Chapter 19
Perioperative Management of Pulmonary Hypertension

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Abstract Any form of pulmonary hypertension (PH) uniformly increases the perioperative risks of both cardiac and noncardiac surgery. Specific perioperative management of PH patients is dependent upon the etiology and severity of disease as well as the planned operation. A detailed understanding of right ventricular (RV) physiology and the impact of chronic as well as acute-on-chronic PH is paramount to decisions on selection for surgery, preoperative preparation, anesthetic plan and postoperative care. The highest risk PH patients should be referred to PH centers where a multidisciplinary approach to patient care can be planned and where expertise exists in using a multitude of inhaled and systemic pulmonary vasodilators, as well as pharmacological and emergent mechanical interventions for right ventricular failure. This chapter is intended to be a guide for all physicians managing the perioperative care of patients with pulmonary hypertension, with an emphasis on noncardiac surgery.

Keywords Pulmonary hypertension • Perioperative management • Anesthesia • High-risk surgery • Right ventricle • Pulmonary vascular resistance

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J.R. Klinger, R.P. Frantz (eds.), *Diagnosis and Management of Pulmonary Hypertension*, Respiratory Medicine 12, DOI 10.1007/978-1-4939-2636-7_19

Abbreviations

BiPAP	Bi-level positive airway pressure
CI	Cardiac index
CPAP	Continuous positive airway pressure
DVT	Deep venous thrombosis
ERA	Endothelin receptor antagonists
ES	Eisenmenger's Syndrome
HFpEF	Heart failure with preserved ejection fraction
HPV	Hypoxic pulmonary vasoconstriction
ILD	Interstitial lung disease
iNO	Inhaled nitric oxide
LAP	Left atrial pressure
LV	Left ventricle, left ventricular
LVEDP	Left ventricular end-diastolic pressure
mPAP	Mean pulmonary artery pressure
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension WHO Group 1 PH
PASP	Pulmonary artery systolic pressure
PCWP	Pulmonary capillary wedge pressure
PDG	Pulmonary diastolic gradient
PDE5-I	Phosphodiesterase 5 inhibitors
PE	Pulmonary embolism
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
Ppm	Parts per million
PPV	Pulse-pressure variation
PV	Pressure–volume (relationship)
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RHC	Right heart catheterization
RV	Right ventricle, right ventricular
RVH	Right ventricular hypertrophy
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion
TEE	Transesophageal echocardiography
TPG	Transpulmonary gradient
WU	Wood Units

Introduction

Pulmonary arterial hypertension (PAH, WHO Group 1 PH) has traditionally been thought of as a rare disease and therefore of concern only to a small group of cardiovascular and pulmonary specialists. However, many patients with various

comorbidities are adversely affected by pulmonary vascular disease. For example, PAH has been associated with stories of doomed Eisenmenger's Syndrome (ES) parturients facing exorbitant mortality rates [1–3]. Pulmonary venous hypertension (WHO Group 2 PH) is a known final common pathway for many untreated cardiac lesions, resulting in higher morbidity and mortality when repaired [4–9]. PH associated with respiratory insufficiency (WHO Group 3) including obesity related hypoventilation, sleep apnea, and parenchymal lung diseases is also a marker of perioperative morbidity [10]. In recent years, an increased understanding of the pathogenesis and pathophysiology of PAH as well as advances in drug therapies have greatly improved survival. Furthermore, an increased awareness of PH in general, has led to more diagnoses of various degrees of non WHO Group 1 PH in the entire population, many of whom go on to surgery. Hospital based specialists are modifying traditional management of acute disease to address coexisting chronic or acute on chronic PH and acute on chronic right ventricular dysfunction. This is particularly evident in the perioperative and peripartum populations requiring anesthesiologists, intensivists, obstetricians, pulmonologists, and cardiologists to have a comprehensive understanding in physiology and treatment of PH and the associated right ventricular dysfunction.

Six retrospective studies have analyzed the outcomes for PH patients undergoing noncardiac surgery [11–15]. The studies used a variety of methods to define PH as well as the severity of disease, so clear conclusions cannot be drawn. What is defined by these studies, however, is a very high rate of perioperative mortality (6–10 %) [12–15]. The rate of complications in all categories were also reported to be extremely elevated. In a more recent prospective international survey of 114 well characterized PAH patients undergoing surgery, Meyer et al. reported a 6.1 % major complication rate (bleeding with estimated blood loss >1 l, systemic inflammatory response or septicemia requiring catecholamine therapy, right heart failure requiring inotropic support, or death), and perioperative mortality of 3.5 % with 15 % (2/13) for emergency procedures vs. 2 % (2/101) for nonemergency procedures [16]. Note is made that some previous studies quoting higher mortality rates (specifically that of Minai et al. 18 %) included mostly patients prior to 2002, before the most PAH specific therapies were available [17]. Also, noteworthy is the fact that a 2 % mortality rate for elective surgery resulted from procedures that were mostly performed at the PH center [16].

Hemodynamics and Perioperative Physiology

The definition and classification of PH has been discussed elsewhere. For the purposes of discussing perioperative management it is useful to review the hemodynamics of PH with reference to pre- vs. post-capillary PH, cardiac output, left atrial and left ventricular end-diastolic pressures, right ventricular systolic and diastolic pressure–volume relationships, interventricular interdependence, and underlying respiratory physiology. The increased pulmonary vascular resistance (PVR) of PAH

produces elevated pulmonary pressures regardless of the left atrial pressures. This "pre-capillary" PH is distinguished by the presence of a PVR ≥3.0 Wood units (WU) with normal pulmonary capillary wedge pressure (PCWP) (i.e., ≤15 mmHg) [18]. In contrast, the "post-capillary" PH will occur due to elevated left atrial filling pressures (LAP) which may be due to left ventricular, valvular abnormalities or a noncompliant left atrium. The elevated LAP is transmitted to the pulmonary veins down their origination at the pulmonary capillaries. Post-capillary PH is characterized by an elevated PCWP (>15–18 mmHg) with normal PVR, transpulmonary gradient (TPG) which is the difference between the mPAP (mean pulmonary artery pressure) and PCWP, and pulmonary diastolic gradient (PDG)—the difference between the pulmonary artery (PA) diastolic pressure and PCWP. In some, the chronic engorgement of the pulmonary vasculature produces vascular remodeling. This results in an elevated TPG, PDG, and PVR. This "mixed" PH is also referred to as "reactive" PH. Mixed PH features PCWP>15 mmHg, PVR≥2.5–3.0 WU, TPG≥12–15 mmHg, and DPG>5 [18–23]. Least common, is a fourth hemodynamic condition in which increased pulmonary blood flow produces PH with normal or minimally increased PVR or increased left heart pressures. This situation arises from systemic-to-pulmonary shunt or high cardiac output states (e.g., anemia, sepsis, portal hypertension, thyrotoxicosis, hemodialysis related large fistula, and myeloproliferative disorders) [18].

Assessment of the hemodynamic phenotype, response to pulmonary and systemic vasodilators, and inodilators should be assessed preoperatively and plans discussed between the pulmonary hypertension specialist, critical care anesthesiologist and intensivist for best recommendations for appropriate use of these agents intraoperatively and postoperatively in the critical care unit.

Perioperative Physiology

For patients suffering from PH, the primary goal throughout the perioperative period is to maintain optimal mechanical matching between the RV and pulmonary circulation. Optimal care requires a comprehensive awareness of intraoperative events that affect RV afterload, inotropy, and oxygen supply–demand relationships.

When interpreting the available data relevant to intraoperative management, it is important to consider a few basic limitations. First, given the relative rarity of PAH in the surgical population, much of the available clinical data are anecdotal and therefore biased to some degree; few clinicians are inclined to report cases in which the outcome was bad. Second, while experimental data are quite useful for demonstrating concepts, there are remarkably few studies in which a model of chronic PAH was used to study perioperative physiology. Finally, as with all studies involving RV physiology, it is important to appreciate that some methods developed for characterization of left ventricular (LV) mechanical performance may not be directly applicable to the RV. For example, as shown in Fig. 19.1, under normal circumstances, the RV pressure–volume relationship is distinctly different than that of the

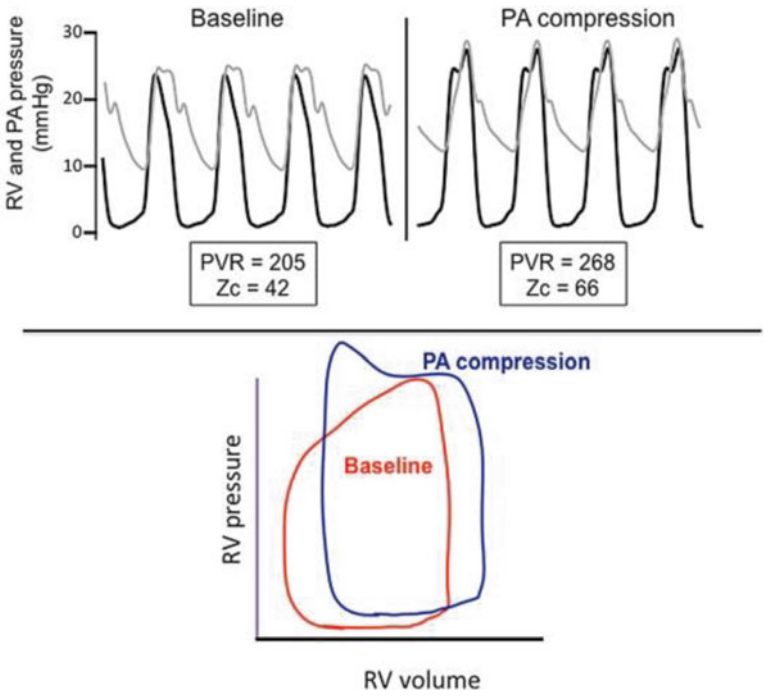

Fig. 19.1 *Top panel*. Right ventricular (RV) and pulmonary arterial (PA) pressures before and after compression of the left PA in an experimental animal (swine). Changes in both the amplitude and morphology of the pressure waveforms are evident. *Bottom panel*. Changes in the RV pressure–volume relationship produced by compression of the left PA are depicted

LV, particularly in regard to a clearly defined end-systolic point, and the period of isovolumic relaxation (of which the RV normally has little).

These differences reflect fundamental properties of each chamber in regard to the pattern of free wall contraction (the RV shows sequential shortening from the inflow to outflow tract), septal motion, the timing of peak pressure (early for the RV, late for the LV), and the contribution of inertia to maintaining flow out of the ventricle late in systole (minimal for the LV) [24, 25]. For a normal RV ejecting into a normal pulmonary circulation, these differences may complicate simple application of principles derived for characterization of LV systolic function such as the linear end-systolic pressure–volume relationship based upon automated detection of a discrete end-systolic point from pressure–volume loop analysis, and the myocardial performance index based in part upon echocardiographic assessment of isovolumic relaxation time. However, in the setting of PAH, RV free wall shortening can become more synchronous, ventricular interdependence changes, peak pressure occurs later in systole, and the inertial component of blood flow into the PA is diminished [24, 25]. As shown in Fig. 19.1, under these conditions the RV pressure–volume relationship resembles that for the LV with a more clearly defined end-systolic point and an isovolumic relaxation period.

Preoperative Evaluation

In 2007, the American College of Cardiology and the American Heart Association published the most current guidelines for perioperative cardiovascular evaluation for noncardiac surgery. This expert consensus document stratifies patients into three categories of risk factors: major, intermediate, and minor clinical predictors. Similarly the guidelines also categorize the type of surgery as high, intermediate, or low risk [26]. This type of risk calculation can be used to consider the specific perioperative risk for PH patients.

Assessing Surgical Risk with PH

For general practitioners and many cardiologists, the specifics of surgical procedures may not be known. The ACC/AHA guidelines define high-risk procedures to include emergent major operations, aortic and major vascular surgery, peripheral vascular surgery, and anticipated prolonged procedures associated with large blood loss or fluid shifts [26]. For PH patients this list must be expanded to include procedures with risk for venous embolism (air, fat, cement), elevations in venous pressures (laparoscopy, Trendelenburg positioning), reduction in pulmonary vascular volume (lung compression or resection), perioperative systemic inflammatory response, and emergency procedures (Table 19.1). Again, effective communication between the PH specialist, surgeon and anesthesiologist can determine the risks and benefits of the proposed surgery or surgical technique. This will be revisited below.

Assessing Patient Risk Factors in PH

A known history of PH will prompt an evaluation of functional status, cardiac function (especially RV function), pulmonary function and current severity of disease. Echocardiography and right heart catheterization are essential to make these assessments. Meyer et al. reviewed major risk factors as being, an elevated right atrial (RA) pressure, a 6 min walking distance <399 m at the last evaluation and need for emergency surgery [16]. The discerning physician must also identify patients with risk factors for PH who as yet may have gone undiagnosed such as patients with scleroderma spectrum of disease, obstructive sleep apnea, cardiac valvular lesions, depressed left ventricular function, heart failure with preserved ejection fraction (HFpEF) or interstitial lung disease (ILD). At a minimum, symptoms of pulmonary hypertension or RV failure should be elicited (shortness of breath, abnormal cardiac silhouette on chest radiograph, elevated jugular venous distension, etc.). Intermediate- or high-risk surgeries might prompt a screening echocardiogram.

Table 19.1 Risk factors for morbidity and mortality in noncardiac surgery

Patient factors
• History of PE [14], CAD [12], CKD [11]
• NYHA/WHO FC ≥ II [14]
• Higher ASA class [12]
• RAD on ECG [14]
• Echo parameters: RVH, RVMPI ≥ 0.75 [14]
• Hemodynamics: higher PAP [11, 12], RVSP/SBP ratio >0.66 [14]
Operative factors
• Emergency surgery [13, 14]
• Intermediate- or high-risk operations [12–14]
– Procedures with high risk for venous embolism (air, fat, cement) [79–82]
– Procedures inducing elevation in venous pressure (Trendelenburg positioning, insufflation) [88–94]
– Procedures involving reduction in lung vascular volume (lung compression or resection) [85–87]
– Procedures inducing severe systemic inflammatory response [79]
• Longer duration of anesthesia [13, 14]
• Intra-operative vasopressor use [14]

Summary of the risk factors identified from studies of patients with pulmonary hypertension undergoing noncardiac surgery
PE pulmonary embolism, *CAD* coronary artery disease, *CKD* chronic kidney disease, *NYHA* New York Heart Association, *WHO* World Health Organization, *RAD* right axis deviation, *ECG* electrocardiogram, *RVH* right ventricular hypertrophy, *RVMPI* right ventricular myocardial performance index, *PAP* pulmonary artery pressure, *SBP* systolic blood pressure, *ASA* American Surgical Association

Comorbidities such as coronary artery disease (CAD), chronic renal insufficiency, history of pulmonary embolism, NYHA functional class III/IV have been correlated with increased morbidity and mortality in cardiac surgery. Right ventricular impairment is also a predictor of worse outcome. Right axis deviation (RAD) ($p = 0.02$), RV hypertrophy (RVH) ($p = 0.04$), RV index of myocardial performance (RVMPI) ≥0.075 ($p = 0.03$), RV systolic pressure to systemic systolic blood pressure ratio ≥2/3 ($p = 0.01$) all predict increased postoperative mortality [14].

Evaluation

The preoperative evaluation of a patient with pulmonary hypertension should seek out indications of right ventricular dysfunction to determine areas for potential optimization or disqualification for surgery due to unacceptable risk. This section will review common preoperative testing modalities to highlight their utility in diagnosing right ventricular insufficiency.

History and Physical

The evaluation begins with the history and physical examination. The most common complaints among PH patients, albeit nonspecific, are dyspnea and generalized fatigue [27]. Angina, pre-syncope, and syncope are indications of advanced PAH and may portend a poor prognosis [27, 28]. Physical signs of elevated RV pressure include jugular venous distension, right ventricular S3 gallop, hepatomegaly, ascites, and peripheral edema. By contrast, pulmonary crackles indicate left-sided heart failure or primary lung disease and not PAH.

Echocardiography

Transthoracic echocardiography (TTE) is easy to obtain and an excellent screening tool to estimate pulmonary arterial pressures as well as evaluate cardiac function. A complete assessment of ventricular and valvular pathology provides invaluable data to determine advancement of disease as well as etiology. By measuring the tricuspid regurgitant jet velocity, the PA systolic pressure (PASP) can be estimated. There is limited accuracy of this measurement in PH patients compared to catheterization, but it is useful as a screening tool [29]. Right ventricular dilation and contractility vary depending on severity and chronicity of disease. Objective measurements of RV function include tricuspid annular plane systolic excursion (TAPSE), RV fractional area change, and RV myocardial performance index, and possible use of mid and late systolic RV outflow Doppler notching to assess RV-PA coupling [30, 31]. Patent foramen ovale can be discovered by injection of agitated saline contrast, as well as intracardiac or intrapulmonary shunts, which may have clinical significance in the operative setting.

The elevated RV pressure during systole results in paradoxical ventricular septal flattening, pathognomonic for PH. Similar septal flattening during diastole marks RV volume overload, typically from RV failure with or without severe tricuspid regurgitation. Analysis of the blood flow through the mitral valve and pulmonary veins, as well as tissue Doppler velocities can determine LV filling patterns and identify elevations in left atrial pressure. Of note this technique is limited to patients in normal sinus rhythm. Left atrial size and function are useful to assess for the WHO 2 PH patient.

TTE may be used to suggest the possibility of HFpEF; however, cardiac catheterization is generally used to confirm the diagnosis. Reduced LV systolic function, severe left sided valvular lesions and left atrial enlargement in the presence of PH suggest a post-capillary etiology. Low grade diastolic dysfunction observed on echocardiography may still be attributable to pre-capillary PH and is not uncommon in PAH, parenchymal lung disease or CTEPH, when LV filling is impaired by altered RV function. It is not surprising that markers of significant RV dysfunction (right atrial enlargement, reduced TAPSE, increased interventricular septal flattening) are associated with poor overall prognosis in PAH patients and can probably be extrapolated to expect poor perioperative outcomes as well [31–33].

Heart Catheterization and Preoperative Optimization

Right heart catheterization (RHC) should be considered for PH patients undergoing intermediate- to high-risk operations or patients with moderate or severe PH by history, noninvasive screening, or with related comorbidities (e.g., obesity, sleep apnea, scleroderma, or risk factors for HFpEF such as atrial fibrillation and LAE). Left heart catheterization should also be performed in patients with coexisting left heart disease because of discrepancies between PCWP and left ventricular end-diastolic pressure (LVEDP) that could lead to misclassification of PH and have significant implications in treatment paradigms [34].

Ideally, RHC should be performed well in advance of surgery to allow for an adequate period of optimization for elective and semi-elective surgery. In all other cases, attempts should be made to lower PVR and enhance RV function prior to surgery. Routine vasoreactivity testing is performed during diagnostic RHC to determine candidates for vasodilator therapy [35, 36]. Although inhaled nitric oxide (iNO) is the drug of choice for testing due to lack of systemic effects and ease of administration, intravenous adenosine, epoprostenol, sildenafil, and inhaled iloprost can also be tried. Pre-capillary PH patients may benefit from advancing targeted pulmonary vasodilator therapy. When surgery cannot be delayed, phosphodiesterase 5 inhibitors (PDE5-I) such as sildenafil 20–40 mg three times daily, can provide acute vasodilatory effects and augmentation of right ventricular inotropy [37]. In those with high-risk hemodynamics (high right atrial pressure (RAP), low cardiac index (CI)), initiation of parenteral prostanoids should be considered prior to surgery. Furthermore, this same vasoactive testing is likewise useful in the perioperative period to guide intraoperative and postoperative management, such as the use of iNO, inhaled prostacyclins, and less commonly continuous epoprostenol. Patients with parenchymal lung disease and a component of hypoxic pulmonary vasoconstriction may also experience an improvement in PA pressures via an iNO mediated improvement in V/Q matching. Post-capillary PH patients may not benefit at all from pulmonary vasodilator therapy and moreover treatment may worsen pulmonary edema formation. In these patients, perioperative treatment should focus on diuresis and control of systemic hypertension. Some of the sickest WHO group 2 PH patients may need preoperative inodilators for low output states with aggressive up titration of the systemic vasodilators. WHO group 2 PH patients who have an increase in their PCWP in response to pulmonary vasodilators are at risk for developing worsening pulmonary vascular congestion and an increase in the driving force of left atrial hypertension with use of pulmonary vasodilators. Abnormal pulmonary function should be optimized with treatments such as oxygen, continuous positive airway pressure (CPAP), bronchodilators, antibiotics, and steroids where appropriate. Physical therapy and weight loss in obese patients may be beneficial although usually require a long-term plan [38, 39].

Optimal hemodynamic stability would include: mean arterial pressure (MAP) $\geq$ 60 mmHg, systolic BP $\geq$ 85 mmHg, oxygen saturation > 92 %, RAP < 12, mPAP < 35 (if feasible), PVR/SVR < 0.5 (if feasible), PCW 8–12 (some WHO 2 PH < 18), and CI $\geq$ 2.2 L/min/m^2.

Dyspnea at rest, syncope, hemodynamic findings of severe RV failure (low CI, high RAP >15 mmHg), metabolic acidosis, and marked hypoxemia are all signs of advanced, unstable disease and serious consideration should be given to cancelling or postponing the surgery until/unless improvement and stabilization or pulmonary hypertension can be achieved [37].

Planning for Surgery

Preoperative coordination of care among the multidisciplinary team is crucial for best outcomes. Ideally, all patients except those with the lowest risk PH and lowest risk procedures should be operated on in a tertiary care center, where a multidisciplinary team of specialists experienced in managing patients with PH is available. The multidisciplinary team for preoperative management of PH patients includes anesthesiologist, cardiologists, intensivists and pulmonologists, surgeons, and experienced allied health-care members including respiratory therapists, pharmacy (availability of medications and a pharmacist with experience in administration of PH therapies), as well as nurse managers (systemic prostacyclin administration requires staff training and often is approved only in certain units). Meticulous advanced planning and discussion amongst team members must take place to transition from oral to IV/inhaled therapies where prolonged surgery/intubation/extended NPO periods are expected. Generally, chronic PAH therapies, including PDE5-I (sildenafil, tadalafil), endothelin receptor anatagonists (ERAs) (bosentan, ambrisentan, macitentan), and prostanoids (inhaled, intravenous, subcutaneous, oral) should be continued throughout the perioperative period, with appropriate substitutions as above when necessary (intravenous for oral PDE5-I, intravenous for subcutaneous prostacyclin infusion, etc., depending on the surgery and interference of subcutaneous site,). If inhaled prostacyclin analogues cannot be continued due to intubation appropriate substitution should be planned with iNO, intermittent nebulized prostacyclin, continuous inhaled epoprostenol, vs. occasional conversion to IV prostanoids (there are no significant bleeding complications with IV prostanoids, despite platelet inhibition) [37]. Oral therapies should be resumed as soon as possible after procedure, keeping in mind that compromised absorption can result in low drug levels and rebound PH. Coumadin can usually be discontinued with judicious decision regarding heparin bridging depending on risk/benefit of bleeding vs. clotting (such as hypercoagulable states, pulmonary embolism (PE), or mechanical valves). In high-risk situations (such as major orthopedic surgeries), retrievable preoperative IVC filter placement may be considered [40]. Careful perioperative deep venous thrombosis (DVT) prophylaxis should be instituted and early ambulation is essential for both DVT/PE prevention and avoiding deconditioning.

Meetings with the patient and family must take place preoperatively and include some discussion of modes of anesthesia, need for invasive monitoring, and their role during the recovery period.

Intraoperative Management

The primary physiological concept is to maintain optimal right ventricular-pulmonary arterial coupling and promote adequate left sided filling and systemic perfusion. Thus, all interventions that affect RV preload, RV inotropy, RV afterload including pulmonary vascular resistance, large pulmonary artery capacitance or impedance, thoracic pressures, and oxygen supply and demand relationship need to be taken into consideration.

Right Ventricular Afterload

Pulmonary vascular disease leads to an increase in RV afterload that impedes RV ejection and thereby leads to increased RV wall stress, RV diastolic overload, RV dilation, and in the more chronic state, RVH. In contrast to the LV, the thinner walled RV is subjected to greater wall tension for the same degree of increase in end diastolic volume; this leads to an increase in RV myocardial oxygen demand and consumption.

Although often described simply as PVR (the *steady-state*, mean pressure/mean flow relationship largely dictated by small vessels), the true interaction between the RV and the pulmonary circulation is pulsatile and *dynamic*. Accordingly, the concept of input impedance has been applied as a means to summarize the resistive, elastic, and reflective components of afterload, and provide for some discrimination between the relative contributions of small vessels (steady state resistance) and large elastic ones ("characteristic" impedance) [25]. However, assessment of input impedance requires simultaneous measurement of pressure and flow, and generally involves analysis in the "frequency domain," i.e., mathematical resolution of pressure and flow waves into their individual frequency components and then defining their ratio at set frequencies along a spectrum. Not surprisingly, the complexity of both measuring and interpreting input impedance spectra has limited clinical utility. Nonetheless, there has been general acceptance of "lumped parameter" models such as the Windkessel to help conceptualize the static and dynamic contributions to afterload. Essentially adaptations of electrical circuits, these models incorporate a resistor (PVR), a capacitor (vascular compliance), and an inductor (characteristic impedance) to represent the basic physiological components dictating input impedance. While alternative methods for calculating characteristic impedance as a measure of large vessel load from more conventional "time-domain" measures (PA pressure, PA diameter, and stroke volume) have been described [41], from a clinical perspective, prognostic significance has focused more upon compliance (calculated as stroke volume/pulse pressure) and its reciprocal relationship with PVR [42–45]. Data suggest that early in the course of PAH, a relatively small rise in PVR will be accompanied by a larger relative decline in compliance, while later in the disease course, the fall in compliance elicited by increased PVR will diminish since the vascular wall

approaches maximum stiffness [41]. Functionally, an acute change in compliance will lessen the ability of large elastic vessels to "absorb" pressure waves reflected from more distal potions of the circulation. This effect can be directly observed in the RV and proximal PA pressure waveform as the timing of peak pressure achievement moves from early to late in systole. This "late phase load" produced by summation of reflective pressure components parallels the systolic augmentation described for systemic vessels and contributes to a widened PA pulse pressure. This is particularly relevant to acute insults that may occur during surgery and affect RV pulsatile load, and importantly, may be underestimated by PA catheter tracings where pressure is measured more distal in the circulation. For example, compliance and PVR may be altered by events such as the addition of positive end-expiratory pressure (PEEP) to mechanical ventilation (Fig. 19.2), a change to prone or Trendelenburg positions, pneumoperitoneum during a laparoscopic procedure (Fig. 19.3), venous emboli (including air emboli or particulate matter, i.e., from orthopedic procedures), and any direct compression or displacement of the large PA branches.

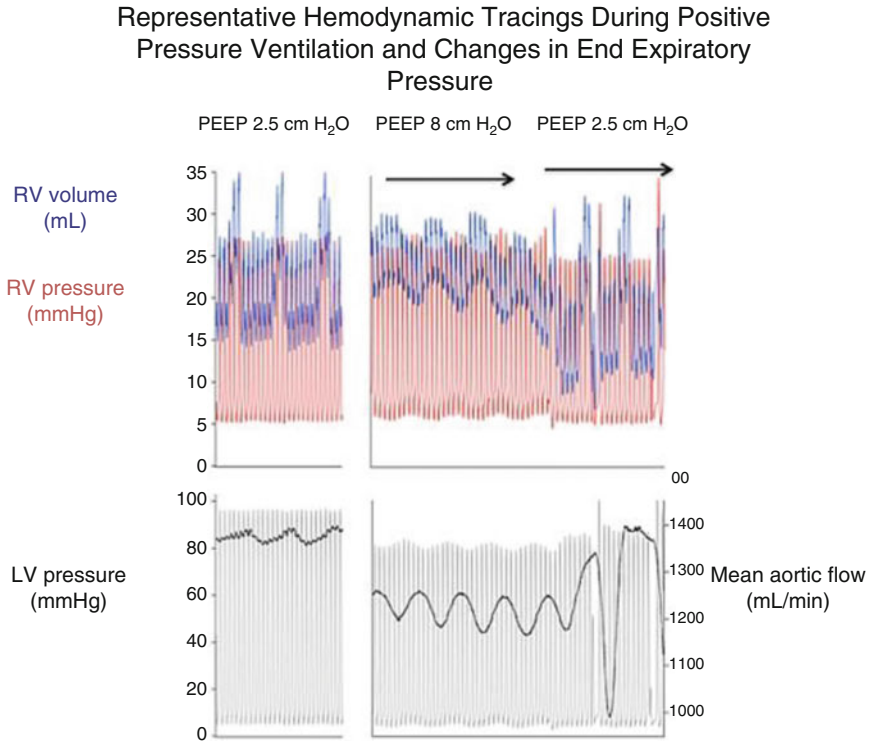

Fig. 19.2 Representative tracings of right (RV) and left (LV) ventricular pressures along with RV volume and aortic blood flow during positive pressure ventilation and variations in positive end-expiratory pressure (PEEP) in an experimental animal (dog). Marked respiratory variation in RV volume and aortic flow is evident, particularly with increased levels of PEEP

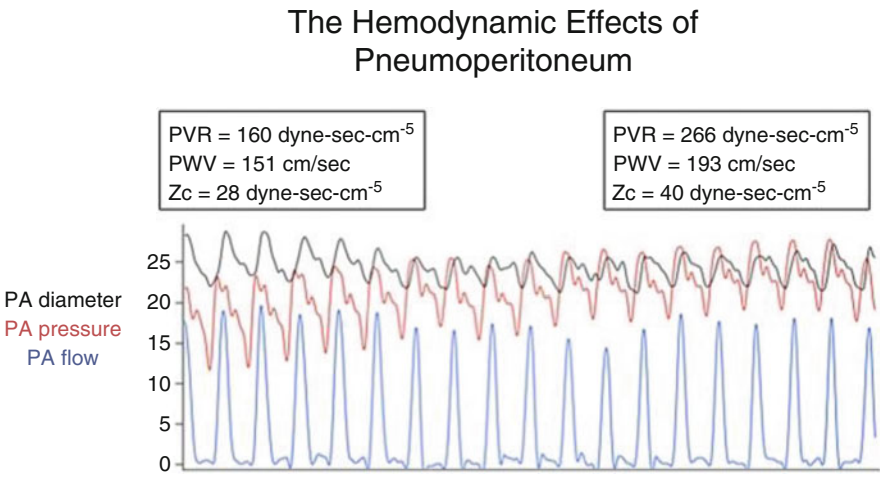

Fig. 19.3 The representative effect of inducing pneumoperitoneum and increasing positive end-expiratory pressure (PEEP) on pulmonary arterial (PA) pressure, diameter, flow, pulse wave velocity (PWV), and characteristic impedance (Zc). The data indicate an acute increase in right ventricular afterload in terms of effects on both pulmonary vascular resistance (PVR, primary determined by small vessels) and characteristic impedance (Zc, primarily determined by large vessels). In addition, the increase in pulse wave velocity (PWV) suggests that pressure waves will be reflected from the distal pulmonary circulation more rapidly, potentially contributing to increased afterload

Changes in Myocardial Supply and Demand

Under normal circumstances the RV intramyocardial pressure is lower than the aortic root pressure and the RV coronary perfusion occurs throughout the cardiac cycle. In PH, due to the elevated RV intramyocardial pressure, coronary flow occurs predominantly during diastole, which further worsens the mismatch between oxygen demand and supply promoting RV ischemia and diminished RV contractility [46, 47]. Low RV oxygen supply is associated with a shift away from aerobic glucose and fatty acid oxidation to the less efficient RV glycolytic pathways [25].

Systemic vasodilatation and hypotension with anesthesia (see Sect. "Choice of Anesthetics") leads to a relative increase in the PVR/SVR ratios, and hypotension induced RV ischemia in the setting of increased oxygen demands [48].

Intraoperative manipulation of the heart and/or great vessels may further contribute to the hypotension.

Interventricular Dependence

The combination of elevated PVR/reduced RV compliance and systemic hypotension may promote RV ischemia resulting in the "lethal combination" of RV dilatation, interventricular septal bulging into the left ventricle, and insufficient left ventricular filling, with resulting progressive decline in CO and further systemic hypotension [49]. Management should be focused on RV unloading with pulmonary vasodilators, optimizing intravascular fluid balance, and maintaining adequate systemic pressure. Combination of RV inotropes and systemic pressors may be needed [50]. Dobutamine may be a preferred RV inotrope in this situation due to less systemic vasodilation as compared to milrinone which may cause further LV unloading and septal displacement; vasopressin may be a good option to maintain systemic pressure although there is some institutional bias as well with the choice of systemic pressors and catecholamine sparing. Ongoing monitoring of arterial pressure, central venous pressure, cardiac output, central venous oxygen saturation, arterial blood gases, and lactate levels are necessary, ideally supplemented by transesophageal echocardiography (TEE) guided assessment of RV/LV filling.

General Anesthetic Management

Preparation

Decision making regarding choice of anesthesia in a PH patient depends on the type of planned surgery, PH severity, comorbidities, and patient's preference. While conscious sedation may result in less anesthetic related problems in a non-PH patient, even mild hypoxia and hypercarbia (frequently associated with conscious sedation) can cause pulmonary vasoconstriction and lead to sudden decompensation in a PH patient. Also, any baseline comorbidity predisposing to hypoxia (sleep apnea, obesity, lung disease) may be an additional indication for a protected airway. Thus, elective intubation and general anesthesia are frequently preferable. Also, any procedures associated with high risk of pulmonary emboli (such as orthopedic procedures) may require intubation, general anesthesia, and invasive hemodynamic monitoring in a PH patient, as to avoid emergent intubation should hemodynamic instability or suboptimal oxygenation be precipitated.

Particular care should be taken to de-air all lines and syringes, as even a small amount of air can cause hemodynamic decompensation in a PH patient [51]; there is also a high risk of passage of air to systemic circulation via PFO. Hypothermia should be avoided as it inhibits physiologic hypoxic pulmonary vasoconstriction (HPV) and may result in worsened VQ mismatch, which may have considerable effect in procedures requiring reduction of lung volume [52].

Airway and Optimal Ventilator Strategies

With any type of non-general anesthesia, airway patency needs to be insured, and an airway access should be planned should ventilation become compromised. With any means of anesthetic administration (face mask, laryngeal airway, or ET) supplemental oxygen must be administered for its direct pulmonary vasodilating effects [53].

With general anesthesia, carefully planning the induction is critical, as uncontrolled ventilation with possibility of hypoxia, and sympathetic stimuli from laryngoscopy can result in acute rise in PVR. Use of 100 % oxygen by mask prior to induction and optimizing depth of anesthesia prior to laryngoscopy and intubation can minimize this effect. In patient with difficult airway, OSA or intrinsic lung disease and poor functional reserve capacity, "awake intubation" with fiberoptic bronchoscopy may be preferable to avoid a period of poor ventilation with regular induction and intubation. Use of systemic pressors to protect against any acute vagal mediated vasodilatory response is often suggested.

After securing airway, ventilator management in PH is focused on use of higher FiO_2, with mild hyperventilation (goal PCO_2 of 35 % or less) and maintenance of lung volumes at normal functional residual capacity (Table 19.2) [54–56]. There is a U-shape relationship between lung volumes and PVR during mechanical ventilation, with PVR being the lowest at functional residual capacity. At low lung volumes, resulting hypercapnia and hypoxia will cause hypoxic vasoconstriction and an increase in PVR, while hyperinflation and high PEEP (preferably <10 mmHg) will result in an undesirable compression of the intra-alveolar vessels which can also lead to increase in PVR [56, 57].

Table 19.2 Perioperative ventilatory conditions to avoid and promote

Avoid pulmonary vasoconstrictors
• Hypoxemia
• Inspiratory pressure >30 mmHg
• High PEEP (>15 mmHg)
• Hypercapnia
• Acidosis
Promote pulmonary vasodilation
• Improve oxygenation (e.g., FiO_2 1.0)
• Permissive hypocapnia (pCO_2 ≤30–35 mmHg)
• Alkalosis (pH N 7.4)
• Optimal ventilatory volume

This table summarizes the conditions to avoid or promote during mechanical ventilation in patients with pulmonary hypertension *PEEP* positive end-expiratory pressure, *FiO_2* fraction of inspired oxygen

Choice of Anesthetics

All anesthetic techniques have been safely employed in PH patients with appropriate judgment and monitoring. However, two anesthetic effects are of special significance when choosing an agent for a PH patient: avoiding direct myocardial depression and unfavorable effects on autonomic tone.

Many anesthetics are known to have myocardial depressant effects [58–62], by the means of directly affecting calcium cycling by myocytes, or the sensitivity of the contractile proteins to calcium, as well as their indirect effect on the autonomic nervous system. Direct myocardial depression is dose dependent. Propofol causes direct myocardial depression but only at relatively high concentrations and can still be used with caution [55, 57]. Studies showed that with frequently used inhaled anesthetics such as isoflurane, sevoflurane, and desflurane, depression of LV systolic function is offset by a decrease in systemic afterload. However, due to a smaller effect on decreasing RV afterload, there is a resulting disparity of LV and RV workload [60–62]. Ketamine has a modest myocardial depressant effect and with optimal ventilation and acid-base balance it may have pulmonary vasodilating properties [63, 64]. However, ketamine may also cause pulmonary vasoconstriction by the means of sympathetic stimulation [51]. With neuraxial (spinal, epidural) anesthesia, blockade of sympathetic nerves can precipitate hypotension. In addition high spinal or epidural anesthesia could result in cardiac sympathetic blockade, with unopposed parasympathetic stimulation from the cranial region [65]. Such an acute shift in autonomic balance in PH patient may result in profound hypotension and severe hemodynamic compromise [65]. In general, gradual epidural dosing or low spinal techniques are safe.

Intraoperative Pharmacological and Inhalation Therapy

Volume Status

Baseline hemodynamics, including “average” resting CVP, PA sat, and CO/CI are very useful at guiding intraoperative and postoperative fluid management [66]. For a normotensive patient, the goal should be to maintain the lowest baseline CVP. Whereas volume resuscitation is often guided by pulse-pressure variation (PPV), this is not feasible in PH patients. With the failing RV, PPV does not predict volume responsiveness and PPV due to increased RV afterload may erroneously suggest volume responsiveness [67, 68]. Although recent studies question the adequacy of both static (CVP) and dynamic (PPV) indices of preload assessment in PH, clinical experience suggests that targeting a CVP of 8–12 mmHg may have utility in managing systemic hypotension.

Pressors and Inotropes

Pressors of choice for the PAH patient include norepinephrine and vasopressin. While many institutions use phenylephrine and it is effective in increasing the coronary artery driving pressure it is less favorable for RV hemodynamics and relative PVR/SVR ratios [69, 70]. With more significant RV dysfunction, vasopressors with inotropic properties, such as norepinephrine and epinephrine, may be preferable. In experimental models, vasopressin was demonstrated to stimulate nitric oxide release and was vasodilating in pulmonary circulation, while causing peripheral vasoconstriction via V1 receptor stimulation [71], providing in vitro rationale for it as a preferable choice. Although there is no definitive clinical trial showing its superiority to catecholamines, there is some clinical experience [72], and applicability of the lessons of vasodilatory shock [73, 74]. For RV inotropy, especially with underfilled LV, dobutamine may be preferable to milrinone due to less arterial vasodilation [75]. For the WHO group 2 patient, milrinone or dobutamine are appropriate, with pressor support with norepinephrine or vasopressin as indicated.

Pulmonary Vasodilators

For WHO Group 1 patients, continuation of chronic pulmonary vasodilators through surgery is essential. Specifically, oral therapies should be given up to and including the day of surgery. Long-term inhaled prostacyclin therapies should be given just prior to surgery and depending on the length of the procedure, arrangements should be made for intraoperative treatments or alternative therapies such as continuous iNO, or continuous inhaled epoprostenol [76, 77]. Patients on intravenous or subcutaneous prostanoids should have lines marked "not to touch," and timely cassette changes planned in advance to avoid sudden interruption of drug delivery. Unlike usual intraoperative titratable medications, prostacyclin and remodulin are not to be titrated upward during the procedure due to risk of systemic hypotension. Inhaled pulmonary vasodilators are more suitable for acute PH management due to their pulmonary selectivity [76, 77]. Down titration of chronic PH therapies due to hypotension is also not recommended due to possibility of abrupt worsening of PVR; rather, pressors should be used as needed for systemic hypotension. Inhaled pulmonary vasodilators have the added benefit of selectively reaching well-ventilated lung areas and diminishing VQ mismatch in patients with intrinsic lung disease. For patients with WHO 2 PH, PO/IV sildenafil may be considered for perioperative PH management, though are unproven (with caution due to possibility of precipitating pulmonary edema), while diuresis and systemic vasodilator remains the mainstay of treatment.

Immediate Postoperative Period

For patients undergoing general anesthesia for major procedures associated with large fluid shifts, it is generally advisable to delay extubation until optimal hemodynamics are accomplished with diuresis vs. volume repletion as needed (with arterial

line and CVP vs. pulmonary artery catheter monitoring). Care should be taken to prevent sympathetic activation with meticulous pain management. Avoidance of hypothermia and shivering aids in maintaining optimal oxygenation and PVR. Aggressive pulmonary toilet is necessary for excessive secretions. Patients with OSA may benefit from postoperative bi-level positive airway pressure (BiPAP) or CPAP to augment ventilation, and their home mask should be made readily available.

Special Considerations

Certain types of surgical procedures may require particularly careful management in PH patients.

Orthopedics

Orthopedic procedures in PH patients may require general anesthesia, as described above [78]. Joint replacement and hip fracture repair are the highest risk orthopedic procedures in PH patients. While hip surgery in the setting of fracture is an urgent and necessary procedure, joint replacement is an elective surgery that, in PH patients, is associated with a high morbidity and mortality due to high potential for pulmonary embolization, and risk and benefits of it have to be carefully considered [79]. The surgical technique of reaming the bone results in extremely high intramedullary pressure that causes bone fragments, marrow, fat, and inflammatory mediators to pass into the bloodstream [79, 80] with exacerbation of PH hemodynamics and systemic vasodilation. If bone cement is used to stabilize the prosthesis, the exothermic reaction of the compound during cementing causes it to expand within intramedullary space, and may results in pressures as high as 5,000 mmHg [81], increasing the potential for particularly large emboli [82]. Multiple pulmonary emboli, even with overall small embolic load, cause a release of pro-inflammatory mediators and result in significant increase in PVR with a possibility of acute RV failure [79, 83].

Preemptive inotropic support needs to be instituted for patients with baseline RV failure [80, 84], and systemic hypotension needs to be aggressively treated with vasopressors.

Thoracic Surgery

Single lung ventilation for lung biopsy or resection may represent a significant risk for PH patients, due to intentional collapse of the operative lung. As the tidal volume is shifted to the ventilated, non-operative lung, hypoxic pulmonary vasoconstriction (HPV) will lead to redistribution of flow away from non-ventilated lung; in PH patients the effects of flow redistribution may result in an acute rise in PA

pressure [85, 86]; iNO or inhaled prostacyclins may aid in optimizing blood flow in the aerated lung thus preventing V/Q mismatch [87]. In this situation, limiting IV pulmonary vasodilators may be beneficial (with dose-appropriate inhaled agent substitution) to minimize HPV inhibition and avoid systemic hypoxia. Even when normal dual lung ventilation is resumed, PA pressure may remain elevated from baseline despite increase in therapies, especially if lung resection took place [86]. In addition, epidural analgesia frequently used in postoperative pain management for thoracic procedures, may cause systemic hypotension by suppressing sympathetic tone, and provoke LV underfilling [51]. Manipulation of the pulmonary artery such as compression and displacement of the large PA branches increases cumulative RV afterload as mentioned above.

Laparoscopy

Insufflation of the abdomen with carbon dioxide during laparoscopy causes diaphragmatic displacement, with resulting need for increased inspiratory pressures and PEEP to prevent atelectasis and maintain ventilation. This may result in a progressive rise of PVR as well as direct PA compression with decreased compliance, increased pulse wave velocity, and an abrupt increase in the pulsatile component of RV afterload (Fig. 19.3) [88].

Prolonged steep Trendelenburg positioning (up to 45°) required for robotic-assisted lower abdominal procedures, such as prostatectomy or hysterectomy, can cause further increases in RV afterload [89–94]. Even in otherwise healthy patients, there is a two to threefold increase in LV and RV filling pressures with resulting PH (as defined by mPAP >35 mmHg) in 75 % of these patients; in otherwise healthy patients there is a corresponding increase in MAP, and overall stable hemodynamics with unchanged CO, and no evidence of RV pressure overload despite 65 % increase of RV stroke work index. [92, 93] It is expected that in PH patients such hemodynamic alterations can be detrimental, although this technique has not been specifically studied in the PH population. Even when pneumoperitoneum is reversed, the PA pressure may not return to baseline for some time due to factors such as atelectasis and subcutaneous emphysema, with gradual CO_2 reabsorption resulting in postoperative hypercarbia [90–94].

Obstetrics

Pregnancy and delivery are known to be associated with high morbidity and mortality in PH patients, especially in the postpartum period with mortality rates available from small case series reported to be 30–70 % [1–3, 15, 95]. Traditionally, avoidance of pregnancy or early termination are strongly recommended. In the last decade, due to careful pregnancy and peripartum care, mortality in IPAH patients has declined to 17 % but in congenital heart disease associated PH and other PH cases, mortality remains as high as 28–33 % [95].

In IPAH, invasive hemodynamic monitoring is frequently necessary in peripartum period to guide therapy [96]. The vaginal route with assisted second stage delivery is preferred (unless there are obstetric indications for a Cesarean section) due to less fluid shifts, and lower incidence of bleeding and infection, although some institutions will prefer scheduled C sections with availability of the most experienced multidisciplinary team. Epidural anesthesia (with slow cautious administration to minimize risk of hypotension) prevents sympathetic activation due to pain. Dobutamine may be used for inotropic RV support, and pressors (preferably vasopressin) can be used as necessary. Availability of backup cardiothoracic surgical team support for emergency ECMO for the sickest patients as a bridge to recovery should be considered. Knowledge that the hemodynamic insult is often at its maximum at 72 h after delivery necessitates the ongoing care of the multidisciplinary team beyond the delivery phase.

Liver Surgery

Anything but mild porto-pulmonary hypertension (PPH) represents a challenge in the setting of liver transplant. Moderate-to-severe PPH (MPAP $\geq$ 35) is diagnosed in up to 10 % of patients referred for liver transplant [97, 98], and has been associated with high complication rates and perioperative mortality [99–101]. Multiple studies in recent years have demonstrated that treatment with pulmonary vasodilators may control and improve the degree of PPH, and reduce perioperative risk [102, 103]. While a significant degree of PPH is considered a contraindication to liver transplant, survival in the absence of transplant is as low as 38 % in 3 years, and 28 % in 5 years, while transplantation can be curative [104–106]. Prostacyclin analogues have been successfully used both preoperatively to reduce the PAP, and intra- and postoperatively to control residual PH [98, 107]. ERAs and PDE5-Is, and various drug combinations have been used preoperatively with some success [108–111]. In these studies, liver transplant was undertaken when MPAP of <35 was accomplished. Epoprostenol was continued throughout surgery and into posttransplant period; some of the patients eventually did not require pulmonary vasodilators [108]. Careful preoperative assessment of RV function with echocardiography, and intraoperative TEE are helpful to assess the RV response to increase in CO and PVR that occur with reperfusion, and to preempt and treat resulting acute RV failure. In many ways, the hemodynamics of liver transplant parallel that of the postpartum woman in the autotransfusion of a high capacitance low resistance circuit into the central volume with an acute rise in the right atrial pressure and potential load on a borderline RV.

Unrecognized PPH can lead to poor clinical outcomes of procedures designed to manage complications of portal hypertension, such as transjugular intrahepatic portosystemic shunt (TIPS). The creation of TIPS causes diversion of the portal flow into the systemic circulation, therefore reducing the incidence of variceal bleeding and refractory ascites; it also causes increase in cardiac index, and rise in PVR, PA pressure, and RAP. One month after TIPS, pulmonary pressure remains elevated.

Currently, absolute contraindications to TIPS include congestive heart failure, severe tricuspid regurgitation, and severe pulmonary hypertension (mean pulmonary pressure >45 mmHg). Whether patients with milder pulmonary hypertension can receive a TIPS safely is unclear [112]. It is important to keep in mind that prevalence of PPH in advanced cirrhosis patients with cirrhosis complications such as refractory ascites may be as high as 16 % [113]; careful pre-procedural screening for significant PPH is essential in preventing TIPS-induced abrupt increase in PVR and RV failure.

Postoperative Management

The postoperative deaths frequently occur in the first few days after surgery, and are frequently sudden, necessitating extended ICU monitoring for PH patients. The hemodynamic deterioration and deaths are attributed to increased sympathetic tone, fluid shifts, worsening pulmonary vasoconstriction (due to hypoxia, hypothermia, acidosis), and pulmonary embolism.

The most feared postoperative complication is RV failure due to PH exacerbation, with resulting LV underfilling, systemic hypotension, and arrhythmias [114–116].

Atrial tachyarrhythmias are usually managed with digoxin and amiodarone; use of beta blockers and calcium channel blockers may occasionally be appropriate (with extreme caution due to negative inotropy); electrical cardioversion is usually reserved for hemodynamically unstable patients, but if catecholamines are markedly elevated and filling pressures are high, recurrences are high.

Any noncardiac complications that increase RV workload (such as infection, anemia, and acidemia) need to be rapidly treated. Acidemia, in particular, increases PVR, while mild alkalosis may be beneficial (Goal pCO_2 is $\leq$30–35 mmHg, and goal pH $\geq$7.4) [117, 118]. Normothermia has to be maintained [52]. Both hypovolemia (bleeding) and volume overload are poorly tolerated in PH patients, as hypertrophied RV requires optimal preload, and excessive volume may precipitate worsening RV failure and septal shift, compromising LV filling. Diuretic use can be guided by CVP (aiming at "best baseline" preoperative CVP, vs. CVP 5–10 for borderline blood pressure, to ensure adequate filling); ultrafiltration can be used for diuretic resistance. PEEP has to be taken in to consideration in hypotensive intubated patients with CVP $\leq$10 mmHg; if lifting patients legs results in increased MAP, fluids are indicated; if CVP $\geq$15 and/or leg rising does not lead to increase in MAP, diuretics are likely needed. Vasopressors and inotropes are used as needed to maintain systemic blood pressure.

While iNO is optimal for the early postoperative period to decrease PVR, it has a potential for formation of toxic metabolites with prolonged use, and is expensive. Weaning to 5 parts per million (ppm) and bridging transition with inhaled prostacyclin derivatives to prevent rebound PH in weaning of the last 3–4 ppm is usually recommended; IV/PO sildenafil used for additional pulmonary vasodilatation may

be helpful in the weaning process and in the highest risk patients, nasally delivered iNO and slower down titration to allow extubation is also feasible. Inhaled milrinone has also been used [119, 120]. The calcium sensitizer levosimendan (available in Europe) showed some promise in optimizing PH hemodynamics in small studies [121] but is not routinely used or available. IV prostanoids may be initiated in the postoperative period in patients with severe PH who are candidates for chronic PH therapies and ideally should have been instituted preoperatively. In patients with WHO group 2 PH, combined systemic and pulmonary vasodilators such as sodium nitroprusside, nitroglycerin, milrinone, nesiritide (and perhaps levosimendan) are beneficial; pulmonary vasodilators can worsen LV failure and pulmonary venous congestion, and precipitate further V/Q mismatch in underlying lung disease.

The multidisciplinary approach is equally essential in the postoperative period as it is in the preoperative and intraoperative settings. Early ambulation and physical therapy, as well as nutritional support for prevention of postoperative complications are routine. Well trained and coordinated multidisciplinary teams have the ability to optimize outcomes and lower mortality in high-risk PH patients. Further studies of anesthesia and surgery in PH patients will help in understanding of the preoperative risks and complications, and refine current treatment strategies.

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