchanger (CCX) family, which has one member of unknown physiological function (184, 1149, 1514). NCX1, NCKX3, and NCKX4 are expressed in vascular smooth muscle (427, 912, 1566, 1796), and NCX1 has been detected by RT-PCR and immunostaining in pulmonary arterial smooth muscle (2013, 2194, 2197). Although NCKX3 mRNA was expressed in human PASMC, NCKX3 protein was not detected, and functional studies suggested that NCKX did not contribute to Na^+/Ca^{2+} exchange in these cells (2197).

NCX are driven by the transsarcolemmal $[Na^+]$ gradient and can operate in either forward (Ca^{2+} efflux) or reverse (Ca^{2+} influx) modes, depending on intra- and extracellular concentrations of the transported ions, membrane potential, and activation state of the exchanger (184, 1149). Activation is regulated by numerous modulators, including H^+, ATP, Na^+, and Ca^{2+} (184, 1149). The regulatory effects of Na^+ and Ca^{2+} are exerted by nontransported ions and are therefore independent of effects on electrochemical gradients, e.g., forward mode operation is inhibited by high intracellular Na^+ concentration ($[Na^+]_i$), reverse mode operation is inhibited by high extracellular Na^+ concentration ($[Na^+]_e$), and both modes are activated by submicromolar $[Ca^{2+}]_i$ (184, 1514) Normally, NCX are thought to be inactive under resting conditions and to operate in forward (Ca^{2+} efflux) mode during evoked increases in $[Ca^{2+}]_i$, thereby tending to limit or reverse the increase in $[Ca^{2+}]_i$; however, inhibition of forward mode operation or operation in reverse (Ca^{2+} influx) mode could occur in response to depolarization, increases in $[Na^+]_i$, or decreases in $[Na^+]_e$. In this case, NCX would tend to increase $[Ca^{2+}]_i$.

The difference between $[Na^+]_e$ (~140 mM) and $[Na^+]_i$ (~20 mM) is due to sarcolemmal Na^+-K^+-ATPase (NKA), which pumps 3 Na^+ out of the cell in exchange for 2 K^+, thereby hyperpolarizing E_m, increasing $[K^+]_i$, and decreasing $[Na^+]_i$ (616). NKA is a P-type ATPase composed of α and β subunits (931), each of which has four isoforms expressed in a species- and tissue-dependent manner (1098). Smooth muscle contains α1 and α2 isoforms, and α2 appears to be coupled spatially and functionally to NCX (912, 913, 1308), such that NKA inhibition causes subsarcolemmal Na^+ accumulation, a degree of depolarization, and secondary increases in $[Ca^{2+}]_i$ through reverse mode operation of NCX (184, 267, 540, 872). Conversely, stimulation of NKA would deplete subsarcolemmal Na^+, hyperpolarize E_m, and decrease $[Ca^{2+}]_i$ through forward mode operation of NCX (1722). Thus NCX and NKA can be considered as a functional unit.

Experimentally, Na^+/Ca^{2+} exchange can be assessed by determining how basal $[Ca^{2+}]_i$ or $[Ca^{2+}]_i$ responses are affected by decreasing the trans-sarcolemmal $[Na^+]$ gradient, inhibiting Na^+/Ca^{2+} exchange, or altering NCX gene expression. In addition, electrophysiological techniques can be used to measure currents generated by Na^+/Ca^{2+} exchange. Because NCX exchange 3 Na^+ for 1 Ca^{2+}, these currents will be inward when the exchangers operate in forward (Ca^{2+} efflux) mode and outward when they operate in reverse (Ca^{2+} influx) mode. Decreasing the $[Na^+]$ gradient is usually accomplished by complete or partial replacement of extracellular Na^+ with choline, *N*-methyl-D-glucamine (NMDG), or Li^+. The gradient can also be decreased, albeit more modestly, by inhibiting NKA with pharmacological antagonists (ouabain, digoxin) or removal of extracellular K^+; however, the relatively modest increases in $[Na^+]_i$ achieved in these cases can inhibit forward-mode Na^+/Ca^{2+} exchange through regulatory effects on NCX. Both approaches could inhibit forward-mode or promote reverse-mode operation of NCX, resulting in augmentation and prolongation of evoked increases in $[Ca^{2+}]_i$, or even increases in basal $[Ca^{2+}]_i$.

The utility of these assessments will depend on *1)* experimental conditions, which ideally should minimize the confounding influences of other pathways contributing to Ca^{2+} homeostasis; *2)* validity of the assumption that choline, NMDG, or Li^+ simply substitute for extracellular Na^+ and do not exert effects of their own; and *3)* specificity of pharmacological agents. The first has been variably considered by investigators, and the second may be unlikely (126, 184). With respect to the third, lack of good antagonists has been a major impediment to investigation of Na^+-Ca^{2+} exchange. Currently, the most widely used agent may be KB-R7943, a putative reverse-mode antagonist (873); however, evidence suggests that KB-R7943 can also inhibit forward-mode Na^+-Ca^{2+} exchange (966), as well as L-type VOCC (174, 1442), store-operated Ca^{2+} entry (48), TRPC channels (994), mitochondrial Ca^{2+} uniporter (1703), and nicotinic ACh receptors (1517). Moreover, low concentrations of KB-R7943 depressed Ca^{2+} transients in electrically stimulated heart tubes from mouse embryos in which the Na^+-Ca^{2+} exchanger was knocked out, confirming effects on other components of Ca^{2+} signaling (1620). Newer agents are being developed and may be more specific (871, 2030),

but have not yet been used to investigate Ca^{2+} signaling in HPV. These considerations emphasize the need for more work, and careful interpretation of work already completed.

In freshly isolated rat distal PASMC, replacement of extracellular Na^+ with Li^+ did not alter basal $[Ca^{2+}]_i$, but augmented magnitude and duration of the transient increase in $[Ca^{2+}]_i$ evoked by brief exposure to 10 mM caffeine + 80 mM K^+ (2013). In cultured human PASMC, the Ca^{2+} ionophore ionomycin caused a transient increase in $[Ca^{2+}]_i$, which was enhanced by simultaneous exposure to Na^+-free perfusate (2194). In rat distal pulmonary arteries perfused with Ca^{2+}-free physiological salt solution containing CPA or thapsigargin to block SERCA, transient exposure to 1.8 mM Ca^{2+} + 30 mM K^+ + 0.44 mM Na^+ (Li^+ substitution) caused a transient increase in $[Ca^{2+}]_i$, which was slightly prolonged if $[Na^+]_e$ were maintained at 0.44 mM (126). In freshly isolated rat distal PASMC subjected to whole cell patch clamp and perfused with Na^+-free salt solution (Li^+ substitution), restoration of extracellular Na^+ caused an inward current with a reversal potential similar to that predicted for NCX (2013). To increase the likelihood that this current was in fact due to Na^+/Ca^{2+} exchange, the investigators clamped E_m and $[Ca^{2+}]_i$ at −60 mV and 1 μM, respectively, and took measures to block Na^+-K^+-ATPase, L-type VOCC, and K^+ channels. In rat PASMC from second- and third-order arteries in which E_m was clamped at −70 mV and K^+ and voltage-dependent Ca^{2+} currents were blocked, H_2O_2 generated an inward current that was abolished by removal of extracellular Na^+ (NMDG substitution) (1096). Furthermore, the general Ca^{2+} antagonist Ni^{2+} (3 mM) and the putative NCX antagonist KB-R7943 (10 μM) inhibited this current, and KB-R7943 also enhanced the increase in $[Ca^{2+}]_i$ caused by H_2O_2 (1096). Collectively, these results suggest that NCX are expressed in PASMC, are inactive during resting conditions, and operate in forward (Ca^{2+} efflux) mode during evoked increases in $[Ca^{2+}]_i$.

Reverse-mode operation may also occur. In human PASMC studied at room temperature after 4–6 passages in growth media, replacement of perfusate Na^+ with Li^+ or NMDG caused a large rapid increase in basal $[Ca^{2+}]_i$, which was unaltered by nifedipine but virtually abolished by KB-R7943 (2194, 2197). This effect was not reported in a previous study of freshly isolated rat PASMC (2013) and was not commonly observed in systemic vascular smooth muscle (962) unless extracellular K^+ was removed to inhibit Na^+-K^+-ATPase (1881). Perhaps Na^+-K^+-ATPase was inactive at room temperature in human PASMC (2194, 2197), permitting elevation of intracellular $[Na^+]$ sufficient to inhibit forward-mode and promote reverse-mode operation of NCX. Similarly, work in systemic arterial or airway smooth muscle cells suggested that endogenous inhibition of Na^+-K^+-ATPase (872) or activation of SOCC and ROCC (70, 783, 1069, 1532), which may be more permeable to Na^+ than Ca^{2+} (1233, 1460), promoted reverse-mode operation of NCX by increasing $[Na^+]_i$. Consistent with this possibility, restoration of extracellular Ca^{2+} in human PASMC perfused with Ca^{2+}-free salt solution containing CPA and nifedipine caused an increase in $[Ca^{2+}]_i$ that was partially inhibited by removal of extracellular Na^+, treatment with KB-R7943, or downregulation of NCX1 by RNA interference (2194, 2197), suggesting that the increase in $[Ca^{2+}]_i$, which normally would be attributed entirely to SOCE, was partially due to reverse (Ca^{2+} influx) mode Na^+/Ca^{2+} exchange.

The effects of hypoxia on Na^+/Ca^{2+} exchange in PASMC have been studied by few investigators. Mild hypoxia (P_{O_2} 50–60 mmHg) did not alter basal $[Ca^{2+}]_i$, but increased the magnitude and duration of the transient elevation of $[Ca^{2+}]_i$ evoked by brief exposure to caffeine and high extracellular $[K^+]$ in rat distal PASMC (2013). These effects were similar to those caused by removal of extracellular Na^+ (Li^+ substitution). The combined effects of mild hypoxia and Na^+ removal were not different from those of hypoxia alone. Moreover, mild hypoxia reduced inward currents generated by restoration of $[Na^+]_e$ to normal in PASMC subjected to perforated patch, voltage clamp (−60 mV), Na^+-free external solution, and blockade of L-type VOCC, K^+ channels, and Na^+-K^+-ATPase. These results suggested that, even though mild hypoxia did not by itself alter basal $[Ca^{2+}]_i$, it nevertheless inhibited forward-mode Na^+/Ca^{2+} exchange, thereby enhancing the increases in $[Ca^{2+}]_i$ caused by other stimuli. Consistent with this possibility, moderate hypoxia (P_{O_2} 25–50 mmHg) eliminated the $[Na^+]_e$-dependent component of relaxation after contraction of bovine pulmonary arteries with high extracellular $[K^+]$ (1698).

In contrast, the contractile response of precontracted rat pulmonary arteries to removal of extracellular Na^+ (NMDG substitution) did not mimic the response to severe hypoxia (0–1% O_2). Furthermore, the combined effects of severe hypoxia (0–1% O_2) and removal of extracellular Na^+ caused greater increases in $[Ca^{2+}]_i$ and contractile force than severe hypoxia alone (126). These results suggest that severe hypoxia did not inhibit (and may have enhanced) forward-mode Na^+/Ca^{2+} exchange. Consistent with this conclusion, treatment of arteries with ouabain plus reduction of $[Na^+]_e$ to 24 mM, which should inhibit Ca^{2+} extrusion by NCX, enhanced HPV. Finally, ouabain and KB-R7943 did not affect HPV, suggesting that reverse-mode NCX activity did not contribute to the response (126). Thus, in precontracted rat pulmonary arteries, NCX appeared to inhibit HPV, as would be expected if it were functioning in forward mode to extrude Ca^{2+}.

Although none of these results suggest that hypoxia promoted reverse-mode Na^+/Ca^{2+} exchange in PASMC, this

possibility remains worthy of pursuit in view of accumulating evidence that hypoxia activates SOCC (see sect. III*B2*, C and D), which are probably permeable to Na^+ and could trigger reverse-mode operation of NCX by increasing $[Na^+]_i$ and membrane potential.

Mechanisms by which hypoxia might alter Na^+/Ca^{2+} exchange have not been investigated. With respect to hypoxic enhancement, it is interesting to note that both severe hypoxia and H_2O_2, which has been proposed to mediate HPV (see sect. III*A2*D), increased forward-mode Na^+/Ca^{2+} exchange in pulmonary arterial smooth muscle (126, 1096). With respect to hypoxic inhibition, decreased mitochondrial ATP production could limit NKA activity, and the resultant increases in $[Na^+]_i$ and membrane potential could increase $[Ca^{2+}]_i$ by decreasing forward mode or promoting reverse-mode NCX operation. Against this possibility, [ATP] was maintained in hypoxic pulmonary arteries through upregulation of glycolysis (1041, 1044, 1045), which is the preferred source of ATP for NKA (250, 1146, 1147, 1480). Also, as noted above, ouabain did not alter HPV in rat pulmonary arteries (126). Consistent with this possibility, at higher pump rates NKA required ATP produced by oxidative phosphorylation (250), which was inhibited by hypoxia in pulmonary arteries (1041, 1044, 1045). Furthermore, ouabain caused vasoconstriction in normoxic canine pulmonary arteries and ferret lungs (500, 1408) and attenuated HPV in isolated rat lungs (769), whereas aldosterone, which stimulates NKA, potentiated HPV in isolated rat lungs (769).

The effects of hypoxia on Na^+/Ca^{2+} exchange in PASMC, the mechanisms of these effects, and the role they play in $[Ca^{2+}]_i$ responses to hypoxia remain unclear.

III) Plasma membrane Ca^{2+}-ATPase. PMCA is a P-type CaM-dependent, relatively low capacity, electrically neutral Ca^{2+}-ATPase that pumps Ca^{2+} out of the cell in exchange for extracellular H^+ (540, 858, 1453, 1846). Thus a decrease in pump activity would tend to increase $[Ca^{2+}]_i$ and pH_i, and vice versa (75). Affinity of PMCA for Ca^{2+} and ATP, expressed as K_m, is ~1 and 50 μM, respectively, and activity may be regulated by cGMP and PKC (670, 1453). Of four known isoforms, two (PMCA1, PMCA4) are expressed in most cell types, including vascular smooth muscle (669, 1171, 1454, 1846); however, detection in PASMC has not been reported. Nonspecificity of pharmacological antagonists (La^{3+}, orthovanadate, eosin, caloxins), low levels of gene expression, and unexpected phenotypes associated with gene knockout and overexpression have complicated evaluation of PMCA function (540, 858, 1453). The role of PMCA in HPV has not been studied directly, and studied indirectly only rarely. For example, potentiation of HPV by orthovanadate in isolated lungs (500, 1240, 1983) was attributed to inhibition of PMCA and/or SERCA (500).

E) MITOCHONDRIA. Since mitochondria are thought to play major roles in both O_2 sensing (see sect. III*A2*) and Ca^{2+} signaling (440, 686, 1384, 1870), it is reasonable to ask whether these organelles contribute to the increased $[Ca^{2+}]_i$ caused by hypoxia in PASMC. Mitochondria take up cytosolic Ca^{2+} by a uniporter and a so-called "rapid mode of calcium uptake (RaM)" (155, 684, 686, 878, 1531) **(FIGURE 9)**. Both mechanisms are driven by the strongly negative potential across the inner mitochondrial membrane ($\Delta\Psi_M$ approximately −180 mV) generated by extrusion of protons during electron transport. Uptake by the uniporter is activated at high $[Ca^{2+}]_i$ (>3 μM), suggesting that this pathway may not contribute to regulation of $[Ca^{2+}]_i$ under physiological conditions; however, mitochondrial $[Ca^{2+}]$ in vascular smooth muscle was found to increase during Ca^{2+} release from SR (434, 1361, 1871), and mitochondria may also take up Ca^{2+} during Ca^{2+} influx (919, 920, 925). Furthermore, mitochondria are found in close association with SR and plasma membrane (635, 1397, 1871). These observations suggest that uptake by the uniporter buffers large local increases in $[Ca^{2+}]_i$ that would otherwise occur during Ca^{2+} release and influx. Such "spatiotemporal shaping" of the $[Ca^{2+}]_i$ signal could alter Ca^{2+}-dependent activation or inactivation of nearby Ca^{2+} channels in SR and sarcolemma. Mitochondrial Ca^{2+} uptake by RaM is initiated rapidly at much lower $[Ca^{2+}]_i$, but the initially high conductivity of this pathway quickly decreases so that steady-state uptake ceases at $[Ca^{2+}]_i$ >180 nM (684, 1531). These characteristics suggest that RaM may play a role in regulation of basal $[Ca^{2+}]_i$ and/or rapid $[Ca^{2+}]_i$ transients. Although observed in several cell types, RaM has not yet been reported to occur in smooth muscle (1531). The molecular identities of the uniporter and RaM remain unknown.

After entering the mitochondrial matrix, Ca^{2+} can either be extruded or enter a high capacity, rapidly mobilizable Ca^{2+} phosphate storage pool (1384) **(FIGURE 9)**. Both processes limit increases in free mitochondrial $[Ca^{2+}]$ ($[Ca^{2+}]_M$), which can cause mitochondrial depolarization (439, 1121). An increase in $[Ca^{2+}]_M$ can also activate several TCA cycle enzymes, leading to increased NADH production, secondary enhancement of electron transport, and repolarization of $\Delta\Psi_M$ (440, 1224). This may be a mechanism by which mitochondria match energy supply to demand. Ca^{2+} can be extruded by the mitochondrial Na^+-Ca^{2+} exchanger (mNCE), mitochondrial H^+-Ca^{2+} exchanger (mHCE), or, under extreme conditions, the permeability transition pore (PTP) (155, 685, 1919) **(FIGURE 9)**. The mHCE is thought to extrude 1 Ca^{2+} ion in the mitochondrial matrix in exchange for 2 H^+ ions in the cytosol. In the case of mNCE, it is unclear whether 1 Ca^{2+} ion in the matrix is exchanged for 2 or 3 Na^+ ions in the cytosol (915). If the latter, this exchanger would be electrogenic, similar to the plasmalemmal NCX, and net entry of 1 positive charge per cycle into the matrix would help supply the energy needed to extrude

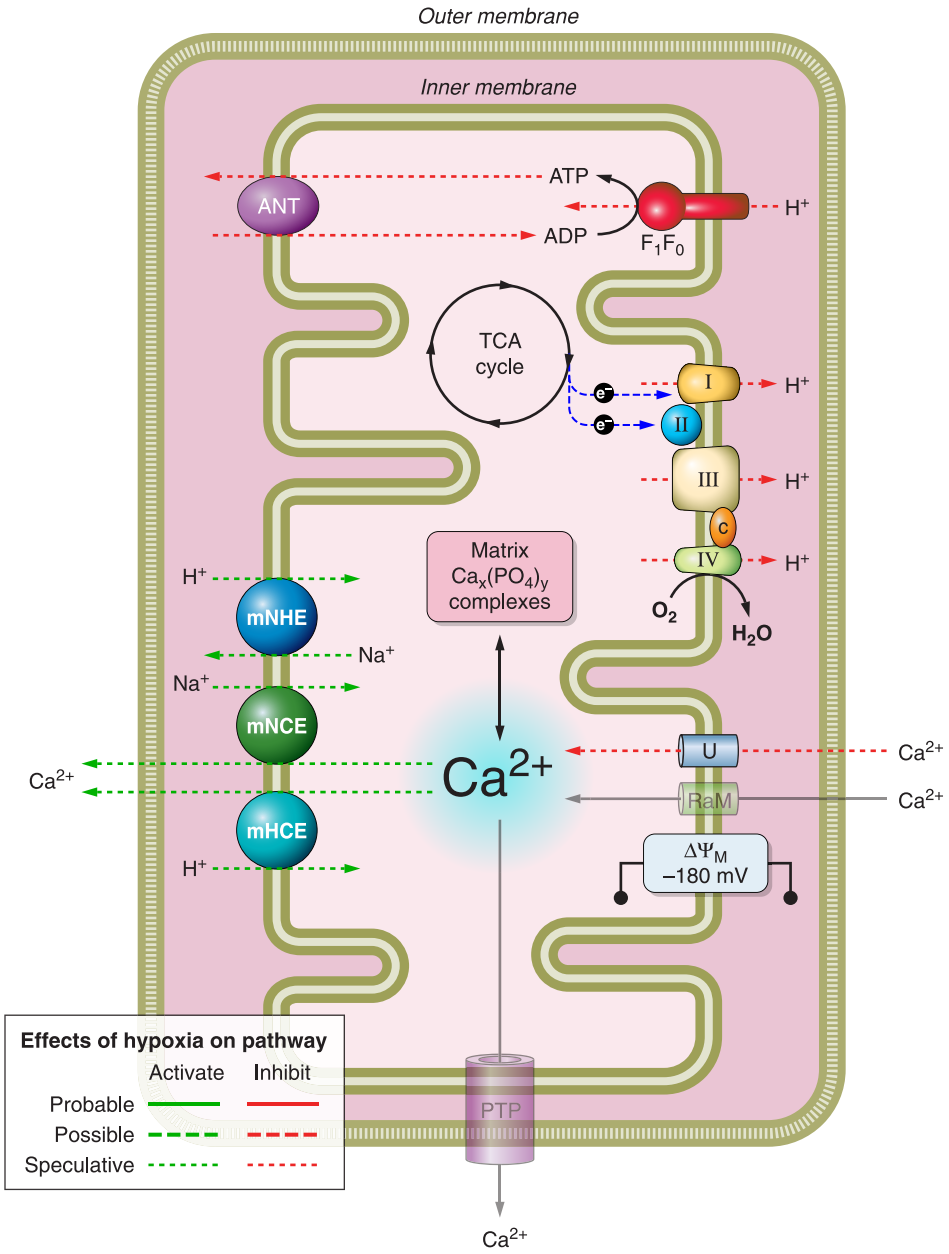


FIGURE 9 Effects of acute hypoxia on mitochondrial Ca^{2+}. Pathways of Ca^{2+} entry include "rapid mode" uptake (RaM) and a uniporter (U). Ca^{2+} can be stored in the matrix as calcium phosphate complexes or leave the organelle through Ca^{2+} efflux pathways, including mitochondrial H-Ca and Na-Ca exchangers (mHCE, mNCE), the latter driven by the mitochondrial Na-H exchanger (mNHE). Under extreme conditions, the "permeability transition pore (PTP)" may also play a role. Hypoxia may activate (green) or inhibit (red) these pathways. The effects shown are highly speculative (dotted lines) rather than probable (solid lines) or possible (dashed lines) and assume that hypoxia decreased mitochondrial electron transport, proton pumping, and membrane potential. Indeed, as discussed in the text, there is some evidence that the opposite may occur. Components of electron transport, proton pumping, and oxidative phosphorylation are also shown, including the tricarboxlic acid (TCA) cycle, electron transport complexes I-IV, F_1F_O ATP synthetase (F_1F_O), and adenine nucleotide translocator (ANT). Mitochondrial membrane potential ($\Delta\Psi_M$), generated by transport of H^+ from the matrix, is shown at its normal value of about −180 mV.

Ca^{2+} against a markedly negative $\Delta\Psi_M$. Na^+ balance is reestablished by a mitochondrial Na^+-H^+ exchanger (mNHE) that exchanges matrix Na^+ 1:1 for H^+, which would now be more abundant in cytosol due to the increased outward proton pumping associated with enhanced electron transport. Eventually the system returns to its "set point," where mitochondrial Ca^{2+} influx and efflux are equal (439, 1384, 1531).

In contrast, homeostasis does not occur when PTP is activated. This "megachannel" is formed when mitochondrial Ca^{2+} concentration is high and stressors such as oxidants,

low concentrations of ATP, and high concentrations of inorganic phosphate are present (440, 685). Upon activation, PTP leads to efflux of Ca^{2+}, cytochrome *c*, and other mitochondrial constituents; collapse of $\Delta\Psi_M$; termination of oxidative phosphorylation; depletion of ATP; mitochondrial swelling and rupture; and cell death. Although PTP may play an important role in cellular necrosis and apoptosis (68, 440), it seems unlikely that the catastrophic events it initiates contribute to the physiological changes in $[Ca^{2+}]_i$ that signal reversible contractile responses in PASMC.

Little is known about the contribution of mitochondria to Ca^{2+} homeostasis in PASMC; however, as noted in section III*A2*E, assessments of energy state in isolated pulmonary arteries suggested that physiological levels of hypoxia decreased the rate of oxidative phosphorylation (1044, 1045, 1767), raising the possibility that $\Delta\Psi_M$ could become less negative during hypoxia as a result of lower electron transport and proton pumping, thereby causing secondary decreases in uptake and/or increases in release of Ca^{2+} by PASMC mitochondria. Only a few studies, however, have investigated the effects of hypoxia on $\Delta\Psi_M$ in PASMC. Tetramethylrhodamine ethyl ester (TMRE) fluorescence, measured in rat PASMC as an index of $\Delta\Psi_M$ [see on-line supplementary data of reference (2032)], indicated that hypoxia (1% O_2) did not alter $\Delta\Psi_M$ while the protonophore FCCP caused depolarization; however, small changes in $\Delta\Psi_M$ due to hypoxia might be difficult to detect using standard fluorescent microscopy in groups of cells because of out-of-focus fluorescence and because dye lost by mitochondria is gained by cytoplasm (443). When $\Delta\Psi_M$ was assessed using the ratiometric dye 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolyl-carbocyanine (JC-1), hypoxia was thought to cause mitochondrial hyperpolarization in PASMC from rats (1278) and rabbits (1814). Hyperpolarization could enhance uptake and/or diminish release of Ca^{2+} by mitochondria; however, the mechanisms by which hypoxia might make $\Delta\Psi_M$ more negative remain unclear.

$[Ca^{2+}]_M$ can be assessed with cationic fluorescent indicators such as rhod 2 (443), but only a single study has measured $[Ca^{2+}]_M$ and $[Ca^{2+}]_i$ simultaneously in PASMC (434). Hypoxia was not studied in these experiments, which were performed in freshly isolated proximal rat PASMC at 20–23°C; however, FCCP prolonged increases in $[Ca^{2+}]_i$ and diminished increases in $[Ca^{2+}]_M$ induced by caffeine or ATP, but did not alter resting $[Ca^{2+}]_i$. These results suggested that mitochondria took up Ca^{2+} released from RyR or IP_3R in SR, but did not contribute to resting Ca^{2+} homeostasis. Since protonophores such as FCCP and CCCP cause dissipation of the $[H^+]$ gradient across the inner mitochondrial membrane and thereby collapse $\Delta\Psi_M$, the absence of an effect on resting $[Ca^{2+}]_i$ suggests that mitochondrial electron transport may already have been inhibited and $\Delta\Psi_M$ depolarized by the low temperatures employed in these experiments. Consistent with this possibility, FCCP caused a rapid initial increase in resting $[Ca^{2+}]_i$ followed by a decrease to an elevated plateau in cultured rat proximal PASMC studied at warmer temperature (33–34°C) (2174). In patched PASMC, FCCP increased outward currents thought to be due to activation of K_{Ca} channels. Neither effect was prevented by removal of extracellular Ca^{2+}, and effects of FCCP on K_{Ca} were not blocked by thapsigargin, suggesting that FCCP released Ca^{2+} primarily from mitochondria (2174). Recordings in cultured rabbit distal PASMC studied at 33–34°C indicated that CCCP increased baseline $[Ca^{2+}]_i$ and augmented $[Ca^{2+}]_i$ responses to caffeine or the combination of hypoxia and removal of extracellular glucose (924). These results suggest that protonophores increased Ca^{2+} release and decreased Ca^{2+} uptake by mitochondria, perhaps through mitochondrial depolarization.

As described in section III*A2*, other agents can block mitochondrial electron transport at Complexes I (rotenone, MPP), II (NPA, TTFA), III preubisemiquinone (myxothiazol), III postubisemiquinone (antimycin A), and IV (cyanide, azide). In all cases, the result is collapse of $\Delta\Psi_M$, termination of oxidative phosphorylation, and depletion of ATP. ATP depletion is further facilitated by reversal of mitochondrial F_1F_0 ATP synthetase, which now consumes ATP to pump H^+ out of the mitochondrial matrix, resulting in some preservation of $\Delta\Psi_M$. Under these conditions, the F_1F_0 ATP synthetase inhibitor, oligomycin, reduces ATP consumption and thereby limits deterioration of energy state; however, this salutary effect comes at the cost of complete mitochondrial depolarization.

Inhibitors of Complex I (rotenone, MPP), Complex II (NPA, TTFA), or Complex III preubisemiquinone (myxothiazol) either did not alter or possibly increased baseline $[Ca^{2+}]_i$, but consistently blocked increases in $[Ca^{2+}]_i$ induced by hypoxia in PASMC (924, 1041, 2010, 2033, 2035). In contrast, inhibitors of Complex III postubisemiquinone (antimycin A) or Complex IV (cyanide, azide) either had no effect or enhanced both baseline $[Ca^{2+}]_i$ and the $[Ca^{2+}]_i$ response to hypoxia (1041, 2009, 2010, 2014, 2033, 2035). Since all of these agents should cause mitochondrial depolarization, deplete ATP, and alter intracellular pH, their different actions on the $[Ca^{2+}]_i$ response to hypoxia are likely due to other factors, such as different effects on ROS production or redox state (see sect. III*A2*, C and D); however, this would not rule out the possibility that alterations of mitochondrial Ca^{2+} balance contribute to the increase in $[Ca^{2+}]_i$ caused by hypoxia. For example, inhibition of mitochondrial Ca^{2+} uptake and facilitation of mitochondrial Ca^{2+} release by hypoxia could amplify the effects of relatively small hypoxia-induced increases in transsarcolemmal Ca^{2+} influx and SR Ca^{2+} release on $[Ca^{2+}]_i$, allowing achievement of the threshold required for HPV. Another possibility is that transsarcolemmal influx of Na^+ through NSCC (see sect. III*B2*D)

could enhance extrusion of mitochondrial Ca^{2+} by mNCE and thereby contribute directly to an increase in $[Ca^{2+}]_i$, as proposed for *Xenopus* motoneurons (2148). Alternatively, if hypoxia does not inhibit mitochondrial Ca^{2+} uptake, these organelles could prevent inactivation of IP_3R and RyR by high $[Ca^{2+}]_i$, and thereby enable depletion of stores sufficient to activate Ca^{2+} influx through SOCC (609, 610). By facilitating transfer of influxing Ca^{2+} to SR, subsarcolemmal mitochondria could control subsarcolemmal $[Ca^{2+}]_i$, and thereby regulate activity of sarcolemmal ion channels and PMCA (559, 1870). Careful measurements of the effects of hypoxia on $\Delta\Psi_M$, $[Ca^{2+}]_M$, and $[Ca^{2+}]_i$ in PASMC should allow these and other possibilities to be evaluated.

F) LYSOSOME-LIKE ORGANELLES. Under acidic conditions, ADP-ribosyl cyclase can use $NADP^+$ rather than NAD^+ as a substrate (1049, 1051). In this case, the product is nicotinic acid adenine dinucleotide phosphate (NAADP) rather than cADPR (see sect. III, *A2*E and *B2*C). NAADP, the most potent Ca^{2+} messenger known (1050), causes Ca^{2+} release by uncertain mechanisms from a store different from those accessed by RyR and IP_3R (581, 1049–1051, 2142). In many cell types, this store is thought to be lysosome-like organelles that sequester Ca^{2+} via a vacuolar H^+-ATPase, which pumps H^+ into the organelle, and a Ca^{2+}-H^+ exchanger, which exchanges organelle H^+ for cytosolic Ca^{2+} (1050, 2142).

In PASMC from second-order rat pulmonary arteries, lysosome-like organelles labeled with a fluorescent acidotropic dye colocalized with RyR labeled with a fluorescent derivative of ryanodine (968). Moreover, intracellular dialysis of NAADP caused local "bursts" of $[Ca^{2+}]_i$. These bursts occurred in a spatial distribution similar to that of lysosome-like organelles and were sometimes followed by global Ca^{2+} waves and contraction (191, 968). Bafilomycin A1, which inhibits vacuolar H^+-ATPase, blocked these responses to NAADP; however, the RyR antagonist ryanodine prevented Ca^{2+} waves and contraction, but not Ca^{2+} bursts, whereas the IP_3R antagonist xestospongin C had no effect (191, 968). These results suggested that NAADP acted via a "two-pool" mechanism (309, 310): local Ca^{2+} release from lysosome-like organelles triggered CICR from nearby RyR, leading to global increases in $[Ca^{2+}]_i$ and contraction. On the other hand, the Ca^{2+} release caused by integrin ligands in rat PASMC was blocked ~50% by ryanodine, 50% by bafilomycin A1, and 100% by ryanodine plus bafilomycin A1, suggesting that releases from RyR and lysosome-like organelles were not coupled, as in CICR, but independent and additive (1955).

Although involvement of lysosome-like organelles in HPV has not been studied directly, indirect evidence does not suggest that they contribute to $[Ca^{2+}]_i$ responses to hypoxia in PASMC. For example, hypoxia-induced Ca^{2+} release was completely blocked by prior depletion of SR Ca^{2+} stores with CPA, norepinephrine, and caffeine, or blockade of SR ryanodine and IP_3 receptors with ryanodine and xestospongin C (2002). Nevertheless, it remains possible that local release of Ca^{2+} from lysosome-like organelles, which was not reflected in measurements of global $[Ca^{2+}]_i$, may be required to facilitate SR Ca^{2+} release by hypoxia.

G) SUMMARY: PASMC Ca^{2+} SIGNALING DURING HYPOXIA. It is well established that acute hypoxia increases $[Ca^{2+}]_i$ in PASMC. As detailed above and diagrammed in **FIGURE 7**, strong evidence indicates that release of Ca^{2+} from RyR in SR and influx of Ca^{2+} through SOCC and VOCC in sarcolemma contribute importantly to this response. It is also possible, but not as well established, that hypoxia-induced Ca^{2+} influx also occurs through ROCC and that hypoxia-induced Ca^{2+} release from SR involves activation of IP_3R. Whether release from lysosome-like organelles and mitochondria or influx via reverse-mode Na^+/Ca^{2+} exchange are involved is unknown. Although there is some evidence that hypoxia may impede Ca^{2+} efflux via forward-mode Na^+/Ca^{2+} exchange in sarcolemma, hypoxic inhibition of efflux by PMCA and uptake by SERCA or mitochondria remain speculative.

In some cases, the steps leading to the effects of hypoxia on particular components of the Ca^{2+} signaling system in PASMC seem clear. For example, hypoxic release of Ca^{2+} from SR leads to Ca^{2+} influx through SOCC, while hypoxic depolarization leads to Ca^{2+} influx through VOCC (see sect. III*B2*, B–D). On the other hand, the sequence, interplay, and importance of the various components of Ca^{2+} signaling in the generation of hypoxic responses are far from clear. As discussed above, the initial event could be release of Ca^{2+} from SR, leading to activation of SOCC and SOCE. Hypoxia may also activate ROCC. Depolarization, resulting directly from activation of these nonspecific cation channels and inhibition of TASK-1 channels, or indirectly from Ca^{2+}-dependent activation of Cl_{Ca} channels and inhibition of K_V channels (317, 542, 1544), could activate VOCC and further increase Ca^{2+} influx. NSCC activation could also increase entry of Na^+, and the resultant increase in $[Na^+]_i$, together with depolarization, could impede Ca^{2+} efflux through forward-mode Na^+-Ca^{2+} exchange or promote Ca^{2+} influx through reverse-mode Na^+-Ca^{2+} exchange.

This sequence predicts that the increase in $[Ca^{2+}]_i$ caused by hypoxia should occur before or without depolarization. This prediction has been tested in two electrophysiological studies of PASMC in whole cell configuration, which are apparently the only studies to have measured the effects of hypoxia on $[Ca^{2+}]_i$ and membrane potential simultaneously in these cells. In the first, severe dithionite-induced hypoxia (P_{O_2} = 5 mmHg) at 36°C increased $[Ca^{2+}]_i$ before it increased membrane potential in PASMC treated with charybdotoxin and niflumic acid to prevent activation of K_{Ca} and Cl_{Ca} channels,

respectively (1544). In the second, authentic hypoxia (P_{O_2} = 26 mmHg) at room temperature increased $[Ca^{2+}]_i$ but did not alter membrane potential in cells treated with charybdotoxin and a $K_V1.5$ antibody (598). Whether these results apply to PASMC under more physiological conditions is unknown. It is also possible that contributions of different components of Ca^{2+} signaling to the acute hypoxic response vary with initial normoxic conditions. For example, depolarization due to hypoxic inhibition of K_V channels and Ca^{2+} influx through VOCC could be of greater importance if normoxic resting membrane potential were relatively high, as it might be in PASMC exposed to priming concentrations of vasoactive agonists (1949).

Finally, other than studies of the effects of hypoxia-induced changes in redox state on K_V channels (see sect. III, *A2*C and *B1*B) and cADPR and ROS on RyR (see sect. III, *A2*, D and E, and *B2*C), there have been few attempts to unravel the molecular mechanisms by which hypoxia acts on various components of the Ca^{2+} signaling system in PASMC. Clearly, more work is needed.

C. Effector Mechanisms

1. Actin-myosin interaction

In smooth muscle, the most obvious effect of increased $[Ca^{2+}]_i$ is contraction, which occurs because at high concentrations Ca^{2+} binds to CaM, and Ca^{2+}-CaM then binds to and activates myosin light-chain kinase (MLCK) **(FIGURE 10)**. Activated MLCK phosphorylates the 20-kDa regulatory

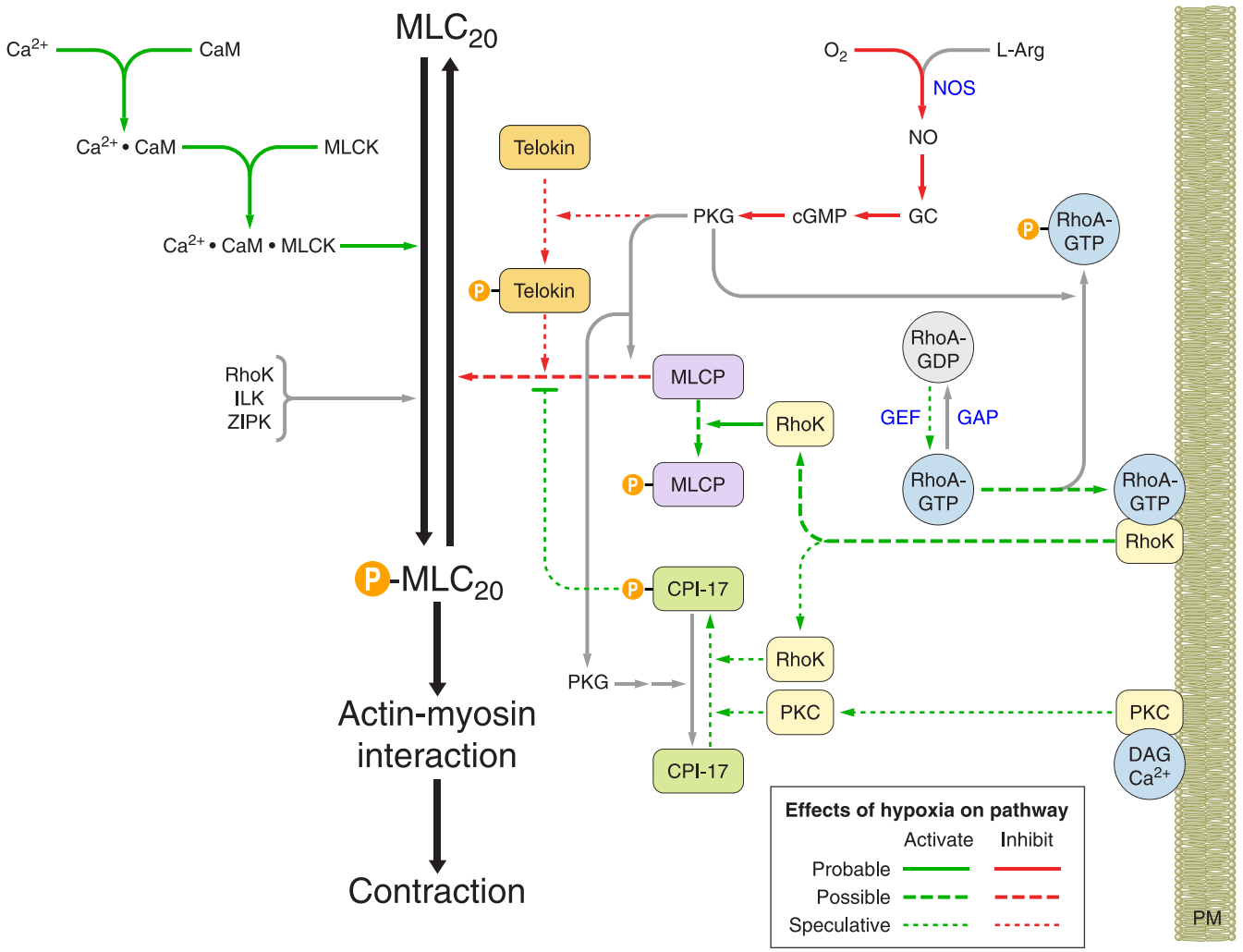


FIGURE 10 Effects of acute hypoxia on determinants of myofilament Ca^{2+} sensitivity in pulmonary arterial smooth muscle. Whether hypoxic activation (green) or inhibition (red) of pathways is probable, possible, or speculative is indicated by solid, dashed, or dotted lines, respectively, as shown in the key at the bottom. CaM, calmodulin; MLCK, myosin light-chain kinase; RhoK, Rho kinase; ILK, integrin-linked kinase; ZIPK, zip kinase; MLC_{20}, 20-kDa regulatory myosin light chain; NOS, NO synthase; GC, guanylate cyclase; PKG, protein kinase G; MLCP, myosin light-chain phosphatase; CPI-17, 17-kDa C-kinase-potentiated phosphatase inhibitor; PKC, protein kinase C; GAP, GTPase-activating proteins; GEF, guanine nucleotide exchange factors; DAG, diacylglycerol. Phosphorylated proteins are indicated by a white "*P*" in a gold circle.

myosin light chain (MLC_{20}) located near the head structure of the myosin crossbridge that binds to actin (921), leading to a conformational change (1964) that allows actin to switch on myosin ATPase activity, crossbridges to cycle, and actin to slide past myosin (245, 678). Although the ultrastructure of the contractile machinery in smooth muscle remains a bit mysterious (1749), it is generally believed that actin filaments are anchored to cytoskeleton at cytoplasmic "dense bodies" and to sarcolemma at "dense plaques" coupled to extracellular matrix; therefore, actin-myosin interaction causes the myocyte to contract (1797).

In smooth muscle cells from extrapulmonary arteries of fetal cow, acute hypoxia (P_{O_2} 25–59 mmHg for 6 min) caused contraction and increased incorporation of ^{32}P into MLC and the concentration of phosphorylated myosin light chains (*P*-MLC_{20}) (1341). Hypoxia had similar effects in myocytes from feline intrapulmonary arteries 200–600 μm in diameter, but not in myocytes from 800 μm pulmonary arteries or cerebral arteries (1160). Subsequent studies confirmed the effects of hypoxia on MLC phosphorylation in rat PASMC (1156, 2015, 2016) as well as precontracted rat extrapulmonary arteries, where hypoxia-induced increases in tissue *P*-MLC_{20} concentration and isometric force were biphasic and correlated, and hypoxic contractions were blocked by the MLCK antagonist ML-9 (2208). In contrast, hypoxia decreased force and *P*-MLC_{20} concentration in rat carotid arteries (2208). Together with the work discussed in section III, *A* and *B*, these results indicate that PASMC contain the essential sensor, transducer, and effector mechanisms required for HPV, and that HPV is effected by Ca^{2+}/CaM-dependent activation of MLCK, MLCK-dependent phosphorylation of MLC_{20}, and *P*-MLC_{20}-dependent activation of actin-myosin interaction.

2. Myofilament Ca^{2+} sensitivity

In smooth muscle, contraction can be triggered not only by an increase in $[Ca^{2+}]_i$ but also by an increase in myofilament Ca^{2+} sensitivity, which is defined by the relation between $[Ca^{2+}]_i$ and contractile force. A shift of this relation to lower $[Ca^{2+}]_i$ and/or higher force indicates an increase in sensitivity, i.e., a higher level of force can be achieved at a lower $[Ca^{2+}]_i$.

Estimates of Ca^{2+} sensitivity in normoxic pulmonary arteries have varied widely, no doubt due to differences among preparations and experimental conditions. The $[Ca^{2+}]_i$ required to generate a half-maximum increase in isometric force (EC_{50}) averaged ~30 nM in endothelium-denuded rat extrapulmonary arteries permeabilized with β-escin and exposed to the PKC activator phorbol-12,13-dibutyrate (PDB) at 30°C (1715); 719 nM in muscle strips dissected from extrapulmonary arteries of fetal rabbits, permeabilized with α-toxin, and studied at 20–22°C (346); 240 nM in endothelium-denuded rat intrapulmonary arteries permeabilized with α-toxin and exposed to the SERCA inhibitor CPA at 26°C (1900); ~80 nM in extralobar branches of endothelium-intact pulmonary arteries from fawn-hooded rats permeabilized with α-toxin and studied at room temperature (1352); and 277 nM in deendothelialized rat distal pulmonary arteries permeabilized with α-toxin and studied at 37°C (2040). In deendothelialized fourth- and fifth-order bovine pulmonary arterial rings permeabilized with α-toxin and studied at 37°C (689), however, measured EC_{50} was extraordinarily high (20,000 nM), suggesting inaccurate estimation of free $[Ca^{2+}]$ in the bathing media or incomplete permeabilization of the vessels.

The effects of hypoxia on myofilament Ca^{2+} sensitivity have been assessed only rarely. In permeabilized endothelium-denuded rat extrapulmonary arteries exposed to PDB, 5–10 min of hypoxia (P_{O_2} = 22 mmHg) did not alter isometric force when administered after force had achieved a steady state at $[Ca^{2+}]_i$ between 3 and 1,000 nM during normoxia (1715); however, it could be argued that an affect of hypoxia was precluded by the use of proximal pulmonary arteries, which have weak contractile responses to hypoxia (1157, 1160, 1740, 1781); the presence of PDB, which could enhance Ca^{2+} sensitivity on its own (562, 1716); or the low temperature at which the experiments were performed (30°C), which is known to inhibit HPV (144, 359, 700). In endothelium-intact rat intrapulmonary arteries precontracted with $PGF_{2\alpha}$ at 37°C, hypoxia (P_{O_2} = 15 mmHg) induced a biphasic contractile response (**FIGURE 3*B***; sect. II*B1*). Phase 1 was associated with a transient increase in $[Ca^{2+}]_i$ (1639); however, the slowly developing phase 2 was associated with a small but unchanging elevation of $[Ca^{2+}]_i$. Moreover, endothelial denudation abolished phase 2 contraction but did not alter the $[Ca^{2+}]_i$ response (1638). These results suggested that hypoxia increased myofilament Ca^{2+} sensitivity indirectly through release of an endothelium-derived factor rather than directly through an effect on PASMC. Consistent with this possibility, hypoxia (P_{O_2} = 8 mmHg) did not alter the relation between increases in $[Ca^{2+}]_i$ and decreases in cell length induced by the Ca^{2+} ionophore 4-bromo-A23187 in freshly isolated distal porcine PASMC at 37°C; however, the load on these cells, which were plated on glass coverslips, may have varied sufficiently to obscure a difference due to hypoxia (1752). At 37°C, hypoxia shifted the $[Ca^{2+}]_i$-isometric force relation to higher force in deendothelialized rat pulmonary arteries permeabilized with α-toxin but did not alter the $[Ca^{2+}]_i$-force relation in similarly treated mesenteric arteries (2040). In the deendothelialized bovine distal pulmonary arteries noted above (689), hypoxia decreased Ca^{2+} EC_{50} from 20,000 to 5,000 nM. Overall, the data suggest that hypoxia increases myofilament Ca^{2+} sensitivity in distal pulmonary arteries through direct effects on PASMC as well as indirect effects on endothelium.

In general, increased Ca^{2+} sensitivity could result from an increase in contractile force occurring without an increase in [*P*-MLC_{20}] or an increase in [*P*-MLC_{20}] occurring without an increase in $[Ca^{2+}]_i$. Perhaps the best known example of the former is the "latch" state, in which agonist-induced increases in force are maintained during continued stimulation even though agonist-induced increases in [*P*-MLC_{20}] and $[Ca^{2+}]_i$ are not (411, 897, 1317). The most enduring explanation for this phenomenon is the latch-bridge hypothesis, which proposes that force maintenance is due to the slow detachment of myosin cross-bridges from actin after cross-bridge dephosphorylation (411, 708, 1340). Other potential mechanisms by which force could change independently of [*P*-MLC_{20}] include regulation of cross-bridge cycling by actin-associated proteins such as calponin, caldesmon, tropomyosin, and SM22 (1318) and regulation of connections and arrangement of thin (actin) and intermediate (vimentin, desmin) filaments that transmit contractile force through the cytoskeleton to adjacent cells and extracellular matrix (683, 1890, 2200). Research in these complex and interesting arenas indicates that regulation of smooth muscle contraction involves much more than actin-myosin interaction but, unfortunately, such investigation has not yet addressed the contractile effects of hypoxia in pulmonary arterial smooth muscle.

An increase in [*P*-MLC_{20}] could occur without an increase in $[Ca^{2+}]_i$ if *1)* kinases other than MLCK phosphorylated MLC_{20} in a Ca^{2+}-independent manner or *2)* myosin light-chain phosphatase (MLCP), the enzyme responsible for dephosphorylation of *P*-MLC_{20}, were inhibited. Several kinases, including Rho kinase (RhoK) (38, 1010), integrin-linked kinase (396), and zip kinase (1389), have been shown to phosphorylate MLC_{20} independently of $[Ca^{2+}]_i$; however, the physiological significance of these actions is not clear. In contrast, inhibition of MLCP is well documented and thought to be a major mechanism of Ca^{2+} sensitization in vascular smooth muscle (781, 1813).

MLCP is composed of three subunits: MYPT1, a 110-kDa protein that targets MLCP to myosin filaments; PP1, the 38-kDa catalytic subunit of the phosphatase; and M20, a 20-kDa noncatalytic subunit (748). MLCP can be inhibited directly via phosphorylation of MYPT1 by RhoK (967), a serine/threonine kinase activated by a small monomeric GTPase known as RhoA. RhoA acts as a molecular switch that is turned on by guanine nucleotide exchange factors (GEF), which exchange RhoA-bound GDP for GTP, and turned off by GTPase-activating proteins (GAP), which hydrolyze RhoA-bound GTP to GDP **(FIGURE 10)**. Many agonist-receptor interactions are thought to activate RhoA by increasing GEF (1813). Activated RhoA then translocates to sarcolemma, where it activates RhoK (630).

PASMC and/or pulmonary arteries express MYPT1 (134, 357, 587, 1110, 1482, 2016) and PP1 (134, 135, 2016), as well as RhoA and RhoK (84, 587, 976, 1110, 1396, 1714, 2015, 2016, 2154). In cultured rat distal PASMC studied at passage 2–5 after 24 h of serum starvation, acute hypoxia (Po_2 = 25–30 mmHg) increased RhoK activity, the ratio of phosphorylated to total MYPT1, [*P*-MLC_{20}], and stress fiber formation, and decreased MLCP activity (2015, 2016). Furthermore, exoenzyme C3 and toxin B, which prevent recruitment of RhoA to sarcolemma (97), blocked hypoxia-induced increases in RhoK activity and [*P*-MLC_{20}] (2015). In addition, the RhoK inhibitors Y-27632 (863, 1953) and HA-1077 (fasudil) (1709) blocked hypoxia-induced increases in [*P*-MLC_{20}] and decreases in MLCP activity (2015, 2016). Y-27632 also reversed (2015) or prevented (1640) phase 2 HPV in precontracted rat pulmonary arteries, and Y-27632 or HA-1077 blocked HPV in isolated lungs from rats (1640, 2008) and mice (494) and pulmonary arterial pressor responses to acute hypoxia in intact rats (78, 264, 1353). Collectively, these results suggest that hypoxia increased myofilament Ca^{2+} sensitivity by activating Rho/RhoK in PASMC, leading to phosphorylation and inactivation of MLCP, increased [*P*-MLC_{20}] for given levels of $[Ca^{2+}]_i$ and rates of MLC_{20} phosphorylation by MLCK. The mechanisms by which hypoxia may have activated Rho/RhoK signaling are unknown.

Other data, however, suggest that such conclusions should be made with caution. First of all, Y-27632 and HA-1077 also blocked the effects of hypoxia on $[Ca^{2+}]_i$, SOCE, and VOCE in PASMC (2008), indicating effects on $[Ca^{2+}]_i$ as well as Ca^{2+} sensitivity. Second, in permeabilized deendothelialized rat distal pulmonary arteries, Y-27632 shifted the $[Ca^{2+}]_i$-force relation to lower force and higher $[Ca^{2+}]_i$ during both normoxia and hypoxia but did not eliminate the normoxic-hypoxic difference, suggesting that Rho/RhoK signaling was a determinant of Ca^{2+} sensitivity in these vessels but was not responsible for enhancement of sensitivity caused by the direct effects of hypoxia on PASMC (2040). Third, phase 2 HPV in pulmonary arteries, which occurred during a small but constant increase in $[Ca^{2+}]_i$ (1638), required an intact endothelium (see sects. II*B1* and IV*B2*), suggesting that endothelial cells exert an indirect but more important influence on Ca^{2+} sensitivity than the direct effects of hypoxia on PASMC.

Another pathway to increased Ca^{2+} sensitivity is phosphorylation of CPI-17 (C kinase-potentiated phosphatase inhibitor) by PKC **(FIGURE 10)**. Phospho-CPI-17, a 17-kDa protein, then inhibits MLCP by interacting with its catalytic PP1 subunit (481, 482). CPI-17 can also be phosphorylated by other kinases (781, 1813), including RhoK (992). The relative importance of the MYPT1 and CPI-17 pathways to MLCP inhibition probably varies among tissues and conditions (780, 781, 971, 1390). In pulmonary arteries, CPI-17 is expressed and appears to be phosphorylated during chronic hypoxia (357, 494). Acute hypoxia enhanced phosphorylation of CPI-17 triggered by KCl or 5-HT in bovine

pulmonary arteries (689); however, the effects of acute hypoxia alone on CPI-17 have not been reported. Inhibitors of PKC have had inconsistent effects during acute hypoxia. For example, hypoxia-induced increases in myofilament Ca^{2+} sensitivity were inhibited by chelerythrine in permeabilized rat pulmonary arteries (1481). In precontracted rat pulmonary arteries, H-7 (900) or calphostin C (2208) had no effect on phase 1 HPV but blocked phase 2, whereas Ro-31–8220 blocked phase 1 HPV but had no effect on phase 2 (1639).

In addition to upregulation of inhibitory pathways, MLCP activity could be reduced, and Ca^{2+} sensitivity enhanced, by downregulation of signaling pathways leading to MLCP activation. The best known of these is PKG, which is activated by cGMP produced upon interaction of NO with soluble guanylate cyclase (sGC) (1097). In permeabilized deendothelialized rat distal pulmonary arteries **(FIGURE 11)**, the NOS antagonist L-NAME shifted the normoxic $[Ca^{2+}]_i$-force relation to higher force but did not alter the hypoxic $[Ca^{2+}]_i$-force relation, thereby eliminating an additional enhancing effect of hypoxia on Ca^{2+} sensitivity (2040). These results suggest that hypoxic enhancement of Ca^{2+} sensitivity in PASMC may result from decreased production of NO by NOS, which requires O_2 as a substrate, leading to secondary decreases in cGMP-dependent activation of PKG and PKG-dependent activation of MLCP.

Major components of the NOS/sGC/PKG system are expressed in pulmonary arterial smooth muscle, including sGC (186, 354, 750, 1078), PKG (587, 1615), and all three isoforms of NOS (neuronal, inducible, endothelial) (382, 523, 1451, 1835, 1968, 2026, 2112, 2113, 2156). Moreover, hypoxia usually decreased production of NO and/or cGMP in the pulmonary vasculature (see sects. III*A4*D and IV*B2*A). Although NOS antagonists generally did not alter pulmonary vasomotor tone during normoxia, they enhanced increases in tone caused by hypoxia (60, 214, 379, 449, 477, 509, 752, 1058, 1107, 1411, 1968). These results suggested that NO activity was negligible during normoxia but significant during hypoxia. The data in **FIGURE 11** are consistent with this conclusion in that neither hypoxia nor inhibition of NOS altered Ca^{2+} sensitivity at normal baseline $[Ca^{2+}]_i$ (~100 nM). At higher $[Ca^{2+}]_i$, however, NOS inhibition increased Ca^{2+} sensitivity during normoxia and eliminated any further effect of hypoxia. These results suggest that the enhancement of HPV caused by NOS inhibition in lungs and pulmonary arteries could not be due to an increase in myofilament Ca^{2+} sensitivity. Rather, it must be due to potentiation of the hypoxia-induced increase in PASMC $[Ca^{2+}]_i$. Consistent with this possibility, NO or NO donors such as nitroprusside and spermine NONOate activated K_V channels, caused hyperpolarization, and inhibited VOCE and the increases in $[Ca^{2+}]_i$ induced by 5-HT or depolarization in PASMC (315, 2171), and attenuated ROCE, SOCE, and the increases in $[Ca^{2+}]_i$ induced by norepinephrine or UTP in pulmonary arteries (328, 893); however, the effects of NO on $[Ca^{2+}]_i$ responses to acute hypoxia in PASMC have not been determined.

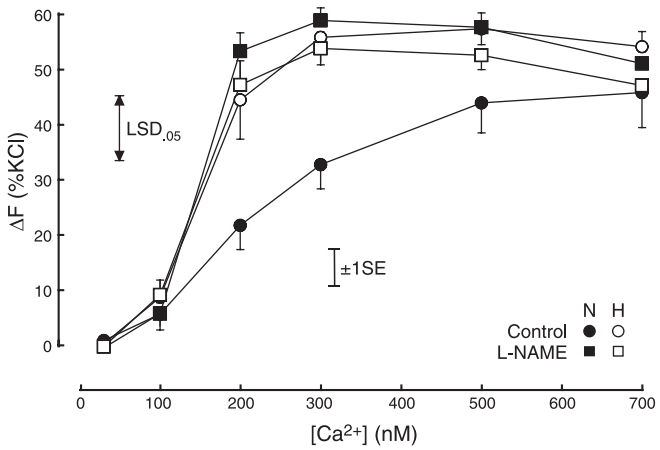


FIGURE 11 Relation between extracellular $[Ca^{2+}]$ and change in isometric force (ΔF) from baseline values measured under Ca^{2+}-free conditions in deendothelialized rat distal pulmonary arteries permeabilized with α-toxin and exposed to normoxia (16% O_2) or hypoxia (1% O_2) (2040). Arteries were otherwise untreated (control) or treated with N^{ω}-nitro-L-arginine methyl ester (L-NAME, 30 μM). ΔF is expressed as a percentage of the contractile response to [KCl] = 80 mM (%KCl_{80}) measured before permeabilization. $LSD_{.05}$ is the protected least significant difference at the 0.05 level.

As shown in **FIGURE 10**, PKG can activate MLCP by *1)* binding to a leucine zipper motif on MYPT1 (1853); *2)* phosphorylating RhoA-GTP, thereby preventing or reversing its activating interaction with RhoK in sarcolemma (1713); *3)* promoting dephosphorylation of the MLCP inhibitor *P*-CPI-17 (483); or *4)* phosphorylating telokin, an independently expressed 17-kDa protein with an amino acid sequence identical to that of the COOH terminus of MLCK, which activates MLCP upon phosphorylation (308, 582, 865, 957, 1000, 1156, 2128). In cats, telokin was more abundantly expressed in myocytes from small distal pulmonary arteries than in large proximal pulmonary arteries, and was not detected at all in cerebral arteries (1156). Moreover, hypoxia decreased phosphorylated telokin concentration ([*P*-telokin]) in concert with increased $[P\text{-}MLC_{20}]$ in small distal but not large proximal PASMC. Since contractile and $[Ca^{2+}]_i$ responses to hypoxia are greater in distal than proximal pulmonary PASMC (1139, 1160, 1963), these results suggest that downregulation of MLCP activity due to decreased [*P*-telokin] might contribute to HPV. How hypoxia decreased [*P*-telokin] was not determined.

In summary, the pulmonary arterial myocyte has intrinsic mechanisms capable of regulating its own Ca^{2+} sensitivity **(FIGURE 10)**. During normoxia, a relatively low Ca^{2+} sensitivity may be the net result of two opposing intrinsic mechanisms: *1)* RhoA/RhoK and/or PKC, which increase sensitivity by inhibiting MLCP; and *2)* NOS/sGC/PKG, which decrease sensitivity by activating MLCP. Thus hy-

poxic enhancement of Ca^{2+} sensitivity may be due to downregulation of intrinsic NO production by NOS, resulting in decreased activity of sGC/PKG, and/or upregulation or maintenance of RhoA/RhoK and/or PKC activity. In both cases, there would be downregulation of MLCP activity, and increased [P-MLC_{20}] at a given level of $[Ca^{2+}]_i$ and MLCK activity.

As discussed in section IV, extrinsic factors could also impact Ca^{2+} sensitivity and/or $[Ca^{2+}]_i$ in PASMC. Indeed, several laboratories found that endothelial denudation prevented contractile responses to hypoxia in isolated pulmonary arteries, suggesting that endothelial factors such as NO and endothelin-1 play a major role in HPV. In vivo, other paracrine or endocrine factors might act similarly. On the other hand, hypoxic contraction has been reported in deendothelialized pulmonary arteries (54, 139, 598, 1207, 2175) and isolated PASMC (see sect. IIC) How extrinsic and intrinsic mechanisms interact in the regulation of Ca^{2+} sensitivity in PASMC during hypoxia needs to be clarified.

IV. MODULATION

Modulation includes mechanisms intrinsic or extrinsic to PASMC that inhibit or facilitate HPV, but are not required for the response. Some of the modulators discussed below were originally investigated as mediators. Although none was confirmed to fulfill this role, many were able to alter HPV. The challenge is to determine which of these mechanisms modulate HPV under physiological and pathophysiological conditions in vivo.

A. Pulmonary Arterial Smooth Muscle Cells

1. K_{ATP} channels

It is unlikely that K_{ATP} channels contribute to resting E_m or hypoxic depolarization in PASMC (see sect. III*B1*A); however, these channels activate as ATP levels decrease and ADP levels increase, linking cellular metabolism to membrane excitability. This metabolic sensitivity suggests that deterioration of PASMC energy state during hypoxia (1044, 1045) could cause K_{ATP} activation and secondary hyperpolarization, inactivation of VOCC, decreased $[Ca^{2+}]_i$, and diminished HPV. Indeed, activation of K_{ATP} channels by decreased [ATP] or release of local mediators is thought to cause vasodilator responses to hypoxia in the systemic vasculature (362, 364, 1254, 1398, 2191). Another endogenous regulator of K_{ATP} activity is cAMP. Activation of adenylyl cyclase, increased intracellular cAMP, and activation of cAMP-dependent protein kinase were demonstrated to activate K_{ATP} channels (363, 972, 973, 1296, 1564), although some investigators question whether this occurs in the pulmonary vasculature (173, 1766). There is also evidence that cGMP plays a role in K_{ATP} activation (1002, 1297, 1339). Conversely, the vasoconstrictor ET-1 inhibited K_{ATP} channels, possibly via activation of PKC (1464). Pharmacologically, K_{ATP} channels can be activated by cromakalim, pinacidil, nicorandil, minoxidil, and diazoxide and inhibited by glibenclamide (312, 314, 1373).

In isolated ferret lungs, which have vigorous HPV (1483, 1852), moderate hypoxia during hypoglycemia caused sustained vasoconstriction, whereas severe hypoxia during hypoglycemia caused vasoconstriction followed by vasodilation (2090, 2091). Hyperglycemia did not alter the sustained vasoconstrictor response to moderate hypoxia, but markedly inhibited the vasodilation phase of the response to severe hypoxia. The effects of hyperglycemia during severe hypoxia were not reproduced by sucrose, pyruvate, 3-O-methylglucose, α-methylglucose, or insulin, suggesting that they were not due to changes in osmotic pressure, glucose metabolism beyond pyruvate, or glucose transport; however, the effects of hyperglycemia were mimicked by the K_{ATP} inhibitor glibenclamide (2092). Glibenclamide also enhanced vasoconstriction (98, 1131, 1715, 2018) or inhibited vasodilation (656, 1767, 2089) caused by severe hypoxia in precontracted pulmonary arteries. Moreover, glucose uptake by PASMC doubled during severe hypoxia in precontracted pulmonary arteries, and the absence of glucose under these conditions caused marked deterioration of energy state, decreased [ATP], and inhibition of HPV (1041, 1045).

These results suggest that decreases in glycolytic ATP production induced by hypoglycemia during severe hypoxia inhibited HPV by activating K_{ATP} channels in PASMC; however, it is also possible that in isolated lungs and arteries the effects of glibenclamide were due to actions on other cells that express K_{ATP} channels, such as endothelial cells (289, 883, 938). In addition, $[Ca^{2+}]_i$ responses of rat pulmonary arteries to severe hypoxia were not altered by the absence of glucose, suggesting that concurrent inhibition of the endothelium-dependent phase 2 HPV was not due to hyperpolarization and decreased Ca^{2+} influx through VOCC in PASMC but rather altered activity of endothelium-derived factors that reduced myofilament Ca^{2+} sensitivity in PASMC (1041). Consistent with this possibility, glibenclamide reversed the inhibitory effect of endothelin receptor antagonists on HPV in intact animals, suggesting that endothelin-mediated suppression of K_{ATP} activity facilitated HPV (1710). It should be noted, however, that the effects of glibenclamide on $[Ca^{2+}]_i$ responses to hypoxia were not tested in rat pulmonary arteries (1041) and that HPV may not require activation of VOCC in this preparation (1641). Finally, glibenclamide did not alter hypoxic responses in several studies of isolated lungs (449, 509, 751, 1636) and precontracted pulmonary arteries (934, 2175). Possibly, this lack of effect was due to shorter or less severe hypoxia, higher glucose concentrations, or less vigorous initial vasoconstriction, all of which could limit depletion of ATP.

Collectively, the data suggest that K_{ATP} channels in PASMC are unlikely to inhibit HPV when glucose concentration is high or hypoxia is not severe and prolonged. More work is needed to clarify when and how K_{ATP} channels in PASMC modulate HPV during severe hypoxia.

2. K_{Ca} channels

An initial proposal that hypoxic depolarization of adult PASMC is mediated by inhibition of K_{Ca} channels (1545) was invalidated by evidence that K_{Ca} channels were not activated at resting E_m in adult PASMC during normoxia (53, 1334, 1438, 1599, 1623, 1776, 1949, 2170, 2179) and vasomotor responses to hypoxia were not altered by K_{Ca} antagonists (622, 934, 2089) or deficiency of BK_{Ca} channels (1663). The latter results, which also suggest that K_{Ca} channels might not modulate HPV, could indicate that the changes in $[Ca^{2+}]_i$ and E_m induced by hypoxia (see sect. III*B*) were too small to achieve K_{Ca} activation. However, K_{Ca} channel activity can also be affected by energy state and phosphorylation (52, 747, 1500, 1637, 1907, 2174, 2177), as well as endothelial-derived factors whose production may be influenced by hypoxia, such as NO, EDHF, prostacyclin, and ET-1. In particular, K_{Ca} channels appear to be a prime target for vasodilators acting via cAMP/PKA (1286, 1685, 1816) and cGMP/PKG (193, 1637, 2098). Modulation of HPV by K_{Ca} channels in PASMC requires further evaluation.

3. Intracellular pH

The effects of hypoxia on pH_i in PASMC have varied considerably. In precontracted porcine proximal intrapulmonary arteries exposed to severe hypoxia (P_{O_2} = 15 mmHg) for 2 h, pH_i fell during the vasodilation component of phase 1 HPV, but recovered to normoxic levels during phase 2 HPV (1044, 1045). In feline PASMC, 5 min of moderate hypoxia (P_{O_2} = 50 mmHg) caused alterations of Cl^-/HCO_3 exchange that induced intracellular alkalinization in myocytes from arteries <600 μm in diameter, which contracted to hypoxia, but acidification in myocytes from arteries >800 μm in diameter, which did not contract to hypoxia (1158, 1159). In rat distal PASMC, 15 min of moderate hypoxia (4% O_2) had no effect on pH_i (1770). This variability could be due to differences in severity and duration of hypoxia, presence of a precontracting agonist, vessel locus within the pulmonary vasculature, species, and other factors.

The effects of changing pH_i on hypoxic responses of PASMC have not been directly evaluated. In normoxic canine PASMC, however, intracellular acidosis increased K_V currents, shifted steady-state K_V activation to more negative potentials, and increased K^+ conductance, whereas intracellular alkalosis had the opposite effects (21). Intracellular alkalosis increased $[Ca^{2+}]_i$ in PASMC (499), caused contraction in isolated pulmonary arteries (995), and increased P_{PA} in isolated lungs (499, 995). On this basis, it was suggested that inhibition of HPV by intracellular acidification in isolated rat lungs (1578) and enhancement of HPV by intracellular alkalinization in isolated rat lungs (1578) and feline distal pulmonary arteries or isolated lamb lungs (638) was due to pH_i-dependent enhancement and inhibition, respectively, of K_V currents in PASMC (21). Against this possibility, intracellular acidosis reduced rather than enhanced K_V currents in rat distal PASMC (147). Furthermore, HPV in isolated and intact lungs (see sect. II*A5*D) was usually attenuated by hypocapnic alkalosis (143, 219, 518, 1114, 1148, 1195, 1733, 1764, 1974, 2140) and enhanced by hypercapnic acidosis (143, 476, 953, 1052, 1645, 1788, 1974, 2141). Further investigation is needed to determine how pH_i changes in PASMC alter HPV.

B. Pulmonary Endothelial Cells

Isolated pulmonary artery preparations provide the ability to directly evaluate the contribution of the endothelium to contractile responses such as HPV. Although a few early studies reported that HPV could be elicited in endothelium-denuded arteries (54, 139, 1207, 2175), most demonstrated that removal of endothelium depressed the vasoconstrictor response to hypoxia while maintaining contractile responses to other agonists (392, 394, 413, 506, 578, 799, 814, 815, 991, 1038, 1043, 1044, 1639, 1652, 1896, 2024), indicating that attenuation was specific for the hypoxic response and not due to reduced contractile ability as a result of smooth muscle cell damage. Although some studies concluded that an endothelium-derived vasoactive substance mediated HPV (799), findings that isolated PASMC (199, 1160, 1341, 1752, 2188) and endothelium-denuded pulmonary arteries (59, 139, 2175) contracted in response to hypoxia suggested that pulmonary arterial endothelial cells (PAEC) modulate rather than mediate HPV.

1. Acute hypoxia in endothelial cells

PAEC are a major source of vasoactive substances in the pulmonary circulation. Endothelial facilitation of PASMC contraction during hypoxia could be due to decreased release of a vasodilator or increased release of a vasoconstrictor. Conversely, endothelial inhibition could be due to increased vasodilator or decreased vasoconstrictor release. There is no question that PAEC sense and respond to changes in oxygen tension **(TABLE 5)**; however, little is known about the mechanisms by which PAEC detect decreases in P_{O_2} and transduce these signals into altered release of vasoactive factors.

A) SENSATION AND TRANSDUCTION OF HYPOXIA. *I) K^+ channels and membrane potential.* Similar to PASMC, PAEC depo-

Table 5 Effects of acute hypoxia on pulmonary vascular endothelial cells

	Variable	Effect of Hypoxia	Preparation	Species	Reference Nos.
Cellular properties	Membrane potential	Depolarization	PAEC	Pig, cow	187, 1836, 2209, 2210
	Calcium	↑	PAEC	Cow	731
		↓	PAEC	Cow, sheep	1836, 1912
	ROS	↓	PAEC	Pig, rat	2149, 2227
		↑	PAEC	Rat	1486, 1672
	DNA modifications	↑	PAEC	Rat	1672, 2221, 2222
	Membrane fluidity	↑	PAEC	Pig	188
	Polyamine transport	↑	PAEC	Rat	77
	Serotonin (5-hydroxy-tryptamine) transport	↑	PAEC	Pig	166, 167
	L-arginine transport	↓	PAEC	Porcine	187, 2209, 2210
Contractile response	Cell stiffness and traction forces on substrate	↑	PMVEC	Rat	42
	Cell surface area	↓	PMVEC	Rat	153
	Matrix deformation	↑	PMVEC	Rat	153
	Actin stress fiber formation	↑	PMVEC	Cow	1470
			PAEC	Pig	2110
	Diameters of poorly or nonmuscularized pulmonary vessels	↓	IPL	Mouse, dog, rat	153, 779, 1876, 2138
Release of vasoactive substances	NO	↑	IPL	Rat	2138
			PAEC	Cow	731
		↓	IPL	Rabbit, pig	260, 344, 379, 663, 846, 927, 1370
			Isolated arteries	Rat, rabbit	903, 1651
	Aracidonic acid metabolites	↑ PGI_2	IPL	Dog, rat	602, 2138
			Lung homogenate	Dog	726
			Isolated arteries	Sheep	1403
			PAEC	Sheep	1403
		↓ ThBX	Lung homogenate	Dog	726
		No change in ThBX	IPL	Ferret, pig, rabbit	647, 712, 845
			PAEC	Cow	1202
		↑ ThBx	PAEC	Cow	497
		↑ Leukotrienes	IPL	Rat	1320
		No change in leukotrienes	IPL	Rat, sheep	1232, 1726, 1727
		↓ 20-HETE	IPL	Rabbit	2215
	ET-1	↑	Intact animal	Human, lamb, rat	257, 324, 458, 474, 1079, 1784
			IPL	Sheep, rat	426, 767
			PAEC	Cow, human	458, 988, 989

IPL, isolated perfused lung; ET-1, endothelin-1; 20-HETE, 20-hydroxyeicosatetraenoic acid; NO, nitric oxide; PAEC, pulmonary artery endothelial cell; PGI_2, prostacylin; PMVEC, pulmonary microvascular endothelial cell; ROS, reactive oxygen species; ThBX, thromboxane.

larized in response to hypoxia (1836); however, the ion channels generating this depolarization probably differ. In cultured bovine pulmonary arterial and microvascular endothelial cells, resting E_m was close to the K^+ reversal potential, suggesting that E_m is controlled mainly by K^+ conductance (10, 11, 1391, 1392, 1778, 1986). Vascular endothelial cells possess several types of K^+ channels, including K_{Ca}, K_V, K_{ATP}, and K_{IR} (10, 11, 1391, 1392). Among these channels, K_{IR} has been suggested to be the main contributor to regulation of E_m (10, 11, 1391, 1392).

The K_{IR} family of channels is composed of several subtypes, and $K_{IR}2.1$ has been identified in pulmonary endothelium (544, 922). K_{IR} channels conduct large sustained inward currents at voltages negative to the K^+ equilibrium potential and much smaller currents at voltages positive to this potential. In support of the possibility that K_{IR} channels contribute significantly to resting E_m in PAEC, inhibition of K_{IR} with Ba^{2+} caused significant depolarization of bovine PAEC (1778, 1986). In the central nervous system, K_{IR} channels have been postulated as O_2 sensors, and in cardiac myocytes, K_{IR} current increases with hypoxia (1675). The sensitivity of these channels to hypoxia has not been explored in PAEC, although conditions that may simulate an hypoxic environment (e.g., KCN) downregulated K_{IR} activity in bovine PAEC (922), suggesting a possible role for these channels in hypoxic depolarization.

Channels in the K_V family, namely, $K_V1.5$, $K_V2.1$, $K_V1.2$, and $K_V9.3$, can form homo- or heteromeric complexes that exhibit decreasing activity as P_{O_2} falls (see sect. III*B1*B). Both pharmacological and molecular evidence indicates expression of K_V channels in endothelial cells (1392), including those from pulmonary vessels (795); however, it is well established that other K^+ channel family members participate in membrane potential regulation, and thus the potential role of K_V channels in hypoxic depolarization of PAEC is probably minimal.

II) Intracellular Ca^{2+} concentration. In PASMC, hypoxic depolarization causes activation of L-type VOCC and Ca^{2+} influx (see sect. III, *B1*B and *B2*D). This does not occur in PAEC, which lack L-type VOCC; however, T-type VOCC have been identified in PAEC (2038, 2125) and can open transiently with depolarization and contribute to Ca^{2+} influx under certain conditions. The major pathways for Ca^{2+} influx in PAEC are thought to be ROCC and SOCC. Usually, depolarization decreases the electrochemical gradient for Ca^{2+} influx through these channels and therefore lowers endothelial cell $[Ca^{2+}]_i$ (763, 764). Conversely, hyperpolarization increases the gradient for Ca^{2+} influx and raises $[Ca^{2+}]_i$ (10, 11, 1140, 1141).

Alteration of $[Ca^{2+}]_i$ is a primary mechanism of endothelial cell signaling. For example, the synthesis and release of several substances, including NO, ET-1, and PGI_2, are directly correlated with an increase in $[Ca^{2+}]_i$. The effects of acute hypoxia on $[Ca^{2+}]_i$ in PAEC, however, have been rarely investigated. In bovine PAEC, measurements at ~1-min intervals during a 15-min exposure to a P_{O_2} of 35 mmHg revealed a progressive decline in $[Ca^{2+}]_i$ to levels well below baseline in association with depolarization and decreased Ca^{2+} influx (1836). Consistent with these findings, $[Ca^{2+}]_i$ in fetal ovine PAEC increased upon switching from hypoxic to normoxic conditions (1912). In contrast, when measurements were made more frequently (60 Hz) in bovine PAEC, a 3- to 5-min exposure to hypoxia (P_{O_2} = 37 mmHg) was found to cause a rapid increase in $[Ca^{2+}]_i$ that returned to baseline within 40 s (731). This response was blocked by ryanodine or thapsigargin but unaffected by removal of extracellular Ca^{2+}, suggesting that it was due to Ca^{2+} release from endoplasmic reticulum rather than influx from extracellular fluid. Together, these results imply that in PAEC hypoxia may cause an initial transient increase in $[Ca^{2+}]_i$ due to Ca^{2+} release from internal stores, followed by a progressive decrease due to depolarization and reduced Ca^{2+} influx. Obviously, more investigation is needed to test these possibilities and determine underlying mechanisms; however, such studies will have to address observations that acute hypoxia can alter calibration of fluorescent Ca^{2+} indicators in PAEC (1837).

III) ROS. In porcine (2149) and rat (2227) PAEC, ROS release was found to decrease 2 h after beginning exposure to anoxia. In contrast, hypoxia (1% O_2 for 6 h) increased mitochondrial ROS production in bovine PAEC, leading to activation of signaling pathways involving NF-κB and transcriptional regulation of IL-6 (1486). As the goals of these studies were to identify pathways involved in hypoxia-reoxygenation injury and inflammatory responses to hypoxia, shorter periods of hypoxia were not examined. ROS production in rat PAEC was found to increase within minutes of exposure to 2% O_2 and to be maintained for 1 h (1672). In these experiments, ROS were measured with dichlorofluorescein, an approach that has generated controversy (see sect. III*A2*D). Nevertheless, taken at face value, the results suggest that hypoxia caused rapid, sustained generation of ROS in PAEC. Consistent with this conclusion, a recent study reported that 24 h of hypoxia (1.5% O_2) increased ROS in distal rat PAEC transfected with RoGFP, a ratiometric green fluorescent protein redox indicator targeted to cytosol (303).

In PASMC, ROS may signal increases in $[Ca^{2+}]_i$ in response to acute hypoxia (see sect. III*A2*D); however, it is not clear whether this occurs in PAEC. Another possible ROS-dependent hypoxic signaling pathway is DNA modification. In PAEC, 3–48 h of hypoxia increased ROS production and induced oxidant-mediated modifications in nuclear DNA, perhaps contributing to regulation of gene expression (665, 1672, 2221, 2222). These hypoxic effects were prevented in cells treated with myxothiazol, an inhibitor of mitochondrial complex III (1672). Both ROS and RhoA activity were increased by 24 h of hypoxia in distal rat PAEC; however, only the increases in ROS were prevented by treatment with an antioxidant, suggesting that ROS did not activate RhoA (303). While the relevance of these observations to HPV, which occurs within minutes, is uncertain, they could have implications for synthesis of factors contributing to endothelial and/or smooth muscle cell contraction during more prolonged hypoxic exposure.

B) ENDOTHELIAL EFFECTS OF ACUTE HYPOXIA. Regulation of synthesis and secretion of vasoactive factors is a prime effect of hypoxia on PAEC; however, other functional responses to hypoxia have been noted. For example, acute exposure to severe hypoxia (P_{O_2} = 13 mmHg) caused contraction of rat pulmonary microvascular endothelial cells, which was rapidly reversed by reoxygenation (153). Consistent with these results, exposure to hypoxia (P_{O_2} ≈30 mmHg) for 4 h increased endothelial cell monolayer permeability, intracellular gap formation, and extracellular matrix proteins; however, these variables fell below normoxic levels after 24 h of hypoxia (1470). Changes in endothelial cell barrier function induced by hypoxia were associated with alterations in actin stress fiber formation, increased cell stiffness, and contraction (42, 351, 2110), all of which appeared to be mediated by activation of MAP kinase and/or Rho kinase (42, 943). These hypoxia-induced alterations in cell shape and structure, and resulting increases in permeability, could facilitate exposure of PASMC to circulating vasoactive substances and/or contribute to development of pulmonary edema, as occurs in animal models of hypoxia and in humans at high altitude (see sect. VC).

Another possible role for hypoxia-induced changes in endothelial cytoskeletal rearrangement is regulation of capillary diameter. Indeed, in pancreatic capillaries, application of norepinephrine caused bulging of the nuclear regions of the endothelial cells into the vascular lumen, indicative of endothelial contraction, and reduced capillary diameter by 50% (1150). Similarly, when treated with an agent that fixed endothelial actin filaments, ischemia-induced reductions in coronary capillary diameter were lost (618). Moreover, experiments using confocal imaging in isolated perfused mouse lungs demonstrated a reduction in diameter of small arterioles and intra-acinar vessels, which typically have very little smooth muscle (153, 1876). These results are consistent with earlier data demonstrating hypoxia-induced contraction of pulmonary arterioles and venules 30–50 μm in diameter (779, 2138) and suggest that while endothelial cell contraction causes intracellular gap formation in a cultured monolayer, it may reduce capillary diameter in vivo and thereby contribute to HPV. This possibility warrants further investigation.

Hypoxia can also change plasmalemmal structure and function in PAEC; for example, hypoxia increased fluidity and transport of 5-HT and polyamines and decreased phospholipid concentration and transport of L-arginine in plasma membranes of PAEC (77, 166, 167, 187, 188, 2209, 2210). Such changes may account for some of the alterations in synthesis, release, or uptake of vasoactive factors by PAEC, which may have an important modulatory role in HPV.

2. Interaction with smooth muscle

A) ENDOTHELIUM-DERIVED RELAXING FACTORS. *I) NO*. NO is produced by oxidation of L-arginine to L-citrulline in a reaction that requires molecular O_2, NADPH, tetrahydrobiopterin (BH_4), and the dioxygenase NOS (1452). NOS is a dimer composed of identical monomers, each containing binding sites for NADPH, FAD, FMN, BH_4, and CaM as well as heme, which binds O_2 (44, 1850). Among the three NOS isoforms, eNOS and nNOS are Ca^{2+}-dependent and constitutively expressed, whereas iNOS is Ca^{2+}-independent and expressed in response to cytokines and other stimuli, including chronic hypoxia (1450, 1451). In endothelial cells, NO synthesis is thought to occur via eNOS or activation of iNOS. NO released from endothelial cells promotes vasodilation by activating sGC in vascular smooth muscle, leading to generation of cGMP and cGMP-dependent decreases in $[Ca^{2+}]_i$ and/or myofilament Ca^{2+} sensitivity (see sect. III, *B2*C and *C2*) that can limit or reverse ongoing contraction (263).

As discussed in section III*A4*D, O_2 affinity measured for purified enzymes in vitro was greatest for eNOS, intermediate for iNOS, and least for nNOS; however, O_2 affinities could be greater in intact cells and tissues, making it possible that NO production by all NOS isoforms could be rate-limited by hypoxia in vivo (470, 1039, 1611, 1612, 1850). Consistent with this possibility, hypoxia reduced exhaled NO and/or perfusate NO metabolites in isolated perfused lungs (16, 260, 344, 379, 663, 846, 927, 1370); exhaled NO in intact animals (16), including humans (457, 1725); cGMP levels in isolated pulmonary arteries (656, 903, 1651, 1758) and PASMC cocultured with PAEC (1757); and NO-induced fluorescence of 4-amino-5-methylamino-2,7-difluorofluorescein in ovine fetal and neonatal pulmonary microvascular endothelial cells (902). Moreover, hypoxia decreased L-arginine transport into PAEC, possibly due to depolarization (187, 1836). As noted above, depolarization could also reduce the driving force for Ca^{2+} entry in PAEC, resulting in decreased $[Ca^{2+}]_i$ and Ca^{2+}-dependent NO production by eNOS. In contrast, hypoxia did not alter exhaled NO concentrations in humans (1940), increased accumulation of NO metabolites in perfusates of bovine PAEC (731) and isolated rat lungs (2138), and increased intracellular metallothionein *S*-nitrosation and cGMP heme iron nitrosylation detected by fluorescence resonance energy transfer in sheep PAEC (153); however, exhaled air may have been contaminated by nasal NO in humans (1940), hypoxia was brief (10 min) in PAEC (153, 731), and normoxic time-control lungs were not studied in rats (2138). Overall, the data indicate that NO production in lungs, pulmonary arteries, and PAEC is reduced by hypoxia (1039).

NO seems to be an important modulator of pulmonary vascular resistance during normoxia in the neonate (335, 425, 640, 1368); however, things are more complicated in the adult. For example, NO antagonists had little if any effect on baseline pulmonary vasomotor tone in intact rats (477) and dogs (114), isolated lungs of rats (477, 509, 512,

752) and dogs (1699), and precontracted rat pulmonary arteries (1043). In contrast, NO antagonists increased normoxic pulmonary vasomotor tone in healthy awake humans (185), intact anesthetized rats (78, 264, 401), isolated rat lungs (114), and precontracted rat pulmonary arteries (1651). These data suggest that the contribution of NO to maintenance of low pulmonary vasomotor tone during normoxia depends on the presence or absence of contractile influences and/or relaxing influences other than NO, which in turn may depend on species, preparation, experimental conditions, and other factors.

In the context of results indicating that hypoxia inhibited NO production, the reported effects of NO inhibition on HPV appear to be contradictory. On the one hand, HPV was enhanced in intact and isolated lungs treated with NOS antagonists (60, 78, 114, 185, 214, 264, 379, 449, 477, 509, 512, 640, 752, 1058, 1107, 1368, 1699, 1825, 1968, 2138) and isolated nonprecontracted pulmonary arteries treated with NOS antagonists, Hb (which binds NO), or inhibitors of soluble guanylyl cyclase (393, 1104, 1411, 1418). Moreover, HPV was exaggerated in transgenic mice with complete or partial eNOS deficiency (495, 1106), but blunted in rat and mouse lungs overexpressing eNOS and/or iNOS (277, 887, 896). These data suggest that HPV was inhibited by NO. On the other hand, NOS antagonists attenuated hypoxic contractions in isolated precontracted pulmonary arteries (477, 506, 656, 814, 934, 991, 1151, 1413, 1430, 1691, 1894, 1896, 1976, 2146). Similar results were obtained with Hb and inhibitors of sGC (656, 903, 1413, 1430, 1651, 1976, 2146). Although a few studies reported that NOS antagonists did not alter hypoxic contractions in precontracted pulmonary arteries (908, 991, 1043), collectively the data suggest that hypoxic responses in this preparation were at least partly due to decreased NO activity.

The apparent contradiction that NOS antagonists enhanced HPV in lungs, but inhibited HPV in precontracted pulmonary arteries, can be explained as follows. In untreated lungs, NO synthesis was reduced during hypoxia, whereas in lungs treated with a NOS antagonist it was virtually eliminated; therefore, HPV was greater in treated lungs. In untreated pulmonary arteries, however, precontraction caused an increase in NO production that limited precontraction tone during normoxia. When NO production was then reduced during hypoxia, precontraction tone increased, a result that was interpreted as HPV. In pulmonary arteries treated with a NOS antagonist, NO production was already eliminated and precontraction tone maximal during normoxia, precluding any further decreases in NO production and associated increases in precontraction tone during hypoxia. This result was interpreted as inhibition of HPV. Whether or not this explanation is correct, the available evidence strongly suggests that endothelium-derived NO limits HPV in vivo.

II) Prostacyclin. Arachidonic acid, a major component of cell membranes, is the precursor of several vasoactive prostaglandin mediators, including the cyclooxygenase product prostacyclin (PGI_2). PGI_2 is released from endothelium and causes vasodilation in both the pulmonary and systemic circulations via stimulation of adenylate cyclase and increased production of cAMP. Decreased synthesis or release of PGI_2 during hypoxia was proposed to contribute to HPV in isolated pulmonary arteries of humans (394) and sheep (393); however, this hypothesis is inconsistent with data demonstrating that lung PGI_2 production increases during hypoxia (602, 726, 1403). Moreover, numerous investigators have shown that cyclooxygenase inhibitors did not prevent HPV (647, 799, 991, 1043, 1058, 1104, 1242, 1652, 1691, 1938, 2057, 2059, 2140, 2146). Indeed, cyclooxygenase inhibitors enhanced hypoxic pressor responses in lungs of dog (32, 719, 1824, 2048), rabbit (1824), rat (1962, 1984), lamb (641, 1583), and goat (1952). Thus PGI_2 is an inhibitory modulator of HPV.

III) Endothelium-derived hyperpolarizing factor. Endothelium-dependent relaxations induced by acetylcholine and other agents were sometimes reduced but not eliminated after inhibition of NO and PGI_2, indicating the presence of additional endothelium-dependent vasodilation pathways (195, 294, 508, 986, 1143). Since these vasodilatory effects occurred in association with smooth muscle hyperpolarization, they have been attributed to release of endothelium-derived hyperpolarizing factors (EDHF). EDHF probably causes hyperpolarization by activating smooth muscle K^+ channels, resulting in closure of VOCC, decreased $[Ca^{2+}]_i$, and vasorelaxation that can be inhibited by blockers of K_{Ca}, K_V, and K_{IR} channels; however, the identity of these EDHF, and whether they act in smooth muscle, endothelium, or both, remains unclear (507, 1143, 1182, 1235, 1512, 2229). Possibilities include a cytochrome *P*-450 product of arachidonic acid metabolism, perhaps an epoxyeicosatrienoic acid (196, 534, 536, 593); H_2O_2 (145, 1210, 1211, 1779); and electrical coupling between endothelium and smooth muscle via myoendothelial gap junctions (291, 507, 659).

Although EDHF appeared to play a role in vasomotor responses of isolated pulmonary arteries (293, 584, 812, 933, 1412, 2193), their role in HPV has been evaluated only in isolated lungs. After treatment with inhibitors of NO and PGI_2, the nonselective K^+ channel blocker TEA and the K_{ATP} blocker glibenclamide prolonged HPV in lungs of normal rats (752), while the K_{Ca} channel antagonists charybdotoxin + apamin completely reversed inhibition of HPV in lungs of rats with hepatic cirrhosis (262). These results suggested that EDHF is an inhibitory modulator of HPV. In contrast, a later study from the same laboratory reported that charybdotoxin + apamin abolished thapsigargin-induced vasodilation, presumed to be due to EDHF, but altered neither baseline P_{PA} nor HPV in normal rat lungs

treated with antagonists of NOS and cyclooxygenase (1321). Similar results were obtained with the *P*-450 inhibitors 7-ethoxyresorufin and sulfaphenazole and the gap junction uncoupler palmitoleic acid. These data suggested that EDHF plays no role in HPV. The inconsistency among these results remains unexplained and the modulatory role of EDHF in HPV is unclear.

B) ENDOTHELIUM-DERIVED CONTRACTING FACTORS. In isolated pulmonary arteries, most evidence indicates that phase 2 hypoxic contraction, which is thought to require an intact endothelium, is caused by increased release of endothelium-derived contracting factors (EDCF) rather than decreased release of endothelium-derived relaxing factors (EDRF).

I) Endothelin-1. Endothelin-1 (ET-1) is a 21-amino acid peptide produced by endothelium and other cells that causes profound pulmonary vasoconstriction in every species tested to date, including cat (1772), dog (111, 429, 2144), ferret (588), guinea pig (256), human (801, 1237, 1500, 1774), horse (137, 138), lamb (1111, 2012), mouse (277), pig (572, 578, 1975), rabbit (570, 571, 573, 1016, 1100, 1154, 1162), and rat (204, 868, 1047, 1650, 1773, 1884). At concentrations as low as 10^{-10} M, ET-1 constricted isolated pulmonary arteries through activation of ET_A or ET_B receptors on PASMC (111, 171, 204, 486, 570, 572, 760, 777, 909, 1016, 1155, 1227, 1229, 1406, 1506, 1711, 1748, 1772, 1884, 2012, 2085). In isolated perfused lungs, infusion of ET-1 caused long-lasting increases in vascular resistance (111, 113, 204, 277, 460, 860, 868, 1100, 1175, 1585, 1650, 1711, 1884, 1918). ET-1 synthesis and release by endothelium can be elicited by numerous stimuli, including increased shear stress and hypoxia (76, 257, 324, 426, 458, 474, 604, 767, 820, 988, 989, 1004, 1079, 1402, 1772, 1784). ET-1 receptor antagonists attenuated or prevented HPV in a variety of species in vivo (27, 39, 297, 298, 323, 324, 419, 548, 800, 802, 803, 822, 1432, 1510, 1710, 1910, 2012, 2096) and in vitro (622, 909, 1104, 1456, 1805, 2189). These findings suggest that ET-1 plays a major role in HPV.

Other data seem inconsistent with this possibility. ET receptor blockade failed to inhibit HPV in precontracted pulmonary arteries (429, 578, 1038, 1691, 2146), isolated lungs (306, 1884), and intact animals (2114), including humans (906). In some studies (419, 1180, 1250, 1508), hypoxia did not increase pulmonary ET-1 production. In others (288, 767, 1175, 1883), both induction of ET-1 production by hypoxia and reversal of pulmonary vasoconstriction induced by ET-1 occurred very slowly, whereas the onset and offset of HPV occur rapidly (see sect. II*A2*).

Studies in porcine PASMC (1752) and pulmonary arteries (1104) suggest a possible resolution of these discrepancies. In untreated PASMC, hypoxia caused small increases in $[Ca^{2+}]_i$ and decreases in length; however, after the cells were "primed" with a low concentration of ET-1 (10^{-10} M) that did not itself alter $[Ca^{2+}]_i$ or cell length, hypoxic contractions were markedly enhanced (1752). Hypoxic contractions were abolished by endothelial denudation or the ET_A antagonist BQ-123 in untreated distal pulmonary arteries studied at constant transmural pressure, and restored by 10^{-10} M ET-1 in endothelium-denuded arteries (1104). These results suggested that full expression of HPV required basal release of ET-1 from endothelium, which facilitated HPV in PASMC. It is possible that other vasomotor agonists share endothelin's ability to facilitate HPV. This could explain why ET-1 receptor antagonists did not block HPV in some studies of precontracted pulmonary arteries, isolated lungs, and intact animals, where such agonists were either given or could be intrinsically produced. Consistent with this possibility, ET-1 receptor antagonists inhibited HPV in isolated lungs perfused with physiological saline solution, but not in lungs costimulated with angiotensin II (1710).

The mechanisms by which ET-1 or other vasoconstrictors exert these facilitating effects could involve alteration of Ca^{2+} signaling or myofilament Ca^{2+} sensitivity in PASMC. The Ca^{2+} signaling pathways leading to ET-1-induced contraction in PASMC are complex and include activation of phospholipase C; membrane depolarization due to PKC-dependent inhibition of K_V channels or Ca^{2+}-dependent activation of Cl_{Ca} channels; and elevation of $[Ca^{2+}]_i$ due to Ca^{2+} influx through VOCC, SOCC, or ROCC; and Ca^{2+} release from both caffeine-sensitive and -insensitive intracellular stores, the latter possibly including balfilomycin-sensitive stores in lysosome-like organelles (87, 111, 843, 968, 980, 1047, 1081, 1175, 1500, 1608, 1694–1696, 1776, 1777, 2201). In rat PASMC, 10^{-10} M ET-1 was sufficient to inhibit K_V currents, cause depolarization, and facilitate further depolarization in response to hypoxia, which otherwise was without effect (1776, 1949). Basal levels of ET-1 may also suppress activation of K_{ATP} channels, thereby facilitating depolarization and/or inhibiting hyperpolarization of PASMC during hypoxia (622, 1131, 1464, 1710). The magnitude of Ca^{2+} current at a given E_m was increased by ET-1 in coronary arterial and portal venous smooth muscle cells (646, 853, 1786), indicating E_m-independent activation of VOCC. If ET-1 had similar effects in PASMC, Ca^{2+} influx through VOCC could be enhanced during hypoxia.

The possibility that facilitation of HPV by ET-1 is due to an increase in Ca^{2+} sensitivity is consistent with observations that both the increased hypoxic contraction caused by 10^{-10} M ET-1 in porcine PASMC (1752) and the abolition of phase 2 HPV caused by endothelial denudation in rat pulmonary arteries (1638, 1639) occurred without alteration of the $[Ca^{2+}]_i$ response to hypoxia. Although it is well documented that higher concentrations of ET-1 enhance Ca^{2+} sensitivity in both systemic (247, 646, 1759, 1760,

1957, 2157) and pulmonary vessels (486, 1505), it is not known whether lower concentrations have this effect. In addition, phase 2 HPV in rat pulmonary arteries was not blocked by antagonists of ET-1 receptors or PKC (1638, 1639), suggesting that the endothelium-dependent increase in Ca^{2+} sensitivity that occurred during phase 2 was due to an EDCF other than endothelin. Nevertheless, the consistency with which ET_A receptor antagonists blocked HPV in vivo is compelling and suggests that ET-1 is an important if not exclusive facilitator of HPV.

II) Thromboxane. Thromboxane or thromboxane mimetics caused vasoconstriction in isolated lungs of ferrets (1585), piglets (520), and rats (528) and in isolated pulmonary arteries of dogs (885), piglets (520), rabbits (1101, 1343), and rats (325). Although thromboxane production was increased by 3% O_2 in bovine PAEC (497), it was not altered by less severe hypoxia in PAEC (1202) or isolated lungs (647, 712, 845), and was decreased in dog lung homogenates (726). Moreover, with few exceptions (814), inhibition of cyclooxygenase, thromboxane A_2 synthase, or thromboxane A_2 receptors did not prevent HPV in lungs of calves (2048), dogs (32, 719, 1058, 1824, 2048), ferrets (647, 1938), goats (1952), lambs (641, 1583), rabbits (1824, 2059), and rats (306, 1242, 1652, 1962, 1984, 2048) or hypoxic contractions in pulmonary arteries of rats (1043, 1413, 1691, 2146) and pigs (799, 991, 1104). These results argue strongly against modulation of HPV by thromboxane.

III) Leukotrienes. Leukotrienes C_4, D_4, and E_4 caused pulmonary vasoconstriction in dogs (1902), guinea pigs (26, 734), humans (736, 1723, 1994), pigs (1062, 1476, 1520), rats (504), and sheep (19, 20, 918, 1726). Early studies appeared to support a role for leukotrienes in mediation of HPV, as hypoxia was reported to increase leukotriene synthesis in rat lungs (1320) and inhibitors of leukotriene synthesis and receptors to decrease HPV in lambs (1583, 1734), pigs (1221), and rats (1319). In contrast, more recent studies demonstrated that hypoxia did not increase leukotriene synthesis in parenchymal lung cells (1475) or isolated lungs (1232, 1726, 1727). Moreover, inhibition of lipoxygenase or leukotriene receptors did not inhibit HPV in lungs of dogs (590, 1124, 1902), ferrets (647, 1938), pigs (1062), rats (1232), and sheep (1485, 1727) or hypoxic contractions in isolated pulmonary arteries of guinea pigs (1926), pigs (1282), and rats (139). These data indicate that leukotrienes neither mediate nor facilitate HPV. Interestingly, moderate hypoxia increased contractile responses of isolated porcine pulmonary arteries to leukotrienes, suggesting an increase in pulmonary vascular responsiveness (1476). If this increased responsiveness occurred during in vivo hypoxia, leukotrienes either were not available in sufficient concentration to cause vasoconstriction or their vasoconstrictive effects were cancelled by vasodilator influences.

IV) Hydroxy- and cis-epoxyeicosatrienoic acids. Arachidonic acid can also be metabolized by cytochrome *P*-450, which produces midchain hydroxyeicosatetraenoic (HETE) and *cis*-epoxyeicosatrienoic (EET) acids in PAEC and PASMC (2184, 2217). HETE and EET can cause either pulmonary vasodilation (175, 877, 1832, 2165) or vasoconstriction (575, 1132, 1832, 2135, 2216), depending in part on the level of pretone (1831). EET can be further metabolized by soluble epoxide hydrolase, forming dihydroxy derivatives (DHET). The possible roles of these metabolites in mediation and modulation of HPV are discussed in section III*A4*C.

V) Other endothelium-derived contracting factors. As noted above, in some studies of isolated precontracted pulmonary arteries, contractile responses to hypoxia were blocked by endothelial denudation, but unaffected by ET_A- and/or combined ET_A/ET_B receptor blockade (429, 578, 1038). In rings of endothelium-denuded porcine pulmonary arteries, insertion of cardiac pulmonic valve leaflets (which are lined with endothelium) into the rings restored hypoxic contractions that were unaffected by indomethacin or L-NAME (578); however, the effects of ET antagonists on this restoration were not determined. More recently, it was reported that factor(s) released into the perfusate of isolated rat lungs during hypoxia caused sustained constriction of isolated normoxic rat pulmonary arteries that was not associated with an increase in $[Ca^{2+}]_i$ or blocked by antagonists of ET receptors or PKC (1643). These results suggested that a diffusible, unidentified EDCF contributed to HPV by increasing myofilament Ca^{2+} sensitivity in PASMC. Consistent with this possibility, rabbit distal pulmonary arteries exposed to 45 min of hypoxia (P_{O_2} = 9 mmHg) exhibited progressive vasoconstriction that did not fully reverse upon resumption of normoxia; however, complete reversal could be achieved by refreshing the myograph bath, and vasoconstriction was subsequently regenerated by reapplication of the original bath solution, suggesting that it contained a soluble vasoconstrictor released from the artery during hypoxia (1886). The source and nature of this vasoconstrictor remains unknown, as the presence of functioning endothelium was not confirmed and pharmacological testing was not performed.

More recently, it was proposed that NO-dependent release of zinc from metallothionein in endothelial cells during hypoxia could contribute to HPV by causing endothelial cell contraction and secondary constriction of nonmuscular pulmonary vessels (153). In support of this proposal, hypoxia was found to constrict intra-acinar pulmonary arteries <40 μm in diameter, contract isolated pulmonary but not aortic endothelial cells, and increase NO production and NO-dependent release of zinc in PAEC. Furthermore, HPV was blunted in isolated lungs of metallothionein-deficient mice and rats or mice treated with a zinc chelator; and enhanced by an NO donor in lungs of mice treated with

antagonists of soluble guanylate cyclase and K_{Ca} channels to block NO-dependent vasodilation (153). However, as discussed in section IV*B2*A, many investigators have shown that HPV not only persists but is enhanced after complete blockade of NOS. On this basis, it seems unlikely that NO-dependent zinc release in endothelium is a major modulator of HPV in muscular pulmonary arteries. To determine whether it has this effect in nonmuscular pulmonary vessels will first require confirmation that constriction of these vessels during hypoxia is active and not simply the passive result of HPV in upstream muscular arteries (see sect. II*A4*B).

C. Local and Blood-Borne Humoral Agents

1. Adenosine

Adenosine, a product of AMP or *S*-adenosylhomocysteine metabolism, is a local regulator of cell function. Binding to its cell surface receptors and transducing signals through G protein-coupled adenylyl cyclase, adenosine has been shown to cause marked vasodilation in most vascular beds (272, 648, 985, 1053, 1209, 1273, 1366, 1586, 1671, 1839, 1875, 1923). Four distinct subtypes of adenosine receptors have been characterized and cloned: A_1, A_{2A}, A_{2B} and A_3. A fifth (A_4) has been proposed, but may be a variation of an already identified subtype. The distribution of receptor subtypes varies with vascular bed; however, most vascular responses to adenosine appear to be mediated by A_1, A_{2A}, and A_{2B}. All three of these receptor subtypes have been characterized in the lung (1218), where adenosine can elicit both relaxation and contraction of pulmonary arteries, depending in part on baseline vasomotor tone (299, 1366, 1656). For example, adenosine caused vasodilation in isolated or intact lungs of cats (1366, 1367), dogs (1265), ferrets (648), humans (574, 1605), lambs (987), rabbits (1484), and rats (761, 1656), and isolated pulmonary arteries of guinea pigs (1656), rabbits (469), and rats (1656); whereas vasoconstriction was reported in intact sheep (169), left lower lobes of intact cats (299, 1365), and isolated pulmonary arteries of guinea pigs (221) and rats (1656).

Hypoxia increased adenosine concentration in dog lungs (1265), and exogenous adenosine or blockers of adenosine uptake strongly inhibited HPV in intact lambs (987), isolated rat (761) and ferret lungs (648), and left lower lobes of intact dogs (1265). These results suggested that adenosine might act as an inhibitory modulator of HPV; however, blockade of adenosine receptors or decreasing endogenous adenosine levels with adenosine deaminase had no effect on HPV in precontracted rat pulmonary arteries (900, 2146) or isolated ferret lungs (648). Thus there is currently no definitive evidence that adenosine modulates HPV.

2. Histamine

Observations that mast cells located near small pulmonary arteries degranulated and released histamine in response to acute hypoxia led to speculation that histamine derived from mast cells made an important contribution to HPV (699). In support of this possibility, acute hypoxia increased plasma histamine levels in guinea pig (699) and dog (1613), and infused histamine caused pulmonary vasoconstriction in cat (104, 369, 755, 1541) and dog (714, 718). Studies in isolated rat and ferret lungs (101, 754, 755) and cat lung lobes perfused in situ (104) reported that antihistamines or depletion of pulmonary histamine stores with the agent compound 48/80 prevented or reduced HPV without affecting responses to other agonists; however, other studies in guinea pig (718), cat (101, 1541), human (1827) and dog (1613, 1948) found that blockade of histamine receptors or depletion of histamine stores had no effect on HPV. Similarly, prestimulation of isolated pulmonary arteries and veins with histamine enhanced hypoxic contraction in some vessels (198, 815, 1282) but not others (198, 506). Finally, lung mast cell density was inversely correlated to HPV in cats (1203); FPL 55618, a disodium cromoglycate analog thought to stabilize mast cells, had no effect on HPV in cats or rats (101); and HPV was unaltered in mice deficient in mast cells (2218). Some of these discrepancies could be related to species differences or drug nonspecificity. For example, only one of three antihistamines inhibited HPV in dogs (1855), and the concentration of compound 48/80 found to attenuate HPV did not affect histamine content in lungs or blood of cats (368). Overall, the results imply that histamine does not play a crucial role in HPV, but could facilitate the response in some species under some circumstances.

3. Angiotensin II

Circulating angiotensin I, a product of the renin-angiotensin system, is converted to the vasoactive peptide angiotensin II (ANG II) in the lung by means of endothelium-bound angiotensin converting enzyme (ACE). Exogenous ANG II caused vasoconstriction in lungs of cats (1552), dogs (625, 1405), humans (258), mice (494), pigs (1221), rabbits (2063), and rats (121, 566, 1240, 2039) as well as in isolated pulmonary arteries of dogs (1887) and rats (200, 1652). Under normoxic conditions, some studies showed that ACE inhibition or angiotensin II receptor blockade reduced pulmonary vasomotor tone (259, 625, 1405), suggesting basal activation of the renin-angiotensin system; however, others failed to confirm these effects (720, 823, 959, 997, 1552).

Investigations of the role of ANG II in HPV have produced inconsistent results. Acute hypoxia was reported to both increase (823, 1089) and decrease (997) plasma renin activity in dogs. Hypoxia had no effect on conversion of ANG I to ANG II in endothelial cells (1874) or fetal lung allografts

in hamster cheek pouch (1765), but decreased ACE activity in anesthetized or conscious dogs (997, 1873) and isolated rabbit lungs (1628), possibly due to an HPV-induced decrease in endothelial surface area (1433). ANG I or ANG II increased normoxic pulmonary vasomotor tone and HPV in cats (1851), dogs (31), and rats (152, 1240, 1851), but not ferrets (1851). Although an initial study in isolated rat lungs perfused with physiological salt solution concluded that enhancement of HPV by ANG II was specific for both HPV and ANG II (152), this was not confirmed by a subsequent study in the same preparation, which found that increases in normoxic pulmonary vasomotor tone, whether caused by ANG II or other interventions, enhanced vasoconstrictor responses to both hypoxia and KCl (1240). Antagonists of ACE or ANG II receptors did not prevent HPV in dogs (720, 823, 997), cats (1552), or isolated rat lungs (509, 1242), but attenuated HPV in humans (259, 958) and neonatal piglets (249). Although the explanation for these discrepancies is unknown, the data suggest that ANG II may sometimes facilitate HPV.

4. 5-Hydroxytryptamine

Pulmonary neuroendocrine cells secrete various vasoactive substances in response to airway hypoxia and hypercapnia, including 5-HT (904, 1037). A 5-HT transporter protein (SERT) in plasma membranes allows circulating 5-HT to be taken up by cells, including pulmonary endothelial cells and platelets, where it is stored and subsequently released during aggregation. 5-HT constricts the pulmonary vasculature, although its potency varies greatly among species (23, 100, 104, 189, 279, 330, 349, 372, 614, 677, 793, 1112, 1152, 1314, 1315, 1541, 1629, 2017, 2052).

Exposure of neuroepithelial bodies to hypoxia caused depletion of 5-HT, which was reversed by normoxia, suggesting hypoxia-induced 5-HT release (563, 944, 945). Pretreatment with 5-HT enhanced HPV in conscious rats (463) and isolated pulmonary arteries (139, 392, 393, 900, 1151, 1959–1961). Increases in right ventricular systolic pressure induced by acute hypoxia were potentiated in mice lacking the SERT gene (459). Dexfenfluramine, an anorexigen whose many effects include competition with 5-HT for uptake by SERT (1153), enhanced HPV in dogs previously unresponsive to hypoxia (1350) and rats (462). These observations suggest that 5-HT could facilitate HPV in vivo; however, 5-HT receptor antagonists, including lysergic acid and ketanserin, blocked pressor responses to 5-HT but did not alter HPV in perfused lungs (100, 766, 1112) or intact dogs (1350), making this possibility unlikely.

D. Pulmonary Nerves

The lung is innervated with autonomic and sensory nerves (35, 246, 532, 1007, 1627). Since HPV occurs in isolated lungs, pulmonary arteries, and PASMC, these nerves are obviously not required for the response; however, they could modulate HPV.

1. Sympathetic nerves

Postganglionic sympathetic nerves originate in cervical and thoracic ganglia, and in many species are most numerous around pulmonary arteries and veins at the hilum, progressively less numerous in more peripheral vessels, and absent in arteries <30–50 μm in diameter. In rat and mouse, however, sympathetic innervation does not extend beyond proximal intrapulmonary vessels near the hilum (273, 430, 530, 701). Although sympathetic nerves typically release norepinephrine, some also release cotransmitters such as ATP and neuropeptides, in particular neuropeptide Y (1007). While ATP is stored and released with norepinephrine, neuropeptides are stored in distinct dense-core vesicles, allowing for differential transmitter release based on stimulation frequency (311). In the guinea pig lung, where colocalization studies have been performed, all adrenergic fibers appear to contain neuropeptide Y, while a small population of neuropeptide Y-containing nonadrenergic nerve fibers also exists (1007).

In normoxic intact animals with controlled pulmonary perfusion, α-adrenergic agonists caused pulmonary vasoconstriction (100, 104, 1539, 1540, 1660, 1787, 1788), while β-adrenergic agonists caused dilation (104, 1540, 1788). In anesthetized cats, sympathetic nerve stimulation caused constriction of pulmonary arteries 200–500 μm in diameter, and this constriction was enhanced by β-adrenergic blockade (propranolol), reversed by α-adrenergic blockade (phentolamine), and eliminated by combined α- and β-adrenergic blockade (1783). In pithed rats, stimulation of preganglionic sympathetic nerves increased PVR during normoxia and enhanced the increase in PVR caused by hypoxia (1287). Moderate hypoxia did not increase circulating norepinephrine or epinephrine levels in humans (623); however, pulmonary sympathetic nerve activity in anesthetized cats did not increase until PaO_2 fell below 45 mmHg and did not reach a maximum (250% of control) until PaO_2 = 15 mmHg (1780). Hypoxic contractions in isolated pulmonary arteries were enhanced by α-adrenergic agonists (60, 139, 198, 876, 991, 1131, 1151, 1413, 1652, 2089, 2206) and inhibited by β-adrenergic agonists (1417, 1418). Collectively, these results suggest that the effect of sympathetic activity on HPV in vivo, if any, would depend on the severity of hypoxia and the balance between α- and β-adrenergic activity.

Most experiments in intact animals suggest that sympathetic activity has no effect on HPV. For example, HPV was not altered by surgical sympathectomy (1872), chemical sympathectomy with 6-hydroxydopamine (722, 1346, 1941), α-receptor blockade (1076, 1168, 1787), β-receptor blockade (1076, 1168, 2102), combined α- and β-receptor blockade (1118), ganglionic blockade (1118), or depletion

of catecholamines with reserpine (100, 623, 1787). Similar findings were obtained in isolated lungs (359, 754, 1112, 1116).

In contrast, HPV was attenuated by blockade of α-adrenergic receptors and enhanced by blockade of β-adrenergic receptors in intact and isolated dog lungs (220, 1112) and cat lungs or lung lobes perfused in situ in anesthetized animals (100, 104, 1539). In intact cats, hypoxic constriction of distal pulmonary arteries and veins was enhanced by propranolol or ganglionic blockade + adrenalectomy (1782). Thus it is possible that sympathetic activity modulates HPV in vivo under certain conditions. One possible example is high-altitude pulmonary edema (see sect. VC2).

2. Parasympathetic nerves

Postganglionic parasympathetic nerves originate from ganglia located along airways and vessels, and release ACh and/or other transmitters such as NO and vasoactive intestinal polypeptide (VIP) (35, 400, 1238). Their vascular distribution is similar to that of sympathetic nerves; however, parasympathetic innervation is generally less dense (274, 468, 701). The extent to which ACh, NO, and VIP colocalize within parasympathetic nerves has not been well studied in the pulmonary vasculature, although NOS-containing axons do not extend as far into the guinea pig lung as do cholinergic axons (701).

In most cases, the parasympathetic nerves appear to relax the pulmonary vasculature, e.g., stimulation of cholinergic nerves in the intact cat lung caused NO-dependent relaxation when tone was enhanced with U46619 (1238). In rat (681), guinea pig (1108, 1109, 1163, 1744), cat (1003), neonatal pig (632), and human (1743), noncholinergic parasympathetic nerves caused pulmonary vasodilation through activation of nNOS, which was detected in nerve fibers surrounding and within walls of conduit pulmonary arteries (681). In some cases, noncholinergic neural relaxation was only partially resistant to NOS inhibition (681, 1743), suggesting that other neurotransmitters participate in the response. One possibility is VIP, which induces vasodilation in precontracted rat lungs that is partially mediated by NO (870).

Only a few studies have examined the role of parasympathetic nerves in HPV. Bilateral cervical vagotomy and/or atropine did not alter HPV in dogs (1068) or fetal lambs (1076), suggesting that parasympathetic nerves do not modulate HPV. Consistent with this possibility, total autonomic blockade with hexamethonium had no effect on HPV in conscious dogs (1118). On the other hand, hypoxemic stimulation of carotid chemoreceptors in anesthetized dogs virtually abolished the diversion of pulmonary blood flow to the right lung that occurred during left lung hypoxia in the absence of chemoreceptor stimulation (2102). Moreover, this inhibition was prevented by vagotomy or atropine. These results suggested that carotid chemoreflexes acting via parasympathetic nerves inhibited HPV. A subsequent study in a similar preparation, however, revealed that this inhibition did not occur if $P_{mv}O_2$ were not allowed to fall to typical levels (15–20 mmHg) during systemic hypoxemia, but were instead maintained >30 mmHg (1492). These results suggested that inhibition of flow diversion by systemic hypoxemia was due to the accompanying decrease in $P_{mv}O_2$, which induced HPV in the normoxic lung, diminished HPV in the hypoxic lung (see sect. II*A*, *2* and *3*), or both. The relative importance of the roles played by $P_{mv}O_2$ and parasympathetic chemoreflexes in the inhibition of HPV by systemic hypoxemia remains unclear.

3. Sensory nerves

Sensory (afferent) nerve fibers, which not only transmit signals to the central nervous system but also produce local effects, have also been described in the lung. Sensory neurons can be identified by sensitivity to capsaicin and production of calcitonin gene-related peptide (CGRP), substance P, neurokinin A, and/or neurokinin B, all of which are derived from the preprotachykinin A gene. In general, pulmonary vascular sensory innervation is not as prevalent as sympathetic or parasympathetic innervation (35, 246, 1007); however, CGRP/substance P-containing fibers can be found around pulmonary arteries in guinea pig (1007), pig (1204), human (35), and rat (246). In some cases, these fibers extend along the vasculature to precapillary arterioles (35) and capillaries (246).

CGRP and substance P have little effect on normal pulmonary tone but cause relaxation of the precontracted pulmonary vasculature (1204, 1223, 1239). Thus it could be hypothesized that activation of sensory nerve fibers might act to limit HPV. However, in the rat, desensitization of sensory nerves with capsaicin had little effect on the pressor response to hypoxia, suggesting that these nerves are not important modulators of HPV (1222). More studies are needed to confirm this conclusion.

V. ROLES

A. Fetal-Neonatal Transition

Fetal gas exchange occurs in the placenta. Of the combined cardiac output from right and left ventricles in the fetus at term, <10% in sheep (1673) and ~25% in humans (1590) enters the lungs. Pulmonary vascular resistance (PVR) is higher than systemic vascular resistance, creating a pressure gradient that drives most of the output of the right ventricle through the ductus arteriosus, which links the main pulmonary artery to the descending aorta. Structural factors, including compression of small pulmonary arteries by fluid-filled alveoli and less numerous, more muscular small pulmonary

arteries, contribute to the high fetal PVR (1673). In late gestation, low fetal blood P_{O_2} may also play a role, possibly by suppressing NO release, since the marked fall in fetal PVR caused by increasing fetal blood oxygenation was inhibited by the NOS antagonist N^G-monomethyl-L-arginine (1589, 1908).

At birth, multiple interacting processes triggered by initiation of lung ventilation and increases in blood P_{O_2} cause a profound fall in PVR and closure of the ductus arteriosus, leading to a rapid and dramatic increase in pulmonary blood flow (265, 367). Factors released from pulmonary endothelium are thought to be crucial for pulmonary vasodilation at birth. Early investigations provided evidence that PGI_2 and possibly other vasodilating prostanoids are important for the response to lung ventilation, but perhaps less important for the response to increasing blood P_{O_2} (5, 1061, 1063, 1915, 1971). Interest in the involvement of NO developed quickly upon its identification as EDRF, and it was found that NOS inhibitors markedly attenuated the perinatal fall in PVR (6, 336, 1313). Although the relative contributions of PGI_2 and NO to this response remain unresolved, the weight of evidence indicates that NO is comparatively more important, except perhaps in the rat (645). Indeed, PGI_2 may act as a pulmonary vasodilator primarily by causing NO release, at least in the late term lamb fetus (2186). Endothelin (869) and the unidentified substance bronchial-derived relaxing factor (136) have also been proposed to promote perinatal NO release. However, despite many pharmacological studies indicating the importance of NO for pulmonary vasodilation at birth, $eNOS^{-/-}$ mice survived birth as well as wild-type control mice, suggesting that other mechanisms are able to replace NO in this respect, at least in this species (1281). Detailed reviews of the roles of PGI_2 and NO and other proposed mediators such as endothelin, PGD_2, and leukotrienes C_4 and D_4 in the hemodynamic transition of the pulmonary circulation from fetal to postnatal life are available (524, 605, 758, 776, 1072, 1073, 1673, 1755, 2220).

Regardless of the effects of these substances on the pulmonary vasculature at birth, it is clear that, as in adults, increases in O_2 can act directly on fetal PASMC to regulate membrane potential and $[Ca^{2+}]_i$ in such a way as to cause vasodilation. Interestingly, however, it is BK_{Ca} rather than K_V channels that seem to mediate the effects of O_2 in the fetus. In cultured PASMC from third-order pulmonary arteries of late gestation fetal lambs, hypoxia caused a gradual increase in $[Ca^{2+}]_i$, which was abolished by exposure to low extracellular $[Ca^{2+}]$ and did not occur in myocytes from main pulmonary or carotid arteries (341). The rise in $[Ca^{2+}]_i$ in these cells was strongly inhibited by verapamil, enhanced by BAY K 8644, and accompanied by membrane depolarization, pointing to involvement of L-type VOCC. Iberiotoxin but not glibenclamide also increased $[Ca^{2+}]_i$, indicating that inhibition of BK_{Ca} channels might explain the effects of hypoxia (340). The hypoxia-induced rise in $[Ca^{2+}]_i$ became transient in the presence of 10^{-7} M ryanodine, consistent with the possibility that P_{O_2} might control BK_{Ca} channel activation by altering Ca^{2+} spark activity (880). Consistent with this possibility, distal fetal PASMC maintained under hypoxic (i.e., fetal) conditions responded to normoxia with a fall in $[Ca^{2+}]_i$ that was abolished by both ryanodine and iberiotoxin. The frequency of STOC, indicative of spark-dependent opening of BK_{Ca} channels, was also increased by normoxia (1543).

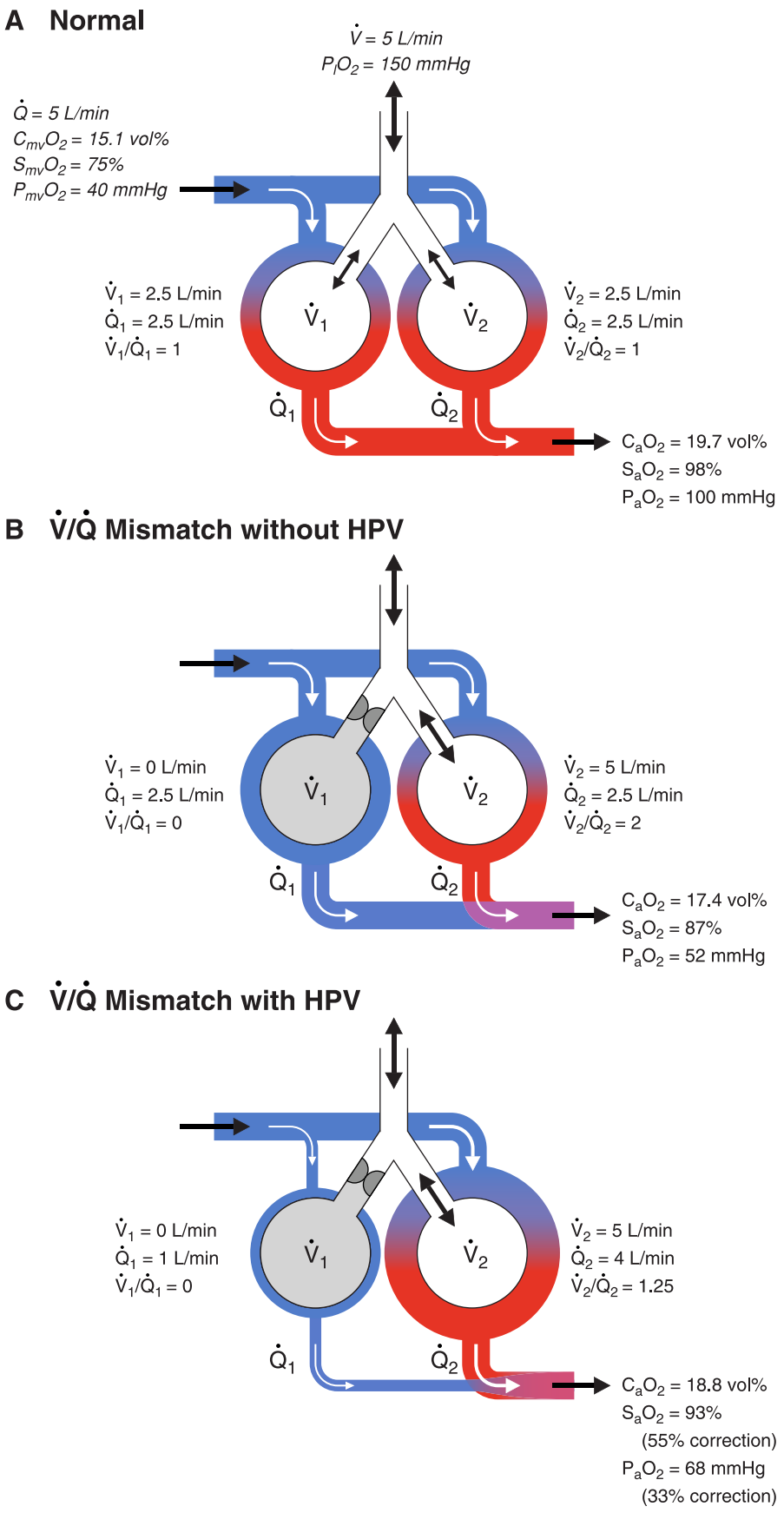
In freshly isolated myocytes from fourth- to fifth-order fetal lamb pulmonary arteries, the K^+ current was small under hypoxic conditions and greatly enhanced by normoxia (338, 1599). Under normoxic conditions, I_K was strongly inhibited by iberiotoxin, charybdotoxin, and TEA, and associated with STOC, indicating that it was carried by BK_{Ca} channels. Normoxia also caused membrane hyperpolarization of ~13 mV. A comparison of fetal and adult PASMC showed that I_K in the latter was larger and more sensitive to the K_V channel inhibitor 4-AP. The response in fetal cells was also blocked by the PKG inhibitor KT5823 and mimicked by NO. It was concluded that O_2 opened BK_{Ca} channels by activating a cyclic nucleotide-dependent protein kinase, possibly PKG (338); however, how hypoxia was able to do this in the absence of endothelium-derived factors was not established. An increase of P_{O_2} from ~40 to ~150 mmHg also increased I_K and caused hyperpolarization (~9 mV) in myocytes from fourth-order rabbit pulmonary arteries (808). The increase in I_K was greatly enhanced if cells were held at a depolarized potential to inactivate K_V currents. Under these conditions, the current was then dramatically reduced by iberiotoxin, indicating that it was predominantly due to activation of BK_{Ca} channels.

In addition to these studies carried out in cells, in vivo experiments established that infusion of BK_{Ca} channel inhibitors into the fetal circulation attenuated the fall of PVR associated with several birth-related stimuli (338, 1707, 1842, 1932). A similar effect was found for ryanodine (1543, 1707). Together with the results in cells, these observations suggest that the direct effects of increasing P_{O_2} on PASMC make an important contribution to perinatal pulmonary vasodilation; however, plasma levels of both NO and PGI_2 also increase at birth, and both factors can activate BK_{Ca} channels. Thus it remains unclear whether inhibition of pulmonary vasodilation at birth by BK_{Ca} channel antagonists was due to blockade of direct activation of BK_{Ca} channels in PASMC by O_2, or indirect activation by NO and PGI_2 (338, 1912).

B. Pulmonary Gas Exchange

1. Overview

In 1922, Haldane pointed out that "the mean composition of the contained air [in a region of lung] will depend on the ratio between the supply of fresh air and the flow of blood. If the supply of fresh air is unusually small in relation to the



supply of venous blood, there will be a lower percentage of oxygen and higher percentage of carbon dioxide in the air of the air sac, and vice versa (715)." In other words, diffusion of O_2 and CO_2 between alveolar gas and pulmonary capillary blood will achieve equilibrium at alveolar partial pressures (P_AO_2, P_ACO_2) determined by inspired and mixed venous partial pressures of O_2 (P_IO_2, $P_{mv}O_2$) and CO_2 (P_ICO_2, $P_{mv}CO_2$) and the ratio of alveolar ventilation to perfusion ($\dot{V}_A/\dot{Q}$). During rest at sea level, P_IO_2 and P_ICO_2 ≈150 and 0 mmHg and $P_{mv}O_2$ and $P_{mv}CO_2$ ≈40 and 43 mmHg, respectively. The normal mean $\dot{V}_A/\dot{Q}$ is ~1, but $\dot{V}_A/\dot{Q}$ of individual lung units can vary from 0 (right-to-left shunt: zero $\dot{V}_A$, finite $\dot{Q}$) to infinity (deadspace: finite $\dot{V}_A$, zero $\dot{Q}$). As $\dot{V}_A/\dot{Q}$ of a lung unit approaches 0, P_AO_2 and P_ACO_2 in that unit approach their mixed venous values. As $\dot{V}_A/\dot{Q}$ approaches infinity, P_AO_2 and P_ACO_2 approach their inspired values.

Regional variation of $\dot{V}_A/\dot{Q}$ in normal lungs is due to gravity, which causes relatively greater perfusion (and thus lower $\dot{V}_A/\dot{Q}$) in dependent lung regions through effects on pleural and vascular pressures; lung structure, which determines the fundamental resistances to regional air and blood flow; and the tone of airway and vascular smooth muscle, which can alter these resistances. Assuming a parallel arrangement of lung units and no extrapulmonary right-to-left shunt, the concentrations of O_2 and CO_2 in systemic arterial blood (C_aO_2, C_aCO_2) are simply the perfusion-weighted means of the O_2 and CO_2 concentrations in blood flowing from each lung unit, and systemic arterial partial pressures (P_aO_2, P_aCO_2) are the partial pressures corresponding to these mean concentrations, i.e., for given levels of inspired and mixed venous partial pressures, P_aO_2 and P_aCO_2 are determined by the $\dot{V}_A/\dot{Q}$ ratios of individual lung units, and the distribution of $\dot{V}_A/\dot{Q}$ among these units. Thus, for the lung to fulfill its major function, pulmonary perfusion and ventilation must be appropriately matched.

An illustration of the effects of $\dot{V}_A/\dot{Q}$ mismatch on P_aO_2 in a simple two-compartment lung is shown in **FIGURE 12.** In a normal lung breathing air at sea level **(FIGURE 12*A*)**, ventilation and perfusion are matched ($\dot{V}_A/\dot{Q}$ = 1) in both compartments, yielding an O_2 concentration of 19.7 vol%, oxyhemoglobin saturation of 98%, and P_{O_2} of 100 mmHg in blood flowing from the compartments. Since systemic arterial blood flow is the sum of compartmental blood flows, C_aO_2, S_aO_2, and P_aO_2 will also equal 19.7 vol%, 98% and 100 mmHg, respectively. However, if ventilation to one compartment were completely obstructed without changing perfusion, $\dot{V}_A/\dot{Q}$ would decrease to 0 in the obstructed compartment (right-to-left shunt) and increase to 2 in the nonobstructed compartment, which would now receive all of the ventilation **(FIGURE 12*B*)**. Under these conditions, O_2 concentration in blood flowing from the obstructed compartment would be the same as that in mixed venous blood (15.1 vol%) while that in blood flowing from the nonobstructed compartment would remain virtually unchanged (19.7 vol%). Thus, with equal blood flow from each compartment, C_aO_2 would be the average of these values, or 17.4 vol%, corresponding to an SaO_2 of 87% and P_aO_2 of 52 mmHg.

The question of how ventilation and perfusion are matched was addressed by von Euler and Liljestrand in 1946 (1987). These investigators found that decreasing P_IO_2 or increasing P_ICO_2 in intact anesthetized cats caused acute increases in P_{PA}, whereas increasing P_IO_2 caused P_{PA} to fall **(FIGURE 2*B*)**. With more insight than evidence, they concluded that these responses were due to changes in pulmonary vasomotor tone triggered by local actions of O_2 and CO_2. In addition, they proposed that "If the blood flow becomes inadequate in relation to ventilation in some parts of the lungs, the corresponding alveolar air will become richer in oxygen and poorer in carbon dioxide than the rest of the lungs. But this will lead to a dilatation of the blood vessels of that part of the lungs with a redistribution of blood flow as a consequence. It is interesting to note that oxygen want and carbon dioxide … call forth a contraction of the lung vessels, thereby increasing the blood flow to better aerated lung areas, which leads to improved conditions for the utilization of alveolar air."

Consistent with this proposal, numerous reports subsequently demonstrated that ventilating a sublobar lung region (653, 1012), lung lobe (103, 141, 143, 422, 1192, 1645, 1761, 1764, 1852), or an individual lung (355, 380, 415, 421, 473, 717, 719, 778, 1192, 1435, 1579, 1823, 1825, 1999) with an hypoxic gas mixture (F_IO_2 = 0–13%) while ventilating the remaining lung with a normoxic or hyperoxic gas mixture decreased blood flow in the hypoxic region by 20–100%. Since total flow was unaltered, these decreases represent diversion of flow from hypoxic to nonhypoxic lung due to HPV in hypoxic lung. From the perspective of pulmonary gas exchange, this diversion im-

FIGURE 12 Effects of ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships on oxygen exchange in a 2-compartment lung during normal conditions (*A*), $\dot{V}/\dot{Q}$ mismatch without hypoxic pulmonary vasoconstriction (HPV) (*B*), and $\dot{V}/\dot{Q}$ mismatch with HPV (*C*). Values for total ventilation ($\dot{V}$), inspired O_2 tension (P_IO_2), total cardiac output ($\dot{Q}$), and mixed venous O_2 concentration ($C_{mv}O_2$), tension ($P_{mv}O_2$), and hemoglobin saturation ($S_{mv}O_2$) shown in A were the same for all conditions. Compartmental ventilation ($\dot{V}_1$, $\dot{V}_2$), perfusion ($\dot{Q}_1$, $\dot{Q}_2$), ventilation-perfusion ratio ($\dot{V}_1/\dot{Q}_1$, $\dot{V}_2/\dot{Q}_2$), the resulting systemic arterial O_2 concentration (C_aO_2, calculated as the perfusion-weighted mean of the O_2 concentrations in blood flowing from each compartment) and corresponding systemic arterial oxyhemoglobin saturation (S_aO_2) and O_2 tension (P_aO_2) are also indicated for each condition. For simplicity, O_2 concentrations were calculated as the product of hemoglobin concentration (15 g/dl), hemoglobin O_2 binding capacity (1.34 vol% per g/dl), and oxyhemoglobin saturation, and ignore the concentration of O_2 physically dissolved in plasma, which would be small at these O_2 tensions. Vol% indicates ml O_2 (STPD)/100 ml blood.

proves P_aO_2 by increasing $\dot{V}_A/\dot{Q}$ (and therefore P_AO_2) in the hypoxic region and decreasing flow from the hypoxic region to the systemic vasculature. These improvements are offset to some extent by decreased $\dot{V}_A/\dot{Q}$ in nonhypoxic lung regions caused by the increase in their perfusion due to diversion, but this effect is usually small.

Using the mismatched two-compartment lung as an example (**FIGURE 12, *B* AND *C***), if HPV reduced perfusion of the obstructed compartment by 60% (i.e., from 2.5 to 1 L/min), its $\dot{V}_A/\dot{Q}$ ratio would remain 0 and O_2 concentration in its exiting blood would remain 15.1 vol%. In the nonobstructed compartment, $\dot{V}_A/\dot{Q}$ would decrease from 2 to 1.25 due to blood flow diversion from the obstructed compartment, but O_2 concentration in its exiting blood would remain virtually unchanged (19.7 vol%). However, blood flow from the nonobstructed and obstructed compartments would now constitute 80 and 20%, respectively, of total blood flow. Since C_aO_2 is the perfusion-weighted average of O_2 concentrations in blood flowing from each compartment, HPV-induced flow diversion would increase C_aO_2 to (0.8)(19.7 vol%) + (0.2)(15.1 vol%), or 18.8 vol%, corresponding to an S_aO_2 of 93% and P_aO_2 of 68 mmHg. Thus HPV corrected the hypoxemia due to ventilation-perfusion mismatch by 55% in terms of S_aO_2 and 33% in terms of P_aO_2.

2. *Effectiveness of pulmonary blood flow diversion by HPV*

The degree to which perfusion is diverted from hypoxic to nonhypoxic lung by HPV will depend on *1)* the magnitude of HPV and *2)* the size of the hypoxic region, both of which are discussed above (see sect. II*A*). In the context of $\dot{V}_A/\dot{Q}$ matching, it is worth emphasizing here that maximum steady-state HPV generally occurs at P_AO_2 of 25–50 mmHg; therefore, blood flow diversion should also be maximum at these O_2 tensions. However, HPV magnitude may decrease at P_AO_2 <25 mmHg, leading to reduced diversion, deterioration of $\dot{V}_A/\dot{Q}$ matching, and worsening hypoxemia. Although such low P_AO_2 is unlikely to occur in normal animals breathing air at sea level, it could occur in the setting of lung disease or exposure to high altitude.

In addition, the effects of P_ACO_2 on HPV magnitude (see sect. II*A5*D) deserve emphasis. If a lung region is ventilated at constant rate and volume with an hypoxic gas mixture not containing CO_2, as in the studies cited above, a decrease in regional perfusion due to HPV will lower regional P_ACO_2 as a consequence of an increased regional $\dot{V}_A/\dot{Q}$ (141, 1012, 1579, 1645, 1761). The vasodilatory effects of local hypocapnia could limit HPV-dependent diversion of regional blood flow. This apparently occurred in lung lobes of dogs (103, 141, 143, 1435) and sheep (1645, 1761, 1764), where addition of CO_2 to the inspired gas enhanced diversion caused by decreases in regional F_IO_2, but not in sublobar lung regions of coati mundi (653), where CO_2 had no effect. Regional hypocapnia may also be responsible for oscillations in flow diversion seen after F_IO_2 is abruptly decreased from 100 to 0% in the absence of inspired CO_2 (141, 655, 1458, 1764).

Normally, however, regional alveolar hypoxia is caused not by a decrease in F_IO_2, but by hypoventilation occuring as a result of airway mucus plugging or bronchospasm. The resulting decrease in $\dot{V}_A/\dot{Q}$ causes regional P_AO_2 to fall and P_ACO_2 to rise toward mixed venous values, as described by the O_2-CO_2 diagram of Rahn and Fenn (1580). In theory, an increase in regional P_ACO_2 could cause pulmonary vasoconstriction and thereby contribute to flow diversion (103, 141, 143, 1435, 1645, 1761, 1764); however, the magnitude of this effect is likely to be small, because the maximum possible increase in P_ACO_2 is small when $P_{mv}CO_2$ is constant. For example, under normal conditions, regional P_ACO_2 would increase from ~38 mmHg at a regional $\dot{V}_A/\dot{Q}$ of 1 to ~43 mmHg as $\dot{V}_A/\dot{Q}$ approached 0, a maximum possible increase of 5 mmHg. In intact awake sheep, such an increase in the right upper lobe decreased its blood flow by ≤10% (1761). In the coati mundi (653), hypoventilation of a sublobar lung region increased regional P_ACO_2 by only 2 mmHg. Thus acute increases in regional P_ACO_2 due to regional hypoventilation at constant F_IO_2 are unlikely to enhance HPV-dependent flow diversion as long as $P_{mv}CO_2$ is unchanged. In contrast, acute decreases in regional P_ACO_2 due to decreased regional F_IO_2 at constant ventilation could be large and therefore limit HPV-dependent flow diversion.

Finally, as noted in section II*A1*, diversion of blood flow from hypoxic to nonhypoxic lung will be diminished and the HPV-dependent augmentation of P_{PA} enhanced as the size of the hypoxic region becomes larger (1191, 1192, 1717). In the limit where 100% of the lung is hypoxic at the same P_AO_2, HPV increases P_{PA}, but causes no diversion of blood flow, and therefore plays no role in $\dot{V}_A/\dot{Q}$ matching. Conversely, as size of the hypoxic region approaches 0, flow diversion is maximized, the increase in P_{PA} is minimized, and HPV becomes most effective at $\dot{V}_A/\dot{Q}$ matching.

3. *Assessment of the role of HPV in $\dot{V}_A/\dot{Q}$ matching*

Although it is clear that HPV can divert blood flow from hypoxic to nonhypoxic lung, thereby redistributing $\dot{Q}$ with respect to $\dot{V}_A/\dot{Q}$, the task remains to quantify the effects of this redistribution of $\dot{Q}$ on pulmonary gas exchange. To make this assessment, an appropriate parameter of gas exchange, such as P_aO_2 or S_aO_2, must be measured under control and experimental conditions with HPV present and absent, or enhanced and reduced. Ideally, alterations of HPV should be accomplished using methods that do not change pulmonary vasomotor responses to stimuli other than hypoxia or alter other determinants of gas exchange. In the case of O_2, these include $P_{mv}O_2$, P_IO_2, $\dot{Q}$, and $\dot{V}_A$.

The need to control these factors complicates the experimental approach to the problem considerably.

A) MODEL ANALYSES. To cope with these complications, many investigators have used computer-based lung models to quantify the role of HPV in $\dot{V}_A/\dot{Q}$ matching. The most frequently used model is composed of 50–100 parallel compartments (1993). Typically, two compartments are assigned $\dot{V}_A/\dot{Q}$ ratios of 0 (shunt) and infinity (deadspace), while the others have $\dot{V}_A/\dot{Q}$ ratios spaced equally on a logarithmic scale between selected lower and upper limits (e.g., $\dot{V}_A/\dot{Q}$ = 0.005 and 100). $\dot{V}_A/\dot{Q}$ inhomogeneity can be imposed by increasing the standard deviation of the distribution of $\dot{Q}$ with respect to the logarithm of $\dot{V}_A/\dot{Q}$ ($\log SD_{\dot{Q}}$) from its normal range of 0.3–0.6 (1992). Observed stimulus-response relationships between O_2 tension and an index of pulmonary vascular resistance can be applied to determine how HPV alters the effects of a perturbation, such as a change in $\log SD_{\dot{Q}}$, on an outcome variable, such as P_aO_2 or S_aO_2. P_aO_2 or S_aO_2 determined in this manner under control conditions (e.g., normal $\log SD_{\dot{Q}}$) can then be compared with values determined under experimental conditions (e.g., increased $\log SD_{\dot{Q}}$) in the presence and absence of HPV.

A key decision in this approach is which determinants of gas exchange to hold constant. To evaluate the role of HPV in pulmonary gas exchange, it is logical to hold $\dot{Q}$ and $\dot{V}_A$ constant, since changes in these variables could alter overall $\dot{V}_A/\dot{Q}$, P_{PA}, and distribution of $\dot{Q}$ with respect to $\dot{V}_A/\dot{Q}$; and thus change P_aO_2 independently of HPV. At first glance, it would seem logical also to hold $\dot{V}O_2$ constant. In this case, however, if $\dot{Q}$ were also constant and HPV did not compensate perfectly for a perturbation, any deterioration of P_aO_2 would be accompanied by a decrease in $P_{mv}O_2$, which could lead to further deterioration of P_aO_2. Allowing $\dot{Q}$ to respond to hypoxia in a physiologically appropriate manner could limit this effect, but again would complicate assessment of the role of HPV. Although it seems most reasonable to hold $\dot{Q}$, $\dot{V}_A$, P_IO_2, and $P_{mv}O_2$ constant when using models to evaluate the role of HPV in pulmonary gas exchange, in fact a variety of conditions have been used, which must be kept in mind when interpreting results.

This is illustrated by the variability among estimates of the degree to which HPV was able to correct hypoxemia caused by increases in $\log SD_{\dot{Q}}$ or shunt fraction in model simulations (217, 654, 1189, 1193, 1761). The data from these studies allow the percent correction of hypoxemia by HPV to be calculated as in **FIGURE 12** above, i.e., percent correction = $[1 - (X_N - X_{H+})/(X_N - X_{H0})]$, where $X = P_aO_2$ or S_aO_2 and the subscripts N, H+, and H0 indicate normoxic control conditions, hypoxia in the presence of HPV, and hypoxia in the absence of HPV, respectively. Depending on the assumed F_IO_2, severity and type of perturbation, HPV stimulus-response relation, whether the size of the hypoxic region was taken into account and whether $\dot{Q}$, $\dot{V}_A$, $\dot{V}O_2$, or $P_{mv}O_2$ were held constant, correction by HPV in these studies varied between 14–48% for P_aO_2 and 51–87% for S_aO_2. As a specific example, one particularly comprehensive analysis used a two-compartment model (test region, remaining lung) that incorporated effects of local P_AO_2 and P_ACO_2 on local blood flow, as determined in awake sheep from measurements of endogenous methane elimination in gas expired from separately ventilated right apical lobe and remaining lung (1761). Assuming that changes in right apical lobe P_AO_2 and P_ACO_2 did not affect cardiac output, P_{PA}, or mixed venous blood gases and pH (as was observed), and that changes in P_{PA} altered conductances of relaxed and constricted pulmonary vascular beds to the same degree, the authors were able to express local blood flow as a function of both compartment size and local P_AO_2 and P_ACO_2. With an F_IO_2 of 21%, constant $\dot{Q}$, $\dot{V}_A$, and mixed venous blood gases, and solutions limited to those consistent with the O_2-CO_2 diagram of Rahn and Fenn (1580), this analysis predicted that removing ventilation from 60% of the lung would decrease P_aO_2 from 104 mmHg (S_aO_2 ≈98%) to 45 mmHg (S_aO_2 ≈81%) in the absence of HPV and to 63 mmHg (S_aO_2 ≈92%) in the presence of HPV, yielding corrections of 30% for P_aO_2 and 65% for S_aO_2.

Despite the disparate conditions and assumptions, three generalizations seem justified on the basis of these calculations and the absolute levels of P_aO_2 and S_aO_2 predicted by the model analyses (217, 654, 1189, 1193, 1761). First, S_aO_2 may be a more appropriate index of the effects of HPV on oxygenation than P_aO_2 because it is more linearly related to the oxygen content of systemic arterial blood. Second, HPV seems designed to prevent S_aO_2 from falling much below 90%. Third, to achieve this goal in the face of severe deterioration of pulmonary O_2 exchange, HPV must occur over a range of PO_2 higher than that associated with oxyhemoglobin desaturation, and this appears to be the case (see sect. II*A3*).

In many model analyses, results were also expressed in terms of feedback control parameters. The most widely used of these is "gain due to feedback (G_{fb})," defined as the absolute value of $([dy/dx]_0/[dy/dx]_+) - 1$, where x is the perturbing (input) variable (e.g., $\log SD_{\dot{Q}}$ or shunt fraction), y is the controlled (output) variable (e.g., S_aO_2 or P_aO_2), dx and dy represent small changes in these variables, and the subscripts + and 0 indicate the presence and absence, respectively, of HPV (654, 1630). Thus, if HPV had no effect on the controlled variable (i.e., if $[dy/dx]_+ = [dy/dx]_0$), G_{fb} would equal 0. If HPV acted to preserve gas exchange through negative feedback ($[dy/dx]_+ < [dy/dx]_0$), as would be expected on the basis of the above data, the magnitude of G_{fb} would exceed 0 in proportion to the degree of preservation. For example, in the limit where negative feedback by HPV completely prevented a change in the controlled

variable, $[dy/dx]_+$ would equal 0, and G_{fb} would equal infinity. Conversely, if HPV acted to worsen gas exchange through positive feedback ($[dy/dx]_+ > [dy/dx]_0$), G_{fb} would approach 1 as $[dy/dx]_+$ became progressively greater than $[dy/dx]_+$ (1630).

In a multicompartment lung model with a normal degree of $\dot{V}_A/\dot{Q}$ inhomogeneity, P_aO_2 as the controlled variable y, $\log SD_{\dot{Q}}$ as the perturbing variable x, and the HPV stimulus-response relation of the coatimundi, HPV decreased $dP_aO_2/d\log SD_{\dot{Q}}$ (negative feedback) and maximum G_{fb} equaled 0.6 when $\dot{Q}$, $\dot{V}_A$, P_IO_2 and $P_{mv}O_2$ were constant at normal values (653, 654). When $\dot{V}O_2$ rather than $P_{mv}O_2$ was constant and the HPV stimulus-response relation in dogs was used, maximum G_{fb} equaled 0.7 (217). Negative feedback with a G_{fb} of 0.6–0.7 indicates that HPV reduced the change in P_aO_2 that would occur in the absence of HPV by ~40%, calculated as $100([dy/dx]_0 - [dy/dx]_+)/[dy/dx]_0$, or $100(1 - [G_{fb} + 1]^{-1})$. With S_aO_2 as the controlled variable, maximum G_{fb} equaled 1.04, indicating an HPV correction of 51% (217). With both P_aO_2 and S_aO_2, however, G_{fb} decreased as $\dot{V}_A/\dot{Q}$ inhomogeneity ($\log SD_{\dot{Q}}$) increased, indicating a progressive decrease in negative feedback, and eventually revealed positive feedback, or worsening of P_aO_2 and S_aO_2 by HPV (217, 654). Positive feedback could occur if *1)* decreases in O_2 tension caused pulmonary vasodilation (i.e., decreased HPV), as might occur at O_2 tensions <25 mmHg **(TABLE 1)**; *2)* HPV in low $\dot{V}_A/\dot{Q}$ regions diverted flow to regions of even lower $\dot{V}_A/\dot{Q}$, where HPV was already maximum or had diminished (654); or *3)* incomplete correction of P_aO_2 by HPV caused progressive decreases in $P_{mv}O_2$ when $\dot{V}O_2$ was constant (217, 654). On this basis, it was concluded that HPV was not a very effective optimizer of $\dot{V}_A/\dot{Q}$ matching (654, 1258).

Steady-state feedback control analysis, however, may not be the best way to clarify function in a system as complex as whole lung, where multiple variables can interact in multiple feedback loops in multiple compartments in a complicated manner that changes over time. One source of confusion might be G_{fb} itself. In a multicompartment lung with constant $\dot{Q}$, $\dot{V}_A$, and $\dot{V}O_2$, an F_IO_2 of 30%, and severe $\dot{V}_A/\dot{Q}$ inhomogeneity ($\log SD_{\dot{Q}} = 2.0$), G_{fb} determined using P_aO_2 as the controlled variable indicated positive feedback with a magnitude of 0.2, while G_{fb} determined under the same conditions using S_aO_2 as the controlled variable indicated reasonably robust negative feedback with a magnitude of 1.2 (217). It was suggested that this discrepancy occurred because with severe $\dot{V}_A/\dot{Q}$ inhomogeneity HPV moved P_aO_2 and S_aO_2 from a lower steeper part of the Hb saturation curve to a higher flatter part of the curve and, as a result, decreased $[dS_aO_2/d\log SD_{\dot{Q}}]_+$ but increased $[dP_aO_2/d\log SD_{\dot{Q}}]_+$ relative to their values in the absence of HPV. Such considerations emphasize that, as a ratio of "instantaneous" derivatives, G_{fb} does not reveal the cumulative effect of HPV on the controlled variable, e.g., if P_AO_2 in every lung region were low enough to cause maximum HPV, then a further decrease in P_AO_2 would not divert blood flow away from any region. Although $G_{fb} = 0$ under these conditions, it would be wrong to conclude that HPV was not effective at diverting flow, just as it would be wrong to conclude that Hb was not effective at carrying O_2 because dC_aO_2/dP_aO_2 measured at very high P_aO_2 was close to 0 and unaltered by an increase in Hb concentration. Although an accurate G_{fb} might help determine the conditions under which HPV is most capable of compensation, it does not express the overall extent to which HPV has restored P_aO_2 or S_aO_2 in response to interventions causing deterioration of pulmonary gas exchange.

Perhaps due to these complexities and ambiguities, the use of feedback control analysis to quantify the role of HPV in $\dot{V}_A/\dot{Q}$ matching in whole lung models has not gained much traction. Rather, most investigators have resorted to model predictions of overall changes in P_aO_2 and S_aO_2 caused by HPV, as described above, or to experimental manipulation of HPV in real lungs, as described below.

B) EXPERIMENTAL APPROACHES. *I) Strategies and measurements*. Numerous studies have been performed to determine how alteration of HPV affects pulmonary gas exchange. The easiest and most specific way to alter HPV is to change F_IO_2; however, this approach has some disadvantages. The most obvious is that changing F_IO_2 would have a far greater effect on O_2 tension in ventilated than in unventilated (shunt) regions.

To completely inhibit HPV in ventilated lung, most investigators raise F_IO_2 to 100%, which could convert regions of low but finite $\dot{V}_A/\dot{Q}$ to shunt via absorbtion atelectasis (361, 1933, 1992). Although increasing F_IO_2 frequently also increases $P_{mv}O_2$, these increases can be small and unpredictable. An increase in $P_{mv}O_2$ can be better accomplished by veno-venous extracorporeal membrane oxygenation (ECMO), which has been occasionally employed experimentally (146, 178). If sufficiently large, increases in $P_{mv}O_2$ could reverse HPV, particularly in regions of shunt or low $\dot{V}_A/\dot{Q}$ ratios.

To enhance HPV by lowering P_IO_2 or $P_{mv}O_2$ is more problematic. Although decreasing P_IO_2 or $P_{mv}O_2$ could further decrease O_2 tension in hypoxic lung regions and thereby improve $\dot{V}_A/\dot{Q}$ matching through greater diversion of flow to less hypoxic regions, this effect could be limited or reversed by widespread development of HPV in previously normoxic regions and/or stable or decreased HPV due to more severe hypoxia in previously hypoxic regions. As a result, decreasing P_IO_2 or $P_{mv}O_2$ is of limited value in assessing the contribution of HPV, since it could improve, worsen, or not alter gas exchange. Changing F_IO_2 could also alter $\dot{V}_A$ and $\dot{Q}$ (94, 96, 342, 579, 1258, 1261, 1522, 1865, 1866, 1922, 1992), might not be feasible in patients,

would not be useful in experiments where $\dot{V}_A/\dot{Q}$ heterogeneity was generated by decreasing regional F_IO_2 and requires measurements other than P_aO_2 and S_aO_2 to assess its effects on gas exchange.

One way to assess pulmonary gas exchange independently of O_2 is the multiple inert gas elimination technique (MIGET), in which steady-state partial pressures of several inert gases of widely varying solubility (e.g., SF_6, ethane, cyclopropane, halothane, diethyl ether, and acetone) are measured in mixed venous blood (P_{mv}), systemic arterial blood (P_a), and mixed expired air (P_E) as a solution of the gases is infused intravenously at a constant rate (1647, 1993). Inert gases provide two major advantages in the study of pulmonary gas exchange. First, unlike O_2 and CO_2, the relation between partial pressure and concentration of an inert gas in blood can be assumed to be linear, i.e., solubility can be assumed to be constant, which greatly simplifies the analysis. Second, elimination of an inert gas from pulmonary blood by ventilation will depend on its solubility; i.e., the greater its solubility, the greater the ventilation required for its elimination. Thus efficient elimination of an inert gas of very low solubility can occur at very low $\dot{V}_A/\dot{Q}$ ratios, whereas efficient elimination of an inert gas of very high solubility will require very high $\dot{V}_A/\dot{Q}$. Stated another way, each inert gas "looks" at a specific range of $\dot{V}_A/\dot{Q}$ ratios determined by its solubility.

Measurements of inert gas partial pressures in expired air (P_E) and arterial and mixed venous blood (P_a, P_{mv}) allow calculation of several direct indices of gas exchange efficiency, all of which decrease when $\dot{V}_A/\dot{Q}$ matching improves. For example, shunt fraction can be determined from the relation between inert gas solubility and retention ($R = P_a/P_{mv}$). Deadspace fraction can be determined from the relation between solubility and excretion ($E = P_E/P_{mv}$). These results can then be used to calculate mean arterial-alveolar or end capillary-alveolar partial pressure gradients normalized to mixed venous partial pressure [$(P_a - P_A)/P_{mv}$, $(P_{ec} - P_A)/P_{mv}$] for each gas (791, 1374, 1866). Closely related to these gradients are so-called "dispersions," estimated as the sum for all inert gases of root mean square differences between measured E and measured R ($DISP_{R-E}$), measured R and calculated R ($DISP_R$), and measured E and calculated E ($DISP_{E*}$), where calculated R and calculated E assume a homogenous lung with the measured $\dot{Q}$ and $\dot{V}_A$ and calculated E is corrected for deadspace (E*) (579).

In addition, iterative least-squares and smoothing techniques can be used to fit MIGET data to the multicompartment lung model described above (1993) to estimate the distribution of $\dot{V}_A$ and $\dot{Q}$ with respect to $\dot{V}_A/\dot{Q}$. Although the distributions obtained can fit the inert gas data to close tolerances, they are not unique solutions. Nevertheless, a variety of indirect indices derived from these distributions have been used to quantify $\dot{V}_A/\dot{Q}$ matching, including the logarithmic standard deviations of the perfusion and ventilation distributions ($logSD_{\dot{V}}$, $logSD_{\dot{Q}}$) and the fraction of perfusion to units with $\dot{V}_A/\dot{Q}$ <0.1 or >10. Again, decreases in these indices indicate improved $\dot{V}_A/\dot{Q}$ matching.

Given values of P_IO_2, $P_{mv}O_2$, $\dot{V}$, and $\dot{Q}$, $\dot{V}_A/\dot{Q}$ distributions derived from MIGET data can also predict P_aO_2 and S_aO_2 with reasonable accuracy (491, 1922, 1989, 1990). Thus, if $\dot{V}$ and $\dot{Q}$ were constant and shunt did not develop during ventilation with 100% O_2, the distribution of $\dot{Q}$ with respect to $\dot{V}_A/\dot{Q}$ determined by MIGET at F_IO_2 = 100% could be used with values of $P_{mv}O_2$ and P_IO_2 measured at a lower F_IO_2 (e.g., 21%) to predict P_aO_2 and S_aO_2 that would exist at the lower F_IO_2 in the absence of HPV. The greater the differences between predicted and measured values of P_aO_2 and S_aO_2, the greater the contribution of HPV to $\dot{V}_A/\dot{Q}$ matching at the lower F_IO_2. Apparently, this approach to quantifying the role of HPV has not been tried.

Other assessments of $\dot{V}_A/\dot{Q}$ matching measured ventilation and perfusion in lung regions of various sizes using tracers delivered via inhalation and intravenous infusion. These included fluoroaerosols and radioactive microspheres (1261, 1263), fluorescent microspheres (790), ^{13}N (467), and ^{81m}Kr (1792).

In addition to raising P_IO_2 or $P_{mv}O_2$, HPV could be inhibited by intravenous infusion of a vasodilator. Although this approach has the advantage of affecting the entire pulmonary vasculature, it could inhibit responses to vasoconstrictor stimuli other than hypoxia. This might not be an issue in normal lungs, where pulmonary vasomotor tone is typically low; however, it could be a problem in diseased lungs, where pulmonary hypertension due to a variety of mechanisms may occur. Intravenous vasodilators could also alter $\dot{V}_A/\dot{Q}$ matching by altering tone of airway smooth muscle and increasing $\dot{Q}$ and $P_{mv}O_2$ through effects on the systemic vasculature. Inhaled agents have been used to minimize systemic effects; however, with the possible exceptions of NO, which is thought to bind rapidly to Hb in lung erythrocytes (660, 1632), and PGE_1, which is rapidly metabolized by the lungs (729, 1521), systemic effects remain possible, particularly in diseased lungs where cells may be injured and metabolic pathways altered. Moreover, it has been proposed that inhaled NO can exert systemic effects via transport to the periphery as NO-derived nitrite or *S*-nitrosothiol proteins, where they are then converted back to NO (406, 592, 612, 1144). Like changes in F_IO_2, inhaled agents affect mainly ventilated lung and, like intravenous agents, may inhibit pulmonary vasoconstrictor responses to stimuli other than hypoxia. Inhaled agents may also be more likely to alter airway smooth muscle tone.

In addition to lowering P_IO_2 or $P_{mv}O_2$, investigators have tried to enhance HPV with pharmacological agents that either antagonize endogenous vasodilator modulation or

potentiate endogenous mediation of HPV. Examples of the former include L-NAME and indomethacin, which inhibit NOS and cyclooxygenase, respectively, leading to decreased synthesis of NO and vasodilator prostaglandins such as PGI_2 and secondary enhancement of HPV (see sect. IV*B2*). These effects, however, are not specific and could enhance vasoconstriction due to other stimuli. Currently, the only example of the latter is the triazine derivative almitrine bismesylate, which is thought to potentiate the ventilatory response to hypoxia through stimulation of arterial chemoreceptors (177, 601, 1015, 1035, 1117, 1214, 1845). The mechanism of this effect is unknown but may involve activation of catecholamine release (37) and/or inhibition of Ca^{2+}-dependent K^+ channels (1128) in arterial chemoreceptor cells. Almitrine can also interfere with mitochondrial oxidative phosphorylation (1631), but whether this action is involved in its effects on chemoreceptor cells has not been determined.

In patients with severe chronic obstructive pulmonary disease breathing room air, almitrine increased ventilation, causing P_aCO_2 to fall and P_aO_2 to rise; however, in some patients almitrine improved blood gases without changing ventilation or ventilatory pattern, leading to speculation that almitrine improved $\dot{V}_A/\dot{Q}$ matching by potentiating HPV (1548). This speculation was subsequently confirmed. At low doses (e.g., $<5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ iv), almitrine potentiated HPV in humans (1255, 1684), dogs (295, 1359, 1657, 1882), and rats (128, 496, 649, 1644, 1678). At higher doses, almitrine caused pulmonary vasoconstriction during normoxia and inhibited HPV during moderate to severe hypoxia (296, 496, 649, 1346, 1359, 1678). Moreover, vasoconstrictor responses to almitrine during normoxia were blocked by hyperoxia (1255, 1359, 1657). Similar dose-dependent effects were seen with the almitrine analogs S1867 and S9581 (128, 1644). Findings like these and observations that interventions known to enhance or inhibit HPV had similar effects on almitrine-induced pulmonary vasoconstriction suggested that hypoxia and almitrine might act through a common mechanism (129, 649, 1631, 1678, 1683); however, almitrine's mechanism of action and specificity remain unclear. Almitrine-triggered chemoreflex effects on the pulmonary vasculature seem an unlikely mechanism of action, since almitrine can enhance HPV in isolated lungs (496, 649, 1678). A direct action on pulmonary arteries is usually assumed, but has not been established. Almitrine depressed contractile responses of guinea pig pulmonary arteries to a number of vasoconstrictor agonists (132) and inhibited pulmonary vasoconstriction to angiotensin II when given in a dose that potentiated HPV in isolated rat lungs (496), suggesting that enhancement of vasoconstriction was specific for HPV. Despite such uncertainties, almitrine has been widely used to potentiate HPV and improve $\dot{V}_A/\dot{Q}$ matching.

The following discussion will rely more heavily on data obtained when interventions designed to alter HPV did not change $\dot{Q}$, $\dot{V}$, or $P_{mv}O_2$. In addition, experiments in which HPV was inhibited by raising P_IO_2 and/or $P_{mv}O_2$ will receive greater weight than those that used less specific interventions.

II) Normal lungs. When total $\dot{Q}$ and $\dot{V}$ were constant in normal lungs, ventilation with hyperoxic gas mixtures sometimes reduced P_{PA} slightly, but did not alter shunt fraction, deadspace, inert gas gradients, or $\dot{V}_A/\dot{Q}$ distributions in anesthetized dogs (329, 1657, 1737) or the steady-state correlation between regional $\dot{Q}$ and $\dot{V}$ in awake sheep (1261). In normal awake humans 21–60 years of age, breathing 100% O_2 for 30 min generated a small shunt (1992), possibly due to absorbtion atelectasis in regions with low $\dot{V}_A/\dot{Q}$ ratios (361, 1933), and also increased $\dot{V}$; however, in a subsequent study of normal adults 21–32 years of age, 100% O_2 had no effect on $\dot{V}$, $\dot{Q}$, P_{PA}, shunt, deadspace, $\log SD_{\dot{Q}}$, or $\log SD_{\dot{V}}$ (1255). These observations suggest that HPV plays little role in matching perfusion to ventilation in normal lungs breathing air during rest at sea level, and that $\dot{V}_A/\dot{Q}$ matching sufficient to maintain normoxia under these conditions is the result of underlying lung structure.

Consistent with these conclusions, less specific pulmonary vasodilators, such as inhaled NO (695, 810, 1522) or intravenous sodium nitroprusside (SNP) (329, 1347) and PGI_2 (615), did not cause deterioration of P_aO_2 or other indices of pulmonary gas exchange in normal lungs. In contrast, intravenous trinitroglycerine (TNG) caused a small decrease in P_aO_2 (96 to 90 mmHg) without altering $\dot{V}$, $\dot{Q}$, or $P_{mv}O_2$ in normal human subjects; however, this finding is probably irrelevant since TNG did not block HPV in these subjects (1347).

Acute exposure of normal awake dogs to simulated high altitude did not change $\dot{Q}$, $\dot{V}$, shunt, or deadspace, but increased P_{PA} and decreased inert gas gradients, suggesting that global lung hypoxia improved $\dot{V}_A/\dot{Q}$ homogeneity (1866). In anesthetized dogs at sea level, however, decreasing F_IO_2 from 21 to 12% increased P_{PA} but did not alter gas exchange (1657). In normal awake humans, acute high altitude exposure (579, 1922) or breathing 12.5% O_2 (1255) also did not affect $\log SD\dot{Q}$, $\log SD\dot{V}$, or inert gas gradients; however, $\dot{Q}$ and/or $\dot{V}$ were increased in these studies and may have altered $\dot{V}_A/\dot{Q}$ matching independently of HPV. In anesthetized dogs, one study reported that reducing F_IO_2 from 50 to 15% improved $\log SD_{\dot{Q}}$, $\log SD_{\dot{V}}$, and inert gas gradients (1865), whereas another showed that gas exchange was the same at F_IO_2 of 100, 40, and 10% (387). In anesthetized pigs, $\dot{V}_A/\dot{Q}$ relationships measured with intravenous and inhaled fluorescent microspheres deteriorated when F_IO_2 was decreased from 21 to 9% (790, 1828). These inconsistencies are probably due in part to differences

in baseline $\dot{V}_A/\dot{Q}$ matching, e.g., lungs with higher $\dot{V}_A/\dot{Q}$ ratios and/or greater $\dot{V}_A/\dot{Q}$ homogeneity would be less affected by a decrease in P_IO_2, since the resultant decreases in regional O_2 tensions might not achieve the threshold for HPV. As noted above, decreasing P_IO_2 is a less reliable way to assess the role of HPV in $\dot{V}_A/\dot{Q}$ matching than ventilation with 100% O_2, which will shut off HPV in all ventilated lung regions regardless of $\dot{V}_A/\dot{Q}$ ratio or degree of $\dot{V}_A/\dot{Q}$ homogeneity.

Pharmacological enhancement of HPV with intravenous almitrine increased P_{PA}, had slight or no effect on P_aO_2, and did not alter inert gas variables in anesthetized dogs (1657) or normal awake humans (1255, 1349), again consistent with little or no $\dot{V}_A/\dot{Q}$ mismatch in normal lungs.

III) Regional hypoxia in normal lungs. As discussed in section V*B*, *1* and *2*, when F_IO_2 is reduced in a region of normal lung, HPV in that region defends P_aO_2 by decreasing regional perfusion, which both limits the fall in regional P_{O_2} by raising regional $\dot{V}_A/\dot{Q}$ and decreases the contribution of regional perfusion to total $\dot{Q}$. In anesthetized dogs, ventilating the left lower lobe with hypoxic gas mixtures containing 3% CO_2 (to minimize changes in regional P_{CO_2}) while continuing to ventilate the remaining lung with 100% O_2 caused increases in P_{PA} and decreases in regional $\dot{Q}$, but did not change total $\dot{Q}$ or any parameter of inert gas exchange measured for whole lung (422). Interestingly, when the left lower lobe and remaining lung were examined separately, $\dot{V}_A/\dot{Q}$ heterogeneity increased in the hypoxic left lower lobe, presumably due to flow diversion by HPV, but decreased in the remaining lung, perhaps due to a higher perfusion pressure. The same group subsequently reported that ventilating the entire left lung with 3% O_2-3% CO_2 while ventilating the right lung with 100% O_2 reduced left lung perfusion by 57–71% without altering total $\dot{Q}$, deadspace, shunt, or fractional perfusion to low $\dot{V}_A/\dot{Q}$ regions (1999). Although fractional perfusion to high $\dot{V}_A/\dot{Q}$ regions showed an overall increase, this could reflect HPV-dependent reductions in regional blood flow in a larger portion of lung. Thus these data suggest that regional HPV was able to maintain overall $\dot{V}_A/\dot{Q}$ matching when hypoxic lung regions were as large as the left lower lobe or even the entire left lung, and that alteration of HPV in this model should cause significant alteration of gas exchange.

Vasodilators including NO or PGI_2 added to gas mixtures ventilating the hypoxic regions (205, 553) and dobutamine (1435), PGE_1 (1012), SNP (355, 778), or TNG (355) infused intravenously increased regional $\dot{Q}$ and/or venous admixture and decreased P_aO_2 in lungs of dogs, pigs, and sheep. In contrast, agents given to enhance HPV, such as almitrine at doses $<5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ (295, 1359, 1882), indomethacin (719, 1823, 1825), L-NAME (553, 1825), or L-NAME + indomethacin (1825) decreased regional $\dot{Q}$ and/or increased P_aO_2 in lungs of dogs, pigs, and rabbits. In these studies, gas mixtures ventilating the hypoxic lung region frequently contained no O_2 at all, and the remaining lung was usually ventilated with 100% O_2; therefore, it may be unwise to extrapolate these results to more typical physiologic or pathophysiologic situations. Nevertheless, the consistency of the data suggests that HPV plays an important role in $\dot{V}_A/\dot{Q}$ matching in this model.

IV) Regional shunt or hypoventilation in normal lungs. When airway obstruction blocks regional ventilation completely, the result is a right-to-left shunt and eventual atelectasis. In this case, regional $\dot{V}_A/\dot{Q} = 0$, $P_AO_2 = P_{mv}O_2$, and $P_ACO_2 = P_{mv}CO_2$. In normal humans breathing room air, complete lobar bronchial occlusion caused lobar P_AO_2 and P_ACO_2 to rapidly achieve mixed venous levels and decreased lobar flow by 47–53% after 5–7 min (1325–1327). There was no diversion of blood flow after bronchial occlusion when airway P_{O_2} was kept above 127 mmHg by prior ventilation with hyperoxic gas mixtures, indicating that diversion after bronchial occlusion during room air breathing was due to regional HPV (1326). Atelectasis of the left lung (424, 613) or left lower lobe (103, 140) decreased regional perfusion by 39–72%. This diversion of blood flow was due to regional HPV, since it was reversed by increasing $P_{mv}O_2$ to 105–135 mmHg (424) and unaltered by reexpansion of atelectatic lung with 95% N_2-5% CO_2 (140). Consistent with this conclusion, almitrine improved P_aO_2 in patients subjected to one-lung ventilation (358, 1332).

Diversion of blood flow from a region of shunt by HPV would not alter its $\dot{V}_A/\dot{Q}$, since regional $\dot{V}_A$ would remain 0; however, the flow of shunted blood would be reduced and systemic oxygenation improved. Consistent with this effect, pulmonary vasodilation with intravenous PGE_2 or SNP increased venous admixture and decreased P_aO_2 in anesthetized animals with one-lung ventilation (235) or atelectasis (1188). Inhaled NO also decreased shunt and increased P_aO_2 in animals with regional shunt (810, 1840). In this case, vasodilation in ventilated lung probably increased P_aO_2 by "stealing" perfusion from the shunt region, which was not exposed to the inhaled NO. In contrast, inhaled NO did not improve gas exchange in dogs with right lower lobar atelectasis (1188) or patients receiving one-lung ventilation during thoracic surgery (388, 547, 1333, 2106). This lack of effect suggests that *1)* pulmonary vasomotor tone in ventilated regions was minimal in normal lungs and therefore not influenced by inhaled NO; *2)* NO-dependent diversion of perfusion from unventilated to ventilated lung lowered $\dot{V}_A/\dot{Q}$ ratios in ventilated lung sufficiently to prevent improvement in P_aO_2 despite a reduced shunt fraction; or *3)* HPV in the shunt region was inhibited by anesthetics or recirculation of inhaled NO to the shunt region as nitrite or *S*-nitrosothiol proteins in blood (406, 592, 612, 1144).

Pulmonary vasoconstriction with intravenous $PGF_{2\alpha}$ decreased venous admixture and increased P_aO_2 and $P_{mv}O_2$ in

dogs with right lung atelectasis (1188), perhaps due to enhancement of HPV in atelectatic lung (1123, 1188, 1947). Similar to the inconsistency seen with vasodilators, however, the cyclooxygenase antagonist meclofenamate decreased shunt but did not alter P_aO_2 in dogs with left lower lobe atelectasis (591), and NOS2 deficiency or treatment with a NOS2 antagonist did not alter left lung blood flow in mice with occlusion of the left mainstem bronchus (1954).

Despite its physiological and pathophysiological importance, regional hypoventilation (i.e., regional $\dot{V}_A/\dot{Q}$ low but >0) has been studied infrequently. Decreasing regional $\dot{V}_A$ at constant F_IO_2 (21%) reduced regional perfusion in left lower lobes of cats and dogs (103). In the coatimundi (653), decreasing ventilation to a sublobar lung region by 80% caused a 70% fall in perfusion, and reduced regional $\dot{V}_A/\dot{Q}$ from 0.9 to 0.4 and regional P_AO_2 from 110 to 84 mmHg. If regional perfusion had not fallen, $\dot{V}_A/\dot{Q}$ and P_AO_2 in the hypoventilated region would have decreased to 0.2 and 66 mmHg, respectively. Since regional P_ACO_2 changed little, it was concluded that the fall in P_AO_2 caused local HPV, which diverted blood flow from the region, thereby limiting changes in regional $\dot{V}_A/\dot{Q}$ and P_AO_2.

The effects of increasing F_IO_2 to 100% on $\dot{V}_A/\dot{Q}$ matching in normal lungs with regional hypoventilation have not been examined; however, in anesthetized dogs with partial obstruction of a lobar bronchus, decreases in pulmonary vascular resistance induced in the hypoventilated region by inhaled NO were correlated with decreases in P_aO_2 and increases in whole lung $\log SD_{\dot{Q}}$, suggesting that the larger the reversal of regional HPV by NO, the greater its deleterious effects on $\dot{V}_A/\dot{Q}$ matching (810). In anesthetized dogs and cats with hypoventilation of one lobe, intravenous almitrine increased P_{PA}, had variable effects on lobar $\dot{Q}$, and decreased both P_aO_2 and lobar venous $P_{\bar{v}O_2}$ (1988). These results indicate that almitrine decreased vascular resistance in the hypoventilated lobe relative to that in the remaining lung, causing an increase in fractional perfusion to the hypoventilated lobe. This effect may have been due to the high dose of almitrine used (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), which can inhibit HPV and cause pulmonary vasoconstriction during normoxia (296, 496, 649, 1346, 1359, 1678).

Thus, compared with regional hypoxia in normal lungs, data in normal lungs with regional shunt or hypoventilation are limited and inconsistent. The inconsistency may be due to poor control of factors that affect $\dot{V}_A/\dot{Q}$ matching, abnormalities in ventilated lung that obscured effects of HPV in the hypo- or nonventilated lung region, and nonspecificity of interventions employed to alter HPV.

V) Asthma. Asthma is a chronic inflammatory disorder of airways that causes bronchial hyperresponsiveness to a variety of stimuli and recurrent episodes of wheezing, breathlessness, chest tightness, and coughing in association with widespread, variable, and usually reversible airflow obstruction (617, 1363). Hypoxemia is common and associated with increased perfusion of low $\dot{V}_A/\dot{Q}$ regions but usually not shunt (89, 90, 342, 1307, 1653, 1990, 1991).

With the exception of one study of four asymptomatic patients (1990), increasing F_IO_2 to 100% worsened inert gas exchange in asthma, as reflected by increases in $\log SD_{\dot{Q}}$ and perfusion to lung regions with $\dot{V}_A/\dot{Q}$ <0.1 (89, 90, 342, 1653). In a group of severely ill patients mechanically ventilated with an F_IO_2 of 30–50%, 100% O_2 also increased shunt fraction from 1.5 to 8.3% in association with a 17 mmHg increase in $P_{mv}O_2$ (1653); 100% O_2 did not alter indices of airway obstruction (89, 90, 342). These results indicate that HPV contributes significantly to maintenance of $\dot{V}_A/\dot{Q}$ matching in asthma.

Since $\dot{V}_A/\dot{Q}$ mismatching in asthma is thought to be caused by regional hypoventilation secondary to airways obstruction, relief of obstruction would be expected to improve gas exchange; however, this has rarely been true. For example, inhaled isoproterenol improved airways obstruction but worsened hypoxemia and increased perfusion to low $\dot{V}_A/\dot{Q}$ regions in both asthmatic patients (1990) and dogs with bronchospasm induced by inhaled methacholine (1654). Other inhaled adrenergic agonists, such as epinephrine, salbutamol, and terbutaline, had little or no effect on gas exchange (89, 90, 1556, 1654). During methacholine-induced bronchospasm, inhaled NO increased P_aO_2 and decreased shunt in pigs (1556), but worsened hypoxemia in normal humans and asthmatics (1879). Intravenous bronchodilators, such as salbutamol and aminophylline, improved airways obstruction, but salbutamol increased $\log SD_{\dot{Q}}$ and fractional perfusion to low $\dot{V}_A/\dot{Q}$ regions (89), while intravenous aminophylline had no effect on P_aO_2 or inert gas exchange (1307). These results suggest that the salutary effects of these agents on regional airways obstruction can be offset by inhibitory effects on regional HPV, leading to maintenance or worsening of $\dot{V}_A/\dot{Q}$ mismatch. In some cases, an increase in total $\dot{Q}$ due to actions on the heart and systemic vasculature may also contribute (89, 1654).

VI) Chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is a disorder of airways and lung parenchyma, which is caused primarily by cigarette smoking, associated with an abnormal inflammatory response to noxious particles or gases, and manifested by gradually progressive airflow obstruction that is not fully reversible (275, 1562, 1569). Symptoms and signs include chronic cough, sputum production, wheezing, dyspnea, poor exercise tolerance, pulmonary hypertension, and right heart failure. Hypoxemia is thought to result mainly from increased perfusion of lung regions with low but finite $\dot{V}_A/\dot{Q}$ ratios (14, 94, 95, 1256, 1260, 1303, 1989). Right-to-left shunt is usually trivial, possibly due to an increase in collateral ventilation. As determined by MIGET, other gas ex-

change abnormalities include increases in $logSD_{\dot{Q}}$, $logSD_{\dot{V}}$, deadspace, and perfusion to regions with high $\dot{V}_A/\dot{Q}$ ratios.

Increasing F_IO_2 from 21 to 100% caused deterioration of inert gas exchange in both stable outpatients (96) and spontaneously breathing inpatients hospitalized for exacerbation of their disease or surgery (94, 95, 1646). The most common finding was increased $logSD_{\dot{Q}}$ without alteration of shunt. Increased inert gas gradients and increased perfusion to low and high $\dot{V}_A/\dot{Q}$ regions were also reported. 100% O_2 had similar effects in patients already receiving supplemental oxygen (F_IO_2 = 28–40%) both during (1705, 1924) and 30 min after (1924) discontinuation of mechanical ventilation. In these studies, an unchanged minute ventilation, similar deterioration of gas exchange whether $\dot{Q}$ was unchanged (1646, 1705, 1924) or decreased (94–96), and lack of effect on airways obstruction (94) support the conclusion that HPV contributes significantly to $\dot{V}_A/\dot{Q}$ matching in COPD. In contrast, two studies did not demonstrate an effect of 100% O_2 on inert gas exchange. One was performed in only three patients (1303). In the other (1989), it was suspected that the duration of O_2 breathing was insufficient to allow washout of nitrogen from slowly ventilating low $\dot{V}_A/\dot{Q}$ regions, in which case regional P_{O_2} may not have increased enough to inhibit HPV.

Vasodilators such as oral nifedipine (14, 948, 1256, 1337, 1791) and intravenous PGE_1 (444, 1348) and PGI_2 (55) usually decreased P_aO_2 and increased $\dot{Q}$ in patients with COPD. Nifedipine was also found to increase inert gas gradients and $logSD_{\dot{Q}}$ without altering shunt, deadspace, $logSD_{\dot{V}}$, or airways resistance (14, 1256). Oral sildenafil had similar effects on gas exchange, but did not alter $\dot{Q}$ and caused a small but significant increase in FEV_1 (182). Although the hypoxemia caused by these agents is consistent with inhibition of HPV, an increased $\dot{Q}$ or an action on airways, which was not assessed with agents other than nifedipine and sildenafil, may also have contributed.

As expected in the absence of shunt, the effects of inhaled NO on P_aO_2 were variable, with increases (12, 603), decreases (96, 937), and no change (181, 1262, 1303, 2158) being reported. Similarly, inhaled NO either worsened (96) or did not alter (1303) inert gas exchange. Although inhaled NO usually did not alter $\dot{Q}$, its effects on airways obstruction were not determined. As noted above, the net effect of inhaled NO on vascular and airways resistance in normal and hypoventilated regions of varying $\dot{V}_A/\dot{Q}$ is difficult to predict, complicating prediction of its effects on $\dot{V}_A/\dot{Q}$ distribution and P_aO_2.

The effects of almitrine in patients with COPD have been remarkably consistent. Almitrine increased P_aO_2, usually in association with increased P_{PA} and unaltered $\dot{Q}$ (266, 1260, 1683, 1684, 1792, 2108), and improved $\dot{V}_A/\dot{Q}$ homogeneity, as indicated by both MIGET analysis (266, 1260) and ^{81m}Kr gamma scintigraphy (1792). These results suggest that enhancement of HPV in low $\dot{V}_A/\dot{Q}$ regions increased diversion of blood flow to normal $\dot{V}_A/\dot{Q}$ regions, leading to improved $\dot{V}_A/\dot{Q}$ matching.

VII) Acute lung injury and acute respiratory distress syndrome. Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are characterized by the acute onset of severe hypoxemia and bilateral infiltrates on the chest radiograph in the absence of left atrial hypertension (154, 2029). ALI and ARDS are distinguished by the ratio of P_aO_2 (in mmHg) to F_IO_2 (expressed as a decimal fraction), which is <200 in ARDS and <300 in ALI. Injury causes protein-rich edema due to loss of endothelial and epithelial integrity and can be direct, as in pneumonia or aspiration of gastric contents, or indirect, as in sepsis or severe trauma associated with shock and multiple blood transfusions. Hypoxemia is refractory to increases in F_IO_2 because of large right-to-left shunts. In contrast, other gas exchange indices, including $logSD_{\dot{Q}}$, $logSD_{\dot{V}}$, perfusion to low or high $\dot{V}_A/\dot{Q}$ regions, and deadspace, have been frequently normal or only moderately elevated in patients receiving supplemental O_2 on mechanical ventilation (1259, 1573–1575, 1587, 1661, 1705, 1998). Most patients have mild to moderate pulmonary hypertension and normal cardiac outputs. Similar changes occurred in animal models, such as intravenous infusion of oleic acid in dogs (329, 1555, 1557, 1738), endotoxemia in pigs (1213, 1414, 1415), repeated lung lavage in pigs (389, 391), and prolonged hyperoxia in baboons (821).

HPV was inhibited by endotoxemia in dogs (721, 1602, 2049), sheep (529, 838, 1897), and mice (1822, 1954) and acute lung injury induced by oleic acid in dogs (1059) and bleomycin in rats (1219). These results suggest that HPV could be inhibited in ALI/ARDS and therefore unable to contribute to $\dot{V}_A/\dot{Q}$ matching; however, other observations argue against this possibility. Increasing F_IO_2 to 100% in patients with ARDS (1705) and dogs with oleic acid lung injury (329), or increasing $P_{mv}O_2$ by veno-venous extracorporeal membrane oxygenation (ECMO) in patients with ARDS (146) and dogs with oleic acid lung injury (178) increased shunt fraction without altering total $\dot{Q}$, fractional perfusion to low $\dot{V}_A/\dot{Q}$ regions, $logSD_{\dot{Q}}$, $logSD_{\dot{V}}$, or deadspace. The increase in shunt caused by 100% O_2 may have been due in part to absorbtion atelectasis of ventilated regions with low $\dot{V}_A/\dot{Q}$ ratios; however, this would not explain why shunt increased when $P_{mv}O_2$ was increased by 22–41 mmHg during ECMO (146, 178). $P_{mv}O_2$ is the major determinant of P_{O_2} in regions of shunt, which is the predominant gas exchange abnormality in ALI/ARDS; therefore, these ECMO results indicate that vasoconstriction due to HPV diverted perfusion away from shunt regions until it was reduced by the increase in $P_{mv}O_2$. Increases in $P_{mv}O_2$ of 7–19 mmHg also occurred when F_IO_2

was increased to 100% (329, 1705) and may have had similar effects.

Supportive of flow diversion by HPV in ALI/ARDS, intravenous vasodilators such as diltiazem (1259), SNP (46, 329, 1573), and TNG (46, 1574) increased shunt and decreased P_aO_2 without altering $\dot{Q}$. Intravenous PGE_1 (1257, 1554, 1574, 1785) and PGI_2 (389, 1575, 1661) usually increased shunt, but effects on P_aO_2 were variable, probably because these agents also increased $\dot{Q}$, which could increase shunt and decrease P_aO_2 on its own (178, 1668) or increase P_aO_2 by increasing $P_{mv}O_2$. It is also possible that these vasodilators inhibited pulmonary vasoconstrictor influences other than HPV.

The most frequently tested vasodilator in ALI/ARDS has been inhaled NO, which almost always decreased shunt and increased P_aO_2 in association with decreased P_{PA} and unaltered $\dot{Q}$ (181, 391, 417, 583, 695, 981, 1136, 1213, 1414, 1554, 1555, 1557, 1561, 1661, 1668, 1998, 2228). These decreases in shunt and P_{PA} were probably due to NO-induced reversal of vasoconstriction in ventilated lung, causing redistribution of flow to ventilated lung from shunt regions. It seems unlikely that the vasoconstriction reversed by NO was HPV, since baseline F_IO_2 was usually high enough to inhibit HPV in ventilated lung. Inhaled PGE_1 (1267, 1554) and PGI_2 or its analogs (389, 390, 1998, 2228) had effects similar to inhaled NO, and probably for similar reasons.

The beneficial effects of inhaled NO on gas exchange were improved when almitrine was given concurrently (391, 583, 1455, 2130). On its own, lower doses of almitrine increased P_aO_2 and decreased shunt, usually in association with increased P_{PA} and no change in $\dot{Q}$, indicating increased PVR (390, 391, 583, 1621, 1815). These results are consistent with potentiation of HPV in shunt regions and enhanced diversion of perfusion to ventilated lung. In animal models of ALI/ARDS, these effects of almitrine were shared by antagonists of cyclooxygenase (33, 1058, 1060, 1738) but not by antagonists of NOS (1058, 1415, 1555, 1668), which increased PVR but did not alter P_aO_2 or shunt. These results suggest that endogenous production of vasodilator prostaglandins such as PGI_2, and thus their inhibition of HPV and other vasoconstrictor mechanisms, may have been greater in more injured nonventilated lung than in less injured ventilated lung, whereas endogenous production of NO and NO-dependent inhibition of vasoconstriction was similar in ventilated and nonventilated lung.

Overall, the data suggest that HPV can improve $\dot{V}_A/\dot{Q}$ matching in ALI/ARDS; however, other vasoactive influences and inhibition of HPV by the disease may prevent this effect.

VIII) Other lung diseases. Data relevant to the contribution of HPV to $\dot{V}_A/\dot{Q}$ matching in other lung diseases are limited. In acute pulmonary thromboembolism (APTE), hypoxemia is thought to result from *1)* decreased $P_{mv}O_2$ due to decreased systemic transport of O_2 relative to consumption and *2)* diversion of blood flow from embolized regions due to mechanical obstruction and mediator-induced vasospasm, leading to development of deadspace and/or high $\dot{V}_A/\dot{Q}$ ratios in embolized regions, and increased perfusion, decreased $\dot{V}_A/\dot{Q}$ ratios, and lowered P_{O_2} in nonembolized regions (825, 866, 1172, 1173, 1704, 1806). In some patients, shunt develops, possibly due to atelectasis in embolized low $\dot{V}_A/\dot{Q}$ regions caused by bronchospasm, loss of surfactant, edema, or hemorrhage; or shunting through a patent foramen ovale due to increased right atrial pressure (353, 825, 1173). APTE had similar effects on gas exchange in dogs (360, 385, 386) and pigs (1935, 1936). In hospitalized patients with ATPE, increasing F_IO_2 from 21 to 40% decreased both P_{PA} and $\dot{Q}$ without changing PVR and did not alter inert gas exchange (1172). Similarly, varying F_IO_2 between 100, 40, and 10% did not alter shunt, deadspace, inert gas gradients, $logSD_{\dot{Q}}$, or $logSD_{\dot{V}}$ at constant $\dot{Q}$ and $\dot{V}$ in dogs subjected to APTE (387). Lack of an O_2 effect could be due to inhibition of HPV in APTE (387). These observations argue against an important contribution of HPV to $\dot{V}_A/\dot{Q}$ matching in APTE. Consistent with this conclusion, inhibitors of cyclooxygenase enhanced pulmonary hypertension, but worsened inert gas exchange (385). Moreover, intravenous SNP and hydralazine reduced P_{PA} at constant $\dot{Q}$ and $\dot{V}$ without altering P_aO_2 or inert gas exchange (386). Inhaled NO (208) and intravenous nitrite (403) decreased PVR, but neither altered P_aO_2. It seems likely that HPV, if present in APTE, competes with multiple vasomotor and bronchomotor influences on regional perfusion and ventilation.

Hypoxemia in patients with pneumonia was associated with increases in shunt, perfusion to low $\dot{V}_A/\dot{Q}$ regions, and $logSD_{\dot{Q}}$ (513, 595, 1024, 1997). Ventilation with 100% O_2 did not alter perfusion to low $\dot{V}_A/\dot{Q}$ regions or shunt despite an 8–11 mmHg increase in $P_{mv}O_2$, but did increase $logSD_{\dot{Q}}$ slightly (595, 1024). Intravenous almitrine did not alter P_aO_2 (432), and intravenous acetylsalicylic acid (ASA) slightly increased PVR and decreased shunt, but did not alter P_aO_2, perfusion to low $\dot{V}_A/\dot{Q}$ regions, or $logSD_{\dot{Q}}$ (513). These observations suggest that HPV contributes minimally to $\dot{V}_A/\dot{Q}$ matching in patients with pneumonia. Consistent with this conclusion, established pneumonia due to *Pseudomonas aeruginosa* inhibited HPV in rats (651, 1220) and dogs (1093). In the latter species, administration of cyclooxygenase antagonists restored HPV, diverted perfusion away from pneumonic lung regions, decreased shunt, and increased P_aO_2 (735, 1093); however, diversion of perfusion was not altered when restored HPV was subsequently inhibited by SNP or the 5-lipoxygenase antagonist diethylcarbamazine (1093). These results suggested that regional

lung blood flow redistribution in pneumonia was mediated by some mechanism other than HPV. In contrast, HPV appeared to be enhanced and to decrease perfusion of infected lung regions in dogs with acute pneumonia caused by *Streptococcus pneumoniae* (786). Such variability may be related to host species, causative agent, duration of infection, or other factors, which need to be clarified.

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonitis of unknown etiology that usually occurs in males over the age of 50 and is manifested by progressive dyspnea and hypoxemia, restrictive ventilatory defect, decreased pulmonary diffusing capacity, bibasilar reticular infiltrates on the chest radiograph, and a characteristic histologic appearance on lung biopsy (41). Surprisingly, as assessed by MIGET analysis, $\dot{V}_A/\dot{Q}$ matching in IPF was only slightly abnormal, and characterized by small increases in shunt, perfusion to low $\dot{V}_A/\dot{Q}$ regions, and log$SD_{\dot{Q}}$ (15, 607, 687). In one study (15), breathing 100% O_2 increased inert gas gradients, log$SD_{\dot{Q}}$ and perfusion to low $\dot{V}_A/\dot{Q}$ regions, indicating increased $\dot{V}_A/\dot{Q}$ heterogeneity. Moreover, the greater the O_2-induced increase in log$SD_{\dot{Q}}$ (assumed to indicate greater pulmonary vascular reactivity to O_2), the greater the P_aO_2 when breathing room air. These results suggested that HPV-induced changes in pulmonary vasomotor tone acted to optimize $\dot{V}_A/\dot{Q}$ matching in IPF, but that this effect became limited in more advanced disease (15). In support of the latter possibility, nitrendipine altered neither P_aO_2 nor PVR in patients with IPF complicated by pulmonary hypertension (236). On the other hand, intravenous epoprostenol and oral sildenafil decreased PVR in such patients (607), suggesting preservation of vascular reactivity. Interestingly, epoprostenol decreased P_aO_2 in association with increased shunt and perfusion to low $\dot{V}_A/\dot{Q}$ regions, consistent with reversal of HPV in shunt and low $\dot{V}_A/\dot{Q}$ regions. In contrast, sildenafil, an antagonist of phosphodiesterase-5, increased P_aO_2 in association with decreased shunt and perfusion to low $\dot{V}_A/\dot{Q}$ regions, suggesting enhancement of cGMP levels in better ventilated lung regions, where O_2-dependent endogenous production of NO was greater (663, 846, 927, 2088), resulting in local vasodilation and diversion of perfusion to regions with normal or high $\dot{V}_A/\dot{Q}$ ratios (607). Seemingly at odds with this proposal, inhaled NO had little or no effect on inert gas exchange in IPF (607, 687), suggesting that vasomotor tone was already minimal in ventilated lung regions. The contribution of HPV to $\dot{V}_A/\dot{Q}$ matching in IPF remains unclear.

C. High-Altitude Pulmonary Edema

1. Clinical characteristics

High-altitude pulmonary edema (HAPE), first described by Ravenhill in 1913 (1593), develops within 2–4 days of arrival at high altitude and is characterized by symptoms such as dyspnea at rest, cough, weakness or decreased exercise tolerance, and chest tightness or congestion as well as signs such as rales or wheezing in at least one lung field, central cyanosis, and resting tachycardia and tachypnea (702). Fever and hemoptysis may also occur. Findings on chest radiography can be variable, but usually include patchy alveolar infiltrates, which may become diffuse as the disease progresses (1200, 1981). The ECG may indicate right ventricular strain (704, 835, 1497, 2107). Cardiac catheterization demonstrates moderate to severe pulmonary hypertension in association with normal to low cardiac output and normal pulmonary artery wedge pressure, indicating increased PVR (552, 834, 982, 1165, 1497, 1669).

The risk of HAPE is increased by a prior history of the disease (118, 835), rapid ascent to an altitude >2,500 m (119), strenuous exercise (817, 1264, 1795), male gender (833, 1817), younger age (1741), reentry of high-altitude residents after a sojourn at low altitude (835, 1741), cold temperature (1604, 1817), current respiratory infection (456), and preexisting medical conditions such as primary pulmonary hypertension (1345), atrial or ventricular septal defects (956, 2095), and congenital absence of a pulmonary artery (703). Estimates of overall prevalence vary from 0.01% at 2,500 m (1817) to 16% at 3,400–5,500 m (1795); however, subclinical pulmonary edema may be much more common. For example, clinically defined HAPE did not develop in healthy young soldiers participating in a field exercise at 3,000–4,300 m, but there were immediate sustained decreases in forced vital capacity and transthoracic electrical impedance and clockwise rotations of the transpulmonary pressure-lung volume relation, followed over the next 3 days by gradual increases in lung closing capacity and residual volume (879). Similar increases in closing volume were reported in 74% of climbers without clinical HAPE who reached the summit of Monte Rosa (4559 m) within 24 h (343). These findings suggest an abrupt increase in thoracic intravascular volume upon arrival at high altitude, followed by more gradual accumulation of edema fluid in the interstitial spaces of the lung.

2. Enhancement of HPV

The pivotal role of HPV in the pathophysiology of HAPE is indicated by several lines of evidence, not the least of which is the rapid resolution of pulmonary hypertension and edema that occurs with treatment aimed at increasing P_AO_2, such as descent to low altitude and ventilation with 100% O_2 (834, 1497). If descent and O_2 are not available, temporary improvement can be achieved with use of a portable hyperbaric chamber (117, 556, 936). With mild to moderate HAPE at less extreme altitudes, resolution with bed rest and supplemental O_2 is possible without descent (833, 1200, 2181). In addition, HAPE and/or high altitude-induced pulmonary hypertension can be successfully prevented and treated with agents known to inhibit HPV, including nifedipine (118, 705, 1409, 1410), inhaled NO (43, 1724), and phosphodiesterase-5 (PDE-5) antagonists (606,

1164, 1626). HPV and the increased PVR caused by high altitude were greater (832, 941, 1978) and ventilatory responses to hypoxia smaller (706, 796, 1212) in HAPE-susceptible (HAPE-S) than in HAPE-resistant (HAPE-R) subjects. For given values of P_IO_2 and respiratory exchange ratio ($R = \dot{V}CO_2/\dot{V}O_2$), a smaller ventilatory response to hypoxia would produce a higher P_ACO_2 and lower P_AO_2, and thus a stronger HPV stimulus (840). Conversely, in Tibetans, who are thought to be genetically adapted to their high-altitude environment (1309) and do not get HAPE very often (2126), HPV and pulmonary hypertension were almost absent (674) and hypoxic ventilatory responses nearly normal (2219).

Although pulmonary arterial myocytes play an obvious and key role in HPV, it is not known whether changes in the intrinsic hypoxic reactivity of these cells contribute to enhancement of HPV in HAPE-S subjects. In contrast, there is a fair amount of indirect evidence suggesting contributions by endothelium and possibly other lung cells. Decreased NO/cGMP activity in HAPE-S subjects was indicated by lower NO metabolite concentration in bronchoalveolar lavage fluid (1864), reduced exhaled NO excretion at an altitude of 4559 m (451) and during acute hypoxia at sea level (244) that correlated with increased systolic P_{PA} estimated by echocardiography, and decreases in forearm vasodilator responses to ACh during hypoxia that correlated with increases in systolic P_{PA} and decreases in plasma nitrite concentrations (148). Consistent with these results, inhaled NO (43, 1724) or PDE-5 antagonists (606, 1164, 1626) reversed the pulmonary hypertension induced by high altitude, as noted above; and exhaled NO excretion was greater in Tibetans at 4,200 m than lowlander controls, perhaps explaining lack of pulmonary hypertension in the former (123, 798). Furthermore, plasma endothelin levels were higher in HAPE-S than HAPE-R subjects at 4,559 m and correlated directly with estimates of systolic P_{PA} (1708). Consistent with this result, bosentan, an antagonist of ET_A and ET_B receptors, reduced systolic P_{PA} in healthy subjects after rapid ascent to 4,559 m (1299). Taken together, these data indicate that the enhanced HPV characteristic of HAPE-S subjects may be due to facilitating modulation of HPV by endothelium and other cells.

Other vasomotor influences could also add to or enhance HPV in HAPE. For example, thromboxane B_2 levels in bronchoalveolar lavage fluid were increased in subjects with HAPE, but levels of the prostacyclin metabolite 6-keto-$PGF_{2\alpha}$ were unchanged (1730), suggesting that an imbalance between vasoconstrictor and vasodilator eicosanoids could augment P_{PA}. Sympathetic nerve activity was higher in HAPE-S than HAPE-R subjects during both short-term hypoxia at low-altitude and high-altitude exposure, and was correlated with increases in systolic P_{PA} at high altitude (452). Plasma concentrations and urinary excretion rates of epinephrine and norepinephrine were increased in subjects with HAPE (120, 993), and mean P_{PA} and PVR were reduced by the α-adrenergic antagonist phentolamine (705). In some cases, HAPE was associated with cerebral edema (993), suggesting that increased sympathoadrenal activity at high altitude could be neurogenic, similar to neurogenic pulmonary edema (996). Plasma renin activity, angiotensin II, angiotensin converting enzyme, and aldosterone were increased in HAPE patients (1005, 1088). Furthermore, a recent study of 140 patients and 144 controls found that HAPE was associated with genetic polymorphisms of the renin-angiotensin-aldosterone system (1563); however, such associations were not found in previous smaller studies of different populations (383, 1005).

It is also possible that HPV is enhanced in HAPE-S subjects because the number and/or size of pulmonary vessels, and thus pulmonary vascular cross-sectional area, was structurally smaller than in HAPE-R subjects. Consistent with this possibility, baseline PVR was higher and lung volumes and diffusing capacity lower in HAPE-S subjects (472, 1830). Moreover, HAPE developed at relatively low altitudes in patients with congenital absence of a pulmonary artery (703) or primary pulmonary hypertension (1345).

3. Edema formation

Pulmonary edema is caused by increased filtration of fluid from pulmonary vessels into the lung's extravascular space. As expressed by the Starling equation (1829), filtration rate is equal to $K_f[(P_v - P_{pv}) - \sigma(\pi_v - \pi_{pv})]$, where P_v and P_{pv} are the hydrostatic pressures and π_v and π_{pv} are the osmotic pressures in the vascular (v) and perivascular (pv) spaces at the site of filtration; K_f is the filtration coefficient, which depends on the surface area and hydraulic conductance, or permeability, of the cells and/or membranes through which filtration occurs; and σ is the reflection coefficient, which expresses the effect of the osmotic pressure gradient on filtration relative to that of a hydrostatic pressure gradient of equal magnitude, and thus varies between 0 (no effect) and 1 (equal effect). On this basis, pulmonary edema has traditionally been classified as "hydrostatic" when caused by an increase in hydrostatic pressure gradient, and "permeability" when caused by an increase in permeability, reflected by increases in K_f and/or decreases in σ (1829, 2028). Evidence suggests that HAPE is both a hydrostatic and a permeability edema.

As noted above, P_{PA} was greater at high altitude in HAPE-S than HAPE-R subjects. A major question has been whether the same is true of pulmonary capillary pressure. In humans, pulmonary capillary pressure was estimated by fitting an exponential equation to the slow component of the pressure decay recorded between 0.2 and 2 s after rapid pulmonary artery occlusion by inflation of a balloon at the tip of a pulmonary artery catheter (332). With the assumption that the asymptote of decay is the measured pulmonary arterial wedge pressure, capillary pressure was calculated

from the fitted equation as the pressure predicted to exist at the time of occlusion plus 150 ms. With this method, pulmonary capillary pressure was found to increase from 9 to 19 mmHg in HAPE-S subjects and from 10 to 13 mmHg in control subjects 12–36 h after arrival at 4,559 m (1165).

The accuracy of such estimates will depend on the ability to overcome technical difficulties, such as timing of balloon occlusion and respiratory variation in the pressure waveform, and the validity of the underlying assumptions. Essentially, the method assumes that the pulmonary vasculature is composed of arterial and venous resistances provided by pulmonary arteries and veins that have no compliance, separated by and in series with pulmonary capillaries that have compliance but no resistance. Such assumptions would not be valid in pigs, where the central compliant region also provided a resistance that increased during hypoxia (1648) and included pulmonary arteries as large as 2–3 mm in diameter (1913). Whether they are valid in humans is unknown.

Even if these estimates were accurate, the explanation for the increased pulmonary capillary pressure in HAPE would still be unclear, since the major site of HPV is usually thought to be small pulmonary arteries (see sect. II*A4*). Currently, the preferred solution to this puzzle is regional overperfusion (and therefore increased regional capillary pressure) caused by diversion of blood flow from regions with strong HPV to regions with weak or no HPV (830, 832). Consistent with this possibility are the patchy distributions of pulmonary infiltrates on chest radiographs of subjects with HAPE (1200, 1981) and the increased heterogeneity of pulmonary perfusion caused by hypoxia in both HAPE-S subjects (733, 809) and intact animals (790, 811, 1023, 1174, 1375). Increased perfusion heterogeneity could be due to differences in regional P_AO_2 at a lower P_IO_2, i.e., P_AO_2 could fall from normal to moderately low levels in normal $\dot{V}_A/\dot{Q}$ regions, causing HPV to increase, and from moderately to severely low levels in low $\dot{V}_A/\dot{Q}$ regions, causing HPV to decrease or not change (see sect. V*B*, *1* and *2)*. Alternatively, alteration of HPV by endogenous modulators such as NO could vary among regions (1633, 1634).

Pulmonary capillary pressure could also increase due to HPV in pulmonary veins (1582, 1584, 2206), especially after previous prolonged exposure to hypoxia (1762), but whether this occurs in HAPE is not known. It is also possible that hypoxic contraction of capillary endothelial cells could cause pulmonary capillary constriction (see sects. II*A4*B and IV*B1*B), which might reduce capillary flow and surface area and thereby protect against edema formation. In this case, however, HAPE could result from failure of this mechanism, perhaps due to increased downstream vascular pressures caused by hypoxic venoconstriction or increased left atrial pressure, as might occur during exercise (472). Such an increase could result from decreased left ventricular diastolic compliance secondary to high right ventricular pressures and ventricular interdependence, as may occur in some HAPE patients (34, 156).

In HAPE-S subjects 1 day after arrival at 4,559 m, bronchoalveolar lavage fluid had higher concentrations of erythrocytes, total protein, albumin, and immunoglobulin G than fluid from HAPE-R subjects, whereas concentrations of leukocytes, surfactant protein A, Clara cell protein, and inflammatory mediators including interleukins 1β and 8, TNF, leukotriene B_4, PGE_2, and thromboxane were not different (1864). In subjects with HAPE of longer duration, however, concentrations of neutrophils, arachidonic acid metabolites, and proinflammatory cytokines in bronchoalveolar lavage fluid were elevated (1001, 1729, 1730). In HAPE-R subjects, intense exercise after 24 h at an altitude of 3,800 m caused changes in bronchoalveolar lavage fluid similar to those of early HAPE (471). These results suggest that HAPE is caused by high intravascular pressures that increase not only hydrostatic pressure gradients for filtration but also the permeability of the alveolar-capillary membrane. The latter may result from mechanical stress failure of capillaries and eventual inflammation (119, 2078, 2079); however, involvement of other mechanisms, such as hypoxia-induced release of reactive oxygen species from endothelial cells (856), is also possible.

Many of these conclusions and speculations assume that the increased filtration associated with HAPE occurs in pulmonary capillaries. Such an assumption may not be necessary, as estimates of K_f were similar in pulmonary arteries and capillaries (25, 1467). Since surface area is greater in pulmonary capillaries than arteries, these findings suggest that permeability must be greater in pulmonary arteries than capillaries. In support of this possibility, hydraulic conductance in confluent monolayers of pulmonary arterial endothelial cells was 22 times greater than that in similarly treated pulmonary microvascular endothelial cells (1466). Thus, as proposed more than 40 years ago (2083), HAPE may result in part from filtration of fluid through the walls of pulmonary arteries, where pressure is clearly increased.

Finally, the effects of HPV on fluid filtration and edema formation in HAPE may be amplified by the effects of hypoxia on alveolar fluid clearance. For example, hypoxia decreased absorbtion of fluid instilled into the lung and inhibited activity and expression of the epithelial Na^+ channel and Na^+-K^+-ATPase, which transport Na^+ (and therefore water) from alveoli to interstitium (1166, 1167, 1524, 1980).

D. Pulmonary Hypertension

Pulmonary hypertension, defined as a mean resting $P_{PA} > 25$ mmHg (79), occurs in a wide variety of settings, including

1) so-called pulmonary arterial hypertension (PAH), which occurs with pulmonary capillary wedge or left atrial pressure ≤15 mmHg and can be idiopathic, heritable, or develop as a consequence of exposure to various drugs or toxins, connective tissue diseases, infection with human immunodeficiency virus, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, and pulmonary venoocclusive disease; *2)* left heart disease; *3)* lung diseases and/or hypoxia; *4)* chronic pulmonary thromboembolism; and *5)* other unclear or multifactorial causes (1793). In general, the causes of pulmonary hypertension are poorly understood; however, mutations of type II bone morphogenetic protein receptor have been identified in some cases of idiopathic and heritable PAH (397, 1027, 1930), and global alveolar hypoxia is thought to be a major determinant of pulmonary hypertension associated with high-altitude exposure, sleep-disordered breathing, and lung disorders such as COPD and interstitial lung disease (ILD).

1. Exposure to high altitude

High-altitude pulmonary hypertension (HAPH) in humans is usually not observed at altitudes less than ~2,000 m (P_BO_2 = 604 mmHg; P_IO_2 = 117 mmHg) (831, 1493); thus P_{PA} is normal in residents of Denver, CO (1,600 m) but elevated in residents of Leadville, CO (3,100 m) (1601, 1741). Increases in P_{PA} and PVR occur within hours of arrival at high altitude (34, 832, 999, 1165) and persist upon prolonged exposure (829, 1498, 1664), leading to pulmonary vascular remodeling (67, 1494), right ventricular hypertrophy (1495), and in some cases right ventricular failure (cor pulmonale) (29, 1496).

HAPH is more common in humans indigenous to the Andean plateau, who are thought to have lived at high altitude for ~11,000 years, than in Tibetans, who have resided at similar altitudes for ~25,000 years, suggesting genetic adaptation (47, 122, 674, 798, 1498). Indeed, recent genomic screens of Tibetan highlanders revealed noncoding variants in and around the genes, *HIF2α* (a subtype of the transcription factor, hypoxia inducible factor), *EGLN1* (a regulator of HIF), and *PPARA* (a target of HIF), that were strongly associated with normal rather than elevated levels of blood Hb (1794, 1843, 2155). In addition, resting mean P_{PA} and PVR were normal and HPV minimal in Tibetans (674). Among high-altitude residents of Kyrgyzstan who complained of exertional dyspnea, only 20% had pulmonary hypertension (29). Of those with a normal P_{PA}, 26% were classified as hyperresponsive to acute hypoxia (>2-fold increase in P_{PA} after inhalation of 11% O_2 for 30 min). Repeat right heart catheterization 10 years later revealed that mean resting P_{PA} during normoxia had increased 35% in hyperresponsive subjects, but was unchanged in normally responsive subjects. Among nonhuman species, HPV at sea level was strong and HAPH severe in cow and pig, whereas HPV was weak and HAPH mild in dog and guinea pig (672, 1243, 1483, 1904, 1944, 2094). In calves, the severity of HAPH measured by right heart catheterization 18 days after arrival at high altitude (4572 m) was highly correlated with the magnitude of HPV measured at low altitude (2094). Collectively, these correlations between severity of HAPH and magnitude of HPV suggest that HPV contributes significantly to HAPH. Against this possibility, HAPH did not develop in the coatimundi, which has vigorous HPV (737, 738), and was more severe in the Hilltop than Madison strain of Sprague-Dawley rat, which has greater HPV (1440).

If HAPH were due to HPV, it should be reversed by normoxia; however, after high-altitude exposures as short as 12–36 h, HAPH in humans was reduced but not normalized by inhaled O_2 (43, 621, 832, 999, 1165) or agents known to inhibit HPV, such as nifedipine (118, 621, 705, 1409, 1410) and inhaled NO (43, 1724). In healthy subjects residing at high altitude for at least 5 years, inhalation of 100% O_2 for 10–15 min reduced mean P_{PA} and PVR by 26 and 18%, respectively (828). Similar results were obtained after inhalation of 35% O_2 for 15 min in subjects born and residing at high altitude, in whom acute decreases in P_{PA} and PVR averaged only ~50% of those eventually achieved after 2 years at sea level (1789). Upon return of normal subjects to sea level after 30 days of progressive decompression to 243 mmHg (simulated altitude ≈8,800 m) in a hypobaric chamber, the systolic pressure gradient between the right ventricle and right atrium estimated by echocardiography fell by ~50% of its maximum increase at high altitude (209). In climbers who ascended to 4,250–5,545 m (P_B ≈460–390 mmHg) over 5–16 days, this gradient decreased from 20 to 13 mmHg 5 min after oxyhemoglobin saturation was increased to ≥98% by inhalation of O_2 (437). In contrast, acute hyperoxia did not alter the increased PVR that occurred in healthy subjects after 40 days of progressive decompression to 240 mmHg in a hypobaric chamber (675) or a 2-day sojourn at an altitude of 3,810 m (P_B = 484 mmHg) (472). These data suggest that HPV contributes to HAPH in humans, but that other factors are involved.

The most common animal model of pulmonary hypertension is the chronically hypoxic rat, in which P_IO_2 is typically reduced from 150 to 70 mmHg for a period of 2–6 wk, resulting in progressive pulmonary hypertension, right ventricular hypertrophy, polycythemia, and pulmonary vascular remodeling (297, 366, 1269, 1440, 1570–1572, 1810). As in humans with HAPH, acute exposure of chronically hypoxic rats to normoxia significantly reduced but did not normalize P_{PA} (1028, 1440, 1513). Similar observations have been made in other species. For example, brief inhalation of 100% O_2 decreased P_{PA} from 124 to 74 mmHg in steers kept at an altitude of 3,870 m (P_B ≈480 mmHg) for 9 wk (673). In beagles kept at high altitude for 6–19 mo, acute normoxia reduced P_{PA} to sea level values, but PVR

remained elevated (672). During normoxic recovery of chronically hypoxic rats, P_{PA} decreased gradually after an intial rapid fall, requiring as long as 6–20 wk to achieve normoxic baseline values (558, 770, 1571). Even then, some features of vascular remodeling persisted, including neomuscularization, increased medial thickness, and decreased lumenal diameter of preacinar arteries (558, 770, 787, 1571).

Direct assessment of pulmonary vascular reactivity in isolated rat lungs indicated that chronic hypoxia could suppress, enhance, or not alter HPV. In male Wistar rats exposed to 10% O_2, pulmonary pressor responses of blood-perfused lungs to acute hypoxia were suppressed after 15 h or 2 days, not altered after 7 days, and enhanced after 3–6 wk (475, 2202). In the same preparation, HPV was suppressed after 2 days and enhanced after 2–3 wk in juvenile animals, but not altered in mature animals (99, 130). Neither was HPV altered in buffer-perfused lungs of male Wistar rats kept at an altitude of 2,400 m ($P_B \approx 580$ mmHg) from 4 to 24 wk of age (71). Exposure to a simulated altitude of 4,270 m ($P_B = 440$ mmHg) suppressed HPV after 40 h in blood-perfused lungs of adult Sprague-Dawley rats (1246) and after 4–6 wk in lungs of Sprague-Dawley and Wistar rats (1247). Suppression of HPV was also observed in buffer-perfused lungs of Sprague-Dawley rats exposed to simulated altitudes of 4,500 m ($P_B = 430$ mmHg) for 7 days (72) or ~6,600 m ($P_B = 340$ mmHg) for 3–4 wk (730, 857). After 6 wk at 5,486 m ($P_B \approx 395$ mmHg), HPV suppression was less in juvenile than mature rats (1945). Lungs of Sprague-Dawley and Wistar rats exposed to high altitude for 5–20 wk demonstrated enhanced HPV 3 days after returning to low altitude (71, 1247).

Similar inconsistency exists among studies of intact animals. For example, acute vasoconstrictor responses to hypoxia were enhanced in Sprague-Dawley rats after 10 days at a simulated altitude of ~5,800 m ($P_B = 380$) (557) and beagles after 12–19 mo at 3,100 m ($P_B = 525$ mmHg) (672). In contrast, 4 wk of chronic hypoxia suppressed pulmonary vasoconstrictor responses to 7% O_2 in intact rats (1854). The reasons for this variability are unknown but could include differences in severity and duration of hypoxic exposure; species, strain, and age of the animals (130, 1440, 1956); posthypoxic time before measurements (71, 1247); and other factors. Taken together, the data in animals, as in humans, suggest that HPV contributes to chronic hypoxic pulmonary hypertension, but that other factors are involved.

In general, HAPH could result from *1)* enhancement of pulmonary vasomotor tone due to HPV or other vasomotor influences and/or *2)* loss and lumenal narrowing of small pulmonary vessels due to vascular remodeling (788, 1271, 1272, 1570). The inability of O_2 and other pulmonary vasodilators to reverse HAPH completely led many investigators to conclude that HAPH was caused mainly by remodeling; however, recent studies in intact chronically hypoxic rats found that intravenous or inhalational administration of Rho kinase inhibitors rapidly reduced P_{PA} to nearly normal levels (494, 1351, 1353). Similar results were obtained in isolated lungs, confirming that the effects of Rho kinase antagonists in intact animals were due to changes in PVR rather than cardiac output or left atrial pressure (844). These results indicated that the main cause of pulmonary hypertension in this model was increased vasomotor tone. In support of this possibility, stereological and confocal microscopy studies demonstrated that chronic hypoxia increased wall thickness but did not alter luminal diameter of intra-acinar vessels, suggesting that smooth muscle hypertrophy occurred in an outward direction without luminal encroachment (819, 844). Moreover, increases in total pulmonary vessel length, volume, endothelial surface area, and endothelial cell numbers suggested that chronic hypoxia caused pulmonary angiogenesis, raising the possibility that total cross-sectional area of the pulmonary vasculature was preserved, as suggested by an early morphological study (942). In this case, the increased muscularity of small pulmonary arteries could increase vasomotor responses without increasing basal PVR, thereby explaining the rapid, nearly complete elimination of chronic hypoxic pulmonary hypertension by Rho kinase inhibitors (494, 844, 1351, 1353).

Basal $[Ca^{2+}]_i$ measured under normoxic conditions in freshly isolated distal PASMC from chronically hypoxic rats was increased (201, 1775). Since increased $[Ca^{2+}]_i$ is usually associated with elevated vasomotor tone, this finding is consistent with the incomplete reversal of HAPH by acute normoxia; however, it is not known if acute changes in P_{O_2} alter $[Ca^{2+}]_i$ or Ca^{2+} sensitivity in PASMC from chronically hypoxic animals. Without such data, it is not possible to conclude that acute reduction of vasomotor tone by normoxia was due to reduction of HPV or to know how the mechanisms that mediate and modulate HPV may have been altered by chronic hypoxia. For example, it is possible that reduction of chronic hypoxic pulmonary hypertension by acute normoxia was due to an O_2-dependent increase in NO production by NOS, the expression of which was increased by chronic hypoxia. Consistent with this possibility, NO or NO donors decreased PASMC $[Ca^{2+}]_i$ and Ca^{2+} sensitivity in pulmonary arterial smooth muscle (328, 1713, 2178) and right ventricular hypertrophy in chronically hypoxic animals (813, 2057); chronic hypoxia increased expression of eNOS, nNOS, and iNOS in pulmonary vessels (1040, 1617, 1619, 1756, 2134); NO production in chronically hypoxic rats was high during normoxia and low during hypoxia (1712); iNOS expression was HIF-dependent in pulmonary arterial endothelial cells (1451); NOS antagonists enhanced chronic hypoxic pulmonary hypertension (1677) and revealed ET-1-dependent vasoconstriction in normoxic lungs from chronically hypoxic rats (1335); and

chronic hypoxic pulmonary hypertension was enhanced in eNOS-deficient mice (493, 1834).

Similarly, it is also possible that the nearly complete reversal of chronic hypoxic pulmonary hypertension by Rho kinase inhibitors was due to normalization of PASMC $[Ca^{2+}]_i$ and/or Ca^{2+} sensitivity, which had been increased during chronic hypoxia by endothelin-1 (ET-1). Several observations are consistent with this possibility. ET-1 caused contraction and increased $[Ca^{2+}]_i$, Ca^{2+} sensitivity, and RhoA expression in pulmonary arterial smooth muscle (110, 486, 843, 894, 1047, 1226, 1773, 2041). Chronic hypoxia increased expression of ET-1 and its receptors in lung and pulmonary arteries (458, 474, 1079, 1358). ET-1 expression and chronic hypoxic pulmonary hypertension were HIF-dependent (820, 2087, 2164). ET-1 antagonists prevented or reversed chronic hypoxic pulmonary hypertension (170, 297, 298, 404, 461, 716, 1956) and reversed the increase in membrane-to-cytosol Rho A expression ratio found in pulmonary arteries of chronically hypoxic rats (806). Finally Rho kinase antagonists reduced ET-1-induced $[Ca^{2+}]_i$-dependent and -independent contractions in pulmonary arteries from chronically hypoxic rats (110, 894, 2041).

Differences in the net effects of ET-1 and NO, and possibly other stimulatory and inhibitory vasomotor influences, could also explain variability in both the severity of HAPH and how it is acutely affected by normoxia. More investigation is needed to evaluate such speculations, which may also be relevant to lung disorders associated with chronic hypoxia.

2. Sleep-disordered breathing

The most common and best studied type of sleep-disordered breathing is obstructive sleep apnea (OSA), which is characterized by symptoms and signs of disturbed sleep during daytime, such as somnolence, fatigue, snoring, and restlessness, and five or more episodes per hour of obstructive apnea, hypopnea, and/or arousals related to ventilatory efforts during sleep (478, 1848). Obstructive apnea is the absence or near absence of airflow in the presence of persistent ventilatory effort. Hypopnea is a decrease in airflow $\geq$30% from baseline for at least 10 s accompanied by a decrease in oxyhemoglobin saturation $\geq$4%. The prevalence of mild and moderate/severe OSA in the adult population has been estimated at 20 and 7%, respectively (889, 2159). Prevalence increases with age, male gender, and African-American ethnicity. Risk factors include obesity, skeletal and soft tissue abnormalities of the upper airway, smoking, and use of alcohol (2160). The physiological consequences of OSA result from repetitive collapse of the upper airway, which can occur hundreds of times per night, leading to intermittent hypoxemia, hypercapnia, large swings in intrathoracic pressure, and increased sympathetic activity. OSA is associated with systemic hypertension and an increased incidence of stroke, myocardial infarction, and arrhythmias, as well as pulmonary hypertension and right ventricular failure (74, 395, 1249, 1687, 1812).

Early studies of patients with OSA demonstrated significant transient perturbations in pulmonary hemodynamics during sleep. Whereas normal subjects exhibited only slight changes in P_{PA} (4–5 mmHg) with no variation during the different stages of sleep (998), patients with OSA exhibited large swings in P_{PA} during apneic events, and a generally progressive increase in P_{PA} overnight (232, 1185, 1534, 1751) with systolic P_{PA} often reaching 50–60 mmHg (232, 1388, 1909). Although some studies found no correlation between sleep stage and severity of pulmonary hypertension (1751), most found that extreme increases in P_{PA} tended to occur during periods of rapid-eye-movement (REM) sleep (321, 1388, 1720, 1841), probably because airway obstruction and arterial O_2 desaturation were most severe during this time (321, 1186, 1720).

The possibility that HPV plays a role in OSA was suggested by the correlation during sleep between the transient increases in P_{PA} and transient decreases in SaO_2 (211), which can reach levels as low as 50% (232, 1388, 1909). Later studies confirmed these findings and reported that nocturnal elevations of P_{PA} were alleviated in patients treated with tracheostomy or continuous positive airway pressure (CPAP), which reduce or prevent the obstructive apneas and associated desaturation of oxyhemoglobin (28, 66, 322, 538, 1183, 1186, 1187, 1329, 1688). Moreover, with some exceptions (1184), supplemental O_2 blunted the decreases in S_aO_2 and eliminated the increases in P_{PA} (211, 538). Consistent with these findings, hyperoxia completely blocked increases in P_{PA} induced by obstructive apnea in canine models of OSA, indicating that the increases were due to hypoxia (874, 1728). Thus HPV contributes to the transient increases in P_{PA} during sleep caused by OSA. Other possible contributors include vascular reflexes and the large negative swings in pleural pressure, which could increase pulmonary wedge pressure (and thus P_{PA}) by decreasing left ventricular diastolic compliance through augmentation of venous return and secondary enlargement of the right ventricle or by increasing left ventricular afterload through elevation of the systolic transmural pressure gradient across the left ventricular wall (1687, 1720).

Moderate to severe OSA can also be associated with pulmonary hypertension during daytime (213, 287, 539, 1020, 1702, 1750, 2069), even in patients without clinically significant heart or lung disease (28, 66, 81, 1686, 1688, 1689); however, some of these patients also exhibited daytime hypoxemia (81, 1686) or evidence of small airway dysfunction (1689), suggesting that factors other than nocturnal hypoxemia could be involved. In the absence of systemic hypertension, heart disease, lung disease, or daytime hypoxemia, 21–43% of OSA patients had daytime pulmo-

nary hypertension, defined as a resting mean P_{PA} >20 mmHg (28, 1688) or systolic P_{PA} >30 mmHg (66). In OSA patients without pulmonary hypertension, mean P_{PA} was nevertheless greater than in normal control subjects matched for age and body mass index (28). Treatment with CPAP for 3–6 mo reduced P_{PA} in all OSA patients, but the decrease was greater in those with baseline pulmonary hypertension (28, 66, 1688). CPAP did not alter the ratio of forced expired volume at 1 s to forced vital capacity, pulmonary diffusing capacity, daytime P_aO_2, left ventricular diastolic function, or body mass index (28, 66, 1688). These results suggest that OSA can by itself increase daytime P_{PA}. In support of this possibility, mice and rats exposed to repeated short cycles of intermittent hypoxia during sleep developed persistent pulmonary hypertension and right ventricular hypertrophy (251, 492, 1236, 1364).

In patients with OSA, 4 mo of CPAP also reduced the increase in P_{PA} caused by acute hypoxia, and acute inhalation of 50% O_2 decreased P_{PA} (16.8 to 13.5 mmHg) as much as 4 mo of CPAP (1688). These findings suggest that OSA enhances HPV, and that HPV contributes significantly to the daytime pulmonary hypertension caused by OSA. It was also found that P_{PA} measured during inhalation of 50% O_2 before CPAP therapy was higher than that after CPAP therapy (13.5 vs. 11.6 mmHg). If the latter measurement represents basal P_{PA}, these data suggest that HPV accounts for ~60% of the daytime pulmonary hypertension caused by OSA, and ~40% must be due to other mechanisms.

As with chronic hypoxic pulmonary hypertension (see sect. V*D1*), these mechanisms include pulmonary vascular remodeling and increased vasomotor tone generated by signaling pathways other than those normally responsible for HPV. Remodeling clearly occurs in rodents exposed to intermittent hypoxia (492, 1394, 1809); however, its contribution to pulmonary hypertension in this model is unknown (207). Data from both patients and animals suggest that intermittent hypoxia can upregulate vasoconstrictors and/or downregulate vasodilators. For example, plasma ET-1 levels were increased in patients with OSA (1516) and rats exposed to intermittent hypoxia (923), whereas serum nitrate/nitrite levels in OSA patients (854) and nitrosyl-Hb concentrations in mice exposed to intermittent hypoxia (1394) were reduced. Moreover, CPAP therapy in patients with OSA decreased plasma ET-1 (1516) and increased serum nitrate/nitrite (854), as well as the concentration ratio of prostacyclin to thromboxane metabolites in urine (965). Whether these or other factors contribute to the daytime pulmonary hypertension in OSA is unknown.

Since pulmonary hypertension associated with OSA is mild, additional mechanisms or comorbid conditions may be necessary for it to achieve clinical significance. For example, patients with both OSA and chronic obstructive lung disease (the so-called "overlap syndrome") have greater hypoxemia and hypercapnia during sleep, are more likely to develop clinically significant pulmonary hypertension and, in the absence of CPAP therapy, die at a higher rate than patients with either disorder alone (1178).

3. Lung disease

Pulmonary hypertension has been estimated to occur in 25–90% of patients with COPD, the most common lung disease associated with this disorder (241, 286, 1721, 1877, 2068). Elevation of P_{PA} is usually mild to moderate (2068) and is assumed to result from pulmonary vascular remodeling and increased vasomotor tone due to HPV and other vasomotor influences. Remodeling occurs even in patients with mild COPD (1706, 2119) and differs from the medial hypertrophy and neomuscularization of pulmonary arteries caused by chronic hypoxia in that COPD also causes intimal thickening due to collagen-elastin deposition and smooth muscle hyperplasia, possibly as a result of inflammation due to repeated infections and/or exposure to cigarette smoke (1161, 1706, 2093, 2120, 2121).

The acute effects of O_2 and other vasodilators on the pulmonary vasculature in patients have usually been evaluated by measuring PVR $[(P_{PA} - P_w)/\dot{Q}$, where $\dot{Q}$ is cardiac output]; however, as discussed in section II*A1*, interpretation of changes in PVR is complicated by the curvilinearity of the $(P_{PA} - P_w)$-$\dot{Q}$ relation, which defines the resistive properties of the pulmonary vasculature. Since this relation is convex to its pressure axis, increases or decreases in $\dot{Q}$ along an unchanged $(P_{PA} - P_w)$-$\dot{Q}$ curve will cause, respectively, decreases or increases in PVR. In this case, a decrease in PVR would not indicate pulmonary vasodilation, and an increase would not indicate vasoconstriction. One way to eliminate this ambiguity is shown in **FIGURE 13,** where values of $(P_{PA} - P_w)$ and $\dot{Q}$ measured after acute administration of O_2 or other vasodilators are plotted as percentages of their respective control values. The shaded area is determined by two straight lines drawn though the control point $[(P_{PA} - P_w) = 100\%; \dot{Q} = 100\%]$, one from the origin and one from the control value of $(P_{PA} - P_w)$ on the pressure axis $[(P_{PA} - P_w) = 100\%; \dot{Q} = 0\%]$. This area represents the loci of all possible points on the control $(P_{PA} - P_w)$-$\dot{Q}$ relation, only one of which is known $[(P_{PA} - P_w) = 100\%; \dot{Q} = 100\%]$. Thus interventions that move the control point to the left of the shaded area have caused vasodilation, while interventions that move it to the right have caused vasoconstriction. If the control point is moved within the shaded area, the intervention may not have altered the control $(P_{PA} - P_w)$-$\dot{Q}$ curve, and thus cannot be confirmed to have caused either vasodilation or vasoconstriction.

The acute effects of O_2 inhalation reported in 14 studies of patients with COPD (7, 96, 381, 480, 804, 836, 940, 948, 1066, 1303, 1489, 1791, 1937, 2158) are shown by the filled circles in the upper part of **FIGURE 13**. In 11 of these studies, O_2 moved the average $(P_{PA} - P_w)$-$\dot{Q}$ point to the left

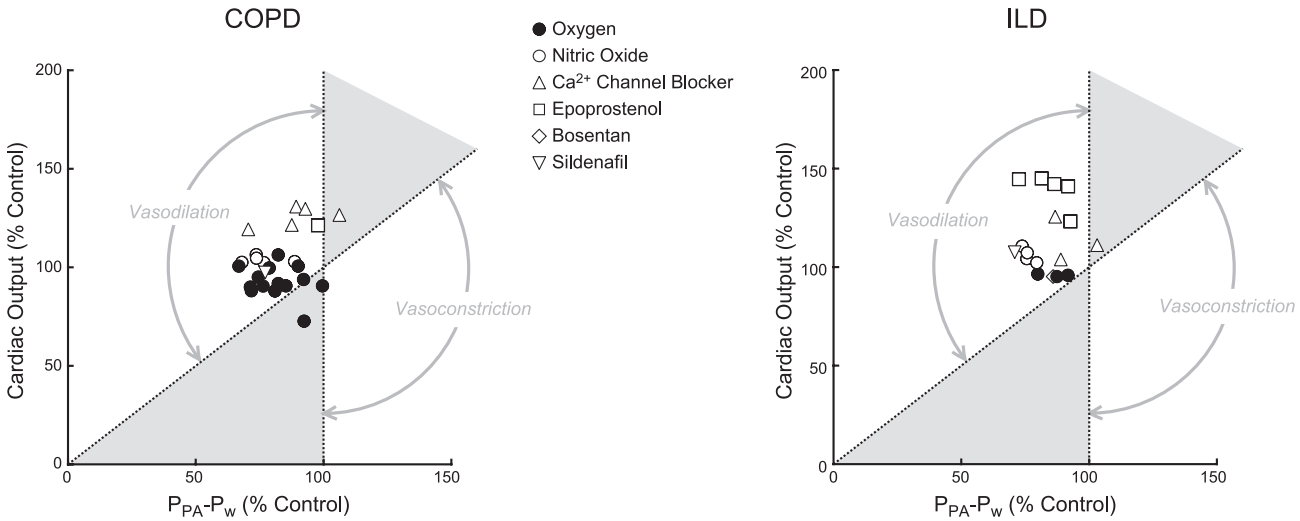


FIGURE 13 Relation between cardiac output and the difference between mean pulmonary arterial and wedge pressures (P_{PA}-P_W) measured in patients with lung disease. Each point represents the acute effects of inhaled O_2 or another vasodilator (see legend) on mean cardiac output and (P_{PA}-P_W) expressed as a percent of control values in groups of patients with chronic obstructive lung disease (COPD, *left*) (7, 14, 96, 182, 381, 480, 804, 836, 907, 940, 948, 1066, 1256, 1303, 1337, 1489, 1791, 1937, 2158) or interstitial lung disease (ILD, *right*) (15, 236, 531, 607, 687, 907, 1426, 1551). The shaded areas represent all possible loci of points on the control (P_{PA}-P_W) vs. cardiac output relation, only one of which is known [(P_{PA}-P_W) = 100; cardiac output = 100]; therefore, movement of the control point to the left of the shaded area indicates pulmonary vasodilation, while movement to the right indicates vasoconstriction.

of the shaded area, indicating vasodilation. In three studies (381, 940, 2158), the average ($P_{PA} - P_w$)-$\dot{Q}$ point fell within or very close to the shaded area, indicating little or no effect. In one of these (2158), O_2 was administered via nasal cannula at only 1 l/min for 10 min. In another (381), F_IO_2 was increased to only 28%. In a subsequent study (1066), this concentration was found not to alter P_{PA} in COPD patients, whereas 40% O_2 caused a significant decrease. Similarly, inhaled NO (12, 96, 181, 1303, 2158), sildenafil (182), intravenous epoprostenol (907) and, with one exception (14), sublingual nifedipine (948, 1256, 1337, 1791) caused acute pulmonary vasodilation. With respect to the exception, nifedipine was found to cause marked pulmonary vasodilation in the same patients after P_{PA} and $\dot{Q}$ had been increased by exercise (14). Overall, these results indicate that vasomotor tone contributes significantly to the pulmonary hypertension associated with COPD. Furthermore, the comparability of the acute effects of O_2 and the other vasodilators suggest that HPV plays a significant role.

For the COPD data shown in **FIGURE 13**, O_2 and the other vasodilators did not alter average $\dot{Q}$ but decreased average P_{PA} from 32 to 28 mmHg. With the assumption that vasodilation was complete and that the upper range of normal for mean P_{PA} is ~20 mmHg, this implies that about one-third of the pulmonary hypertension associated with COPD is due to increased vasomotor tone. Furthermore, long-term continuous O_2 therapy, which improves survival in COPD and can slow or reverse development of pulmonary hypertension, infrequently normalizes P_{PA} (1251, 1399, 2070, 2223). Thus most authorities believe that irreversible morphological changes, such as loss of vessels due to destruction of lung tissue, also contribute significantly to pulmonary hypertension in COPD.

ILD is also associated with global alveolar hypoxia and pulmonary hypertension. This heterogeneous group of disorders is characterized by a restrictive ventilatory pattern and impaired O_2 exchange. Examples include idiopathic and other forms of pulmonary fibrosis, sarcoidosis, and interstitial pneumonitis. Pulmonary hypertension in ILD is usually moderate, has a prevalence of 5–84%, and may contribute to mortality, depending on the type and stage of disease (1362, 1404, 2067). Only a few studies have examined the acute effects of inhaled O_2 on the pulmonary vasculature in ILD (15, 236, 1426). In each case, however, oxygen caused pulmonary vasodilation, as indicated by the shift of the control ($P_{PA} - P_w$)-$\dot{Q}$ point to the left of the shaded area in **FIGURE 13**. Nitric oxide (607, 687, 1426, 1551), Ca^{2+} channel antagonists (1426, 1551), epoprostenol (531, 607, 907, 1426, 1551), bosentan (687), and sildenafil (607) had similar effects; however, the decrease in average P_{PA} in these patients may have been greater than that caused by O_2, and in many cases was associated with an increase in $\dot{Q}$, suggesting more potent vasodilation. In one study (236), nitrendipine moved the control point within the shaded area, suggesting no effect on the ($P_{PA} - P_w$)-$\dot{Q}$ relation. Overall, however, the data suggest that HPV and other vasomotor influences contributed to the pulmonary hypertension associated with ILD. As with COPD, structural changes in the vasculature probably may also have played a role.

Quantitatively, the relative contributions of vascular tone and structure to pulmonary hypertension associated with COPD and ILD remain unclear. As with chronic hypoxic pulmonary hypertension in animals (see sect. V*D1*), it is possible that complete acute vasodilation was not achieved with O_2 or other vasodilators but might be achieved with Rho kinase antagonists. Interestingly, these agents acutely normalized or markedly reduced P_{PA} in other animal models of pulmonary hypertension associated with altered vascular morphology, including monocrotaline-treated rats with or without pneumonectomy (805, 1351), fawn-hooded rats raised in Denver, CO (1351, 1352), and chronically hypoxic rats treated with Sugen-5416, a blocker of VEGF receptors (1420). In a study of eight patients with severe PAH, the acute pulmonary vasodilation caused by Rho kinase antagonists was not impressive (862), suggesting that vasomotor tone did not play an important role; however, the effects of these antagonists in patients with the more moderate pulmonary hypertension typical of COPD and ILD has not been evaluated.

VI. FUTURE DIRECTIONS

Although understanding of HPV has improved significantly, much remains unclear or unknown. With respect to mediation, the primary O_2 sensor for HPV appears to be the PASMC mitochondrion, which increases ROS production when P_{O_2} falls; however, the mechanisms of this effect remain unclear. Furthermore, it is not known if and how signals from this sensor interact with possible secondary or redundant ROS-producing sensors, such as sarcolemmal NADPH oxidase, or with accessory signals, such as altered redox and energy states. The transduction pathways that link increased ROS production to increased $[Ca^{2+}]_i$ and depolarization are also unknown. Because hypoxic signaling in PASMC is likely to occur in microdomains occupied by mitochondria, SR, and sarcolemma, a complete understanding of HPV will require accurate intracellular indicators of ROS and Ca^{2+} targeted to specific organelles. Ideally, such probes would distinguish among superoxide, peroxide, and other species, which might activate different transduction pathways. Although current data suggest that hypoxia increases PASMC $[Ca^{2+}]_i$ via Ca^{2+} release from SR followed by Ca^{2+} influx through SOCC and VOCC, the temporal relationship and coordination among these events needs to be confirmed. It remains unclear whether hypoxic depolarization of PASMC is caused by activation of nonselective cation and Cl_{Ca} channels or inhibition of TASK and K_V channels. The mechanisms by which hypoxia inhibits or activates these channels need to be clarified. The relatively small increases in PASMC $[Ca^{2+}]_i$ usually caused by hypoxia suggest that augmentation of myofilament Ca^{2+} sensitivity may play an equal, or even more important, role than $[Ca^{2+}]_i$ in HPV; yet, how and to what extent hypoxia alters Ca^{2+} sensitivity remains incompletely understood. In addition, there is no information about the effects of hypoxia on PASMC-PASMC and PASMC-matrix interactions, or what role these interactions might play in HPV.

With respect to modulation, many endogenous agents are known to enhance or inhibit HPV; however, the physiological and pathophysiological significance and mechanisms of these effects are unclear. Other than PASMC, PAEC are the cells most likely to modulate HPV, through either altered release of contracting and relaxing factors or possibly direct PAEC-PASMC interaction. Furthermore, it is probable that in vivo expression of HPV depends on such interactions. Nevertheless, the effects of acute hypoxia in PAEC, the sensor and transduction mechanisms involved, the factors released, and the mechanisms by which these factors alter HPV remain uncertain or unexplored. Since hypoxia can cause active contraction of pulmonary microvascular endothelial cells and constriction of nonmuscular intra-acinar vessels, the possibility that endothelial cells, along with intra-acinar pericytes and intermediate cells, contribute directly to HPV needs to be evaluated.

With respect to physiological and pathophysiological roles, indirect evidence suggests that HPV matches pulmonary perfusion to ventilation in normal lungs with regional hypoxia and in certain lung diseases, such as asthma and COPD; however, its contribution in normal lungs with regional shunt or hypoventilation and in diseases such as acute lung injury and ARDS remains unclear. Similarly, HPV plays an important role in high-altitude pulmonary edema, but may only partially explain pulmonary hypertension associated with obstructive sleep apnea, COPD, and interstitial lung diseases. The direct evidence required to confirm the roles of HPV in normal and diseased lungs is unlikely to be forthcoming until the precise mechanisms of HPV are better understood. For example, the increased vasomotor tone responsible for pulmonary hypertension developing after weeks to months of hypoxia is generated by mechanisms different from those responsible for HPV developing after 5–60 min. How, when, and where these mechanisms change in the transition from acute to chronic hypoxia is not known.

Given the complexity of HPV, the benchmark for future investigations must be the intact or isolated lung, where hypotheses based on cellular and molecular results can be tested for relevance.

ACKNOWLEDGMENTS

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GRANTS

The authors' work discussed in this review was supported by National Heart, Lung, and Blood Institute Grants HL-51912 and HL-75113 (to J. T. Sylvester) and HL-67191 and HL-73859 (to L. A. Shimoda) as well as Wellcome Trust Grants 078075 and 087776 and British Heart Foundation Grants FS/06/003 and PG/06/151/21995 (to J. P. T. Ward and P. I. Aaronson).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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