20
Diseases of the Pulmonary Vascular System

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Introduction

Although historically considered the *lesser circulation*, pathology of the pulmonary circulation is a great source of pediatric morbidity and mortality. This is most commonly displayed in neonates with persistent pulmonary hypertension; neonates, infants, and children with congenital heart disease; and adolescents and young adults with primary pulmonary hypertension. Recent evidence indicates that normal pulmonary vascular tone is regulated by a complex interaction of vasoactive substances that are locally produced by the vascular endothelium [1–6]. These substances, such as nitric oxide (NO) and endothelin-1 (ET-1), are capable of producing vascular relaxation and/or constriction, modulating the propensity of blood to clot, and inducing and/or inhibiting smooth muscle cell migration and replication [6–20]. In fact, mounting data implicate endothelial injury and the subsequent aberration in the endogenous production of these substances in the pathophysiology of pulmonary hypertensive disorders [21–25]. This chapter discusses the normal regulation of the fetal, transitional, and postnatal pulmonary circulations, the pathophysiology of pediatric pulmonary hypertensive disorders, and new therapeutic and preventative strategies for pulmonary hypertension. Particular emphasis is placed on the role of the pulmonary vascular endothelium in these processes and treatment modalities.

Regulation of the Fetal, Transitional, and Postnatal Pulmonary Circulations

The Normal Fetal Circulation

In the fetus, gas exchange occurs in the placenta and pulmonary blood flow is low, measuring approximately 100 mL/100 g wet lung weight in the near-term lamb [26]. The majority of right ventricular output, which represents two thirds of total combined ventricular output, is diverted away from the lungs through the widely patent ductus arteriosus to the descending thoracic aorta [27]. Midway through gestation, pulmonary blood flow is approximately 3%–4% of the total combined ventricular output. This value increases progressively, reaching about 6% at 80% gestation, when the release of surface active material into lung fluid begins and up to a maximum of 8%–10% at or near term [21,28,29]. Fetal pulmonary arterial pressure also increases with advancing gestation. At term, mean pulmonary arterial pressure is about 50 mm Hg, generally exceeding the mean descending aortic pressure by 1–2 mm Hg [28,30]. Pulmonary vascular resistance, which is extremely high in early gestation, falls progressively as pulmonary arterial development advances, which increases the cross-sectional area of the pulmonary circulation; however, the pulmonary vascular resistance of the fetus is still much higher than that of the neonate after birth [27,31]. A number of mechanisms have been implicated in the maintenance of the high pulmonary vascular resistance and pulmonary arterial pressure during fetal life. These include mechanical factors, the low oxygen tension of fetal pulmonary and systemic blood, leukotrienes, thromboxane, ET-1, NO, prostaglandin (PG) I_2, platelet-derived growth factor (PDGF), and K^+ channels (32).

The Transitional Circulation

The transition from the fetal to the neonatal pulmonary circulation is marked by a dramatic fall in pulmonary vascular resistance and rise in pulmonary blood flow, which increases 8–10-fold (up to 300–400 mL/min/kg body weight). These changes are associated with the initiation of ventilation of the lungs and the subsequent increase in pulmonary and systemic arterial blood oxygen tensions. The increase in pulmonary blood flow increases pulmonary venous return and left atrial pressure, allowing the foramen ovale to close. In addition, the ductus arteriosus constricts, functionally closing within several hours after birth, which effectively separates the pulmonary and systemic circulations. Mean pulmonary arterial pressure decreases, and by 24 hr of age is approximately 50% of mean systemic arterial pressure. Under normal conditions, adult values are reached 2–6 weeks after birth [29].

The decrease in pulmonary vascular resistance with ventilation and oxygenation at birth is regulated by a complex and incompletely understood interplay between metabolic and mechanical factors. In experiments, physical expansion of the fetal lamb lung without changing oxygen tension increases fetal pulmonary blood

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flow and decreases pulmonary vascular resistance but not to newborn values [33]. A proportion of this decrease relates to alterations in the physical architecture of the alveoli and small pulmonary vessels that occur with mechanical distention [34]. In addition, physical expansion of the lung results in the release of vasoactive substances, such as PGI_2, which increases pulmonary blood flow and decreases pulmonary vascular resistance in the fetal goat and lamb independent of the changes in oxygen tension [35–40].

When ventilation is accompanied by changes in oxygen tension (i.e., ventilation with ambient air or supplemental oxygen), fetal pulmonary blood flow increases and pulmonary vascular resistance falls to newborn values. The exact mechanisms of this oxygen-induced pulmonary vasodilation remain unclear. Alveolar and/or arterial oxygen may directly dilate pulmonary resistance vessels or may trigger the release of vasoactive substances, such as PGI_2 or NO. In fact, data indicate that NO, in particular, participates in the decrease in pulmonary vascular resistance that accompanies increases in alveolar and arterial oxygen tension [7,12] However, despite its important role, inhibition of NO does not impair the immediate fall in pulmonary vascular resistance seen after birth, further suggesting that multiple mechanisms are involved in this transitional physiology. In fact, recent data implicate fluid shear forces across endothelial cells, which result in the production of both NO and PGI_2, as an additional mechanism by which vasodilation occurs after birth [32]. It is possible that this particular mechanism acts to maintain pulmonary vasodilation once it has been established by the mechanisms described earlier.

In general, the dramatic increase in pulmonary blood flow with the initiation of ventilation and oxygenation at birth reflects a shift from active pulmonary vasoconstriction in the fetus to active pulmonary vasodilatation in the newborn. Failure to undergo this normal transition contributes substantially to the pathophysiology of many neonatal pulmonary hypertensive disorders, including bronchopulmonary dysplasia, persistent pulmonary hypertension of the newborn, chronic lung disease, and congenital heart disease [25,40–64].

The Postnatal Pulmonary Circulation

The successful transition from the fetal to the postnatal pulmonary circulation is marked by the maintenance of the pulmonary vasculature in a dilated, low-resistance state [65]. Recent evidence suggests that basal NO release, and the subsequent increase in smooth muscle cell cyclic guanosine monophosphate (cGMP) concentrations, in part mediate the low resting pulmonary vascular resistance of the newborn [66]. Other vasoactive substances, including histamine, 5-hydroxytryptamine, bradykinin, and metabolites of arachidonic acid by the cyclooxygenase and lipoxygenase pathways, have also been implicated in mediating postnatal pulmonary vascular tone; however, their roles are not well elucidated. Two of the most important factors affecting pulmonary vascular resistance in the postnatal period are oxygen concentration and pH. Decreasing oxygen tension and decreases in pH elicit pulmonary vasoconstriction [67]. Alveolar hypoxia constricts pulmonary arterioles, diverting blood flow away from hypoxic lung segments, toward well-oxygenated segments, thus enhancing ventilation–perfusion matching [68]. This response to hypoxia, unique to the pulmonary vasculature, is greater in the younger animal than in the adult [69]. Indeed, in most vascular beds (e.g., cerebral vasculature), hypoxia is a potent vasodilator. The exact mechanism of hypoxic pulmonary vasoconstriction remains incompletely understood but likely involves changes in the local concentration of reactive oxygen species that in turn regulate voltage-gated potassium channels and calcium channels [66,70]. Acidosis potentiates hypoxic pulmonary vasoconstriction, whereas alkalosis reduces it [71]. The exact mechanism of pH-mediated pulmonary vascular reactivity also remains incompletely understood but appears to be independent of $PaCO_2$ [72]. Recent data suggest that potassium channels play an important role in mediating these responses as well [73]. Manipulating alveolar oxygen tension and systemic arterial pH are fundamental approaches to changing pulmonary vascular tone in the critical care setting. Alveolar hyperoxia and alkalosis are often used to decrease pulmonary vascular tone because they generally relieve pulmonary vasoconstriction with little effect on the systemic circulation as a whole. However, severe alkalosis is generally avoided because of the detrimental effects of severe hypocarbia or alkalosis on cerebral and myocardial blood flow (see General Treatment Approach, later) [6,8].

Despite extensive innervation of the lung, neural input is not a major determinant of basal pulmonary vascular tone. However, pulmonary neurohumoral receptors are sensitive to α-adrenergic, β-adrenergic, and dopaminergic agonists [74,75]. Therefore, vasoactive agents that stimulate these receptors will affect the vascular tone of both the pulmonary and systemic circulations. Alterations in vascular tone, in response to a given agent, are dependent on the relative tone of the vascular bed at a given time. Therefore, the response of these agents is difficult to predict in an individual critically ill patient.

Determinants of Pulmonary Vascular Resistance

Pulmonary vascular resistance changes throughout gestation and after birth. The resistance of the pulmonary circulation at any one time is related to several factors and can be estimated by applying the resistance equation and the Poiseuille-Hagen relationship [76]. The resistance equation (the hydraulic equivalent of Ohm's law) states that the resistance to flow between two points along a tube equals the decrease in pressure between the two points divided by the flow [77,78]. For the pulmonary vascular bed, where Rp is pulmonary vascular resistance and Qp is pulmonary blood flow, the decrease in mean pressure is from the pulmonary artery (Ppa) to the pulmonary vein (Ppv) or left atrium, where la is mean left atrial pressure:

$$Rp = [Ppa - Ppv \text{ or } la \text{ (mean)}]/Qp$$

Therefore, the calculated pulmonary vascular resistance increases when pulmonary arterial pressure increases or when pulmonary blood flow decreases. Changes in pulmonary venous pressure or mean left atrial pressure are somewhat more complicated. In isolation, increases in pulmonary venous pressure and left atrial pressure would decrease the calculated pulmonary vascular resistance. However, increases in pulmonary venous pressure are generally accompanied by a greater increase in pulmonary arterial pressure (which maintains driving pressure), resulting in an increase in the calculated resistance across the pulmonary vascular bed. Furthermore, changes in left atrial pressure, which occur independent of alterations in pulmonary vascular resistance, must be considered. For example, large intracardiac shunts (e.g., ventricular septal defect) may result in congestive heart failure with an elevation in left atrial pressure. Closure of the ventricular septal defect may acutely decrease left atrial pressure, resulting in an elevation

in the calculated pulmonary vascular resistance (provided that pulmonary arterial pressure does not decrease to the same extent), when in fact no change in pulmonary vascular tone has occurred [79].

Other factors that affect pulmonary vascular resistance can be defined by applying a modification of the Poiseuille-Hagen relationship, which describes the resistance (R) to flow of a Newtonian fluid through a system of round, straight glass tubes of constant cross sectional area:

$$Rp = 8 \cdot l \cdot \eta / n\pi r^4$$

where l is length of the system of vessels, n is vessel number, r is the internal radius of the system of vessels, and η is the viscosity of the fluid. According to this relationship, increasing the viscosity of blood perfusing the lungs or decreasing the radius or cross-sectional area (πr^4) of the pulmonary vascular bed increases pulmonary vascular resistance. Because the above equations describe steady, laminar flow of a Newtonian fluid in rigid, glass tubes, differences between physical and biologic systems should be considered. First, blood is not a Newtonian fluid. However, this is probably of little importance at normal hematocrit levels [80]. The viscosity of blood is related to red cell number, fibrinogen concentration, and red cell deformability. An increased hematocrit (secondary to fetal hypoxemia, twin-to-twin transfusion, maternal-to-fetal transfusion, or delayed clamping of the umbilical cord) will increase viscosity [80,81] as pulmonary vascular resistance increases logarithmically when the hematocrit increases. Second, pulmonary vessels are not rigid tubes. Their walls are deformable, and their size and shape are influenced by transmural pressure. For example, as pulmonary blood flow or left atrial pressure increases, vessel diameter may change, and/or the recruitment of additional pulmonary vessels may occur. Therefore, the fall in calculated pulmonary vascular resistance with increases in pulmonary blood flow is nonlinear [65,82,83]. Third, blood flow through the pulmonary circulation is pulsatile, not laminar, and the small pulmonary arteries are branched, curved, and tapered, not smooth [76]. In addition, the small pulmonary arteries are in parallel, and the radii of these arteries may differ in different lung zones.

Despite these differences from physical models, the general effects of changes in physical factors, such as viscosity and radius, do apply [76–78]. In fact, a change in luminal radius is the major factor responsible for maintaining a high pulmonary vascular resistance in the fetus. Consideration of these factors, particularly viscosity and cross-sectional area of the vascular bed, is important in evaluating the pathophysiology of pulmonary hypertensive disorders.

Finally, it is important to note the overall relationship between lung volume and pulmonary vascular resistance, which has been described by several investigators [84,85]. These studies have shown that this relationship to be U-shaped (Figure 20.1) with minimal pulmonary vascular resistance noted at functional residual capacity. Using an open-chest model, pulmonary vascular resistance decreased as lungs were inflated from a collapsed state and then progressively increased at higher lung volumes, which was thought to be related to inflation pressure on the alveolar vessels. These observations support the concept that lung inflation may have a variable effect on the distribution of pulmonary blood flow.

When pressure is expressed in mm of Hg and flow in L/min, units of resistance are derived as mm of Hg/L/min (Wood unit, U). However, comparisons among patients of differing weight and age

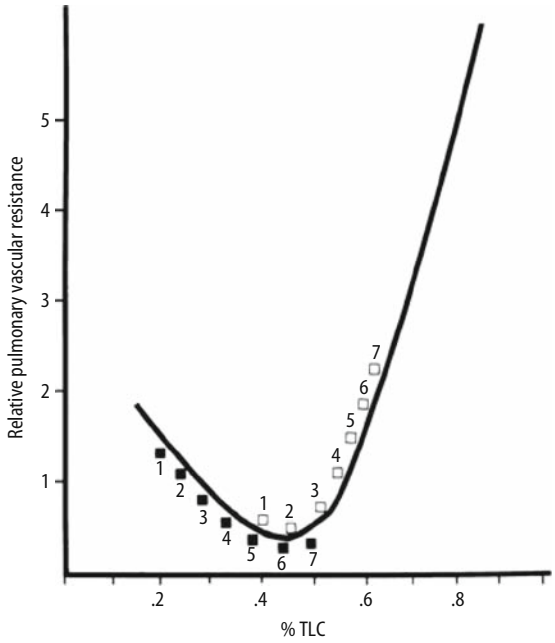

Figure 20.1. Diagrammatic plot to illustrate the U-shaped relationship between relative pulmonary vascular resistance (PVR) and relative lung volume (% total lung capacity [TLC]). Regions of the lung are numbered from top (region 7) to bottom (region 1) of the lung for both low (closed squares) and high (open squares) overall lung volumes. (From Baile et al. [84]. Copyright 1982 from American Physiological Socity. Reprinted with perrmission.)

are problematic. Therefore, resistance is more commonly expressed in relation to body surface area, as U·m^2. Multiplying U by 80 converts to dynes/sec/cm^{-5}, a common form utilized to express resistance in other settings. Pulmonary vascular resistance may be as high as 8–10 U·m^2 immediately after birth and then, under normal conditions, falls as previously described to adult levels of 1–3 U·m^2 by 6 to 8 weeks of life [27,31].

Pulmonary Hypertensive Disorders

Pulmonary hypertensive disorders are a significant source of morbidity and mortality in the pediatric population. Pulmonary hypertension is defined as a mean pulmonary artery pressure of greater than 25 mm of Hg at rest or greater than 30 mm of Hg during exercise. In addition, a calculated pulmonary vascular resistance of greater than 3 U is generally considered abnormal. In neonates, the most common etiology results from a failure to undergo the normal fall in pulmonary vascular resistance at birth termed *persistent pulmonary hypertension of the newborn* (PPHN) that has an incidence of ~1 per 1,000 live births. However, other pulmonary abnormalities, such as congenital diaphragmatic hernia, respiratory distress syndrome, and bronchopulmonary dysplasia, may also result in neonatal pulmonary hypertension. Beyond the neonatal period, the majority of pediatric pulmonary hypertensive disorders are associated with congenital heart defects. Other, less common causes of pediatric pulmonary vascular disease include primary (idiopathic) pulmonary hypertension, hypoxia-induced pulmonary vascular disease, rheumatologic disorders, sickle cell disease, portal hypertension, chronic thromboembolic disease, human immunodeficiency virus disease, and drug-toxin induced disease. A number of clinical classification systems for

Table 20.1. Clinical classification of pulmonary hypertension.

Pulmonary arterial hypertension (PAH)
Idiopathic (IPAH)
Familial (FPAH)
Related to risk factors or associated conditions (APAH)
Collagen vascular disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
Human immunodeficiency virus infection
Drugs and toxins
Other: thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
Associated with venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Pulmonary hypertension associated with lung disease and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Proximal pulmonary arteries
Distal pulmonary arteries
Nonthrombotic embolism (tumor, parasites, foreign material)
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels

Source: Adapted from Simonneau et al. [227].

pulmonary hypertension have been proposed, most recently at the 2003 Third World Symposium on Pulmonary Arterial Hypertension (Table 20.1).

Pathobiology of the Pulmonary Vasculature

Vascular endothelial cells are capable of producing a variety of vasoactive substances that participate in the regulation of normal vascular tone. A schematic of some of these endothelial factors is shown in Figure 20.2. These substances, such as NO, ET-1, and prostacyclin are capable of producing vascular relaxation and/or constriction, modulating the propensity of the blood to clot, and inducing and/or inhibiting smooth muscle cell migration and replication [6–20].

Nitric oxide is a labile humoral factor produced by nitric oxide synthase (NOS) from L-arginine in the vascular endothelial cell [86–88]. Nitric oxide diffuses into the smooth muscle cell and produces vascular relaxation by increasing concentrations of guanosine 3′5′-monophosphate (cGMP) via the activation of soluble guanylate cyclase [89,90]. Nitric oxide is released in response to a variety of factors, including shear stress (flow) and the binding of certain endothelium-dependent vasodilators (such as acetylcholine, adenosine triphosphate [ATP], and bradykinin) to receptors on the endothelial cell [4,91]. Basal NO release is an important mediator of both resting pulmonary and systemic vascular tone in the fetus, newborn, and adult, as well as a mediator of the normal fall in pulmonary vascular resistance that occurs immediately after birth 32,87,92]. In addition, aberrant NO–cGMP signaling is integral to the pathophysiology of pulmonary hypertension, as well as a number of other biologic vascular disorders [10,11,23,25,44,45,48,52].

Endothelin-1 is a 21 amino acid polypeptide also produced by vascular endothelial cells [2]. The vasoactive properties of ET-1 are complex, and studies have shown varying hemodynamic effects on different vascular beds [16–20]. However, its most striking property is its sustained hypertensive action. In fact, ET-1 is the most potent vasoconstricting agent discovered, with a potency 10 times that of angiotensin II. The hemodynamic effects of ET-1 are mediated by at least two distinct receptor populations, ET_A and ET_B [93,94]. The ET_A receptors are located on vascular smooth muscle cells and mediate vasoconstriction, whereas the ET_B receptors are located on endothelial cells and smooth muscle cells and thus may mediate both vasodilation and vasoconstriction, respectively. Individual endothelins occur in low levels in the plasma, generally below their vasoactive thresholds. This suggests that they are primarily effective at the local site of release. Even at these levels, they may potentiate the effects of other vasoconstrictors, such as norepinephrine and serotonin [95]. The role of endogenous ET-1 in the regulation of normal vascular tone is unclear at present [96]. Nevertheless, alterations in ET-1 have been implicated in the pathophysiology of a number of disease states, including pulmonary hypertensive disorders, and has been implicated in the so-called rebound effect of inhaled NO [24,25,54,60,97].

Endothelial-derived hyperpolarizing factor (EDHF), a diffusible substance that causes vascular relaxation by hyperpolarizing the smooth muscle cell, is another important endothelial factor.

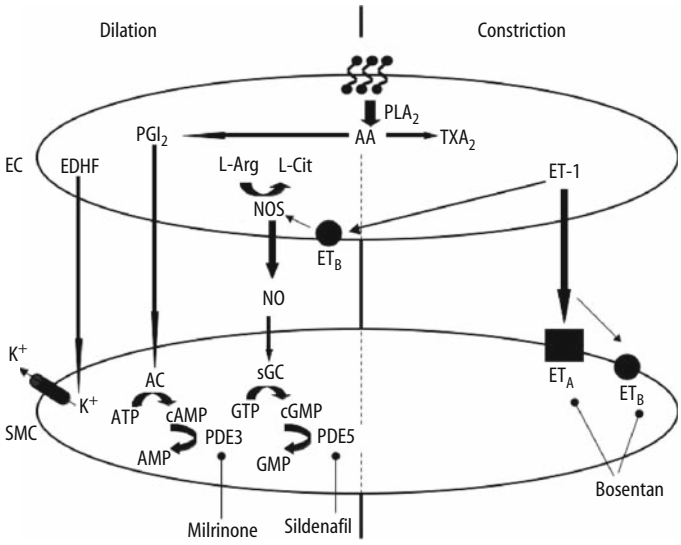

Figure 20.2. Schematic of some endothelial-derived factors. EC, pulmonary vascular endothelial cell; SMC, pulmonary vascular smooth muscle cell; EDHF, endothelial-derived hyperpolarizing factor; PGI_2, prostaglandin I_2; PLA_2, phospholipase A_2; AA, arachidonic acid; TXA_2, thromboxane A_2; L-Arg, L-arginine; L-Cit, L-citrulline; NOS, nitric oxide synthase; ET-1, endothelin-1; ET_A, endothelin A receptor; ET_B, endothelin B receptor; NO, nitric oxide; sGC, soluble guanylate cyclase; GTP, guanosine-5′-triphosphate; cGMP, guanosine-3′-5′-cyclic monophosphate; GMP, guanosine monophosphate; AC, adenylate cyclase; ATP, adenosine-5′-triphosphate; cAMP, adenosine-3′-5′-monophosphate; AMP, adenosine monophosphate; PDE, phosphodiesterase (types 3 and 5 shown); K^+, potassium channels. Also shown are sites of action of milrinone (phosphodiesterase 3 inhibitor), sildenafil (phosphodiesterase 5 inhibitor), and bosentan (ET_A and ET_B antagonists).

Endothelial-derived hyperpolarizing factor has not yet been identified, but current evidence suggests that its action is dependent on K^+ channels [97]. Activation of potassium channels in the vascular smooth muscle results in cell membrane hyperpolarization, closure of voltage-dependent calcium channels, and ultimately vasodilation. Potassium channels are also present in endothelial cells. Activation within the endothelium results in changes in calcium flux and may be important in the release of NO, prostacyclin, and EDHF. Potassium channel subtypes include ATP-sensitive K^+ channels, Ca^{2+}-dependent K^+ channels, voltage-dependent K^+ channels, and inward-rectifier K^+ channels [97].

The breakdown of phospholipids within vascular endothelial cells results in the production of the important byproducts of arachidonic acid, including prostacyclin (PGI_2) and thromboxane (TXA_2). Prostacyclin activates adenylate cyclase, resulting in increased cAMP production and subsequent vasodilation, whereas TXA_2 results in vasoconstriction via phospholipase C signaling. Other prostaglandins and leukotrienes also have potent vasoactive properties. Increasing evidence suggests that endothelial injury and the resulting alteration in the balance of these and other vasoactive substances has a significant role in the development of pulmonary hypertension and increased vascular reactivity [22,98,99]. Support for this hypothesis is strengthened by observations that endothelial injury precedes pulmonary hypertension and its associated vascular remodeling in several animal models of pulmonary hypertension [61,100]. In humans, endothelial dysfunction, including histologic abnormalities of the endothelium, impairment of endothelium-dependent pulmonary vasodilation, and increased plasma ET-1 concentrations have been described in children with congenital heart defects and pulmonary hypertension before the development of significant vascular remodeling [22,98,101]. In addition, neonates with PPHN and adults with advanced pulmonary vascular disease have evidence of endothelial dysfunction, impairment of endothelium-dependent pulmonary vasodilation, increased plasma ET-1 concentrations, and decreased prostacyclin production [23,24,62,99]. The mechanism of injury to the vascular endothelium is unclear but is likely multifactorial and in part dependent on the etiology of the pulmonary hypertension. For example, in children with congenital heart disease and increased pulmonary blood flow, the initiating endothelial injury is likely mediated by increased shear stress. However, once pulmonary arterial pressure is elevated, shear stress-mediated endothelial injury appears to promote the progression of the disease, independent of the underlying etiology. Finally, a genetic disposition appears to be important in some subtypes of pulmonary vascular disease and remains an area of active research. For example, up to 60% of patients with familial idiopathic pulmonary hypertension have mutations resulting in the loss of function of bone morphogenetic protein receptor II [102–105].

Following an initial endothelial injury, smooth muscle proliferation and progressive structural remodeling occurs. The progression of anatomic changes is best characterized in congenital heart disease (see later discussion) [106–109]. However, regardless of the etiology, advanced disease is characterized by medial hypertrophy, intimal hyperplasia, angiomatoid formation, in situ thrombi, and eventual vascular obliteration. If the underlying stress remains untreated (e.g., delayed repair of cardiac shunt), these structural changes can progress to the point of becoming functionally "fixed" or irreversible. An important goal of therapy is to halt this progression and reverse the early vascular remodeling if possible.

General Treatment Approach

Regardless of the underlying etiology, the general treatment approach is similar and can be subdivided into four major goals: (1) prevent and acutely treat active pulmonary vasoconstriction, (2) support the failing right ventricle, (3) treat the underlying etiology, and (4) chronically promote, if possible, the regression of pulmonary vascular remodeling.

Prevent and Acutely Treat Active Pulmonary Vasoconstriction

In the intensive care setting, the prevention and treatment of active pulmonary vasoconstriction is a primary focus for the care of patients with underlying pulmonary vascular disease. It is well appreciated that these patients have augmented pulmonary vasoconstriction in response to such stimuli as hypoxia, acidosis, the catecholamine-mediated α_1-adrenergic stimulation associated with pain and agitation, and increases in intrathoracic pressure [110–112]. In fact, acute increases in pulmonary vascular resistance can lead to significant cardiopulmonary compromise (i.e., a pulmonary hypertensive crisis). The pathophysiology of such a crisis in outlined in Figure 20.3. Following an acute increase in pulmonary arterial pressure, there is an acute increase in right ventricular afterload, producing right ventricular ischemia and, ultimately, failure [113,114]. The resulting increase in right ventricular end diastolic volume shifts the intraventricular septum to the left, decreasing left ventricular volume and cardiac output. Decreased cardiac output results in decreased systemic perfusion and metabolic acidosis. Increased pulmonary vascular resistance and right ventricular failure also decrease pulmonary blood flow, increasing dead space ventilation. Distention of the pulmonary arteries and perivascular edema produce large and small airways obstruction, respectively, which impairs ventilation–perfusion matching and decreases lung compliance. In fact, the decrease in lung compliance can be so dramatic that chest wall movement is impaired, even with manual ventilation. The ensuing hypoxemia, hypercapnia, and acidosis (metabolic and/or respiratory) further increase pulmonary vascular resistance and perpetuate this cascade.

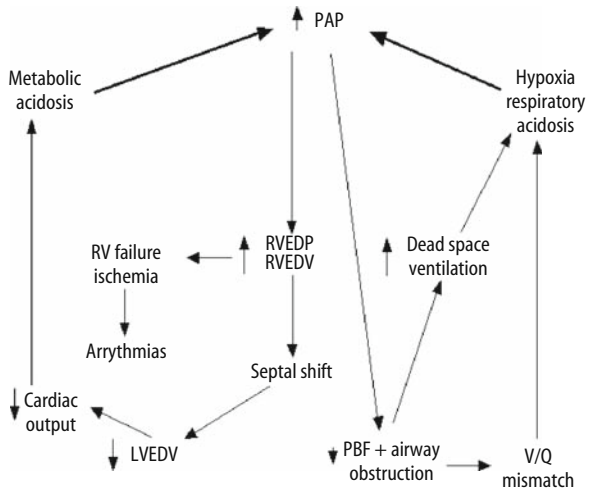

Figure 20.3. The cardiopulmonary effects of acute pulmonary hypertension. CO, cardiac output; LVEDV, left ventricular end diastolic volume; PAP, pulmonary arterial pressure; RV, right ventricle; RVEDP, right ventricular end diastolic pressure; RVEDV, right ventricular end diastolic volume; V/Q, ventilation/perfusion.

Prevention of pulmonary hypertensive crises may be accomplished by avoiding stimuli known to increase pulmonary vascular resistance, including hypoxia, acidosis, agitation, pulmonary overdistention, and polycythemia [112]. Various regimens have been utilized for this purpose, including the judicious use of supplemental oxygen, analgesics, sedatives, and muscle relaxants (especially before noxious stimuli, such as suctioning); the maintenance of an alkalotic pH with the use of controlled ventilation and buffer; aggressive evacuation of pneumothoraces and pleural effusions; the utilization of low lung volume ventilator strategies; the minimization of positive end-expiratory pressures; and the maintenance of the hematocrit below 55% [85,115]. In addition, data suggest that the use of pulmonary vasodilator therapy may decrease the incidence of pulmonary hypertensive crises [116–128].

Treatment of active pulmonary vasoconstriction is accomplished with the use of pulmonary vasodilator therapy. The mainstay of acute pulmonary vasodilator therapy remains supplemental oxygen and moderate alkalosis, as these therapies have minimal effects on the systemic vasculature. Interestingly, the dose-dependent response of the pulmonary vasculature to these agents has not been well established. Studies in newborn lambs demonstrate dose-dependent pulmonary vasodilation in response to increasing pH from 7.30 to 7.60, and a dose-dependent response to increasing inspired oxygen concentrations from 0.21 to 0.5, with minimal effects at higher concentrations [129]. Several intravenous agents have been utilized to promote pulmonary vasodilation, including tolazoline, sodium nitroprusside, nitroglycerin, prostacyclin, prostaglandin E_1, nifedipine, and α-adrenergic antagonists, such as phenoxybenzamine [130–137]. The efficacies of these agents are variable, at least in part because of their effects on the systemic vasculature. Systemic afterload reduction can be advantageous in the setting of left ventricular dysfunction; however, significant reductions in pulmonary arterial pressure without unacceptable systemic hypotension are often not possible [138–140]. In addition, intravenous vasodilators can override intrinsic hypoxic pulmonary vasoconstriction, resulting in an increase in dead space ventilation, which may not be tolerated in some critically ill patients [141–145].

More recent treatment modalities, most notably inhaled NO, deliver short-acting vasodilators to the pulmonary vasculature via an inhalational route [116–128]. When administered to the lung in its natural gaseous form, NO diffuses through the alveolar wall to reach small pulmonary arteries. It then enters vascular smooth muscle cells, initiating a cascade that results in pulmonary vasodilation via increases in cGMP. After entering the blood vessel lumen, NO is rapidly inactivated by hemoglobin, which confines its effects to the pulmonary vasculature. Because of these properties, inhaled NO has several advantages over other vasodilators, including (1) selective pulmonary vasodilation caused by rapid inactivation by hemoglobin, (2) rapid onset and elimination, and (3) an improvement in ventilation–perfusion matching because of the limitation of delivery to well-ventilated lung regions. Accordingly, inhaled NO has become a mainstay of treatment for acute pulmonary hypertensive disorders and the assessment of pulmonary vascular reactivity. Inhaled prostacyclin has similar pulmonary selectivity, secondary to rapid inactivation by hemoglobin. Its vasodilating effects are secondary to increasing cAMP concentrations. Currently, studies on the use of inhaled prostacyclin for pediatric pulmonary hypertension are sparse, and comparison studies between inhaled NO and inhaled prostacyclin are lacking [146–156].

Inhibitors of phosphodiesterases (PDEs), a family of enzymes that hydrolyze the cyclic nucleotides cAMP and cGMP, are a relatively new class of agents that have potent vasodilating and inotropic effects [157]. Milrinone is a PDE 3 inhibitor that increases cAMP concentrations. Animal and human data demonstrate pulmonary vasodilation in response to milrinone that can be in excess of its systemic effects if the pulmonary vasculature is constricted [158–161]. In addition, a large, randomized study demonstrates that its use decreases the incidence of low cardiac output syndrome following surgery for congenital heart disease [162]. Given these properties, milrinone is increasingly utilized in the postoperative management of patients with congenital heart disease and pulmonary hypertension.

Sildenafil, a PDE5 inhibitor, which increases cGMP concentrations, also has potent pulmonary vasodilating effects [163]. The oral formulation is currently being investigated for chronic pulmonary hypertensive therapy, and recent short-term studies demonstrate beneficial effects in children with advanced pulmonary vascular disease [164]. The intravenous formulation is currently being investigated for acute pediatric pulmonary hypertensive disorders (PPHN and perioperative pulmonary hypertension) [165,166].

Increasing data implicate alterations in ET-1 in the pathophysiology of pulmonary hypertension (see earlier) and suggest that ET-receptor antagonism may be a useful therapeutic strategy [24,25,54,60,97]. In fact, bosentan, an oral combined ET_A and ET_B receptor antagonist, has demonstrated efficacy as a chronic therapy for advanced pulmonary vascular disease [167,168]. To date, there have been no large studies on the use of ET receptor antagonists for acute pulmonary hypertensive disorders. In addition, the use of selective ET receptor antagonism is under investigation but has not yet reached clinical trials.

Support the Failing Right Ventricle

A significant component of the pathophysiology of both acute and chronic pulmonary hypertension is the development of right ventricular dysfunction, which often requires pharmacologic support. Maintenance of adequate preload is necessary to optimize cardiac output in patients with pulmonary hypertension. Continuous central venous pressure monitoring may be helpful to guide volume therapy, keeping in mind that patients with a poorly compliant right ventricle or increased right ventricular afterload may require elevated central venous pressures to maintain an adequate cardiac output. Frequent clinical assessment of liver size can be helpful, particularly in infants.

Despite adequate preload, cardiac output may be compromised secondary to elevated right ventricular afterload and/or biventricular myocardial dysfunction after cardiac surgery and cardiopulmonary bypass, necessitating the use of inotropic agents [111,169]. These agents increase stroke volume at a given preload and afterload by stimulating $ß_1$-adrenergic receptors [170,171]. However, some of these agents also stimulate $ß_2$- or α_1-adrenergic receptors, which are found on the smooth muscle cells of both the pulmonary and systemic arteries. Agents that stimulate $ß_2$-adrenergic receptors decrease both pulmonary and systemic vascular resistance and improve right and left ventricular function [172,173]. Agents that stimulate α_1-adrenergic receptors may increase both systemic and pulmonary vascular resistance. Therefore, a rational approach to using inotropic agents in the setting of pulmonary hypertension is to utilize agents with $ß_2$-receptor selectivity and minimal α_1-

adrenergic stimulation (i.e., dobutamine). Although animal studies have shown that high doses of dopamine increase pulmonary vascular resistance, human studies have shown increased cardiac output with minimal effects on pulmonary vascular resistance [130,174]. Milrinone is also a useful therapy for patients with pulmonary hypertension and myocardial dysfunction, given its vasodilatory and inotropic properties [162].

In the setting of pulmonary hypertension secondary to congenital heart defects, an atrial communication can be beneficial in that it allows the failing right ventricle to decompress when right atrial pressure rises [175]. Accordingly, atrial septal defects can be left unclosed (i.e., patent foramen ovale) or created at the time of surgery. The existence of an atrial level communication decreases the risk of right ventricular failure and maintains left-sided cardiac output. The resulting right-to-left shunt is generally well tolerated, particularly if high hemoglobin concentrations are maintained. As right ventricular function improves, right-to-left shunting decreases and oxygenation improves. Atrial septostomy as a part of management for chronic pulmonary hypertension (e.g., primary pulmonary hypertension) has been advocated but must be considered carefully on an individual basis [176–180].

In patients with refractory pulmonary hypertension, short-term postoperative extracorporeal support has been useful during the postoperative period of extreme vasoreactivity. However, its use should be limited to support those patients in which the underlying pulmonary vascular disease is deemed reversible.

Treat the Underlying Etiology

Whenever possible, treatment of the underlying disorder must coincide with symptomatic treatment for pulmonary hypertension if attenuation and/ reversal of the disease are to be successful. For example, in neonates, this may involve correction of underlying metabolic disturbances, antibiotics for infectious etiologies, and exchange transfusions for polycythemia. For patients with congenital heart disease, repair of the underlying defect, after determining that the pulmonary vascular disease is reversible (see later), is mandatory. For hypoxia-induced disease, tonsillectomy and adenoidectomy may be required for sleep apnea, and a descent to sea level may be needed for high-altitude–related disease. Finally, for rheumatologic disease, immunosuppression may be required.

Chronically Promote, if Possible, the Regression of Pulmonary Vascular Remodeling

The mainstay of chronic therapy has been aimed at decreasing pulmonary vascular resistance, thereby assisting right ventricular function and perhaps attenuating the progression of vascular remodeling by decreasing the pressure to which the vasculature is exposed. The continuous infusion of prostacyclin (epoprostin) has been the most successful therapy to date in this regard [181–185]. In fact, several studies in humans with advanced pulmonary vascular disease demonstrate improved 5-year survival and improved exercise tolerance. Interestingly, even those patients without an initial vasodilating response to the infusion show significant long-term benefit, suggesting that effects beyond vasodilation, such as antiplatelet effects, cAMP-mediated inhibition of smooth muscle cell growth, or other unknown mechanisms may be responsible for the treatment effect [186]. Despite the impressive results, several factors limit its utilization, including the need for chronic intravascular assess with the associated infectious and thrombotic risks, and many other untoward effects, including headache, flushing, and acute cardiopulmonary compromise with disruption of the infusion [187].

With the increasing appreciation for the role of ET-1 in the pathophysiology of pulmonary vascular disease, ET receptor antagonists have been developed as a potential treatment modality. To date, bosentan, a combined ET_A and ET_B receptor antagonist, is the most widely studied agent and is the only receptor antagonist approved for the treatment of pulmonary hypertension [167,168]. Recent studies in adults with primary pulmonary hypertension demonstrate similar improvements in survival and exercise tolerance as those demonstrated with epoprostenol [188]. The use of ET receptor antagonists for pediatric pulmonary hypertensive disorders is currently under investigation.

Deficiencies in the NO–cGMP cascade in pulmonary vascular disease are well documented. In addition, the vasodilating effects, antiplatelet effects, and antiproliferative effects of augmenting this cascade are well appreciated. Therefore, new chronic therapies that augment NO–cGMP signaling, which include chronic inhaled NO delivered by nasal cannula and sildenafil, are currently under investigation [187]. In fact, the short-term benefit of sildenafil in children with advanced pulmonary hypertension has recently been reported [164].

Data indicate that several of these new oral therapies, such as bosentan and sildenafil, may offer additional benefit by virtue of their ability to inhibit vascular smooth muscle growth and fibrosis [187]. A number of other treatment strategies, including combination drug therapies, are currently under investigation. To date they have been used predominantly in advanced pulmonary vascular disease, but, due to these favorable characteristics, several potential applications warrant investigation. This includes their use in lung hypoplastic syndromes, in hypoxia-associated disease, and in congenital heart disease in order to improve the operability of patients with modest vascular changes [189].

Persistent Pulmonary Hypertension of the Newborn

In a number of clinical conditions, pulmonary vascular resistance does not decrease normally at birth. As a result, pulmonary blood flow remains reduced and pulmonary arterial pressure remains high. The pathophysiologic effects are hypoxemia, myocardial dysfunction, and a resulting reduction in systemic oxygen delivery. The hypoxemia is most often secondary to extrapulmonary right-to-left shunting of blood at the atrial and/or ductal levels but may also be secondary to intrapulmonary right-to-left shunting of blood when associated with parenchymal lung disease. The pathophysiologic mechanisms preventing the normal pulmonary vasodilatation at birth remain unclear and are most likely multifactorial in etiology.

Within this definition of PPHN, three major subgroups are often characterized: those with underdevelopment of the lung, those with maladaptation of the lung, and those with maldevelopment of the lung [58]. These subgroups represent a spectrum of etiologies and pathophysiology. For example, underdevelopment of the lung represents disorders of vascular hypoplasia, which are usually associated with varying degrees of lung hypoplasia. Within this subgroup, patients with congenital diaphragmatic hernia have been most thoroughly investigated. Although the structural abnormalities are greatest on the side of the hernia, both of the lungs of these patients are smaller and have fewer alveoli than do lungs from a normal control population [190–192]. Their lungs also have fewer vessels per unit of lung [192]. Thus, the total cross-sectional area

of the vascular bed is markedly decreased. Furthermore, the existing pulmonary arteries have increased muscle mass with medial hypertrophy in normally muscularized arteries and an abnormal extension of muscle into the intra-acinar arteries. The increased muscularization may explain the labile, right-to-left extrapulmonary shunting of blood seen in such patients [193,194]. The response to therapy and long-term outcome is dictated by the degree of hypoplasia of the underlying vasculature. Following acute therapies, which often include surgical repair, mechanical ventilation with inhaled NO, and extracorporeal support, subacute and chronic pulmonary hypertension has been increasingly recognized as a major outcome variable in these patients. Because ultimately lung and vascular growth are necessary to reverse the disease process, aggressive long-term support with agents that inhibit vascular remodeling (i.e., ET receptor antagonists and PDE inhibitors) is an emerging treatment approach to support these infants as they grow.

Maladaptation of the lung represents a stress event at the time of delivery that does not allow the normal dilating stimuli, such as increases in systemic arterial pH and oxygen tension, to occur. This may occur in the setting of apnea, pneumonia, sepsis, and aspiration of meconium or amniotic fluid [195–197]. The underlying pulmonary vasculature is often normal, and, thus, these neonates are likely to respond to vasodilator therapy and the correction of contributory metabolic abnormalities.

Maldevelopment of the lung represents a group of conditions in which the vasculature is thickened and abnormally distributed. For example, some newborns who die from persistent pulmonary hypertension have abnormally muscular pulmonary vascular beds, even when they die on the first day of life. In particular, they have thickened muscular coats in the normally muscular preacinar arteries, and extension of muscle into the normally nonmuscular intra-acinar arteries [56,57]. Because vascular remodeling takes time to develop, it has been hypothesized that this increased muscularization is caused by a chronic intrauterine stress. In animal models, this pathophysiology can be mimicked by chronic placental insufficiency, fetal hypoxemia, chronic constriction of the ductus arteriosus, and chronic NO inhibition [40,55,198–203]. Interestingly, PPHN has been associated with maternal indomethacin use, which causes constriction of the ductus arteriosus [204,205]. The response to therapy in neonates with maldevelopment of the lung is variable and may be related to the extent and type of underlying structural vascular pathology.

The primary therapeutic approach is to decrease pulmonary vascular resistance and support myocardial function. The specific treatment modality depends on the underlying etiology. If the cause is perinatal asphyxia, correcting alveolar hypoxia, hypercarbia, and metabolic acidosis by ventilation with 100% oxygen, and by administration of buffer, should decrease pulmonary vascular tone toward normal levels. If parenchymal disease (i.e., respiratory distress syndrome, meconium aspiration, or pneumonia) is causing pulmonary vasospasm due to alveolar hypoxia and hypercarbia, then inflation of the alveoli with positive end-expiratory pressure, surfactant administration, and mechanical ventilation may reverse the pulmonary hypertension [206–208]. The near-term child can exert substantial intrathoracic pressure opposing mechanical ventilation; thus, sedation and occasionally muscle paralysis may be necessary to obtain stable mechanical ventilation [209].

When treatment of the underlying pulmonary parenchymal, infectious, or inflammatory disease is ineffective, or if there is no such underlying disease, therapy is directed at reversing abnormal pulmonary vasoconstriction. This is generally accomplished with sedation, mechanical ventilation with 100% oxygen, and alkalinization. When further pulmonary vasodilation is needed, inhaled NO is utilized with or without high-frequency ventilation. In fact, several multicentered, randomized trials have demonstrated that inhaled NO improves oxygenation and decreases the need for extracorporeal life support in newborns with persistent pulmonary hypertension [117,121,126), although no differences in mortality were noted. The use of extracorporeal membrane oxygenation has substantially decreased overall mortality for most subsets of PPHN. However, overall mortality rates remain substantial at 5%–15% [210–213].

Pulmonary Hypertension Associated with Congenital Heart Disease

The development of pulmonary hypertension and increased pulmonary vascular reactivity is associated with two major types of congenital heart disease: (1) those with increased pulmonary blood flow and pulmonary arterial pressure and (2) those with increased pulmonary venous pressure [110–112,169]. After birth, large communications at the level of the ventricles or great vessels result in increased pulmonary blood flow and pulmonary arterial pressure, which produces progressive structural and functional abnormalities of the pulmonary vasculature [59,106–110,214–217]. Similarly, elevated pulmonary venous pressure results in progressive increases in pulmonary venous and arterial pressure, which produces structural abnormalities of the pulmonary vasculature. Heath and Edwards first described the progression of these pulmonary vascular changes in 1958 [217]. In their classification, changes progress from medial hypertrophy (grade I) to intimal hyperplasia (grade II), lumen occlusion (grade III), arterial dilatation (grade IV), angiomatoid formation (grade V) and fibrinoid necrosis (grade VI). In addition, morphometric analysis shows progression of disturbed arterial growth and remodeling of the pulmonary vascular bed, which correlates with the aberrant hemodynamic state of the pulmonary circulation [108,109,214–216]. These changes are characterized by (1) abnormal extension of vascular smooth muscle into small peripheral pulmonary arteries and mild medial hypertrophy of normally muscular arteries (grade A), (2) severe medial hypertrophy of normally muscular arteries (grade B), and (3) decreased pulmonary arterial number (grade C). Uncorrected, these vascular changes result in decreased cross-sectional area and obliteration of the pulmonary vascular bed and death secondary to severe cyanosis or myocardial failure.

Different congenital heart defects vary considerably in the frequency and severity of pulmonary hypertension. The risks and frequencies of developing advanced pulmonary vascular disease (PVD) for particular heart defects are summarized in Table 20.2. Importantly, children with trisomy 21 and congenital heart defects often have an accelerated development of advanced pulmonary vascular disease [218]. This may be secondary to confounding factors such as airway obstruction or another unidentified predisposition. After surgical correction, early vascular changes (grades I–III, grades A, B) are reversible; however, more severe changes are irreversible and progressive. Therefore, the pathophysiologic state of the pulmonary circulation is the main determinant of the clinical course and the success of surgical treatment, and it explains the trend toward early repair of congenital heart defects [169].

Although early surgical repair of congenital heart defects has decreased the incidence of irreversible pulmonary vascular disease,

Table 20.2. Risks and frequencies of developing advanced pulmonary vascular disease (PVD) in the presence of a heart defect.

Defect	Risk of PVD	Age
Increased pulmonary blood flow		
Truncus arteriosus	~100%	<2 years
Atrioventricular canal	~100%	~2 years
Ventricular septal defect (VSD)	~15%–20%	>2 years
Patent ductus arteriosus	~15%–20%	>2 years
Transposition of the great arteries with VSD	~70%–100%	1–2 years
Atrial septal defect	~20%	>20 years
Increased pulmonary venous pressure		
Obstructed TAPVR (total anomalous pulmonary venous return)	Variable	Variable
Cor triatriatum	Variable	Variable
Mitral stenosis	Variable	Variable

even those children with reversible vascular changes suffer morbidity and mortality in the perioperative period secondary to chronic and/or acute elevations in pulmonary vascular resistance [10–112,219]. Chronic elevations are related to the structural changes that decrease the cross-sectional area of the pulmonary vascular bed. These alterations may take several months to normalize following surgical repair. Acute elevations in pulmonary vascular resistance are often seen immediately following surgery with cardiopulmonary bypass, when there is often a period of enhanced pulmonary vascular reactivity [8,22,98]. This period may last up to 5–7 days and is most likely a manifestation of preexisting aberrant endothelial cell–smooth muscle cell interactions that are exacerbated at the time of surgery. During cardiopulmonary bypass, several factors including the disruption of pulmonary blood flow, complement activation, and neutrophil activation induce pulmonary vascular endothelial dysfunction. This results in an increase in the production and/or release of endothelial factors that promote vasoconstriction, such ET-1 and TXA_2, and a decrease in endothelial relaxing factors, most importantly NO [220]. This period of extreme reactivity may produce severe hypoxemia, acidosis, low cardiac output, and death if not treated immediately.

Classically, a preoperative determination of pulmonary vascular reactivity is made in the cardiac catheterization laboratory in order to assess the operability of a given patient, that is, the degree to which the pulmonary vascular disease is reversible, as well as the postoperative risk. This testing involves measuring pulmonary arterial pressure and calculating pulmonary vascular resistance under varying conditions. The vascular resistance following acute maximal vasodilator therapy (e.g., oxygen and NO) represents the degree of structural pulmonary vascular disease that is present. Despite the frequent utilization of such testing, there is no absolute pulmonary vascular resistance that is universally considered inoperable. In general, a larger reduction in resistance in response to vasodilator therapy correlates with an increased chance of reversibility and a lower risk of perioperative morbidity from pulmonary hypertension. Recent studies suggest that the combination of 100% oxygen and inhaled NO produces maximal pulmonary vasodilation and has some perioperative predictive value [221,222]. In fact, a 20% decrease in the ratio of the pulmonary-to-systemic vascular resistance with vasodilator therapy, and a nadir in this ratio of less than 33%, was 97% sensitive and 90% accurate in predicting a good surgical outcome. Therefore, the combination of oxygen and inhaled NO is now most commonly used for pulmonary vascular reactivity testing. Reactivity testing may also be helpful in the intensive care unit in the setting of a persistent postoperative elevation of pulmonary arterial pressure in order to differentiate between residual anatomic defects and prolonged periods of increased tone [118].

The optimal treatment for perioperative pulmonary hypertensive morbidity is prevention with early surgical repair. It is increasingly clear that the longer the pulmonary vasculature is exposed to the abnormal forces associated with increased blood flow and/or pressure, the greater the risk of perioperative pulmonary vascular reactivity. Following surgery, the goal of perioperative management is to minimize active pulmonary vasoconstriction during the period of exaggerated reactivity and support the right ventricle. To this end, avoidance of those stimuli that increase pulmonary vascular resistance (hypoxia, acidosis, pain, agitation, increased intrathoracic pressure) is critical. Continuous pulmonary arterial and right atrial pressure monitoring is often helpful by allowing prompt recognition of pulmonary hypertensive crises and evaluation of the response to therapeutic maneuvers. Monitoring systemic arterial pressure and systemic arterial oxygen saturation is essential in that it allows changes in pulmonary arterial pressure to be interpreted in the context of the total cardiopulmonary response. For example, if systemic and pulmonary arterial pressures increase in response to pain and agitation, but right atrial pressure does not increase, and systemic perfusion and oxygen saturation remain adequate, then specific treatment directed at the pulmonary vasculature is not necessary. Conversely, increases in pulmonary arterial pressure that are associated with increased right atrial pressure, decreased systemic pressure, and/or decreased systemic saturation might herald imminent collapse.

The objective of vasodilator therapy is to decrease right ventricular afterload and prevent acute increases in pulmonary arterial pressure. Inhaled NO, in combination with oxygen, has been increasingly utilized because of its potent vasodilating effects, pulmonary selectivity, and rapid onset and elimination (see earlier). Several studies demonstrate its potent vasodilating effects in this population [223–226]; however, large, randomized trails are lacking. One randomized trial did demonstrate that inhaled NO decreased postoperative pulmonary vascular resistance, the incidence of pulmonary hypertensive crises, and the days of mechanical ventilation compared with placebo [226]. In patients with a history of pulmonary venous hypertension (total anomalous pulmonary venous return, mitral valve disease), aggressive diuresis may be helpful because interstitial pulmonary edema may contribute significantly to elevations in pulmonary vascular resistance.

Therapies that maintain an adequate cardiac output in this patient population are not dissimilar to therapies utilized in other patient populations, with the exception of the particular emphasis placed on right ventricular afterload reduction and support. It is noteworthy that patients with a poorly compliant right ventricle or with increased right ventricular afterload may require elevated central venous pressures to maintain an adequate preload. In addition, the use of inotropic agents with significant α_1-adrenergic effect should be minimized to avoid the associated pulmonary vasoconstriction. Agents such as dobutamine, milrinone, and dopamine are routinely utilized.

The use of high levels of positive end-expiratory pressure (PEEP) is somewhat controversial. Mechanical hyperventilation with high PEEP increases intrathoracic pressure and pulmonary vascular resistance [85,115]. This therapy should be avoided if adequate systemic arterial saturation can be achieved by other means. However, at low lung volumes, the use of PEEP may increase lung volume

toward functional residual capacity and, thus, improve gas exchange and may lower pulmonary vascular resistance. Mechanical ventilation without PEEP (especially in patients after partial and total caval-pulmonary shunts) predisposes patients to atelectasis, worsens ventilation–perfusion matching, results in systemic arterial hypoxemia, and increases pulmonary vascular resistance [85]. Thus, low levels of PEEP (3–4 cm H_2O), which have minimal effects on pulmonary vascular resistance, should be used to prevent atelectasis in this patient population.

Primary Pulmonary Hypertension

Until very recently, pulmonary arterial hypertension of unknown etiology was termed *primary pulmonary hypertension*. However, recent evidence indicates a genetic disposition in a subset of patients with primary pulmonary hypertension, and a number of diseases that lead to pulmonary arterial hypertension with similar histological and pathophysiologic features have been uncovered [102–105]. Thus, at the 2003 Third World Symposium on Pulmonary Arterial Hypertension, a new classification was proposed to further classify primary pulmonary hypertension into the following subgroups: (1) idiopathic pulmonary arterial hypertension (IPAH), (2) familial pulmonary arterial hypertension (FPAH), and (3) pulmonary arterial hypertension related to risk factors or associated conditions (APAH) [227].

Unfortunately, mortality from primary pulmonary hypertension remains high and may be higher for children than adults. In fact, the Primary Pulmonary Hypertension National Institutes of Health Registry reports a median survival of only 10 months for pediatric patients [228]. However, recent data suggest that pediatric patients may respond differently than adults to new therapies and that these differences may portend a better outcome in younger patients [229,230]. The frequency of primary pulmonary hypertension in pediatric patients is not known, but it appears that the number of confirmed cases is increasing. The incidence is slightly increased in females [231]. The most common causes of death in children with primary pulmonary hypertension are right ventricular failure and sudden death, which may be related to malignant cardiac arrhythmias, pulmonary emboli, or acute right ventricular ischemia [228]. Physicians caring for children in an intensive care unit setting must be cognizant of this disorder, albeit rare, because relatively benign disease processes, such as pneumonia, can be life threatening for children with primary pulmonary hypertension, which may not have been previously identified.

As opposed to adults with primary pulmonary hypertension, who often have severe plexiform lesions resulting in relatively fixed vascular changes, children display greater medial hypertrophy with less intimal fibrosis and fewer plexiform lesions [187,229]. In addition, pediatric patients have a decreased pulmonary arterial number and increased pulmonary vascular reactivity compared with adult patients. The molecular mechanisms underlying primary pulmonary hypertension remain speculative; however, studies suggest an integral role for endothelial dysfunction, resulting in an increase in factors that favor both vasoconstriction and mitogenesis, such as ET-1 and TXA_2, and a decrease in factors that promote vasodilation and smooth muscle antiproliferation, such as NO and prostacyclin [23,101,187,232–235]. Other mechanisms have been investigated including, altered gene expression, coagulation abnormalities (resulting in intravascular thrombosis), and defects of pulmonary vascular smooth muscle cell potassium channels [236–238].

Recent advances in the understanding of pulmonary hypertension have established an association with a number of disease processes and toxins. Thus, it is now known that pulmonary hypertension can be related to collagen vascular disease, portal hypertension, human immunodeficiency virus infection, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitudes, thromboembolic disease, sickle cell disease, *Schistosomiasis*, sarcoidosis, thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, myeloproliferative disorders, and pulmonary capillary hemangiomatosis. In addition, drugs or toxins, most notably anorexigens, have been associated with the development of pulmonary hypertension [187,227]. In general the diagnostic work-up includes history and physical examination, electrocardiography, chest radiography, echocardiography, and cardiac catheterization. Serologic evaluation in order to exclude secondary causes is required, and V/Q scanning to evaluate for pulmonary emboli may be necessary.

Treatment strategies for pediatric pulmonary arterial hypertension are evolving. When the disease is associated with a known disorder, treatment must include specific therapy aimed at the underlying condition. However, general treatments include the approach reviewed above, with oxygen, calcium channel blockers, anticoagulation, ET receptor antagonists, prostacyclin analogues, acute and chronic inhaled NO, PDE type 5 inhibitors, atrial septostomy, and lung or heart–lung transplant considerations as indicated [187].

Patients with pulmonary arterial hypertension have histologic evidence of in situ pulmonary vascular thrombosis, which is the rationale for anticoagulation therapy. Although several adult studies have demonstrated its efficacy, pediatric studies are lacking [239,240]. Currently, warfarin is the treatment of choice for adult patients and in large pediatric centers with significant experience with pediatric pulmonary arterial hypertension. Low-molecular-weight heparin is another alternative [241]; aspirin does not have any demonstrated efficacy.

Chronic calcium channel blockade is efficacious for a subset of adults and children with pulmonary arterial hypertension. In fact, whereas less than 25% of adults respond to calcium channel blockers, up to 40% of children are positive responders [186,242]. It is worth noting that calcium channel blockers are not utilized in the management of other common causes of pediatric pulmonary hypertension, such as PPHN and congenital heart disease. Indeed, calcium channel blockade should be avoided in neonates and after congenital heart surgery. However, studies indicate that long-acting calcium channel blockers, such as nifedipine and amlodipine, are well tolerated in children with primary pulmonary hypertension. An important caveat is that a positive response to calcium channel blockers (i.e., an acute reduction in pulmonary arterial pressure) must be demonstrated as a part of acute vasodilator reactivity testing. Children without a positive acute response do not benefit from chronic treatment.

Prostaglandins are a mainstay of therapy for patients with pulmonary arterial hypertension. In general, prostacyclin (epoprostenol) is administered as a continuous infusion, necessitating a permanent indwelling central catheter, with its associated risks [181–185]. However, various other formulations including oral, inhaled, and subcutaneous prostacyclin analogues have been developed and are in various stages of clinical investigation [243–246].

Supplemental oxygen, cardiac glycosides, antiarrhythmic therapy, and inotropic agents are also variably utilized in certain patients [187,247]. Diuretic therapy is also often beneficial, keeping in mind that these patients may require elevated right ventricular preload. Based on an expanding understanding of the disease process, future therapies might include elastase inhibitors and gene therapy [248,249]. As noted previously, atrial septostomy may have a role in the management of a select group of patients [250]. However, atrial septostomy in the setting of an acute exacerbation of chronic pulmonary hypertension may lead to unacceptable hypoxemia because of excess right-to-left atrial shunting. Finally, heart–lung, single-lung, or bilateral lung transplantation has been successful in pediatric patients with terminal pulmonary hypertension [251,252]. The International Society for Heart and Lung Transplantation reports survival of approximately 50% at 5 years in pediatric patients [253]. Consensus is lacking as to the best type of transplant.

Other

Hypoxia

Increases in pulmonary arterial pressure in response to hypoxia are well described. Clinical and experimental evidence suggests that prolonged exposure or chronic intermittent exposure to hypoxia can result in functional and structural derangements of the pulmonary vasculature, leading to pulmonary hypertension [254–256]. Fortunately, elevations in pulmonary arterial pressure that occur in response to acute hypoxia (such as an acute ascent in altitude) are rapidly reversible. Interestingly, there is great clinical variability in the response to hypoxia. For example, increased susceptibility to high-altitude pulmonary edema, which is associated with increased pulmonary arterial pressure, has been linked to certain major histocompatibility complexes [257,258]. The mechanisms of hypoxia-induced pulmonary hypertension continue to be an area of intense investigation. To date the precise mechanisms remain unclear, but it is known that a number of endothelial derived factors, such as NO, ET-1, leukotrienes, and potassium channels, participate [10,259–262]. Furthermore, additional genetic polymorphisms are also under investigation. Pediatricians must consider this physiology in patients with conditions such as upper airway obstruction, central hypoventilation, and neuromuscular disorders that affect ventilation. In fact, many of these patients do develop evidence of pulmonary hypertension, with right ventricular enlargement. In most cases, addressing the underlying pathology is curative, but it can take some time to fully reverse the structural changes that have occurred.

Acute Lung Injury

The pathophysiology of acute lung injury involves damage to both the alveolar epithelium and pulmonary vascular endothelium. Vascular endothelial injury accounts for key features of acute lung injury, including intravascular thrombosis and capillary permeability that increases alveolar fluid [263]. In fact, pulmonary vascular injury, in the setting of acute lung injury, can lead to pulmonary arterial hypertension, resulting in increased intrapulmonary shunting, hypoxia, pulmonary edema, and right ventricular dysfunction [264–267]. In children with acute lung injury, persistently elevated pulmonary arterial pressures have been associated with worse outcomes [268]; therefore, vasodilators have been utilized in the management of these patients. However, intravenous vasodilators that dilate both the systemic and pulmonary vasculature have significant problems, including systemic hypotension, right ventricular ischemia, increased intrapulmonary shunting (i.e., increased V/Q mismatch), and increased hypoxemia [141–145]. Consequently, selective pulmonary vasodilation with inhaled NO has been utilized, as it improves V/Q matching and oxygenation without untoward systemic effects [269,270]. Unfortunately, improvements in oxygenation associated with inhaled NO are transient, and large randomized trials have failed to demonstrate an improvement in mortality with its use [120,271,272]. The routine use of inhaled NO in patients with acute lung injury, therefore, cannot be justified; however, it may be indicated in individual patients, particularly those with an acute hemodynamic compromise and refractory hypoxemia caused by elevated pulmonary arterial pressures. Clearly, physicians caring for pediatric patients with acute lung injury must include an awareness of the pulmonary vascular aberrations associated with the disease in their management considerations.

Conclusion

Historically, diseases of the pulmonary vasculature, although not uncommon, have been underrecognized. This was caused, in part, by the paucity of effective treatments as well as an incomplete understanding of the vascular biologic mechanisms. In fact, over the past decade, the therapeutic gold standard has been the continuous infusion of prostacyclin. Although certainly extending and improving the lives of many patients, intravenous prostacyclin administration has been predominantly limited to patients with irreversible disease, given the inconvenience and morbidity associated with its delivery. Fortunately, an expanded understanding of the vascular endothelium, vascular smooth muscle cells, and the role of their interactions in the pathophysiology of pulmonary vascular disease have resulted in new effective treatments, with additional potential therapies evolving rapidly. Oral agents such as bosentan and sildenafil are two examples with great promise. In addition, accumulated experience and focused research have uncovered a multitude of disease processes that contribute directly or indirectly to the development of pulmonary hypertension. Physicians caring for critically ill children must be aware of these illnesses, the pathophysiology of pulmonary hypertension, and the available treatment options in order to translate these advances into improved outcomes for patients.

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