REVIEW ARTICLE

Management of Pulmonary Hypertension: Physiological and Pharmacological Considerations for Anesthesiologists

Lars G. Fischer, MD, Hugo Van Aken, MD, PhD, FRCA, FANZCA, and Hartmut Bürkle, MD, PhD

Department of Anesthesiology and Intensive Care, Universitätsklinikum Münster, Münster, Germany

For decades the pulmonary circulation was not considered as important as the systemic ("greater") circulation. However, pulmonary hypertension can arise because of many diseases of the heart and lung. Therefore, increasing efforts in research have been undertaken leading to a profound increase in understanding pulmonary vascular physiology and pathophysiology. This review discusses basic physiology, clinical concepts, and treatment options for pulmonary hypertension and the related right ventricular heart failure focusing on secondary pulmonary hypertension in patients during anesthetic procedures.

Physiology of Pulmonary Circulation

The pulmonary vascular bed is a high-flow, low-pressure circulation system. Pulmonary vessels have less resistance in comparison to the systemic circulation under normal conditions because of higher compliance of pulmonary precapillary arterioles with a thinner media and less smooth muscle cells (SMCs) compared with the corresponding systemic arterioles. In addition, the cross-sectional area of the pulmonary vascular bed is large and highly distensible with recruitable vessels available to accommodate increase in flow resulting in low pressure and low resistance.

In contrast to the systemic arteries, pulmonary vessels constrict with hypoxia (Euler-Liljestrand reflex) and relax in the presence of hyperoxia. Furthermore, changes in cardiac output (CO), airway pressure, and gravity affect the pulmonary more than the systemic circulation. Increases in CO distend open vessels and recruit previously closed vessels. Therefore, the cross-sectional area of pulmonary circulation enlarges and results in a decrease in pulmonary vascular resistance (PVR). An increase in CO has very little effect on pulmonary arterial pressure (PAP) because of the recruitment and distension of pulmonary vessels. An increased PAP or left atrial pressure (LAP) may also distend and recruit pulmonary vessels. Clinically, this means that enhanced CO caused by the administration of inotropic drugs or enlarged blood volume will passively decrease PVR.

The contribution of intra- and extraalveolar vessels accounts for the unique U-shaped relationship between lung volume and PVR, which is minimal at functional residual capacity and increased at large and small lung volumes (Fig. 1). Clinically, this may be observed when hyperinflation of the lungs greatly increases PVR.

Gravity influences the distribution of blood flow in the pulmonary circulation. Blood flow as well as ventilation increases in the dependent areas of the lung. The relationship between alveolar and hydrostatic pressure implies important clinical consequences. Patients with unilateral lung disease should be positioned with the diseased side up as was already shown by Remolina et al. (1). Lying with the sick lung dependent resulted in the worst gas exchange and the lowest arterial oxygen pressure (1).

Application of high levels of positive end-expiratory pressure (PEEP) will narrow the capillaries in the well-ventilated lung areas and divert flow to less well-ventilated or nonventilated areas. Therefore, a decrease in Pao_2 is the consequence.

Constantly changing hemodynamics, mechanical forces, and hormonal environment influence the vascular endothelium and the underlying SMCs. Under normal circumstances, the interaction between endothelium and SMCs results in a low vascular resistance in the pulmonary circulation. An increasing number of molecules seem to be involved in these biochemical transductions: L-arginine-nitric oxide (NO)-cyclic-3'-5'guanosine monophosphate (cGMP) pathway seems to have a predominant role (2). Physiological agonists such as bradykinin and acetylcholine as well as mechanical stress derived from pulmonary blood flow can activate endothelial cells. This results in oxidation

LGF supported by Grant Fi-6-2-98-01 from Innovative Medizinische Forschung Münster, Germany.

Accepted for publication February 3, 2003.

Address correspondence and reprint requests to Lars G. Fischer, MD, Department of Anesthesiology and Intensive Care, Universitätsklinikum Münster, Münster, Germany. Address e-mail to fischer-l@anit.uni-muenster.de.

DOI: 10.1213/01.ANE.0000062523.67426.0B

0003-2999/03

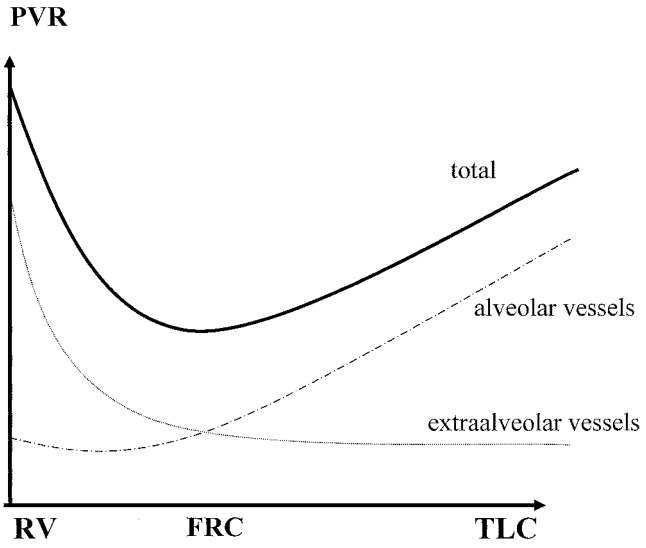

Figure 1. Relationship between lung volume and pulmonary vascular resistance (PVR) (123). RV = residual volume, FRC = functional residual capacity, TLC = total lung capacity.

of the guanidino-nitrogen atom of the amino acid L-arginine by the constitutive NO synthase to form and release NO. NO diffuses from endothelial cells to the SMCs, and produces relaxation by activating guanylate cyclase with increasing intracellular cGMP (2).

Pulmonary endothelial cells (surface area of 200 m^2 in the adult) have a very strategic location: they are exposed to the entire CO, link the pulmonary and systemic circulation, and also regulate SMC tone by signaling to the vascular wall. Endothelial cells both seem to sense local shear stress and to initiate a response (e.g., production of NO) in order to accommodate rapid changes of blood flow. NO and prostacyclin (PGI_2) support oxygenation and lung inflation in dilating the pulmonary vasculature after birth, keeping a key regulatory role in the lung because of its prompt, local powerful action compared with a brief half-life time (3).

Pathophysiology of Pulmonary Hypertension

It is now understood that the balance between vasoconstrictors and vasodilators and mitogenic and antimitogenic factors derived from the endothelium is disturbed in situations with an increase in PAP (4, 5).

Endothelial dysfunction is promoted by hypoxia, acidosis, free radicals (6), inflammatory mediators, shear stress caused by increased pulmonary blood flow from left-to-right intracardiac shunt (7), and fibrin from thromboembolism (8).

There is no widely accepted range for normal PAP. However, mean PAP >25 mm Hg (normal 15 mm Hg) at rest or >30 mm Hg with exercise is generally accepted as indicative for pulmonary hypertension (9). The enhanced pressure in the pulmonary circulation is associated with an increase in PVR and results in a progressive inability of the right ventricle (RV) to sustain its output leading to RV hypertrophy and RV failure depending from acute or chronic changes (4). In a study by Vizza et al. (10), prevalence of RV dysfunction (defined as RV ejection fraction [RVEF] <45%) was significantly higher in patients with pulmonary hypertension compared with all other groups with end-stage pulmonary disease.

Determination of PVR is difficult in clinical settings even if the respective variables such as LAP, mean PAP, pulmonary capillary wedge pressure (PCWP), and thermodilution CO are measured directly because of their intrinsic inaccuracies.

Therefore, indirect estimations use the equation:

$$PVR = [\text{mean PAP} - \text{LAP}/\text{pulmonary artery flow (CO)}]$$

Normal PVR is approximately 1.1–1. 4 Wood units or about 90–120 $\text{dynes} \cdot \text{s} \cdot \text{cm}^{-5}$, and a PVR >300 $\text{dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ is indicative of pulmonary hypertension. Pulmonary blood flow and volume are not always equal to or correlated with CO, because of intracardiac or other shunts.

Vascular Remodeling

Chronic pulmonary hypertension leads to structural alterations of the pulmonary vasculature and to a progression of histological changes known as "vascular remodeling" (11). Under physiological conditions, pulmonary arterioles are thin-walled vessels with the media occupying only 7% of the vessel thickness. The major finding in remodeled vessels caused by a chronic stimulus like hypoxia is the increase in SMCs in already muscularized arteries and extension of SMCs into vessels that are normally thin and nonmuscular (12) and thickening of the adventitial layer (13). Thickening of the adventitial layer is the result of marked proliferation of the fibroblasts, which has been shown to be modulated by protein kinase C and mitogen-activated protein kinase (14). After the proliferative response, there is an increase in adventitial connective tissue including a switch in SMC phenotype to a more synthetic cell that is responsible for deposition of increased connective tissue (12). This deposition of most notably collagen is probably a protective mechanism strengthening the vascular wall against the increase in intravascular pressure (15). Additionally, damage to intimal endothelium as well as intimal hyperplasia and fibrosis can be detected (5). The central regulatory function of the pulmonary endothelium is underlined by the fact that a dysfunctional endothelium can influence the development of pulmonary hypertension at the levels of coagulation control, vasomotor tone, and pulmonary vascular remodeling (16).

The major stimulus for remodeling is hypoxia (17). The increase in PVR is predominantly caused by the hypoxic pulmonary vasoconstriction (HPV), which resides primarily distal to lobar arteries and proximal to the capillaries and occurs in resistance arterioles 30–300 μm in diameter (18). Pulmonary arteriolar SMC oxygen-sensitive voltage-dependent potassium channels seem to have an important role for initiating HPV (19). Inhibition of these channels by decreased Po_2 inhibits outward potassium current, causing membrane depolarization and calcium entry through voltage-dependent calcium channels (19). The main determinant of HPV is alveolar Po_2, but mixed venous Po_2 contributes to approximately 20% of the response (19). HPV is inhibited by substances such as substance P, atrial natriuretic peptides, by mediators such as PGI_2 and NO, by increased LAP, by increased alveolar pressure, and by alkalosis. Enhanced HPV, however, could be observed with acidosis, by using epidural anesthesia and by inhibition of cyclooxygenase or NO synthase (19). Subsequent increases in PAP are predominantly caused by vascular remodeling as well as secondary polycythemia. Proliferation and differentiation of pericytes and intermediate cells to SMCs are a consequence of chronic exposure to hypoxia followed by elastin and collagen synthesis and deposition (20). In addition, vasomotor function may be altered in these remodeled vessels (20). Among the candidates of biochemical mediators of hypoxia-induced pulmonary hypertension are voltage-gated potassium channels, mitochondrial oxygen sensing, and an imbalance in vasoactive factors (see below) (21).

Remodeling also happens in inflammation secondary to sepsis (22) and in patients with chronic lung disease (23) and adult respiratory distress syndrome (ARDS) (24). The inflammation process and increased blood flow lead to vascular remodeling by damaging endothelial cells and disturbs the sensitive balance of pulmonary tone. Under physiological conditions, these cells eliminate factors that initiate SMC proliferation such as angiotensin II, endothelin, thromboxane A_2, prostaglandin H_2 and O_2^- (25). Alternatively, damaged endothelial cells may fail to produce inhibitory factors, possible heparin-like substances, which normally decrease SMC proliferation. Removal of the inciting stimulus can lead to reversal of structural changes.

Etiology of Pulmonary Hypertension

Pulmonary hypertension is caused by a variety of acute and chronic pulmonary diseases with an increase in PAP (Table 1). In contrast to secondary pulmonary hypertension, primary pulmonary hypertension (PPH) is not related to a known underlying disease.

Table 1. World Health Organization Diagnostic Classification of Pulmonary Hypertension (1998) (21)

- I. Pulmonary arterial hypertension
  - 1.1 Primary pulmonary hypertension
    - (a) Sporadic
    - (b) Familial
  - 1.2 Related to:
    - (a) Collagen vascular disease
    - (b) Congenital systemic-to-pulmonary shunts
    - (c) Portal hypertension
    - (d) Human immunodeficiency virus infection
    - (e) Drugs/toxins
      1. Anorexigens
      2. Other
    - (f) Persistent pulmonary hypertension of the newborn
    - (g) Other
- II. Pulmonary venous hypertension
  - 2.1 Left-sided atrial or ventricular heart disease
  - 2.2 Left-sided valvular heart disease
  - 2.3 Extrinsic compression of central pulmonary veins
    - (a) Fibrosing mediastinitis
    - (b) Adenopathy/tumors
  - 2.4 Pulmonary venoocclusive disease
  - 2.5 Other
- III. Pulmonary hypertension with disorders of the respiratory system and/or hypoxemia
  - 3.1 Chronic obstructive pulmonary disease
  - 3.2 Interstitial lung disease
  - 3.3 Sleep disordered breathing
  - 3.4 Alveolar hypoventilation disorders
  - 3.5 Chronic exposure to high altitude
  - 3.6 Neonatal lung disease
  - 3.7 Alveolar-capillary dysplasia
  - 3.8 Other
- IV. Pulmonary hypertension caused by chronic thrombotic and/or embolic disease
  - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
  - 4.2 Obstruction of distal pulmonary arteries
    - (a) Pulmonary embolism (thrombus, tumor, etc.)
    - (b) *In situ* thrombosis
    - (c) Sickle cell disease
- V. Pulmonary hypertension caused by disorders affecting the pulmonary vasculature directly
  - 5.1 Inflammatory
    - (a) Schistosomiasis
    - (b) Sarcoidosis
    - (c) Other
  - 5.2 Pulmonary capillary hemangiomatosis

PPH

PPH is rare (1–2 per million in the general population), affects more women than men (1.7:1), sometimes has a familial link (6% of all cases), and has a poor prognosis (median survival 2–3 yr after diagnosis). PAP usually is >60 mm Hg in these patients (9, 26). PPH is a diagnosis of exclusion, because it is idiopathic. Hypoxemia and increased PVR resulting in an increased PAP can lead to RV failure and death.

Altered vasoreactivity alone is not responsible for PPH. Vascular remodeling contributes to the vasculopathic process. However, regression of extensive changes caused by hypertension can occur.

Secondary Pulmonary Hypertension

Secondary pulmonary hypertension is more common, the increases in PAP are generally less severe (mean PAP <40 mm Hg) (26), and it is also more frequently seen in the perioperative period. Therefore, in this review, we have focused on secondary forms of pulmonary hypertension. Most cases of pulmonary hypertension are secondary to cardiac or pulmonary disease (Table 1) and may be reversible in some cases. Clinical manifestations might be overshadowed by the symptoms of the underlying disease (Table 2). Blood vessel changes are not confined to PPH but are also found in many forms of secondary pulmonary hypertension. Congenital cardiac disease with an atrial or ventricular septal defect causes an increase in pulmonary blood flow. Over time, in response to the increased blood flow, the PVR is increased and eventually will exceed systemic vascular resistance (SVR). Under these conditions, blood flow is shunted from right to left, often referred to as Eisenmenger syndrome. In contrast, high-pressure shunts such as those associated with truncus arteriosus, ventricular septal defects, or patent ductus arteriosus (28) cause pulmonary hypertension much earlier and it is often more severe.

The relevance of pulmonary hypertension in the perioperative period was shown in a study by Reich et al. (29). In patients undergoing coronary artery bypass grafting with cardiopulmonary bypass (CPB), the development of pulmonary hypertension was a significant predictor of increased mortality and perioperative myocardial infarction (29).

The severity of the observed vasoconstriction correlates with the extent of CPB-induced endothelial injury (30). Levels of thromboxane A_2 (31) and endothelin (32) were increased after CPB, whereas PGI_2 and NO levels were reduced (33). For a long time, it was thought that CPB did not cause any pulmonary endothelial injury due to ischemia-reperfusion because of the protection via the vasa vasorum of the bronchial circulation. It has been shown, however, that total CPB may cause complete cessation and reestablishment of pulmonary artery flow, with inadequate pulmonary endothelial blood supply by the vasa vasorum, resulting in an ischemia-reperfusion injury (34).

The intraoperative injury and postoperative endothelial dysfunction of the pulmonary endothelium is promoted by the following factors (2):

- **Preoperative status** of the pulmonary vascular bed, i.e., pulmonary hypertension, valvular pathology; chronic obstructive pulmonary disease, pulmonary thromboembolism, and shear stress caused by increases in pulmonary blood flow and pressure of left-right intracardiac shunt. Bando et al. (35) demonstrated in patients with congenital heart disease that preoperative pulmonary hypertension, absence of mixed venous saturation monitoring, and absence of prophylactic α-blockade significantly increased postoperative pulmonary hypertension.
- **Intraoperative** vasospastic stimuli, such as hypoxia, hypercarbia, acidosis, duration of total CPB, ischemia-reperfusion injury, free radical formation, inflammatory mediators, pulmonary leukosequestration, excess thromboxane or endothelin production, and microemboli.
- **Postoperative factors** such as adrenergic tone, atelectasis, and HPV.

Other examples of pulmonary hypertension during anesthesia are shown in Table 3.

Symptoms and Diagnosis of Pulmonary Hypertension

The most common clinical signs of pulmonary hypertension are dyspnea and fatigue (9) (see also Table 2). These major symptoms might be explained through the associated decrease in CO; however, an exact etiology is still missing.

On physical examination, a prominent P_2 heart sound, a tricuspid regurgitation murmur, an atrial (S_3), or ventricular (S_4) heart sound might be heard. The chest radiograph can display an enlarged main pulmonary artery and enlarged hilar vessels, whereas the electrocardiogram shows a right axis deviation suggesting right ventricular hypertrophy. However, the validity of acute changes in the electrocardiogram attributed to right heart insufficiency in the intraoperative period is limited. Transesophageal echocardiography (TEE) as a more advanced technique diagnoses pulmonary hypertension indirectly attributed to RV enlargement, paradoxical interatrial and interventricular movement, partial systolic closure of pulmonary valve, tricuspid regurgitation, and an increased RV systolic pressure (Fig. 2). There are two approaches to obtaining hemodynamic measurements using TEE. By using spatial imaging methods, cardiac chamber volumes can be estimated to obtain both preload and stroke volume. In addition, Doppler-based methods can be used to estimate both right ventricular filling and CO (37). Because of the inherent difficulty in developing a simple geometric model of the RV, regression equations may inaccurately predict ventricular volumes. In addition, TEE measurements are further altered by changing loading conditions, which alter both the size and geometry of the RV. Although

Table 2. Common Symptoms and Signs of Pulmonary Hypertension (27)

• Dyspnea	• Normal to low blood pressure (occasionally high)
• Fatigue	• Jugular venous distension with prominent A and V waves
• Leg swelling	• Lung findings (dependent and parenchymal involvement)
• Weakness	• Right ventricular lift
• Palpitations	• Right ventricular fourth and/or third heart sound
• Abdominal fullness	• Pulmonic ejection click
• Angina	• Ascites
• Syncope and presyncope	• Peripheral edema
• Cyanosis	• Hepatomegalia (often pulsatile)

Table 3. Occurrence of Pulmonary Hypertension During Anesthesia (36)

• Thromboembolism	Thrombectomy of deep veins, pregnancy, childbirth
• CO_2 embolism	Laparoscopy
• Air embolism	Surgery with patient in sitting position (e.g., neurosurgery)
• Bone cement (Pallacos©)	Orthopedics
• Protamine	Cardiac surgery
• Extracorporeal circulation	Cardiac surgery
• Ischemia-reperfusion syndrome	Clamping/declamping of the aorta (e.g., liver transplantation)
• Loss of lung vessels	Pneumectomy

TEE evaluation of RV volume can be difficult to determine in adults, high-quality images are routinely obtained in pediatric patients. One of the main limitations on further use of TEE is the availability of equipment as well as costs of echocardiography machines and probes, and expertise (37). The definitive diagnosis is obtained by right heart catheterization with direct measurement of PAP, right atrial pressure (RAP), PCWP, and CO.

RV and Pulmonary Hypertension

Like the pulmonary circulation, the RV was not considered as important as the left ventricle (LV) in maintaining normal hemodynamics and counted for a long time as a "quantite negliable" (38). Today it is recognized that RV and LV are interdependent and both have vitally important functions. The RV is a thin-walled, highly compliant, but poorly contractile chamber. Under normal loading conditions and when function is not compromised, RV ejects blood against 25% of the afterload of the LV, resulting in a smaller RV wall thickness (39).

The RV is bound by the RV free wall and the interventricular septum. Failure of the septum (e.g., because of ischemia) to contract normally will decrease RV systolic function. Blood supply for the RV and the septum depends mostly on whether a right or left dominant, or a "balanced" coronary circulation is present. Usually the right and the left anterior descending coronary artery supply the septum and parts of the free wall of the RV. The continuous pressure gradient between the aorta and the RV (coronary perfusion pressure) is responsible for the coronary blood flow to the RV free wall throughout systole and diastole (40). Therefore, the RV blood/oxygen supply is

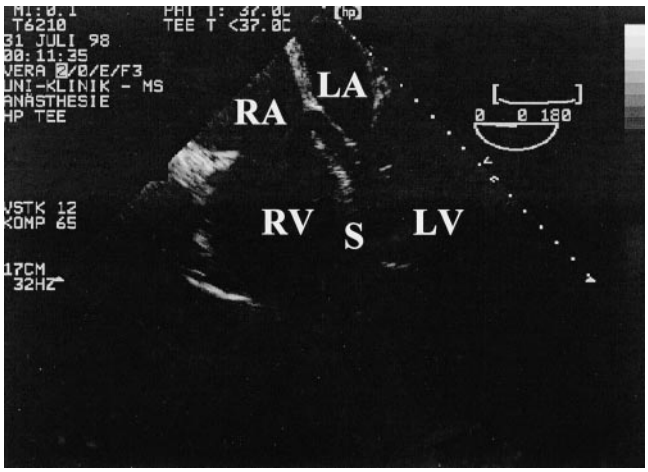

Figure 2. Transesophageal echocardiography for diagnosis of pulmonary hypertension. Dilated right ventricle (RV) in the midesophageal four chamber view. The figure shows the classical septal (S) interventricular shift to the left side. RA = right atrium, LA = left atrium, LV = left ventricle.

proportional to the systemic pressure but inversely proportional to the RV pressure. Systemic hypotension or increased RV pressure results in a decreased RV coronary perfusion pressure (41). Vlahakes et al. (42) previously showed that right heart performance is directly related to systemic pressure during pulmonary hypertension. RV function is very sensitive to increased RV preload or afterload, septic shock, coexistent LV dysfunction, or right coronary artery occlusive disease (43, 44). In a fundamental study, Urabe et al. (45) demonstrated that an increase in the afterload of the RV resulted in a rightward shift of the relationship between perfusion pressure and regional shortening. Also, end-diastolic segment lengths increased significantly after banding of the pulmonary artery. In

contrast to LV performance, RV function is relatively sensitive to increases in afterload. Acute increase in mean PAP above approximately 40 mm Hg results in a significant decrease in RVEF even in the presence of a normal RV contractility. However, gradual increases in afterload are well tolerated, because the RV has time to assemble new sarcomeres in parallel to increase wall thickness (39).

In the presence of decreased RV contractility, the RV is even more susceptible to acute increases in afterload. The decrease in RVEF results from a disproportionate increase in end-systolic volume compared with end-diastolic volume (41).

The RV is less preload-responsive than the LV such that a given increase in preload results in a smaller increase in stroke work. Therefore, attempts at volume loading may be less effective in increasing RV output compared with volume loading of the LV. In addition, volume loading may even worsen the ratio of RV oxygen demand/supply (41).

Vlahakes (46) concluded that two important principles emerged in the management of right heart failure: First, RV afterload must be reduced and second, systemic pressure must be maintained or increased.

Normal atrioventricular conduction and contraction are essential for maintaining normal RV function (47). The maintenance of sinoatrial activity is as important for RV efficiency as it is for LV efficiency (47). RV pump performance is determined by both intrinsic factors (contractile state of the RV myocardium) as well as extrinsic factors (preload, afterload, constraining effects of the pericardium, intrapericardiac pressure, right coronary artery perfusion pressure, LV performance, and the contractile state of the interventricular septum) (48).

All abnormalities of the LV function like coronary artery disease, congestive heart failure, valvular heart disease, or systemic hypertension influence RV function by ventricular interdependence. Also, a dilated RV and right atrium can shift the interatrial and interventricular septum and compress the left atrium and reduce LV end-diastolic volume.

Central venous pressure does not provide accurate information on RV transmural filling pressure and volume because it is dependent on the compliance of the RV and/or abnormalities in the tricuspid valve apparatus. Angiography, echocardiography, radionuclide methods, thermodilution, and magnetic resonance imaging are better and more reliable modalities in measuring the RV performance.

RV dysfunction caused by increased PAP was demonstrated in patients with chronic obstructed pulmonary disease (COPD) (49), ARDS (50), and in patients receiving protamine infusion (51, 52). Mechanical ventilation can also impair RV performance. PEEP (30 cm H_2O) shifts the interventricular septum producing paradoxical motion, resulting in right heart dilation and decreased LV chamber size (53). In postoperative ventilated patients, a decrease in RVEF is observed at PEEP levels >15 cm H_2O because of compression of alveolar vessels and accompanying increase in RV afterload (54). A significant inverse correlation was noted between RVEF and increasing amounts of airway pressure delivered by high-frequency jet ventilation (55).

Treatment

Treatment of the underlying disease has priority. Because symptoms often arise late in pulmonary hypertension, the average life expectancy after occurrence of signs of manifest RV insufficiency is <1 yr (56).

Basic Considerations

Antiobstructive therapy in COPD, corticoids for interstitial lung disease, as well as systemic anticoagulation for chronic lung embolism are fundamentals of therapy of pulmonary hypertension. Elimination of ventilation/perfusion mismatch, which causes dystelectasis and atelectasis and antibiotic therapy for pneumonia can also improve symptoms. Early definitive repair of congenital heart diseases can reduce morbidity and mortality from postoperative pulmonary hypertension (35).

A common clinical problem is the decompensation of the right heart because of chronic left heart insufficiency. In this situation, therapy of the LV has priority. Infarction of the right heart needs immediate revascularization by means of thrombolysis, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting.

Symptomatic Therapy

Symptomatic therapy supports causal treatment and should reduce PVR, which can be achieved with the following active and passive factors influencing the pulmonary circulation:

- Improving oxygenation with 100% oxygen
- Avoidance of respiratory acidosis, moderate hyperventilation ($Paco_2$ 30–35 mm Hg)
- Correction of a metabolic acidosis (aim: pH >7.4)
- Recruitment maneuvers, to avoid ventilation/perfusion mismatch
- Adaptation of respiratory therapy, avoiding overinflation of the lung alveolae
- Avoidance of catecholamine release caused by stress situations: adequate analgesia and sedation
- Avoidance of shivering: body temperature 37°C

Specific Treatment

Treatment options for RV dysfunction with increased PVR include vasodilative drugs, whereas positive inotropic drugs are the treatment of choice in RV dysfunction with normal PVR.

Optimization of RV Preload. Optimization of RV preload should be considered if central venous pressure is <10 mm Hg (57). It is recommended, however, that preload of the RV should be estimated by a simple "endogenous volume loading" test (i.e., raising patients' legs) in every single patient. "Responders" show an increase in mean arterial blood pressure (MAP) and can increase RVEF with volume therapy, if RV contractility is normal and PAP is increased only slightly (57).

However, administration of volume also can have deleterious effects in patients with hemodynamically relevant right heart infarction. Routine treatment in our institution includes diuretics for "nonresponders" (defined as patients showing no increase in MAP to the above-mentioned "volume loading" test) who present with central venous pressure <20 mm Hg.

Reduction of RV Afterload. Reduction of the cross-section of the pulmonary circulation of >60%–70% decreases CO and induces RV failure (58). As previously mentioned, baseline support, IV or inhaled vasodilators should be used, keeping in mind to avoid a significant decrease in SVR. If the decrease in SVR exceeds the improvement in RV stroke volume, greater systemic hypotension can be the consequence.

Magnesium is thought to produce vasodilation by blocking calcium channels (59). Magnesium has other beneficial properties such as the ability to enhance NO synthase activity, activate adenylate cyclase, and release PGI_2 (59).

Adenosine stimulates purine receptors in both endothelial and SMCs. Relaxation of SMCs is mediated by both release of NO and direct stimulation of SMCs (60). Adenosine has a short half-life (9 s), therefore it is relatively selective for the pulmonary circulation. It has been shown to be a potent vasodilator and predictive of other drugs to produce pulmonary vasodilation in studies of patients with PPH (61, 62). Ventilation/perfusion mismatching remains a problem, but there are no arrhythmias observed because of the small dosing schedule (50–200 μg/kg body weight/min).

Angiotensin-converting enzyme inhibitors: In contrast to long-term treatment (3–6 mo) with oral captopril that led to reduced PAP and PVR in patients with secondary pulmonary hypertension (63), short-term treatment did not show any improvement (64). This difference might be explained by the fact that angiotensin-converting enzyme inhibitors depend on their ability to reduce vascular remodeling (65).

The angiotensin receptor antagonist losartan successfully reduced PAP and PVR in patients with secondary pulmonary hypertension 4 h after application (66).

Calcium antagonists have been shown to be effective in the treatment of pulmonary hypertension secondary to connective tissue vascular disease (67), but not in patients with COPD (68), where treatment was limited because of the deleterious effects on venous admixture (69). The effectiveness of therapy with calcium antagonists in secondary pulmonary hypertension seems to depend on the initial level of PAP, i.e., the higher the initial level of PAP, the less effective the drug (67, 68). A metaanalysis of eight long-term trials (70) to investigate the effectiveness of nifedipine on reducing PAP in patients with pulmonary hypertensive disorders showed that a reduction in PAP occurred in seven of eight trials. The largest reduction in PAP occurred in patients treated with the largest dosages and the reduction in PAP corresponded with subjective clinical improvement.

Although these drugs have clearly shown their efficacy, they have severe adverse outcomes if used improperly; therefore, it is recommended that initial calcium antagonist treatment should be limited to specialized centers to avoid complications (71). Patients with pulmonary hypertension and severe clinical right heart failure (mean RAP >20 mm Hg, CO <2 L/min) should be excluded from treatment with calcium antagonists because of the negative inotropic effects of these drugs.

Milrinone/amrinone (phosphodiesterase [PDE] inhibitors) act by inhibiting one or more enzymes responsible for the breakdown of cyclic 3'-5'-adenosine monophosphate (cAMP)/cGMP leading to an increased amount of these cyclic nucleotides with increased LV contractility and pulmonary vasodilation. Both PDE inhibitors, given IV, have been used successfully in patients with pulmonary hypertension after cardiac surgery (72). Inhaled aerosolized milrinone was shown for cardiac surgical patients with increased PVR to induce selective pulmonary vasodilation without systemic effects. It also seems to have an additive pulmonary vasodilatory effect to inhaled PGI_2 (73).

PGI_2: The potent vasodilator PGI_2 was first reported in 1980 to reduce PAP in PPH (74). It is produced mainly by the vascular endothelium and acts via specific prostaglandin receptors linked to adenylate cyclase with following increase of cAMP. PGI_2 production is impaired in patients with pulmonary hypertension (75), so therapeutical addition of PGI_2 may act in part to replace these deficiencies. Additional beneficial effects are an inhibition of both platelet aggregation and SMC proliferation (76). Apart from treatment of PPH, PGI_2 or its stable analog iloprost also decreases PAP in persistent pulmonary hypertension of the newborn (77), pulmonary hypertension after heart surgery in infants (78), ARDS (79), or pulmonary hypertension secondary to connective tissue diseases in adults (80). However, PGI_2 treatment in patients with pulmonary hypertension secondary to COPD was not successful because it was associated with a significant decrease in Pao_2 but no increase in

systemic oxygen transport (81). PGI_2 has to be administered IV continuously because of its short half-life (2–3 min) in the circulation. It is not selective for the pulmonary circulation, hence adverse effects are hypotension, flushing warmth, and headaches (82). Another disadvantage is the cost of the drug (83).

Similar therapeutic effects of PGI_2/iloprost can be achieved by inhalation in aerosol form or by administering an oral analog without losing the potency to decrease PAP and PVR in PPH and secondary pulmonary hypertension (84). PGI_2 exerts no toxic effects and several investigators have reported selective vasodilation by inhaled PGI_2 in patients with pulmonary hypertension of various etiologies (83–86). Beraprost, an orally active PGI_2 analog and a second alternative to IV PGI_2, has a half-life of 1 h and therefore must be given several times a day (86).

Alprostadil (PGE_1) is a product of the arachidonic acid metabolism and causes vasodilation by increasing intracellular cAMP. It has been shown to reduce PVR and improve arterial oxygenation in patients with ARDS (87): Reversibility of pulmonary hypertension was studied in patients with congestive heart failure and severe pulmonary hypertension. In another study in patients undergoing cardiac transplantation, PGE_1 was the only drug that significantly decreased transpulmonary pressure gradient (mean PAP − mean PCWP) and showed the largest decline of PVR compared with nitroglycerin, nitroprusside, dobutamine, and enoximone. The authors concluded that PGE_1 may be more efficient than the other studied drugs for acute reversal of pulmonary hypertension in congestive heart failure (88).

To summarize, all IV administered pulmonary vasodilators more or less lack pulmonary selectivity. Consequences are a concomitantly decreased SVR and a decline in RV coronary perfusion. An assessment of the efficacy of pulmonary vasodilators is calculation of the PVR/SVR ratio.

Inhaled NO (INO): This therapy was first administered to patients with pulmonary hypertension in 1991 (89). INO has been shown to decrease PVR in pulmonary hypertension secondary to COPD (90), congenital heart disease (91), ARDS (92), and after the use of CPB during open heart surgery after protamine infusion. NO is an endothelium-derived vasodilator, which contributes to the low pulmonary vascular tone under physiological conditions (93). The endothelial NO pathway, like PGI_2, is impaired in various types of pulmonary hypertension (94). It causes relaxation of vascular SMCs by activating guanylate cyclase and increasing intracellular cGMP. Comparable to PGI_2, pulmonary selectivity is achieved by virtue of the application way (i.e., inhalation) and the physicochemical properties, such as high lipid solubility and fast binding (and therefore inactivation) by oxyhemoglobin. Administration by inhalation also has the advantage of increasing Pao_2 because it selectively reaches well-ventilated regions of the lung.

The therapeutic benefit of NO in adults is less clear than in infants. Studies showed that only 50% of patients improved oxygenation and/or decreased PVR. Patients with septic shock and ARDS were less likely to respond (95); the greatest benefit was seen in ARDS patients with most severe hypoxemia (96). Additionally, prospective studies failed to demonstrate a reduction in mortality in ARDS patients because of treatment with INO (97). In patients with COPD, INO only improved Pao_2 during exercise (98).

Perioperative INO is valuable in circumstances when PVR is increased, for example, during the use of the CPB, when endothelial damage takes place (94). INO is useful in children undergoing corrective cardiac surgery for congenital cardiac defects (99) as well as in adults undergoing lung or heart/lung transplantation (100). In these situations, INO can reduce PAP (101) and improve oxygenation (102) until abnormalities are corrected.

Potential problems with the administration of NO are an increased bleeding time (103) caused by the inhibition of platelet aggregation and adhesion, negative inotropic effects, and the formation of potentially toxic products (i.e., peroxynitrite, nitrogen dioxide, and methemoglobin) (104). Therefore, INO requires specialized delivery systems and monitoring (73). Methemoglobinemia should be considered very carefully in near-term and preterm infants because of their reduced activity of methemoglobin reductase.

A recent study from Nagaya et al. (105) suggested that oral supplementation of L-arginine, the precursor of NO, may have beneficial effects on hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. Supplemental L-arginine produced a 9% decrease in mean PAP and a 16% decrease in PVR but only a slightly decreased mean systemic arterial pressure (−5%).

Enhancement of Right-Coronary Perfusion Pressure. During experimentally induced acute RV failure, increasing aortic pressure succeeded in improving systolic RV pressure and decreasing diastolic RV pressure (42). Vlahakes et al. (42) emphasize the importance of the coronary perfusion pressure in their study. Vasoconstrictors seem to be superior to volume and/or inotropic drugs in the clinical settings of RV failure and cardiogenic shock (106). Norepinephrine is the vasoconstrictor of choice, because the ratio of its vasoconstrictive α-mimetic effects to the β-adrenergic component is well balanced. However, the indication for norepinephrine is critically dependent on a marked decrease of the systemic blood pressure and respectively coronary perfusion pressure. Otherwise,

the increase in PAP caused by the vasoconstrictive drug worsens the situation even more.

Catecholamines: Enoximone and a combination of dobutamine and nitroglycerine was evaluated in patients with mitral valve regurgitation and pulmonary venous hypertension (107). Both regimens had comparable effects for the mean systemic arterial pressure and heart rate, but enoximone was more effective in reducing mean PAP.

Norepinephrine was useful in the treatment of RV failure after acute pulmonary hypertension (107): Cardiac index increased accompanied by the reduction of pulmonary pressure and the increase of the systemic pressure (108). In patients with chronic pulmonary hypertension, either phenylephrine or norepinephrine was used for treatment of systemic hypotension during the induction of anesthesia (109). In contrast to phenylephrine, norepinephrine decreased the ratio of PAP to systemic blood pressure without a change in cardiac index. Norepinephrine was recommended for the treatment of hypotension in patients with chronic pulmonary hypertension (109).

Improvement of RV Contractility. Dependent from the limitation of RV contractility, dobutamine can be recommended in slight contractility limitations (110). Epinephrine is the drug of choice in situations with severe contractility disorders (111). In patients with shock and serious systemic hypotension, norepinephrine is the preferred catecholamine, as mentioned above.

An increased PVR in association with the contractility limitations is the indication for PDE-III inhibitors (112). They can be added to catecholamine therapy to optimize efficiency because of their different pharmacological mode of action.

Assist Devices. The routine use of NO has reduced the incidence of RV failure requiring right-sided circulatory support. The decision regarding implantation of an RV assist device remains difficult (57). In the operation room, a careful review of all hemodynamic variables after maximal inotropic and vasodilator support starts after several unsuccessful attempts to separate the patient from CPB. This assessment includes a review of RV and LV function and size by TEE, status of mediastinal bleeding, oxygenation, presence of arrhythmias, and urinary output. With the observation of a small hyperdynamic LV, a dilated RV, marginal urinary output, atrial or ventricular arrhythmias, or coagulopathy, insertion of an RV assist device should be taken into consideration (57).

Respiratory Management of Increased PVR. Hyperventilation ($Paco_2$ <30 mm Hg) accompanied by an increase in pH (>7.6) decreases PVR and leads subsequently to an improved oxygenation (113). In this instance, reduction in H^+ rather than in $Paco_2$ is the most important factor. There is no evidence that $Paco_2$ has any direct effect on the pulmonary microvasculature (114). In contrast to the situation before CPB, only slight decreases in PVR caused by increasing fraction of inspired oxygen could be observed after CPB.

In patients with obstructive sleep apnea, continuous positive airway pressure treatment decreased daytime PAP and PVR (115).

In the operation room as well as in the intensive care unit, the implications of treating pulmonary hypertension must be carefully evaluated. The treatment can cause physiological changes that have major impact on systemic hemodynamic status and gas exchange. Reduction of PAP causes a decrease in CO. With lung disease primarily localized in the dependent zones, there is a decreased blood flow to the well-ventilated upper zones but no change in the flow to the diseased lung. The proportion of blood flowing through the hypoxic areas of the lung will increase and results in a decrease in Pao_2. Also, PEEP can narrow the capillaries in the well-ventilated areas and may distribute flow to less-ventilated areas with a possible decrease in Pao_2, and increase in PVR.

Despite all progress in knowledge and understanding of the pathophysiology of pulmonary hypertension, anesthetic management is still a clinical challenge in these patients. Normal physiological changes during anesthesia and surgery can lead to acute increases in PVR and RV failure. Risks associated with PPH are more frequent than those related to secondary pulmonary hypertension (116).

Patients with pulmonary hypertension should be evaluated for vasodilator responsiveness when they are candidates for heart transplantation (117) or major noncardiac surgery (118). However, there are no generally accepted criteria for a beneficial response. The pulmonary circulation exhibits spontaneous variability in PAP and PVR without drug intervention (119). Optimally, reductions in PAP or increases in CO are observed with constant systemic pressure. None of the mentioned therapeutical options is ideal. Therefore, choice of anesthetic medication should be governed primarily by individual and institutional preferences.

Factors that increase PVR can also extend into the postoperative period. Hypoxemia, acidosis, hypercapnia, hypothermia, and increased sympathetic stimulation can worsen pulmonary hypertension as described previously.

Influence of Various Anesthetic Drugs on Pulmonary Vascular Tone and Right Heart Function in Humans

Anesthetic management cannot change the component of PVR increases related to structure, but they can

produce changes in PVR, RV afterload, and potentially, intracardiac shunting. Many anesthetics and techniques have both direct and indirect effects on the PVR through alterations of CO and pulmonary blood flow. With fixed PVR, an increase in CO leads to increases in PAP. Conversely, increases in PVR attenuate RV output to consequently also reduce pulmonary blood flow and LV output.

In the following, only studies performed in humans are cited.

IV Anesthetics

Hammaren and Hynynen (120) studied hemodynamic effects of propofol for sedation after CPB. After an initial loading dose of propofol (0.5 mg/kg) followed by a continuous infusion of propofol (20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for 55 min, mean PAP, PVR, as well as MAP decreased significantly compared with control.

During one-lung ventilation (OLV) in patients undergoing esophageal surgery, anesthesia with propofol was associated with a higher Pao_2 and lower shunt fraction values compared with anesthesia with isoflurane and sevoflurane (121). The impact of propofol on RV function is controversial. Boyd et al. (122) showed improved RV performance compared with isoflurane in a cross-over study, whereas Kellow et al. (123) verified a reduced mean cardiac index and RVEF in patients during OLV compared with isoflurane. However, propofol was not associated with a significant increase in shunt fraction during OLV, in contrast to isoflurane, where shunt fraction increased threefold (123).

A comparison between thoracic epidural anesthesia (TEA) combined with inhaled anesthetics (isoflurane) and total IV anesthesia (propofol and fentanyl) in patients undergoing elective lung surgery showed that the TEA regimen did not impair arterial oxygenation to the same extent as total IV anesthesia (124). Fentanyl and sufentanil have no appreciable influence on pulmonary tone (125). Hachenberg et al. (126) showed, in accordance to Von Dossow et al. (124), that TEA did not influence development of shunt before and after induction of general anesthesia.

OLV with ketamine resulted in a more stable Pao_2 and pulmonary shunt when compared with volatile anesthetics (127, 128). Ketamine increased PVR in adults during spontaneous respiration (129). In spontaneously breathing and normocarbic infants, PVR index was little changed by ketamine administration during spontaneous breathing with either normal or increased baseline PVR index (130). Thiopental (10 mg/kg) decreases PVR (125).

In summary, IV anesthetics have minimal effects on HPV, pulmonary vascular tone, and oxygenation as demonstrated during OLV.

Volatile Anesthetics

In patients, 1–1.2 MAC levels of isoflurane did not affect HPV and Pao_2, when one lung was ventilated with an hypoxic air mixture (fraction of inspired oxygen 8%) compared with ventilation with 100% O_2 (131). Halothane decreased pulmonary blood flow and left PVR unchanged (125, 132).

During OLV, Pao_2 under anesthesia with 1 MAC isoflurane was higher than with enflurane (133). In patients with pulmonary emphysema, arterial oxygenation was not affected by small isoflurane concentrations (0.5%–2%) during OLV (134).

In patients undergoing intracranial aneurysm clipping, PVR was significantly less in the enflurane group compared with a barbiturate group (135). In burned patients, induction with both enflurane and isoflurane decreased cardiac index and PAP to the same extent, whereas PVR did not change (136).

In a comparative study in humans between desflurane and isoflurane before OLV, Pagel et al. (137) demonstrated for desflurane a significantly increased PAP and PVR with unchanged SVR. Isoflurane increased PAP but did not alter PVR and CO.

In healthy volunteers, sevoflurane caused a larger decrease in mean PAP compared with isoflurane with similar myocardial depression (138). Inada et al. (139) found an increase in PAP, PCWP, and cardiac index after surgical incision in patients anesthestized with sevoflurane or isoflurane.

After CPB for valve surgery, nitrous oxide (FiN_2O 50%) increased PVR and RAP (140). If CO was maintained in the presence of the anesthetic (e.g., N_2O), HPV seems to be attenuated *in vivo* (141). In patients with pulmonary hypertension before elective mitral valve replacement, N_2O (FiN_2O 50%) increased PVR. However, this increase was not associated with alterations in other hemodynamic variables. Therefore, the authors did not discourage from using N_2O in these patients. Interestingly, in children, even in the presence of pulmonary hypertension, PVR was not increased when N_2O was used (142). The preoperative degree of PVR is of more importance for the pulmonary vascular response to N_2O than the influence of background anesthesia (143).

The specific anesthetic procedure seems relatively unimportant in that various anesthetics and techniques have been used with success in patients with pulmonary hypertension. Also isoflurane, recommended for anesthesia in patients with pulmonary hypertension (144), may have significant negative inotropic effects impairing RV function when given at clinical concentrations (145). Most anesthetics have little effects on the pulmonary circulation with the exception of ketamine and N_2O.

Summary

Endothelial dysfunction and vascular remodeling are two important processes explaining the development of pulmonary hypertension. Therapeutic management of pulmonary hypertension has progressed rapidly in the last years. However, there is still no ideal treatment for this disease. Strategies for the future could include improved methods of administering current drugs, combination of current available drugs, new drug groups, and the possibility for gene therapy. The influence of the RV on cardiorespiratory stability under this circumstance was emphasized in this article. Different treatment options were presented and discussed.

We are grateful to Dr. C. Schmidt for providing excellent transesophageal echocardiographical pictures. We thank Prof. G. F. Rich for helpful discussions.

References

1. Remolina C, Khan AU, Santiago TV, Edelman NH. Positional hypoxemia in unilateral lung disease. N Engl J Med 1981;304:523–5.
2. Riedel B. The pathophysiology and management of perioperative pulmonary hypertension with specific emphasis on the period following cardiac surgery. Int Anesthesiol Clin 1999;37:55–79.
3. Kinsella JP, Abman SH. Physiological and therapeutic roles of nitric oxide in the transitional pulmonary circulation. In: Weir EK, Archer SL, Reeves JT, eds. Nitric oxide and radicals in the pulmonary vasculature. Armonk, NY: Futura Publishing, 1996:447–62.
4. Wanstall JC, Jeffery TK. Recognition and management of pulmonary hypertension. Drugs 1998;56:989–1007.
5. Loscalzo J. Endothelial dysfunction in pulmonary hypertension. N Engl J Med 1992;327:117–9.
6. Marczin N, Ryan US, Catravas JD. Effects of oxidant stress on endothelium-derived relaxing factor-induced and nitrovasodilator-induced cGMP accumulation in vascular cells in culture. Circ Res 1992;70:326–40.
7. Haworth SG. Pulmonary vascular disease in different types of congenital heart disease. Implications for interpretation of lung biopsy findings in early childhood. Br Heart J 1984;52:557–71.
8. Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection, and therapeutic implications. Am Heart J 1995;130:1276–82.
9. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987;107:216–23.
10. Vizza CD, Lynch JP, Ochoa LL, et al. Right and left ventricular dysfunction in patients with severe pulmonary disease. Chest 1998;113:576–83.
11. Stenmark KR, Mecham RP. Cellular and molecular mechanisms of pulmonary vascular remodeling. Ann Rev Physiol 1997;59:89–144.
12. Meyrick B. The pathology of pulmonary artery hypertension. Clin Chest Med 2001;22:393–404.
13. Grover RF, Wagner WW, McMurtry IF, Reeves JT. Pulmonary circulation. In: Shepherd JT, Abboud FM, eds. Handbook of physiology. Vol. 3. Bethesda, MD: American Physiological Society, 1983:103–36.
14. Das M, Dempsey EC, Bouchey D, et al. Chronic hypoxia induces exaggerated growth responses in pulmonary artery adventitial fibroblasts: potential contribution of specific protein kinase C isozymes. Am J Respir Cell Mol Biol 2000;22:15–25.
15. Tozzi CA, Christiansen DL, Poiani GJ, Riley DJ. Excess collagen in hypertensive pulmonary arteries decreases vascular distensibility. Am J Respir Crit Care Med 1994;149:1317–26.
16. Tuder RM, Cool CD, Yeager M, et al. The pathobiology of pulmonary hypertension: endothelium. Clin Chest Med 2001;22:405–18.
17. Herget J, Wilhelm J, Novotna J, et al. A possible role of the oxidant tissue injury in the development of hypoxic pulmonary hypertension. Physiol Res 2000;49:493–501.
18. Dumas JP, Bardou M, Goirand F, Dumas M. Hypoxic pulmonary vasoconstriction. Gen Pharmacol 1999;33:289–97.
19. Naeije R, Brimioulle S. Physiology in medicine: importance of hypoxic pulmonary vasoconstriction in maintaining arterial oxygenation during acute respiratory failure. Crit Care 2002;5:67–71.
20. Rabinovitch M. Investigational approaches to pulmonary hypertension. Toxicol Pathol 1991;19:458–69.
21. Strange JW, Wharton J, Phillips PG, Wilkins MR. Recent insights into the pathogenesis and therapeutics of pulmonary hypertension. Clin Sci (Lond) 2002;102:253–68.
22. Jones R, Kirton OC. Lung microvessel injury from peritoneal abscesses and Gram-negative bacteremia. Microvasc Res 1996;52:84–100.
23. Weitzenblum E, Kessler R, Oswald M, Fraisse P. Medical treatment of pulmonary hypertension in chronic lung disease. Eur Respir J 1994;7:148–52.
24. Snow RL, Davies P, Pontoppidan H, et al. Pulmonary vascular remodeling in adult respiratory distress syndrome. Am Rev Respir Dis 1982;126:887–92.
25. Gossage JR, Christman BW. Mediators of acute and chronic pulmonary hypertension (part 1). Sem Respir Crit Care Med 1994;15:190–8.
26. Salvaterra CG, Rubin LJ. Investigation and management of pulmonary hypertension in chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;148:1414–7.
27. Ricciardi MJ, Rubenfire M. How to manage primary pulmonary hypertension: giving hope to patients with a life-threatening illness. Postgrad Med 1999;105:45–8.
28. Ricciardi MJ, Rubenfire M. How to manage secondary pulmonary hypertension. Postgrad Med 1999;105:183–90.
29. Reich DL, Bodian CA, Krol M, et al. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg 1999;89:814–22.
30. Koul B, Wollmer P, Willen H, et al. Venoarterial extracorporeal membrane oxygenation: how safe is it? Evaluation with a new experimental model. J Thorac Cardiovasc Surg 1992;104:579–84.
31. Hashimoto K, Miyamoto H, Suzuki K, et al. Evidence of organ damage after cardiopulmonary bypass: the role of elastase and vasoactive mediators. J Thorac Cardiovasc Surg 1992;104:666–73.
32. Knothe C, Boldt J, Zickmann B, et al. Endothelin plasma levels in old and young patients during open heart surgery: correlations to cardiopulmonary and endocrinology parameters. J Cardiovasc Pharmacol 1992;20:664–70.
33. Morita K, Ihnken K, Buckberg GD, et al. Pulmonary vasoconstriction due to impaired nitric oxide production after cardiopulmonary bypass. Ann Thorac Surg 1996;61:1775–80.
34. Verrier ED, Boyle EM Jr. Endothelial cell injury in cardiovascular surgery. Ann Thorac Surg 1996;62:915–22.
35. Bando K, Turrentine MW, Sharp TG, et al. Pulmonary hypertension after operations for congenital heart disease: analysis of risk factors and management. J Thorac Cardiovasc Surg 1996;112:1600–7.
36. Martin GS, Bernard GR. Airway and lung in sepsis. Intensive Care Med 2001;27(Suppl 1):S63–S79.

37. Brown JM. Use of echocardiography for hemodynamic monitoring. Crit Care Med 2002;30:1361–4.
38. Zwissler B. [Acute right heart failure: etiology—pathophysiology—diagnosis—therapy]. Anaesthesist 2000;49:788–808.
39. Bristow MR, Zisman LS, Lowes BD, et al. The pressure-overloaded right ventricle in pulmonary hypertension. Chest 1998;114:101S–6.
40. Berne RLM. Coronary circulation and cardiac metabolism. In: Berne RLM, ed. Cardiovascular physiology. St. Louis: CV Mosby, 1977:198–208.
41. Calvin JE. Acute right heart failure: pathophysiology, recognition, and pharmacological management. J Cardiothorac Vasc Anesth 1991;5:507–13.
42. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. Circulation 1981;63:87–95.
43. Hoffman MJ, Greenfield LJ, Sugerman HJ, Tatum JL. Unsuspected right ventricular dysfunction in shock and sepsis. Ann Surg 1983;198:307–19.
44. Grose R, Strain J, Yipintosoi T. Right ventricular function in valvular heart disease: relation to pulmonary artery pressure. J Am Coll Cardiol 1983;2:225–32.
45. Urabe Y, Tomoike H, Ohzono K, et al. Role of afterload in determining regional right ventricular performance during coronary underperfusion in dogs. Circ Res 1985;57:96–104.
46. Vlahakes GJ. Management of pulmonary hypertension and right ventricular failure: another step forward. Ann Thorac Surg 1996;61:1051–2.
47. Hines R. Right ventricular function and failure: a review. Yale J Biol Med 1991;64:295–307.
48. Hines RL, Barash PG. Right ventricular performance. In: Kaplan JA, ed. Cardiac anesthesia. Philadelphia: WB Saunders, 1993:1095–121.
49. Matthay RA, Berger HJ. Cardiovascular performance in chronic obstructive pulmonary diseases. Med Clin North Am 1981;65:489–524.
50. Sibbald WJ, Paterson NA, Holliday RL, et al. Pulmonary hypertension in sepsis: measurement by the pulmonary arterial diastolic-pulmonary wedge pressure gradient and the influence of passive and active factors. Chest 1978;73:583–91.
51. Lowenstein E, Johnston WE, Lappas DG, et al. Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 1983;59:470–3.
52. Conahan TJ, Andrews RW, MacVaugh H. Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981;60:33–6.
53. Jardin F, Farcot JC, Boisante L, et al. Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 1981;304:387–92.
54. Biondi JW, Schulman DS, Soufer R, et al. The effect of incremental positive end-expiratory pressure on right ventricular hemodynamics and ejection fraction. Anesth Analg 1988;67:144–51.
55. Biondi J, Hines R, Rafferty T, et al. The effect of high frequency positive pressure ventilation on right and left ventricular function. Anesth Analg 1986;65:679–82.
56. Beuckelmann DJ. Pulmonary hypertension [in German]. Internist (Berl) 1997;38:1020–33.
57. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001;38:923–31.
58. Zwissler B. Der "kranke" rechte Ventrikel. Intensivmed 2001;38:264–77.
59. Patole SK, Finer NN. Experimental and clinical effects of magnesium infusion in the treatment of neonatal pulmonary hypertension. Magnes Res 1995;8:373–88.
60. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524–6.
61. Inbar S, Schrader BJ, Kaufmann E, et al. Effects of adenosine in combination with calcium channel blockers in patients with primary pulmonary hypertension. J Am Coll Cardiol 1993;21:413–8.
62. Nootens M, Schrader B, Kaufmann E, et al. Comparative acute effects of adenosine and prostacyclin in primary pulmonary hypertension. Chest 1995;107:54–7.
63. Alpert MA, Pressly TA, Mukerji V, et al. Short- and long-term hemodynamic effects of captopril in patients with pulmonary hypertension and selected connective tissue disease. Chest 1992;102:1407–12.
64. Waller DG. ACE inhibitors. In: Peacock AJ, ed. Pulmonary circulation: a handbook for clinicians. London: Chapman and Hall, 1996:141–53.
65. Morrell NW, Morris KG, Stenmark KR. Role of angiotensin-converting enzyme and angiotensin II in development of hypoxic pulmonary hypertension. Am J Physiol 1995;269:H1186–94.
66. Kiely DG, Cargill RI, Wheeldon NM, et al. Haemodynamic and endocrine effects of type 1 angiotensin II receptor blockade in patients with hypoxaemic cor pulmonale. Cardiovasc Res 1997;33:201–8.
67. Alpert MA, Pressly TA, Mukerji V, et al. Acute and long-term effects of nifedipine on pulmonary and systemic hemodynamics in patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease. Am J Cardiol 1991;68:1687–91.
68. Nootens M, Kaufmann E, Rich S. Short-term effectiveness of nifedipine in secondary pulmonary hypertension. Am J Cardiol 1993;71:1475–6.
69. Kalra L, Bone MF. Effect of nifedipine on physiologic shunting and oxygenation in chronic obstructive pulmonary disease. Am J Med 1993;94:419–23.
70. Malik AS, Warshafsky S, Lehrman S. Meta-analysis of the long-term effect of nifedipine for pulmonary hypertension. Arch Int Med 1997;157:621–5.
71. Rich S. Calcium channel blockers for the treatment of primary pulmonary hypertension. Eur Respir Rev 1995;29:252–4.
72. Jenkins IR, Dolman J, O'Connor JP, Ansley DM. Amrinone versus dobutamine in cardiac surgical patients with severe pulmonary hypertension after cardiopulmonary bypass: a prospective, randomized double-blinded trial. Anaesth Intensive Care 1997;25:245–9.
73. Haraldsson A, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. Anesth Analg 2001;93:1439–45.
74. Watkins WD, Peterson MB, Crone RK, et al. Prostacyclin and prostaglandin E1 for severe idiopathic pulmonary artery hypertension [letter]. Lancet 1980;1:1083.
75. Badesch DB. Clinical trials in pulmonary hypertension. Annu Rev Med 1997;48:399–408.
76. Hinderliter AL, Willis PW, Barst RJ, et al. 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.
77. Eronen M, Pohjavuori M, Andersson S, et al. Prostacyclin treatment for persistent pulmonary hypertension of the newborn. Pediatr Cardiol 1997;18:3–7.
78. Schranz D, Zepp F, Iversen S, et al. Effects of tolazoline and prostacyclin on pulmonary hypertension in infants after cardiac surgery. Crit Care Med 1992;20:1243–9.
79. Radermacher P, Santak B, Wust HJ, et al. Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: effects on pulmonary capillary pressure and ventilation-perfusion distributions. Anesthesiology 1990;72:238–44.
80. Menon N, McAlpine L, Peacock AJ, Madhok R. The acute effects of prostacyclin on pulmonary hemodynamics in patients with pulmonary hypertension secondary to systemic sclerosis. Arthritis Rheum 1998;41:466–9.

81. Archer SL, Mike D, Crow J, et al. A placebo-controlled trial of prostacyclin in acute respiratory failure in COPD. Chest 1996; 109:750–5.
82. Magnani B, Galie N. Prostacyclin in primary pulmonary hypertension. Eur Heart J 1996;17:18–24.
83. Peacock AJ. Treatment of pulmonary hypertension. Drugs Today 1995;31:201–11.
84. Olschewski H, Walmrath D, Schermuly R, et al. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. Ann Intern Med 1996;124:820–4.
85. Mikhail G, Gibbs J, Richardson M, et al. An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. Eur Heart J 1997;18:1499–504.
86. Saji T, Ozawa Y, Ishikita T, et al. Short-term hemodynamic effect of a new oral PGI_2 analogue, beraprost, in primary and secondary pulmonary hypertension. Am J Cardiol 1996;78: 244–7.
87. Kunimoto F, Arai K, Isa Y, et al. A comparative study of the vasodilator effects of prostaglandin E1 in patients with pulmonary hypertension after mitral valve replacement and with adult respiratory distress syndrome. Anesth Analg 1997;85: 507–13.
88. Murali S, Uretsky BF, Reddy PS, et al. Reversibility of pulmonary hypertension in congestive heart failure patients evaluated for cardiac transplantation: comparative effects of various pharmacologic agents. Am Heart J 1991;122:1375–81.
89. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, et al. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 1991;338:1173–4.
90. Yoshida M, Taguchi O, Gabazza EC, et al. Combined inhalation of nitric oxide and oxygen in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155:526–9.
91. Kovalchin JP, Mott AR, Rosen KL, Feltes TF. Nitric oxide for the evaluation and treatment of pulmonary hypertension in congenital heart disease. Tex Heart Inst J 1997;24:308–16.
92. Papazian L, Roch A, Bregeon F, et al. Inhaled nitric oxide and vasoconstrictors in acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;160:473–9.
93. Cremona G, Wood AM, Hall LW, et al. Effect of inhibitors of nitric oxide release and action on vascular tone in isolated lungs of pig, sheep, dog and man [published erratum appears in J Physiol (Lond) 1994;481:811]. J Physiol 1994;481:185–95.
94. Wessel DL, Adatia I, Giglia TM, et al. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation 1993;88:2128–38.
95. Manktelow C, Bigatello LM, Hess D, Hurford WE. Physiologic determinants of the response to inhaled nitric oxide in patients with acute respiratory distress syndrome. Anesthesiology 1997;87:297–307.
96. Treggiari-Venzi M, Ricou B, Romand JA, Suter PM. The response to repeated nitric oxide inhalation is inconsistent in patients with acute respiratory distress syndrome. Anesthesiology 1998;88:634–41.
97. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26:15–23.
98. Roger N, Barbera JA, Roca J, et al. Nitric oxide inhalation during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;156:800–6.
99. Beghetti M, Habre W, Friedli B, Berner M. Continuous low dose inhaled nitric oxide for treatment of severe pulmonary hypertension after cardiac surgery in paediatric patients. Br Heart J 1995;73:65–8.
100. Adatia I, Lillehei C, Arnold JH, et al. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. Ann Thorac Surg 1994;57:1311–8.
101. Jois D, Pouard P, Mauriat P, et al. Inhaled nitric oxide as a therapy for pulmonary hypertension after operations for congenital heart defects. J Thorac Cardiovasc Surg 1994;107: 1129–35.
102. Shah AS, Smerling AJ, Quaegebeur JM, Michler RE. Nitric oxide treatment for pulmonary hypertension after neonatal cardiac operation. Ann Thorac Surg 1995;60:1791–3.
103. Ferrer R, Masclans JR, Angles R, et al. Anticoagulative effect of nitric oxide inhalation in ARDS. Intensive Care Med 1998;24: 837–8.
104. Mariani G, Barefield ES, Carlo WA. The role of nitric oxide in the treatment of neonatal pulmonary hypertension. Curr Opin Pediatr 1996;8:118–25.
105. Nagaya N, Uematsu M, Oya H, et al. Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. Am J Respir Crit Care Med 2001;163:887–91.
106. 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.
107. Hachenberg T, Mollhoff T, Holst D, et al. Cardiopulmonary effects of enoximone or dobutamine and nitroglycerin on mitral valve regurgitation and pulmonary venous hypertension. J Cardiothorac Vasc Anesth 1997;11:453–7.
108. Bertolissi M, Bassi F, Da Broi U. Norepinephrine can be useful for the treatment of right ventricular failure combined with acute pulmonary hypertension and systemic hypotension: a case report. Minerva Anestesiol 2001;67:79–84.
109. 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.
110. Elatrous S, Nouira S, Besbes-Ouanes L, et al. Dobutamine in severe scorpion envenomation: effects on standard hemodynamics, right ventricular performance, and tissue oxygenation. Chest 1999;116:748–53.
111. Le Tulzo Y, Seguin P, Gacouin A, et al. Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. Intensive Care Med 1997;23:664–70.
112. Hines R. Right ventricular function and failure: a review. Yale J Biol Med 1991;64:295–307.
113. Richter JA, Barankay A. Pulmonary hypertension and right ventricular dysfunction after operations for congenital heart disease. Acta Anaesthesiol Scand 1997;111:31–3.
114. Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. J Clin Invest 1966;45:399–411.
115. Sajkov D, Wang T, Saunders NA, et al. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2002;165:152–8.
116. Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy: a lethal combination. Anaesth Intensive Care 1990; 18:366–74.
117. Addonizio LJ, Gersony WM, Robbins RC, et al. Elevated pulmonary vascular resistance and cardiac transplantation. Circulation 1987;76:V52–5.
118. Rodriguez RM, Pearl RG. Pulmonary hypertension and major surgery. Anesth Analg 1998;87:812–5.
119. Rich S, D'Alonzo GE, Dantzker DR, Levy PS. Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. Am J Cardiol 1985;55:159–63.
120. Hammaren E, Hynynen M. Haemodynamic effects of propofol infusion for sedation after coronary artery surgery. Br J Anaesth 1995;75:47–50.
121. Abe K, Shimizu T, Takashina M, et al. The effects of propofol, isoflurane, and sevoflurane on oxygenation and shunt fraction during one-lung ventilation. Anesth Analg 1998;87:1164–9.
122. Boyd O, Murdoch LJ, Mackay CJ, et al. The cardiovascular changes associated with equipotent anaesthesia with either propofol or isoflurane: particular emphasis on right ventricular function. Acta Anaesthesiol Scand 1994;38:357–62.

123. Kellow NH, Scott AD, White SA, Feneck RO. Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery. Br J Anaesth 1995;75:578–82.
124. Von Dossow V, Welte M, Zaune U, et al. Thoracic epidural anesthesia combined with general anesthesia: the preferred anesthetic technique for thoracic surgery. Anesth Analg 2001; 92:848–54.
125. Sykes MK. Effects of anesthetics and drugs used during anesthesia on the pulmonary circulation. In: Altura B, Halevy S, eds. Cardiovascular actions of anesthetics and drugs used in anesthesia. Basel, Switzerland: Karger, 1986:92–125.
126. Hachenberg T, Holst D, Ebel C, et al. Effect of thoracic epidural anaesthesia on ventilation-perfusion distribution and intrathoracic blood volume before and after induction of general anaesthesia. Acta Anaesthesiol Scand 1997;41:1142–8.
127. Lumb PD, Silvay G, Weinreich AI, Shiang H. A comparison of the effects of continuous ketamine infusion and halothane on oxygenation during one-lung anaesthesia in dogs. Can Anaesth Soc J 1979;26:394–401.
128. Rees DI, Gaines GY. One-lung anesthesia: a comparison of pulmonary gas exchange during anesthesia with ketamine or enflurane. Anesth Analg 1984;63:521–5.
129. Wiedemann K, Diestelhorst C. [The effect of sedation on pulmonary function]. Anaesthesist 1995;44(Suppl 3):S588–93.
130. Hickey PR, Hansen DD, Cramolini GM, et al. Pulmonary and systemic hemodynamic responses to ketamine in infants with normal and elevated pulmonary vascular resistance. Anesthesiology 1985;62:287–93.
131. Carlsson AJ, Bindslev L, Hedenstierna G. Hypoxia-induced pulmonary vasoconstriction in the human lung: the effect of isoflurane anesthesia. Anesthesiology 1987;66:312–6.
132. Harris P, Heath D, eds. The human pulmonary circulation. New York: Churchill Livingstone, 1986.
133. Slinger P, Scott WA. Arterial oxygenation during one-lung ventilation: a comparison of enflurane and isoflurane. Anesthesiology 1995;82:940–6.
134. Satoh D, Sato M, Kaise A, et al. Effects of isoflurane on oxygenation during one-lung ventilation in pulmonary emphysema patients. Acta Anaesthesiol Scand 1998;42:1145–8.
135. Sokoll MD, Gergis SD, Kassell NF. Comparative effects of barbiturate or enflurane anesthesia with induced hypotension on intrapulmonary shunting. J Neurosurg 1984;60:248–51.
136. Gregoretti S, Gelman S, Dimick A, Bradley ELJ. Hemodynamic changes and oxygen consumption in burned patients during enflurane or isoflurane anesthesia. Anesth Analg 1989;69: 431–6.
137. Pagel PS, Fu JL, Damask MC, et al. Desflurane and isoflurane produce similar alterations in systemic and pulmonary hemodynamics and arterial oxygenation in patients undergoing one-lung ventilation during thoracotomy. Anesth Analg 1998;87: 800–7.
138. Malan TPJ, DiNardo JA, Isner RJ, et al. Cardiovascular effects of sevoflurane compared with those of isoflurane in volunteers. Anesthesiology 1995;83:918–28.
139. Inada T, Inada K, Kawachi S, et al. Haemodynamic comparison of sevoflurane and isoflurane anaesthesia in surgical patients. Can J Anaesth 1997;44:140–5.
140. Tempe D, Mohan JC, Cooper A, et al. Myocardial depressant effect of nitrous oxide after valve surgery [published erratum appears in Eur J Anaesthesiol 1997;14:672]. Eur J Anaesthesiol 1994;11:353–8.
141. Sykes MK, Hurtig JB, Tait AR, Chakrabarti MK. Reduction of hypoxic pulmonary vasoconstriction in the dog during administration of nitrous oxide. Br J Anaesth 1977;49:301–7.
142. Hickey PR, Hansen DD, Strafford M, et al. Pulmonary and systemic hemodynamic effects of nitrous oxide in infants with normal and elevated pulmonary vascular resistance. Anesthesiology 1986;65:374–8.
143. Schulte-Sasse U, Hess W, Tarnow J. Pulmonary vascular responses to nitrous oxide in patients with normal and high pulmonary vascular resistance. Anesthesiology 1982;57:9–13.
144. Cheng DC, Edelist G. Isoflurane and primary pulmonary hypertension. Anaesthesia 1988;43:22–4.
145. Ewalenko P, Brimioulle S, Delcroix M, et al. Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension. Br J Anaesth 1997;79:625–30.