Postoperative Pulmonary Hypertension: Etiology and Treatment of a Dangerous Complication

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Postoperative pulmonary hypertension is a challenging and feared complication of many types of surgery, including lung and heart transplantation, pulmonary thromboendarterectomy, congenital-heart-disease repair, and others. The most severe manifestation is acute right heart syndrome, characterized by right heart failure and cardiovascular collapse—a daunting therapeutic challenge associated with a high mortality. Patients with postoperative pulmonary hypertension must be carefully evaluated to identify reversible contributing factors such as fluid and metabolic imbalance, hypoxemia, and right heart ischemia. A pulmonary arterial catheter and echocardiogram are recommended for evaluation, although their value has not been established in carefully designed trials. Basic principles of management include maintenance of systemic perfusion pressure, optimization of cardiac inotropy, use of lung-protective ventilator strategies, and attempting to reduce right-ventricular afterload using pulmonary vasodilators. Unfortunately, controlled trials upon which to base therapy are lacking, and most approaches are supported only by uncontrolled or anecdotal evidence. Better understanding of the pathophysiology of right heart failure and controlled trials testing therapeutic approaches are needed if we are to make progress in treating this heretofore highly mortal condition. *Key words: postoperative pulmonary hypertension, surgery, acute right heart syndrome, lung transplantation, heart transplantation, thromboendarterectomy*. [Respir Care 2009;54(7):958–968.

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Introduction

Postoperative pulmonary hypertension is a feared complication of many surgeries, contributing to increased morbidity and mortality.[1] Because it occurs sporadically in individual institutions, the epidemiology and therapy of postoperative pulmonary hypertension have not been well studied. Nonetheless, certain management principles are widely accepted. The following will discuss the classification, epidemiology, pathophysiology, evaluation, and management of postoperative pulmonary hypertension, pointing out the many areas where additional work needs to be done.

Definition and Classification

By consensus, pulmonary hypertension is defined as a mean pulmonary arterial (PA) pressure $\geq$ 25 mm Hg at rest or $\geq$ 30 mm Hg with exercise.[2] The World Health Organization classifies pulmonary hypertension into 5 groups: PA hypertension (PAH), characterized by an elevated PA pressure with a wedge pressure $\leq$ 15 mm Hg; pulmonary venous hypertension, characterized by a PA wedge pressure $>$ 15 mm Hg; pulmonary hypertension associated with chronic hypoxia or parenchymal lung disease; pulmonary hypertension caused by emboli; and miscellaneous.[2] Individuals with postoperative pulmonary hypertension could fall into any of the above categories, although the majority fall into group 1 (ie, congenital heart disease or portopulmonary hypertension pre-liver transplant) or group 2 (ie, chronic heart failure pre-transplant or left-ventricular diastolic dysfunction). Others may have multiple contributing factors and thus do not fall easily into any one group.

Epidemiology

Postoperative pulmonary hypertension occurs predictably after certain types of surgery, such as for correction of congenital left-to-right heart shunts[3] or repair or replacement of diseased mitral valves[4] (Table 1). These patients, who typically have pulmonary hypertension preoperatively, require careful preoperative evaluation to ascertain that their surgical risk is not excessive. Postoperative pulmonary hypertension also commonly persists, at least transiently, after surgery to treat pulmonary hypertension itself, such as thromboendarterectomy for chronic thromboembolic pulmonary hypertension or lung transplantation.[5,6]

Table 1. Surgeries Commonly Associated With Postoperative Pulmonary Hypertension

Transplantation
Heart: follows chronic heart failure
Lung: especially if done for pulmonary hypertension
Liver: preoperative portopulmonary hypertension
Kidney: long-term ($>$ 2 y) hemodialysis
Cardiac
Valve repair/replacement
Mitral most common
Aortic less often
Congenital heart
Congenital intracardiac shunts (ventricular septal defect more than atrial septal defect)
Left-ventricular-assist devices
Lung resection
Pneumonectomy more than lobectomy
Thromboendarterectomy
Chronic thromboembolic pulmonary hypertension

Some surgeries are done on populations at risk for pulmonary hypertension, such as heart, liver, and kidney transplants. Chronic left-sided heart failure can alter pulmonary vascular structure and tone so that persistent pulmonary hypertension can complicate the postoperative course.[7] Left-ventricular assist devices can also precipitate pulmonary hypertensive episodes, probably because of the same mechanism.[8] Portopulmonary hypertension occurs in up to 10% of patients with liver cirrhosis,[9] and a recent study demonstrated that 58% of end-stage renal failure patients on hemodialysis for at least 2 years have right-ventricular systolic pressure $>$ 35 mm Hg.[10] Thus, a low threshold for obtaining screening echocardiograms is prudent in these pre-transplant populations.

Other surgeries may precipitate pulmonary hypertension, such as when a lobectomy, or more often a pneumonectomy, is performed in a patient with insufficient pulmonary vascular reserve. Similarly, underlying pulmonary hypertension may first become apparent at the time of surgery. But more often the presence of pulmonary hypertension is known and the surgery is deemed necessary, even taking into account the greater risk.[11-13]

Pulmonary hypertension may also occur postoperatively related to factors, elucidated below, indirectly associated with the surgery. These factors may also enhance the severity of pre-existing pulmonary hypertension. Thus, although precise numbers on occurrence are lacking, pulmonary hypertension is seen in many different postoper-

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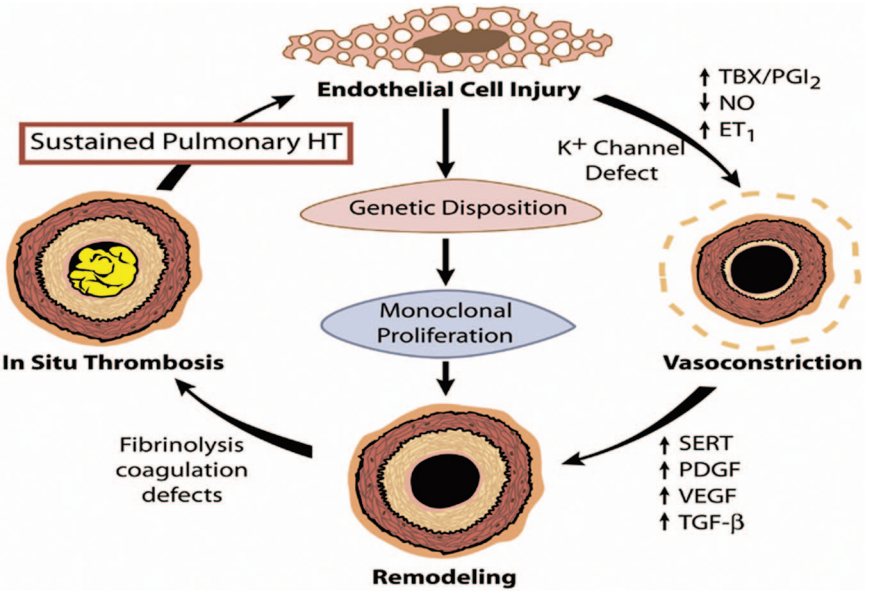

Fig. 1. Important pathophysiologic features of the development of pulmonary arterial hypertension. In the presence of a genetic predisposition, endothelial cell injury causes an imbalance of vasoactive mediators, which leads to vasoconstriction. Growth factors promote cell proliferation and may inhibit apoptosis, which favors remodeling. Hemostatic defects predispose to in situ thrombosis, which intensifies the severity of the pulmonary hypertension, which may further injure the endothelium and exacerbate the situation. TBX = thromboxane A2. PGI_2 = prostacyclin. ET-1 = endothelin 1. NO = nitric oxide. SERT = serotonin transporter. PDGF = platelet-derived growth factor. VEGF = vascular endothelial growth factor. TGFα = transforming growth factor.

ative settings and is a not-uncommon challenge for clinicians working in critical care units.

Pathophysiology

Postoperative pulmonary hypertension is best understood in the context of pulmonary hypertension generally. Much has been learned about the pathophysiology of PAH (Fig. 1), but much remains to be learned. Pulmonary endothelial injury plays a central role, altering the balance of vasoactive mediators to increase vascular tone rather than maintain its normal low level.[14] Such mediators include thromboxane, prostaglandin, and prostacyclin. Analysis of these mediators indicate that thromboxane is manufactured out of proportion to prostacyclin, favoring constriction.[15] The dysfunctional endothelium releases less of the vasodilator mediator, nitric oxide (NO), produced from L-arginine via the action of NO synthase,[16] and expression of the vasoconstrictor peptide endothelin-1 (ET-1) is increased.[17] In addition to their vasoactivity, some agents, such as ET-1, are also mitogens, driving vessel-wall remodeling (growth of smooth muscle in the media). When pulmonary hypertension is advanced, in situ thrombosis may also play a role, providing a rationale for long-term anticoagulants in many such patients.

A genetic basis for the familial form of PAH was established in 2000 with the discovery of mutations in the "pulmonary hypertension gene"—the bone morphogenic protein receptor 2 gene, which also occur in perhaps 20% of those with the sporadic idiopathic form.[18] This receptor plays a role in regulation of cellular proliferation, and it is theorized that mutations predispose to dysregulated growth of pulmonary vascular smooth muscle, leading to vessel wall remodeling. Although a genetic predisposition may play a role in the occurrence of other forms of pulmonary hypertension in the postoperative setting, this possibility requires additional study.

Table 2. Potentially Reversible Pathophysiologic Factors Contributing to Postoperative Pulmonary Hypertension

Preoperative pulmonary hypertension
Fluid overload
Left-ventricular failure: systolic or diastolic
Acute lung injury/acute respiratory distress syndrome
Pulmonary emboli
Acidosis
Hypoxia

Many other factors can contribute to postoperative development or worsening of pulmonary hypertension (Table 2).[19] The anesthesia or surgery itself may have deleterious effects via direct actions on the vasculature, or indirectly via the release of cytokines and other inflammatory mediators that depress cardiac function, injure the pulmonary endothelium, and modulate NO or endothelin-1 release, increasing pulmonary vascular tone. If endothelial

damage is sufficient to alter the permeability barrier, the acute respiratory distress syndrome (ARDS) can result. Overzealous fluid administration during surgery can be damaging in such patients, or in those with chronic systolic or diastolic heart failure.

Ultimately the cause of death in most patients with postoperative pulmonary hypertension is right-heart failure. The ability of the right heart to handle the added strain of augmented pulmonary pressure in the postoperative setting may be the most important determinant of survival. Under normal circumstances, the right heart operates under low pressures, relative to the left heart, and can accommodate large swings in volume, but not pressure. In response to acute increases in afterload, which might occur with massive pulmonary embolism, for example, the previously normal right-ventricle is capable of sustaining increases in PA pressure only up to a mean of approximately 40 mm Hg.[20] However, over time it adapts by hypertrophying and becoming more of a pressure generator. This process is not well understood, nor is it understood why some right-ventricles fail when others can cope quite well with pressures that approach or even equal systemic levels.

Hypoxia and cardiac ischemia probably contribute when the right ventricle fails. Underlying coronary atherosclerosis may contribute, but, more alarmingly, a drop in the systemic below the PA blood pressure can compromise right-ventricular perfusion. Right-ventricular ischemia and cardiovascular collapse may ensue. This scenario is sometimes referred to as a pulmonary hypertensive crisis or the acute right heart syndrome,[21] characterized by right-ventricular dilatation and hypocontractility by echocardiogram, elevation of right atrial pressure, and systemic hypotension. Unless prompt measures are taken to ameliorate the situation, patients who develop this syndrome become profoundly hypotensive, with worsening hypoxia and metabolic acidosis leading inexorably to death.

Risk Factors for Postoperative Complications

When pulmonary hypertension is known preoperatively, risk factors for postoperative complications can be assessed to aid in deciding whether to proceed with the surgery and how to prepare for potential complications (Table 3). A number of studies have examined risk factors for operating on children or adults with congenital heart disease. Patients with excessively high baseline pulmonary vascular resistance ($>$ 6 Wood units [1 Wood unit = 80 dyn $\cdot$ s $\cdot$ cm^{-5}]) or those without substantial vasodilator responsiveness (inability to reduce pulmonary vascular resistance to below 3 Wood units) are considered poor surgical candidates.[3] A more recent study[22] examined the combination of inhaled NO and oxygen supplementation in patients undergoing corrective cardiac surgery or heart transplantation. They found that a decrease in the ratio of pulmonary to systemic vascular resistance (an index of pulmonary specificity) of at least 20%, to below 0.33, reliably identified patients at low risk of complications. Although not yet firmly established, this approach appears to be helpful in the evaluation of pre-transplant or cardiac surgery patients.

Table 3. Risk Factors for Postoperative Complications in Patients With Preoperative Pulmonary Hypertension

Cardiac surgery: congenital shunt repair
High preoperative pulmonary vascular resistance ($>$ 6 Wood units)
Less vasoreactivity ($<$ 20% drop in pulmonary vascular resistance to acute vasodilator)
Lack of pulmonary specificity (ratio of pulmonary to systemic vascular resistance fails to drop below 0.33 in response to vasodilators)
Non-cardiac surgery
High estimated pulmonary arterial systolic pressure ($>$ 70 mm Hg)
Underlying coronary artery disease
Emergency surgery
Intermediate to high risk surgery
New York Heart Association functional class $\geq$ 2
History of pulmonary embolism
Prolonged anesthesia ($>$ 3 h)
Right-axis deviation or right-ventricular hypertrophy on electrocardiogram
Ratio of right-ventricular to systemic systolic blood pressure $>$ 0.66
Need for vasopressor

(Adapted from References 12, 13, and 22.)

Other investigators have identified risk factors in patients with underlying pulmonary hypertension undergoing non-cardiac surgery.[11-13] Surgical mortality rates ranged from 7% to 24% in such patients,[11,13] with morbidity rates approaching 50%. Right-heart failure was responsible for most of the mortality, but complications such as aspiration pneumonia, sepsis, and renal failure also contributed.[11] In a case control study that compared 62 patients with preoperative estimated PA systolic pressures $>$ 70 mm Hg with a matched group whose PA systolic pressures were estimated at $<$ 35 mm Hg, Lai et al[12] found that emergency surgery, underlying coronary artery disease, and a higher systolic PA pressure were all risk factors for mortality. Ramikrishna et al[13] identified 145 patients with estimated PA systolic pressure by echocardiogram $\geq$ 35 mm Hg who had undergone surgery at the Mayo Clinic since 1991. Risk factors for mortality included right-axis deviation and right-ventricular hypertrophy on the electrocardiogram, a history of pulmonary embolism, a ratio of right-ventricular to systemic systolic pressure $>$ 0.66, the need for vasopressors, and anesthesia without nitrous oxide.

These investigations demonstrate that preoperative identification of patients at risk is possible. Not surprisingly,

higher PA pressure, indices of poor right-ventricle function, and hemodynamic instability are important predictors, but none of the studies indicated that the type of anesthesia (spinal vs general) made any difference. Also, none of the studies assessed the effects of preoperative treatment of the pulmonary hypertension on surgical outcome—something that would be of great interest in the future.

Evaluation

Preoperative detection of pulmonary hypertension and assessment of the risk for postoperative complications are ideal, but pulmonary hypertension may be undetected preoperatively or arise perioperatively or postoperatively, rendering management more challenging. Patients at risk of having pulmonary hypertension should be screened with an echocardiogram to determine not only estimated PA systolic pressure, but, more importantly, functional status of the right ventricle. It is important to recognize that estimates of PA systolic pressure via transthoracic echocardiogram can be inaccurate, and that PA pressure may not be markedly elevated when the right ventricle is failing. Thus, regardless of the PA pressure estimate, detection of a dilated right ventricle with paradoxical septal motion gives incontrovertible evidence of a serious problem. Brain natriuretic peptide and functional capacity, as determined with a 6-min walk, are also helpful in assessing cardiovascular reserve. Ultimately, though, patients with echocardiographic evidence of substantial pulmonary hypertension should undergo a right-heart catheterization for confirmation and characterization. Right-heart catheterization gives direct measurements of PA pressure, as well as right-atrial and PA wedge pressure, to determine filling characteristics of the right and left heart, respectively. A high right-atrial pressure, especially when combined with a low cardiac index, indicates a failing right ventricle and should raise serious concerns about the advisability of doing surgery.

Additional studies that can be done at the time of catheterization include vasoreactivity testing with relatively specific pulmonary vasodilators such as inhaled NO or intravenous adenosine. The utility of eliciting a "significant" vasodilator response has already been discussed for the identification of patients at high or low risk following cardiac surgery.[22] Exercise is also useful at the time of catheterization, to assess cardiac reserve and the ability of the pulmonary circulation to accommodate increases in blood flow. A left-heart catheterization may be useful if there is doubt about the patency of the coronary arteries or the measurement of left-ventricular filling pressure based on the right-heart catheterization.

Although the effect on outcomes of monitoring central hemodynamics with a right-heart catheter during surgery has not been established, our practice is to insert one preoperatively in patients with moderate to severe pulmonary hypertension. This permits monitoring not only of PA pressure but also of ventricular filling pressure and cardiac output—measurements that might be very helpful in the presence of hemodynamic instability.

When pulmonary hypertension arises or intensifies postoperatively, additional testing should be contemplated. Fluid volume should be assessed with a careful bedside evaluation, measurement of central venous pressure, and consideration of right-heart catheter placement if not already done. Brain natriuretic peptide measurement lacks specificity in this situation, but marked elevations (above 1,000 μg/mL) suggest dysfunction of not just the right but also left ventricle. In addition, superimposed pulmonary thromboembolism should always be considered as a potential complicating factor. Thromboembolic events occur most commonly 3 or 4 days postoperatively, but may occur sooner. Ventilation-perfusion lung scanning is more sensitive than computed tomography in detecting distal clots, but in the presence of parenchymal abnormalities on a standard chest radiograph, computed tomography with the pulmonary embolism protocol is the preferred study.

Management of Postoperative Pulmonary Hypertension

Management of postoperative pulmonary hypertension depends on its severity and the results of a careful evaluation. If a patient has mild to moderate pulmonary hypertension, preservation of right-heart function, and is otherwise clinically stable, then the pulmonary hypertension can merely be observed, assuming fluid status, left-side filling pressure, and systemic blood pressure are optimized. On the other hand, the acute right heart syndrome constitutes an emergency that demands aggressive treatment. Although few randomized studies have been performed to determine optimal management practices, certain principles of management are based on experience and are widely accepted (Table 4).

Treatment of Predisposing Factors

A careful and systematic evaluation of predisposing factors, as outlined above, is obligatory in managing postoperative pulmonary hypertension, and dictates subsequent management. Obviously, if the patient is in respiratory failure or has underlying pulmonary embolism, specific therapies for these conditions should be instituted immediately.

Certain predisposing factors should be addressed in any patient with the acute right heart syndrome, before consideration of specific pulmonary hypertension therapies. Fluid balance is critically important because of the dangers

Table 4. Basic Principles of Managing Postoperative Pulmonary Hypertension

Optimize fluid balance
Avoid excessive fluid in patient with distended inferior vena cava and right ventricle
Optimize metabolic state
Correct acidosis, hypoxemia, anemia
Treat respiratory failure
Intubated patient
Lung-protective ventilation strategy (tidal volume 6 mL/kg, plateau pressure < 30 cm H_2O)
Optimize oxygenation
Maintain systemic perfusion pressure
Mean systemic blood pressure $>$ mean pulmonary arterial pressure
Pressors if necessary
Optimize cardiac output
Use inotropes to maintain cardiac index > 2 L/min/m^2
Attempt to reduce right-ventricular afterload
Avoid systemic vasodilators
Use pulmonary vasodilators: inhaled vasodilators are less likely to have adverse effects on systemic blood pressure or oxygenation.
Consider combinations

of both under-hydration and over-hydration. Under-hydration can precipitate systemic hypotension due to low cardiac output related to inadequate ventricular filling during diastole. But over-hydration can impede cardiac performance due to the principle of ventricular interdependence. When the right ventricle is markedly dilated, it impinges on the left ventricle and interferes with left-ventricular filling. Aggressive fluid resuscitation can exacerbate this problem by further increasing right-ventricular volume. For this reason, bolus administration of crystalloid solutions in 250–500 mL quantities, followed by careful reassessments, is preferred to larger, sustained infusions of fluid. If a bolus of fluids improves cardiac output and systemic blood pressure, then further boluses are given until an end point is reached, such as a certain perfusion target or adverse effects.

Although its value is no better established in this setting than in patients with sepsis or ARDS, we advocate insertion of a right-heart catheter to monitor pressure, cardiac output, and central hemoglobin saturations. These are helpful in assessing ventricular filling pressure, although care must be exercised in interpretation. Because of the problem of ventricular interdependence, the pulmonary artery wedge pressure can be elevated in the presence of a small left-ventricular end-diastolic volume due to the encroaching right ventricle, creating the illusion of excessive left-heart filling. Transthoracic echocardiography can be helpful in this situation, although it may not reliably detect small but clinically important changes in right-ventricle volume. If the inferior vena cava is markedly dilated on transthoracic echocardiography, fluids are unlikely to help. Also, obese patients and those with emphysema pose challenges in finding adequate echocardiographic windows. For the latter reason, transesophageal echography may be preferable to transthoracic echocardiography to evaluate right-ventricular function in these patients.[23]

Other factors to consider include hemoglobin concentration, which can be insufficient or excessive. An insufficient hemoglobin concentration compromises oxygen delivery, which can already be limited by a low cardiac output and can become critical in the right ventricle, where the perfusion gradient may already be marginal. An excessive hemoglobin concentration is associated with a high hematocrit, the major determinant of blood viscosity, which increases resistance to blood flow.[24] Transfusion or phlebotomy, depending on the initial value, can help to restore stability. The optimal hemoglobin concentration for patients with the acute right heart syndrome is unknown, but values below 9 g/dL or greater than 18 g/dL are probably undesirable.

High-tidal-volume mechanical ventilation also appears to contribute to right-ventricular dysfunction. In 1985, an echocardiographic study reported a 61% incidence of acute cor pulmonale (a manifestation of the acute right heart syndrome denoting a pulmonary precipitant, defined in the study as a right-ventricular-to-left-ventricular surface-area ratio of > 0.6) in patients receiving mechanical ventilation for ARDS.[25] In 2001, a study from the same critical care unit found that the incidence of acute cor pulmonale in such patients had dropped to 25%, in association with the adoption of lung-protective ventilation for ARDS in the late 1990s.[26] The likely explanation for the drop is that in 1985 the use of excessive tidal volumes overdistended the lung, not only contributing to volutrauma and acute lung injury, but also increasing pulmonary vascular resistance and thereby right-ventricular afterload. Lower tidal volume and a lung-protective ventilation strategy protect not only the lungs but also the heart, helping to keep right-ventricular impedance lower. For ventilation of ARDS patients, current recommendations are to use tidal volume of no more than 6 mL/kg and plateau pressure of < 30 cm H_2O.[27] The same recommendations would apply to patients with pulmonary hypertension in the postoperative setting receiving mechanical ventilation, although we acknowledge that confirmatory studies have not been done in this setting.

Maintain Systemic Perfusion Pressure

For preservation of right-ventricle perfusion, maintenance of an adequate systemic blood pressure is paramount in managing postoperative pulmonary hypertension. If systemic hypotension persists despite optimization of fluid volume and ventilator settings, then vasopressors must be promptly initiated. Systemic blood pressure should be

maintained above PA pressure if possible, but overzealous use of pressors should also be avoided, because they can increase right-ventricular afterload and myocardial oxygen consumption.

No single vasopressor has demonstrated superiority over another. During the late 1980s, Angle et al[28] reported on the advantages of norepinephrine in a dog model of pulmonary hypertension induced by pulmonary emboli. This pressor maintained systemic blood pressure by increasing stroke volume and cardiac output, but without altering renal perfusion or pulmonary vascular resistance. Dopamine, at an intravenous infusion rate $\geq$ 5 μg/min,[29] and epinephrine[30] are both effective pressors but tend to increase heart rate and myocardial oxygen consumption more than norepinephrine. A report of the successful use of vasopressin to treat systemic hypotension in 2 patients with severe idiopathic PA hypertension undergoing Caesarian section suggested that vasopressin might be particularly attractive in this situation because it is not only a systemic vasopressor but can also dilate pulmonary arteries.[31] However, no firm recommendations regarding specific agents can be made because none has been tested adequately in patients with postoperative pulmonary hypertension.

Maintain Cardiac Output

The systemic hypotension seen in the acute right heart syndrome is associated with a low cardiac output, as the right ventricle fails in the presence of high impedance. Inotropes (agents that increase cardiac contractility) can be very helpful in restoring cardiac output, and, occasionally, the improvement in flow can restore systemic perfusion pressure without the need for pressors. However, inotropes are also systemic vasodilators, and combination with pressors is usually necessary.

Inotropes commonly used to treat the acute right heart syndrome fall into 2 main categories: catecholamines and phosphodiesterase-3 inhibitors. No clear advantage of one class over the other has been established, although there are differences.[32] The positively inotropic catecholamines (dobutamine, low-dose dopamine and epinephrine) all act mainly via β_1 and β_2 adrenergic receptors, increasing contractility as well as heart rate, and vasodilating systemic blood vessels. Dobutamine is usually the preferred catecholaminergic inotrope because of greater β-receptor agonism relative to α agonism. Especially at higher doses, both dopamine and epinephrine are greater α agonists, which may increase systemic vascular impedance.[30]

The phosphodiesterase-3 inhibitors (amrinone and milrinone), on the other hand, slow the metabolism of the intracellular second messenger, cyclic adenosine monophosphate, enhancing its actions, which include, among many others, increasing cardiac contractility. Although the hemodynamic effects of the 2 classes of agents in patients with low-cardiac-output syndromes are quite similar, the phosphodiesterase-3 inhibitors tend to increase heart rate less and augment stroke volume more than the catecholeminergic agents.[32,33] Whether these tendencies impact outcomes in patients with postoperative pulmonary hypertension is unknown.

Levosimendan is another positive inotrope that has theoretical advantages in the treatment of the acute right heart syndrome. It is available in nearly 50 countries worldwide but has not been approved by the Food and Drug Administration (FDA) in the United States. A calcium sensitizer, it enhances contractility without increasing myocardial oxygen consumption.[34] It also has pulmonary and systemic vasodilator effects via actions on vascular smooth muscle potassium channels as well as anti-ischemic effects via actions on mitochondrial K^+-adenosine triphosphate channels.[35] Several case reports have described its successful use in patients with severe pulmonary hypertension following mitral valve surgery.[36,37] However, in the absence of larger more systematic studies, its effectiveness for patients with postoperative pulmonary hypertension remains largely unknown.

Pulmonary Vasodilators

Once treatable predisposing factors, systemic and right-ventricular perfusion, and cardiac output have been optimized or at least stabilized, attempts at lowering PA pressure can be made. To attempt this earlier is inadvisable because many of the pulmonary vasodilating agents are also systemic vasodilators and can further destabilize systemic hemodynamics. Also, normalization of elevated left-ventricular filling pressure can sometimes eliminate pulmonary hypertension without any need for pulmonary vasodilators. Unfortunately, few studies are available on use of pulmonary vasodilators to treat postoperative pulmonary hypertension. The following synopsis will therefore rely on evidence obtained from studies performed on patients with PA hypertension in the long-term setting as well as studies on the acute right heart syndrome.

The main goal of pulmonary vasodilation in patients with pulmonary hypertension is to lower right-ventricular impedance, thus decreasing afterload and improving ventricular performance. Cardiac output should thereby increase, improving systemic perfusion, including that of the right ventricle. Unfortunately, this goal is often difficult to achieve, because patients often have "fixed" pulmonary hypertension, with little or no capacity to relax. In contrast to the systemic circulation, merely raising the vasodilator dose may not only fail to dilate the pulmonary vessels but may in fact potentiate systemic vasodilation, which can worsen the hemodynamic crisis. In addition, systemic vasodilation can increase blood flow through right-to-left

shunts, such as a patent foramen ovale, worsening oxygenation. Thus, pulmonary vasodilators must be administered with extreme caution, with close monitoring of hemodynamics and oxygenation.

Presently, 6 pharmacotherapeutic agents have been approved by the FDA for therapy of PAH, representing 3 pharmacologic pathways: the prostacyclins, intravenous epoprostenol, subcutaneous or intravenous treprostinil, and inhaled iloprost, which act by stimulating adenylate cyclase to generate cyclic adenosine monophosphate; the endothelin receptor antagonists, including oral bosentan and oral ambrisentan, which block the vasoconstrictor and mitogenic actions of endothelin-1; and the phosphodiesterase-5 inhibitors, including sildenafil and possibly tadalafil (under consideration by the FDA), which slow the metabolism of cyclic guanosine monophosphate (GMP), intensifying its vasodilator and antiproliferative actions. A detailed discussion of these agents is beyond the scope of this review and can be found elsewhere.[38,39] We will focus only on aspects relevant to the management of postoperative pulmonary hypertension. We will also consider agents that have been reported to be potentially useful in this setting, even if they have not been specifically approved for this indication by the FDA.

Systemic Vasodilators

One of the earliest reports on the management of postoperative pulmonary hypertension described 3 pediatric patients who underwent repair of ventricular septal defects and developed right-heart failure and responded favorably to tolazaline, an α adrenergic receptor blocker.[40] Unfortunately, subsequent experience has been less favorable. These agents, including intravenous nitroglycerin and nitroprusside, calcium channel blockers, angiotensin-converting-enzyme inhibitors, and hydralazine, often vasodilate systemic vessels more than pulmonary vessels, aggravating systemic hypotension and worsening hypoxemia in these very tenuous patients, and should be avoided.

Prostacyclins

Infused prostacyclins are potent pulmonary vasodilators and are commonly used as "rescue" therapies for patients with very severe PA hypertension, including the acute right heart syndrome. Of the 2 intravenous prostacyclins available, eposprostenol is the preferred one for acute right heart syndrome because its shorter half-life (3–4 min, as opposed to 3–4 h with treprostinil) makes it safer in unstable patients. In one study after heart transplantation, intravenous prostacyclin was an effective pulmonary vasodilator, lowering PA pressure more than nitroglycerin and the same as nitroprusside, but it had no more specificity as a pulmonary vasodilator.[41] This lack of pulmonary specificity can be a serious limitation of infused prostacyclins, because they can worsen systemic hypotension and oxygenation.

When administered via inhalation, however, prostacyclins have much greater pulmonary specificity. Not only are they much less likely to worsen systemic hypotension than when given via the infused route, but they may also enhance oxygenation by increasing blood flow to ventilated areas, thus improving the ventilation-perfusion ratio.[42] Accordingly, inhaled iloprost has been used as a vasodilator in the postoperative setting. In one study,[43] 11 patients were treated with a 25-μg inhalation of iloprost, and pulmonary vascular resistance dropped from 503 $dyn \cdot s \cdot cm^{-5}$ to 328 $dyn \cdot s \cdot cm^{-5}$ 30 min later. There was no significant change in a group of controls treated with inhaled saline. In a second series of 20 patients treated with a 25-μg inhalation of iloprost after mitral valve repair, pulmonary vascular resistance dropped from 422 $dyn \cdot s \cdot cm^{-5}$ to 208 $dyn \cdot s \cdot cm^{-5}$, right-ventricular ejection fraction improved, and the effect was more pulmonary-specific than that of intravenous nitroglycerin.[44]

Interest has also been growing in the use of inhaled epoprostenol for the acute right heart syndrome, because it has a shorter half-life than iloprost (3–4 min vs 20 min) and thus might offer a safety margin in very unstable patients. It is provided via continuous nebulization, via the ventilator tubing in intubated patients, or via face mask. In one series of 126 patients with mild to moderate pulmonary hypertension (mean PA pressure $>$ 30 mm Hg) following various kinds of surgery, including cardiac, lung transplants, and lung resections, inhaled epoprostenol lowered mean PA pressure from 35 mm Hg to 24 mm Hg and improved cardiac output, with no change in oxygenation or systemic blood pressure.[42] The relative pulmonary vasodilator efficacy, comparable dosing, and suitability for longer-term administration of inhaled versus intravenous epoprostenol have not been adequately investigated.

Endothelin Receptor Antagonists

Bosentan and ambrisentan are generally considered long-term therapies for pulmonary hypertension. Bosentan inhibits acute hypoxic pulmonary hypertension and has acute favorable effects in patients with chronic heart failure,[45] but has not been studied for acute pulmonary hypertension in a clinical setting. The tendency of these agents to promote fluid retention could be a limitation for longer-term use in these patients.

Nitric Oxide/Cyclic GMP Pathway

NO stimulates guanylate cyclase to generate cyclic GMP, which mediates vasodilation and inhibits smooth muscle cell proliferation. Because it combines the advantages of

potent pulmonary vasodilation, virtual absence of systemic effects, by virtue of its immediate inactivation by hemoglobin, and ability to improve oxygenation like other inhaled agents, some have considered inhaled NO the "drug of choice" for intraoperative pulmonary hypertension.[19] It offers a safety margin, and with a commercially available delivery device (INO Therapeutics, Clinton, New Jersey) is easy to administer and titrate, either via mechanical ventilator or face mask. Numerous case reports and small series and a few randomized trials have been reported on its application for acute right heart syndrome, both in the postoperative setting and otherwise. However, in a Cochrane analysis of 4 randomized trials in children who underwent surgery for congenital heart disease complicated by pulmonary hypertension, those authors found no significant effects on mortality or hemodynamics, including mean PA pressure or oxygenation.[46] Furthermore, in a series of 26 patients with the acute right heart syndrome, Bhorade et al[21] found that only 54% responded favorably ($>$ 20% drop in pulmonary vascular resistance) and two thirds subsequently developed a withdrawal syndrome (consisting of systemic hypotension and worsened oxygenation) when inhaled NO was tapered. Furthermore, mortality was 80% among the responders and only 50% among non-responders. Considering that inhaled NO costs up to $3,000 per day and the lack of clinical data to support its efficacy, it must be acknowledged that labeling it the "drug of choice" is a bit premature.

By slowing the metabolism of cyclic GMP, sildenafil potentiates the beneficial effects of NO. A number of case reports and small series have demonstrated that sildenafil is a potent acute vasodilator in patients with pulmonary hypertension. One study showed that sildenafil is comparable to intravenous epoprostenol as a pulmonary vasodilator, lowering mean PA pressure and pulmonary vascular resistance in such patients by 12% and 30%, respectively.[47] In 13 patients following heart transplantation complicated by pulmonary hypertension, sildenafil (3 mg/kg/d up to 250 mg) was given via nasogastric tube. Pulmonary vascular resistance dropped from 832 $dyn \cdot s \cdot cm^{-5}$ to 448 $dyn \cdot s \cdot cm^{-5}$, without systemic hypertension, and all patients weaned from mechanical ventilation within 3 days.[48] In another series of 10 patients who developed pulmonary hypertension after placement of a left-ventricular assist device, sildenafil (25–50 mg orally) lowered mean PA pressure without affecting systemic pressure.[49] Thus, sildenafil is a promising agent to treat postoperative pulmonary hypertension, by virtue of its rapid onset, potent vasodilatory effect, and relative pulmonary specificity. However, it is not devoid of systemic effects, and worsening of systemic hypotension remains a concern in unstable patients.

Combination Therapy

Considering that no one agent has demonstrated superiority to treat postoperative pulmonary hypertension, and multiple agents have potential favorable actions, numerous combinations have been tried in an attempt to get additive effects to treat the condition. One popular combination is to add a vasodilator agent such as inhaled NO to an inotrope such as dobutamine, which can provide complementary benefits.[50] Combining specific pulmonary hypertension therapies that work via different pathways is also attractive. A report on the combination of intravenous epoprostenol and inhaled NO used to treat a patient after liver transplantation supports this approach.[51] A twist on this theme is to combine inhaled iloprost with inhaled NO to enhance pulmonary specificity. A case report demonstrated additive effects of this combination following thromboendarterectomy.[52] Sildenafil combined with inhaled NO has also become popular, not only because the 2 have additive effects,[47] but also because sildenafil reduces the likelihood of withdrawal from inhaled NO.[53] Sildenafil also potentiates the action of brain natriuretic peptide, a vasodilatory cardiac hormone that is synthesized and released by ventricular cardiomyocytes in response to stress and other stimulatory factors.[54] By slowing the metabolism of cyclic GMP, sildenafil synergizes the stimulatory action of brain natriuretic peptide on particulate guanylate cyclase and enhances pulmonary vasodilation with only minor effects on systemic blood pressure.[54] It could prove to be useful in treating acute right heart deterioration, but hasn't been adequately tested in clinical settings.

Summary

Postoperative pulmonary hypertension complicates many types of surgery, including lung and heart transplantation, pulmonary thromboendarterectomy, congenital heart-disease repair, and others. If sufficiently severe to provoke acute right heart syndrome, postoperative pulmonary hypertension poses a daunting therapeutic challenge associated with a high mortality. Patients must be carefully evaluated with an eye to identifying and ameliorating reversible contributing factors such as fluid and metabolic imbalance, hypoxemia and ischemia. A PA catheter and echocardiogram are recommended, although their value has not been established. Basic principles of management include maintenance of systemic perfusion pressure, optimization of cardiac inotropy, a lung-protective ventilation strategy, and attempting to reduce right-ventricular afterload with pulmonary vasodilators. Unfortunately, controlled trials upon which to base therapy are lacking, and most approaches are supported only by uncontrolled or anecdotal evidence. Better understanding of the pathophysiology of right-heart failure and controlled trials of thera-

pies are needed if we are to make progress in treating this heretofore highly mortal condition.

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