Pulmonary Hypertension

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Peter Oishi, Sanjeev A. Datar, and Jeffrey R. Fineman

Abstract

Neonates, infants, and children may present to critical care settings primarily due to pulmonary hypertension, or pulmonary hypertension may complicate the course of another illness. In advanced pulmonary hypertension, progressive pulmonary vascular functional and structural changes ultimately cause increased pulmonary vascular impedance, increased right ventricular afterload, right ventricular failure, and death. In addition, in the setting of certain critical illnesses severe pulmonary hypertension can develop rapidly (i.e. pulmonary hypertensive crisis) or pulmonary vascular dysfunction can complicate the course, even in the absence of preexisting frank pulmonary hypertension. Management includes: the prevention and/or treatment of active pulmonary vasoconstriction, the support of right ventricular function, and treatment of the underlying disease, if possible. Most available therapies that target the pulmonary vasculature promote vascular relaxation by augmenting or inhibiting factors, or mediators of their downstream signaling cascades, that originate in the pulmonary vascular endothelium. These pathways include: nitric-oxide-cGMP, prostacyclin, and endothelin-1. This chapter will provide a brief overview of the disease processes associated with pulmonary hypertension, review the key pathophysiologic principles, and describe a general therapeutic approach, with an emphasis on the critical care setting.

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) of greater than or equal to 25 mmHg. This simple definition belies the complexity and variety of pathophysiologic situations that can cause PH in critically ill pediatric patients. Moreover, pulmonary vascular dysfunction can complicate the course of patients before the definition of PH is satisfied. This chapter will provide a brief overview of the disease processes associated with PH, review the key pathophysiologic principles, and describe a general therapeutic approach, with an emphasis on the critical care setting.

P. Oishi, MD • S.A. Datar, MD, PhD • J.R. Fineman, MD (✉)
Department of Pediatrics, University of California San Francisco, Benioff Children's Hospital,
513 Parnassus Avenue, San Francisco, CA 94143, USA
e-mail: peter.oishi@ucsf.edu; sanjeev.datar@ucsf.edu; jeff.fineman@ucsf.edu

Clinical Classification and Etiology

Over the past 40 years, clinical classification schemes have evolved in order to keep pace with the expanding number of disease processes identified to be associated with PH. The initial classification endorsed by the World Health Organization in 1973 divided PH into only two categories – primary and secondary PH. The most recent classification, which followed the 5th World Symposium on PH in 2013, divided PH into 5 groups, with 28 subgroups (Table 15.1) [1].

The prevalence of PH in pediatric patients is not known precisely. A French registry estimated the prevalence of PH to be 3.7 cases/million [2]. In that cohort, the majority (60 %) had idiopathic PH, 24 % had PH associated with congenital heart disease, and 10 % had familial PH [2]. An earlier report from the UK Pulmonary Hypertension Service for Children from 2001 to 2006 described 216 children with PH [3]. In that cohort, 28 % of the patients had idiopathic PH, 31 % had Eisenmenger physiology, 30 % had postoperative PH, 19 %

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Table 15.1 Clinical classification of pulmonary hypertension[1]

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension associated with lung disease and/or hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Other: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

[1]Adapted from Simonneau et al. [1]. With permission Elsevier

had PH associated with lung disease, 9 % had PH associated with miscellaneous disorders including HIV, bone marrow transplant and metabolic disease, 6 % had connective tissue disease, and 5 % had PH associated with complex unoperated or palliated congenital heart disease [3].

In the neonatal population, persistent pulmonary hypertension of the newborn (PPHN) warrants particular attention. The incidence of PPHN has been estimated to be approximately 2 per 1,000 live births [4]. PPHN may occur as a primary disorder of the fetal pulmonary circulation, or may be secondary to pathologic processes that cause a maladaptive transition from the fetal to neonatal circulation, such as sepsis, meconium aspiration or surfactant deficiency, or diseases that result in abnormalities of lung development, such as congenital diaphragmatic hernia [5]. Furthermore, PH is also associated with chronic lung disorders, including bronchopulmonary dysplasia [6–9].

It is important to recognize that patients may have significant pulmonary vascular disease without resting PAPs that meet the definition of PH [10]. For example, patients with congenital cardiac defects resulting in either increased pulmonary blood flow or impaired pulmonary venous drainage are prone to episodes of acute reactive pulmonary vasoconstriction, even when baseline PAPs are normal, that can result in catastrophic cardiopulmonary collapse, particularly in the postoperative period after exposure to cardiopulmonary bypass [11, 12]. In addition, certain disease processes can create pulmonary vascular disease in patients without preexisting abnormalities. For example, acute lung injury (ALI) is associated with pulmonary vascular endothelial injury, that can lead to vascular obstruction from intravascular thrombi, segmental atelectasis, and/or increased hypoxic pulmonary vasoconstriction [13, 14]. In some patients this can progress to PH and right ventricular failure [13–16]. In a

cohort of 23 children with ALI, Katz and colleagues found that PAP, pulmonary vascular resistance (PVR), and intrapulmonary shunt fractions were higher in non-survivors than in survivors [17]. More recently, Bull and colleagues evaluated the transpulmonary gradient (PAP – pulmonary capillary wedge pressure) and the PVR index in 475 and 470 (respectively) adult patients with ALI, and found that pulmonary vascular dysfunction was common and independently associated with poor outcome [18].

Diagnosis

Invasive and noninvasive techniques are used in order to diagnose, classify, and manage PH. Indwelling pulmonary artery catheters provide the most direct information, allowing for measurements of vascular pressures and cardiac output, and calculations of PVR. However, these catheters are used infrequently in critically ill pediatric patients, owing to size limitations and a lack of evidence that justifies their routine use.

Standard noninvasive studies include ECG and transthoracic echocardiography. The chief finding of interest on an ECG is evidence of right ventricular hypertrophy, although studies of patients with known PH have demonstrated that ECG alone lacks adequate sensitivity and specificity [19, 20].

The important data that may be obtained by echocardiography are: an estimate of systolic pulmonary arterial pressure (sPAP), right and left ventricular function, and cardiac anatomy, including determinations of chamber sizes, valvular function, and intracardiac shunts. In general, the sPAP is considered equivalent to the right ventricular systolic pressure (RVSP), unless there is right ventricular outflow tract obstruction or pulmonary valve stenosis. With the use of Doppler echocardiography, RVSP is estimated by determining the velocity of flow across the tricuspid valve during systole (tricuspid regurgitation jet, TR jet). A modification of the Bernoulli equation is used to estimate the RVSP, as follows: $\text{RVSP} = 4v^2 + \text{RAP}$, where v is the velocity of the TR jet in meters per second, and RAP is the right atrial pressure that is ether standardized or estimated by echocardiography. Multiple studies have validated estimates of sPAP determined by echocardiography using right-heart catheterization as confirmation [21–29]. In the absence of a measurable TR jet, parameters related to right ventricular outflow patterns and time intervals could be assessed by Doppler echocardiography with demonstrated accuracy compared to right-heart catheterization [30–33]. Recently, Arkles and colleagues found that the shape of the right ventricular Doppler envelope predicted hemodynamics and right heart function in adult PH patients [34]. The same group in an earlier study demonstrated that another echocardiographic estimate of right heart function, the tricuspid annular plane systolic excursion (TAPSE), was reflective of RV function when compared to right heart catheterization, and predicted survival in a cohort of 63 adult PH patients [35].

Cardiac catheterization remains the "gold standard" for the diagnosis of pulmonary hypertension. In addition to measuring PAP and PVR, cardiac catheterization can assess for intracardiac and extracardiac shunts, evaluate the pulmonary vascular anatomy (such as assessments of pulmonary venous abnormalities), and measure intracardiac pressures and cardiac output. Furthermore, pulmonary vascular reactivity testing is essential in selecting appropriate therapy. Indeed, children who are responsive to acute vasodilator testing (evoked by short acting agents such as inhaled nitric oxide (iNO) or iloprost, and intravenous epoprostenol or adenosine) which is defined as a ≥20 % decrease in PAP without a decrease in cardiac output, have been shown to have improved survival [36]. In addition, responsiveness to acute vasodilator testing predicts a favorable response to long-term therapies, such as calcium channel blockers [37, 38]. Conversely, calcium channel blockers may be deleterious for patients not responsive to vasodilator therapy, which exemplifies the value of this information [39, 40]. However, the timing of cardiac catheterization is often less clear. Indeed, catheterization may not be safe in critically ill patients suffering from severe acute PH.

Other diagnostic modalities include V/Q scan, CT scan, and MRI. Thromboembolic disease may present with pulmonary hypertension, and can be evaluated by V/Q scan. Several studies found that V/Q scanning was highly sensitive and specific in differentiating between idiopathic pulmonary hypertension and thromboembolic disease [41–43]. Contrast enhanced CT scan and/or MRI can help identify causes of pulmonary hypertension. Thromboembolic disease may be visualized by both modalities [44]. In addition, both imaging techniques can help identify other pulmonary pathology, such as interstitial disease, masses or vasculitis [45]. Findings on CT scan, such as pulmonary artery size, may contribute to the diagnosis of pulmonary hypertension, but do not replace Doppler echocardiography [46–49]. MRI can better delineate the cardiac anatomy, particularly chamber sizes and wall thickness, and MRI measurements can detect PH [50–52]. However, like CT, it is not clear that MRI offers significant advantages for diagnosis compared to Doppler echocardiography.

Pathophysiology

The pathophysiology of PH is multifactorial, complex, and incompletely understood. Various etiologies are associated with different particular mechanisms of disease, and a unifying construct has not been identified. However, several pathways common to a number of etiologies have been elucidated.

Hemodynamics and Morphology

From a hemodynamic standpoint, the morbidity and mortality associated with PH relates to increased right ventricular afterload. Over some period of time, compensatory mechanisms fail leading to right heart failure and death. It is important to note that the tempo of this clinical sequence varies across etiologies and individual patients. For example, right ventricular failure can develop rapidly in an infant following cardiac surgery (i.e. postoperative pulmonary hypertensive crisis) or may progress over years in other patients (e.g. Eisenmenger's).

Although right ventricular failure is a common potential endpoint for patients with PH, the location of the disease within the pulmonary vasculature depends upon the particular etiology. This is important when considering available therapies, since therapies appropriate for one group of patients may be deleterious for another. For example, iNO may be effective for patients suffering from acute pulmonary arteriolar constriction (e.g. pulmonary arterial hypertension (PAH); or PH owing to lung diseases and/or hypoxia), but may be entirely ineffective or even harmful in patients with pulmonary veno-occlusive disease or left heart failure [53–55].

Among the various PH groups, the mechanisms that result in increased right ventricular afterload are best understood in PAH. However, left heart disease is a common cause of PH, at least in adults [56]. In these patients, elevations in PAP relate to the transmission of elevated left atrial pressures. PVR may be normal. Although subsets of patients with left heart disease develop PAH, the associated mechanisms are less well understood and specific therapies for these patients have not been adequately studied [57–60]. Likewise, the pulmonary vascular changes associated with pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and congenital cardiac defects associated with pulmonary venous obstruction are less well studied, but the initial elevations in PAP relate to the backward transmission of pressure across the pulmonary vasculature, a situation that is not likely to benefit from pharmacologic pulmonary arteriolar dilation [61–63].

In PAH, increased right ventricular afterload relates to increased PVR and decreased compliance [64, 65]. Traditionally, hemodynamic assessments focused on measuring PAP and calculating PVR in PH patients, but more recent data have demonstrated value in measuring pulmonary vascular impedance, which combines resistance and compliance [66–68]. Increased PVR and decreased compliance in PAH relates to several basic mechanisms: increased pulmonary vascular reactivity, sustained pulmonary vasoconstriction, vascular remodeling, and luminal obstruction, due to *in situ* thrombosis and/or obstructive neointimal and plexiform lesions. In 1958, Heath and Edwards first described the histopathology of pulmonary vascular changes associated with congenital cardiac defects, and devised a six grade classification [69]. 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). Rabinovitch and colleagues followed with a morphometric classification system, based on lung biopsies taken from patients (aged 2 days to 30 years, with a median age of 1 year) with congenital cardiac defects [70]. This morphometric analysis showed progression of disturbed arterial growth and remodeling of the pulmonary vascular bed that correlated with the aberrant hemodynamic state of the pulmonary circulation. These changes were characterized by: (i) abnormal extension of vascular smooth muscle into small peripheral pulmonary arteries and mild medial hypertrophy of normally muscular arteries (Grade A), (ii) severe medial hypertrophy of normally muscular arteries (Grade B) and (ii) decreased pulmonary arterial number (Grade C) (Fig. 15.1). These vascular changes tend to progress in a stepwise fashion, and in severe disease obliterate portions of the pulmonary circulation at the level of the distal precapillary resistance arterioles. It is recognized that this sequence represents a pathologic framework, but that significant heterogeneity exists in terms of the precise pathology of PAH [71]. Furthermore, the degree to which these changes are reversible remains unclear, but likely depends in part upon the etiology, and may be influenced by age [72]. For example, in a seminal study, Rabinovitch and colleagues demonstrated that age at surgery, lung morphometric analysis, and the Heath-Edwards system grade predicted the reversibility of structural and functional pulmonary vascular changes secondary to congenital cardiac defects with increased pulmonary blood flow after surgical repair [73]. In addition, it must be remembered that even early reversible pulmonary vascular disease can contribute to morbidity and mortality. An important study by Celermajer and colleagues, for example, demonstrated that children with increased pulmonary blood flow due to intracardiac shunting had a selective impairment of endothelium-dependent pulmonary vascular relaxation, before their baseline PAP or PVR increased significantly [10].

In addition, extravascular forces also influence PAP and pulmonary vascular impedance. The relationship between intravascular pressures and alveolar pressures are well described [74, 75]. Pulmonary vessels are termed extra-alveolar, corner, or intra-alveolar. Extra-alveolar and corner vessels increase their size with lung expansion, due to radial traction placed on their walls by the lung parenchyma. Intra-alveolar vessels, however, are directly associated with alveoli and thus are subject to compression with alveolar expansion. This results in the classic U-shaped curve describing the relationship between PVR and lung inflation, wherein PVR is lowest at functional residual capacity, but increased with under- and over-inflation of the lung (Fig. 15.2). West further

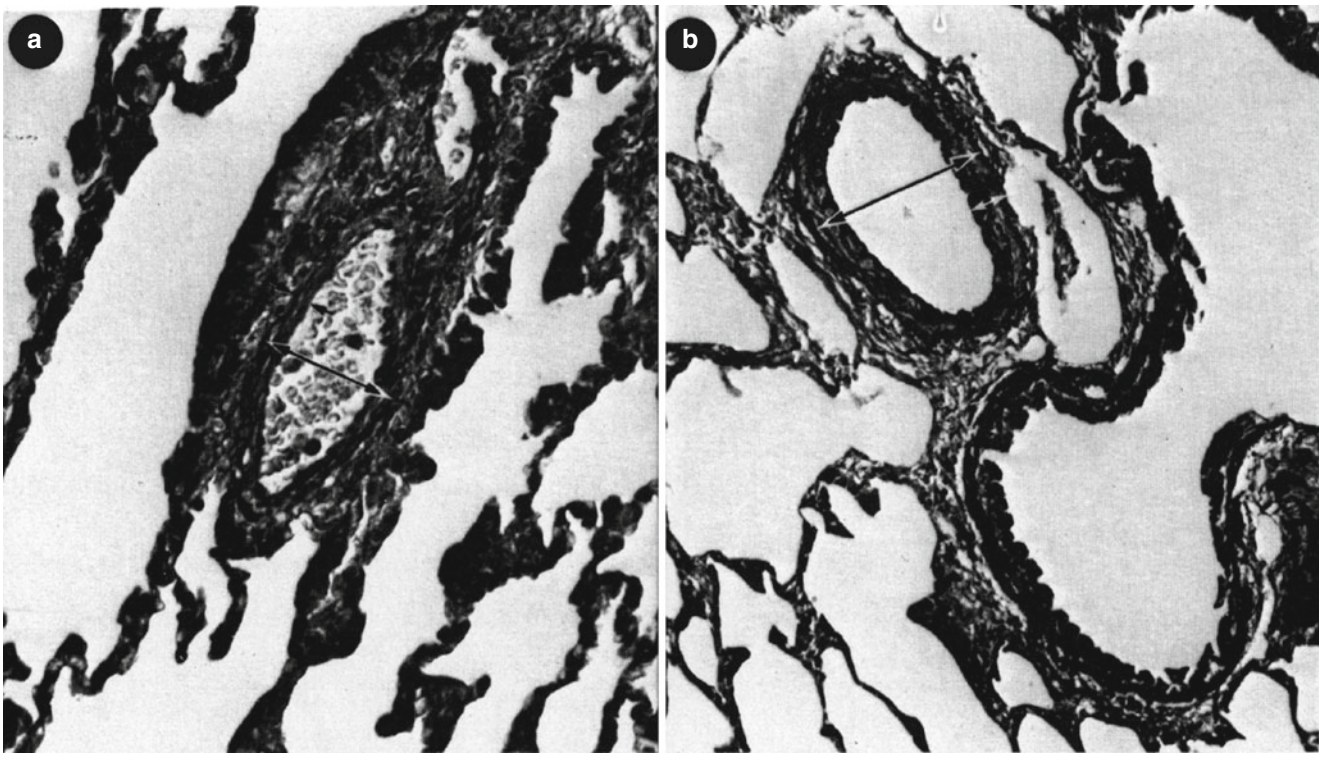

Fig. 15.1 Examples of morphometric analysis done on lung biopsies taken from a patient with a small ventricular septal defect (**a**) and a patient with an atrioventricular septal defect and pulmonary hypertension (**b**). A cross section from arteries at the same level are shown (Elastic Van Geison stain, magnification × 100). The wall thickness is increased in the patient with pulmonary hypertension (**b**). *Arrows* indicate wall thickness and external diameter (Reprinted from Rabinovitch et al. [70]. With permission from Wolter Kluwers Health.)

characterized this relationship by dividing the lung into three theoretical zones, which move down the lung from the apex to the base, in an upright subject. These zones are based on the relationship between pulmonary artery pressure (PAP), or inflow pressure, alveolar pressure (P_{av}), and pulmonary venous pressure (P_{ven}), or outflow pressure. In theory, no blood flows to zone I because P_{av} exceeds PAP, or $P_{av} > PAP > P_{ven}$. In this zone, intra-alveolar vessels are collapsed. Clinically, zone I conditions are negligible in a healthy lung, as pulmonary blood flow does occur at the apex. The fact that extra-alveolar and corner vessels are patent in this zone may help maintain blood flow. In Zone II, PAP exceeds P_{av} and blood flow occurs independent of outflow pressures, or $PAP > P_{av} > P_{ven}$. In this zone, blood flow increases down the lung, since PAP, but not P_{av}, is influenced by gravity. In Zone III, blood flow is dictated by the normal relationship of PAP to P_{ven}, or inflow pressure minus outflow pressure. In this zone, blood flow does not change dramatically down the lung as it does in zone II because gravity affects PAP and P_{ven} equally, or $PAP > P_{ven} > P_{av}$. Subsequently, an additional zone, zone IV, has been described where pulmonary blood flow decreases at the extreme base of the lung. This is due to the impact of the weight of the lung on the extra-alveolar and corner vessels, which causes compression thereby increasing resistance to flow; furthermore, the decrease in ventilation that occurs at the base results in areas of relative hypoxia with resultant hypoxic pulmonary vasoconstriction.

Under normal conditions, pulmonary blood flow is largely determined by zone III conditions. It is important to stress that these zones are conceptual and that in disease states a number of factors in addition to gravity influence V/Q matching; in addition, critically ill patients are rarely upright, but rather are supine or prone [76]. Particularly pertinent to pediatric critical care are the effects of positive pressure ventilation with high levels of peak end expiratory pressure. Increased alveolar pressure, may expand zone II and allow zone I conditions to be realized, resulting in mismatching of ventilation and perfusion and intrapulmonary shunting with hypoxia and hypercapnia. Likewise, pathology such as pneumothorax, hemothorax, pleural effusion, pneumonia and pulmonary edema, along with other conditions, can increase zone IV conditions within the lung. Finally, hypotension from multiple etiologies, such as hemorrhage, can expand zone I and zone II conditions.

Pulmonary Vascular Endothelium

It is now accepted that increased pulmonary vasoconstriction and impaired relaxation in PH is mediated in large part by

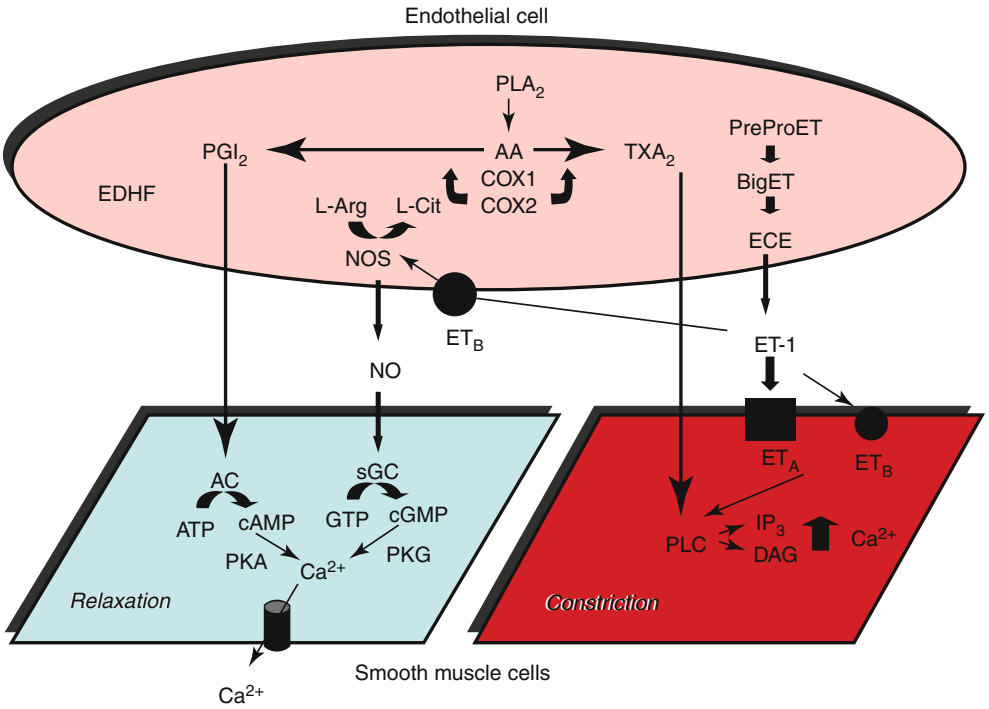

Fig. 15.2 A schematic of some endothelial derived factors. These factors may cause decreased (relaxation) and/or increased (constriction) smooth muscle cell contraction. *PLA2* phospholipase A2, *PGI2* prostaglandin I2, *AA* arachidonic acid, *TXA2* thromboxane A2, *ECE* endothelin converting enzyme, *L-Arg* L-arginine, *L-Cit* L-citrulline, *NOS* nitric oxide synthase, *ET-1* endothelin-1, *ETA* endothelin A receptor, *ETB* 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, *PDE* phosphodiesterase (type 5 shown), *PLC* phospholipase C, *IP3* inositol 1,4,5-trisphosphate, *DAG* diacylglycerol, *Ca2+* calcium

aberrant endothelial function, wherein endogenous vasodilators, such as nitric oxide (NO) and prostacyclin (PGI_2), are decreased while endogenous vasoconstrictors, such as endothelin (ET-1) and serotonin (5-HT), are increased (Fig. 15.2) [77–82]. Indeed, the majority of approved therapies for PH target these endothelial-derived factors or their signaling pathways in some way (Fig. 15.3).

NO is produced in the vascular endothelium by the enzyme endothelial NO synthase (eNOS), from the precursor L-arginine. Once formed, NO diffuses into the adjacent smooth muscle cell and activates soluble guanylate cyclase (sGC), producing cGMP. cGMP results in smooth muscle cell relaxation through protein kinase G (PKG). cGMP is broken down by a family of phosphodiesterases (PDE), with PDE5 being prominent in the pulmonary vasculature (Fig. 15.2).

Arachidonic acid metabolism within vascular endothelial cells, results in the production of PGI_2 and thromboxane (TXA_2). PGI_2 activates adenylate cyclase, resulting in increased cAMP production, activation of protein kinase A, and subsequent vasodilation, whereas TXA_2 results in vasoconstriction via phospholipase C signaling (Fig. 15.2). PGI_2 also binds to platelet receptors, which inhibits their activation.

ET-1 is a 21 amino acid polypeptide also produced by vascular endothelial cells [83]. The vasoactive properties of ET-1 are complex [84–88]. However, its most striking property is its sustained hypertensive action. The hemodynamic effects of ET-1 are mediated by at least two distinct receptor populations, ET_A and ET_B [89, 90]. The ET_A receptors are located on vascular smooth muscle cells, and mediate vasoconstriction, whereas the ET_B receptors are located on endothelial and smooth muscle cells, and thus may mediate both vasodilation and vasoconstriction, respectively (Fig. 15.2). In addition, ET_B receptors are involved in the clearance of ET-1.

An important area of active research is focused on understanding the mechanisms responsible for endothelial injury or dysfunction in PH. Some important mechanisms include: alterations in mechanical forces (such as increased pulmonary blood flow associated with congenital cardiac defects, or altered flow velocities that are associated with areas of luminal narrowing) that result in increased vascular wall shear stress, hypoxia, oxidative stress, and inflammation [91–99]. Additional factors that contribute to endothelial injury in some patients include, infection, such as HIV and Schistosomiasis, as well as injury from drugs or toxins [100–102].

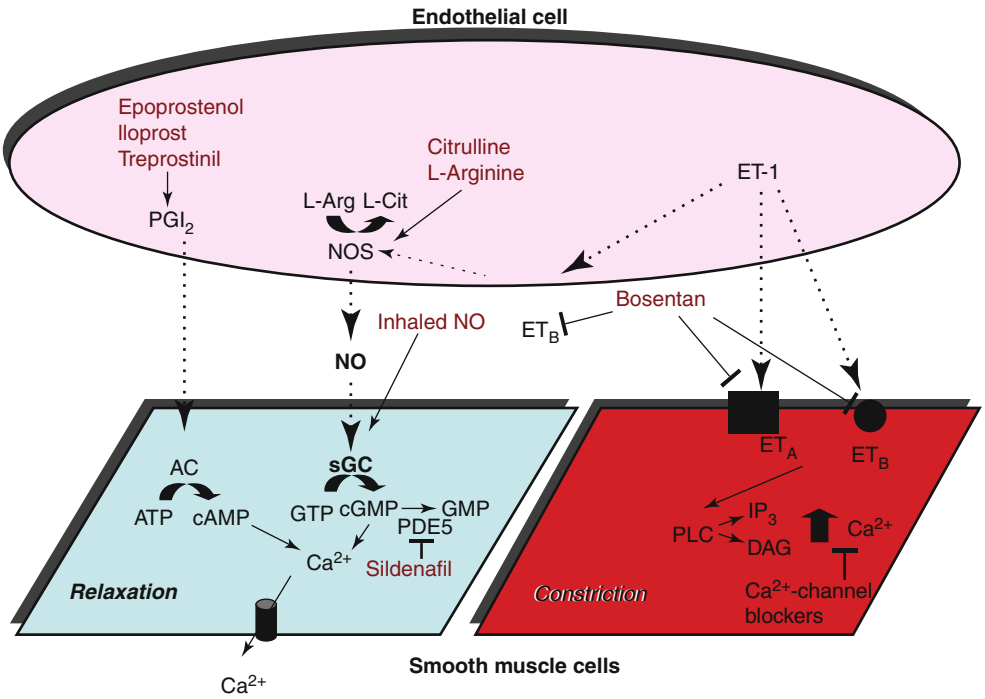

Fig. 15.3 A schematic of the sites of action of some endothelial and smooth muscle cell based therapies. *Arrows* indicate activation and (*T*) indicate inhibition

Moreover, it is known that endothelial derived factors, such as NO, PGI_2, and ET-1, are integral to processes beyond the regulation of vascular smooth muscle cell tone. Nitric oxide and PGI_2 are key regulators of vascular homeostasis, having antithrombotic and antiproliferative properties, in addition to their effects on vascular tone. Conversely, the mitogenic properties of ET-1 are well described. Indeed, endothelial injury or dysfunction likely contributes to alterations in inflammatory cascades, growth factors, and transcriptional factors that are increasingly recognized as key mediators of the vascular remodeling associated with PH [99].

Pulmonary Vascular Smooth Muscle

Considerable efforts have been made to understand the processes responsible for smooth muscle cell hypertrophy and proliferation that accompany PH. It is clear that a complex interplay exists between endothelial and smooth muscle cells. Some known mechanisms include: increased pericyte differentiation, smooth muscle cell migration, endothelial cell transdifferentiation, smooth muscle cell proliferation, smooth muscle cell hypertrophy, and inflammation [103, 104]. The extracellular matrix and matrix metalloproteinases (MMPs) are known to participate in these processes, with a cascade that involves the release of mitogens, such as basic fibroblast growth factor [105–107]. Multiple putative mechanisms and mediators are currently under investigation, many of which involve abnormalities in apoptosis with some sharing features with neoplastic processes [108]. In addition, genetic abnormalities participate in the development of PH in some patients, most prominently, mutations in bone morphogenetic protein receptor 2 (BMPR2) [109–114].

Management Strategies and Therapeutic Options

The basic elements of PH management include: the prevention and/or treatment of active pulmonary vasoconstriction, the support of right ventricle function and, when possible, treatment of the underlying disease. The ultimate treatment would involve the regression of advanced pulmonary vascular structural remodeling, but to date this remains an unattained goal.

In the critical care setting, avoidance, recognition and treatment of pulmonary hypertensive crises are paramount. Pulmonary hypertensive crises are most commonly observed in susceptible patients after cardiac surgery, but can occur in a number of settings. These life-threatening events involve: acute elevations in pulmonary vascular impedance, that cause an increase in right ventricular afterload, right ventricular ischemia, and decreased cardiac output [115, 116]. Decreased cardiac output results from the associated increase in right ventricular end diastolic volume that shifts the intraventricular septum to the left, decreasing left ventricular end diastolic volume and stroke volume. Decreased cardiac output results in decreased systemic oxygen delivery and metabolic acidosis. In addition, decreased pulmonary blood flow increases dead space ventilation. Distention of the pulmonary

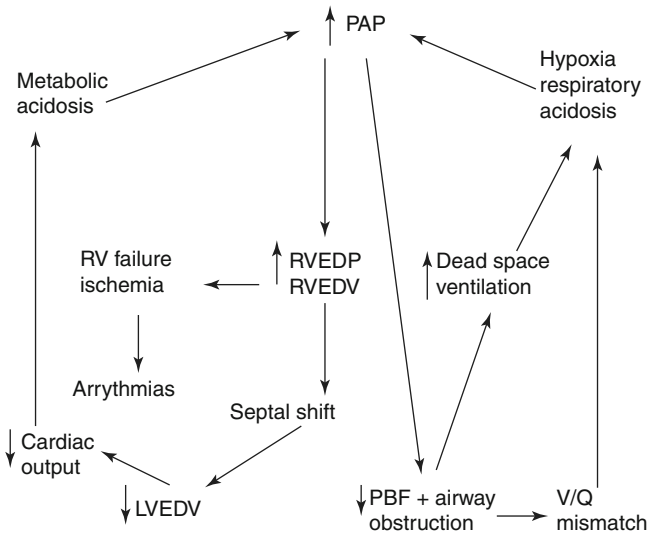

Fig. 15.4 A schematic of a pulmonary hypertensive crisis. An acute increase in pulmonary arterial pressure (*PAP*) results in a decrease in pulmonary blood flow (*PBF*) and airway obstruction due to distention of pulmonary arteries proximal to the maximally constricted resistance arterioles and perivascular edema. This results in an increase in dead space ventilation and ventilation-perfusion (*V/Q*) mismatch, both of which contribute to respiratory acidosis. In addition, right ventricular end-diastolic pressure (*RVEDP*) and volume (*RVEDV*) increase, which can result in failure of the right ventricle (*RV*) and movement of the intraventricular septum leftward, with compromise of left ventricular filling (decreased left ventricular end-diastolic volume (*LVEDV*)). This can impair cardiac output, resulting in metabolic acidosis. The resultant hypoxia (via hypoxic pulmonary vasoconstriction) and respiratory and metabolic acidosis can further increase PAP, causing a downward cycle

arteries and perivascular edema produce large and small airway obstruction, respectively, which further 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. A cycle of worsening hypoxemia, hypercapnia, and acidosis (metabolic and/or respiratory) that results in further increases pulmonary vascular impedance develops that ultimately ends with right heart failure and death if left untreated (Fig. 15.4) [117–121].

Prevention and/or Treatment of Active Pulmonary Vasoconstriction

Increased pulmonary vascular reactivity is an early feature of PH, which manifests clinically as augmented pulmonary vasoconstriction in response to such stimuli as hypoxia, acidosis, catecholamine-mediated α_1-adrenergic stimulation associated with pain and/or agitation, and increases in intrathoracic pressure [121–123].

In critical care settings, acute PH is often first treated with pain control, sedation, oxygenation, and alkalinization. Indeed, recently published clinical practice guidelines for the hemodynamic support of pediatric and neonatal septic shock, specifically addressed the risk of elevated PAP/PVR and right heart failure in neonates with sepsis, and the potential need for metabolic and respiratory alkalinization as a part of the initial resuscitative strategy [124]. Decreasing oxygen tension and decreases in pH elicit pulmonary vasoconstriction. Alveolar hypoxia constricts pulmonary arterioles, diverting blood flow away from hypoxic lung segments, toward well-oxygenated segments, thus enhancing ventilation-perfusion matching. This response to hypoxia is unique to the pulmonary vasculature. Indeed, in all other vascular beds 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 [125]. Acidosis potentiates hypoxic pulmonary vasoconstriction, while alkalosis reduces it [126]. The exact mechanism of pH-mediated pulmonary vascular reactivity also remains incompletely understood, but appears to be independent of PaCO2. Recent data suggest that potassium channels play an important role in mediating these responses as well [127].

Vasodilator Therapy

The most widely used therapies for PH work by altering one of three endothelial signaling cascades: NO-cGMP, PGI_2, and ET-1. Figure 15.3 is a simplified depiction of the various sites of action of the therapies. In the critical care setting, augmentation of NO-cGMP signaling is most common, but the use of PGI_2 analogs is increasing. For the treatment of chronic PH, combination therapy is often required, and in fact may also be necessary in severe PH in the critical care setting [128–132]. Calcium channel blockers have demonstrated efficacy in the chronic treatment of subsets of PH patients, although their use may be decreasing [37, 40]. However, in the acute care setting the effects on the systemic circulation are of great concern, particularly in the face of right heart failure, and thus they are rarely used [133].

NO-cGMP Cascade

Inhaled NO (iNO) is the best-studied and most widely used agent for acute selective pulmonary vasodilation. When delivered by inhalation, NO diffuses across the alveolus into the smooth muscle of the accompanying capillary, resulting in relaxation. NO then diffuses into the blood vessel where it is rapidly inactivated by its interaction with hemoglobin. In this way, the effects of iNO are relatively confined to the pulmonary circulation and to ventilated areas of the lung, thus optimizing VQ matching. In large trials, iNO was found

to decrease the need for extracorporeal life support in neonates with PPHN and hypoxic respiratory failure, and these data led to its FDA approval [134–136]. Despite this initial indication, iNO is used to treat many other forms of PH and for diagnostic purposes. For example, several studies have investigated the use of iNO in pediatric patients undergoing cardiac surgery [12, 137–140]. These studies indicated that iNO was effective in lowering PAP and PVR in the postoperative period, but the data were less clear about the impact on outcome [141]. Likewise, investigators have examined the utility of iNO in the particular situations of bidirectional cavopulmonary connections and after Fontan completion [142–144]. In these patients, iNO decreased central venous pressure and transpulmonary gradient, and increased oxygen saturations. In addition, the pulmonary vascular response to iNO has been studied as a part of the assessment for operability in patients with PH associated with congenital heart disease [145–148]. These studies found that the combination of 100 % oxygen and iNO (80 ppm) produced maximal pulmonary vasodilation and was more predictive than either treatment alone for postoperative outcome [145–148].

Sildenafil is a PDE5 inhibitor and, as such, its mechanism of action is to augment NO-cGMP signaling by inhibiting the degradation of cGMP. Increased cGMP results in pulmonary vascular relaxation. It should be noted, however, that sildenafil has both pulmonary and systemic effects. In addition, the effects of PDE5 inhibition may not be restricted to the vasculature. For example, a recent study found that PDE5 was upregulated in the hypertrophied right ventricle and that PDE5 inhibition improved contractility [149]. Several studies have demonstrated the efficacy of sildenafil for the treatment of chronic PH [150–154]. Despite limited data, the use of sildenafil in infants and children with PH after cardiac surgery is increasing. Three small studies found that enteral sildenafil facilitated weaning from iNO in pediatric patients with congenital heart disease undergoing therapy for postoperative PH [155–157]. Two studies examined the effects of intravenous sildenafil in pediatric patients after cardiac surgery [158, 159]. Both studies found that intravenous sildenafil decreased PAP and PVR either to a greater extent than iNO or synergistically, but that its use was associated with increased intrapulmonary shunting and decreased systemic arterial pressures.

The administration of additional substrate for NOS with arginine and citrulline is another approach that has been taken to augment the NO-cGMP cascade, with some success [160–167].

Prostanoids

Higenbottam and colleagues, first described the long-term use of intravenous PGI_2 for the treatment of PH almost 30years ago [168]. Despite the many recent advances in therapy, intravenous PGI_2, epoprostenol, remains the best-proven and most effective therapy for chronic PH [169–173]. Complications associated with long-term epoprostenol are well known and include: thrombosis and infection secondary to the required indwelling central venous catheter, the need for dose escalation over time, and life threatening rebound PH with abrupt discontinuation of the infusion.

Given the success of chronic intravenous epoprostenol therapy, recent efforts have focused on developing additional agents and delivery approaches, in large part in order to address the complications and limitations associated with chronic intravenous infusions. In order to achieve selective pulmonary vascular relaxation, various investigations have focused on delivering prostanoids via the inhalational route [174–176]. This route (in large part due to the potential for selective pulmonary vascular relaxation) is particularly useful in the intensive care setting. Iloprost is a PGI_2 analog that is FDA approved for administration by nebulization. Ivy and colleagues studied iloprost in 22 children with PH [177]. They found that inhaled iloprost decreased PAP to a degree equivalent to iNO with oxygen. Likewise, Rimensberger and colleagues administered inhaled iloprost and iNO, alone and in combination, to 15 children with PH secondary to congenital cardiac defects [178]. Both agents decreased the PVR:SVR ratio to a similar degree, and there was no added benefit from a combination of the treatments. Furthermore, in an interesting study by Limsuwan and colleagues done in Thailand, which has relatively less access to iNO, inhaled iloprost decreased mean PAP and increased systemic saturations without decreasing systemic blood pressure in eight children suffering from acute increases in PAP after repair of congenital heart disease [179].

Other dosing strategies for prostanoids include subcutaneous and oral routes of administration, although these are less likely to be useful in critically ill children [180–185]. In children, an important impediment to the use of subcutaneous treprostinil relates to pain at the site of injection, but nonetheless it has been used successfully in these patients [186, 187].

Endothelin-1

Unlike augmentation of the NO-cGMP and prostanoid cascades, inhibition of ET-1 signaling does not reliably cause acute pulmonary vascular relaxation, and thus ET receptor antagonists are considered chronic therapies. However, in a small study that included seven infants that had undergone surgical repair of left-to-right intracardiac shunts, Schulze-Neick and colleagues demonstrated that an intravenous infusion of a selective ET_A-receptor antagonist resulted in an acute decrease in PVR [188]. Notably, the addition of iNO

had no effect, and the decrease in PVR correlated with left atrial ET-1 levels. But, currently, intravenous ET receptor antagonists are restricted to experimental settings.

Presently, the most common ET receptor antagonist is bosentan, an oral dual ET receptor antagonist. A number of studies have demonstrated the efficacy of bosentan in patients with chronic PAH, including children [189–192]. Bosentan is a sulfonamide-based agent metabolized by cytochrome P450 enzymes and thus monitoring liver function is important due to potential hepatic toxicity [193, 194]. Newer agents include selective ET_A-receptor antagonists [195–198].

The Support of Right Ventricular Function

Mortality from PH is most directly related to right ventricular function. The therapies outlined above may improve right ventricular function to the extent that they decrease right ventricular afterload, although emerging data suggest that some of these therapies, such as PDE5 inhibition and ET-1 receptor antagonism, may also enhance or impair (respectively) contractility of the hypertrophied right ventricle [149, 199]. However, in addition to afterload reduction, other therapies that support the right ventricle may be necessary, especially in acute care settings.

Under conditions of increased afterload, the contractility of right ventricular cardiomyocytes increases initially, due to changes in sarcomere length-tension relationships, increased Ca^{+2} sensitivity, and alterations in force-frequency relationships [200, 201]. In addition, the time course over which right ventricular afterload increases with the state of the right ventricle (in particular, right ventricular mass) together influence the degree to which the right ventricle can compensate [202]. For example, patients with Eisenmenger's syndrome tolerate elevated right ventricular afterload far better than patients with normal right ventricles who suffer an acute pulmonary embolism [200, 203].

Nonetheless, over some period of time (acutely or chronically) compensatory mechanisms fail, leading to elevations in right ventricular end-diastolic volume and decreased output. Due to ventricular interdependence, increases in right ventricular end-diastolic volume result directly in decreased left ventricular filling and decreased systemic output [204]. In fact, diastolic ventricular interactions, with decreases in left ventricular end-diastolic volumes, have been demonstrated to be more closely related to stroke volume than PAP in patients with PAH [205]. It is also important to recognize that right and left ventricular contractility are directly related. The ventricles share muscle fibers, the interventricular septum, and the pericardial space. Based on studies that used electrically isolated right heart preparations and experimental aortic constriction, it is estimated that 20–40 % of right ventricular systolic pressure is due to left ventricular contraction [206–208]. In addition, right coronary artery perfusion is dependent, in large part, on the pressure gradient between the aortic root and right ventricle.

Taken together, then, the principles of right ventricular support are: a reduction in right ventricular afterload (i.e. a reduction in pulmonary vascular impedance), optimization of right ventricular volume, augmentation of right ventricular contractility, and maintenance of left ventricular contractility and systemic vascular resistance. Importantly, this strategy requires adequate left ventricular function. The physiology associated with PH due to left heart failure, is quite different. Left heart failure is associated with elevations in left ventricular end-diastolic volume and pressure, the reverse situation of right heart failure due to PAH. Moreover, in this situation decreased right ventricular afterload and/or increased systemic vascular resistance could result in clinical deterioration, with pulmonary edema or impaired cardiac output [53, 54, 209]. Interestingly, however, sildenafil has been shown to increase cardiac output in patients with PH secondary to left heart failure, presumably due to reductions in pulmonary and systemic vascular resistance [210, 211].

The optimization of right ventricular volume presents a significant clinical challenge, as the proper management is dependent on the particular situation [212–217]. Although volume loading may be necessary in some situations, excessive volume may provoke adverse diastolic ventricular interactions. Management aimed at decreasing right ventricular volume (e.g. diuretics) may be necessary [217, 218].

Inotropes are often necessary in order to augment right ventricular contractility, however it remains unclear if one agent is superior. Although dopamine has been shown to increase cardiac output in patients with PH, Liet and colleagues found that dopamine increased the PVR to systemic vascular resistance ratio in preterm infants with a widely patent ductus arteriosus [219, 220]. Based on animal studies, epinephrine may have a superior hemodynamic profile in the setting of PH compared to dopamine, including a decrease in the PVR to systemic vascular resistance ratio, but direct clinical evidence is sparse [221]. Dobutamine, at low doses, may result in a reduction in PVR, while increasing right ventricular contractility. Several clinical studies have demonstrated the efficacy of dobutamine in adult patients with PH [222–224]. Likewise, milrinone, a PDE3 inhibitor and inodilator that augments ventricular contractility while decreasing PVR and systemic vascular resistance, has been shown to improve right ventricular output in adult patients with PH [225–227]. The decrease in systemic vascular resistance may not be desirable and thus may need to be addressed by the addition of a vasopressor. Finally, the drug levosimendan, which is a Ca^{2+} sensitizing agent and PDE3 inhibitor, holds great promise. Levosimendan has been shown to decrease PVR and improve right ventricular output in adult patients

with RV failure secondary to a number of conditions including PH [228–232].

The role of vasopressors is to increase systemic vascular resistance in order to augment right ventricular output through an elevation in left ventricular systolic pressure, and to maintain right coronary perfusion. Norepinephrine has been validated as a useful agent in a number of animal studies [233, 234]. Tourneux and colleagues demonstrated that norepinephrine increased left ventricular output, systemic arterial pressure, and pulmonary blood flow, while decreasing the pulmonary to systemic pressure ratio in 18 newborns with PPHN [235]. Phenylephrine has been shown to increase right coronary blood flow in the setting of increased right ventricular pressures, but may also increase PVR [236, 237]. Vasopressin, a systemic vasoconstrictor and pulmonary vasodilator, has been advocated in the treatment of right ventricular failure secondary to PH, with several positive clinical studies [238–243].

Finally, atrial septostomy as a part of management for chronic pulmonary hypertension has been advocated in order to allow for decompression of the right ventricle due to right-to-left shunting [231, 244–249]. Severe hypoxemia with this approach remains a concern. Recently, Labombarda and colleagues described favorable results with the placement of a Potts anastomosis (descending aorta to left pulmonary artery) in two children with severe idiopathic PH, thereby directing desaturated blood to the lower body [250].

Treatment of Underlying Disease

The ability to impact the course of PH by treating associated conditions is highly variable. Early repair of congenital cardiac defects represents the most successful effort to alter the natural history of PH [73, 122, 251, 252]. Likewise, PH related to treatable left heart disease would be expected to resolve in most cases, depending on the timing of the repair. However, treatment for other associated conditions may not decrease the incidence of PH. For example, PH can develop with Schistosomiasis and HIV infection despite treatment [253, 254]. The reversal of PH associated with portal hypertension after liver transplant has been described, but not in large series [255, 256]. Likewise, the reversal of PH associated with systemic lupus erythematosus after hematopoietic stem cell transplantation has been described, but only as case reports [257]. The use of steroids has been successful in the treatment of some patients with autoimmune disease, mixed connective tissue disease, POEMS syndrome, Langerhans' cell granulomatosis, and sarcoidosis [133, 258–261]. Advances in the management of sickle cell disease may decrease the incidence of associated PH, but definitive studies are lacking [262].

Subsets of newborns with PPHN are often treatable, and can ultimately survive without PH [263]. Several reports have described the reversal of PH after tonsillectomy or adenoidectomy for the treatment of obstructive sleep apnea [264, 265, 266]. In addition, PH related to high altitude can be reversed when patients move to sea level [267]. Home oxygen therapy is a relatively common treatment for pediatric patients with PH or at risk for developing PH. But, the data are conflicting about whether oxygen therapy alters the disease course, likely due to differences between the diseases that are studied [268, 269]. Finally, an increasing number of metabolic conditions have been found to be associated with PH. For example, the association between thyroid disorders and PH is now well established, and in fact therapy has been shown to reverse PH in these patients [270].

Future Directions

Right heart failure due to elevated pulmonary vascular impedance is the ultimate cause of mortality in most patients with PH. The majority of patients with advanced disease do not respond to acute pulmonary vasodilators, and yet most available therapies either augment pathways that cause vasodilation or inhibit pathways that cause vasoconstriction. Taken together it can be seen that an approach aimed at promoting the regression of structural pulmonary vascular remodeling may be a fundamentally more effective paradigm for patients with PH not associated with treatable conditions or with advanced PH. For critically ill patients with impending right heart failure, novel therapies may yet promote acute pulmonary vascular relaxation in patients that do not respond to the currently available treatments, by targeting new pathways within endothelial and/or smooth muscle cells.

Novel therapies in various stages of development include: direct sGC activators, eNOS couplers, antioxidants, cell-based therapy, vasoactive intestinal peptide, adrenomedullin, Rho-kinase inhibitors, tyrosine kinase inhibitors, statins, peroxisome proliferator–activated receptor agonists, elastase inhibitors, epidermal growth factor receptor inhibitors, and dichloroacetate.

Conclusions

Neonates, infants, and children may present to critical care settings primarily due to PH, or PH may complicate the course of another illness. A basic understanding of pulmonary vascular biology, the pathobiology and pathophysiology of PH, and the therapeutic approach is essential for intensive care physicians caring for these vulnerable patients. Early attention to right heart function is absolutely essential.

References

1. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34–41.
2. Fraisse A, Jais X, Schleich JM, di Filippo S, Maragnes P, Beghetti M, Gressin V, Voisin M, Dauphin C, Clerson P, Godart F, Bonnet D. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. Arch Cardiovasc Dis. 2010;103:66–74.
3. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK pulmonary hypertension service for children 2001–2006. Heart. 2009;95:312–7.
4. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, Verter J, Stoll BJ, Lemons JA, Papile LA, Shankaran S, Donovan EF, Oh W, Ehrenkranz RA, Fanaroff AA. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. 2000;105:14–20.
5. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2006:CD000399.
6. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr. 2009;154:379–84, 384e371–2.
7. Hislop AA, Haworth SG. Pulmonary vascular damage and the development of cor pulmonale following hyaline membrane disease. Pediatr Pulmonol. 1990;9:152–61.
8. Goodman G, Perkin RM, Anas NG, Sperling DR, Hicks DA, Rowen M. Pulmonary hypertension in infants with bronchopulmonary dysplasia. J Pediatr. 1988;112:67–72.
9. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, Mullen MP. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics. 2007;120:1260–9.
10. Celermajer DS, Cullen S, Deanfield JE. Impairment of endothelium-dependent pulmonary artery relaxation in children with congenital heart disease and abnormal pulmonary hemodynamics. Circulation. 1993;87:440–6.
11. Lincoln CR, Rigby ML, Mercanti C, Al-Fagih M, Joseph MC, Miller GA, Shinebourne EA. Surgical risk factors in total anomalous pulmonary venous connection. Am J Cardiol. 1988;61:608–11.
12. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet. 2000;356:1464–9.
13. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342:1334–49.
14. Tomashefski Jr JF, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. Am J Pathol. 1983;112:112–26.
15. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med. 1977;296:476–80.
16. Sibbald WJ, Driedger AA, Myers ML, Short AI, Wells GA. Biventricular function in the adult respiratory distress syndrome. Chest. 1983;84:126–34.
17. Katz R, Pollack M, Spady D. Cardiopulmonary abnormalities in severe acute respiratory failure. J Pediatr. 1984;104:357–64.
18. Bull TM, Clark B, McFann K, Moss M. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. Am J Respir Crit Care Med. 2010;182:1123–8.
19. Ahearn GS, Tapson VF, Rebeiz A, Greenfield Jr JC. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. Chest. 2002;122:524–7.
20. Battle RW, Davitt MA, Cooper SM, Buckley LM, Leib ES, Beglin PA, Tischler MD. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. Chest. 1996;110:1515–9.
21. Grunig E, Janssen B, Mereles D, Barth U, Borst MM, Vogt IR, Fischer C, Olschewski H, Kuecherer HF, Kubler W. Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. Circulation. 2000;102:1145–50.
22. Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three doppler ultrasound methods in the prediction of pulmonary artery pressure. J Am Coll Cardiol. 1987;9:549–54.
23. Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, Reeder GS, Nishimura RA, Tajik AJ. Continuous wave doppler determination of right ventricular pressure: a simultaneous doppler-catheterization study in 127 patients. J Am Coll Cardiol. 1985;6:750–6.
24. Denton CP, Cailes JB, Phillips GD, Wells AU, Black CM, Bois RM. Comparison of doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic Sclerosis. Br J Rheumatol. 1997;36:239–43.
25. Hinderliter AL, Willis PW, Barst RJ, Rich S, Rubin LJ, Badesch DB, Groves BM, McGoon MD, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Koch G, Li S, Clayton LM, Jobsis MM, Blackburn Jr SD, Crow JW, Long WA. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Primary pulmonary hypertension study group. Circulation. 1997;95:1479–86.
26. Kim WR, Krowka MJ, Plevak DJ, Lee J, Rettke SR, Frantz RP, Wiesner RH. Accuracy of doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. Liver Transpl. 2000;6:453–8.
27. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann XJ, Georgiou D, Mandayam S, Ginzton LE, Brundage BH. Primary pulmonary hypertension: Improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am Coll Cardiol. 1997;30:343–9.
28. Shen JY, Chen SL, Wu YX, Tao RQ, Gu YY, Bao CD, Wang Q. Pulmonary hypertension in systemic lupus erythematosus. Rheumatol Int. 1999;18:147–51.
29. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by doppler ultrasound in patients with tricuspid regurgitation. Circulation. 1984;70:657–62.
30. Chotivittayatarakorn P, Pathmanand C, Thisyakorn C, Sueblinvong V. Doppler echocardiographic predictions of pulmonary artery pressure in children with congenital heart disease. J Med Assoc Thai. 1992;75:79–84.
31. Fernandes R, Bjorkhem G, Lundstrom NR. Echocardiographic estimation of pulmonary artery pressure in infants and children with congenital heart disease. Eur J Cardiol. 1980;11:473–81.
32. Kosturakis D, Goldberg SJ, Allen HD, Loeber C. Doppler echocardiographic prediction of pulmonary arterial hypertension in congenital heart disease. Am J Cardiol. 1984;53:1110–5.
33. Mirrakhimov MM, Tenenbaum AM, Moldotashev IK, Niazova ZA, Zlatkovsky ML. New approaches to noninvasive assessment of pulmonary artery pressure. Clin Cardiol. 1992;15:811–6.
34. Arkles JS, Opotowsky AR, Ojeda J, Rogers F, Liu T, Prassana V, Marzec L, Palevsky HI, Ferrari VA, Forfia PR. Shape of the right ventricular doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Respir Crit Care Med. 2011;183:268–76.
35. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM. Tricuspid annular displacement

predicts survival in pulmonary hypertension. Am J Respir Crit Care Med. 2006;174:1034–41.
36. Kawut SM, Horn EM, Berekashvili KK, Garofano RP, Goldsmith RL, Widlitz AC, Rosenzweig EB, Kerstein D, Barst RJ. New predictors of outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol. 2005;95:199–203.
37. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med. 1992;327:76–81.
38. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99: 1197–208.
39. Packer M, Greenberg B, Massie B, Dash H. Deleterious effects of hydralazine in patients with pulmonary hypertension. N Engl J Med. 1982;306:1326–31.
40. Montani D, Savale L, Natali D, Jais X, Herve P, Garcia G, Humbert M, Simonneau G, Sitbon O. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. Eur Heart J. 2010;31:1898–907.
41. D'Alonzo GE, Bower JS, Dantzker DR. Differentiation of patients with primary and thromboembolic pulmonary hypertension. Chest. 1984;85:457–61.
42. Bergin CJ, Hauschildt J, Rios G, Belezzuoli EV, Huynh T, Channick RN. Accuracy of MR angiography compared with radionuclide scanning in identifying the cause of pulmonary arterial hypertension. AJR Am J Roentgenol. 1997;168:1549–55.
43. Worsley DF, Palevsky HI, Alavi A. Ventilation-perfusion lung scanning in the evaluation of pulmonary hypertension. J Nucl Med. 1994;35:793–6.
44. Bergin CJ, Sirlin CB, Hauschildt JP, Huynh TV, Auger WR, Fedullo PF, Kapelanski DP. Chronic thromboembolism: diagnosis with helical ct and mr imaging with angiographic and surgical correlation. Radiology. 1997;204:695–702.
45. Bergin CJ, Hauschildt JP, Brown MA, Channick RN, Fedullo PF. Identifying the cause of unilateral hypoperfusion in patients suspected to have chronic pulmonary thromboembolism: diagnostic accuracy of helical ct and conventional angiography. Radiology. 1999;213:743–9.
46. Choe KO, Hong YK, Kim HJ, Joo SH, Cho BK, Chang BC, Cho SY, Shim WH, Chung NS. The use of high-resolution computed tomography in the evaluation of pulmonary hemodynamics in patients with congenital heart disease: in pulmonary vessels larger than 1 mm in diameter. Pediatr Cardiol. 2000;21:202–10.
47. Kuriyama K, Gamsu G, Stern RG, Cann CE, Herfkens RJ, Brundage BH. Ct-determined pulmonary artery diameters in predicting pulmonary hypertension. Invest Radiol. 1984;19:16–22.
48. Ng CS, Wells AU, Padley SP. A ct sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. J Thorac Imaging. 1999;14:270–8.
49. Tan RT, Kuzo R, Goodman LR, Siegel R, Haasler GB, Presberg KW. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. Medical college of Wisconsin lung transplant group. Chest. 1998;113: 1250–6.
50. Boxt LM, Katz J, Kolb T, Czegledy FP, Barst RJ. Direct quantitation of right and left ventricular volumes with nuclear magnetic resonance imaging in patients with primary pulmonary hypertension. J Am Coll Cardiol. 1992;19:1508–15.
51. Katz J, Whang J, Boxt LM, Barst RJ. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. J Am Coll Cardiol. 1993;21:1475–81.
52. Murray TI, Boxt LM, Katz J, Reagan K, Barst RJ. Estimation of pulmonary artery pressure in patients with primary pulmonary hypertension by quantitative analysis of magnetic resonance images. J Thorac Imaging. 1994;9:198–204.
53. Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW, Fifer MA. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol. 1994;24:982–8.
54. Loh E, Stamler JS, Hare JM, Loscalzo J, Colucci WS. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. Circulation. 1994;90:2780–5.
55. Creagh-Brown BC, Nicholson AG, Showkathali R, Gibbs JS, Howard LS. Pulmonary veno-occlusive disease presenting with recurrent pulmonary oedema and the use of nitric oxide to predict response to sildenafil. Thorax. 2008;63:933–4.
56. Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med. 2007;28:233–41, x.
57. Delgado JF, Conde E, Sanchez V, Lopez-Rios F, Gomez-Sanchez MA, Escribano P, Sotelo T, Gomez de la Camara A, Cortina J, de la Calzada CS. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail. 2005;7:1011–6.
58. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation. 2000;102: 1718–23.
59. Cody RJ, Haas GJ, Binkley PF, Capers Q, Kelley R. Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation. 1992;85:504–9.
60. Ben Driss A, Devaux C, Henrion D, Duriez M, Thuillez C, Levy BI, Michel JB. Hemodynamic stresses induce endothelial dysfunction and remodeling of pulmonary artery in experimental compensated heart failure. Circulation. 2000;101:2764–70.
61. Maeda K, Yamaki S, Yokota M, Murakami A, Takamoto S. Hypoplasia of the small pulmonary arteries in total anomalous pulmonary venous connection with obstructed pulmonary venous drainage. J Thorac Cardiovasc Surg. 2004;127:448–56.
62. Endo M, Yamaki S, Ohmi M, Tabayashi K. Pulmonary vascular changes induced by congenital obstruction of pulmonary venous return. Ann Thorac Surg. 2000;69:193–7.
63. Lantuejoul S, Sheppard MN, Corrin B, Burke MM, Nicholson AG. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: a clinicopathologic study of 35 cases. Am J Surg Pathol. 2006;30:850–7.
64. Gan CT, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JW, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest. 2007;132:1906–12.
65. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2006;47:799–803.
66. Dyer K, Lanning C, Das B, Lee PF, Ivy DD, Valdes-Cruz L, Shandas R. Noninvasive doppler tissue measurement of pulmonary artery compliance in children with pulmonary hypertension. J Am Soc Echocardiogr. 2006;19:403–12.
67. Hunter KS, Lee PF, Lanning CJ, Ivy DD, Kirby KS, Claussen LR, Chan KC, Shandas R. Pulmonary vascular input impedance is a combined measure of pulmonary vascular resistance and stiffness and predicts clinical outcomes better than pulmonary vascular resistance alone in pediatric patients with pulmonary hypertension. Am Heart J. 2008;155:166–74.
68. Weinberg CE, Hertzberg JR, Ivy DD, Kirby KS, Chan KC, Valdes-Cruz L, Shandas R. Extraction of pulmonary vascular compliance, pulmonary vascular resistance, and right ventricular work from single-pressure and doppler flow measurements in children with pulmonary hypertension: a new method for evaluating reactivity: in vitro and clinical studies. Circulation. 2004;110:2609–17.
69. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes

in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation. 1958;18:533–47.
70. Rabinovitch M, Haworth SG, Castaneda AR, Nadas AS, Reid LM. Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease. Circulation. 1978;58: 1107–22.
71. Tuder RM. Pathology of pulmonary arterial hypertension. Semin Respir Crit Care Med. 2009;30:376–85.
72. Yamaki S, Wagenvoort CA. Comparison of primary plexogenic arteriopathy in adults and children. A morphometric study in 40 patients. Br Heart J. 1985;54:428–34.
73. Rabinovitch M, Keane JF, Norwood WI, Castaneda AR, Reid L. Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects. Circulation. 1984;69:655–67.
74. Baile EM, Pare PD, Brooks LA, Hogg JC. Relationship between regional lung volume and regional pulmonary vascular resistance. J Appl Physiol. 1982;52:914–20.
75. Whittenberger JL, Mc GM, Berglund E, Borst HG. Influence of state of inflation of the lung on pulmonary vascular resistance. J Appl Physiol. 1960;15:878–82.
76. Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. Br J Anaesth. 2007;98:420–8.
77. Giaid A. Nitric oxide and endothelin-1 in pulmonary hypertension. Chest. 1998;114:208S–12.
78. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med. 1995;333:214–21.
79. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, Stewart DJ. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med. 1993;328:1732–9.
80. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med. 1992;327:70–5.
81. Adatia I, Barrow SE, Stratton PD, Miall-Allen VM, Ritter JM, Haworth SG. Thromboxane a2 and prostacyclin biosynthesis in children and adolescents with pulmonary vascular disease. Circulation. 1993;88:2117–22.
82. Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. Circulation. 2004;109:159–65.
83. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature. 1988;332:411–5.
84. Bradley LM, Czaja JF, Goldstein RE. Circulatory effects of endothelin in newborn piglets. Am J Physiol. 1990;259:H1613–7.
85. Cassin S, Kristova V, Davis T, Kadowitz P, Gause G. Tone-dependent responses to endothelin in the isolated perfused fetal sheep pulmonary circulation in situ. J Appl Physiol. 1991;70:1228–34.
86. Wong J, Vanderford PA, Fineman JR, Chang R, Soifer SJ. Endothelin-1 produces pulmonary vasodilation in the intact newborn lamb. Am J Physiol. 1993;265:H1318–25.
87. Wong J, Vanderford PA, Fineman JR, Soifer SJ. Developmental effects of endothelin-1 on the pulmonary circulation in sheep. Pediatr Res. 1994;36:394–401.
88. Perreault T, De Marte J. Maturational changes in endothelium-derived relaxations in newborn piglet pulmonary circulation. Am J Physiol. 1993;264:H302–9.
89. Arai H, Hori S, Aramori I, Ohkubo H, Nakanishi S. Cloning and expression of a cDNA encoding an endothelin receptor. Nature. 1990;348:730–2.
90. Sakurai T, Yanagisawa M, Takuwa Y, Miyazaki H, Kimura S, Goto K, Masaki T. Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor. Nature. 1990;348: 732–5.
91. Morris CR, Vichinsky EP. Pulmonary hypertension in thalassemia. Ann N Y Acad Sci. 2010;1202:205–13.
92. Crosswhite P, Sun Z. Nitric oxide, oxidative stress and inflammation in pulmonary arterial hypertension. J Hypertens. 2010;28:201–12.
93. Spiekermann S, Schenk K, Hoeper MM. Increased xanthine oxidase activity in idiopathic pulmonary arterial hypertension. Eur Respir J. 2009;34:276.
94. Gupte SA, Wolin MS. Oxidant and redox signaling in vascular oxygen sensing: implications for systemic and pulmonary hypertension. Antioxid Redox Signal. 2008;10:1137–52.
95. Black SM, Fineman JR. Oxidative and nitrosative stress in pediatric pulmonary hypertension: roles of endothelin-1 and nitric oxide. Vascul Pharmacol. 2006;45:308–16.
96. Birukov KG. Cyclic stretch, reactive oxygen species, and vascular remodeling. Antioxid Redox Signal. 2009;11:1651–67.
97. Durmowicz AG, St Cyr JA, Clarke DR, Stenmark KR. Unilateral pulmonary hypertension as a result of chronic high flow to one lung. Am Rev Respir Dis. 1990;142:230–3.
98. Ghorishi Z, Milstein JM, Poulain FR, Moon-Grady A, Tacy T, Bennett SH, Fineman JR, Eldridge MW. Shear stress paradigm for perinatal fractal arterial network remodeling in lambs with pulmonary hypertension and increased pulmonary blood flow. Am J Physiol Heart Circ Physiol. 2007;292:H3006–18.
99. Hassoun PM, Mouthon L, Barbera JA, Eddahibi S, Flores SC, Grimminger F, Jones PL, Maitland ML, Michelakis ED, Morrell NW, Newman JH, Rabinovitch M, Schermuly R, Stenmark KR, Voelkel NF, Yuan JX, Humbert M. Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol. 2009;54:S10–9.
100. Marecki JC, Cool CD, Parr JE, Beckey VE, Luciw PA, Tarantal AF, Carville A, Shannon RP, Cota-Gomez A, Tuder RM, Voelkel NF, Flores SC. Hiv-1 nef is associated with complex pulmonary vascular lesions in shiv-nef-infected macaques. Am J Respir Crit Care Med. 2006;174:437–45.
101. Graham BB, Mentink-Kane MM, El-Haddad H, Purnell S, Zhang L, Zaiman A, Redente EF, Riches DW, Hassoun PM, Bandeira A, Champion HC, Butrous G, Wynn TA, Tuder RM. Schistosomiasis-induced experimental pulmonary hypertension: role of interleukin-13 signaling. Am J Pathol. 2010;177:1549–61.
102. Souza R, Humbert M, Sztrymf B, Jais X, Yaici A, Le Pavec J, Parent F, Herve P, Soubrier F, Sitbon O, Simonneau G. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. Eur Respir J. 2008;31:343–8.
103. Pak O, Aldashev A, Welsh D, Peacock A. The effects of hypoxia on the cells of the pulmonary vasculature. Eur Respir J. 2007;30: 364–72.
104. Jeffery TK, Wanstall JC. Pulmonary vascular remodeling: a target for therapeutic intervention in pulmonary hypertension. Pharmacol Ther. 2001;92:1–20.
105. Cowan KN, Heilbut A, Humpl T, Lam C, Ito S, Rabinovitch M. Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor. Nat Med. 2000;6:698–702.
106. Cowan KN, Jones PL, Rabinovitch M. Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-c antisense prevents progression, of vascular disease. J Clin Invest. 2000;105:21–34.
107. Merklinger SL, Jones PL, Martinez EC, Rabinovitch M. Epidermal growth factor receptor blockade mediates smooth muscle cell apoptosis and improves survival in rats with pulmonary hypertension. Circulation. 2005;112:423–31.
108. Michelakis ED, Wilkins MR, Rabinovitch M. Emerging concepts and translational priorities in pulmonary arterial hypertension. Circulation. 2008;118:1486–95.
109. Atkinson C, Stewart S, Upton PD, Machado R, Thomson JR, Trembath RC, Morrell NW. Primary pulmonary hypertension is

associated with reduced pulmonary vascular expression of type ii bone morphogenetic protein receptor. Circulation. 2002;105: 1672–8.
110. Lane KB, Machado RD, Pauciulo MW, Thomson JR, Phillips 3rd JA, Loyd JE, Nichols WC, Trembath RC. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. The international PPH consortium. Nat Genet. 2000;26:81–4.
111. Machado RD, Pauciulo MW, Thomson JR, Lane KB, Morgan NV, Wheeler L, Phillips 3rd JA, Newman J, Williams D, Galie N, Manes A, McNeil K, Yacoub M, Mikhail G, Rogers P, Corris P, Humbert M, Donnai D, Martensson G, Tranebjaerg L, Loyd JE, Trembath RC, Nichols WC. Bmpr2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. Am J Hum Genet. 2001;68:92–102.
112. Morse JH, Deng Z, Knowles JA. Genetic aspects of pulmonary arterial hypertension. Ann Med. 2001;33:596–603.
113. Newman JH, Wheeler L, Lane KB, Loyd E, Gaddipati R, Phillips 3rd JA, Loyd JE. Mutation in the gene for bone morphogenetic protein receptor ii as a cause of primary pulmonary hypertension in a large kindred. N Engl J Med. 2001;345:319–24.
114. Thomson JR, Machado RD, Pauciulo MW, Morgan NV, Humbert M, Elliott GC, Ward K, Yacoub M, Mikhail G, Rogers P, Newman J, Wheeler L, Higenbottam T, Gibbs JS, Egan J, Crozier A, Peacock A, Allcock R, Corris P, Loyd JE, Trembath RC, Nichols WC. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding bmpr-ii, a receptor member of the TGF-beta family. J Med Genet. 2000;37:741–5.
115. Rowe RD, Hoffman T. Transient myocardial ischemia of the newborn infant: a form of severe cardiorespiratory distress in full-term infants. J Pediatr. 1972;81:243–50.
116. Turner-Gomes SO, Izukawa T, Rowe RD. Persistence of atrioventricular valve regurgitation and electrocardiographic abnormalities following transient myocardial ischemia of the newborn. Pediatr Cardiol. 1989;10:191–4.
117. Scott JP, Higenbottam TW, Smyth RL, Wallwork J. Acute pulmonary hypertensive crisis in a patient with primary pulmonary hypertension treated by both epoprostenol (prostacyclin) and nitroprusside. Chest. 1991;99:1284–5.
118. Pelech AN, Neish SR. Sudden death in congenital heart disease. Pediatr Clin North Am. 2004;51:1257–71.
119. Allman KG, Young JD, Stevens JE, Archer LN. Nitric oxide treatment for fulminant pulmonary hypertension. Arch Dis Child. 1993;69:449–50.
120. Hopkins RA, Bull C, Haworth SG, de Leval MR, Stark J. Pulmonary hypertensive crises following surgery for congenital heart defects in young children. Eur J Cardiothorac Surg. 1991;5:628–34.
121. Wheller J, George BL, Mulder DG, Jarmakani JM. Diagnosis and management of postoperative pulmonary hypertensive crisis. Circulation. 1979;60:1640–4.
122. Hoffman JI, Rudolph AM, Heymann MA. Pulmonary vascular disease with congenital heart lesions: pathologic features and causes. Circulation. 1981;64:873–7.
123. Burrows FA, Klinck JR, Rabinovitch M, Bohn DJ. Pulmonary hypertension in children: perioperative management. Can Anaesth Soc J. 1986;33:606–28.
124. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA, Duncan A, Evans B, Feldman J, Felmet K, Fisher G, Frankel L, Jeffries H, Greenwald B, Gutierrez J, Hall M, Han YY, Hanson J, Hazelzet J, Hernan L, Kiff J, Kissoon N, Kon A, Irazuzta J, Lin J, Lorts A, Mariscalco M, Mehta R, Nadel S, Nguyen T, Nicholson C, Peters M, Okhuysen-Cawley R, Poulton T, Relves M, Rodriguez A, Rozenfeld R, Schnitzler E, Shanley T, Kache S, Skippen P, Torres A, von Dessauer B, Weingarten J, Yeh T, Zaritsky A, Stojadinovic B, Zimmerman J, Zuckerberg A. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the american college of critical care medicine. Crit Care Med. 2009;37:666–88.
125. Moudgil R, Michelakis ED, Archer SL. Hypoxic pulmonary vasoconstriction. J Appl Physiol. 2005;98:390–403.
126. Schreiber MD, Heymann MA, Soifer SJ. Increased arterial ph, not decreased paco2, attenuates hypoxia-induced pulmonary vasoconstriction in newborn lambs. Pediatr Res. 1986;20:113–7.
127. Cornfield DN, Resnik ER, Herron JM, Reinhartz O, Fineman JR. Pulmonary vascular k+ channel expression and vasoreactivity in a model of congenital heart disease. Am J Physiol Lung Cell Mol Physiol. 2002;283:L1210–9.
128. Hoeper MM, Leuchte H, Halank M, Wilkens H, Meyer FJ, Seyfarth HJ, Wensel R, Ripken F, Bremer H, Kluge S, Hoeffken G, Behr J. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2006;28:691–4.
129. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006;174:1257–63.
130. Channick RN, Olschewski H, Seeger W, Staub T, Voswinckel R, Rubin LJ. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. J Am Coll Cardiol. 2006;48:1433–7.
131. Simonneau G, Rubin LJ, Galie N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med. 2008;149: 521–30.
132. Ghofrani HA, Rose F, Schermuly RT, Olschewski H, Wiedemann R, Kreckel A, Weissmann N, Ghofrani S, Enke B, Seeger W, Grimminger F. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. J Am Coll Cardiol. 2003;42:158–64.
133. Adatia I, Shekerdemian L. The role of calcium channel blockers, steroids, anticoagulation, antiplatelet drugs, and endothelin receptor antagonists. Pediatr Crit Care Med. 2010;11:S46–52.
134. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. The neonatal inhaled nitric oxide study group. N Engl J Med. 1997;336:597–604.
135. Clark R, Kueser T, Walker M, Southgate W, Huckaby J, Perez J, Roy B, Keszler M, Kinsella J. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical inhaled nitric oxide research group. N Engl J Med. 2000;342:469–74.
136. Roberts Jr JD, Fineman JR, Morin 3rd FC, Shaul PW, Rimar S, Schreiber MD, Polin RA, Zwass MS, Zayek MM, Gross I, Heymann MA, Zapol WM. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The inhaled nitric oxide study group. N Engl J Med. 1997;336:605–10.
137. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation. 1993;88:2128–38.
138. Curran RD, Mavroudis C, Backer CL, Sautel M, Zales VR, Wessel DL. Inhaled nitric oxide for children with congenital heart disease and pulmonary hypertension. Ann Thorac Surg. 1995;60:1765–71.
139. Russell IA, Zwass MS, Fineman JR, Balea M, Rouine-Rapp K, Brook M, Hanley FL, Silverman NH, Cahalan MK. The effects of inhaled nitric oxide on postoperative pulmonary hypertension in infants and children undergoing surgical repair of congenital heart disease. Anesth Analg. 1998;87:46–51.

140. Day RW, Allen EM, Witte MK. A randomized, controlled study of the 1-hour and 24-hour effects of inhaled nitric oxide therapy in children with acute hypoxemic respiratory failure. Chest. 1997;112:1324–31.
141. Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev. 2005:CD005055.
142. Goldman AP, Delius RE, Deanfield JE, Miller OI, de Leval MR, Sigston PE, Macrae DJ. Pharmacological control of pulmonary blood flow with inhaled nitric oxide after the fenestrated fontan operation. Circulation. 1996;94:II44–8.
143. Gamillscheg A, Zobel G, Urlesberger B, Berger J, Dacar D, Stein JI, Rigler B, Metzler H, Beitzke A. Inhaled nitric oxide in patients with critical pulmonary perfusion after fontan-type procedures and bidirectional Glenn anastomosis. J Thorac Cardiovasc Surg. 1997;113:435–42.
144. Cai J, Su Z, Shi Z, Zhou Y, Xu Z, Yang Y. Nitric oxide and milrinone: combined effect on pulmonary circulation after fontan-type procedure: a prospective, randomized study. Ann Thorac Surg. 2008;86:882–8. discussion 882–888.
145. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, Kaine SF, Ivy DD, Webber SA, Rothman A, Ross RD, Aggarwal S, Takahashi M, Waldman JD. Inhaled nitric oxide as a preoperative test (Inop Test I): the inop test study group. Circulation. 2002;106:I76–81.
146. Adatia I, Perry S, Landzberg M, Moore P, Thompson JE, Wessel DL. Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. J Am Coll Cardiol. 1995;25:1656–64.
147. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. J Am Coll Cardiol. 1999;33:813–9.
148. Barst RJ, Agnoletti G, Fraisse A, Baldassarre J, Wessel DL. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol. 2010;31:598–606.
149. Nagendran J, Archer SL, Soliman D, Gurtu V, Moudgil R, Haromy A, St Aubin C, Webster L, Rebeyka IM, Ross DB, Light PE, Dyck JR, Michelakis ED. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation. 2007;116:238–48.
150. Bharani A, Mathew V, Sahu A, Lunia B. The efficacy and tolerability of sildenafil in patients with moderate-to-severe pulmonary hypertension. Indian Heart J. 2003;55:55–9.
151. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353:2148–57.
152. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. J Am Coll Cardiol. 2004;43:1149–53.
153. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. Am Heart J. 2006;151:851. e851–855.
154. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation. 2005;111:3274–80.
155. Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. Anesthesiology. 1999;91:307–10.
156. Namachivayam P, Theilen U, Butt WW, Cooper SM, Penny DJ, Shekerdemian LS. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. Am J Respir Crit Care Med. 2006;174:1042–7.
157. Lee JE, Hillier SC, Knoderer CA. Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. J Intensive Care Med. 2008;23:329–34.
158. Schulze-Neick I, Hartenstein P, Li J, Stiller B, Nagdyman N, Hubler M, Butrous G, Petros A, Lange P, Redington AN. Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease. Circulation. 2003;108 Suppl 1:II167–73.
159. Stocker C, Penny DJ, Brizard CP, Cochrane AD, Soto R, Shekerdemian LS. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. Intensive Care Med. 2003;29:1996–2003.
160. Vosatka RJ, Kashyap S, Trifiletti RR. Arginine deficiency accompanies persistent pulmonary hypertension of the newborn. Biol Neonate. 1994;66:65–70.
161. Morris CR, Kuypers FA, Larkin S, Vichinsky EP, Styles LA. Patterns of arginine and nitric oxide in patients with sickle cell disease with vaso-occlusive crisis and acute chest syndrome. J Pediatr Hematol Oncol. 2000;22:515–20.
162. Pearson DL, Dawling S, Walsh WF, Haines JL, Christman BW, Bazyk A, Scott N, Summar ML. Neonatal pulmonary hypertension–urea-cycle intermediates, nitric oxide production, and carbamoyl-phosphate synthetase function. N Engl J Med. 2001;344:1832–8.
163. Barr FE, Beverley H, VanHook K, Cermak E, Christian K, Drinkwater D, Dyer K, Raggio NT, Moore JH, Christman B, Summar M. Effect of cardiopulmonary bypass on urea cycle intermediates and nitric oxide levels after congenital heart surgery. J Pediatr. 2003;142:26–30.
164. McCaffrey MJ, Bose CL, Reiter PD, Stiles AD. Effect of l-arginine infusion on infants with persistent pulmonary hypertension of the newborn. Biol Neonate. 1995;67:240–3.
165. Morris CR, Morris Jr SM, Hagar W, Van Warmerdam J, Claster S, Kepka-Lenhart D, Machado L, Kuypers FA, Vichinsky EP. Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? Am J Respir Crit Care Med. 2003;168:63–9.
166. Schulze-Neick I, Penny DJ, Rigby ML, Morgan C, Kelleher A, Collins P, Li J, Bush A, Shinebourne EA, Redington AN. L-arginine and substance p reverse the pulmonary endothelial dysfunction caused by congenital heart surgery. Circulation. 1999;100:749–55.
167. Smith HA, Canter JA, Christian KG, Drinkwater DC, Scholl FG, Christman BW, Rice GD, Barr FE, Summar ML. Nitric oxide precursors and congenital heart surgery: a randomized controlled trial of oral citrulline. J Thorac Cardiovasc Surg. 2006;132:58–65.
168. Higenbottam T, Wheeldon D, Wells F, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). Lancet. 1984;1:1046–7.
169. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. N Engl J Med. 1996;334:296–302.
170. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002;40:780–8.
171. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med. 1998;338:273–7.
172. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110:660–5.
173. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation. 1999;99:1858–65.

174. Katz SL, Adatia I, Louca E, Leung K, Humpl T, Reyes JT, Coates AL. Nebulized therapies for childhood pulmonary hypertension: an in vitro model. Pediatr Pulmonol. 2006;41:666–73.
175. Kelly LK, Porta NF, Goodman DM, Carroll CL, Steinhorn RH. Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. J Pediatr. 2002;141:830–2.
176. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, Hamm M, Fabel H. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med. 2000;342:1866–70.
177. Ivy DD, Doran AK, Smith KJ, Mallory Jr GB, Beghetti M, Barst RJ, Brady D, Law Y, Parker D, Claussen L, Abman SH. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2008;51:161–9.
178. Rimensberger PC, Spahr-Schopfer I, Berner M, Jaeggi E, Kalangos A, Friedli B, Beghetti M. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation. 2001;103:544–8.
179. Limsuwan A, Wanitkul S, Khosithset A, Attanavanich S, Samankatiwat P. Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol. 2008;129:333–8.
180. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165:800–4.
181. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, Rubin LJ. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28:1195–203.
182. Lang I, Gomez-Sanchez M, Kneussl M, Naeije R, Escribano P, Skoro-Sajer N, Vachiery JL. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest. 2006;129:1636–43.
183. Gomberg-Maitland M, Tapson VF, Benza RL, McLaughlin VV, Krichman A, Widlitz AC, Barst RJ. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005;172:1586–9.
184. Oudiz RJ, Schilz RJ, Barst RJ, Galie N, Rich S, Rubin LJ, Simonneau G. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. Chest. 2004;126:420–7.
185. McLaughlin VV, Gaine SP, Barst RJ, Oudiz RJ, Bourge RC, Frost A, Robbins IM, Tapson VF, McGoon MD, Badesch DB, Sigman J, Roscigno R, Blackburn SD, Arneson C, Rubin LJ, Rich S. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. J Cardiovasc Pharmacol. 2003;41:293–9.
186. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr. 2011;158(4):584–8.
187. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol. 2010;106:1332–8.
188. Schulze-Neick I, Li J, Reader JA, Shekerdemian L, Redington AN, Penny DJ. The endothelin antagonist bq123 reduces pulmonary vascular resistance after surgical intervention for congenital heart disease. J Thorac Cardiovasc Surg. 2002;124:435–41.
189. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, Rubin LJ. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet. 2001;358:1119–23.
190. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346:896–903.
191. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114:48–54.
192. Maiya S, Hislop AA, Flynn Y, Haworth SG. Response to bosentan in children with pulmonary hypertension. Heart. 2006;92:664–70.
193. Dingemanse J, van Giersbergen PL. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. Clin Pharmacokinet. 2004;43:1089–115.
194. Horn EM, Widlitz AC, Barst RJ. Sitaxsentan, a selective endothelin-a receptor antagonist for the treatment of pulmonary arterial hypertension. Expert Opin Investig Drugs. 2004;13:1483–92.
195. Benza RL, Barst RJ, Galie N, Frost A, Girgis RE, Highland KB, Strange C, Black CM, Badesch DB, Rubin L, Fleming TR, Naeije R. Sitaxsentan for the treatment of pulmonary arterial hypertension: a 1-year, prospective, open-label observation of outcome and survival. Chest. 2008;134:775–82.
196. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N. Treatment of pulmonary arterial hypertension with the selective endothelin-a receptor antagonist sitaxsentan. J Am Coll Cardiol. 2006;47:2049–56.
197. Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, McLaughlin V, Hill N, Tapson VF, Robbins IM, Zwicke D, Duncan B, Dixon RA, Frumkin LR. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004;169:441–7.
198. Barst RJ, Rich S, Widlitz A, Horn EM, McLaughlin V, McFarlin J. Clinical efficacy of sitaxsentan, an endothelin-a receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. Chest. 2002;121:1860–8.
199. Nagendran J, Sutendra G, Haromy A, Fu DZ, Ross DB, Rebeyka IM, Michelakis ED. Endothelin receptor inhibitors decrease contractility in the hypertrophied right ventricle. Am J Respir Crit Care Med. 2007;179:A4141.
200. Yerebakan C, Klopsch C, Niefeldt S, Zeisig V, Vollmar B, Liebold A, Sandica E, Steinhoff G. Acute and chronic response of the right ventricle to surgically induced pressure and volume overload–an analysis of pressure-volume relations. Interact Cardiovasc Thorac Surg. 2010;10:519–25.
201. de Vroomen M, Cardozo RH, Steendijk P, van Bel F, Baan J. Improved contractile performance of right ventricle in response to increased RV afterload in newborn lamb. Am J Physiol Heart Circ Physiol. 2000;278:H100–5.
202. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. Am J Cardiol. 2002;89:34–8.
203. Watts JA, Marchick MR, Kline JA. Right ventricular heart failure from pulmonary embolism: key distinctions from chronic pulmonary hypertension. J Card Fail. 2010;16:250–9.
204. Belenkie I, Dani R, Smith ER, Tyberg JV. Ventricular interaction during experimental acute pulmonary embolism. Circulation. 1988;78:761–8.
205. Gan CT, Lankhaar JW, Marcus JT, Westerhof N, Marques KM, Bronzwaer JG, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. Am J Physiol Heart Circ Physiol. 2006;290:H1528–33.
206. Belenkie I, Horne SG, Dani R, Smith ER, Tyberg JV. Effects of aortic constriction during experimental acute right ventricular

pressure loading. Further insights into diastolic and systolic ventricular interaction. Circulation. 1995;92:546–54.
207. Yamaguchi S, Harasawa H, Li KS, Zhu D, Santamore WP. Comparative significance in systolic ventricular interaction. Cardiovasc Res. 1991;25:774–83.
208. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. Prog Cardiovasc Dis. 1998;40:289–308.
209. Chockalingam A, Mehra A, Dorairajan S, Dellsperger KC. Acute left ventricular dysfunction in the critically ill. Chest. 2010;138:198–207.
210. Lepore JJ, Maroo A, Bigatello LM, Dec GW, Zapol WM, Bloch KD, Semigran MJ. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. Chest. 2005;127:1647–53.
211. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007;116:1555–62.
212. Mathru M, Venus B, Smith RA, Shirakawa Y, Sugiura A. Treatment of low cardiac output complicating acute pulmonary hypertension in normovolemic goats. Crit Care Med. 1986;14:120–4.
213. Molloy WD, Lee KY, Girling L, Schick U, Prewitt RM. Treatment of shock in a canine model of pulmonary embolism. Am Rev Respir Dis. 1984;130:870–4.
214. Ghignone M, Girling L, Prewitt RM. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. Anesthesiology. 1984;60:132–5.
215. Belenkie I, Dani R, Smith ER, Tyberg JV. Effects of volume loading during experimental acute pulmonary embolism. Circulation. 1989;80:178–88.
216. Mercat A, Diehl JL, Meyer G, Teboul JL, Sors H. Hemodynamic effects of fluid loading in acute massive pulmonary embolism. Crit Care Med. 1999;27:540–4.
217. Siva A, Shah AM. Moderate mitral stenosis in pregnancy: the haemodynamic impact of diuresis. Heart. 2005;91:e3.
218. Ducas J, Prewitt RM. Pathophysiology and therapy of right ventricular dysfunction due to pulmonary embolism. Cardiovasc Clin. 1987;17:191–202.
219. Holloway EL, Polumbo RA, Harrison DC. Acute circulatory effects of dopamine in patients with pulmonary hypertension. Br Heart J. 1975;37:482–5.
220. Liet JM, Boscher C, Gras-Leguen C, Gournay V, Debillon T, Roze JC. Dopamine effects on pulmonary artery pressure in hypotensive preterm infants with patent ductus arteriosus. J Pediatr. 2002;140:373–5.
221. Barrington KJ, Finer NN, Chan WK. A blind, randomized comparison of the circulatory effects of dopamine and epinephrine infusions in the newborn piglet during normoxia and hypoxia. Crit Care Med. 1995;23:740–8.
222. Leier CV, Heban PT, Huss P, Bush CA, Lewis RP. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation. 1978;58:466–75.
223. Acosta F, Sansano T, Palenciano CG, Falcon L, Domenech P, Robles R, Bueno FS, Ramirez P, Parrilla P. Effects of dobutamine on right ventricular function and pulmonary circulation in pulmonary hypertension during liver transplantation. Transplant Proc. 2005;37:3869–70.
224. Ferrario M, Poli A, Previtali M, Lanzarini L, Fetiveau R, Diotallevi P, Mussini A, Montemartini C. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. Am J Cardiol. 1994;74:329–33.
225. Kihara S, Kawai A, Fukuda T, Yamamoto N, Aomi S, Nishida H, Endo M, Koyanagi H. Effects of milrinone for right ventricular failure after left ventricular assist device implantation. Heart Vessels. 2002;16:69–71.
226. Fukazawa K, Poliac LC, Pretto EA. Rapid assessment and safe management of severe pulmonary hypertension with milrinone during orthotopic liver transplantation. Clin Transplant. 2010;24:515–9.
227. Eichhorn EJ, Konstam MA, Weiland DS, Roberts DJ, Martin TT, Stransky NB, Salem DN. Differential effects of milrinone and dobutamine on right ventricular preload, afterload and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1987;60:1329–33.
228. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, Hutchins S, Leier CV, LeJemtel TH, Loh E, Nicklas J, Ogilby D, Singh BN, Smith W. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study investigators. Circulation. 2000;102:2222–7.
229. Russ MA, Prondzinsky R, Carter JM, Schlitt A, Ebelt H, Schmidt H, Lemm H, Heinroth K, Soeffker G, Winkler M, Werdan K, Buerke M. Right ventricular function in myocardial infarction complicated by cardiogenic shock: improvement with levosimendan. Crit Care Med. 2009;37:3017–23.
230. Poelzl G, Zwick RH, Grander W, Metzler B, Jonetzko P, Frick M, Ulmer H, Pachinger O, Roithinger FX. Safety and effectiveness of levosimendan in patients with predominant right heart failure. Herz. 2008;33:368–73.
231. Cicekcioglu F, Parlar AI, Ersoy O, Yay K, Hijazi A, Katircioglu SF. Levosimendan and severe pulmonary hypertension during open heart surgery. Gen Thorac Cardiovasc Surg. 2008;56:563–5.
232. Kleber FX, Bollmann T, Borst MM, Costard-Jackle A, Ewert R, Kivikko M, Petterson T, Pohjanjousi P, Sonntag S, Wikstrom G. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study. J Clin Pharmacol. 2009;49:109–15.
233. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, Naeije R, Brimioulle S. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. Crit Care Med. 2004;32:1035–40.
234. Hirsch LJ, Rooney MW, Wat SS, Kleinmann B, Mathru M. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. Chest. 1991;100:796–801.
235. Tourneux P, Rakza T, Bouissou A, Krim G, Storme L. Pulmonary circulatory effects of norepinephrine in newborn infants with persistent pulmonary hypertension. J Pediatr. 2008;153:345–9.
236. Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension*. Anaesthesia. 2002;57:9–14.
237. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. Circulation. 1981;63:87–95.
238. Tayama E, Ueda T, Shojima T, Akasu K, Oda T, Fukunaga S, Akashi H, Aoyagi S. Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. Interact Cardiovasc Thorac Surg. 2007;6:715–9.
239. Jeon Y, Ryu JH, Lim YJ, Kim CS, Bahk JH, Yoon SZ, Choi JY. Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients. Eur J Cardiothorac Surg. 2006;29:952–6.
240. Smith AM, Elliot CM, Kiely DG, Channer KS. The role of vasopressin in cardiorespiratory arrest and pulmonary hypertension. QJM. 2006;99:127–33.

241. Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877–87.
242. Walker BR, Haynes Jr J, Wang HL, Voelkel NF. Vasopressin-induced pulmonary vasodilation in rats. Am J Physiol. 1989;257:H415–22.
243. Eichinger MR, Walker BR. Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats. Am J Physiol. 1994;267:H2413–9.
244. Rich S, Lam W. Atrial septostomy as palliative therapy for refractory primary pulmonary hypertension. Am J Cardiol. 1983;51:1560–1.
245. Mullins CE, Nihill MR, Vick 3rd GW, Ludomirsky A, O'Laughlin MP, Bricker JT, Judd VE. Double balloon technique for dilation of valvular or vessel stenosis in congenital and acquired heart disease. J Am Coll Cardiol. 1987;10:107–14.
246. Hausknecht MJ, Sims RE, Nihill MR, Cashion WR. Successful palliation of primary pulmonary hypertension by atrial septostomy. Am J Cardiol. 1990;65:1045–6.
247. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation. 1995;91:2028–35.
248. Sandoval J, Gaspar J, Pulido T, Bautista E, Martinez-Guerra ML, Zeballos M, Palomar A, Gomez A. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol. 1998;32:297–304.
249. Barst RJ. Role of atrial septostomy in the treatment of pulmonary vascular disease. Thorax. 2000;55:95–6.
250. Labombarda F, Maragnes P, Dupont-Chauvet P, Serraf A. Potts anastomosis for children with idiopathic pulmonary hypertension. Pediatr Cardiol. 2009;30:1143–5.
251. Hoffman JI. Natural history of congenital heart disease. Problems in its assessment with special reference to ventricular septal defects. Circulation. 1968;37:97–125.
252. Hanley FL, Heinemann MK, Jonas RA, Mayer Jr JE, Cook NR, Wessel DL, Castaneda AR. Repair of truncus arteriosus in the neonate. J Thorac Cardiovasc Surg. 1993;105:1047–56.
253. Kolosionek E, Crosby A, Harhay MO, Morrell N, Butrous G. Pulmonary vascular disease associated with schistosomiasis. Expert Rev Anti Infect Ther. 2010;8:1467–73.
254. Cicalini S, Almodovar S, Grilli E, Flores S. Pulmonary hypertension and human immunodeficiency virus infection: epidemiology, pathogenesis, and clinical approach. Clin Microbiol Infect. 2011;17:25–33.
255. Bandara M, Gordon FD, Sarwar A, Knauft ME, Pomfret EA, Freeman RB, Wirth JA. Successful outcomes following living donor liver transplantation for portopulmonary hypertension. Liver Transpl. 2010;16:983–9.
256. Saleemi S. Portopulmonary hypertension. Ann Thorac Med. 2010;5:5–9.
257. Traynor AE, Corbridge TC, Eagan AE, Barr WG, Liu Q, Oyama Y, Burt RK. Prevalence and reversibility of pulmonary dysfunction in refractory systemic lupus: improvement correlates with disease remission following hematopoietic stem cell transplantation. Chest. 2005;127:1680–9.
258. Kamata Y, Nara H, Sato H, Masuyama JI, Minota S, Yoshio T. Effect of steroid pulse therapy on mixed connective tissue disease with pulmonary arterial hypertension. Ann Rheum Dis. 2005;64:1236–7.
259. Jouve P, Humbert M, Chauveheid MP, Jais X, Papo T. Poems syndrome-related pulmonary hypertension is steroid-responsive. Respir Med. 2007;101:353–5.
260. Benyounes B, Crestani B, Couvelard A, Vissuzaine C, Aubier M. Steroid-responsive pulmonary hypertension in a patient with Langerhans' cell granulomatosis (histiocytosis x). Chest. 1996;110:284–6.
261. Rodman DM, Lindenfeld J. Successful treatment of sarcoidosis-associated pulmonary hypertension with corticosteroids. Chest. 1990;97:500–2.
262. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018–31.
263. Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatr Clin North Am. 2009;56:579–600, Table of Contents.
264. Gozal D, Kheirandish-Gozal L, Serpero LD, Sans Capdevila O, Dayyat E. Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy. Circulation. 2007;116:2307–14.
265. Yilmaz MD, Onrat E, Altuntas A, Kaya D, Kahveci OK, Ozel O, Derekoy S, Celik A. The effects of tonsillectomy and adenoidectomy on pulmonary arterial pressure in children. Am J Otolaryngol. 2005;26:18–21.
266. Mucklow ES. Obstructive sleep apnoea causing severe pulmonary hypertension reversed by emergency tonsillectomy. Br J Clin Pract. 1989;43:260–3.
267. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation. 2007;115:1132–46.
268. Munhoz AS, Adde FV, Nakaie CM, Doria Filho U, Silva Filho LV, Rodrigues JC. Long-term home oxygen therapy in children and adolescents: analysis of clinical use and costs of a home care program. J Pediatr (Rio J). 2011;87(1):13–8.
269. Ohashi N, Matsushima M, Maeda M, Yamaki S. Advantages of oxygen inhalation therapy for postoperative pulmonary hypertension. Pediatr Cardiol. 2005;26:90–2.
270. Marvisi M, Zambrelli P, Brianti M, Civardi G, Lampugnani R, Delsignore R. Pulmonary hypertension is frequent in hyperthyroidism and normalizes after therapy. Eur J Intern Med. 2006;17:267–71.