Current Anesthesiology Reports (2018) 8:44–51
https://doi.org/10.1007/s40140-018-0251-z

PREOPERATIVE EVALUATION (BJ SWEITZER, SECTION EDITOR)

Pre-operative Evaluation of Patients with Pulmonary Hypertension

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Published online: 13 February 2018

Abstract

Purpose of Review To highlight some clinical information and recent findings about pulmonary hypertension (PH) and use them as a resource to improve perioperative care in patients affected with this disease.

Recent Findings The last PH Consensus was held in Nice (2013) and continues to classify PH in five major groups. Although transthoracic Doppler echocardiography is often used as a first screening tool, right heart catheterization is mandatory to accurately make the diagnosis. As the natural history of PH has been changed by modern drug therapies, with current median survival rate reaching up to 9 years in low-risk patients, it is likely that anesthesiologists will need to evaluate PH patients more often. Their perioperative management remains challenging, and patients should be preferentially cared for in specialized centers.

Summary Although the perioperative mortality of PH patients has significantly decreased over the years, morbidity remains high. Thus, a careful pre-operative evaluation and risk stratification by a multidisciplinary team is strongly encouraged as it may improve outcomes after surgery.

Keywords Pulmonary hypertension · Pre-operative management · Perioperative outcomes · Right ventricular function

Introduction

Pulmonary hypertension (PH) is a rare, progressive, and lethal disease with an estimated prevalence of 15 to 124 patients per million habitants or 0.001 to 0.01% [1]. Time from onset of symptoms to diagnosis is approximately 2 years, and survival without therapy is only 2.8 years [1]. Initial reports of this disorder date back from the end of the nineteenth century, when it was defined as pulmonary sclerosis [2]. Detailed clinical and pathological descriptions appeared in the early 1950s with Dresdale and in 1970 with Wagenvoort's autopsy studies [2]. The first National Registry was done in the early 1970s, and the natural history of the disease could be followed more closely. The discovery of prostacyclins (1976), nitric oxide (1986), and endothelins (1988) and their role in the pathophysiology of PH led to many specific target drug therapies that are currently used [3••]. Quality of life and exercise tolerance have improved, as well as survival with some of these drugs. Lung transplantation remains an option for more advanced stages.

Eventually, PH patients may need surgery, either elective or urgent. Pre-operative evaluation and planning is challenging, and a multidisciplinary approach is highly encouraged. The anesthesiologist's role in this process should not be overlooked, as he or she is the one who will ultimately manage these patients during surgery. The goal of this review is to provide current knowledge about PH in order to perform a systematic and evidence-based pre-operative evaluation, which can potentially lead to improved perioperative outcomes.

This article is part of the Topical Collection on *Preoperative Evaluation*

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Clinical Findings and Diagnosis

The clinical findings of PH vary greatly at presentation [3••]. Patients may be nearly asymptomatic to exhibiting overt right heart failure symptoms. Dyspnea, near syncope or syncope, peripheral edema, and chest pain are frequent complaints. Because symptoms are non-specific, a high index of suspicion is warranted in order to diagnose PH.

The normal value for mean pulmonary artery pressure (mPAP) is 14 ± 3.3 mmHg [3••, 4]. The upper normal limit is 20 mmHg (i.e., 2 SD above the mean). PH is defined as a mPAP ≥ 25 mmHg at rest [4]. Values between 20 and 24 mmHg belong to a "gray zone," and it is currently unknown whether they have clinical significance, with some arguing that they represent a stage of "pre-PH."

Although pulmonary artery catheterization is needed for definite diagnosis, transthoracic Doppler echocardiography (TTE) is usually the first-line screening method. At the bedside, the clinician is able to estimate the pulmonary artery systolic pressure (PASP) by measuring the regurgitant tricuspid jet flow velocity [5]. The modified *Bernoulli* equation is then applied:

$$\Delta P = 4 \times V^2$$

Where ΔP is the pressure gradient between two chambers and V is the flow velocity of a turbulent jet across the two chambers, in this case, the tricuspid regurgitant jet. This is measured by the echocardiographer using continuous Doppler. Herein, ΔP is the difference between the right ventricle and the right atrial pressures (RVP and RAP, respectively). The equation then turns out to be:

$$\mathrm{RVP}-\mathrm{RAP} = 4 \times V^2$$
$$\mathrm{RVP} = 4 \times V^2 + \mathrm{RAP}$$

Usually, the RAP is estimated using changes in the inferior vena cava diameter during spontaneous inspiration [5]. If there is no variation at all, the RAP is said to be 15 mmHg ("hypervolemic"); if variations exceed more than 50% of the baseline diameter, RAP is equal to 5 mmHg ("hypovolemic"); otherwise, RAP is 10 mmHg ("normovolemic").

RVP is then calculated after solving for the equation above. If there is no obstruction to the right ventricular outflow tract (e.g., infundibular or pulmonary stenosis), the RVP is similar to PASP.

The sensitivity and specificity of TTE in diagnosing PH is 83 and 72%, respectively [5]. Importantly, TTE has a high negative predictive value if a cutoff value of PASP less than 50 mmHg is used, highlighting its usefulness as a screening tool. Further evaluation with right heart catheterization (RHC) is considered when the estimated PASP is greater than 45–50 mmHg. However, it should be noted that positive predictive values are fair, which means that some patients with an estimated PASP higher than 50 mmHg will not have PH with RHC.

Clinically, PH can be classified into five major groups (Table 1) [6]. Group 1 consists of systemic diseases that may evolve to PH, such as HIV infection (0.5% of the patients), scleroderma (8–12%), portal hypertension (4–10%), and others. The former primary pulmonary hypertension is now called idiopathic and also belongs to this group. The term pulmonary arterial hypertension (PAH) is synonymous for group 1 PH. Group 2 is PH secondary to left heart diseases. Group 3 is associated with lung disorders (pulmonary fibrosis,

Table 1 Pulmonary hypertension is classified in five major groups (last revised in Nice, 2013)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic
1.2. Heritable
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1". Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1. Left ventricular systolic dysfunction
2.2. Left ventricular diastolic dysfunction
2.3. Valvular disease
2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleimoyomatosis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

chronic obstructive pulmonary disease) or chronic hypoxia, such as found in patients with severe sleep-disordered breathing. Group 4 is due to chronic thromboembolism, also known as chronic thromboembolism pulmonary hypertension (CTEPH). Finally, a number of diseases that are associated with PH but without a clear pathophysiological mechanism are classified as group 5. Examples include pulmonary sarcoidosis, chronic hemolytic anemia, and other myeloproliferative disorders.

While groups 2 and 3 are the most frequently diagnosed in the western world, only group 1 has specific target therapies. The only successful and curative treatment for group 4 PH (CTEPH) is pulmonary artery thromboendarterectomy, though percutaneous balloon pulmonary angioplasty dilatation may be an option in selected patients [7•]. Care should be taken on evaluating these patients as residual pulmonary hypertension may persist after either procedure (15% of the patients). Rescue therapy with drugs used in group 1 PH might be used in these patients [8].

The functional status of PH patients is useful for overall risk assessment and prognosis. It can be evaluated by the functional class (FC), 6-min walk distance (6MWD), and cardiopulmonary exercise testing (CPET). The FC is stratified according to the World Health Organization (WHO) classification [9], which is quite similar to the New York Heart Association (NYHA) classification for heart failure. WHO FC I patients have good exercise capacity whereas class IV patients have very limited reserve. More objectively, the 6MWD is widely used to quantify exercise capacity in this setting [10]. Healthy individuals are able to walk more than 600 m in 6 min. Symptomatic PH patients rarely achieve this distance, and values less than 300 m are a marker for poor prognosis [10]. Low-risk (estimated 1-year mortality less than 5%) patients walk above 440 m. Improvements in the 6MWD have been used as a surrogate for successful drug therapy. The CPET, usually performed as a maximal exercise test, provides information on exercise capacity as well as on gas exchange, ventilator efficacy, and cardiac function during exercise.

Hemodynamic Measurements

RHC is the standard method to diagnose PH. Apart from directly measuring the mPAP, it yields other useful hemodynamic data. For instance, the cardiac output (CO) can be measured and the pulmonary vascular resistance (PVR) calculated according to *Ohm*'s law:

$$\mathrm{CO} = \Delta\mathrm{P}/\mathrm{PVR}$$
$$\textit{Or}$$
$$\mathrm{PVR} = \Delta\mathrm{P}/\mathrm{CO}$$

ΔP is the downstream pressure gradient across the pulmonary vasculature: (mPAP − PAWP). Most patients with PH have PVR higher than 3 Woods Units (WU). A low CO is a marker of poor prognosis.

It may be useful to distinguish between pre- and post-capillary PH using the pulmonary artery wedge pressure (PAWP) values. If PAWP is less than 15 mmHg, PH is said to be pre-capillary. When PAWP is greater than 15 mmHg, it is post-capillary, which is the hallmark of left heart disease [11•].

While the majority of patients will have isolated post-capillary PH (ISO-PH), some will combine both post- and pre-capillary PH (Cpc-PH). The gradient between the pulmonary artery diastolic pressure (PADP) and PAWP (diastolic pressure gradient) is useful to differentiate them [4, 11•]. If PADP-PAWP is higher than 7 mmHg along with a PAWP greater than 15 mmHg and PVR > 3 WU, then Cpc-PH type is present. This is important, because therapy can be properly adjusted.

A vasodilator challenge, usually with inhaled nitric oxide (iNO), is recommended at the time of RHC in selected subgroups (idiopathic, heritable, drug induced) to test pulmonary vascular reactivity and detect patients who can be safely treated with high doses of a calcium channel blocker (CCB). A 10-mmHg decrease in baseline mPAP resulting in mPAP 40 mmHg or less, with preserved or increased cardiac output is considered a positive response [12]. However, only about 10% of patients will respond to a vasodilator challenge, and only 50% of these patients will eventually respond to CCB therapy.

Therapy

Major advances in PH therapy have been made over the last 20 years. Median survival rates have markedly improved and may reach up to 9 years in low-risk patients [13••].

In the late 1990s, clinical drug trials used mostly functional parameters like the 6MWD as primary end-points. An increase in 20 m walking distance is usually clinically relevant [10, 14]. Unfortunately, these end-points have not clearly translated into improved survival [14]. PH is a rare disease, and trials with a large number of patients and long-term follow-up are expensive to perform, particularly when survival is chosen as the primary event.

More recent trials have used composite clinical end-points, and results have been encouraging. The concept of "hit hard and hit early" has been suggested [15•], and initial target therapy is likely to become more aggressive in an attempt to halt disease progression. In this regard, dual or triple up-front therapy has been increasingly used.

Because PH is a broad-spectrum disease with sometimes complex hemodynamic overlapping situations, RHC is mandatory before initiation of drug therapy. Unfortunately, in a

recent review, up to 40% of referred patients were on drug therapy despite not having a previous RHC [16], clearly showing that the clinical care of these patients may be improved.

Importantly, general "ancillary" care should not be overlooked in patients with PH, such as physical rehabilitation, oxygen therapy, diuretics, and anticoagulants. Anticoagulants are not only used in group 4 (CTEPH) patients. They also have shown some benefits in selected patients with group 1 disease. A recent European Society of Cardiology and European Respiratory Society Consensus has classified oral anticoagulants as class IIb-C drugs in patients with PAH (idiopathic), heritable or due to anorexigens [17].

With regard to specific target therapy, a number of drugs have been used over the last two decades, particularly in group 1 PH. Despite different mechanisms of action, all of them eventually lead to pulmonary vasodilation, as shown in Fig. 1. A description of these drugs follows:

Calcium Channel Blockers CCB is represented mostly by nifedipine, amlodipine, and diltiazem; this class of drugs only works in half of those 10% of PH patients who have a positive vasodilatory response on RHC [12, 17]. The other 90% who are non-responders should not be considered for this therapy. Their low cost and widespread availability are attractive, and the reasons they are considered initial agents. Because they are not selective pulmonary vasodilators, systemic side effects often occur. High-risk patients (WHO class III/IV) are not candidates for this therapy, requiring more potent and selective drugs.

Prostaglandin Analogs These analogs produce vasodilation through second messengers, leading to increased cAMP levels. Prostacyclin is the most studied. Because of its very short half-life, it has to be infused continuously through a central line. It has been shown to reduce PVR and improve 6MWD and survival [18]. However, the demanding delivery method, high cost (30 to 200,000 dollars annually per patient), and significant side effects (nausea, headaches, pain on injection, catheter-related infection, flushing, jaw pain, and systemic hypotension) preclude its widespread use. Inhaled prostacyclin (iloprost) has been successfully used, particularly in the perioperative setting [19]. However, despite the improvement in the route of administration, side effects (cough) and cost remain high. Also, its long-term benefits are less clear and titration is difficult to accomplish. Oral formulation such as treprostinil has shown some promising results, but it has so far been approved only for monotherapy in treatment-naïve patients [20].

More recently, the non-prostacyclin selective IP receptor agonist selexipag has been developed. It is given orally as a pro-drug. It has been tested with favorable results, reducing composite end-points in the large GRIPHON phase III trial

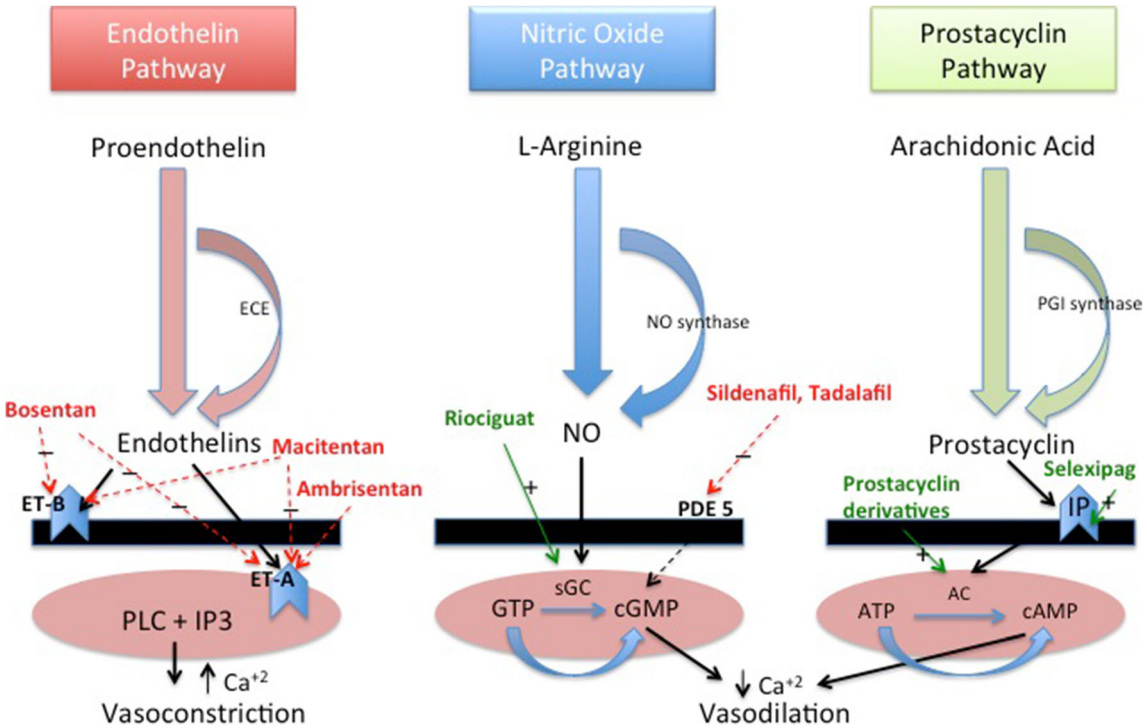

Fig. 1 Target therapies for pulmonary hypertension. All classes of drugs belong to one of the pathways described, and the end result is decreased pulmonary vascular resistance. Antagonists are highlighted in red while agonists are in green. ECE, endothelin converting enzyme; ET-A, endothelin receptor A; ET-B, endothelin receptor B; PLC, phospholipase C; IP3, inositol triphosphate; NO, nitric oxide; PDE 5, phosphodiesterase 5; sGC, soluble guanylate cyclase; AC, adenylate cyclase

[21••]. In the USA, it has received FDA approval for the treatment of WHO group I patients, to halt disease progression. In Europe, it has been recommended for WHO groups II and III patients. Again, costs and side effects remain significant. In the future, nanotechnology may enhance these drugs by delivering them encapsulated directly to their final target in the pulmonary circulation [22].

Inhaled Nitric Oxide A selective pulmonary vasodilator with well-documented use in the perioperative setting and favorable results overall. Dose regimens vary widely among patients, ranging between 5 and 40 ppm, though higher doses may be required [23]. A dedicated apparatus is needed to deliver iNO into the ventilator circuit, which is not readily available outside of specialized centers. Toxic metabolites may accumulate and continuous monitoring is mandatory. Also, it can cause rebound pulmonary hypertension after prolonged exposure [23]. Thus, slowly weaning iNO is strongly advised while the patient resumes oral medications.

Phosphodiesterase Inhibitors Sildenafil and tadalafil inhibit the phosphodiesterase (PDE)-5 enzyme. This causes cGMP levels to build up, ultimately leading to increased intracellular NO signaling and vasodilation. Currently, these drugs are most often used in combination with others to enhance their effects [24]. Their relatively low cost (when compared with other drugs used in PH) is advantageous, but tolerance may develop requiring frequent dose adjustments.

Guanylate Cyclase Stimulators Riociguat stimulates the soluble enzyme guanylate cyclase, which increases cGMP production inside the cell. Preliminary studies have been encouraging, including improved survival [25]. Riociguat has received FDA approval for use in inoperable patients with CPEPH [26]. It improves 6MWD test, functional class, hemodynamic parameters, and the B-type natriuretic peptide (BNP) preform, the N-terminal pro-BNP (NT-proBNP). Side effects include hypotension in 9% of patients.

Endothelin Receptor Antagonists Endothelin (ET) is a potent vasoconstrictor and plays a significant role in the pathophysiology of PH. It binds to specific A (vascular muscle cell) and B (endothelial) receptors, modulating vascular tone. Drugs that block these receptors have been developed and include bosentan, ambrisentan, and macitetan, all given orally. Improvements in hemodynamics and functional capacity have been shown with these drugs. Side effects include hepatotoxicity and thrombocytopenia. Up-front dual therapy with ambrisentan and tadalafil has shown promising results as reported in the AMBITION trial [27••].

Pre-operative Management PH patients have increased perioperative morbidity and mortality when compared with controls [28•]. This should be clearly discussed with patients and their relatives, particularly when elective surgery is planned. Overall, mortality rates range from 1 to 18%, while morbidity may reach 40% [28•]. Most causes of mortality are related to RV failure in the post-operative period. Respiratory failure and sepsis also contribute significantly.

In retrospective studies conducted more than 10 years ago, a 7% mortality rate was reported in PH patients undergoing non-cardiac surgery [29]. More recently, a case-control study reported a lower mortality rate of 1%, though morbidity was ten times higher than controls [30]. Memtsoudis et al. [31] reviewed a large national database of PH patients (n = 3302) undergoing total knee or hip arthroplasty. Mortality was 4–4.5 times greater when compared with matched controls, with the subgroup of PAH having the higher mortality rate. Data regarding anesthetic technique (regional vs. general) were not reported.

Differences between studies may be due to patient selection and pre-operative drug therapy regimen. In fact, the specific target drugs for PH were not clinically available in old studies. Furthermore, in some studies, many PH patients were in group 2, which may have a different outcome profile when compared with group 1 patients.

Most often the patient will present to surgery with appropriate follow-up by a referral center. Elective surgery should be postponed pending complete evaluation for patients with a new diagnosis of PH.

Successful perioperative management of these patients requires seven steps [32]: (1) recognizing the disease; (2) determining the etiology; (3) assessing severity; (4) balancing the risks and benefits of anesthesia and the surgical procedure; (5) developing an anesthetic plan; (6) managing the anticipated complications of systemic hypotension and right heart failure; and (7) arranging appropriate and specialized care for the post-operative period. A multidisciplinary approach is highly encouraged. Risk assessment is focused on the type of surgery (minor, intermediate, or high-risk), the severity of PH and degree of right ventricle (RV) impairment and functional capacity of the patient, as measured by WHO classification and the 6MWD. BNP and NT-proBNP values are biochemical markers that usually follow hemodynamic and functional responses to PH therapies [33]. They have been well documented as prognostic markers for perioperative morbidity and mortality in heart failure patients [34], though data specifically on PH are still lacking.

Physical examination, electrocardiography (ECG) and chest radiography may indicate RV overload. Lung ventilation/perfusion (V/Q) scans are useful for diagnosis of group 4 PH (CTEPH). Some patients use anticoagulants to prevent pulmonary embolism, and these need to be managed in advance of surgery. Usually, a bridge to heparin is not necessary, unless for patients who are on secondary prophylaxis (previous documented deep venous or pulmonary

embolism or group 4 disease). Thromboembolism prophylaxis is indicated post-operatively as recommended per institutional protocols. All other drugs used to treat PH should be continued throughout the perioperative period.

A careful review of a recent TTE is mandatory, as it objectively evaluates RV function, which is of paramount importance to stratify perioperative risk. As mentioned above, the PASP can be estimated by measuring the regurgitant tricuspid jet flow velocity. In addition, the RV fractional area change (RVFAC: normal > 40%); RV myocardial performance index (RVMPI) or RV *Tei* index (normal < 0.55); and tricuspid annular plane systolic excursion (TAPSE; normal > 18 mm) are typically measured. RVMPI > 0.83 is associated with poor outcomes [35] and TAPSE < 18 mm is a predictor of mortality in patients with PH [36]. Pericardial effusion is associated with poor prognosis as well. The presence of RV hypertrophy is significant, as these patients tolerate systemic hypotension very poorly, carrying a high risk or RV ischemia and failure [37•].

While most WHO FC 1 and 2 patients will tolerate minor and intermediate-risk procedures relatively well, WHO classes 3 and 4 patients should have elective surgery with extreme caution, because perioperative mortality is as high as 40% [38]. Predictors of 30-day mortality and morbidity include [38, 39]:

- NYHA FC > 2;
- History of pulmonary embolism or sleep apnea;
- Right axis deviation on ECG;
- RV hypertrophy;
- Emergency or high-risk surgery (particularly thoracic and major orthopedic procedures);
- Intraoperative use of epinephrine or dopamine;
- Anesthesia lasting > 3 h.

It is strongly recommended that surgery be done only in specialized centers with specialists and anesthesiologists familiar with PH. Also, these patients should be prepared in advance regarding the anesthetic plan and whether invasive monitoring will be used or not. An arterial line is useful before induction of general anesthesia, since systemic hypotension requires be aggressive treatment. Norepinephrine and vasopressin are the first-line agents, with a better profile than phenylephrine in terms of RV hemodynamics [40].

Perioperative hemodynamic goals are highlighted in Table 2. Despite its long controversy, the pulmonary artery catheter (PAC) is frequently used to follow closely the PAP, PVR, and CO during surgery. Transesophageal echocardiography (TEE) is useful to monitor RV function and may be used with a PAC. Importantly, TEE and PAC are not mutually exclusive but rather complementary monitors, as they yield integrated data that are useful to track changes in RV function. If advanced monitoring is not used, central venous pressure (CVP) trends can be followed as a surrogate for RV performance.

Table 2 Perioperative hemodynamic goals in PH patients

mPAP	Within 15% of baseline
PASP	Less than 40 mmHg of SAP
PVR	Less than ½ of SVR or close to baseline
CI	> 2.2 l min^{-1} m^2
MAP	≥ 65 or 20 mmHg above mPAP
RAP	The lowest value possible to allow systemic perfusion

mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; SAP, systolic arterial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; CI, cardiac index; MAP, mean arterial pressure; RAP, right atrial pressure

Sevoflurane seems to provide better RV hemodynamics when compared with isoflurane and desflurane [41]. In patients under one lung ventilation, propofol infusion was associated with a lower RV ejection fraction (RVEF) when compared with isoflurane [42]. However, in the setting of liver transplantation, RVEF was similar between propofol and isoflurane groups [43]. If used, propofol should be carefully titrated to avoid hypotension. Etomidate is an attractive choice particularly when RV function is compromised. Ketamine and nitrous oxide (NO_2) should be avoided since they might increase PVR. Opioids have minimal consequences on RV and pulmonary hemodynamics. In animal models, remifentanil has mild pulmonary vasodilating properties likely mediated by histamine release, but its clinical significance is unclear [44]. On the other hand, opioids may induce respiratory depression potentially leading to hypercarbia and elevated PVR, particularly in the post-operative period. As a result, post-operative pain management with opioid sparing techniques such as regional blocks is desirable.

Central neuroaxial anesthesia is highly controversial. Although it has been used successfully in selected patients, RV homeometric regulation is likely to be impaired after sympathetic blockade [45]. This regulation is responsible for coupling RV performance with acute increases in afterload. If this coupling is not successful, afterload mismatch occurs and RV dysfunction follows. Thus, if neuroaxial anesthesia is to be considered, it should be used with extreme caution in these patients.

Conclusions

PH is a rare disease with a complex pathophysiological mechanism and broad clinical spectrum. It is likely that in the near future, improvements in drug therapy will lead to increased survival in these patients, who may eventually undergo surgical procedures. As a result, anesthesiologists will need to evaluate these patients more often, which can be challenging. Clinical knowledge about PH is crucial in order to

perform an oriented and evidence-based pre-operative evaluation, with the ultimate goal of improving outcomes after surgery. A multidisciplinary approach in a tertiary center is strongly encouraged and the role of anesthesiologists in this context is essential.

Compliance with Ethical Standards

Conflict of Interest Glauber Gouvêa, Camila Santos Spiller, Rodrigo Diaz, Daniel Waetge, and Fabiano Gouvêa declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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