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Pulmonary Arterial Hypertension

Pathophysiology and Anesthetic Approach

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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 molecules[4]; 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.[3]

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 constric-

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§World Symposium on Primary Pulmonary Hypertension, 1998. Available at: http://www.who.int/ncd/cvd/pph.homl. Accessed December 5, 2000.

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 venoocclusion 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 α_1 receptors.[16,17] There are α_2-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 α_2 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.[39,40] 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.[41–43] 5-HT promotes SMC proliferation, pulmonary arterial vasoconstriction, and local microthrombosis.[44] 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.[45] 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,[46,47] Raynaud phenomenon, and collagen vascular disease.[42] In human pulmonary arteries, serotonin acts mainly *via* 5-HT_{1B} and not *via* 5-HT_{2A} receptors.[48,49] This explains the lack of effect of ketanserin, a 5-HT_{2A} receptor antagonist, on pulmonary hypertension in humans. Pulmonary vasoconstriction is mainly evoked through activation of the 5-HT_{1B} receptor, and smooth muscle proliferation is induced through activation of the 5-HT_{2A} 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[50–53] 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 A_2 metabolites and reduced excretion of prostacyclin metabolites.[54] Endothelial nitric oxide synthase expression is reduced in the pulmonary circulation of patients with PPH compared to control subjects[55]; however, this is still controversial.[56]

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 K_v channel in pulmonary artery SMC
4. Excess endothelial production of constrictors (ET-1, TXA_2) *versus* dilator mediators (nitric oxide, prostaglandin)
5. Serotonin excess
6. Thrombosis *in situ*

BMPR2 = bone morphogenic protein receptor type 2; ET-1 = endothelin-1; K_v = voltage-gated potassium channel; SMC = smooth muscle cell; TXA_2 = thromboxane A_2.

Endothelin-1 is a potent vasoconstrictor and mitogen. Its concentrations are increased in experimental pulmonary hypertension[57,58] and in human PAH.[59–64] ET-1 produced by pulmonary endothelial cells may contribute to increased PVR and to the pathogenesis of PPH.[65]

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 Ca^{2+} channel.[66] Ca^{2+} 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.[67,68] In humans with PPH, Kv1.5 mRNA concentrations are reduced in pulmonary artery SMC.[69] It is possible that decreased expression or function of K^+ 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.[70] 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.[71,72] 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[4] (table 2).

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 factor 2 receptor potentiates hypoxic pulmonary hypertension,[77] and cell-based gene transfer of vascular endothelial growth factor attenuates experimental pulmonary hypertension.[78]

Pulmonary hypertension can be induced by different drugs and pathologic conditions. The first association between the anorexigen aminorex and pulmonary hypertension was observed in the 1960s.[79,80] PAH was later associated with fenfluramine or dexfenfluramine intake, and it was subsequently shown that PAH occurs approximately 30 times more frequently in patients receiving these anorectic agents for more than 3 months compared to the general population.[81,82] Fenfluramine releases 5-HT from platelets and inhibits its reuptake into platelets and pulmonary endothelial cells.[83,84] Fenfluramine was widely coprescribed with phentermine, a combination that became known as "fen/phen." Phentermine can prolong the effect of 5-HT and increase the concentration of 5-HT by inhibiting monoamine oxidase B, which metabolizes 5-HT. The fen/phen association has been shown to induce valvular disease[85] similar to that observed after exposure to 5-HT–like drugs, such as ergotamine and methysergide, and to increased 5-HT concentrations found in carcinoid syndrome. Most of the anorexigens are also serotonin-transporter substrates[86] and thus get translocated into pulmonary vascular cells, where their effects may become amplified. Anorexigens are also Kv channel blockers,[87] and one of their targets is Kv2.1.[69,88] Anorexigen-induced Kv channel inhibition and membrane depolarization might contribute to pulmonary vasoconstriction.[89,90] In addition to its effect on Ca^{2+} entry *via* the L-type Ca^{2+} channel, dexfenfluramine also promotes vasoconstriction by enhancing Ca^{2+} release from the sarcoplasmic reticulum.[88,91] Furthermore, fenfluramine reduces Kv1.5 mRNA concentrations by 50% in pulmonary artery SMC from normotensive patients,[92] suggesting that inhibited gene transcription and expression of Kv channels may play an important role in anorexigen-induced PAH. In addition to a synergistic interaction between fenfluramine and phentermine favoring PAH and cardiac vascular disease,[93] fenfluramine may precipitate secondary forms of PAH. Fenfluramine and dexfenfluramine are no longer available for clinical use.

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

Symptoms and Evaluation

Careful diagnostic evaluation aimed at identifying various etiologies is essential for appropriate management of pulmonary hypertension. Symptoms are not specific, and the most frequent symptom is progressive dyspnea. Other 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 prognosis[94,95] (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 decrescendo 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 4. Recommended Complementary Examinations before Anesthesia in Patients with Pulmonary Hypertension

1. Electrocardiography
2. Chest radiology
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.[96] 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.[94] 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.[1]

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.[97] 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.[98–100] 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 prostacyclin 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.[101,102] 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,[103] 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.[104] 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 amlodipine, 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 ($0.06\ mg \cdot kg^{-1} \cdot min^{-1}$) infusion and a changing fraction of inspired oxygen (F_{IO_2}) was evaluated in patients with pulmonary hypertension secondary to chronic obstructive disease. Nicardipine reduces pulmonary resistance and increases cardiac index independent of F_{IO_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 vasodilatation 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 muscles *via* 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 phosphodiesterase-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) I_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 trepostinil, 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 *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.[65] 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.[146] ET-A receptors on smooth muscle mediate vasoconstriction and promote SMC proliferation. ET-B receptors seem to be involved in ET-1 clearance,[147,148] and a subpopulation of ET-B receptors located in the endothelium mediates vasodilation through the release of nitric oxide and prostacyclin.[149] There may be an advantage to selectively block the ET-A receptor, leaving ET-B receptor function intact.[132] Clinical trials with bosentan, a nonselective inhibitor, already suggest a beneficial effect in patients with PAH,[150–152] 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.[153]

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[154] or regression of established pulmonary vascular remodelling.[155–157] 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.[158,159] Gene therapy directed at the pulmonary bed, using nitric oxide synthase,[160] prostacyclin synthase,[9] 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 management of PPH or secondary PAH is a challenge for the anesthesiologist because the risk of right-sided heart failure is markedly increased. Knowledge of the pathophysiology of the disease and the therapeutic possibility of treating patients in the perioperative phase are essential.

The anesthetic management of patients with PAH is generally described in case reports of obstetric anesthesia and cardiac surgery.[161–163] 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.[164] 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.[165] 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 commonly 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.[2] 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 ($Paco_2$) and increasing pH produce a consistent and reproducible decrease in PVR in infants with pulmonary hypertension.[166] 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.[95]

Calcium channel blockers given as treatment of chronic pulmonary hypertension should be continued despite any possible interaction with anesthetics on myocardium or vascular resistance.[167,168] Particular attention should be paid to maintain sinus rhythm. Patients

Table 5. Treatment of Pulmonary Hypertension during Surgery

Inhaled nitric oxide: 20–40 ppm.[226,227]
Milrinone (phosphodiesterase III inhibitor): 50=μg/kg bolus followed by a perfusion of 0.5–0.75 $\mu g \cdot kg^{-1} \cdot /min^{-1}$
Dypiridamole: 0.2–0.6 mg/kg intravenously over 15 min; to be repeated every 12 hours.[228–232]
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.[226,233–235]
2. Continuous administration at a concentration of $50\ ng \cdot kg^{-1} \cdot min^{-1}$.[236]
   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.[237]
   If no nebulizing device is available, prostacyclin can be infused intravenously at a dose between 4 and $10\ ng \cdot kg^{-1} \cdot min^{-1}$.[238]
   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.

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 $Paco_2$ may induce arrhythmias during general anesthesia, especially in the presence of some anesthetics (*e.g.*, halothane). Increased $Paco_2$ 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 euvolemia, 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.[169] 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.[170] 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.[171–173] Successful weaning for CPB in patients with acute pulmonary hypertension has been achieved with left atrial norepinephrine infusion combined with inhaled nitric oxide or PGE_1 infusion (table 6).[174,175] Concomitant administration of inhaled nitric oxide or inhaled prostacyclin may be helpful.[176] 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.[177] 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.[120,122]

Epidural anesthesia has been used successfully for cesarean delivery in patients with pulmonary hypertension.[163] 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 α_1-adrenergic receptors are present in the pulmonary circulation.[178,179] 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 6. Anesthetic Considerations

Preoperative medications
Maintain all pulmonary vasodilators, such as intravenous or inhaled prostacyclin, Ca^{++} antagonists, phosphodiesterase-5 inhibitors (sildenafil, dypiridamole), 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.

thesia, from the first to the fifth thoracic level, blocks cardiac afferent and efferent sympathetic fibers with loss of chronotropic and inotropic drive to the myocardium.[180] Heart rate may decrease as a result of blockade of the cardioaccelerator fibers arising from T1 to T4. The heart rate may decrease as a result of a decrease in right atrial filling, which reduces outflow from intrinsic chronotropic stretch receptors located in the right atrium.[181]

Postoperative Period

Patients with pulmonary hypertension who undergo surgery often die suddenly during the first postoperative days.[182] Possible etiologies include a progressive increase in pulmonary vascular tone, acute pulmonary vasospasm, 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.

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.[183,184] Horibe *et al.*[185] 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.[186] In a canine model, propofol had no effect on basal pulmonary vascular tone but increased the pulmonary response to vasoconstrictors.[187] 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.[188]

Ketamine may produce sympathetic nervous system activation and increased concentrations of epinephrine and norepinephrine in plasma.[189] *In vitro*, ketamine increases PVR in rat lung.[190] 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.[191] 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.*[192] 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.*[193] 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

Table 7. Summary of Recent Case Reports of Perioperative Management of Pulmonary Hypertension

Cause of Pulmonary Hypertension and Surgical Intervention	Anesthesia Technique and Medication Used	Outcome
Eisenmenger syndrome[239]	103 Anesthesia 68 General anesthesia 19 Neuroaxial anesthesia 16 Combined anesthesia	Mortality 14% Mortality 18% Mortality 5% Mortality 7%
Major surgery: cesarean delivery, hysterectomy, laparotomy, vascular surgery		Mortality 24%
Minor surgery: hernia repair, tubal ligation, dental work, dilatation and curettage, extremity surgery		Mortality 4%
PPH Cesarean delivery[225]	EDA 18 mg ropivacaine + 5 mg morphine Postoperative analgesia Epidural morphine Oral calcium channel blockers and low-molecular-weight heparin	Hypotension Bradycardia 0.25 mg atropine 10 mg ephedrine 1.7 mg phenylephrine Immediate outcome good Patient died 19 months later, waiting for heart–lung transplantation
PPH Lung transplantion[240]	General anesthesia 250 μg fentanyl 3.6 mg midazolam 70 mg succinylcholine 0.5–1% isoflurane TEE Dilatation of RV Major T regurgitation Underfilling of LV Shift of IV septum	Acute pulmonary hypertension after intubation, low CO (1.2 l/min) Treatment Epinephrine 2×50 μg + perfusion 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Cardiac arrest after thoracotomy, open chest cardiac massage, catheterization of femoral vessels Beginning of CPB Good final outcome
PPH Cesarean delivery[163]	EDA 300 mg lidocaine, 1% 70 mg bupivacaine, 0.5% 0.1 mg fentanyl 20 mg aerosolized iloprost Furosemide for positive volume into postoperative period	Good outcome
PPH Lung transplantation[240]	General anesthesia Sufentanil Etomidate Rocuronium	Cardiac arrest Cardiac massage Canulation of femoral vessels CPB Good outcome
PPH Cesarean delivery[219]	Nitroglycerine 50–100 mg/h *via* PA catheter to reduce PAP 1 mg alfentanil 16 mg etomidate 100 mg succinylcholine Isoflurane 50%/50% N_2/O_2 After delivery 5 U oxytocin Nitroglycerin replaced by 2–5 ng $\cdot kg^{-1} \cdot min^{-1}$ intravenous prostacyclin Because of vaginal bleeding Intravenous prostacyclin was aerosolized at 60,000 ng/h Finally, 30 mg oral nefedipin and weaning from prostacyclin	Good outcome

(*Table continues*)

Table 7. (continued)

Cause of Pulmonary Hypertension and Surgical Intervention	Anesthesia Technique and Medication Used	Outcome
Severe pulmonary hypertension due to valvular heart disease[188] (mitral stenosis and regurgitation, aortic and tricuspid regurgitation) Cesarean delivery	General anesthesia: TCI 8 ng/ml remifentanil 2.5 μg/ml propofol 40 mg rocuronium Postsurgical pain management 3-ml/h infusion of a mixture of 0.06% bupivacaine 1 μg/ml sulfentanil	Good outcome; valves repaired 1 month after surgery
Primary and secondary hypertension[241]	Epidural anesthesia	Good outcome
Vaginal delivery: seven patients Cesarean delivery: one patient	General anesthesia 200 mg thiopenthal 100 mg succinylcholine 100 μg fentanyl 0.5% halothane 50%/50% N_2O/O_2	Death 12 h after admission to ICU
PPH Cesarean delivery[163]	Epidural anesthesia 300 mg lidocaine, 2% 70 mg bupivacaine, 0.5% 100 μg fentanyl 20 μg aerosolized iloprost Perfusion of 2,400 ml Ringer's lactate Postoperative treatment Iloprost inhalation 6 times/day Furosemide to treat 1,600 positive balance Analgesia Intravenous paracetamol and morphine	Good outcome

CO = cardiac output; CPB = cardiopulmonary bypass; EDA = epidural analgesia; ICU = intensive care unit; IV = intravenous; LV = left ventricle; N_2O/O_2 = nitrous oxideoxygen ratio; PA = pulmonary artery; PAP = pulmonary artery pressure; PPH = primary pulmonary hypertension; RV = right ventricle; TEE = transesophageal echocardiography. TCI = target-controlled infusion.

of the response.[194] 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.[193]

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 β_1 adrenoceptor activation. However, it has no effect on the vasoconstriction response to α_1 adrenoreceptor activation.[195,196]

Adenosine triphosphate–sensitive potassium channels play an important role in the regulation of vascular smooth muscle tone.[197] Adenosine triphosphate–sensitive potassium channel activation mediates the vasodilator effect of many endogenous mediators, such as adenosine, PGI_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 PGI_2. It has no effect on baseline pulmonary circulation tone.[198] 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.[199]

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

adenosine triphosphate–sensitive potassium channel agonists.[200] Desflurane shares this latter feature, unlike sevoflurane, which has no effect. Desflurane potentiates pulmonary vasoconstriction in response to adrenoceptor activation, in contrast to isoflurane.[201]

Sykes *et al.*[202] demonstrated in the dog lung that nitrous oxide seemed to attenuate hypoxic pulmonary vasoconstriction. Other investigators have obtained little or no action when nitrous oxide is added to inhaled gas mixtures.[203] Nitrous oxide has minimal effects on hemodynamics but can still depress myocardial contractility.[204] In infants, nitrous oxide does not produce the increases in PAP and PVR observed in adults.[205] Nitrous oxide should be used with caution in adult patients with increased PVR, particularly in the presence of right ventricular dysfunction.[206] In a dog model, nitrous oxide had no effect on pulmonary vascular tone in an isolated lobe but increased PVR in intact animals.[207] Despite a moderate impact on pulmonary pressure, nitrous oxide has been used several times without detrimental results in patients with pulmonary hypertension.[206,208,209]

Anesthesia for Special Procedures

Immediate Preoperative Preparation

All medications specially prescribed for treating pulmonary hypertension, such as prostacyclin, Ca^{2+} antagonists, phosphodiesterase inhibitors, ET receptor antagonists, and oxygen therapy, should be continued until the procedure and after surgery. Coumadin should be changed to heparin before the procedure.

If the patient has had no specific treatment for pulmonary hypertension and if the surgery cannot be delayed to establish the best treatment, phosphodiesterase inhibitors (50–100 mg sildenafil) should be given daily, with L-arginine supplementation (15 g/day). This is especially indicated if the patient has clinical signs of pulmonary hypertension and demonstrates poor exercise tolerance. For premedication, a sedative, such as benzodiazepine, is administered to decrease anxiety.

Anesthesia for Bilateral Lung Transplantation

Induction of anesthesia can be accomplished with opioids (5–10 μg/kg fentanyl or 0.5–1 μg/kg sufentanil), 1 mg/kg lidocaine, 2–3 mg/kg pentothal, or 0.5–1 mg/kg propofol with muscle relaxants. Muscles relaxants releasing histamine such as atracurium or cisatracurium should be avoided. Mask ventilation with 100% O_2 and a volatile anesthetic such as isoflurane could be used to deepen the level of anesthesia before intubation. If necessary, norepinephrine should be infused to treat hypotension evoked by induction agents. If the patient is not fastened (this situation is not frequent because it takes some time to organize the transplantation), rapid-sequence induction can be used after hyperventilation to reduce $Paco_2$ and increase $Paco_2$. However, in this alternative, 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 the lung deflate and avoid thoracic hyperinflation with reduction of venous return.[210] Anesthesia maintenance is based on opioids, volatile agents, and muscle relaxants. Total intravenous anesthesia could also be used. Specific pulmonary vasodilators, such as inhaled nitric oxide and inhaled prostacyclin, should be immediately available in the operating room.

The most difficult part of the anesthesia usually occurs during one-lung ventilation of the native lung. Acute exacerbation of pulmonary hypertension can occur because total cardiac output is going only to one lung. A pulmonary vasodilator, such as inhaled nitric oxide, may be useful. However, CPB is often needed to complete the procedure. Inhaled nitric oxide can be administered before reperfusion because it decreases reperfusion injury.[211–213] After the procedure, there is usually no problem of pulmonary hypertension, and if patients were on PG infusion before surgery, it can be weaned rapidly after transplantation. The management then becomes similar to that for other major thoracic procedures. Epidural thoracic analgesia is indicated as soon as coagulation status is in the normal range.

Anesthesia for Cardiac Procedures

The use of CPB induces a pulmonary inflammatory response (acute lung injury) marked by pulmonary hypertension and hypoxemia. The inflammatory response can be prevented by inhaled nitric oxide and nitric oxide administered through the CPB machine; 20 parts per million (ppm) NO should be given throughout the procedure.[214–216] Phosphodiesterase-3 inhibitors, such as milrinone, are helpful to wean from CPB, and a bolus can be added to the CPB reservoir before weaning. The dosage for milrinone is a 25- to 50-μg/kg bolus, followed by infusion at 0.375–0.750 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Hypotension and low cardiac output should be treated with norepinephrine.

If pulmonary pressure remains high despite treatment with inhaled nitric oxide, right ventricular failure may occur. The latter can be diagnosed with use of direct myocardial vision, measurement of pulmonary hemodynamics, and transesophageal echocardiography and can be treated with a phosphodiesterase-5 inhibitor (dipyridamole). Finally, inhaled prostacyclin should be given if the previous treatment has not sufficiently decreased pulmonary pressure. Weaning from inhaled nitric oxide should be performed progressively while following the PAP response. The process can be facilitated by phosphodiesterase-5 inhibitors or L-arginine (table 5).

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,[217] and prostacyclin inhibits platelet aggregation *in vitro*.[218] In patients with PPH, platelet aggregation was increased because of a higher concentration of thromboxane A_2 and 5-HT, and this abnormality was corrected in 80% of patients treated with continuous intravenous prostacyclin.[131] 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.[219] Inhaled prostacyclin has no effect on platelet function and on bleeding after cardiac surgery.[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.[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

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 sinusal 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.

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.[222–224]

Cesarean Delivery

Both general and epidural anesthesia have been used for cesarean delivery in patients with pulmonary hypertension.[163,188,219,225] 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.

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