**Review**

**Chronic Hypoxic Pulmonary Hypertension**

**Cell Biology to Pathophysiology**

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*(Chest 1994; 106:236-43)*

| AHPR=acute hypoxic pressor response; cGMP=guanosine cyclic monophosphate; NO=nitric oxide; PAP=pulmonary arterial pressure; PVR=pulmonary vascular resistance; PVS=vascular smooth muscle cell |

Pulmonary hypertension is a frequent hemodynamic complication associated with a wide variety of respiratory systems disorders whose only common physiologic abnormalities are alveolar hypoxia and consequent arterial hypoxemia of long-term duration. Such disease processes include the alveolar hypoventilation syndromes, neuromuscular disorders, kyphoscoliosis, and severe obstructive lung diseases. Similar findings have been observed in humans residing at high altitude. In contrast to the pulmonary circulatory response to acute hypoxia, prolonged durations of hypoxic exposure experimentally or associated with human disease states cause a persistent elevation in pulmonary arterial pressure (PAP) which is not immediately or totally correctable upon improvement in oxygen concentrations to normal values. A variety of influences can contribute to the increase in PAP, including acute respiratory acidosis and the common systemic response of secondary polycythemia. However, the focus of this review will center on the local effects of chronic alveolar hypoxia on the pulmonary vasculature directly, which are in major part the main determinants of the increase in pulmonary vascular resistance (PVR). The sustained elevation in PAP is thought to be mediated through two pathophysiologic vascular mechanisms: (1) persistent vasoconstriction and (2) vascular structural remodeling. The combination of these processes causes vascular luminal narrowing and vessel obliteration that reduce pulmonary vascular surface area to the critical degree necessary for the development of pulmonary hypertension. Although the exact contribution of either mechanism to the elevation in PVR will vary from case to case and from disease to disease, their combined effect on PAP is an established cause of morbidity resulting from cor pulmonale. Given the importance of each individual process, a detailed review of relevant or probable etiologic mechanisms seemed warranted with special emphasis directed toward current and future therapies.

**Comparisons: Clinical and Experimental**

Accurately defining the complexity of the pulmonary vascular response to prolonged durations of reduced oxygen tension has been complicated by the myriad of factors demonstrated to have significance in disease development, both clinically and experimentally. Interspecies and intraspecies variation has been observed in virtually every aspect of study ranging from experimental protocol to results. Bovine and porcine species are quite susceptible to the pulmonary hemodynamic complications of hypoxia in contrast to the hyporesponsiveness of dogs and sheep. Within the same species, neonatal calves exhibit brisk hemodynamic responses and dramatic structural changes when raised at altitude compared with similarly exposed adult animals. Similar age and sex differences in this same response have been noted in rats. In small animal species, reductions in inspired oxygen concentrations to approximately half-normal (normobaric or hypobaric) consistently elicit structural and hemodynamic alterations evident as early as 3 days following exposure with full development at 2 weeks. Interestingly, intermittent hypoxic exposure in rats for as little as 4 h/d is equally effective in producing vascular abnormalities as those evident upon continuous exposure.

Less severe degrees of hypobaric hypoxia will produce sustained pulmonary hypertension in cattle. However, susceptibility to the effects of prolonged hypoxia in this species is not universal but appears to be determined...
somewhat by genetic influences since selective breeding can segregate animals into either hypoxia-resistant or hypoxia-sensitive groups.8

Obligatory disparities exist between experimental animal studies and the development of pulmonary circulatory changes observed in human disease states. Excluding residence at high altitude, the development of chronic hypoxic pulmonary hypertension in humans does not represent a distinct disease entity, but rather occurs as a complication of another primary disease process with its own unique set of associated variables. For example, the interaction of inflammatory cytokines associated with chronic bronchitis may be an additional stimulus modulating vascular abnormalities.9 For the most part, the progressive deterioration in alveolar oxygen concentrations is thought to represent a chronic, slowly evolving process associated with local inhomogeneity in the degree of hypoxia. This contrasts with the abrupt onset and short duration of generalized hypoxia employed experimentally. In addition, defined thresholds in the levels of alveolar hypoxia necessary for the induction of either vascular process have not been established in humans. Finally, the late onset of clinical manifestations resulting from this hemodynamic abnormality and the lack of identifiable indices predictive of disease development suggest that studies and therapies directed at established disease may not truly reflect earlier etiologic mechanisms.

**VASOCONSTRICTION: GENERAL CHARACTERISTICS**

In experimental animals maintained under prolonged hypoxic conditions or in human disease states associated with chronic alveolar hypoxia, an abnormally heightened tone appears to persist in the resistance-sized vessels of the pulmonary circulation. This sustained vasospasm is mediated through the contraction of smooth muscle cells located in the precapillary arterioles and represents a potentially reversible physiologic process regardless of disease duration or severity. The demonstrated ability of a variety of nonspecific and mechanistically distinct vasodilators to cause acute reductions in PVR in clinically stable patients and experimental animals with established hypoxia-related pulmonary hypertension supports the concept of at least a minor reversible component of vasospasm in the chronic situation. The list of such agents include acetylcholine, captopril, hydralazine, isosorbide dinitrate, nifedipine, phenolamine, prostaclycin, prostaclandins E1, terbutaline, and urapidil. In most cases, however, major hemodynamic improvement is rarely observed and any amelioration following long-term pharmacologic administration is usually transient.10 Even the addition of relatively high levels of inspired oxygen concentrations (80 to 100 percent O₂) to patients in a stable condition with established pulmonary hypertension resulting from chronic hypoxia generally fails to achieve any immediate hemodynamic improvement despite significant increases in arterial oxygen values.11 Any benefit in pulmonary hemodynamics in these patients after lower levels of supplemental oxygen administration or in experimental animals exposed long term to hypoxia and then allowed to recover occur only after a long latency period, is rarely of dramatic degree, and infrequently results in normalization of PAP.12 Results obtained from patients enrolled in the Nocturnal Oxygen Therapeutic Trial study demonstrated a mean reduction in resting PVR of only 11 percent and an associated average decrement in mean PAP of approximately 2 mm Hg.13 Of interest, in this same study, the subgroup of patients with less severe grades of pulmonary hypertension defined as a mean PAP less than 27 mm Hg demonstrated improved survival not evident in patients with values above this level. The implications of this observation independent of other disease variables are unknown.

**VASOCONSTRICTION: ACUTE AND CHRONIC COMPARISON**

Acute hypoxic vasoconstriction is an inherent property of the lung designed to divert blood flow from poorly ventilated alveoli and improve local ventilation/perfusion relationships. When generalized, this same process can result in significant increases in PVR and consequent right ventricular strain. Short-term exposure of the pulmonary circulation to reduced levels of oxygen tension both in vivo and in vitro elicits an immediate vasoconstrictive response that is totally reversible upon return to normal concentrations of oxygen.14 The acute hypoxic pressure response (AHPR) is a local property intrinsic to the pulmonary vascular smooth muscle cell (PVSMC) independent of neural influences or circulating humoral substances.15 The AHPR is associated with graded membrane depolarization and depends on the influx of calcium from extracellular sources through dihydropyridine-sensitive voltage-gated channels.16 Recent studies have proposed a direct role of potassium channel inhibition in mediating these effects. The addition of K+-channel antagonists to the perfusate of isolated lungs will effect similar degrees of elevation in PAP as that achieved upon hypoxic exposure alone. In addition, in isolated pulmonary arterial smooth muscle cells switching from normoxic to hypoxic conditions causes a reduction in the amplitude of outwardly directed Ca2+-sensitive potassium currents as measured by patchclamp technique.17

Dependent on experimental conditions and animal species, this response may be partially mediated or at
least modulated by the actions of locally released endothelial cell-derived vasodilator or vasoconstrictor compounds. A recent study using conduit human pulmonary arterial segments has demonstrated an endothelial cell dependency for hypoxia-induced contraction.18 The threshold for initiation of this response is also variable, but in general, an AHPR is observed in vitro at inspired oxygen concentrations between 10 to 12 percent O2 and in vitro at dissolved oxygen partial pressures of approximately 40 to 50 mm Hg. The intracellular sensing mechanisms responsible for initiating the series of reactions culminating in smooth muscle cell contraction remains unknown. Endothelium independent activation of smooth muscle guanylate cyclase through a hydrogen peroxide-mediated mechanism with resultant increases in guanosine cyclic monophosphate (cGMP) appears to be necessary in the relaxation response to reoxygenation following short periods of induced hypoxia.19 As a corollary, it is hypothesized that reductions in these same parameters by hypoxia could represent the internal smooth muscle signal for contraction. Finally, maintenance of hypoxic conditions for subacute durations causes blunting or even loss of the acute pressor effect.

The waning of pressor effect and immediate reversibility characteristic of acute hypoxic exposure situations appear to contrast with the sustained vasospasm and lack of reversibility seen under prolonged conditions of reduced oxygen tension. Despite the apparent common property of both the acute and chronic vasoconstrictor responses being inhibited by calcium channel blockers, it does not necessarily follow that they represent similar physiologic mechanisms.20 In addition, a temporal continuum for both responses has not yet been conclusively demonstrated. However, preservation of the classic AHPR under conditions of prolonged hypoxia has been clearly demonstrated both clinically and experimentally. Acute worsening of chronically abnormal alveolar or arterial oxygen status will cause further deterioration in pulmonary hemodynamics, sometimes of dramatic degree.21 Such situations are commonly observed in chronically ill patients who suffer acute exacerbating changes in their usually stable and compensated disease status. As expected, correction of this acute change by measures to improve lung function or addition of increased levels of supplemental oxygen will cause PAP to revert back to baseline values. Similar findings have been noted in experimental animals with chronically remodeled pulmonary vessels. In these animals, the imposition of an acute hypoxic challenge has been shown to elicit increases in PAP of similar or even greater magnitude than that observed in normal controls.22 These combined observations might actually seem to suggest a dissociation in mechanisms between the chronologically different vasoconstrictive properties.

**Sustained Vasospasm: Mechanisms**

Basal pulmonary circulatory tone is maintained by a dynamic balance of vasoconstrictor and vasodilatory influences acting on the PVSMC located in the precapillary resistance vessels of the lung. This interaction is controlled by factors both intrinsic and extrinsic to the smooth muscle itself. Under conditions of chronic generalized alveolar hypoxia, there is a shift favoring PVSMC contraction and a heightened overall vascular tone. Mechanistically, this imbalance could result from either an increase or excess of the various vasoconstrictor components or a defect or reduction in appropriately adaptive relaxation mechanisms. The requisite inciting factors or membrane abnormalities that could potentially mediate the onset of PVSMC contraction have not yet been defined but most probably will be integrally linked to some dysfunction in calcium homeostasis.23

Most studies actually suggest that defects in pulmonary vasodilatation may be the essential element accounting for the persistently abnormal tone, specifically failure of endothelium-mediated PVSMC relaxation. Pulmonary arterial segments harvested from animals exposed long term to environments of reduced oxygen tension demonstrate consistent abnormalities of their vasodilatory capacity in response to agents known to exert this effect through endothelial cell-derived relaxing factor production and release (acetylcholine, adenosine diphosphate, calcium ionophore A23187).24 In these same studies, responses to nonendothelium-dependent vasodilatation using agents such as sodium nitroprusside and 8-bromo-cGMP were well preserved. Nitric oxide (NO) has been identified as the major biochemical compound mediating endothelium dependent vascular relaxation. Nitric oxide is synthesized from the terminal guanidine nitrogen atom(s) of L-arginine and exerts its vasodilatory effect through the generation of guanosine 3',5'-cyclic monophosphate (cGMP) by activation of soluble guanylyl cyclase. Not surprisingly, hypoxia-induced impairment of this enzyme has been observed in segments of proximal pulmonary arteries from rats exposed to 10 percent O2 for durations of 2 and 7 days.25 Conflicting data have been obtained regarding correction of this abnormality in NO-mediated relaxation through exogenous supplementation with L-arginine, a necessary precursor for NO synthesis. In addition, surgical specimens of pulmonary arteries recovered from patients with severe hypoxic lung disease undergoing transplantation similarly exhibited deficiencies in relaxation responses to acetylcholine and adenosine diphosphate, but normal sodium nitro-
prusside-mediated responses.\textsuperscript{26} Still, a degree of caution needs be observed in the overall interpretation of these data, since even within the same study, differences between \textit{in vitro} and \textit{in vivo} responsiveness to acetylcholine-induced endothelium-mediated vasodilatation have been observed.\textsuperscript{27} Whether this defect in endothelium-directed vasoregulation represents a selective abnormality or merely a reflection of overall endothelial cell dysfunction resulting from hypoxia remains to be determined.

**Structural Remodeling: General Characteristics**

Under conditions of chronic generalized alveolar hypoxia, the complexity of pathologic structural remodeling has been demonstrated throughout the entirety of the pulmonary circulation and all the structural layers of the arterial wall. The changes common to all chronically hypoxic disorders regardless of disease etiology or experimental condition include (1) the abnormal deposition of increased amounts of collagen and elastin within the adventitia, (2) medial smooth muscle cell hypertrophy and hyperplasia, and (3) the differentiation of normally poorly developed precursor smooth muscle cells into mature-appearing cells at the precapillary and alveolar levels (termed neomuscularization).\textsuperscript{28,29} In human disease states of severe emphysema, there is the additional appearance of longitudinally oriented smooth muscle cells within the intima and the occasional development of eccentric elastosis.\textsuperscript{30} This latter finding is probably a mechanical response to the stretching and distortion unique to that specific disease anatomy. Presumably, this occurs as a result of smooth muscle cell migration from the media into the intima. Characteristically, there is an absence of vascular necrosis or signs of toxicity besides the transient occurrence of endothelial cell blebs noted within the first few hours of exposure.\textsuperscript{31} In addition, there is a lack of evidence suggesting an inflammatory or reparative process. Pathologic studies of established disease have failed to reveal findings of platelet deposition or vascular thrombosis and organization.

As stated, however, late definition of specific anatomic abnormalities may not represent an accurate reflection of earlier events in disease onset and progression. Indeed, electron microscopic studies have shown a rapid and profuse accumulation of platelets within the microcirculation of rat lungs as soon as 1 h following 10 percent O\textsubscript{2} exposure which peak in number at 48 h duration but then disappear.\textsuperscript{32} These findings suggest that the anatomic vascular changes of chronic alveolar hypoxia are truly adaptive in nature and not the result of tissue injury from specific toxins, anoxia, or damage resulting from shearing forces. These compensatory anatomic changes increase vascular resistance not only as a result of luminal narrowing and obliteration, but also because of their ability to decrease vessel wall compliance and heighten vascular reactivity.\textsuperscript{33} This reduced vascular profusion was one of the earliest findings following radiographic analysis of barium-gelatin perfused lungs recovered from long-term exposed experimental animals.\textsuperscript{29}

**Structural Remodeling: Matrix Components**

The importance of extracellular matrix deposition in contributing directly to the elevation in PVR was first demonstrated in animal studies utilizing the nonspecific lathyrogen (B-aminopropionitrile) to inhibit both collagen and elastin formation.\textsuperscript{34} This pharmacologic intervention resulted in significant structural and hemodynamic improvement. Subsequent studies by these same investigators later demonstrated equal efficacy with the collagen-specific inhibitor cis-hydroxyproline not only in disease prevention but also in terms of significant amelioration when administered after pulmonary hypertension was established.\textsuperscript{35}

More recent studies have shown a potential autocrine function to the smooth muscle cells themselves in the control of this accelerated matrix production and deposition. Conditioned media recovered from cultured smooth muscle cells harvested from calves raised at altitude appeared to contain a unique elastogenic factor not found in cellular media from control animals. This factor served the dual role of enhancing elastin synthesis in committed cells and inducing differentiation of noncommitted cells into an elastin-expressing phenotype.\textsuperscript{36} However, \textit{in vitro} exposure of isolated PVSMC to reduced oxygen tension alone paradoxically elicits a decrease in the production rates of collagen, elastin, and their encoding messenger RNA.\textsuperscript{37}

These results suggest that hypoxia is not sufficient in itself to stimulate the increased production of these various matrix components. The other critical component in promoting this aspect of structural adaptation appears to be transmural mechanical stress resulting from the elevations in arterial pressure. Acute of cyclic application or stretch tension to vascular segments of the pulmonary artery for 4-h periods causes increased rates of collagen and elastin synthesis which interestingly appears to be endothelium dependent.\textsuperscript{38} Similar accelerated rates of matrix production have also been noted in explants of proximal pulmonary arterial segments removed from rats quite early following onset of hypoxic conditions that correlates closely in time with the onset of pulmonary hypertension.\textsuperscript{39} Furthermore, \textit{in vivo} animal studies have demonstrated that banding of one pulmonary
artery in rats prior to long-term hypoxic exposure significantly ameliorates the subsequent structural changes without affecting expected findings on the nonbanded side. These combined studies strongly support mechanical stress as an additional important stimulus to structural remodeling. The presence of these insoluble compounds could theoretically serve the dual purpose of increasing vascular wall rigidity/stiffness and establishing the appropriate local milieu permissive for mesenchymal cell proliferation and further matrix elaboration.

**Structural Remodeling: Smooth Muscle Cell Abnormality**

The changes in smooth muscle cell histologic features are thought to represent abnormalities of growth; replication and hypertrophy in large-sized vessels and maturation and development in smaller ones. *In vitro* studies have clearly demonstrated that hypoxia alone is incapable of directly stimulating PVSMC DNA synthesis and replication. Consequently, the potential role of currently known cellular mitogens and other growth regulatory substances as being etiologically implicated in mediating this stimulated growth has received active investigation. The polyamines are a group of organic cations with major regulatory roles in cellular growth and differentiation. Increased concentrations of the polyamines (putrescine, spermidine, spermine) have been demonstrated in rat lungs following prolonged durations of hypoxic exposure sufficient to effect sustained elevations in pulmonary arterial pressure. No such changes were found in the serum or liver of these same animals. Increased expression of platelet-derived growth factor A and B chain genes has also been noted in rat lungs as early as 3 days following hypoxic exposure which then remained elevated for the entire 21 days of study. This observation is similar to *in vitro* studies employing human umbilical vein endothelial cells showing the ability of oxygen tension to regulate gene expression for this mitogen. The exact relationship of these findings to the anatomic changes still awaits definition, but the demonstrated presence of growth-promoting substances relatively early in disease onset provides a rational hypothesis for the later development of fixed structural alterations.

A variety of pharmacologic manipulations have been efficacious in inhibiting these anatomic abnormalities. *In vitro* studies in experimental animals have demonstrated the abilities of heparin and the calcium channel inhibitors, nifedipine and nifedipine, to blunt the accelerated smooth muscle cell proliferative response and limit the degree of neomuscularization with subsequent beneficial effects on pulmonary hemodynamics. Heparin presumably mediates this action through its ability to intrinsically inhibit smooth muscle cell proliferation independent of its anticoagulant properties, since warfarin was without effect. The mechanism of the beneficial action exerted by the calcium channel blockers remains undefined but adds circumstantial support to the theory that the structural changes represent an adaptive response to the stresses induced by persistent vasoconstriction. Similar observations following modulation of different vasoregulatory metabolites of arachidonic acid likewise strengthen such a contention. Significant improvement in structural and hemodynamic parameters has been observed following inhibition of leukotriene synthesis by diethyldiamazine and stimulation of prostacyclin formation by continuous infusion of angiotensin II. This latter result conflicts with data from another study showing beneficial effects from angiotensin-converting enzyme inhibition and leaves open the possibility that any ameliorative action may occur through agonist of angiotensin II-directed stimulation of smooth muscle cell hyperplasia and hypertrophy rather than by blocking its vasoconstrictive capability.

In contrast to the documented effects of endothelial cell-derived substances on vascular reactivity, their role in mediating aberrant smooth muscle cell growth is debated. Using disparate in *vitro* techniques, investigators have shown that hypoxia-induced endothelial cell-derived factors can either inhibit or stimulate cultured PVSMC DNA synthesis and replication under similar co-culture conditions. However, confirmatory studies of either proposed mechanism have not yet been devised for *in vivo* models, thus rendering both sets of data purely speculative.

**Therapy: Preventive**

Conceptually, as a result of local inhomogeneity, the multitude of peripheral airways along with their accompanying vessels are exposed to variable levels of oxygen concentration dependent on the degree of reduction in inspired oxygen concentration, the degree of obstruction in chronic airway disorders, or the degree of ineffective ventilation associated with nonparenchymal respiratory diseases. In humans, a threshold or critical value of oxygen reduction at the alveolus has not yet been identified that will initiate either the chronic vasospastic or structural changes. Indeed, it is not even clear that the same magnitude of abnormality is required for both. Theoretically, as each disease process worsens in severity, more and more areas of the pulmonary vasculature are exposed to oxygen levels below that critical threshold, thereby setting up the nidus for the subsequent development of each pathophysiologic process. Consequently, even minor improvements in oxygen concentration around
and within a particular focal area have the potential to return oxygen levels above the critical level and prevent or at least retard further disease progression. Treating the primary initiating disease process at a stage before the development signs and symptoms suggesting significant vascular disease is the most obvious preventive therapeutic measure. Such established therapies include the following: (1) smoking cessation and institution of bronchodilatory drugs in chronic obstructive airway disorders; (2) tracheostomy or nasal continuous positive airway pressure in cases of obstructive sleep apnea; or (3) initiation of mechanical ventilatory assistance to patients suffering from progressive respiratory muscle weakness or chest wall disorders prior to the onset of overt respiratory failure and aggressive respiratory support of this same group of patients during situations of acute complicating lung diseases.

**Therapy: Established Pulmonary Hypertension**

Even once manifest, initial treatment of pulmonary hypertension in clinically stable situations remains directed at the primary disease with hopes of secondary improvement in its hemodynamic sequelae. Once this aspect of therapy is optimized or the disease reaches a stage deemed irreversible, then specific efforts may be directed toward the pulmonary vascular processes *per se*. Current options are limited to vasodilators or addition of supplemental oxygen. However, it must be realized that either therapy rarely returns PVR or pressure values to normal levels.

Despite isolated reports of major improvements following addition of long-term oxygen therapy in patients with hypoxic pulmonary hypertension, most large studies have shown only small decrements in either PVR or PAP. These findings raise the speculation that correction of alveolar hypoxia is ineffective at alleviating the demonstrated abnormalities once overt or that supplemental oxygen is unable to achieve adequate concentrations at the alveolar level to reverse or limit disease progression. Clinical data support the former contention. The addition of long-term domiciliary supplemental oxygen therapy to patients with stable hypoxic conditions and chronic obstructive lung disease improves arterial oxygen values and prevents hemodynamic deterioration but fails to achieve any significant differences in vascular abnormalities when compared with matched patients not receiving this form of therapy. However, more detailed studies of this latter point are probably warranted. Nevertheless, long-term oxygen therapy has clearly been proved to be of benefit in terms of overall morbidity and mortality for this group of patients.

In contrast to supplemental oxygen therapy, the utilization of vasodilator therapy in this same group of patients is without uniformly established efficacy in terms of either sustained hemodynamic improvement or mortality. Most of the vasodilatory drugs studied lacked specificity for the pulmonary circulation and frequently resulted in the complications of systemic hypotension or shock at dosages required to effect even small improvement in PVR. In addition, vasodilator therapy carries the risk of potentiating the degree of arterial hypoxemia due to alterations of adaptive ventilation/perfusion relationships with the possibility of worsening systemic oxygen delivery and exacerbating pulmonary hemodynamics because of decrements in oxygen at the alveolar and microvascular gas exchange areas. Since recent studies appear to have demonstrated selective pulmonary circulatory abnormalities in endothelial cell-derived relaxing factor (NO) production and release under conditions of chronic hypoxia, it would seem most plausible that NO administration or measures to correct this defect would be ideal therapeutic modalities. Given its pharmacologic property of rapid systemic deactivation by binding to hemoglobin, NO should also be free of unwanted systemic vasodilatation. Continuous inhalation of NO has been demonstrated to reverse acute hypoxic vasoconstriction in animals and to relieve some degree of pulmonary hypertension complicating human cases of acute lung injury and primary pulmonary hypertension. However, the extremely short biologic activity of this compound necessitates continuous delivery which is most impractical for the large number of patients with chronic hypoxic pulmonary hypertension. Furthermore, the established safety of this novel therapeutic modality has not been proved.

Clearly our lack of understanding specific etiologic factors and mechanisms for each of the individual components that contribute to the elevation in PAP resulting from prolonged alveolar hypoxia has hindered the development and use of more specifically targeted therapies. As this information becomes available, it would not be surprising that such studies will soon be forthcoming. However, the potential crossover of such interventions in terms of overt toxicity or disruption of normal organ function and repair will need to be monitored closely and their ultimate beneficial effects on morbidity and mortality critically assessed.

**Conclusion**

In conclusion, pulmonary hypertension is a frequent hemodynamic complication of a wide spectrum of disease processes whose only common abnormality is chronic alveolar hypoxia. The development of the increase in PAP is mediated by two interdependent vascular mechanisms: (1) persistent
vasospasm and (2) structural remodeling. The combination of these physiologic and pathologic processes imposes a mechanical and obliterative burden on the pulmonary circulation that cannot be dissipated by normal adaptive properties. The various etiologic components in terms of initiating and modifying influences are slowly being unraveled. This knowledge could dramatically alter future therapies. However, current management remains standardized, namely appropriate treatment of the primary disease process and institution of supplemental oxygen when indicated by established criteria.

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