Pulmonary Hypertension and Noncardiac Surgery: Implications for the Anesthesiologist

Leila Hosseinian, MD

The perioperative management of patients with pulmonary hypertension (PH) is a growing concern for anesthesiologists worldwide as more patients with PH are presenting for elective noncardiac surgery. As a direct result of increased awareness and discovery of new medical therapies, patients with PH not only have a longer life expectancy, but also an improved quality of life. Despite these recent advances, surgery still poses a significant risk for patients with PH. A considerable amount of data already have been published showing increased mortality and morbidity in patients undergoing cardiac surgery with PH. There are, however, much less data investigating the outcomes of patients with PH in the setting of noncardiac surgery. In a retrospective study by Ramakrishna et al, 42% of PH patients who underwent noncardiac surgery had 1 or more short-term morbid events, and 7% of patients had early death, which was due primarily to respiratory or right ventricular (RV) failure. These outcomes have been compared to other high-risk populations undergoing noncardiac surgery such as elderly patients older than 80 years of age who experienced a mortality of 4.6%, or those older than 65 years who experienced a mortality of 3.4%. This review will discuss the classifications, pathophysiology, and the anesthetic management of patients with PH for noncardiac surgery.

CASE PRESENTATION

A 67-year-old woman with World Health Organization (WHO) group 1 PH (pulmonary artery pressure 72/44/30 mmHg) presented for a below-the-knee amputation. Her exercise tolerance was poor, showing signs of dyspnea on minimal exertion, New York Heart Association (NYHA) class III. The patient had a history of calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome. The anesthesiologist was notified by the surgeon about the medical complexity of this case a few weeks in advance in order to properly prepare and initiate a thorough preoperative workup. Her chest computed tomography (CT) scan showed evidence of severe bronchiectasis. Her pulmonary function test (PFT) results were normal with the exception of her diffusion capacity of the lung for carbon monoxide (DLCO) being severely reduced (36% of predicted). She required supplemental oxygen at home. Her transthoracic echocardiogram (TTE) showed normal left ventricular (LV) size and performance, severe RV dilation with moderate hypertrophy and severely reduced function. On her right-heart catheterization, her pulmonary artery pressures (PAPs) were unresponsive to the treatment trials of a variety of therapies for PH, so her cardiac regimen only included aspirin, diuretics and digoxin. She was taking coumadin for prevention of thromboembolic events. Considering her comorbidities, the amputation had been delayed by the surgeon, but her leg had now become gangrenous, making the amputation relatively urgent.

The patient had been optimized medically prior to the day of surgery. A regional anesthetic had been agreed upon by the patient, anesthesiologist, and surgeon. In lieu of this, the patient was to stop coumadin 5 days prior to surgery. Since the indication for coumadin was her severely reduced RV function, her cardiologist did not deem it necessary to bridge her with low-molecular-weight heparins (LMWHs). It was decided that an epidural anesthetic would be the ideal technique, as it could be used intraoperatively as well as postoperatively for pain control without resulting in respiratory compromise. The patient, however, was very anxious and did not want to be fully aware during the procedure. A dexmedetomidine infusion was administered in order to decrease the patient’s level of awareness without causing any respiratory depression, which could cause an unwanted elevation of pulmonary vascular resistance (PVR). Intraoperative monitoring included an indwelling arterial catheter and a central venous line. The arterial catheter was placed prior to the administration of any sedation or epidural placement. After the successful placement of a catheter into the epidural space, a 7-French triple-lumen catheter was inserted into the patient’s right internal jugular vein. The epidural anesthetic was injected. In anticipation of local-anesthetic-induced sympathetic blockade, the patient’s hemodynamic status was monitored closely and shifts were corrected promptly with intravenous vasoadilatory medications. The central venous pressure (CVP) during the case was kept close to the baseline CVP (15 mmHg) upon placement of the central venous line. In addition to monitoring the CVP, the central line provided the anesthesia team with secure vascular access in case the administration of vasoadilatory medications became necessary. Pulmonary vasodilators were not used since the patient’s right-heart catheterization had shown no improvement with their use.

Intraoperatively, the case proceeded smoothly; hypoxia, hypercarbia, acidosis, and pain were avoided. Hemodynamically, intravascular fluid administration was only to compensate for the small amount of blood lost. The patient went to the intensive care unit (ICU) for close monitoring postoperatively. She did well during her ICU stay until the epidural catheter was removed. Pain control without the epidural was challenging. On postoperative day 6, the patient developed respiratory distress, which resulted very precipitously in cardiac arrest from which she could not be resuscitated. An autopsy showed that the patient suffered from a saddle embolus in her pulmonary artery.
DEFINITION AND CLASSIFICATION

Pulmonary hypertension is defined as a persistent elevation of mean PAP at rest of 25 mmHg or greater.12–14 PH was categorized by the World Health Organization (WHO) in 2008 into 5 different groups (Table 1).12–14 The group classification is determined by the underlying pathophysiology. This diversity results in the need for different treatments and management strategies that are group-specific. WHO Group 1, pulmonary arterial hypertension (PAH), is a disease of the distal pulmonary arteries. This disease results in changes to the pulmonary vasculature, which include pulmonary arterial vasoconstriction, smooth muscle hypertrophy, intimal and adventitial proliferation with eventual fibrosis, complex plexiform lesions, and thrombotic lesions.15–17 The changes in the pulmonary vasculature cause increases in PAP and PVR without an elevation of the pulmonary capillary wedge pressure (PCWP). Initially, the vascular remodeling can be characterized as reversible vasoconstriction; however, eventually it will progress to a fixed disease process, unresponsive to pulmonary vasodilator therapy.18

These pathologic pulmonary arterial changes usually are not evident in WHO Group 2, which is a more common form of PH. When elevated pulmonary artery systolic pressures (PASP) are detected on echocardiography, the etiology is most likely pulmonary venous hypertension due to left-heart disease. WHO Group 2 makes up more than 65% of all patients diagnosed by echocardiography with PH.19 Although left-heart disease is the most common cause of PH, there is a paucity of data on the frequency of pathologic pulmonary vascular changes in this heterogeneous group of patients.15,20 In this setting, post-capillary PH-elevated PA pressures may be due to passive back pressure due to elevations in left-heart pressures (Fig 1).21–23 Mixed PH includes increases in PAP due to elevated left heart filling pressures with “reactive” changes due to superimposed pulmonary vasoconstriction and vascular remodeling.24–26 Groups 3, 4, and 5 represent a similar pathophysiology as in Group 1 since they all result in elevations of PAP and PVR with normal PCWP. The treatment strategies are also similar for groups 1, 3, 4, and 5 compared to 2. Of note, although obstructive sleep apnea (OSA) is a cause of PH Group 3, only a minority of patients with OSA actually develop PH. A recent retrospective study found only a 17% incidence of PH among OSA patients.27 Patients with OSA are more likely to progress to PH if they have an additional underlying pulmonary disease.27 The presence of PH, regardless of group classification, has been shown to be a marker of poor prognosis and increased mortality in patients with heart failure.21,26,28

Signs and symptoms of pulmonary hypertension are non-specific and similar to those of heart failure, often resulting in delayed diagnosis (Table 2). Since exertional dyspnea and fatigue are the most common initial complaints, patients often discount their symptoms and wait to seek medical attention.29 Eventually, when the RV is affected and starts to fail, PH patients will experience peripheral edema, hepatomegaly, ascites, and elevated jugular venous pressures.27,30

Table 1. World Health Organization Classification of Pulmonary Hypertension (2008)12

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Examples</th>
<th>Classification</th>
<th>Hemodynamics</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Pulmonary arterial hypertension</td>
<td>Idiopathic, heritable, drug- and toxin-induced, associated with connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, persistent pulmonary hypertension of the newborn</td>
<td>Pre-capillary PH</td>
<td>Mean PAP (mmHg): &gt; 25 PCWP or LVEDP (mmHg): &lt; 15 PVR (dynes·s·cm⁻²): &gt; 240</td>
</tr>
<tr>
<td>1'</td>
<td>PVOD and/or PCH</td>
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<tr>
<td>2</td>
<td>PH due to left-heart disease</td>
<td>Chronic severe left-sided valve disease, left ventricular systolic or diastolic heart failure</td>
<td>Post-capillary PH Mixed PH</td>
<td>Mean PAP (mmHg): &gt; 25 PCWP or LVEDP (mmHg): &lt; 15 PVR (dynes·s·cm⁻²): &gt; 240 Post-capillary PH PVR (dynes·s·cm⁻²): &gt; 240</td>
</tr>
<tr>
<td>3</td>
<td>PH due to lung disease and/or hypoxia</td>
<td>COPD, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation, chronic exposure to high altitudes</td>
<td>Pre-capillary PH</td>
<td>Mean PAP (mmHg): &gt; 25 PCWP or LVEDP (mmHg): &lt; 15 PVR (dynes·s·cm⁻²): &gt; 240</td>
</tr>
<tr>
<td>4</td>
<td>Chronic thromboembolic PH</td>
<td>Thrombotic obstruction of the pulmonary arteries</td>
<td>Pre-capillary PH</td>
<td>Mean PAP (mmHg): &gt; 25 PCWP or LVEDP (mmHg): &lt; 15 PVR (dynes·s·cm⁻²): &gt; 240</td>
</tr>
<tr>
<td>5</td>
<td>PH with unclear or multifactorial mechanisms</td>
<td>Myeloproliferative disorders, splenectomy, sarcoidosis, glycerol storage disease, neurofibromatosis, vasculitis, thyroid disease, chronic renal failure on dialysis, tumor obstruction, fibrosing mediastinitis</td>
<td>Pre-capillary PH</td>
<td>Mean PAP (mmHg): &gt; 25 PCWP or LVEDP (mmHg): &lt; 15 PVR (dynes·s·cm⁻²): &gt; 240</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery pressures; PH, pulmonary hypertension; PVOD, pulmonary venoocclusive disease; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.
Electrocardiogram (ECG) and chest x-ray (CXR) findings lack the sensitivity or specificity necessary to use them as a screening method. Although the gold standard for diagnosing a patient with PH requires the use of right-heart catheterization, a TTE is the best first-line noninvasive screening test. Echocardiography can provide an estimate of PASP by utilizing the simplified Bernoulli equation. A pressure gradient between the RV and right atrium (RA) can be obtained by measuring the peak velocity of the tricuspid regurgitation jet. By inserting this velocity into the equation below, a gradient between the 2 chambers can be derived. Finally, by adding this value to an estimate of the right atrial pressure the PASP can be determined.

\[
\Delta P = 4 \times V^2
\]
\[
PASP = \Delta P + CVP
\]

In addition, TTE noninvasively can determine RV and LV size and function and the presence of valvular disease, helping to determine the cause of PH and effects of PH on the heart. Fisher et al performed a prospective study comparing TTE results within 1 hour after right-heart catheterization to compare hemodynamic estimates. In 48% of cases, there was either an overestimation or underestimation of PAP by less than 10 mmHg. In studies in which TTE correlation to right-heart catheterization data have been assessed, correlation coefficients ranged between 0.31-0.93. The largest discrepancies occurred when PAP was less than 50 mmHg or greater than 100 mmHg. The ability to obtain accurate Doppler tricuspid jet velocities is very much operator-dependent and is what most limits the accuracy of echocardiography.

Right-sided cardiac catheterization is the gold standard for evaluating PH. Left ventricular end-diastolic pressure (LVEDP), PCWP, left atrial pressure (LAP), and PVR can all be measured, allowing clinicians to better determine the classification of PH. Pulmonary-specific vasodilators are given during the procedure to determine the degree of vasoreactivity. These results are extremely useful to guide treatment modalities.

**PATHOPHYSIOLOGY**

A thorough understanding of the pathophysiology of PH is imperative to the successful anesthetic management of these patients. The fundamental problem for patients with PH is the ability of the RV to pump enough blood across the pulmonary vasculature to meet the demands of the systemic circulation. This results in a pulmonary arterial hypertension, which can be caused by various factors such as left heart disease, lung disease, and chronic hypoxia. The right ventricle must then work harder to pump blood against this increased gradient, leading to right ventricular hypertrophy and eventually right ventricular failure. The symptoms of PH can include exertional dyspnea, fatigue, reduced exercise tolerance, angina, syncope, and peripheral edema. The diagnosis of PH is often made using right-heart catheterization, which provides direct measurements of hemodynamics and allows for the administration of vasodilators to assess the response to treatment. Echocardiography can provide noninvasive estimates of pulmonary artery pressure and the presence of valvular disease. The pathophysiology of PH is complex, and a thorough understanding of its underlying mechanisms is essential for effective anesthetic management.
pulmonary bed, thus guaranteeing adequate LV preload. All therapeutic interventions and management strategies should focus on this task.

The RV is a thin-walled (<5mm), highly compliant, afterload-sensitive, and geometrically–complex structure accustomed to contracting against the low-resistance pulmonary circulation.35 Chronically elevated pressures in the pulmonary circulation stimulate the RV to concentric hypertrophy in order to maintain cardiac output in the face of elevated afterload.35–37 The right ventricular ejection fraction (RVEF) will precipitously decline if an acute increase in afterload is encountered (eg, massive pulmonary embolism).35,36 Any perturbation causing an increase in PAP, PVR, or depression of contractility, as can happen during anesthesia and surgery, increases the risk of acute RV failure.

The RV also is prone to ischemia in patients with PH, especially those with RV hypertrophy since there is a greater dependence on diastolic coronary flow as RV pressures and systolic wall tension rise (Table 3).17,36,38 RV coronary perfusion pressure is decreased with systemic hypotension or increased RV pressure (RV hypertrophy) since blood flow through the right coronary artery is determined by a pressure gradient between the aorta and the RV. The RV stroke work also is increased markedly due to RV hypertrophy, making it more susceptible to ischemia.

As discussed above, concentric hypertrophy is the first compensatory mechanism to combat an increase in afterload. If this increase in afterload is not recognized and treated, the RV will begin to dilate. As the RV dilates, so does the tricuspid valve annulus, which in turn leads to valvular incompetence, further exacerbating the volume status and ultimately leading to RV failure.57 This cycle is further perpetuated by a shift of the interventricular septum from the right to the left, resulting in compression of the LV and reduction of LV end-diastolic volume.39–41 Consequently, cardiac output will decline, and the patient will show signs of inadequate tissue perfusion (Fig 3A and 3B) (Video clips 1 and 2).30 Interventricular interdependence is an important concept demonstrating the coupling of LV and RV systolic functions.36,40

The effect of PH and RV failure is not only a problem of reduced forward flow but also that of increased back pressure (ie, CVP). End-organ perfusion is compromised severely in the setting of low systemic blood pressure and elevated filling pressures.

End Organ Perfusion Pressure = Mean arterial pressure (MAP) – CVP

Hypoperfusion of the kidneys leads to reduced urine production, resulting in increased activity of the renin-angiotensin-aldosterone system, which in turn promotes renal sodium and water retention and increases the release of arginine vasopressin.42 This further accentuates the volume

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<table>
<thead>
<tr>
<th>BP systolic</th>
<th>BP diastolic</th>
<th>CPP systole</th>
<th>CPP diastole</th>
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<tbody>
<tr>
<td>RV</td>
<td>25 mmHg</td>
<td>5 mmHg</td>
<td>95 mmHg</td>
</tr>
<tr>
<td>LV</td>
<td>120 mmHg</td>
<td>5 mmHg</td>
<td>0 mmHg</td>
</tr>
<tr>
<td>Ao</td>
<td>120 mmHg</td>
<td>80 mmHg</td>
<td></td>
</tr>
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Abbreviations: Ao, aorta; BP, blood pressure; CPP, coronary perfusion pressure; LV, left ventricle; RV, right ventricle.

Fig 2. The anesthetic management of PH requires maintenance of RV contractility, avoidance of hypotension and hypervolemia, and elevations of PAP. CPP, coronary perfusion pressure; RV, right ventricle; PAP, pulmonary artery pressure; PA, pulmonary artery; RR, respiratory rate; FRC, functional residual capacity.

Table 3. Ventricular Perfusion
status, leading to a vicious cycle of increased cardiac filling pressures, worsening RV dilation, and RV failure.

Liver dysfunction also reflects the status of heart failure. Passive hepatic congestion due to increased CVP, as occurs in right heart failure, primarily will cause elevations in bilirubin. A low-cardiac-output state or hypotension is associated with hepatic ischemia and will result in elevations in serum amino-transferases. Hyperbilirubinemia is a strong independent predictor of an adverse prognosis in patients with pulmonary hypertension.

**MANAGEMENT IN THE OPERATING ROOM**

**Preoperative Considerations**

When assessing a patient with PH, the preoperative evaluation should include assessment of the type of surgery, patient’s functional status, severity of disease, and the patient’s comorbidities. Discussions with consultants, including cardiologists and pulmonologists, may be necessary to assure full optimization prior to surgery. The patient’s primary care physician (PCP) as well as many of the consultants frequently have developed a long-standing relationship with the patient and, consequently, are able to provide the anesthesiologist with the longitudinal/historic background of the patient’s disease. Information derived from previous interventions, which might not be documented in the current chart, can be obtained and utilized to further optimize the patient’s perioperative plan.

Serious consideration of cancelling or postponing surgery should be made in patients with an exacerbation of heart failure symptoms, marked hypoxia, or metabolic acidosis. These patients should be optimized medically prior to any elective procedures. All of the appropriate testing, volume optimization, and symptom management, including the use of systemic vasodilators and inotropes, should be confirmed before the day of surgery. Useful preoperative tests include basic laboratory studies, ECG, echocardiography, CXR, and right-heart catheterization. PFTs and arterial blood gas analysis can be useful in patients with significant lung disease. The necessity of these studies depends on the severity of disease and type of surgery.

Patients with PH undergoing noncardiac surgery are at increased risk of morbidity and mortality. Predictors of morbidity and mortality include history of pulmonary embolism, chronic kidney disease, NYHA functional class II or greater, intermediate-to-high risk or emergency surgery, surgery duration greater than 3 hours, high PAP, right-axis deviation, RV hypertrophy, RV myocardial performance index greater than 0.75, RV systolic pressure/systolic blood pressure ratio greater than 0.66, and intraoperative vasopressor use. Perioperative morbidity occurred in 15% to 42% of patients and included congestive heart failure, hemodynamic instability, sepsis, respiratory failure, longer need for ventilator support, longer ICU length of stay, and more frequent 30-day readmission rate. A full discussion regarding the increased risk of morbidity and mortality must be explained to the patient.

**Monitoring**

Next, decisions need to be made regarding intraoperative monitoring. The placement of invasive arterial lines is useful, allowing for rapid recognition of hemodynamic deterioration and arterial blood gas monitoring in order to facilitate maintenance of adequate oxygenation and normocarbia. It must be emphasized that aside from the numeric values, there is a plethora of information that can be obtained by inspecting the waveform of the arterial pulse. Patients in cardiac failure show a diminished pulse pressure resulting from low stroke volume. In addition, respiratory fluctuations in the arterial waveform can be indicative of hypovolemia or tamponade. It is important, however, not to become fixated on one monitoring value, but use multiple clinical and laboratory parameters to obtain the
true clinical picture. Central venous pressure measurement monitors right heart filling pressures and can be helpful in guiding volume management and optimizing end-organ perfusion.\textsuperscript{18} The utility of pulmonary artery (PA) catheterization recently has been questioned by the results of numerous trials, showing either no benefit or pulmonary artery catheterization versus standard central venous catheterization or even an increased risk of adverse outcomes.\textsuperscript{47-49} In addition, there is a greater risk of PA rupture when floating a PA catheter in a patient with PH.\textsuperscript{50} While these studies have investigated the utility of PA catheters in high-risk surgical patients and critically ill patients, there is a paucity of data exploring the benefit of PA catheters in the PH subgroup. The ability to monitor PA pressures and assess therapeutic interventions could be of potential benefit in this group of patients.

The use of transesophageal echo (TEE) allows for real-time monitoring of cardiac contractility and noninvasive estimation of systolic PAPs and volume status. It enables continuous real-time monitoring, allowing the anesthesiologist to diagnose acute changes in cardiac function. Therapeutic interventions swiftly can be implemented should signs of hemodynamic compromise arise.\textsuperscript{51} Currently, no guidelines exist for the role of TEE as an intraoperative monitor for patients with pulmonary hypertension.

**Anesthetic Techniques**

There are no specific anesthetic techniques proven to be safest in patients with PH.\textsuperscript{18,35,52,53} Regional or neuraxial anesthesia may be useful because they block sympathetic tone, thereby preventing precipitous increases in PVR, which, in turn, can lead to decreased flow across the pulmonary bed, resulting in a decline in LV preload. This anesthetic method, however, must be used cautiously due to potential hypotension from a loss of vascular tone. Epidural anesthesia has the advantage over a spinal because it can be bolused slowly, allowing titration to hemodynamics. Postoperatively, regional techniques allow for superb pain control without depressing respiratory drive as is often encountered with the use of systemic narcotics.\textsuperscript{55} Avoidance of hypoxia and hypercarbia in this case improves PVR. Unfortunately, not all patients are candidates for neuraxial anesthesia because these techniques are contraindicated in patients being anticoagulated or receiving certain antiplatelet medications.\textsuperscript{35} Monitored anesthesia care (MAC) with conscious sedation can prove to be more challenging as hypoxia and hypercarbia are not well tolerated in patients with PH. A general anesthetic with a secure airway allows the anesthesiologist to have greatest control over the patient’s respiratory status. Since there is no proven benefit to any anesthetic technique, the decision regarding which technique is used depends on the type of surgery, patient preference, and comorbidities.\textsuperscript{55}

**Intraoperative Management Goals**

Regardless of chosen anesthetic technique, the clinician must understand that patients with PH have marginal cardiac reserve. Periods of arterial hypotension commonly are encountered during both neuraxial as well as general anesthesia. While heart-healthy patients can tolerate these brief periods of systemic hypotension, patients with PH have a much more limited cardiac reserve and brief periods of hypotension will inadvertently lead to RV ischemia, further promoting systemic hypotension, which, in turn, will eventually lead to hemodynamic collapse. Extreme vigilance is required by the anesthesiologist to promptly recognize the etiology responsible for the systemic hypotension and swiftly implement therapeutic interventions. The etiology of systemic hypotension is always the result of an abnormality in one, or in a combination, of the following 5 factors: Afterload, preload, contractility, rhythm, and rate.

**Afterload**

Hypoxia, hypercarbia, acidosis, hyperinflation or hypoinflation of the lungs, and hypothermia all result in pulmonary vasoconstriction. PVR is lowest at lung volumes closest to functional residual capacity (FRC).\textsuperscript{55,56} Hyperinflation of the lungs or atelectasis results in compression of intra-alveolar and extra-alveolar vessels.\textsuperscript{57} High positive end-expiratory pressure (PEEP) greater than 15 mmHg also compresses the vasculature in well-ventilated areas of the lung, resulting in increased blood flow to less-ventilated areas. This, in turn, causes an increased ventilation/perfusion (V/Q) mismatch, resulting in decreased PaO\textsubscript{2} and an increase in PVR.\textsuperscript{35,58}

**Preload**

Maintaining normal RV function in patients with pulmonary hypertension presents the clinician with the difficult task of carefully balancing intraoperative fluid administration. Both hypovolemia as well as hypervolemia will lead to a suboptimal position on Starling’s curve. The ability of the RV to compensate for acute changes in volume status is compromised in patients with PH. Only a perfectly optimized (euvolemic) RV will maintain its ability to contract against the increased afterload of the pulmonary circulation.\textsuperscript{56} The CVP often is cited as a marker to assess volume status. It must be stressed, however, that the relationship between filling pressure and ventricular volume only can be determined if ventricular compliance is known. This usually is not the case in patients with PH since many chronic compensatory mechanisms have taken place to tolerate elevated PA pressures. Devices that are based on pulse contour analysis (FloTrac\textsuperscript{TM}/Vigileo\textsuperscript{TM} and the PiCCOplus\textsuperscript{TM}) also have been shown to reliably assess volume status in healthy patients. Unfortunately, there are no data investigating their effectiveness and reliability in the PH subgroup.\textsuperscript{56} While echocardiography can assess ventricular size and function, it must be noted that ventricular size can be misleading since many “sick” hearts have the tendency to remodel. Ventricular remodeling can increase end-diastolic volume by a manifold, making a snapshot acquisition of ventricular size difficult to interpret. Consequently, in patients with chronic cardiac pathology, it is better to follow trends rather than one-time absolute values. These trends should be correlated to hemodynamics (blood pressure, heart rate) and laboratory values (mixed venous saturation, lactate) and require constant fine-tuning until the “sweet spot” can be found. Despite a plethora of monitors, the assessment of volume status
remains one of the most challenging aspects of modern-day anesthetic care and is, in most part, dependent on the skill and experience of the clinician taking care of the patient.

**Contractility**

The ejection fraction (EF) frequently is used as a surrogate marker to describe the intrinsic contractile strength of the myocardium. While it makes sense from a didactic standpoint to look at preload, afterload, contractility, rhythm, and rate as isolated parameters; in reality, they are all intertwined. For example, a rapid increase in RV afterload (eg, pulmonary embolism) inadvertently will lead to a significant reduction in RV contractility. Many anesthetic agents have negative inotropic effects and can further depress an already strained RV.

**Rhythm**

Maintaining sinus rhythm is ideal during the perioperative period. Atrioventricular coupling is essential in optimizing preload of the RV as it improves RV diastolic filling. A loss of sinus rhythm, as can be seen in atrial fibrillation, may lead to acute hemodynamic deterioration. Depending upon the degree of compromise, rapid synchronized direct current cardioversion or pharmacologic rate and/or rhythm control will be necessary.56

**PHARMACOLOGIC MANAGEMENT**

The fundamental principal of pharmacologic treatment of PH intraoperatively centers on the use of pulmonary vasodilators to decrease RV afterload, inotropes to support RV contractility, and vasoconstrictors to support coronary perfusion and volume optimization (Fig 2). Currently, the majority of drug development has focused on patients with WHO Group-1 PAH.46,59 At this time, pulmonary vasodilator therapy only has been approved for WHO Group 1 but also is being used-off label in other groups without the evidence obtained through large randomized controlled trials (Table 4).60,61 Smaller trials have indicated a potential use for phosphodiesterase-5 inhibitors in WHO Group-2 patients.60,62,63 The pathophysiology that is unique to WHO Group-1 patients focuses on the findings that the vascular endothelium of these patients has reduced levels of NO synthase and prostacyclin, resulting in the inability of these vessels to properly vasodilate.64 In addition, these patients have elevated levels of thromboxane and endothelin-1, both of which result in vasoconstriction.18 Consequently, the equipoise between vasodilator and vasoconstrictor influences has been shifted towards the side of vasoconstriction, resulting in an increase in PVR. The results obtained from right-heart catheterization are essential in understanding the reactivity of the individual patient’s pulmonary vasculature so that the clinician can tailor treatment accordingly.

| Table 4. Pulmonary Vasodilators 25,63,65,75–77 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| **Group** | **Names** | **PVR** | **mPAP** | **CI** | **SVR** | **Administration** | **Side Effects** |
| Vasodilator | Nitroprusside | ↓↓↓ | ↓ | ↑↑ | ↓↓↓ | IV | Arrhythmias |
| | Nitroglycerin | | | | | | |
| | Nesiritide | | | | | | |
| PDE-3 inhibitor | Milrinone | ↓↓↓ | ↓ | ↑↑↑ | ↓↓↓ | IV or inhaled | Tachyphylaxis, jaw pain, flushing, headache, nausea, vomiting, diarrhea |
| | Epoprostenol | ↓↓↓ | ↓ | ↑↑ | ↓↓↓ | IV | |
| Prostacyclin analogs | Iloprost | ↓↓↓ | ↓ | ↑↑ | ↓ | Inhaled | |
| | Treprostinil | ↓↓↓ | ↓ | ↑ | ↓ | SQ/IV/inhaled | |
| Nitric Oxide | INO | ↓↓↓ | ↓ | ↓ | ↓ | Inhaled | Methemoglobinemia; rebound PH; expensive |

Abbreviations: CI, cardiac index; INO, inhaled nitric oxide; IV, intravenous; mPAP, mean pulmonary artery pressure; PDE-3, phosphodiesterase-3 inhibitor; PVR, pulmonary vascular resistance; SQ, subcutaneous; SVR, systemic venous resistance.
can tailor treatment options towards the patient’s individual pathophysiologic picture.

**RV Afterload Reduction**

**Calcium Channel Blockers (Nifedipine, Diltiazem)**

Systemic vasodilators have limited use in treating PH as only a small subset of patients are vasoreactive to CCBs. CCBs cause vasodilation and a decline in PAP and have various degrees of negative inotropic effects. Systemic hypotension that results can cause significant hemodynamic compromise. A small fraction of patients with PH are responsive to these drugs. They are not useful intraoperatively for acutely reducing PAP. Patients taking them preoperatively should continue their use perioperatively.

**Vasodilators (Nitroglycerin, Nitroprusside, Nesiritide)**

These agents lower PAP by increasing venous capacitance, which reduces the hydrostatic component of PH secondary to left-heart disease. These IV agents can be used intraoperatively with caution as they can result in a decline in SVR (Table 4).

**Phosphodiesterase-3 and -5 Inhibitors (PDE3 and 5)**

PDE-3 inhibitors, milrinone, amrinone, and enoximone increase intracellular cyclic adenosine monophosphate (cAMP), enhancing cardiac contractility (Table 4). They also cause direct pulmonary and systemic vasodilation. IV milrinone can be used intraoperatively both as an inotrope and pulmonary vasodilator; however, systemic hypotension and arrhythmias are side effects that may restrict its use. Trials with oral enoximone in heart failure patients have failed to demonstrate improvement in outcomes, so it has not been approved for use in the United States.

PDE-5 inhibitors prevent cyclic guanosine monophosphate (cGMP) degradation, leading to reductions in intracellular calcium levels, smooth muscle relaxation, and inhibition of cellular proliferation. PDE5 is highly expressed in the lung. Sildenafil was the first PDE-5 inhibitor to be approved by the FDA to augment pulmonary vasodilation. Systemic vasodilation is modest although a greater problem with intravenous administration. In a recent small randomized control trial of patients with heart failure with preserved ejection fraction who had evidence of reactive PH, they showed decreased PVR and improved LV diastolic function, RV function, and quality of life when treated with sildenafil. It has also been shown to have direct positive inotropic effects on the RV. This is the only class of pulmonary vasodilator for which there is some evidence to support its use in WHO Group-2 patients. Other PDE-5 inhibitors less widely used include tadalafil and vardenafil.

**Endothelin-Receptor Antagonists (ERAs) (Bosentan, Ambrisentan)**

Endothelin is a potent endogenous vasoconstrictor that stimulates vascular smooth muscle cell proliferation and induces fibrosis. ETA receptors are found on vascular smooth muscle cells and mediate vasoconstriction and proliferation. ETB receptors are found on endothelial cells and vascular smooth muscle cells and induce NO synthase and other vasodilators. ETA receptors are upregulated and ETB receptors are downregulated in PH. There is little evidence to support their use in Group-2 PH; however, they are useful in PH Group 1. Both bosentan and ambrisentan are oral medications and should be continued perioperatively but are not useful for treating acute exacerbation of PH in the operating room.

**Prostacyclin (Epoprostenol, Illoprost)**

Prostacyclin is a product of endothelial arachadonic acid metabolism and causes smooth muscle relaxation by increasing production of cAMP, inhibits smooth muscle proliferation, and inhibits platelet aggregation. Epoprostenol is FDA approved for the treatment of PH. It has a short half-life (3 minutes) so it is administered as a continuous IV infusion, or it can be inhaled. Epoprostenol acutely improves PAP and PVR, making it useful in the OR. It can be used on an outpatient basis, but it needs to be administered through a permanent tunneled catheter. Treprostinil is a prostacyclin analog with an extended elimination half-life. It can be administered via inhalation, a continuous subcutaneous infusion, or an intravenous infusion. Iloprost is a prostacyclin analog, which is aerosolized. Because it is inhaled, it has the potential to improve ventilation perfusion matching by increasing blood flow to well-ventilated areas of the lung. Its short half-life (20-30 minutes) requires it to be administered 6 to 9 times daily (Table 4).

**Inhaled NO (iNO)**

Through activation of cGMP, iNO relaxes pulmonary vessels. It rapidly acts to decrease PVR, so it is a particularly useful drug intraoperatively. It dilates the pulmonary bed without decreasing SVR because it is delivered as a rapidly-acting gas and is deactivated immediately when it binds with hemoglobin in red blood cells. Because it is only delivered to ventilated regions of the lung, iNO can improve V/Q mismatch, so only the vasculature involved with ventilation is dilated. It can be delivered via facemask, nasal cannula, and endotracheal tube. Because of the risk of rebound pulmonary hypertension, iNO should never be discontinued abruptly (Table 4).

**Inotropes**

Inotropes should be considered when there is evidence of inadequate oxygen delivery due to the inability of the myocardium to contract against increased PVR. There are a variety of drugs that are able to enhance RV contractility. Dopamine activates dopaminergic receptors at doses less than 5 μg/kg/min, β1-receptors at doses between 5 to 10 μg/kg/min, and α1-receptors at doses greater than 10 μg/kg/min. Although the routine use of dopamine has not been supported in this setting, at low doses (up to 16 μg/kg/min), it can improve CO without increasing PVR. Its ability to improve RV ejection fraction, however, has not been proven. Isoproterenol is a nonselective β-agonist. It has both positive inotropic and chronotropic properties, thereby increasing cardiac output. It also produces pulmonary and peripheral vasodilation. Its use in pulmonary hypertension is limited secondary to it causing tachycardia, arrhythmias, and increasing myocardial oxygen consumption.
Dobutamine is primarily a beta-agonist with minimal alpha-receptor agonist activity. It works through β₁-receptor-mediated increases in myocardial contractility and β₂ stimulation, which induces vasodilatation and decreases afterload. Dobutamine functions by increasing cAMP levels, resulting in inotropic stimulation. At doses up to 5 μg/kg/min, it increases myocardial contractility and reduces PVR and SVR. At doses exceeding 10 μg/kg/min, dobutamine leads to tachycardia and increased oxygen consumption without providing any additional improvement in PVR. Epinephrine is a potent, nonselective α- and β-agonist. It is an inotrope that maintains SVR because of its α₁ activity. It causes increased cardiac output without altering the PVR/SVR ratio. Its use has not been well-studied in PH; however, it has been shown to improve RV contractility in patients with RV dysfunction in septic shock.

Milrinone is a PDE-3 inhibitor. It is particularly useful in PH because it exerts positive inotropic action as well as a vascular smooth muscle relaxing effect, resulting in decreasing PVR, SVR, and increasing RV contractility. Milrinone and dobutamine can work synergistically as both drugs increase cAMP levels via 2 separate mechanisms. Levosimendan sensitizes troponin-C to intracellular calcium, resulting in increased contractility without increased oxygen consumption. It also has a vasodilatory effect by opening ATP-sensitive potassium channels in smooth muscle cells to cause smooth muscle relaxation. This results in improved diastolic function, decrease in PVR, and improved myocardial contractility without increasing oxygen consumption. A recent large-scale trial, Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), showed no statistically significant benefit of levosimendan over dobutamine on all-cause mortality at 31 or 180 days. However, in a post hoc analysis of the data, levosimendan may be superior at reducing mortality during the first few weeks of treatment compared to dobutamine in patients with a history of congestive heart failure who were taking beta-blocker therapy when they were hospitalized with acute decompensations. Levosimendan has not yet been approved in the United States; however, is used in Europe and South America.

POSTOPERATIVE MANAGEMENT

Close monitoring of these patients postoperatively is critical as this is the time period in which most unwanted events occur. Morbidity and mortality usually are seen several days postoperatively due to volume shifts, progressive increase in PVR and worsening RV function. Depending on the invasiveness of surgery and severity of disease, patients may need to be admitted to an ICU for closer monitoring. Vaso-dilator therapy started in the OR should be continued in the ICU and eventually transitioned to the patient’s outpatient regimen. Respiratory failure is the most common postoperative complication. A plan for pain control should be established to avoid catecholamine-induced pulmonary vasoconstriction. However, high doses of opioid-based analgesics should be avoided as they can result in respiratory depression. As in the operating room, hypoxia, hypercarbia, and acidosis need to be avoided.

CONCLUSION

Despite increased understanding and better medical management of patients with PH, their perioperative care continues to represent a challenge. The case presented in this review highlights the importance of anesthesiologists participating not only in the intraoperative care but also in the preoperative workup and postoperative management of this highly complex patient population. Taking care of these patients perioperatively demands a multidisciplinary approach with excellent communication among anesthesiologist, surgeon, and consultants. As experts in physiology and pharmacology, anesthesiologists possess a unique skill set that enables them to take on a leading role when caring for patients with PH undergoing surgical or interventional procedures. Anesthesiologists should not shy away but embrace this challenge.

APPENDIX A. SUPPORTING INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2013.11.017.
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