Pulmonary Hypertension and Management of Perioperative Right Ventricular Failure

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Learning Objectives:
As a result of completing this activity, the participant will be able to
- Discuss pulmonary hypertension (PH) as a disease entity including its definition, pathogenesis, classification, diagnosis, and treatment options
- Describe the pathophysiology of acute perioperative right ventricular (RV) failure in patients with PH
- Explain the principles of treatment for acute perioperative RV failure

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Pulmonary hypertension (PH) and the associated right ventricular (RV) dysfunction are increasingly being encountered in the perioperative period. Managing these patients is challenging, but a thorough understanding of the pathophysiology of PH and the related RV dysfunction allows the practitioner to anticipate, prevent, and successfully manage many of the perioperative risks.

Normal systolic, diastolic, and mean pulmonary artery pressures are 25, 10, and 15 mmHg, respectively; the normal range for pulmonary vascular resistance (PVR) is 0.9 to 1.4 Wood units or 90 to 120 dynes s/cm². The PVR is the quotient represented by PVR = (ΔP)/flow, where ΔP represents the mean pulmonary artery pressure (mPAP) minus the left atrial pressure (LAP), and flow equals cardiac output (CO). The gradient between mPAP and LAP is commonly referred to as the transpulmonary gradient. If the gradient is elevated, there is an increase in PVR; in contrast, if the transpulmonary gradient is not elevated, the increase in mPAP is caused by an elevation in LAP resulting from left heart pathology (left ventricular [LV] systolic/diastolic dysfunction, mitral and/or aortic valve abnormality). Thus, PVR = (mPAP − LAP)/CO, or mPAP = LAP + (CO × PVR). Therefore, only three physiological factors could lead to a rise in mPAP: (1) an increase in LAP (due to left heart pathology); (2) an increase in CO (resulting from congenital heart disease with left-to-right shunt, fluid overload, or hyperdynamic states); and (3) an increase in PVR (caused by pulmonary parenchymal/airway disease, hypoxia, interstitial lung disease, thromboembolic disease, or idiopathic pulmonary artery hypertension).¹ (Supplemental Digital Content 1, http://links.lww.com/ASA/A291).

Because of pulmonary vascular remodeling, even factors 1 and 2 could eventually lead to an increased PVR, and the associated rise in mPAP will reflect both an increase in LAP.

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and an eventual elevation in PVR over time. For example, patients with mitral valve stenosis who have an increased mPAP solely because of elevated LAP (without increased PVR—i.e., early or “reversible” PH) usually have an uncomplicated mitral valve replacement with little risk of RV failure after cardiopulmonary bypass. In comparison, patients with mitral valve stenosis associated with a preoperative increase in LAP, mPAP, and PVR (secondary to pulmonary vascular remodeling—i.e., “fixed” PH) may have severe RV failure after mitral valve replacement, which could lead to difficulty in weaning from cardiopulmonary bypass.

Acute on top of chronic increases in PVR are common in the perioperative period and can lead to acute decompensation in RV function. Some of the factors responsible for acute exacerbations in PVR are hypoxia, hypercapnia, acidosis, hypothermia (shivering), increased sympathetic tone (pain, anxiety), and exogenous or endogenous pulmonary vasoconstrictors such as catecholamines, serotonin (pain, catechols), drugs, blood, others. Early recognition and reversal of these causes of acute deterioration could be lifesaving.

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**PULMONARY HYPERTENSION**

**Definition and Classification**

Normal mPAP at rest is 14 ± 3 mmHg, with an upper limit of 20 mmHg. The significance of mPAP between 21 and 24 mmHg is unclear. The European Society of Cardiology and the European Respiratory Society define precapillary PH as a persistent increase in mPAP ≥ 25 mmHg at rest as assessed by right heart catheterization in the setting of a normal pulmonary capillary wedge pressure (PCWP) of ≤ 15 mmHg, PVR ≥ 3 Wood units, and normal or reduced CO. They define postcapillary PH as a persistent increase in mPAP ≥ 25 mmHg at rest as assessed by right heart catheterization in the setting of an increased PCWP ≥ 15 mmHg, PVR ≥ 3 Wood units, and normal or reduced CO. The definition of PH according to the American College of Cardiology/American Heart Association 2009 Expert Consensus Document on Pulmonary Hypertension is a measurement, by right heart catheterization, of a resting mPAP ≥ 25 mmHg, PCWP/LAP ≤ 15 mmHg, and PVR ≥ 3 Wood units.

PH has undergone several reclassifications over the past 20 years. The most recent, the Dana Point Classification, is shown schematically in Figure 1. There are five major categories: (1) pulmonary arterial disease; (2) left heart disease; (3) lung disease/hypoxemia; (4) chronic thromboembolic disease; and (5) unclear and/or multifactorial causes. Because the World Health Organization classification is not based on a physiological approach, classification into precapillary, postcapillary, and mixed PH may be more useful in the perioperative period (Figure 2).

**Pathogenesis**

PH is a syndrome resulting from a pathological increase in PVR that leads to restricted flow through the pulmonary arterial circulation and, ultimately, RV failure. The loss of vascular cross-section due to remodeling is the predominant reason for the rise in PVR; however, excessive vasoconstriction may be a significant contributing factor in about 20% of patients. The vasculopathy, which predominantly affects small resistance pulmonary arteries, consists of intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombus *in situ*, and varying degrees of inflammation. Mutations in three genes in the transforming growth factor β superfamily receptor...
pathway are part of the pathogenesis of hereditary PH. These include BMPR-2, activin receptor–like kinase-1, and endoglin. The lack of penetrance in families with PH suggests that some form of second "insult" is required, in addition to the mutation, for PH to be manifested. Environmental factors associated with the development of PH include hypoxia, anorexigenics, and central nervous system stimulants. Hypoxia causes vasodilatation of systemic vessels but vasoconstriction of the pulmonary vasculature, in part through the action of endothelin and serotonin. Acute hypoxia further inhibits the function of voltage-gated K\(^+\)-ATP channels of the pulmonary artery smooth muscle cells, resulting in membrane depolarization, an increase in cytoplasmic calcium concentration, vasoconstriction, and eventually PH. Endothelial dysfunction contributing to PH involves increased production of vasoconstrictor and mitogenic compounds such as endothelin-1, angiotensin II, serotonin, thromboxane A2, vasoactive intestinal peptide, and deficient production of vasodilators including prostacyclin and nitric oxide.\(^6\) Prostacyclin, normally a potent local vasodilator, inhibits platelet activation and has antiproliferative properties. These mechanisms are thought to be associated with PH that complicates the use of appetite suppressants and, in PH of the newborn, the use of selective serotonin reuptake inhibitors during pregnancy (Supplemental Digital Content 2, http://links.lww.com/ASA/A292).

**Diagnosis and Investigations**

The most common presenting symptoms are fatigue, dyspnea on exertion, chest pain, presyncopy, syncope, palpitations, and lower extremity swelling. Syncopy is a particularly ominous sign that usually predicts a poor prognosis. Signs of PH and RV failure include tachypnea, tachycardia, distended neck veins, left parasternal lift, an audible tricuspid regurgitation murmur, RV S3 gallop, hepatomegaly, ascites, and lower extremity edema. The American Heart Association proposed dividing the investigations into pivotal and contingency tests, and these are shown in Figure 3.\(^3\) An electrocardiogram, chest x-ray, and echocardiogram may display signs suggestive of PH. An echocardiogram should be considered once PH is suspected by history taking, clinical examination, and assessment of risk factors. Possible causes of PH that can be excluded or confirmed by echocardiography are congenital and acquired valvular disease, LV systolic and diastolic dysfunction, large pulmonary embolus, dilated RV, and congenital disease with shunts. It is important to rule out chronic thromboembolic pulmonary hypertension (CTEPH), as 50% of patients with a diagnosis of CTEPH have no history of acute pulmonary embolism. The screening test of choice is radionuclide perfusion scanning. A normal or very low–probability scan essentially excludes CTEPH, whereas a high-probability scan warrants further evaluation with a pulmonary angiogram. A spiral computed tomography scan, although excellent in ruling out an acute pulmonary embolus, is less sensitive than perfusion scanning in excluding CTEPH. Generally, right heart catheterization should be performed in patients with unexplained preoperative dyspnea or confirmatory findings on echocardiography (RV systolic pressure greater than 40 mmHg, right atrial enlargement, RV hypertrophy/dilatation, or flattening of the interventricular septum) to better
delineate the hemodynamic profile and assess the response to vasodilator therapy.

**Medical Therapy**

A treatment algorithm for PH is shown in Figure 4. General treatment goals include the improvement of symptoms and functional capacity (6-minute walk test and cardiopulmonary exercise testing), lowering mPAP, normalizing CO, slowing the rate of progression of the underlying disease, and, ultimately, improvement in survival. Low-level aerobic exercise (walking) is encouraged. Avoidance of high altitudes and oxygen supplementation on commercial aircraft for patients with room air saturations less than 92% is advised. Oxygen therapy is indicated if oxygen saturation is less than 90% in room air. Ideally, pregnancy should be avoided. Routine anticoagulation with warfarin may improve survival. Diuretics and a sodium-restricted diet are indicated in RV dysfunction or overt failure. Digoxin is often added, although outcome studies are lacking. Calcium-channel blockers are indicated in a small, select group of patients with idiopathic pulmonary arterial hypertension who show acute vasodilator responsiveness on right heart catheterization. Patients with chronic obstructive pulmonary disease may benefit from the addition of oxygen, bronchodilators, steroids, and antibiotics if indicated. Use of biphasic positive airway pressure may improve PVR and RV function among patients with obstructive sleep apnea.

Prostanoids are the mainstay therapy for many patients. The three available for treatment of PH include intravenous epoprostenol (*i.e.*, prostacyclin or PGI2), subcutaneous treprostinil, and inhaled iloprost. Several studies have shown improvement in symptoms, exercise tolerance, hemodynamics, quality of life, and survival with prostanoid therapy. Although tachyphylaxis with the need for frequent dose adjustments occurs, the beneficial effects of prostanoids can be sustained for years; as a result, many patients have been removed from heart–lung transplantation lists.

Activation of endothelin A receptors causes pulmonary vasoconstriction, and activation of endothelin B receptors causes pulmonary vasodilatation. The endothelin-receptor antagonists bosentan and sitaxsentan are increasingly used as first-line oral therapy. Bosentan is a nonselective, competitive endothelin A and B receptor antagonist that promotes pulmonary vasodilatation. Sitaxsentan is a selective endothelin A receptor blocker that preserves endothelin B receptor–dependent nitric oxide–mediated vasodilatation.

The phosphodiesterases (PDEs) are another important class of agents. PDE-3 and -5 are enzymes that inactivate cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), respectively, the principal second messengers of prostacyclins and nitric oxide. These PDEs augment cAMP- and cGMP-mediated intracellular signaling, respectively, leading to vasodilation and decreased PVR. The PDE class of agents have an increasing role in acute PH crises in the perioperative period. This will be discussed in a later section.

**Invasive Therapy**

Patients with PH associated with Eisenmenger syndrome (*i.e.*, right-to-left shunting through an atrial or ventricular septal defect) generally have superior survival rates compared with patients with idiopathic PH, mainly because of decompression of a pressure-overloaded RV, improved LV filling, and a resulting increase in CO. Atrial septostomy is considered a palliative procedure and may be a bridge to lung or heart–lung transplantation in patients with intractable RV failure despite maximal medical therapy. The shunt causes a decrease in systemic arterial oxygen saturation that is compensated for by increases in CO and systemic oxygen delivery. Pulmonary endarterectomy is indicated for patients with a positive perfusion scan or

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**Figure 4.** American Heart Association’s treatment algorithm for patients with PH. From McLaughlin et al.3 Copyright © 2009, with permission of Elsevier. CCB = calcium-channel blockers; ERA = endothelin-receptor antagonists; PDE-5I = phosphodiesterase-5 inhibitors; PH = pulmonary hypertension.
positive pulmonary angiogram who have surgically accessible disease and an acceptable surgical risk. The goal is to remove sufficient material to lower PVR and increase CO. The underlying abnormality in CTEPH includes initial thrombus obstruction, thrombus organization, fibrous obstruction of proximal arteries, and vascular remodeling in patent distal arteries. Therefore, it is a disease with a proximal mechanical component (amenable to surgery) and a variable degree of distal small vessel arteriopathy (amenable to medical therapy). Identification of these patients is important, as CTEPH is generally underdiagnosed as a cause of PH and has a poor prognosis if untreated. Bilateral lung transplantation (and occasionally heart–lung transplantation) is the final option for a minority of patients in whom medical therapy has failed. Although effective medical therapy has reduced the rate of transplantation, death rates on waiting lists are high because of a global shortage of donor organs. Only approximately 4% of lung and combined heart–lung transplantations performed annually worldwide are for patients with PH.

Extracorporeal support may occasionally be a rescue option for acute RV failure and hypoxemia caused by massive pulmonary embolus. It is also used as a bridge to lung transplantation, for support after lung transplantation, in the treatment of severe reperfusion pulmonary edema after pulmonary endarterectomy, and for RV failure unresponsive to conventional medical therapy. Patients with end-stage RV failure due to idiopathic PH have traditionally responded poorly to RV assist devices, as the increased flow (high dP/dT ratio) potentially damages the pulmonary microcirculation, causing even greater increases in mPAP and PVR.

Prognosis
Predictors of poor prognosis include advanced NYHA Functional Class 3 or 4, rapid symptom progression, poor exercise capacity, significant RV dysfunction, low CO, elevated brain natriuretic peptide, and an associated diagnosis of scleroderma. The best survival rates are seen in patients with congenital heart disease associated with PH. The natural history of idiopathic PH reveals a median survival of 2.8 years with 1-, 3-, and 5-year survival rates of 68, 48, and 34%, respectively.

PERIOPERATIVE RV FAILURE IN PATIENTS WITH PH
Although often preventable, acute decompensation of patients with PH during the perioperative period is relatively common, is frequently fatal, and occurs as a result of acute RV failure. In 2002, patients with Eisenmenger syndrome undergoing cesarean section were reported to have a perioperative mortality rate of about 70%. In 2005, patients with PH undergoing liver transplantation had a reported mortality rate as high as 80%. However, it is noteworthy that the perioperative risks associated with PH have improved steadily over the past decade, likely as a result of better understanding and management of these patients (Figure 5).

Emergency procedures, American Society of Anesthesiologists class greater than 2, intermediate- or high-risk surgery, longer duration of surgery and anesthesia (more than 3 hours), coronary artery disease, chronic renal insufficiency, history of pulmonary embolism, and NYHA Functional Class of 2 or greater have all been identified as independent predictors of morbidity and mortality in patients with PH undergoing noncardiac surgery. High-risk surgical procedures include those that are potentially associated with significant perioperative systemic inflammatory response and rapid blood loss (cardiac surgery), high possibility of venous air or CO₂ emboli (laparoscopic surgery), fat or cement emboli (orthopedic surgery), and loss of lung blood vessels (lung resection).

Serious consideration should be given to cancelling or delaying surgery if the PVR is largely fixed on vasodilator testing with inhaled nitric oxide (iNO), if moderate to severe PH with significant RV dysfunction is present, and if high-risk surgery is planned. Some of the important factors that impact these decisions are shown in Figure 5. All attempts must be made to optimize PVR before surgery, including maximizing medical therapy and preventing conditions that may cause acute deterioration. Patients on chronic therapy for PH ideally should continue their regimen throughout the perioperative period, as discontinuation can precipitate an acute pulmonary hypertensive crisis. Intravenous prostacyclin has potent antiplatelet properties, and changing to inhaled therapy preoperatively should be considered, especially if increased

### Table: Patient risk factors

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<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>NYHA/WHO class ≥2</td>
<td>Moderate to severe functional class</td>
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<tr>
<td>Right axis deviation on ECG</td>
<td>Right heart strain</td>
</tr>
<tr>
<td>Echo: Right ventricular hypertrophy</td>
<td>RV hypertrophy</td>
</tr>
<tr>
<td>High CVP, RAP, RVSP/SBP &gt;0.66</td>
<td>Elevated RV pressures</td>
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### Table: Operative risk factors

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<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>Intermediate- or high-risk surgery</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Higher ASA class</td>
<td>ASA ≥3</td>
</tr>
<tr>
<td>Long duration of surgery</td>
<td>More than 3 hours</td>
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<tr>
<td>Significant intraoperative vasopressor use</td>
<td>High CVP, RAP</td>
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### Figure 5. Factors affecting perioperative morbidity and mortality in patients with PH undergoing surgery. After McGlothlin et al.16 ASA = American Society of Anesthesiologists; PH = pulmonary hypertension; WHO = World Health Organization.
blood loss is anticipated. In selected patients not on PH-specific therapies, a preoperative right heart catheterization, vasodilator trial, and PH-specific therapy may be indicated.

**Serious consideration should be given to cancelling or delaying surgery if the PVR is largely fixed on vasodilator testing with iNO, if moderate to severe PH with significant RV dysfunction is present, and if high-risk surgery is planned.**

Acute perioperative decompensation and the subsequent acute, rapid, potentially lethal RV failure are frequently underrecognized or misdiagnosed. Shock caused by acute RV failure is schematically presented in Figure 6.

Acute RV failure (low end-organ inflow pressure due to reduced LV stroke volume and high end-organ outflow pressure due to elevated right atrial pressure) has a worse prognosis than shock due to acute LV failure (only low end-organ inflow pressure) because of the “double-hit” on end-organs, leading to rapid multiorgan failure. In addition, elevation in right atrial pressure may cause hypoxemia by right-to-left shunting across a patent foramen ovale. It is important to note that tricuspid regurgitation is common in acute and chronic RV failure; hence, thermodilution CO measurements may be misleading. However, pulmonary artery pressure measurements may still be useful to monitor the effect of pulmonary artery vasodilators or systemic vasopressors (Supplemental Digital Content 3, http://links.lww.com/ASA/A293).

Many issues in the perioperative period, some of them “minor” by themselves, can critically affect the outcome of these patients. These include, among others, the timing of extubation, meticulous management of mechanical ventilation, the surgical acumen and outcome, fluid and electrolyte shifts, balancing the positive versus negative effects of transfusion,

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**Figure 6.** A, The “double-hit” phenomenon of RV cardiogenic shock. B, The lethal cycle of RV failure.
intravascular volume optimization, acid–base optimization (pH > 7.4, PaCO₂ 30 to 35 mmHg, PaO₂ > 100 mmHg), temperature control, optimized analgesia, and early restarting of noninvasive ventilation (Supplemental Digital Content 4, http://links.lww.com/ASA/A294).

**Prevention and Treatment**

**Optimize Heart Rate and Rhythm.** Restoring and maintaining sinus rhythm is important for optimal filling of a hypertrophied/dilated RV. Because of the association of RV failure with tricuspid valve regurgitation, higher heart rates (80 to 100 bpm) may be desirable to reduce end-diastolic volume. Furthermore, because an increase in RV stroke volume is limited by the increase in RV afterload, it is best to avoid bradycardia as the RV CO becomes rate dependent. Where appropriate, early synchronized cardioversion should be considered, as loss of sinus rhythm may lead to acute hemodynamic decompensation. If cardiac pacing is possible, atrial or atroventricular sequential pacing leads to improved RV diastolic filling compared with ventricular pacing alone. Serum potassium and magnesium levels must be optimized to prevent arrhythmias and efforts must be made to mitigate mechanical irritation of the cardiac chambers by central lines (i.e., make certain the distal end of the central venous catheter does not enter the right atrium, and ensure early removal of the pulmonary artery catheter in case of ventricular irritability or dysrhythmias).

**Optimize RV Filling.** Perioperative central venous pressure (CVP) monitoring is important; in general, when the CVP is low, the RV must be “coping” even if the pulmonary artery pressure and PVR are elevated (i.e., the RV must have been “primed” [hypertrophied] and exposed to a progressively higher pulmonary artery pressure and PVR over time, or it is truly underfilled). In contrast, progressive elevation in CVP may imply a failing RV, especially when accompanied by increasing size of V waves (worsening tricuspid regurgitation) and decrease in pulmonary artery pressure and CO. The compromised RV will tolerate neither hypovolemia nor overfilling; therefore, an optimal position has to be determined and maintained on the (compromised) RV Frank–Starling curve. Because the RV is mainly a “volume chamber,” it is less dependent on preload compared with the LV. Thus, for a given increase in preload, a smaller increase in stroke volume is expected. However, because it is thin walled, the RV is much more afterload dependent than the LV, and RV CO decreases significantly with an acute increase in mPAP.

Past teachings have often suggested that the RV be filled aggressively to passively increase pulmonary blood flow and CO. This may hold true when the PVR is normal (Fontan physiology) but not when it is high. Excess volume loading in these circumstances will result in acute RV distention, increased tricuspid regurgitation, right-to-left shift of the interventricular septum, and impaired LV end-diastolic filling, leading to a decrease in stroke volume and CO (diastolic ventricular interdependence). The resultant drop in systemic blood pressure causes decreased right coronary artery perfusion and a decline in the transseptal pressure gradient (TSG) and, eventually, hemodynamic collapse. This is especially true once the CVP reaches values of 15 to 20 mmHg. Assessment of optimal RV filling can be very difficult. Options include a fluid bolus (250 mL of lactated Ringer solution) or autotransfusion (by elevation of the patient’s legs). Ongoing fluid boluses are indicated if leg elevation causes a modest (2 to 5 mmHg) increase in CVP and a corresponding increase in PCWP, CO, and/or blood pressure; an increase in only the CVP (with minimal or no change in PCWP, CO, or mean arterial pressure) likely indicates RV distention and precludes further fluid boluses. A relatively underfilled RV is likely the lesser of the two evils. Repeated bedside echocardiographic assessments could prove invaluable. In patients with a pulmonary artery catheter, monitoring RV filling pressures through continuous transducing of the RV pressure tracing is an underused but invaluable tool (Figure 7).

**Maintain RV Myocardial Performance.** This includes maintenance of RV coronary perfusion pressure and RV inotropic therapy. Normally, RV coronary perfusion occurs during systole and diastole. However, as the PVR and RV systolic pressure increase, flow through the right coronary artery occurs mainly in diastole, similar to left coronary artery perfusion. RV subendocardial ischemia caused by myocardial oxygen supply–demand imbalance is common in PH. Therefore, systemic hypotension and excessive increases in RV systolic pressure, contractility, and heart rate must be avoided. When acute RV failure is suspected, the systemic blood pressure must be increased immediately to ensure adequate right coronary artery perfusion pressure and restoration of the TSG. This can be achieved by optimizing volume status and with early use of norepinephrine with or without vasopressin. Accumulating clinical experience as well as animal data suggest that vasopressin causes less of an increase in PVR than does norepinephrine and reduces the dose of norepinephrine required to maintain an adequate systemic blood pressure. Vasopressin binds to peripheral V1 receptors and causes systemic vasoconstriction while stimulating nitric oxide release and vasodilation in the pulmonary circulation.

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**When acute RV failure is suspected, the systemic blood pressure must be increased immediately to ensure adequate right coronary artery perfusion pressure and restoration of the TSG.**
The choice of anesthetic technique (general vs. regional) and the anesthetic agents used are much less important than understanding the possible physiological perturbations that may result from their use. All anesthetic agents cause varying degrees of myocardial and autonomic nervous system depression. In this regard, volatile agents, propofol, thiopental, narcotics, ketamine, and etomidate can all be used in the appropriate manner. Contractility may need to be enhanced in the acutely failing RV with either a β-adrenoreceptor agonist (dobutamine), PDE-3 inhibitor (milrinone), or calcium sensitizer (levosimendan), all of which also reduce pulmonary and systemic vascular resistance. Thus, if the increase in RV CO does not offset the reduction in systemic vascular resistance, the systemic blood pressure will decrease with resultant decline in right coronary artery perfusion pressure and TSG. The combination of low-dose dobutamine and low-dose milrinone is synergistic in inotropy and has fewer negative effects on systemic vascular resistance. Levosimendan is a cardiac inotrope that binds to troponin C and sensitizes the cell to calcium, leading to increased contractility without raising intracellular calcium levels. Monitoring overall RV function with continuous RV pressure transduction through the RV port of the pulmonary artery catheter is invaluable (Figure 7).

**Maintain the TSG and RV Geometry.** At normal systolic pressure (RV 25 mmHg, LV 125 mmHg), there is a large TSG (TSG = 100 mmHg) that is responsible for the normal configuration of the interventricular septum; this provides a buttress for the free wall to contract against (bellows effect). The septal contraction (septal twist) accounts for more than 50% of overall RV systolic function, and the maximum RV developed pressure is reduced by 30% with septal inactivation. Therefore, conditions that reduce LV systolic pressure (systemic hypotension) or increase RV systolic pressure will reverse the TSG and severely compromise RV function: not only will septal function be compromised because of misalignment of the obliquely oriented septal myofibrils to a transverse configuration, resulting in less contractile force, but the free wall will lose its buttress as the distance between the free wall and the septum increases (the result of leftward septal bowing). To restore the TSG, the PVR needs to be reduced and LV systolic pressure needs to be aggressively maintained or increased.

**Reduce PVR.** Perioperative hypoxemia, hypercapnia, atelectasis, pleural effusions, hypothermia, fluid overload, pain, and anxiety all cause acute increases in PVR with resultant RV decompensation. Patients on chronic therapy for PH should continue their established treatment during the perioperative period. The combination of nitrous oxide and protamine increases PVR and should be avoided. Functional residual capacity must be carefully maintained, as both hyperinflation and atelectasis can lead to an increase in PVR. The important relationship between lung volume and functional residual capacity during mechanical ventilation is U-shaped, with PVR being the lowest at functional residual capacity (Figure 8). At low lung volumes, hypoxia and hypercapnia cause hypoxic pulmonary vasoconstriction; in contrast, hyperinflation causes compression of intra-alveolar vessels with a resultant increase in PVR in both circumstances. A positive end-expiratory pressure greater than 15 mmHg also leads to an increase in PVR. In contrast to systemic arteries, pulmonary vessels constrict with hypoxia (Euler–LiJestrand reflex) and dilate with hyperoxia. Therefore, perioperative ventilation strategies for patients with PH should incorporate high concentrations of oxygen, low tidal volumes (6 mL/kg of predicted body weight), a respiratory rate sufficient to achieve mild hypocapnia, and optimum levels of positive end-expiratory pressure (5 to 10 cm H\(_2\)O). Early drainage of pleural effusions and recruitment maneuvers should be considered. Intravenous air or particulate material (precipitated drugs) should be avoided because of the
potential for right-to-left embolization through an open foramen ovale.

**Patients on chronic therapy for PH should continue their established treatment during the perioperative period.**

Apart from the aforementioned physiological considerations, the PVR can be reduced by selective pulmonary artery vasodilators. Unfortunately, none of the intravenously administered agents are selective enough not to cause accompanying systemic vasodilation; these agents could also potentially worsen hypoxia by inhibiting hypoxic pulmonary vasoconstriction. The PDE-3 inhibitor milrinone decreases the PVR and has positive inotropic effects (inodilator). Pulmonary artery vasodilation with intravenous nitroglycerin, sodium nitroprusside, or citrulline (all metabolized to nitric oxide) can be useful provided simultaneous systemic hypotension is anticipated and treated. Intravenous epoprostenol (iPGI2) has been successfully used to treat protamine-induced PH and to facilitate weaning patients with PH from cardiopulmonary bypass. It is, however, a powerful antiplatelet agent and must be used cautiously in the face of surgical bleeding.

Inhaled pulmonary artery vasodilators improve V/Q matching and arterial oxygen saturation, which in itself decreases PVR. An algorithm for their use is shown in Figure 9. Unlike the intravenous pulmonary artery vasodilators, these agents have little effect on systemic vascular resistance. iNO is a selective pulmonary artery vasodilator (increases cGMP production) that is almost immediately inactivated by binding to hemoglobin; inhaled epoprostenol (iPGI2) promotes pulmonary artery vasodilation by increasing cAMP in smooth muscle cells. iNO and iPGI2 are equally effective in decreasing mPAP and PVR, and overly fast weaning of both can lead to rebound PH. Inhaled iloprost is a water-soluble analog of prostacyclin with a longer half-life, which makes it suitable for intermittent nebulization. Inhaled milrinone is associated with less systemic hypotension but a smaller decrease in PVR when compared with intravenous administration.

The PDE-5 inhibitor sildenafil, administered sublingually or orally, has been used to manage acute RV dysfunction in heart transplant recipients, wean patients from iNO, reduce the duration of mechanical ventilation, and prevent pulmonary endothelial cell dysfunction after prolonged cardiopulmonary bypass. It also extends and

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**Figure 8.** The critical and clinically important relationship between lung volume and PVR. The PVR is lowest at FRC: both hypoinflation/atelectasis and hyperinflation can cause a clinically significant elevation in PVR. FRC = functional residual capacity; PVR = pulmonary vascular resistance; RV = residual volume; TLC = total lung capacity.

**Figure 9.** An algorithm for the rational use of “selective” pulmonary artery vasodilators in the perioperative period. From Strumpher and Jacobsohn.1 Copyright © 2011, with permission from Elsevier. iNO = inhaled nitric oxide; iPGI2 = inhaled epoprostenol; PAP = pulmonary artery pressure; PDE-5I = phosphodiesterase-5 inhibitor; RV = right ventricle.
potentiates the effects of iNO. The sublingual route, although not specifically studied in the perioperative period, is potentially an excellent ancillary in conjunction with the inhaled agents (Supplemental Digital Content 5, http://links.lww.com/ASA/A295).

CONCLUSIONS

The perioperative management of patients with PH and associated RV dysfunction is complex and requires a thorough understanding of the pathophysiology involved. Failure to make an early diagnosis of RV failure and institute the correct therapy will lead to high perioperative morbidity and mortality. The anesthesiologist must be aware of the potential treatment strategies including optimizing physiological parameters, use of selective pulmonary artery vasodilators, inotropic support, and systemic blood pressure maintenance. Wherever possible, these patients should be cared for in specialty centers.

REFERENCES