IN 1998, the World Health Organization sponsored a symposium on pulmonary hypertension at which a new, more clinically useful classification system was adopted.§ Traditionally, pulmonary hypertension had been classified as being primary or secondary. The classification proposed at the World Health Organization symposium divides pulmonary hypertension into five distinct categories (table 1): (1) pulmonary arterial hypertension (PAH) associated primary pulmonary hypertension (PPH) (familial and sporadic) and PAH related to collagen vascular disease, congenital systemic to pulmonary shunts, HIV infection, portopulmonary hypertension, drugs such as anorexigens, and toxins; (2) PAH linked with disorders of the respiratory system and/or hypoxemia; (3) pulmonary venous hypertension, including mitral valve disease, chronic left ventricular dysfunction, and pulmonary venoocclusive disease; (4) PAH due to chronic thrombotic and/or embolic disease; and (5) PAH attributed to disorders directly affecting the pulmonary vasculature (inflammatory pulmonary capillary hemangiomatosis).

Pathophysiology

Pulmonary arterial hypertension is characterized by a progressive increase in pulmonary arterial pressure (PAP; mean pressure > 25 mmHg at rest or 30 mmHg during exercise) in association with variable degrees of pulmonary vascular remodelling, vasoconstriction, and in situ thrombosis.¹ No underlying cause can be found for some PAH, and secondary forms of PAH are related to collagen vascular disease, congenital systemic to pulmonary shunts, HIV infection, portopulmonary hypertension, and drugs.²

Primary pulmonary hypertension is a rare disease with an annual incidence of 1–2 per million. Six to 12% of cases are inherited in an autosomal dominant manner with reduced penetrance. PPH occurs three times more frequently in women than in men.³ Recently, mutations of the bone morphogenetic protein receptor type 2 gene (BMPR2) have been identified as causing many cases of familial PPH. BMPR2 encodes a type II receptor member of the transforming growth factor B superfamily of cell-signaling molecules⁴; after ligand binding, type II receptors form heteromeric complexes with membrane-bound type I receptors initiating phosphorylation of the type I receptor.⁵ This pathway seems to be critical in both cell differentiation and cell growth, with specificity mediated through transcriptional factors. The sporadic form of PPH is also associated with mutations of the gene encoding the protein receptor BMPR2 in at least 26% of cases.⁶–⁸ The 2000 International PPH Consortium pointed to the possibility that additional factors, either environmental or genetic, are required for disease pathogenesis. Recent publications have confirmed the important role of heredity in the disease.⁹,¹⁰ The sex bias for disease presentation suggests a role for either hormonal factors or an X-linked locus.¹¹

In the normal pulmonary circulation, pressure and resistance are 80–90% lower than in the systemic circulation. Pulmonary arteries larger than 1 mm in ID are elastic in nature and have well-developed internal and external laminae with a less distinct medial layer than systemic arteries. Most pulmonary arteries run adjacent to the airways. Distal to the respiratory bronchioles, the smooth muscle layer is reduced, and the arteries are only partially muscularized or nonmuscularized.¹¹ Vascular tone is normally very low, even if the pulmonary vessels are highly reactive to hypoxia and endogenous constrict-
Table 1. Diagnosis Classification of Pulmonary Hypertension
Proposed at the World Symposium on Primary Pulmonary Hypertension, 1998

| Pulmonary arterial hypertension                  |
|-------------------------------------------------|
| Primary pulmonary hypertension (sporadic, familial) |
| Pulmonary arterial hypertension related to collagen vascular disease (scleroderma, lupus, rheumatoid arthritis) |
| Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome), portopulmonary hypertension |
| HIV infection, drugs, and toxins                  |
| Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia |
| Parenchymal lung disease (chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and cystic fibrosis) |
| Chronic alveolar hypoxemia (exposure to long-term low oxygen tension such as in high altitudes) |
| Pulmonary venous hypertension                    |
| Mitral valve disease                             |
| Chronic left ventricular dysfunction             |
| Pulmonary venoocclusive disease                  |
| Pulmonary hypertension due to chronic thrombotic and/or embolic disease |
| Thromboembolic obstruction of proximal pulmonary arteries |
| Obstruction of distal pulmonary arteries         |
| Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature |
| Inflammatory                                    |
| Pulmonary capillary hemangiomatosis              |

World Symposium on Primary Pulmonary Hypertension, 1998. Available at: http://www.who.int/ncd/cvd/pph.html. Accessed May 12, 2000.

...tors.12–15 Sympathetic innervation of the pulmonary circulation does exist, and its activation increases pulmonary tone, although there are still controversies regarding the presence of α2 receptors.16,17 There are α2-adrenergic receptors in human pulmonary tissue. However, their specific localization (nerves, vessels, bronchi) is not known.18 We are not aware of studies of the effects of α2 agonists on isolated pulmonary vessels. Both PPH and other forms of PAH may share a common pathophysiology. It has been proposed that muscularization of the terminal portion of the pulmonary arterial vascular tree, caused by smooth muscle cell (SMC) hyperplasia, is the earliest change.19 There is great heterogeneity in the phenotype of pulmonary vascular SMCs,20 depending on the size and location of the pulmonary arteries. Different phenotypes respond differently to vasoactive factors and exhibit differential pharmacology. For example, K+ channels are differentially distributed,21 and cell-specific differences are in the endothelin-1 (ET-1) system.22 In established PAH, the pulmonary arteries are characterized by intimal fibrosis, medial hypertrophy, adventitial proliferation, and obliteration of small arteries. Plexiform lesions are found in many PAH cases. These lesions resemble renal glomeruli with multiple channels lined by endothelial cells. There is a suggestion from the work of Tuder et al.23–24 that this is a form of neoplastic lesion reflecting dysregulation of endothelial cell growth, rather than a smooth muscle abnormality, the principal event in PPH. The plexiform lesions are monoclonal in PPH, and polyclonal in other forms of PAH.25,26 Plexiform lesions might also represent an angiogenic response to local ischemia or hypoxia.27

Acute pulmonary hypertension induces a severe and sudden increase of right ventricular afterload, with an increased end-diastolic volume, a reduced ejection fraction, and a decreased stroke volume of the right ventricle.28 However, chronic pulmonary hypertension leads to progressive systolic pressure overload of the right ventricle that dilates and hypertrophies, resulting in gradual right ventricular dysfunction.29 In acute pulmonary hypertension, when pulmonary vascular resistance (PVR) increases abruptly, it is unusual for the right ventricle to be able to generate a mean pressure greater than 40 mmHg.30–32 In the presence of more severe vascular obstruction, the heightened PVR induces a decrease in the cardiac index. In chronic pulmonary hypertension, increases in PVR gradually worsen right ventricular failure.33 The ejection fraction of the right ventricle is also gradually reduced.

Decreased venous return compromises right ventricular preload and pulmonary blood flow. It may result from positive intrathoracic pressure during mechanical ventilation, such as positive end-expiratory pressure. High positive end-expiratory pressure also evokes alveolar overdistension and compression of the capillary network in the alveolar wall and interstitium. This condition increases PVR and reduces pulmonary blood flow.34

In pulmonary hypertension, the increased PVR limits right ventricular stroke volume and the volume available for left ventricular filling. The left ventricle is also compressed as the intraventricular septum moves paradoxically to the left during systole. Left ventricular septal bowing reduces left ventricular volume in early diastole and can impair left ventricular filling in the most important phase of rapid filling.35–37 Both mechanisms lead to low cardiac output and reduced arterial pressure. Decreased systemic vascular resistance, which occurs after anesthetic administration, depresses systemic arterial pressure. Hypotension reduces coronary perfusion pressure, which can result in myocardial ischemia and cause right-sided heart failure. The right ventricle normally receives coronary blood flow in both systole and diastole. During pulmonary hypertension and augmented right ventricular wall stress, coronary blood flow to the right ventricle is dramatically decreased during systole if right ventricular systolic pressure is equal to or higher than systemic pressure, and could also become limited during diastole if right ventricular end-diastolic pressures are increased.

Hypoxemia can occur in conjunction with reduced cardiac output and pulmonary blood flow. It can also result from right-to-left intracardiac shunting. As many as 30% of adults have a patent foramen ovale.38 Normally, there is no right-to-left shunting across the foramen ovale. If right atrial pressure exceeds left atrial pressure,
right-to-left shunting can occur, culminating in systemic oxygen desaturation. Finally, patients may have a restrictive pattern on pulmonary function tests or a low carbon monoxide diffusion capacity, leading to more severe hypoxemia and pulmonary hypertension.

**Biology**

In PAH, platelet activity is enhanced; serotonin, plasminogen activator inhibitor, and fibrinopeptide A concentrations are increased; and thrombomodulin is decreased. Thrombosis is often found *in situ* in pulmonary arterioles of PAH patients. The role of serotonin (5-hydroxytryptamine [5-HT]) in the development of PAH has been an enigma. 5-HT promotes SMC proliferation, pulmonary arterial vasoconstriction, and local microthrombosis. Alterations in 5-HT turnover, leading to an increased availability of free 5-HT in the vicinity of the pulmonary artery wall, have been proposed to be a pathophysiologic process. The major source of stored 5-HT is the platelet-dense granule. There is evidence that alterations in platelet 5-HT storage and/or heightened platelet consumption by the lung may trigger the development of PAH. Decreased platelet 5-HT concentration with enhanced plasma concentrations of free 5-HT has been reported in many disorders associated with PAH, including anorexigen intake, portal hypertension, Raynaud phenomenon, and collagen vascular disease. In human pulmonary arteries, serotonin acts mainly via 5-HT1B and not via 5-HT2A receptors. This explains the lack of effect of ketanserin, a 5-HT2A receptor antagonist, on pulmonary hypertension in humans. Pulmonary vasoconstriction is mainly evoked through activation of the 5-HT1B receptor, and smooth muscle proliferation is induced through activation of the 5-HT2A receptor. 5-HT is taken up by SMC through the serotonin transporter. The involvement of the 5-HT transporter in vascular disease has been postulated to be a pathophysiologic process. The major source of stored 5-HT is the platelet-dense granule. There is evidence that alterations in platelet 5-HT storage and/or heightened platelet consumption by the lung may trigger the development of PAH. Decreased platelet 5-HT concentration with enhanced plasma concentrations of free 5-HT has been reported in many disorders associated with PAH, including anorexigen intake, portal hypertension, Raynaud phenomenon, and collagen vascular disease. In human pulmonary arteries, serotonin acts mainly via 5-HT1B and not via 5-HT2A receptors. This explains the lack of effect of ketanserin, a 5-HT2A receptor antagonist, on pulmonary hypertension in humans. Pulmonary vasoconstriction is mainly evoked through activation of the 5-HT1B receptor, and smooth muscle proliferation is induced through activation of the 5-HT2A receptor. 5-HT is taken up by SMC through the 5-HT transporter. The involvement of the 5-HT transporter in pulmonary hypertension and remodelling is based on several experimental observations and suggests that it plays a major role in hypoxia-induced vascular remodelling through its ability to mediate the mitogenic action of 5-HT.

Besides 5-HT and coagulation, several other mechanisms controlling pulmonary vascular tone and plasticity can be altered in pulmonary hypertension. The balance between endothelium-dependent vasodilators, such as prostacyclin and nitric oxide, and vasoconstrictors, such as ET-1 and thromboxane, is modified toward higher concentrations of vasoconstrictors and lower concentrations of vasodilators. Patients with either PPH or secondary pulmonary hypertension have increased excretion of thromboxane A2 metabolites and reduced excretion of prostacyclin metabolites. Endothelial nitric oxide synthase expression is reduced in the pulmonary circulation of patients with PPH compared to control subjects; however, this is still controversial.

**Table 2. Possible Causes of Primary Pulmonary Hypertension**

| 1. BMPR2 mutation and vascular smooth muscle cell proliferation |
| 2. Monoclonal proliferation of endothelial cells in plexiform lesions |
| 3. Inhibition or down-regulation of the Kᵥ channel in pulmonary artery SMC |
| 4. Excess endothelial production of constrictors (ET-1, TXA₂) versus dilator mediators (nitric oxide, prostaglandin) |
| 5. Serotonin excess |
| 6. Thrombosis *in situ* |

Endothelin-1 is a potent vasoconstrictor and mitogen. Its concentrations are increased in experimental pulmonary hypertension and in human PAH. ET-1 produced by pulmonary endothelial cells may contribute to increased PVR and to the pathogenesis of PPH. K⁺ channels are transmembrane-spanning proteins that contain a pore with great selectivity for the K⁺ ion. They are tonically active in vascular smooth muscle, allowing a slow efflux of K⁺ along their intracellular/extracellular concentration gradient of 145/5 mM. There are several types of K⁺ channels; one of them, the voltage gated (Kᵥ), has a voltage sensor and contributes to membrane potential in SMC. Inhibition of Kᵥ channels results in accumulation of positively charged K⁺ ions within cells, raising the membrane potential to more positive levels (depolarization), which activates the voltage-gated L-type Ca²⁺ channel. Ca²⁺ then enters the cells, activating their contractile apparatus, leading to vasoconstriction and possibly initiating cell proliferation. Inhibition of Kv could be one of the mechanisms of hypoxic pulmonary vasoconstriction. In humans with PPH, Kv1.5 mRNA concentrations are reduced in pulmonary artery SMC. It is possible that decreased expression or function of Kᵥ channels in pulmonary artery SMC of patients with PPH could initiate and/or maintain pulmonary hypertension and play a role in the pathogenesis of PPH. It is intriguing that Kv2.1 is also inhibited by dexfenfluramine, a weight-loss drug that is associated with the development of PAH.

Vascular remodelling is a prominent feature of PPH. BMPR2, a member of the tumor growth factor (TGF)-β receptor family, regulates cell proliferation in response to ligand binding. The ligands for the TGF-β receptor family include TGF-β, bone morphogenetic protein, and activin. These growth factors have pleiotropic effects on endothelial cells and vascular SMCs depending on the context of the signal and the specific TGF receptor family members to which they bind. It has been postulated that mutations in BMPR2 in patients with PPH lead to loss of the inhibitory action of bone morphogenetic protein on the growth and the proliferative response of vascular endothelial and smooth cells in the pulmonary vasculature. Primary pulmonary hypertension is also characterized...
by endothelial cell proliferation. Migration and proliferation of pulmonary endothelial cells and angiogenesis might be the initial phenomenon in the pathogenesis of PPH. This view is supported by the expression of BMPR2 on endothelial cells and plexiform lesions. Mutations in this receptor are likely to affect bone morphogenetic protein signaling in endothelial cells and myofibroblasts within obliteration lesions in PPH.73

Moreover, the endothelial cell proliferation might be explained by mutations in activin receptor-like kinase (ALK)-1 found abundantly in the pulmonary vasculature. Normally, TGF-β binding ALK-1 attenuates the endothelial proliferative response induced by TGF-β binding to ALK-5.74 Trembath et al.75 have recently identified amino acid changes in ALK-1 in patients with pulmonary hypertension associated with hereditary hemorrhagic telangiectasia, which might result in unopposed TGF-β signaling through ALK-5 and endothelial cell proliferation. The role of vascular endothelial growth factor in the pathophysiology of PAH is controversial because the expression of vascular endothelial growth factor and its receptor are closely correlated with the formation of the plexiform lesion in human pulmonary hypertension,76 and on the opposite, blockade of the vascular endothelial growth factor2 receptor potentiates hypoxic pulmonary hypertension.77 and cell-based gene transfer of vascular endothelial growth factor 2 receptor potentiates hypoxic pulmonary hypertension. Symptoms are not specific, and the most frequent symptom is progressive dyspnea. Common signs and symptoms include chest pain secondary to right ventricular ischemia, fatigue, peripheral edema, near syncope, and syncope. Syncope is a serious complication of pulmonary hypertension and portends a poor prognosis94,95 (table 3).

Clinical examination can help to detect pulmonary hypertension and right-sided heart failure. The signs of pulmonary hypertension depend on the severity of the disorder. A loud pulmonic component of the second heart sound is suggestive of increased PAP. Patients with right-sided heart overload may have a left parasternal heave.

A murmur of tricuspid regurgitation that may increase in intensity during inspiration can develop as the right ventricle dilates. Signs such as an increase in jugular venous pressure, neck veins pulsations (giant systolic V waves), peripheral edema, hepatomegaly, and ascites are indicative of right-sided heart failure. Dilatation of the pulmonary valve annulus produces the diastolic decrease-murdo murmur of pulmonary valve regurgitation, the Graham Steell murmur. Right ventricular S3 gallop is characteristic of advanced right ventricle failure and has a poor prognosis.96

The diagnostic evaluation of patients with suspected pulmonary hypertension includes echocardiography, electrocardiography, chest radiographs, pulmonary function tests, ventilation/perfusion scanning, pulmonary angiography, spiral computed tomography, serologic testing, and liver function testing (table 4). Echocardiography is the screening method of choice.

### Table 3. Signs of Disease Severity

| 1. | Dyspnea at rest |
| 2. | Low cardiac output with metabolic acidosis |
| 3. | Hypoxemia |
| 4. | Signs of right heart failure (large V wave on jugularis vein, peripheral edema, hepatomegaly) |
| 5. | Syncope |

Anesthesiology, V 99, No 6, Dec 2003

---

**Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.**
Table 4. Recommended Complementary Examinations before Anesthesia in Patients with Pulmonary Hypertension

1. Electrocardiography
2. Chest radiography
3. Measurement of arterial blood gases
4. Echocardiography: information obtained includes size of right heart (dilation or hypertrophy), tricuspid regurgitation, myocardial function, shift of intravenous septum, patency of foramen ovale, estimation of pulmonary pressure, left heart function
5. Cardiac catheterization: information obtained includes pulmonary pressure, cardiac output, response to vasodilators, patency of foramen ovale, status of coronary circulation

Anatomic and functional data involving ventricular function, valvular abnormalities, and intracardiac shunts can be assessed. Echocardiography may show right ventricular hypertrophy, dilatation of the right heart chamber with impairment of left ventricular filling, and paradoxical motion of the interventricular septum. Doppler studies provide an estimate of pulmonary artery systolic pressure by measuring regurgitant flow across the tricuspid valve or by directly measuring systolic flow velocity across the pulmonary valve. Electrocardiographic abnormalities reflect right ventricular and right atrial enlargement as well as right ventricular hypertrophy. Chest radiography may show enlarged central and right and left pulmonary arteries. Increased size of the cardiac silhouette may reflect an enlarged right ventricle and right atrium. Ventilation/perfusion scans, pulmonary angiograms, and spiral computed tomograms are useful to identify thromboembolic disease. Serologic tests may indicate collagen vascular diseases such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis, HIV infection, liver diseases, and other rare conditions.

Cardiac catheterization remains the gold standard for the assessment of PAH. Right-sided heart catheterization confirms the presence of increased pressure (mean PAP > 25 mmHg), and the absence of pulmonary venous hypertension is suggested by normal mean capillary wedge pressure (< 15 mmHg). Central venous pressure is an important parameter to follow because it indicates the degree of right-sided heart failure. A low cardiac index is also of important prognostic significance. Hemodynamic abnormalities predict survival in patients with PPH. Finally, right-sided heart catheterization is necessary for testing the efficacy of vasodilator drugs.

Vasodilator trials are performed using short-acting vasodilators such as nitric oxide, epoprostenol, or adenosine. The ideal response to these substances is pulmonary arterial vasodilatation with an increase in cardiac output, a decrease and a reduction of pulmonary resistance. Acute testing is only indicative of the acutely reversible component of pulmonary hypertension. As discussed above, some chronic therapies such as prosta-

Cyclin and nitric oxide may show benefit, even in the absence of an acute response.

Treatment Options

Until recently, the medical treatment of pulmonary hypertension was limited to anticoagulation, oxygen, and high-dose calcium channel blockers for responders, in association with diuretics and digoxin where indicated.

Thrombosis of small pulmonary arteries (in situ thrombosis) is seen in most patients who are dying of pulmonary hypertension. Evidence of thrombin activity and fibrinogen consumption has been found in patients with PPH. Anticoagulation therapy has been studied in uncontrolled case series, and, indeed, the long-term use of warfarin is associated with improved survival. Warfarin is administered in doses to maintain the international normalized ratio at 2–2.5 times the control level. The use of unfractionated or low-molecular-weight heparin has not been examined. Heparin might provide similar antithrombotic efficacy and potentially offer some benefit through inhibition of SMC proliferation. However, heparin has a synergistic effect on endothelial proliferation when combined with endothelial cell growth factor, and, given the importance of endothelial proliferation in PAH, its application must be carefully examined. Oxygen therapy may be useful if arterial desaturation occurs at rest (hemoglobin saturation < 90%) or during physical activity.

High-dose calcium channel blockers were the first class of drugs that were shown to have dramatic, beneficial, long-term effects in selected patients with PPH. The presumed mechanism is through vasodilatation and the subsequent decrease in mean PAP. Cardiac output may increase as a result of right ventricular afterload reduction. Patients tend to be responders or nonresponders to high doses of Ca$^{2+}$ channel blockers, with only approximately 15–25% of patients responding. Only nifedipine and diltiazem have been tested rigorously. It is not known whether Ca$^{2+}$ channel blockers that release nitric oxide, such as amlopidine, are more effective than other classes of medications. In patients who are responsive (defined as > 20% reduction of PVR and > 20% decrease in PAP), a dose–response relation seems to exist in terms of magnitude of action. High doses of Ca$^{2+}$ channel blockers are necessary to achieve maximum benefit, and once achieved, the beneficial effect may be stable for many years. The indiscriminate use of calcium channel blockers in patients with PPH also has great potential for harm. There is no evidence that nonresponders benefit from them. Systemic hypotension producing reflex tachycardia, sympathetic stimulation, and right ventricular ischemia are detrimental effects of calcium channel blockers that ultimately may worsen sur-
vival. Acute vasodilation testing with nitric oxide and prostacyclin has been used as a technique to identify patients who may respond to high-dose calcium channel blockers. In a clinical trial, pulmonary and systemic effects of a nicardipine (0.06 mg · kg\(^{-1}\) · min\(^{-1}\)) infusion and a changing fraction of inspired oxygen (Fi\(\text{O}_2\)) was evaluated in patients with pulmonary hypertension secondary to chronic obstructive disease. Nicardipine reduces pulmonary resistance and increases cardiac index independent of Fi\(\text{O}_2\) without changing arterial and mixed venous content.\(^{105}\) No controlled studies have examined the effect of calcium channel blockers in PAH secondary to causes other than PPH.

Nitric oxide used as an inhaled gas is a selective pulmonary vasodilator.\(^{106}\) It acts by stimulating soluble guanylate cyclase and increasing cyclic guanosine monophosphate. The vasodilator response to inhaled nitric oxide is an index of the reversibility of pulmonary hypertension.\(^{107}\) Long-term treatment of PAH with inhaled nitric oxide has been studied in some patients.\(^{108}\) However, inhaled nitric oxide therapy is currently cumbersome and expensive and requires a fairly sophisticated system because it is administered only during the initial part of the inspiration phase.\(^{109–111}\) Patient mobility is limited by the need for a gas cylinder and an injector to provide nitric oxide. Because the effect of inhaled nitric oxide is mainly limited to the pulmonary circulation, there is no systemic vasodilation and hypotension. The influence of inhaled nitric oxide on pulmonary remodeling has not definitively been established. If inhaled nitric oxide inhibits remodeling in newborn rats treated with monocrotaline,\(^{112}\) inhaled nitric oxide has no effect on pulmonary remodeling in adults rats treated with monocrotaline.\(^{113,114}\) Nitric oxide could inhibit pulmonary vascular remodeling by two possibilities\(^{115}\): (1) a reduction in pressure/shear stress,\(^{2}\) a direct antimitogenic effect on smooth muscle v\(\text{ia}\) inhibition of the expression/production of ET-1 and/or platelet-derived growth factor,\(^{116}\) or inhibition of serine elastase.\(^{117}\) The effect of inhaled nitric oxide may be potentiated by phosphodies- terase-5 inhibitors, which specifically suppress cyclic guanosine monophosphate catabolism and prolong its action. Two medications that inhibit phosphodiesterase-5 are available: dipyridamole and sildenafil.\(^{118–126}\) Sildenafil has already been described in case reports as a therapy for severe pulmonary hypertension.\(^{127}\) Its effect might be explained by two mechanisms of action: increased cyclic guanosine monophosphate concentration and opening of \(K^+\) channels.\(^{128}\)

Prostaglandins such as epoprostenol sodium (the synthetic salt of prostacyclin), a U.S. Food and Drug Administration-approved treatment for PPH, have been studied extensively over the past decade in patients with PPH and secondary PAH. Prostacyclin increases cyclic adenosine monophosphate by stimulating adenylate cyclase, leading to vasodilatation. It increases cardiac output and heart rate and decreases mean PAP and right atrial pressure.\(^{129,130}\) Epoprostenol may have beneficial effects other than vasodilatation when given chronically, possibly because of its antiplatelet or antiproliferative properties.\(^{131,132}\) Lack of an acute vasodilator response does not preclude a positive effect of chronic treatment, and many patients with a poor acute response have greatly benefited from chronic therapy. In fact, epoprostenol is not intended for patients with an acute response to vasodilator therapy.\(^{133}\) The epoprostenol dose must be increased gradually during the first year of therapy to prevent symptom recurrence. Its half-life in the blood is short (3–5 min), and it must be administered intravenously. Inhaled epoprostenol is experimental and not approved. Continuous epoprostenol infusion requires the placement of an indwelling venous catheter and is associated with the risk of infection. Epoprostenol therapy leads to a marked improvement in functional capacity and in the survival of patients with PPH,\(^{134,135}\) with improvement in functional capacity and hemodynamics in patients with PAH related to scleroderma-type diseases.\(^{136}\) Despite the huge increase in price of inhaled nitric oxide treatment in some countries, epoprostenol treatment is more expensive than inhaled nitric oxide.\(^{108}\) Intravenous use of prostaglandin (PG) \(E_2\) is somewhat limited by its many adverse effects, including systemic hypotension, flushing, chest pain, headache, and diarrhea.

Treprostinil is a more stable analog of prostacyclin at room temperature with a longer half-life and can be administered subcutaneously. The Food and Drug Administration Advisory Committee has recommended its approval, and a recent trial has demonstrated that its long-term use improves exercise tolerance in patients with PPH.\(^{137}\) Continuous infusion of treprostinil, another stable prostacyclin analog, has improved function in patients with PAH.\(^{138}\) Iloprost is a prostacyclin analog that can be administered by inhalation. The major advantage of this inhalation strategy is that lower doses of the drug, with minimal systemic effects, can be used.\(^{139,140}\) Unfortunately, its short half-life requires frequent inhalation, and it is unclear whether the magnitude of long-term effects is sustained. Inhaled prostacyclin treatment could be combined with a phosphodiesterase-5 inhibitor such as sildenafil such that lower doses of drug can be used and the adverse effects can be minimized.\(^{125,141–144}\)

Wilkens \textit{et al.}\(^{120}\) conclude that sildenafil causes a long-lasting reduction in mean PAP and PVR, with further additional improvement after inhalation of iloprost. These data suggest that small doses of a phosphodiesterase type V inhibitor may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension. Beraprost, an oral prostacyclin analog, is reasonably well absorbed and produces beneficial effects in patients with PPH.\(^{145}\) Its efficacy is currently being examined in controlled clinical investigations.
The role of ET-1 as a mediator of PAH has been suggested. Antagonists that are nonselective (block both endothelin-A [ET-A] and endothelin-B [ET-B] receptors) or are ET-A receptor selective have been developed and tested in animal models of pulmonary hypertension. ET-A receptors on smooth muscle mediate vasoconstriction and promote SMC proliferation. ET-B receptors seem to be involved in ET-1 clearance, and a subpopulation of ET-B receptors located in the endothelium mediates vasodilation through the release of nitric oxide and prostacyclin. There may be an advantage to selectively block the ET-A receptor, leaving ET-B receptor function intact. Clinical trials with bosentan, a nonselective inhibitor, already suggest a beneficial effect in patients with PAH as do studies with sitaxsentan, an ET-A selective inhibitor. Bosentan has recently been approved by the Food and Drug Administration for the oral treatment of PPH.

It is likely that combination therapy using several medications acting through different and complementary pathways, for example, prostacyclin (intravenous or inhaled), inhaled nitric oxide, ET-A blockers, and phosphodiesterase inhibitors will be shown to be useful in the medical management of pulmonary hypertension.

Finally, the advances in our understanding of the pathogenesis of PAH will eventually lead to the development of novel approaches focusing directly on abnormal proliferation of endothelial cells or regression of established pulmonary vascular remodelling. Genes for prostacyclin synthase and nitric oxide synthase have been transfected into the airways as well as small pulmonary arteries, and transiently overexpressed in mice. Gene therapy directed at the pulmonary bed, using nitric oxide synthase, or perhaps BMPR2 is a possible future approach. Antiangiogenic therapy may also prove to be beneficial when given in the presence of endothelial proliferation.

**Perioperative Care**

The anesthetic management of patients with PAH is generally described in case reports of obstetric anesthesia and cardiac surgery. In PAH, several mechanisms are implicated in right-sided heart failure, such as inadequate preload of the right ventricle, increased afterload of the right ventricle, hypotension, and hypoxemia. During anesthesia, all of these situations can occur. It is essential that the anesthesiologist avoid precipitating right-sided heart failure, resulting in low cardiac output.

Before anesthesia, chronic medical treatment already being administered for pulmonary hypertension and right-sided heart failure should be continued. If already being given, continuous intravenous epoprostenol therapy should be maintained at the same dose because it offers hemodynamic benefit and abrupt discontinuation of the drug can lead to syncope and death. Oxygen is useful in patients with hypoxemia (oxygen saturation < 90%) because hypoxemia causes pulmonary vasoconstriction and increases PVR. Cardiac glycosides, such as digoxin, may improve cardiac output in patients with PPH and right ventricular failure and induce a significant reduction in circulating norepinephrine. However, digitalis glycosides have a narrow therapeutic range. Digoxin blood concentration and blood electrolytes should be monitored as the risk of toxicity increases with hypokalemia. Diuretics should be used judiciously to control edema from right-sided heart dysfunction. Excessive diuresis may be extremely dangerous through a reduction of right ventricular preload. If overdiuresis occurs in the presence of acute right-sided heart failure secondary to acute myocardial infarction, it is less common an issue in the hypertrophied right side of the heart in chronic pulmonary hypertension. Fluid administration and induction of diuresis during anesthesia should be based on careful hemodynamic monitoring, surveillance of filling pressure, cardiac chamber volume, intracardiac flow pattern (determined by echocardiography), and clinical response.

Vasoactive medication should be added with caution. Sedatives should be administered with care, avoiding any drugs that potentially decrease systemic blood pressure. The anesthesiologist must try to maintain optimal pulmonary blood flow. All factors that increase PVR should be avoided and corrected if they occur. Because hypoxia and hypercarbia augment PVR, ventilation and oxygenation should be controlled, and acidosis should be corrected. Changes in PVR in response to acidosis are small in the presence of normal alveolar oxygen tensions, but in the presence of alveolar hypoxia, they are greatly enhanced. Therefore, vasoconstriction may be augmented by increases in arterial hydrogen ion concentration, alveolar partial pressure of carbon dioxide, or both. Reducing arterial carbon dioxide tension (Paco₂) and increasing pH produce a consistent and reproducible decrease in PVR in infants with pulmonary hypertension. Most of the sedative drugs and general anesthetic agents reduce systemic vascular resistance, which may lead, particularly in fixed cardiac output states, to decreased systemic arterial pressure and coronary perfusion.

Calcium channel blockers given as treatment of chronic pulmonary hypertension should be continued despite any possible interaction with anesthetics on myocardium or vascular resistance. Particular attention should be paid to maintain sinus rhythm. Patients...
may deteriorate rapidly with the onset of atrial fibrillation or flutter because the atrial component to ventricular filling can be critical in maintaining cardiac output. High PaCO₂ may induce arrhythmias during general anesthesia, especially in the presence of some anesthetics (e.g., halothane). Increased PaCO₂ with acidosis can increase PAP and right ventricular afterload.

Insertion of catheters or wires into the central circulation may provoke cardiac arrhythmia, so flow-directed thermodilution catheters should be introduced carefully. Difficulties may be encountered in passing the catheters into the pulmonary artery in patients with severe pulmonary hypertension.

If hypotension occurs despite cuveolaemia, inotropic agents are essential to improve cardiac output. Dobutamine is a β-adrenergic agent that increases cyclic adenosine monophosphate concentrations in both myocardium and vascular smooth muscle, resulting in inotropic, chronotropic, systemic, and pulmonary vasodilator effects. Dobutamine has been used extensively in patients with pulmonary hypertension after cardiopulmonary bypass (CPB) and for the evaluation of pulmonary vascular reactivity before cardiac transplantation. This agent decreases PVR in experimental pulmonary hypertension. Phosphodiesterase-3 inhibitors, such as milrinone, reduce both systemic vascular resistance and PVR and augment contractility by increasing intracellular concentrations of cyclic adenosine monophosphate concentration. They may be useful in supporting patients with pulmonary hypertension. Systemic hypotension is the limiting factor because of a lack of pulmonary specificity. Most of the medications used to treat pulmonary hypertension are vasodilators; their effects on systemic arterial pressure are difficult to predict because they are due to a balance among the decrease in pulmonary and systemic resistance, their impact on cardiac function, and oxygenation. As a consequence, therapy must be individualized to the patient’s response.

In case of persistent hypotension, the use of vasoconstrictors such as phenylephrine and norepinephrine can augment coronary perfusion pressure and avoid right ventricular ischemia. Norepinephrine also provides inotropic support. Norepinephrine is metabolized by the pulmonary vascular endothelium. Therefore, its metabolism is reduced in PPH, and its concentrations increase. Successful weaning for CPB in patients with acute pulmonary hypertension has been achieved with left atrial norepinephrine infusion combined with inhaled nitric oxide or PGE₁ infusion (table 6).

Concomitant administration of inhaled nitric oxide or inhaled prostacyclin may be helpful. Reductions in PVR and mean PAP with enhanced cardiac performance and minimal or no effects on systemic pressure have been reported. Nitric oxide and prostacyclin act via different signaling pathways, and their effects are additive without increased toxicity. Prostacyclin decreases PVR and augments cardiac output and systemic oxygen delivery when acutely administered to patients with PPH. The effect of inhaled nitric oxide and inhaled prostacyclin could be improved by phosphodiesterase inhibitors, such as dipyridamole and sildenafil.

Epidural anesthesia has been used successfully for cesarean delivery in patients with pulmonary hypertension. The most significant risk in this situation is the reduction of venous return and arterial pressure consequent to sympathetic blockade. Also, the rapid changes in vascular volume and vascular tone peripartum pose a significant challenge. Few reports have described the effect of thoracic epidural anesthesia on PVR. Sympathetic innervation of the pulmonary circulation has been elaborated. No α₁-adrenergic receptors are present in the pulmonary circulation. Therefore, sympathetic innervation does not contribute to basal vasomotor tone. Thoracic epidural has no impact on basal pulmonary artery tone. However, thoracic epidural anesthesia has cardiac effects that can be deleterious in patients with pulmonary hypertension. High thoracic epidural anes-

Table 5. Treatment of Pulmonary Hypertension during Surgery

| Inhalation nitric oxide: 20–40 ppm. | Milrinone (phosphodiesterase III inhibitor): 50 μg/kg bolus followed by a perfusion of 0.5–0.75 μg kg⁻¹ min⁻¹ | Dipyridamole: 0.2–0.6 mg/kg intravenously over 15 min; to be repeated every 12 hours. |
|-------------------------------|-------------------------------------------------|---------------------------------------------|
| **Inhaled prostacyclin:** two modalities of application | 1. Intermittent administration: 50 μg is diluted in 50 ml saline and nebulized in 15 min, which aerosolizes a dose between 14 and 17 μg; this treatment must be repeated every hour. | 2. Continuous administration at a concentration of 50 ng · kg⁻¹ · min⁻¹. Prostacyclin, 1.5 mg, can be dissolved in 100 ml sterile glycine buffer (final concentration, 15 μg/ml); the drug is administered by means of an inline nebulizer connected to the inspiratory line. |
| If no nebulizing device is available, prostacyclin can be infused intravenously at a dose between 4 and 10 ng · kg⁻¹ · min⁻¹. These medications should be weaned slowly after the pulmonary hemodynamic response in the postoperative period. | Regional anesthesia can be provided using nerve block, brachial plexus block, and lumbar plexus block. Epidural anesthesia should be induced slowly, and a mixture of local anesthetics and opioids should be given to reduce the dose of local anesthetics and then the hypotension. Hypotension during the procedure should be treated according to the etiology (bleeding etc.). Phenylephrine and norepinephrine have been used to treat persistent systemic hypertension; norepinephrine has the advantages of being both a vasoconstrictor and a positive inotropic agent. This medication should be titrated according to the clinical response. | If regional anesthesia is used, arterial and CVP lines are recommended, and specific treatment for pulmonary hypertension is required. |

CVP = central venous pressure; ppm = parts per million.
Table 6. Anesthetic Considerations

| Preoperative medications | Maintenance all pulmonary vasodilators, such as intravenous or inhaled prostacyclin, Ca++ antagonists, phosphodiesterase-5 inhibitors (sildenafil, dipyridamole), endothelin receptor antagonists (Bosentan), and oxygen. If pulmonary hypertension has been discovered in the immediate preoperative period and if the surgery cannot be delayed, a treatment with sildenafil (50–100 mg daily) and L-arginine (15 g daily) should be started as soon as possible. Heparin should replace indirect anticoagulant until the surgical procedure. Premedication: Slight sedation (midazolam) is allowed as long as respiratory acidosis is not induced. Induction Opioids, such as fentanyl, alfentanil, sufentanil, and remifentanil, should be used at a dose to block the cardiorespiratory response of intubation. They have no direct vascular effect on pulmonary vessels. Lidocaine, 1 mg/kg, can also suppress the response to intubation. Propofol, 1–2 mg/kg; pentothal, 1–2 mg/kg; or etomidate, 0.2–0.4 mg/kg, may be used. Depolarizing or nondepolarizing muscle relaxants could be used. Maintenance Volatile anesthetics, such as isoflurane, desflurane, or sevoflurane, can be administered (isoflurane has been the most commonly used). Opioids should be maintained at a surgical analgesic level. Muscle relaxation should be maintained. Monitoring Arterial line; CVP or pulmonary artery catheter; TEE if available Postoperative treatment Hospitalization in an intensive care unit Optimal analgesia with continuous epidural, regional block, or parenteral opioids CVP = central venous pressure; TEE = transesophageal echocardiography. | PULMONARY ARTERIAL HYPERTENSION |
---|---|

Pulmonary Vasoreactivity to Anesthetic Agents

Few studies have been performed on the intrinsic action of anesthetic agents on the vasoreactivity of the pulmonary vasculature. The effect of propofol on the pulmonary circulation is controversial. Propofol has been reported to cause either an increase in PVR or pulmonary vasodilation in transplant patients. Horibe et al. have recently studied the effects of propofol on the pulmonary vascular response to endothelium-dependent and -independent vasodilators in a canine model. They tested the hypothesis that propofol could attenuate endothelium-dependent pulmonary vasodilatation. Propofol reduces acetylcholine-induced pulmonary vasodilatation. However, it does not change the response to bradykinin. Acetylcholine and bradykinin stimulate endothelium-dependent pulmonary vasodilation, but by different mechanisms. Bradykinin-induced pulmonary vasodilation is mediated by nitric oxide and prostacyclin. Acetylcholine-induced vasodilatation is mediated by nitric oxide and a cytochrome P-450 metabolite that could be endothelium-derived hyperpolarizing factor. Propofol has no effect on the pulmonary vasodilatation induced by nitric oxide, implying that it does not influence guanylyl cyclase activity in pulmonary vascular smooth muscle. The normal response to nitric oxide and bradykinin indicates that propofol has a selective effect on the endothelial signaling pathway for acetylcholine-induced vasodilatation. In a canine model, propofol had no effect on basal pulmonary vascular tone but increased the pulmonary response to vasoconstrictors. It is not known whether the same response could occur in humans. Propofol has been used as an induction agent without problems in patients with PPH. Ketamine may produce sympathetic nervous system activation and increased concentrations of epinephrine and norepinephrine in plasma. In vitro, ketamine increases PVR in rat lung. However, a study performed using isolated rabbit pulmonary arteries showed a relaxant effect of ketamine, suggesting an intrinsic endothelium-independent vasodilator action on the pulmonary circulation. Relaxation caused by ketamine could be mediated by inhibition of calcium release from intracellular storage sites, or by a calcium channel-blocking effect. In a rat thoracic aorta model, Miyawaki et al. found that ketamine inhibited acetylcholine-induced relaxation but not sodium nitroprusside-induced relaxation, implying that it suppressed nitric oxide formation in the endothelium. Ogawa et al. have shown recently in canine pulmonary artery preparations that ketamine attenuates endothelium-dependent pulmonary vasorelaxation in response to acetylcholine and bradykinin by inhibiting both the nitric oxide and the endothelium-derived hyperpolarizing factor components.

Postoperative Period

Patients with pulmonary hypertension who undergo surgery often die suddenly during the first postoperative days. Possible etiologies include a progressive increase in pulmonary vascular tone, acute pulmonary vasoconstriction, pulmonary thromboembolism, cardiac arrhythmia, heightened sympathetic tone, and fluid shifts. All precautions should be taken to avoid hypoxemia, hypotension, and hypovolemia. Postoperative control of pain should be effective. Any therapy to decrease PVR and improve pulmonary blood flow should be weaned with caution.
| Cause of Pulmonary Hypertension and Surgical Intervention | Anesthesia Technique and Medication Used | Outcome |
|---------------------------------------------------------|----------------------------------------|---------|
| Eisenmenger syndrome<sup>239</sup>                     | 103 Anesthesia                         | Mortality 14% |
| Major surgery: cesarean delivery, hysterectomy, laparotomy, vascular surgery | 68 General anesthesia | Mortality 18% |
| Minor surgery: hernia repair, tubal ligation, dental work, dilatation and curettage, extremity surgery | 19 Neuroaxial anesthesia | Mortality 5% |
| 16 Combined anesthesia                                  |                                        | Mortality 7% |
| 239                                                      | Mortality 24%                          |         |
| Major surgery: cesarean delivery, hysterectomy, laparotomy, vascular surgery | 68 General anesthesia | Mortality 18% |
| Minor surgery: hernia repair, tubal ligation, dental work, dilatation and curettage, extremity surgery | 19 Neuroaxial anesthesia | Mortality 5% |
| 16 Combined anesthesia                                  |                                        | Mortality 7% |
| 239                                                      | Mortality 24%                          |         |

PPH

| Cesarean delivery<sup>225</sup> | EDA | 18 mg ropivacaine + 5 mg morphine | Hypotension |
|----------------------------------|-----|----------------------------------|------------|
|                                  |     | Postoperative analgesia          | Bradycardia|
|                                  |     | Epidural morphine                | 0.25 mg atropine |
|                                  |     | Oral calcium channel blockers and low-molecular-weight heparin | 10 mg ephedrine |
|                                  |     | Immediate outcome good           | 1.7 mg phenylephrine |
|                                  |     |                                   |             |
| Lung transplantation<sup>240</sup> | General anesthesia | 250 µg fentanyl | Patient died 19 months later, waiting for heart-lung transplantation |
|                                  |     | 3.6 mg midazolam                 |              |
|                                  |     | 70 mg succinylcholine            |              |
|                                  |     | 0.5–1% isoflurane                |              |
|                                  |     | TEE Dilation of RV              | Immediate outcome good |
|                                  |     | Major T regurgitation            | Cardiac arrest after thoracotomy, open chest cardiac massage, catheterization of femoral vessels |
|                                  |     | Underfilling of LV              | Beginning of CPB |
|                                  |     | Shift of IV septum               | Good final outcome |
|                                  |     |                                  | Good outcome |

PPH

| Cesarean delivery<sup>463</sup> | EDA | 300 mg lidocaine, 1% | Hypotension |
|----------------------------------|-----|---------------------|------------|
|                                  |     | 70 mg bupivacaine, 0.5% | Cardiac arrest |
|                                  |     | 0.1 mg fentanyl     | Cardiac massage |
|                                  |     | 20 mg aerosolized iloprost | Canulation of femoral vessels |
|                                  |     | Furosemide for positive volume into postoperative period | CPB |
|                                  |     | TEE Dilation of RV | Good outcome |
|                                  |     | Major T regurgitation |              |
|                                  |     | Underfilling of LV |              |
|                                  |     | Shift of IV septum |              |

PPH

| Lung transplantation<sup>240</sup> | General anesthesia | Sufentanil | 0.01 µg · kg<sup>−1</sup> · min<sup>−1</sup> | Cardiac arrest |
|------------------------------------|--------------------|------------|--------------------------------------------|---------------|
|                                    |                    | Etomidate  | 2 × 50 µg + perfusion                      | Cardiac massage |
|                                    |                    | Rocuronium |                                                   | Canulation of femoral vessels |
|                                    |                    | Nitroglycerine |                                                  | CPB |

PPH

| Cesarean delivery<sup>219</sup> | Nitroglycerine | 50–100 mg/h via PA catheter to reduce PAP | Good outcome |
|----------------------------------|----------------|------------------------------------------|--------------|
|                                  | 1 mg alfentanil |                                          |              |
|                                  | 16 mg etomidate |                                          |              |
|                                  | 100 mg succinylcholine |                      |              |
|                                  | Isoflurane      |                                          |              |
| After delivery                    | 5 U oxytocin    | Nitroglycerin replaced by 2–5 ng · kg<sup>−1</sup> · min<sup>−1</sup> intravenous prostacyclin |              |
|                                  | Nitroglycerine | Because of vaginal bleeding |              |
|                                  | 50–100 mg/h     | Intravenous prostacyclin was aerosolized at 60,000 ng/h |              |
|                                  | Nitroglycerin  | Initially 30 mg oral nIfedipin and weaning from prostacyclin |              |

(Table continues)
of the response. These results reveal the differential reactivity of the pulmonary vascular bed and that the clinical effect of an agent is always mediated via the integration of several systems. Like ketamine, etomidate selectively attenuates endothelium-dependent canine pulmonary vasorelaxation by inhibiting the nitric oxide and endothelium-derived hyperpolarizing factor components of the response. It seems likely that etomidate and ketamine suppress the pulmonary vasorelaxant response to acetylcholine and bradykinin by reducing the increase in endothelial Ca\(^{2+}\), an essential step in the production of nitric oxide and endothelium-derived hyperpolarizing factor in response to receptor activation.

### Inhalational Anesthetic Agents

Isoflurane anesthesia exerts differential effects on the vasoreactivity of the pulmonary circulation. It attenuates the magnitude of hypoxic pulmonary vasoconstriction. Isoflurane potentiates the vasodilator response to \(\beta_1\) adrenoceptor activation. However, it has no effect on the vasoconstriction response to \(\alpha_1\) adrenoceptor activation. Adenosine triphosphate-sensitive potassium channels play an important role in the regulation of vascular smooth muscle tone. Adenosine triphosphate-sensitive potassium channel activation mediates the vasodilator effect of many endogenous mediators, such as adenosine, PG\(_I_2\), and nitric oxide. Isoflurane inhibits endothelium-dependent relaxation in aorta as well as in isolated pulmonary arteries. It selectively attenuates the pulmonary vasorelaxant response by inhibiting the activity of the adenosine triphosphate-sensitive potassium channels, which regulate the synergy between nitric oxide and PG\(_I_2\). It has no effect on baseline pulmonary circulation tone. Conversely, isoflurane suppresses the pulmonary vasoconstrictor response to hypotension. In this situation, it does not modify the influence of endogenous potassium-channel activation on the pulmonary vascular response to hypotension. Possibly, isoflurane may attenuate the pulmonary vasoconstrictor response to hypotension through a differential effect on sympathetic adrenoceptors in the pulmonary vasculature.

Neither halothane nor enflurane exerts any action on the baseline pulmonary circulation, but these agents reduce the pulmonary vasodilator effect mediated by...
adeno

Anesthesia for Special Procedures

Immediate Preoperative Preparation

All medications specially prescribed for treating pul-

Anesthesia for Cardiac Procedures

The use of CPB induces a pulmonary inflammatory response (acute lung injury) marked by pulmonary hy-

Anesthesia for Bilateral Lung Transplantation

Induction of anesthesia can be accomplished with opio-

Mechanical ventilation should allow enough time to let

reduce $\text{Paco}_2$ and increase $\text{Paco}_2$. However, in this alter-

natives, the induction is not as smooth, and it is more
difficult to control the pulmonary and systemic hemodynamics.

Mechanical ventilation should allow enough time to let

reduce $\text{Paco}_2$ and increase $\text{Paco}_2$. However, in this alter-

natives, the induction is not as smooth, and it is more
difficult to control the pulmonary and systemic hemodynamics.

Mechanical ventilation should allow enough time to let

reduce $\text{Paco}_2$ and increase $\text{Paco}_2$. However, in this alter-

natives, the induction is not as smooth, and it is more
difficult to control the pulmonary and systemic hemodynamics.
Anesthesia for Peripheral and General Surgery

Peripheral surgery can be completed under regional block (e.g., brachial plexus, lumbar plexus nerve block). Epidural anesthesia can be used. Prostacyclin and nitric oxide have a synergistic inhibitory effect on platelet function,\textsuperscript{217} and prostacyclin inhibits platelet aggregation \textit{in vitro}.\textsuperscript{218} In patients with PPH, platelet aggregation was increased because of a higher concentration of thromboxane $\Lambda_2$ and 5-HT, and this abnormality was corrected in 80% of patients treated with continuous intravenous prostacyclin.\textsuperscript{151} In one patient, vaginal bleeding after delivery was enhanced after treatment by intravenous prostacyclin. The bleeding stopped after changing the route of administration of the drug to inhalation from intravenous.\textsuperscript{219} Inhaled prostacyclin has no effect on platelet function and on bleeding after cardiac surgery.\textsuperscript{220} There are no data on the safety of epidural anesthesia in patients treated with intravenous prostacyclin. The reduction of vaginal bleeding after changing the route of prostacyclin administration (intravenous vs. inhaled) could be due to an effect on platelet function or a change in uterine tone. There are no reports that long-term intravenous infusion of prostacyclin produces epidural bleeding after regional anesthesia. If inhaled, prostacyclin treatment is not a contraindication to epidural anesthesia. Platelet function testing, if easily available, would give useful information before proceeding with epidural anesthesia if the patients are treated with intravenous prostacyclin. The induction of epidural anesthesia should be progressive to avoid sudden hypotension, and morphine or morphine derivatives should be added to local anesthetics to improve analgesia and reduce the amount of local anesthetics as well as the hemodynamic consequences of regional block. Spinal anesthesia with local anesthetics is not the technique of choice because the hemodynamic changes at induction and during recession of the block can be rapid and poorly tolerated. Systemic hypotension may be treated with either phenylephrine or norepinephrine. Norepinephrine acting primarily through B$_1$-adrenergic receptors has a positive inotropic effect on the myocardium.\textsuperscript{171,172,221} A central intravenous line or pulmonary artery catheter and an arterial cannula are useful to monitor hemodynamics and to administer medications.

If general anesthesia is required, induction can be completed using a mixture of opioids, hypnotics, and volatile anesthetics, as previously explained, and maintenance comprising a mixture of volatile anesthetics, opioids, and muscle relaxants. A combination of epidural and general anesthesia is a good choice, and the epidural can also be used for postoperative analgesia. Inhaled nitric oxide should be available and given (concentration 20–40 ppm) to treat pulmonary hypertension crises. If this treatment is inefficient, dipyridamole should be administered to potentiate inhaled nitric oxide. Finally, aerosolized prostacyclin could add its effect to the previously mentioned medications to decrease pulmonary pressure.

Patients should be admitted to the intensive care unit in the postoperative period and monitored closely. Pain management should be optimal, and inhaled nitric oxide, if used during the procedure, should be weaned progressively.

Anesthesia in the Obstetrics Population

\textit{Epidural Anesthesia for Delivery}

Several hemodynamic objectives should be reached: maintain the pulmonary pressure as low as possible and the systemic pressure within the 15% above and below the basal level (the systemic pressure should always be higher than pulmonary pressure), avoid dysrhythmias and tachycardia, and maintain sinus rhythm. An arterial line and a central venous or pulmonary catheter should be used for monitoring or for drug administration. Patients should be admitted to the intensive care unit after delivery.

\textit{Epidural Anesthesia for Vaginal Delivery}

Pain induced by labor should be treated in these patients with epidural analgesia via a mixture of local anesthetics and opioids in a low concentration because it produces good analgesia, keeps sufficient muscle tone, and has a minor effect on blood pressure. Forceps delivery, which decreases patient effort and has hemodynamic consequences, is the technique of choice.\textsuperscript{222–224}

\textit{Cesarean Delivery}

Both general and epidural anesthesia have been used for cesarean delivery in patients with pulmonary hypertension.\textsuperscript{165,188,219,225} Special care should be taken to avoid perioperative hemodynamic instability. Patient positioning is important.

The surgical procedure can lead to excessive bleeding and hypovolemia. Uterine contraction after delivery may return a large bolus of blood to the circulation. This can be poorly tolerated in patients with severe pulmonary hypertension and mitral stenosis. The sudden hypervolemia can be treated with vasodilators, such as nitroglycerine, and diuretics.

A blood pressure cuff inflated between the arterial and venous pressures around the thighs, can suddenly and reversibly decrease right ventricular filling by reducing venous return. Air or amniotic fluid embolism could acutely increase pulmonary pressure.

Induction of general anesthesia is based on opioids: fentanyl, sufentanil, or remifentanil. Lidocaine (1 mg/kg) reduces pulmonary and hemodynamic reactions during intubation. Induction can be further achieved by pentothal, propofol, or etomidate. Succinylcholine can be used for intubation. Anesthesia is maintained with use of...
sufentanil or remifentanil infusion (if these opioids have been used for induction), volatile anesthetics such as isoflurane, or propofol infusion.

If long-acting opioids have been used (fentanyl or sufentanil), the resuscitation team must be prepared to intubate and ventilate the newborn, who will have depressed respiration; naloxone has been administered in some cases (a special team should be ready to take care of the newborn). Postoperative analgesia may be achieved by intravenous, epidural, or intrathecal opioids. If the epidural approach is taken, a mixture of opioids and low-dose bupivacaine can be infused continuously (table 7).

Summary

Pulmonary arterial hypertension is a serious clinical problem associated with significant morbidity and mortality. A better understanding of disease pathophysiology will contribute to the development of new therapies and improve the long-term prognosis of patients. Selective pulmonary vasodilators are available and can be given separately or in combination. Hemodynamic monitoring and transesophageal echocardiography are diagnostic tools that are essential for the diagnosis but also give direct information on the efficacy of the therapeutic used.

References

1. Rubin JI: Primary pulmonary hypertension. N Engl J Med 1997; 336:111–7
2. Gaine S: Pulmonary hypertension. JAMA 2000; 284:3160–8
3. Loyd JE, Butler MG, Foroud TM, Connolly FM, Phillips JA III, Newman JH: Genetic anticipation and abnormal gender ratio at birth in familial primary pulmonary hypertension. Am J Respir Crit Care Med 1995; 152:93–7
4. Liu F, Ventura F, Dood J, Massague J: Human type II receptor for bone morphogenetic proteins (BMPs): Extension of the two-kinase receptor model to the BMPs. Mol Cell Biol 1995; 15:3479–86
5. Massague J, Chen YC: Controlling TGF-beta signaling. Genes Dev 2000; 14:627–44
6. Thomson JR, Machado RD, Paucillo MW, Morgan NV, Humbert M, Elliott GC, Ward K, Yacoub M, Mikhail G, Rogers P, Newman J, Wheeler J, Higebottom T, Gibbs JS, Egan J, Croizer A, Peacock A, 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
7. Deng Z, Morse JH, Slager SL, Cuervo N, Kalachikov S, Cayanis E, Fischer SG, Barst RJ, Hodge SE, Knowles JA: Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic proteins (BMPs): Extension of the two-kinase receptor model to the BMPs. Mol Cell Biol 1995; 15:3479–86
8. Thomson RD, Paucillo MW, Thomson JR, Lane KB, Morgan NV, Wheeler L, Phillips JA III, Newman J, Williams D, Galie N, Manes A, McNeil K, Yacoub M, Mikhail G, Rogers P, Corris P, Humbert M, Donnai D, Martinsson G, Tranhejre L, Loyd JE, Trembath RC, Nichols WC. BMPR2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. Am J Hum Genet 2000; 67:757–44
9. Geraci MW, Hoshikawa Y, Yeager M, Golpion H, Gesell T, Tudor RM, Voelkel NF. Gene expression profiles in pulmonary hypertension. Chest 2002; 121:1045–55
10. Geuna E, Merelle D, Arnold K, Benz A, Olschewski H, Miltenberger-Miltiényi G, Borst MM, Ashushi A, Seeger W, Winkler J, Hopfer MM, Bartram CR, Kuhler W, Janssen B: Primary pulmonary hypertension is predominantly a hereditary disease. Chest 2002; 121:815–25
11. Meyrick B: Pulmonary hypertension: Anatomical and physiologic correlates. Clin Chest Med 1983; 4:199–217
12. McMurtry IF, Hockway BW, Roos S: Red blood cells play a crucial role in maintaining vascular reactivity to hypoxia in isolated rat lungs. Chest 1977; 71:253–6
13. Barer G, Emery C, Stewart A, Bee D, Howard P: Endothelial control of the pulmonary circulation in normal and chronically hypoxic rats. J Physiol 1993; 465:1–16
14. McLean MR, McCulloch KM, Baird M: Endothelin ETA and ETB-receptor-mediated vasconstriction in rat pulmonary arteries and arterioles. J Cardiovasc Pharmacol 1994; 23:838–45
15. McCulloch KM, Docherty CC, Morecroft I, McLean MR: EndothelinB receptor-mediated contraction in human pulmonary resistance arteries. Br J Pharmacol 1996; 119:1125–30
16. Troncy E, Franoceur M, Salazkin I, Yang F, Charbonneau M, Leclerc G, Vinay P, Blaise G: Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine. Br J Anaesth 1997; 79:631–8
17. Helb C: Motor innervation of the pulmonary blood vessels of mammals. The Pulmonary Circulation and Intestitrial Space. Edited by Fishman AP, Hecht HH. Chicago, University of Chicago Press, 1969, pp 195–217
18. Berkowitz DE, Price DT, Belo EA, Page SO, Schwinn DA: Localization of messenger RNA for three distinct alpha 2-adrenergic receptor subtypes in human tissues: Evidence for species heterogeneity and implications for human pharmacology. Anesthesiology 1994; 81:1235–44
19. Heath D, Smith P, Gosney J, Mulcahy D, Fox K, Yacoub M, Harris P. The pathology of the early and late stages of primary pulmonary hypertension. Br Heart J 1987; 58:204–13
20. Frid MG, Moiseeva EP, Stenmark KR. Multiple phenotypically distinct smooth muscle cell populations exist in the adult and developing bovine pulmonary arterial media in vivo. Circ Res 1994; 75:669–81
21. Michelakis ED, Reeve HL, Huang JM, Tolarova S, Nelson DP, Weir EK, Archer SL: Potassium channel diversity in vascular smooth muscle cells. Can J Physiol Pharmacol 1997; 75:880–97
22. Tchekepeva E, Lawrence ML, Meyrick B: Cell-specific differences in ET-system in adjacent layers of main pulmonary artery: A new source of ET-1. Am J Physiol Lung Cell Mol Physiol 2000; 278:L813–L821
23. Tudor RM, Chacon M, Alper L, Wang J, Tarasievic EST, Kasahara Y, Cool CD, Bishop AE, Geraci M, Semenza G, Yacoub M, Polak JM, Voelkel NF. Expression of angiogenesis-related molecules in plexiform lesions in severe pulmonary hypertension: Evidence for a process of disordered angiogenesis. Am J Pathol 2001; 159:507–24
24. Tudor RM, Voelkel NF. Plexiform lesion in severe pulmonary hypertension: Association with glomeruloid lesion. Am J Pathol 2001; 159:382–3
25. Voelkel NF, Cool C, Lee SD, Wright L, Geraci MW, Tudor RM. Primary pulmonary hypertension between inflammation and cancer. Chest 1998; 114:2255–60.
26. Lee SD, Shroyer KR, Markham NE, Cool CD, Voelkel NF, Tudor RM. Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. J Clin Invest 1998; 101:927–54
27. Cool CD, Stewart JS, Warthera P, Miller GJ, Williams RL, Voelkel NF, Tudor RM. Three-dimensional reconstruction of pulmonary arteries in plexiform pulmonary hypertension using cell-specific markers. Evidence for a dynamic and heterogeneous process of pulmonary endothelial cell growth. Am J Pathol 1999; 155:411–9
28. Mercat A, Meyer G. Embolie pulmonaire grave, Insuffisance circulatoire aigue. Edited by Rich C, Vincent JL. Paris, Arnette, 1994, pp 313–29
29. Morpurgo M. Le coeur dans l’hypertension arterielle pulmonaire. Hypertension arterielle pulmonaire. Edited by Weitzenblum E, Denollin H. Paris, Masson, 1995, pp 117–27
30. Benotti JR, Dalen JE. The natural history of pulmonary embolism. Clin Chest Med 1984; 5:403–10
31. Dalen JE, Banas JS Jr, Brooks HL, Evans GL, Paraskos JA, Dexter L. Resolution rate of acute pulmonary embolism in man. N Engl J Med 1969, 280:1194–9
32. McIntyre KM, Sashahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971; 28:288–94
33. Wiedemann HP, Matthay MA. The management of acute and chronic cor pulmonale. Heart-Lung Interactions in Health and Disease. Edited by Scarf SM, Cassidy SS. New-York, Marcel Dekker, 1991, pp 915–82
34. Jenkins J, Lynn A, Edmonds J, Barker G. Effects of mechanical ventilation on cardiotocographic function in children after open-heart surgery. Crit Care Med 1985; 13:77–80
35. Boxx LM, Katz J, Kolb T, Czegedy FP, Barst RJ: Direct quantification of right and left ventricular volumes with nuclear magnetic resonance imaging in patients with primary pulmonary hypertension. Am J Cardiol 1992; 70:1508–15
36. Louis R, Dick S, Bronquelo BH. Doppler echocardiographic assessment of impaired left ventricular filling in patients with right ventricular pressure overload due to primary pulmonary hypertension. Am J Cardiol 1986; 58:298–306
37. Marcus JT, Vonk NA, Rooseland RJ, Postmus PE, Heerthaar RM, Van Rossum AC, Boonstra A. Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: Noninvasive monitoring using MRI. Chest 2001; 119:1761–7
38. Iagaru PT, Schulz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. Mayo Clin Proc 1984; 59:17–20
39. Frank H, Milzoch J, Huber K, Schuster E, Guttner HP, Kneussl M. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest 1997; 112:714–21

Anesthesiology, V 99, No 6, Dec 2005
constriction: The tale of two channels. FASEB J 1995; 9:183.

Well, Massachusetts, Kluwer/Plenum, 2001.

Patients with pulmonary hypertension associated with congenital heart defects:
Association with acute hypoxic pulmonary vasoreactivity. Am Rev Respir Dis 1995; 151:161–8.

Fenfluramine elevates systemic blood pressure by inhibiting potassium current in vitro. Circ Res 1999; 85:93–4.

Post JM, Hume JR, Archer SL, Weir EK. Direct role for potassium channel inactivation in hypoxic pulmonary vasoreactivity. Am J Physiol 1992; 262:C882–C889.

Michelakis ED, Weir EK. The pathology of pulmonary hypertension: Smooth muscle cells and ion channels. Clin Chest Med 2001; 22:419–32.

Archer SL, Soul E, Dinh-Xuan AT, Schreemler B, Mercier JC, El Yagoubi A, Artero-Sanchez L, Reeve HL, Trump V. Molecular identification of the role of voltage-gated K+ channels, Kv1.5 and Kv1.1, in hypoxic pulmonary vasoconstriction and control of resting membrane potential in rat pulmonary artery myocytes. J Clin Invest 1998; 101:2319–30.

Perret MS, Vassali JD, Montesano R. Biphasic effect of transforming growth factor-beta 1 on in vitro angiogenesis. Exp Cell Res 1993; 205:356–63.

Battegay EJ, Raines EW, Seifert RA, Bowen-Pope DF, Ross R. TGF-beta induces bimodal proliferation of connective tissue cells via complex control of an autocrine TGF-beta loop. Cell 1996; 84:193–202.

Akinobin C, Stewart S, Imanura T, Trembath RC, Morrell NW. Immunolocalization of BMPR-II and TGF-B type II and II receptors in primary plexogenic pulmonary hypertension. J Heart Lung Transplant 2001; 20:149.

Oh SP, Seki T, Goss KA, Imanura T, Yi Y, Donahoe PK, Li L, Miyazono K, ten Dijke P, Kim S, Li E. Activin receptor-like kinase 1 modulates transforming growth factor-beta 1 signaling in the regulation of angiogenesis. Proc Natl Acad Sci USA 2000; 97:2620–31.

Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, Winship I, Simonneau G, Galie N, Lyon JE, Humbert M, Nichols WC, Morrell NW, Berg J, Mames A, McQuaughran J, Pauciuolo M, Wheeler C. Local and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. Eur Respir J 1999; 14:600–8.

Hirose S, Hosoda Y, Furuya S, Otsuki T, Ikeda E. Expression of vascular endothelial growth factor and its receptors correlates closely with formation of the plexiform lesion in human pulmonary hypertension. Pathol Int 2000; 50:472–82.

Tarasavciei-Stewart L, Kusahara Y, Alger L, Hirth P, Mc MG, Waltertenberg J, Voelkel NF, Tuder RM. Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and pulmonary hypertension in mice lacking the 5-HT2B receptor. J Clin Invest 2000; 105:1555–62.

Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Adnot S. Induction of serotonin transporter by hypoxia in pulmonary vascular smooth muscle cells: Relationship with the mitogenic action of serotonin. Circ Res 1999; 84:529–36.

Eddahibi S, Raffestin B, Pham I, Launay JM, Aegerter P, Sibton M, Adnot S. Treatment with 5-HT3 potentiates development of pulmonary hypertension in chronically hypoxic rats. Am J Physiol 1997; 272:H1173–81.

Eddahibi S, Hanoun N, Leflamey L, Lesk CP, Raffestin B, Hamon M, Adnot S. Antisense pulmonary hypertension in mice lacking the 5-HT3 receptor transporter gene. J Clin Invest 2000; 105:1555–62.

Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, Simonneau G, Dartevelle P, Hamon M, Adnot S. Hyperplasia of pulmonary artery medial muscle in mice lacking the 5-HT1B receptor. Br J Pharmacol 1999; 128:730–34.

Eddahibi S, Dietrich F, Bristow MR, Troisi V, Bonic B, Matsumoto M, J. Treatment with 5-HT potentiates development of pulmonary hypertension in mice lacking the 5-HT1B receptor transporter gene. J Clin Invest 1999; 105:1555–62.

Induction of serotonin transporter by hypoxia in pulmonary vascular smooth muscle cells: Relationship with the mitogenic action of serotonin. Circ Res 1999; 84:529–36.

Eddahibi S, Raffestin B, Pham I, Launay JM, Aegerter P, Sibton M, Adnot S. Induction of serotonin transporter by hypoxia in pulmonary vascular smooth muscle cells: Relationship with the mitogenic action of serotonin. Circ Res 1999; 84:529–36.

Induction of serotonin transporter by hypoxia in pulmonary vascular smooth muscle cells: Relationship with the mitogenic action of serotonin. Circ Res 1999; 84:529–36.

Tension: Association with acute hypoxic pulmonary vasoreactivity. Am Rev Respir Dis 1995; 151:161–8.
Fishman AP, Goldring RM, Groves BM, Koerner SK. Primary pulmonary hypertension: A national prospective study. Ann Intern Med 1987; 107:216–23

109. Yacoub MH. Pulmonary and systemic arterial pressure changes during syncpe in primary pulmonary hypertension. Circulation 2001; 104:1326–7

110. McGoon MD, Fuster V, Freeman WK, Edwards WD, Scott JP. Pulmonary hypertension: Practice of Cardiology, 3rd edition. Edited by Guittani ER, St. Louis, Mosby, 1996, pp 1815–36.

111. D’Alonzo GE, Barst RJ, Ayres SM, Bergsfsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kerns JT. Survival in patients with primary pulmonary hypertension: Results from a national prospective registry. Ann Intern Med 1991; 115:543–9

112. Sibton O, Brentz F, Denjean A, Bergeron A, Parent F, Azarian R, Herve P, Raffestin B, Simonneau G. Inhaled nitric oxide as a screening vasodilator in patients with primary pulmonary hypertension: A prospective study and comparison with prosta-cyanin. Am J Respir Crit Care Med 1995; 151:384–9

113. Sibthon O, Humbert M, Jagot JL, Taravella O, Fartohlk M, Parent F, Herve P, Simonneau G. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J 1998; 12:265–70

114. Pekpe-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J: Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 1991; 338:1173–4

115. Langleben D, Moroz LA, McGregor M, Lisbona R. Decreased half-life of fibrinogen in primary pulmonary hypertension. Thromb Res 1985; 40:577–80

116. Eisenberg PR, Lucore C, Kaufman L, Sobel BE, Jaffe AS. Rich: S. Fibro-nectin peptide A levels indicative of pulmonary vascular thrombosis in patients with primary pulmonary hypertension. Circulation 1990; 82:841–7

117. Weatherford DA, Sackman J, Redick TT, Freeman MB, Stevens SL, Goldman MH. Vascular endothelial growth factor and heparin in a biologic response to human aortic endothelial cell proliferation with aortic smooth muscle cell inhibition. Surgery 1986; 102:439–9

118. 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; 327:706–14

119. Saadaian A, Philp-Joet F, Hot B, Reynaud-Gaubert M, Durand A, Levy S, Arnaud A. Effects of nicardipine on pulmonary and systemic vascular reactivity to oxygen in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease. Eur J Pharmacol 1987; 139:171–7

120. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, Roy BJ, Keszler M, Kinsella JP. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clin Inhaled Nitric Oxide Research Group. N Engl J Med 2000; 342:469–76

121. Ricciardi MJ, Knight BP, Martinez RF, Rubenfiel DF. Nitric oxide inhalation decreases pulmonary artery remodeling in the injured lungs of rat pups. Circ Res 2000; 87:140–7

122. Navarro P: One-year continuous inhaled nitric oxide for primary pulmonary hypertension. Clinical Inhaled Nitric Oxide Research. Anesthesiology, V 99, No 6, Dec 2003

123. Eisenberg PR, Lucore C, Kaufman L, Sobel BE, Jaffe AS, Rich S. Fibro-nectin peptide A levels indicative of pulmonary vascular thrombosis in patients with primary pulmonary hypertension. Circulation 1990; 82:841–7

124. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, Roy BJ, Keszler M, Kinsella JP. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clin Inhaled Nitric Oxide Research Group. N Engl J Med 2000; 342:469–76

125. Ricciardi MJ, Knight BP, Martinez RF, Rubenfiel DF. Nitric oxide inhalation decreases pulmonary artery remodeling in the injured lungs of rat pups. Circ Res 2000; 87:140–7

126. Dweik RA, Laskowski D, Abu-Soud HM, Kaneko F, Hutter R, Stuehr DJ, Erzurnu SC. Nitric oxide synthesis in the lung: Regulation by oxygen through a kinetic mechanism. J Clin Invest 1998; 101:660–6

127. Prasad S, Wilkinson J, Gatzoulis MA: Sildenafil in primary pulmonary hypertension (letter). N Engl J Med 2000; 343:154–7

128. Medina P, Segarra G, Torondel B, Chuan P, Domenech C, Vila JM, Lluch S. Inhibition of neuroreceptor transmission in human vas deferens by sildenafil. Br J Pharmacol 2000; 131:871–4

129. Michels S, McLaughlin MM. The effects of chronic prosta-cyanin therapy on cardiac output and symptoms in primary pulmonary hypertension. J Am Coll Cardiol 1999; 34:1184–7

130. Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE: Prostacyclin-induced acute pulmonary vasodilatation in patients with primary pulmonary hypertension. Circulation 1982; 66:334–8

131. Friedman R, Mears JG, Barst RJ: Continuous infusion of prosta-cyanin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 1997; 95:71–8

132. Langleben D, Barst RJ, Badesch D, Groves BM, Tapson VF, Murali S, Bourge RC, Ettinger N, Shalit E, Clayton LM, Jobms BB, Blackburn SD, Crow JW, Stewart DJ, Long W. Continuous infusion of epoprostenol improves the net balance between pulmonary endothelin-1 clearance and release in primary pulmonary hypertension. Circulation 1999; 99:3266–71

133. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH. A comparison of continuous intravenous epoprostenol (prosta-cyanin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996; 334:296–302

134. Barst RJ, Rubin LJ, McGoon MD, Caldwell DJ, Long WA, Levy PS: Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med 1994; 121:409–15

135. Wax D, Garofano R, Barst RJ: Effects of long-term infusion of prosta-cyanin on exercise performance in patients with primary pulmonary hypertension. Chest 1999; 116:914–20

136. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral JM, Jobms MM, Loyde J, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin MM, Roberts JM, Rein J, Starnes VA, Sraiani A, Murali S. Continuous intravenous epoprostenol pulmonary hypertension for the scleroderma spectrum of disease: A randomized, controlled trial. Ann Intern Med 2000; 132:125–34

137. McLaughlin VV, Gaine SP, Barst RJ, Oudiz RJ, Bourge RC, Frost A, Robbins IM, Tapson VF, McGoon MD, Badesch DB, Sigman J, Roscigino R, Blackburn SD, Arneson C, Rubin LJ, Rich S: Efficacy and safety 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

138. Olschewski H, Walmrath D, Schermuly R, Ghorani H, Grimmer F, Seeger W. Aerosolized prosta-cyanin in severe pulmonary hypertension (letter). N Engl J Med 2001; 345:1285–8

139. Olschewski H, Walmrath D, Schermuly R, Ghorani H, Grimmer F, Seeger W. Aerosolized prosta-cyanin in severe pulmonary hypertension. Circulation 2001; 104:820–4

140. Hoepner MM, Olschewski H, Ghorani H, Wilkens H, Winkler J, Borst MM, Niedermeyer J, Fabel H, Seeger W. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH Study Group. J Am Coll Cardiol 2000; 35:176–82

141. Schermuly RT, Krupnik E, Tenor H, Schulte D, Meinrath S, Rose F, Grimmer F, Seeger W, Walmrath D, Ghorani H: Coagulation of plasma platelets and platelet aggregation in patients with primary pulmonary hypertension treated with inhaled iloprost in experimental pulmonary hypertension: Maintenance of lung selectivity. Am J Respir Crit Care Med 2001; 164:1694–700

142. Weimann J, Ulrich R, Hromy J, Fujino Y, Clark MW, Bloch KD, Zapol WM: Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension. Anesthesiology 2000; 92:1702–12
143. Zhao L, Mason NA, Morrill NW, Kojonzabavazh B, Sadyov A, Maripov A, Mirzakhimov MM, Aledashv A, Wilkins MR: Sildenafil inhibits hypoxia-induced pulmonary hypertension. Circulation 2002; 106:242–51.

144. Lodato RF: Viagran for impotence of vasodilatory therapy? Am J Respir Crit Care Med 2001; 163:312–3.

145. Nagaya N, Uematsu M, Okano Y, Satoh T, Kyotani S, Sakamaki F, Nakano M, Aquate D, Kunieda T: Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. J Am Coll Cardiol 1999; 34:1188–92.

146. Chen SJ, Chen YF, Oggenfuss TJ, Wessale JL, Meng QC, Durand J, DiGiovanna VS, Opolar S: The orally active neuropeptide endothelin receptor antagonist A-127,722 prevents and reverses hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling in Sprague-Dawley rats. J Cardiovasc Pharmacol 1997; 29:714–25.

147. Duperj J, Crambeck P, Tardif JC, Stewart DJ, Gosselin G, Dynda I, Bonan R, Crepeau J: Reduced pulmonary clearance of endothelin-1 in pulmonary hypertension. Am Heart J 1998; 155:614–20.

148. Duperj J, Jasmin JF, Pne S, Crambeck P: Importance of local production of endothelin-1 of the ET(B) receptor in the regulation of pulmonary vascular tone. Pulm Pharmacol Ther 2000; 13:15–40.

149. de Nucci G, Thomas R, D’Ore качмпасте Juste P, Antunes E, Waldier C, Warner TD, Vane JR: Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci USA 1988, 85:9797–800.

150. Channick RN, Simonneau G. Sitbon O, Robbins TM, Prowant VF, Badesch DB, Roux S, Raimisio M, Bodin F, Rubini LF: Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: A randomised placebo-controlled study. Lancet 2003; 361:1119–23.

151. Newman JH: Treatment of primary pulmonary hypertension: The next generation. N Engl J Med 2002; 346:933–9.

152. Schraer JA, Crambeck P, Rabinovitch M, Bohn DJ: Pulmonary hypertension in children. Perioperative management. Can Anesth Soc J 1986; 33:600–28.

153. Rousj B, Arvieux A, Leger P, Arthaud M, Landault C, Vicaut E, Maigre E, Eurin J, Gandhich J, Vaisier P: Peripheral vascular effects of thiopeptin and propofol in humans with artificial hearts. Anesthesiology 1991; 75:32–42.

154. Claesly MA, Gepts E, Camu F: Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1998; 80:3–4.

155. Rousj B, Arvieux A, Leger P, Arthaud M, Landault C, Vicaut E, Maigre E, Eurin J, Gandhich J, Vaisier P: Peripheral vascular effects of thiopeptin and propofol in patients with artificial hearts. Anesthesiology 1991; 75:32–42.

156. Veering BF, Cousins MJ: Cardiovascular and pulmonary effects of epinephrine. Anaesthesia Intensive Care 2000; 28:620–635.

157. Pollard JB: Common mechanisms and strategies for prevention of cardiac arrest during epidural anaesthesia. J Clin Anesth 2002; 14:52–6.

158. Zucolor W, Klinkov BA, Klinkov MJ, Bohn DJ: Pulmonary hypertension in patients with cpulmonary venous obstruction. Anesthesiology 2000; 93:457–65.

159. Kondo U, Kim SO, Murray PA: Propofol selectively attenuates endothelin-dependent pulmonary vasodilation in chronically instrumented dogs. Anesthesiology 2000; 93:457–66.

156. Bradford KK, Deb B, Pearl RG: Combination therapy with inhaled nitric oxide and intravenous dobutamine during pulmonary hypertension in the rabbit. Can J Anaesth 2002; 49:51–4.

157. Tanaka H, Tajima K, Moritoune O, Kobyashi K, Okada K: Effects of milrinone on pulmonary vasculature in normal dogs and in dogs with pulmonary hypertension. Crit Care Med 1999; 27:68–74.

158. Angle MB, Molloy DW, Penner B, Jones D, Prewitt RM: The cardipulmonary and renal hemodynamic effects of norepinephrine in canine pulmonary embolism. Chest 1989; 95:1333–7.

159. Hirsch LJ, Rowehe MW, Wat SS, Kleinman L, Mathur M: Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. Chest 1991; 100:796–802.

160. Kwak YL, Lee CS, Park YH, Hong YW: The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. Anaesthesia 2003; 58:7–14.

161. Trappepe L, Voci P, Cogliati AA, Pasotti E, Papula U, Menichetti A: Successful weaning from cardiopulmonary bypass with central venous prostaglandin E1 and left atrial norepinephrine infusion in patients with acute pulmonary hypertension. Crit Care Med 1999; 27:2180–3.

162. Scherler RF: Viagra for impotence of pulmonary vasodilator therapy? Am J Respir Crit Care Med 1996; 153:991–6.

163. Troncy E, Francois M, Salazkin I, Yang F, Charlbonneau M, Leclerc G, Vinay P, Blaise G: Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine. Br J Anaesth 1997; 79:631–40.

164. Troncy E, Blaise G: Phenylephrine and inhaled nitric oxide. Anesthesiology 1998; 89:538–40.

165. Veering BF, Cousins MJ: Cardiovascular and pulmonary effects of nitric oxide. Anesthesia Intensive Care 2000; 28:620–635.

166. Pollard JB: Common mechanisms and strategies for prevention of cardiac arrest during epidural anaesthesia. J Clin Anesth 2002; 14:52–6.

167. Zucolor W, Klinkov BA, Klinkov MJ, Bohn DJ: Pulmonary hypertension in patients with cpulmonary venous obstruction. Anesthesiology 2000; 93:457–65.

168. Lynch CJ: Are volatile anesthetics really calcium entry blockers? Anesthesiology 1984; 61:644–6.
interaction between nitric oxide and prostacyclin. Anesthesiology 1997; 86: 946–44.

199. Fujiwara Y, Murray PA: Effects of isoflurane anesthesia on pulmonary vascular response to K+ ATP channel activation and circulatory hypotension in chronically instrumented dogs. Anesthesiology 1999; 90:799–811

200. Seki S, Sato K, Nakayama M, Murray PA: Halothane and enflurane attenuate pulmonary vasodilation mediated by adenosine triphosphate–sensitive potassium channels compared to the conscious state. Anesthesiology 1999; 92:35–35

201. Nakayama M, Kondo U, Murray PA: Pulmonary vasodilator response to adenosine triphosphate–sensitive potassium channel activation is attenuated during desflurane but preserved during sevoflurane anesthesia compared with the conscious state. Anesthesiology 1998; 88:1023–35

202. Sykes MK, Hurrig JB, Tait AR, Chakrabarti MK: Reduction of hypoxic pulmonary vasoconstriction in the dog during administration of nitrous oxide. Br J Anaesth 1979; 43:301–7.

203. Benuomof JL, Wahrenbrock EA: Local effects of anesthetics on regional hypoxic pulmonary vasoconstriction. Anesthesiology 1975; 43:525–52

204. Pagan PS, Kampe JP, Schmeling WT, Warther DC: Effects of nitric oxide on myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 1999; 73: 1145–55.

205. Hickey PR, Hansen DD, Strafford M, Thompson JE, Jonas RE, Mayer JE: Pulmonary and systemic hemodynamic effects of nitric oxide in infants with normal and elevated pulmonary vascular resistance. Anesthesiology 1981; 65:

206. Schulte-Sasse U, Hess W, Tarnow J: Pulmonary vascular responses to nitric oxide in patients with normal and high pulmonary vascular resistance. Anesthesiology 1982: 57:9–13

207. Heedrt PM, Caldwell RW: The mechanism of nitric oxide-induced changes in pulmonary vascular resistance in a dog model of left atrial outflow obstruction. J Cardiothorac Anesth 1989; 3:568–73

208. Hilgenberg JC, McCammon RL, Stoelting RK: Pulmonary and systemic vascular responses to nitric oxide in patients with mitral stenosis and pulmonary hypertension. Anesth Analg 1980; 53:235–6

209. Konstadt SN, Reich DL, Thris DM: Nitric oxide does not exacerbate pulmonary hypertension or ventricular dysfunction in patients with mitral valvular disease. Can J Anaesth 1990; 37:615–7

210. Robinson RJ, Shenbuhl H, Neurell C: Slow-rate, high-pressure ventilation: A method of management of difficult transplant recipients during sequential double lung transplantation for cystic fibrosis. J Heart Lung Transplant 1994; 13:779–84

211. Ardebali A, Laks H, Levine M, Shpiner R, Shpiner E, Laks H: Pulmonary and systemic response to nitric oxide in patients with normal and elevated pulmonary vascular resistance. Anesthesiology 1981; 65:

212. Kemming GI, Merkel MJ, Schallerer A, Habler OP, Kleen MS, Haller M, Bregel J, Vogelmeier C, Furst H, Reichart B, Zwissler B: Inhaled nitric oxide (NO) in the treatment of early allograft failure after lung transplantation. Munich Lung Transplant Group. Intensive Care Med 1998; 24:1173–80

213. Thubat G, Brugiere O, Leschege G, Stern JB, Fradj K, Herve P, Jebra G, Marvautis T, Fourmier M, Mal H: Preventive effect of inhaled nitric oxide and pentoxifylline on ischemia/reperfusion injury after lung transplantation. Transplantation 2001; 71:1295–300

214. Miller OL, Tang SP, Keetch 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; 356:1466–9

215. Hubert BP, Blaise GA. Inhaled NO given peroperatively improves oxygenation and decreases pulmonary arterial resistance following cardiopulmonary bypass in a pig model (abstract). Anesthesiology 2001; 95:A-566

216. Hubert BP, Radomski A, Blaise GA: Does inhaled nitric oxide (inhNO) affect matrix-metalloproteinase (MMP) concentration in bronchoalveolar lavage fluid (BAL) after cardiopulmonary bypass (CPB)? (abstract). Anesthesiology 2001; 95:A-440

217. Radomski MW, Palmer RM, Moncada S: Comparative pharmacology of endothelin-derived relaxing factor, nitric oxide and prostacyclin in platelets. Br J Pharmacol 1997; 92:181–7.

218. van Heerden PV, Gibbins NM, Michalopoulos N: Effect of low concentra-
tions of prostacyclin on platelet function in vitro. Anaesth Intensive Care 1997; 25:543–6

219. O'Hare R, McLoughlin C, Milligan K, McNamara D, Sidhu H: Anaesthesia for caesarean section in the presence of severe primary pulmonary hypertension. Br J Anaesth 1998; 81:790–2

220. van Heerden PV, Barden A, Michalopoulos N, Bulsara MK, Roberts BL: Dose-response to inhaled acetylsalicylic acid for hypoxemia due to ARDS. Chest 2000; 117:819–27

221. Wood KE. Major pulmonary embolism: Review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002; 121:877–905

222. Easterling TR, Ralph DP, Schmucker BC: Pulmonary hypertension in pregnancy: Treatment with pulmonary vasodilators. Obstet Gynecol 1999; 93: 494–8

223. Nelson DM, Main E, Crafford W, Ahumada GG: Peripartum heart failure due to primary pulmonary hypertension. Obstet Gynecol 1983; 62:588–638

224. Metcalfe J, McAnulty J, Ueland K: Burwell and Metcalfe’s Heart Disease and Pregnancy: Physiology and Management, 2nd edition. Boston, Little, Brown, 1986 pp 265–77.

225. Olofsson C, Bremme K, Forsell G, Ohqvist G: Cesarean section under epidural ropivacaine 0.75% in a parturient with severe pulmonary hypertension. Acta Anesthesiol Scand 2001; 45:258–60

226. Hoeper MM, Maier R, Tongers J, Niedermeyer J, Hohlfeld JM, Hamm M, Fabel H: Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. Am J Respir Crit Care Med 1995; 151:584–9

227. alAlyvan S, alOmran A, Dyer T: The use of phosphodiesterase inhibitor (diprydramole) to wean from inhaled nitric oxide. Intensive Care Med 1996; 22:1093–5

228. Buyse C, Fonteyne C, Dewy H, De Laet MH, Biarent D: The use of diprydramole to wean from inhaled nitric oxide in congenital diaphragmatic hernia. J Pediatr Surg 2001; 36:1864–5

229. Fullerton DA, Jaggars J, Piedalue F, Grover FL, McIntyre RJ: Effective control of refractory pulmonary hypertension after cardiac operations. J Thorac Cardiovasc Surg 1997; 113:363–8

230. Ivy DD, Kinsella JP, Ziegler JW, Abman SH: Diprydramole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease. J Thorac Cardiovasc Surg 1998; 115:875–82

231. Jiang ZY, Costachescu T, Derouin M, Blaise G: Treatment of pulmonary hypertension during surgery with nitric oxide and vasodilators. Can J Anaesth 2000; 47:582–77

232. Hoeper MM, Schwarzwe E, Ehlerding S, Adler-Schuermeyer A, Spiekeroetter 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.

233. Wilkens H, Guth A, Konig J, Forster C, B, Hennens B, Bohn M, Syrbrecht GW: Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. Circulation 2001; 104:1218–22

234. Rosner B: Fundamental of Biostatistics, 4th edition. Belmont, California, Duxbury, 1995

235. Fischer SM, Cope JT, Kron IL, Caza AK, Long SM, Kern JA, Tibring CB, Lowson SM: Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide for patients with reperfusion injury after lung transplantation. J Thorac Cardiovasc Surg 2001; 121:981–2

236. Hache M, Denault AY, Belisle S, Couture P, Babin D, Tetrault F, Guimond JG: Inhaled prostacyclin (PGI2) is an effective addition to the treatment of pulmonary hypertension and hypoxia in the operating room and intensive care unit. Can J Anaesth 2001; 48:924–9

237. Stewart R, Tuazon D, Olson G, Duarte AG: Pregnancy and primary pulmonary hypertension: Successful outcome with epoprostenol therapy. Chest 2001; 119:973–5

238. Martin JT, Tautz TJ, Antognini JF: Safety of regional anesthesia in Eisenmenger’s syndrome. Reg Anesth Pain Med 2002: 27:509–13

239. Hohn L, Schwarzwe A, Morel DR, Spiliopoulos A, Licker M: Cylindrical failure after anesthesia induction in a patient with severe primary pulmonary hypertension. Anesthesiology 1999; 91:1943–5

240. Smedstad KG, Cramb R, Morison DH: Pulmonary hypertension and pregnancy: A series of eight cases. Can J Anaesth 1994; 41:502–12

Anesthesiology. V 99, No 6, Dec 2003