

# Perioperative Management of Pulmonary Hypertension. A Review

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## ABSTRACT

Pulmonary hypertension is a rare and progressive pathology defined by abnormally high pulmonary artery pressure mediated by a diverse range of aetiologies. It affects up to twenty-six individuals per one million patients currently living in the United Kingdom (UK), with a median life expectancy of 2.8 years in idiopathic pulmonary hypertension. The diagnosis of pulmonary hypertension is often delayed due to the presentation of non-specific symptoms, leading to a delay in referral to specialists services. The complexity of treatment necessitates a multidisciplinary approach, underpinned by a diverse disease aetiology from managing the underlying disease process to novel specialist treatments. This has led to the formation of dedicated specialist treatment centres within centralised UK cities. The article aimed to provide a concise overview of pulmonary hypertension's clinical perioperative management, including key definitions, epidemiology, pathophysiology, and risk stratification.

**Keywords:** pulmonary hypertension, anaesthesia, pathophysiology, perioperative care

Received: 16 August 2020 / Accepted: 31 January 2021

## INTRODUCTION

Pulmonary hypertension (PH) remains a common comorbid condition in patients presenting for surgery [1]. PH is a chronic progressive disease characterised by an abnormal elevation in pulmonary arterial pressure. This article aims to provide general anaesthetists with an update of the perioperative management for PH for non-cardiac surgery.

### Definitions

The New World Symposium definition of PH is defined following cardiac catheterisation of the right heart as a mean pulmonary arterial pulmonary pressure  $\geq 20$  mmHg at rest and pulmonary vascular resistance  $\geq 3$  Wood Units (WU) [2]. Current treatments are approved for patients with mean PAP  $\geq 25$  mmHg. The severity of PH is classically characterised by pulmonary artery pressure from mild (20-40mmHg) to severe ( $>55$ mmHg) (Table 1).

### Epidemiology

PH is an increasing yet poorly diagnosed disease affecting up to fifty million people worldwide. Idiopathic PH remains the most common aetiology classically affect-

**Table 1. Severity criteria for PH also includes Cardiac Index (severe  $< 2$ ), mean RAP ( $>15$ ), and low mixed venous O<sub>2</sub> saturation and the presence of pericardial effusion. Mean Pulmonary Artery Pressure (mPAP).**

Severity	Mean mPAP (mmHg)
Mild	20-40
Moderate	41-55
Severe	$>55$

ing middle-aged females. The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management reported a higher prevalence in black females than the white female population (5:1 vs 3:1 female to male ratio, respectively) [3]. The UK and Ireland National PH registry also highlighted the higher risk of idiopathic PH in the female population at 45-52 years [4].

PH is a progressive disease leading to premature death. Improved outcomes have been reported over the last 20 years due to improved diagnostics and access to the treatment. Survival varies depending on disease aetiology and progression. The UK PH registry reports a survival rate of 93%, 73%, and 61% at 1, 3 and 5 years following the diagnosis, respectively [4]. A review by Lau et al. [5] reported several independent risk factors

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associated with poor outcome. These were categorised into non-modifiable and modifiable PH aetiology, male gender, age >50, genetic factors (Alterations in Ring Finger Protein (RNF213), mutations in bone morphogenetic protein receptor type 2 (BMP2)) and associated diagnosis (systemic sclerosis, Human Immunodeficiency Virus, Chronic Obstructive Pulmonary Disease, congenital heart disease, pulmonary veno-occlusive disease and porto-pulmonary hypertension) are classified as non-modifiable. While declining lung function, elevated right atrial pressures, and functional status are assigned to modifiable [5,6]. Right ventricle decompensation and arrhythmias due to the progression of PH or an acute rise in pulmonary artery pressures leads to circulatory collapse. Resuscitation events are often unsuccessful due to the irreversibility of the underlying pathology [7].

### Classification

In 2015 the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) updated their guidelines regarding the classification of PH [8]. Five diagnostic groups have been formulated with clear subgroups, aiding clinicians with diagnosis and management (Figure 1). Broadly they are classified into a disease of the [1] pulmonary artery vasculature; [2] respiratory system; [3] left ventricle; [4] those which predispose to pulmonary artery thrombosis; and fi-

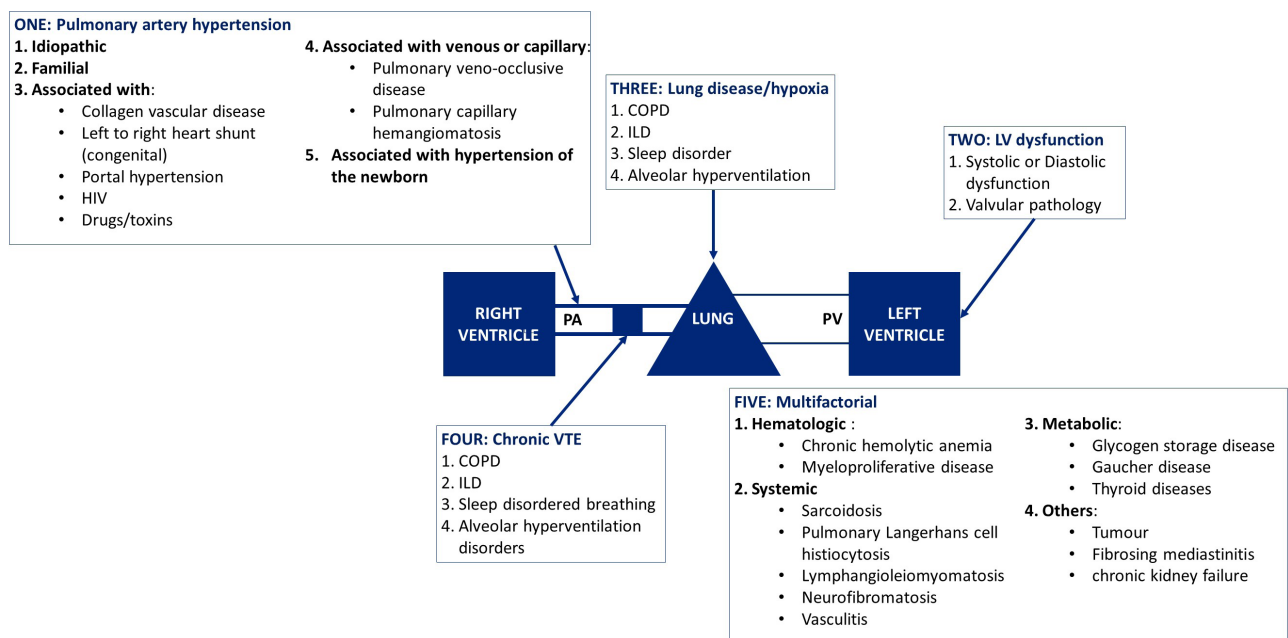
nally [5] multifactorial disease aetiology. Patients in group one are considered to have pulmonary arterial hypertension (PAH), while those in groups two to five are considered to have PH. Haemodynamic characteristics of PH can be defined into pre-capillary PH that includes clinical groups 1, 3, 4 and 5; isolated post-capillary PH – groups 2 and 5; and combined pre and post-capillary PH - groups 2 and 5 [9]. Depending on the “localisation” of PH (pre-, post-capillary or combined), different definitions of PH are available (Table 2).

### Pathophysiology

Ohm's Law can be used to explain the relationship between pressure difference ( $\Delta P$ ), flow (Q) and resistance

**Table 2. Haemodynamic characteristics of pulmonary hypertension. Mean Pulmonary Arterial Pressure (mPAP), Pulmonary Artery Wedge Pressure (PAWP) and Pulmonary Vascular Resistance.**

Classification	Parameter	Value
<b>Pre-capillary</b>	mPAP	> 20mmHg
	PAWP	≤ 15mmHg
	PVR	≥3 WU
<b>Isolated Post capillary</b>	mPAP	>20mmHg
	PAWP	>15mmHg
	PVR	<3 WU
<b>Combined pre- and post-capillary</b>	mPAP	>20mmHg
	PAWP	>15mmHg
	PVR	≥3 WU



**Fig. 1. Aetiology of pre- and post-capillary PH (PA: Pulmonary artery, PV: Pulmonary vein, COPD: Chronic Obstructive Pulmonary Disease, ILD: interstitial lung disease, HIV: Human immunodeficiency virus)**

(R) (i.e.  $(\Delta P = Q \times R)$ ), which enables the calculation of Mean Pulmonary Artery Pressure (mPAP = (right ventricle cardiac output  $\times$  pulmonary vascular resistance) + pulmonary alveolar occlusion pressure) [10]. The main determinant of PH is always elevated pulmonary vascular resistance. Additional factors, such as high flow states and increased pulmonary venous pressure, usually play a minor role.

The aetiology of pre-capillary PH disease is often multifactorial involving endothelial, inflammatory and genetic factors [9]. Clinical group 1 is characterised as a proliferative vasculopathy of the small pulmonary arterioles. Resulting in profound vasoconstriction, hyperplasia and hypertrophy of the vasculature tissue, which progresses to full-thickness vascular fibrosis, and thrombosis [11]. Clinical group 2 disease is secondary to left ventricular (LV) dysfunction results in a persistent elevation in left atrial pressure with associated vasoconstriction, pulmonary vascular remodelling, and persistent elevations in pulmonary vascular resistance [12]. Clinical group 3 involves obstructive/restrictive lung disease and hypoxia. The pathophysiology involves a combination of generalised alveolar hypoxia leading to an upregulation of pulmonary vasomotor tone and increased pulmonary vascular resistance (PVR) [13]. Infiltration of inflammatory cells into the intima leads to remodelling and thickening of the pulmonary vasculature and loss of pulmonary tissue [14]. Finally, clinical group 4 disease describes PH due to pulmonary artery obstruction (i.e. chronic thromboembolic PH). It is based on a two-stage process; firstly, acute obstruction of the pulmonary artery resulting in a rapid elevation in Pulmonary Artery (PA) pressure followed by widespread distal vessel remodelling [15].

### Physiology of right ventricular myocardial perfusion, ischaemia and failure

Right ventricle physiology remains distinct from the LV, a recent review by Crystal et al. highlights these differences [16]. Specialised features of the right ventricle (RV) include; one, Coronary perfusion is directly related to perfusion and occurs throughout the cardiac cycle mediated by nitric oxide [17]. Two, Lower RV oxygen extraction, oxygen consumption and greater total capillary density enables the RV to meet metabolic demands [18]. Three, collateral supply from the left coronary artery (LCA) and Thebesian veins [19]. Finally, uniformly transmural RV blood flow. In contrast to the LV, RV lacks effective pressure-flow autoregulation and

has a reduced RV wall density enabling reduced oxygen demand and utilisation [20].

The thin-walled RV poorly responds to increases in afterload. Acute increases in PA pressure can lead to rapid elevations in systolic and end-diastolic RV pressure, leading to increased myocardial oxygen uptake, ventricular septal displacement, reduced stroke volume, and flow to the left side. This leads to impaired cardiac output, aortic root pressure, and coronary perfusion pressure, thus provoking myocardial ischaemia and cardiovascular collapse. Consequently, emphasis should be placed on optimising RV (preload and contractility), maintaining normocardia, preventing elevations in PAP and maintaining PVR [21,22].

Neural regulation of the coronary circulation encompassing both cholinergic and adrenergic receptor (Alpha ( $\alpha$ ) and Beta ( $\beta$ )) expression.  $\alpha$ 2-adrenergic receptor expression within coronary arterioles mediates dose-dependent vasoconstriction [23].  $\beta$ 2-adrenergic receptor expression within small arterioles mediates vasodilation [24]. Cholinergic stimulation via endogenous acetylcholine, specifically Muscarinic (M) three receptors activation mediates vasodilation [25].

## ■ PREOPERATIVE CARE

### History

Symptoms of early disease are often non-specific and lead to delay in presentation and diagnosis. That is why the first hospital admission relating to PH may present with symptoms of acute heart failure. Initially, patients report dyspnoea, palpitations, and lethargy due to an imbalance between oxygen delivery and demand during physical exertion [26]. As the disease progresses, exertional chest pain (due to subendocardial hypoperfusion from elevated intra-cardiac pressures) and weight gain from water retention in lower limbs and abdomen occurs. Finally, patients develop exertional syncope due to an inability to maintain cardiac output at a time of high demand [27].

### Examination

Initial examination findings are subtle; an increase in the intensity of the second heart sound's pulmonary component may be the only sign. As right ventricle (RV) failure progresses, it leads to an increased preload and an elevation in jugular venous pressure (JVP), with evidence of prominent a and v waves suggestive of el-

evated right atrial pressure and tricuspid regurgitation, respectively. Precordial findings include: left parasternal heave suggestive of right ventricular hypertrophy, a gallop rhythm indicative of fluid overload, wide splitting of the second heart sound and finally a holosystolic murmur of tricuspid regurgitation. Tender hepatomegaly, pleural effusion, ascites, and lower limb oedema is evidence of fluid accumulation and elevated right heart pressures [28].

### Investigations

The ESC guidelines define a diagnostic algorithm for PH [29]. Basic investigations include an electrocardiogram, arterial blood gas and a biochemistry panel to screen patients for evidence of right ventricular strain, type 1 respiratory failure and myocardial dysfunction. Imaging (Chest x-ray, High-resolution computed tomography (HRCT) and echocardiography) and Pulmonary Functional Tests (PFTs) identify patients with severe disease. All patients with evidence of severe PH should be referred to a PH specialist centre who can perform additional investigations which include; Pulmonary Artery Catheterisation (PAC) and additional haematological investigations (i.e. Human immunodeficiency virus (HIV), Toxins, Connective Tissue Diseases (CTDs) and Schistosomiasis) to aid diagnosis of the underlying pathology. Finally, cardio-respiratory function should be assessed by Cardiopulmonary Exercise Testing (CPET) in all patients with moderate to severe disease. Necessary investigations are described below.

A chest x-ray can be used to assess for signs of right ventricular or central pulmonary artery enlargement, pleural effusions or pericardial effusion (Table 3) [30].

Echocardiography is an important screening tool and should be performed by a specialist technician. The British Society of Echocardiography defines criteria to aid the diagnosis of pulmonary hypertension, a full explanation of echocardiographic diagnosis is out of the scope for this article [31]. Diagnosis is confirmed with surrogate pulmonary pressure markers that include at least two positive parameters (right atrium size and inferior vena cava diameter, pulmonary artery diameter and right ventricle size and function in conjugation with tricuspid regurgitation (TR) velocity). The pulmonary artery assessment includes: Firstly, pulmonary artery diameter increases in response to pressure and volume overload with a diameter >25mm being abnormal. Secondly, right ventricle outflow doppler acceleration time of <105ms as PAP increases the ejection time from the RV is reduced. Finally, early diastolic pulmonary regurgitation (PR) velocity >2.2 m/s is a marker of pulmonary artery diastolic pressures [32]. Peak TR velocity correlates with PA pressure at rest, and during exercise, it is measured via a doppler across the tricuspid valve, >2.8 m/s is considered abnormal [32,33].

PFTs assess lung mechanical and gas exchange function. The majority of Group 1 patients exhibit restrictive lung disease [34]. The remainder have a normal total lung capacity with an increased residual volume (RV) to compensate for a reduced vital capacity (VC) [35]. Spirometry results are mixed, but the majority

**Table 3. Perioperative investigations**

	Investigation	Comments
<b>Bedside</b>	ECG	RVH -RBBB, RAD, rSR' complex in V1 RV enlargement - P pulmonale
	ABG	Type one respiratory failure
<b>Bloods*</b>	BNP	RV failure
<b>Imaging</b>	CXR	Dilated pulmonary arteries Right ventricular enlargement
	Echocardiography	PA diameter, >25mm Right ventricle outflow doppler acceleration time, <105ms Early diastolic pulmonary regurgitation (PR) velocity. >2.2 m/s Peak TR velocity, >2.8 m/s
		Cardiac MRI imaging
<b>Additional</b>	Lung function test	Obstructive or restrictive defect Low TLCO a marker of disease severity
	CPET	
	Pulmonary artery catheter	

RV: Right ventricle; RBBB: Right bundle branch block; RAD: Right axis deviation

\*Blood test do not aid diagnosis but identify aetiology of PH and degree of end-organ damage

report normal Forced Expiratory Volume in the first second (FEV1)/Forced Vital Capacity (FVC) ratios [36]. Patients in the second clinical group have low total lung capacity (TLC) and FVC due to increased extravascular lung water and pleural effusion due to left heart failure [37]. The severity of lung disease in clinical group 3 patients does not correlate with the degree of PH. Lung volumes classically vary depending on the obstructive or restrictive lung disease pattern with most cases reporting impaired DLCO. Finally, in group 4 disease, chronic pulmonary emboli lead to localised scarring and thus restrictive lung volume with impaired DLCO from fibrosis and reduced regional blood flow [38].

CPET provides a combined assessment of cardiovascular, respiratory and metabolic physiology for a defined level of work. Key outcomes are subclassified into exercise (Anaerobic threshold, Peak O<sub>2</sub> uptake, peak work rate), cardio-respiratory (VO<sub>2</sub> - work rate slope, Ventilation (VE) and Ventilatory equivalent for O<sub>2</sub>) and resting spirometry variables (FEV1, VC, MV) [39]. Abnormal CPET assessment trends are observed in patients with PH due to a combination of factors [40]. One, lateral displacement of the interventricular septum into the left ventricle due to ventricular interdependence reduces stroke volume and cardiac output. Two, reduced oxyhaemoglobin saturation occurs due to abnormal respiratory capillary transfer. Finally, a right-to-left shunt may occur via an intrapulmonary shunt or patent foramen ovale. These physiological changes result in depressed peak oxygen consumption (VO<sub>2</sub> max, ml/kg/min), causing an imbalance of oxygen supply to skeletal muscle demand. Furthermore, reduced ventilation capacity and increased respiratory dead space lead to an increased output gradient for the CPET curve volume of exhaled carbon dioxide (VCO<sub>2</sub>) (L/min) vs ventilation (VE) (L/min) [41].

PAC is the gold standard technique for measurement of PA pressure [42]. Pre- and post-capillary PH is defined by mean pulmonary arterial pressure (PAPm)  $\geq$  25mmHg at rest. The pre-capillary disease has a PCWP / LVEDP of  $\leq$  15mmHg whilst post-capillary disease is associated with an increase in PCWP / LVEDP of  $>$ 15mmHg [43].

### Differential diagnosis

The differential diagnosis for PH is broad; it can be based on symptoms and indirect markers of elevated pulmonary artery pressure. Firstly, differential diag-

nosis based on symptomatology includes chronic obstructive pulmonary disease, pulmonary embolism, biventricular heart failure and coronary artery disease. Secondly, causes of an elevated pulmonary artery pressure include volume overload states (i.e. heart failure, chronic kidney and liver disease), lung disease (i.e. acute and chronic), sleep disorders (i.e. obstructive sleep apnoea), left-sided heart disease, high cardiac output states (i.e. hyperthyroidism), hypertension and obesity.

### Outpatient management

All chronic pulmonary vasodilator medications should be continued throughout the perioperative period, with the conversion of oral to inhaled or intravenous based preparation where the enteral route is inappropriate. Treatment options vary due to a lack of large scale randomised controlled trials. Treatment strategies for PAH have evolved with the increasing use of upfront combination pulmonary vasodilator therapy to optimise clinical outcomes, guided by clinical risk assessment tools.

Group 1 PAH, vasoreactivity testing can be performed by right heart catheterisation to determine if the patient responds to calcium channel blockers. Non-responders are classed as 'Non-vasoactive' [8]. Such patients can undergo treatment with a phosphodiesterase-5 inhibitor (PDE-5i) (tadalafil or sildenafil), endothelin receptor antagonist (ERA) (ambrisentan, bosentan or macitentan), prostacyclin receptor agonist (selexipag) or a guanylate cyclase inhibitor (e.g. riociguat) [44]. Riociguat should not be prescribed in combination with a PDE-5 inhibitor.

Group 2 disease - secondary to left heart failure - treatment is based on ongoing cardiac management, including diuretics, with little evidence to support PH specific therapies [45].

Group 3 PH - arising from lung disease - intensive treatment of the underlying lung disease is essential [8]. This may include supportive measures: stopping smoking, inhaled treatment for airways disease, anti-fibrotic or anti-inflammatory treatment as appropriate for interstitial lung disease, diuretics, oxygen therapy and vaccination. Selective referral for lung transplantation can be considered for severe disease. Selected Group 3 patients with a pulmonary vascular phenotype can be referred to a PH unit to consider targeted PH therapy, particularly if severe PH identified, out of proportion to the extent of underlying parenchymal lung disease.

Group 4 disease includes patients with chronic thromboembolic disease (CTED) or chronic thromboembolic pulmonary hypertension (CTEPH), require ongoing management with anticoagulation [46]. Careful imaging and multidisciplinary pulmonary vascular assessment of anatomical distribution are required, as surgical treatment with pulmonary thromboendarterectomy (PTE) can be curative. Increasingly, evolving treatment options include PTE, catheter-based balloon pulmonary angioplasty, or medical treatment with Riociguat is improving the outcomes of patients with CTEPH or indeed CTED, lacking PH [47,48]. Finally, both Bosentan and Macitentan have shown improved haemodynamic parameters in inoperable chronic thromboembolic disease [49,50].

PDE-5i such as sildenafil inhibit the breakdown of cyclic guanosine monophosphate (cGMP) by cGMP-specific phosphodiesterase type 5 in vascular smooth muscle. Elevated concentrations of cGMP inhibit calcium entry, mediating smooth muscle relaxation [51]. Effects are widespread and not localised to the pulmonary vasculature, which may lead to peripheral hypotension. Pre-treatment baseline blood pressure observation is essential. Conversely, Riociguat is a novel stimulators of soluble guanylate cyclase (sGC), which improves exercise tolerance and is well tolerated concerning side effects and drug interaction profile [52].

Endothelium receptor antagonists (ERA), such as bosentan and ambrisentan, competitively antagonise endothelium receptors ( $ET_A$ ,  $ET_B$ ) with varying selectivity in a diverse range of tissues. A multicentre placebo-controlled clinical trial of ambrisentan, an oral selective endothelin-A receptor antagonist, reported improved exercise capacity in patients with idiopathic PH [53]. Endothelium release on local smooth muscle is attenuated; these include; vasocontraction and local cell proliferation [54]. ERAs are highly hepatotoxic and teratogenic, and thus monthly liver function monitoring and pregnancy testing are essential [55].

Prostacyclin is naturally occurring prostaglandin with a short half-life and potent vasodilator features [56]. Examples include epoprostenol, iloprost and treprostinil which can be delivered via nebuliser, intravenous and subcutaneous routes. Neurohumoral activation leads to an upregulation of the sympathetic nervous system to enhance pulmonary perfusion. Consequently, beta-blockers should be used with caution due to a reliance on heart rate to maintain cardiac output.

Pulmonary vasodilator therapy (PDE-5i, ERA and prostacyclin) should be continued throughout the perioperative period if required prostacyclin can be converted to intravenous preparations. Drugs interactions between anaesthetic agents and the three major classes of PH medication are negligible. Endothelin receptor antagonists are associated with hepatic enzyme induction, and the prostacyclin-analog iloprost, may precipitate systemic hypotension which can be exacerbated by both volatile and intravenous induction agents.

### Risk stratification

A comprehensive assessment should be performed before the perioperative intervention; no single test provides clear prognostic certainty. A multidimensional structure will enable a holistic assessment.

Risk score stratification tools highlight the disease trajectory from registry outcomes, which includes both European and United States registry data (United Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)) [57,58]. The joint European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of PH developed algorithms to strategies one-year mortality based on three subgroups; low (<5%), medium (5-10%) and high risk (>10%) [29]. The criteria determining risk are based on symptoms and signs of PAH and investigative methods which include; 6-minute walk test or cardiopulmonary exercise testing, biomarkers including NTpro-BNP or BNP, imaging, including echo or cardiac MRI, and finally haemodynamic studies. No current risk assessment tools are devised to assess morbidity and mortality risk following general anaesthesia dedicated to PH patients.

Risk factors associated with a poor outcome are categorised into patient factors, including a history of pulmonary embolism, chronic renal disease, ischaemic heart disease, RV dysfunction and World Health Organisation functional status  $\geq 2$ . Anaesthetic factors including a mean pulmonary pressure <4 after induction and mPAP >50 mm Hg and PVR 58.6 [59,60]. Surgical factors include emergency procedures and prolonged duration of surgery [61,62]. A range of studies in non-cardiac surgery has reported patient morbidity to be between 14% to 42%, with mortality rates up to 18% of patients with mild to severe disease [63,64].

A significant proportion of patients with PH are prothrombotic, abnormalities in coagulation and vascular

thrombosis at post mortem along with standard risks associated with surgery (immobility) have provided the rationale for anticoagulation [65,66]. Studies have reported positive outcomes following anticoagulation in patients with idiopathic PH, heritable PH and pulmonary artery hypertension [65,67]. Anaesthesia associated with neuro-axial blockade of peripheral nerve risk vasculature puncture. Risk assessments must be performed in relation to the surgical intervention, the technique involved, and the procedure's length. There is no definitive guidance concerning long term anticoagulation management. However, high-risk patients with regard to the diagnosis of PH hypertension and surgery implicated should undergo heparin bridging with intravenous or low molecular weight heparin [68,69]. We recommend intravenous heparin when therapeutic bridging is recommended from four to five hours before the procedure. Resuming treatment is based on the risk of post-operative haemostasis and typically occurs from six hours, however individual patient assessment should be performed based on prothrombotic risk, patient factors and anaesthetic technique. Recommencement of normal anticoagulation will occur within twelve to twenty-four hours.

## ■ PERIOPERATIVE OPTIMISATION

### Volume status

Aim for a euvolemic fluid state. Acute RV failure can be participated by cardiovascular effects including sodium/water status, anaemia and arrhythmias. Elevated PA pressure may lead to renal congestion and both deteriorating renal function and diuretic resistance. An elevated hyperdynamic circulation volume will subsequently negatively impact cardio-respiratory function by elevating mean atrial pressure and pulmonary artery pressure and flow through the pulmonary vasculature [70].

Optimisation of volume status can be achieved by a stepwise approach using pharmacological and non-pharmacological methods, including fluid restriction [71]. Pharmacological methods include; Firstly, continue regular diuretics with intermittent loop diuretic doses or infusion. Secondly, improvement of cardiac function by  $\beta_2$  agonists, including dobutamine. Thirdly, the addition of thiazide diuretics, and aldosterone antagonists. Finally, fluid removal by haemodialysis or ultrafiltration.

## PA pressure and cardiovascular support

Perioperative risk factors associated with elevated pulmonary pressure include; increased sympathetic tone, hypoxic, fluid overload, acidosis, lung injury, embolisation (air, fat or haemostatic clot) and finally, LV systolic and diastolic dysfunction. Achieved by medical and non-medical management. A combination of inotropic and vasopressor support may be required to maintain optimal RV function and cardiac output (mPAP <35mmHg, PVR/systemic vascular resistance ratio <0.5) whilst maintaining cardiac output (cardiac index >2.2 l/min/m<sup>2</sup>)[72].

## ■ INTRAOPERATIVE CARE

Intraoperative management of PH is aimed at preventing significant increases in PVR and afterload, resulting in compensatory elevations in RV pressure [73]. Optimisation to reduced PVR can be based on patient factors preventing hypoxia, hypercarbia, acidaemia and hypothermia and anaesthetic technique (regional, central neuro-axial and general anaesthetic) (Table 4).

### Regional techniques vs general anaesthesia

Regional anaesthesia is one of the safest options, both intra- and post-operatively, due to a lack of central cardiovascular and respiratory dysregulation. Common indications include peripheral nerve blockade for limb surgery. Advantages of such techniques include preventing the need for intermittent positive pressure ventilation which result in higher PAP [74]. However, caution should be applied to patients with severe PH who cannot lie supine for long periods and anticoagulation status. The consensus for regional techniques outweighs general anaesthesia, however identifying clear statistically significant outcomes has been challenging, both in obstetric and non-obstetric patient groups [75,76]. Martin et al. (2002) reviewed fifty-seven articles assessing the safety of regional anaesthesia in Eisenmenger's Syndrome, reporting a 13% reduction in mortality compared to general anaesthesia; however, this was not statistically significant [77].

Graded central neuro-axial blockade, including spinal and epidural anaesthesia, is effective and safe with a degree of caution. Sympathetic nerves from the lumbar sympathetic ganglion follow peripheral nerves to the lower limbs. The blockade of such ganglia leads to vascular dilatation, reducing peripheral PVR leading to systemic hypotension, impaired venous return, cardiac

**Table 4. General anaesthetic management principles**

Perioperative management techniques and goals				
<b>Preoperative</b>	Medication	Pulmonary vasodilator agents	Continue	
		Anticoagulation	Switch long term anticoagulation to IV heparin	
<b>Induction</b>	GA	Opioids	Widely used	
		Propofol/thiopentone	Widely used	
	LA	Regional	Widely used	
		Neuro-axial	Widely used	
<b>Intraoperative</b>	Agents	Volatile anaesthetics	Widely used	
		N2O	Avoid	↑PVR
		NMBD	Safe	
	Monitoring	BP/ECG/HR/SaO2/ETCO2	Essential	
		CVP/TTE/PCA Arterial line (+ABG)	Additional	
	Physiology	Respiratory	FIO2 > 0.6	O2 = Pulmonary VD / weak systemic VC
			Hyperventilation	Avoid V/Q mismatch and over-inflation
Recruitment manoeuvres				
Lung protective ventilation (T <sub>v</sub> 6-8ml/kg)				
	Cardiovascular	Preload- normovolemia		
		Heart		
		Rate – Low normal		
		Rhythm- SR		
		Contractility -preserve		
		Afterload – Avoid ↑PVR		
		Haematological	pH >7.35	
		Others	Normothermia	
<b>Post-operative</b>	Location	Level 2/3 care		

(T<sub>v</sub>: Tidal volume, SR: Sinus rhythm, SVR: Systemic vascular resistance, TTE: Transthoracic echo, PCA: Pulse contour analysis)

output, and coronary perfusion pressure. Activation of Bezold–Jarisch reflex following a reduction in venous return and ventricular stretch inhibits the vasomotor centre, blocking sympathetic activity leading to decreased PVR, bradycardia and hypotension [78]. Direct rapid injection into the intrathecal space should be avoided to support cardiovascular stability and reduce the risk of impaired coronary perfusion and acute right ventricular failure. Similarly, epidural anaesthesia should be approached with the same principles: higher thoracic epidurals risk T2–4 nerve blockade and profound bradycardia leading to cardiovascular collapse [79].

General anaesthesia, airway management can be delivered via a supraglottic airway device, enabling spontaneous respiration and thus maintaining a negative pleural pressure allowing distention of the pulmonary vasculature, lower pulmonary artery and pulmonary capillary wedge pressures [80,81]. Conversely, endotracheal intubation provides a secure airway to prevent aspiration and carefully control expired gases, at the disadvantage of higher PAP<sub>m</sub>. It is fundamental to provide a smooth anaesthetic from induction to recovery. The

use of both volatile anaesthetic agents and total Intravenous anaesthesia (TIVA) remain safe. Volatile anaesthetics attenuate hypoxic pulmonary vasoconstriction response, suppress systemic vascular resistance (SVR), and increase end-tidal carbon dioxide concentrations. In addition to vasodilation of the systemic circulation which may lead to haemodynamic compromise following a reduction in coronary perfusion pressure to the right ventricle. Isoflurane and desflurane have dose-dependent reductions in RV contractility and marginally increase PVR, impairing RV afterload and thus RV pulmonary artery coupling [82].

Similarly, sevoflurane reduces RV contractility whilst having little influence on PVR [83]. However, nitrous oxide should be avoided as it increases PVR. Intravenous induction drugs, including opioids, can be safely employed in patients with PH. Propofol mediates a range of cardiovascular effects, including negative inotropy, chronotropy and reduced peripheral and pulmonary vascular resistance [84]. Muscle relaxants with high histamine release such as atracurium should be avoided [85].



## Monitoring

Monitoring and intraoperative care should follow the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidance for basic monitoring which includes; blood pressure, heart rate, respiratory rate, oxygen saturation and capnography [86]. Additional invasive monitoring options include invasive blood pressure assessment, pulmonary artery catheterisation and trans-oesophageal echocardiography. The goals of cardio-respiratory parameters are defined in table 5.

## Cardiovascular support

Intraoperative pharmacological therapy to control pulmonary pressure is essential [87]. Treatments are two-fold, to increase RV afterload and improve myocardial perfusion (Table 6). Treatments to maintain myocardial perfusion may require a combination of agents. Vasopressors which include vasopressin or low dose noradrenaline are first-line agents which enhance venous return and perfusion of the right ventricle, whilst increasing SVR, PVR, RV afterload and decreasing pulmonary vascular compliance. Inotropic agents are used to offset enhanced RV afterload by increasing RV contractility. Examples include levosimendan which sensitises myocardial troponin C to calcium during ventricular systole and milrinone, a phosphodiesterase

**Table 5. Goals for perioperative cardio-respiratory parameters**

Severity	Mean MAP (mmHg)	Units
SBP (or Above sPAP)	≥90 (40)	mmHg
MAP (or Above mPAP)	≥65 (20)	
mPAP (or lower than MAP)	<35 (25)	mmHg
PVR/SVR	<0.5	
Cardiac Index	>2.2	l/min/m <sup>2</sup>

SBP: Systolic Blood Pressure; sPAP: systolic Pulmonary Arterial Pressure; MAP: Mean Arterial Pressure; PVR: Pulmonary Vascular resistance; SVR: Systemic Vascular Resistance

**Table 6. Perioperative management of PH**

	Agent	Physiological response
↓ RV Afterload	<b>Inhalational</b>	
	Prostanoids	
	Nitric oxide	↓PVR/ SVR
↑ Myocardial perfusion	<b>Intravenous</b>	
	Prostanoids (epoprostenol, treprostinil)	
	<b>Inotropes</b>	
	Milrinone / levosimendan	Positive inotropic (<-> HR)
	Dobutamine / epinephrine	Positive inotropic (↑HR)
	<b>Vasopressors</b>	
	Norepinephrine / vasopressin / terlipressin	↑SVR/PVR/RV load

RV: Right ventricle, HR: Heart rate, SVR: Systemic vascular resistance, PVR: Pulmonary vascular resistance

III inhibitor, inhibiting cAMP breakdown and enhancing protein kinase A (PKA) activation mediating myocardial contraction and reducing both systemic and pulmonary vascular tone [88–90]. The use of dobutamine and adrenaline is limited by the  $\beta_2$  effects causing persistent tachycardia, which may, in turn, impair myocardial perfusion.

Treatments to reduce RV afterload in Group 1 disease include inhaled therapies (nitric oxide, prostaglandin I<sub>2</sub>) or continuous low dose intravenous infusions (prostaglandin I<sub>2</sub>). Caution should be applied, particularly with intravenous prostanoids, due to the risk of systemic hypotension and profound pulmonary vascular dilation, resulting in fulminant pulmonary oedema, secondary to downstream occlusion from left atrial hypertension, pulmonary vein stenosis or veno-occlusive disease. Acute RVF in group 2 patients, with left-sided heart disease, who risk developing pulmonary oedema from a non-compliant left atrium and ventricle, should undergo diuresis to reduce PCWP [88]. The role of nitric oxide is not clear; however, prostaglandins should be avoided.

## Pulmonary hypertensive crisis

Pulmonary hypertensive crisis (PH crisis) is characterised by an elevated mean arterial pulmonary pressure above mean systolic arterial pressure, mediated by abrupt elevations in PVR, leading to acute RV dysfunction and systemic hypotension [91,92]. Risk factors associated with the development of PH crisis are broad and account for over 40% of acute decompensations, some of which are associated with a poor prognosis [93]. Cardiovascular factors include developing supraventricular arrhythmias secondary to hypovolaemia or atrial dilation, which are classically managed by the adult life support (ALS) algorithm and are a poor prognostic sign. Moreover, negative inotropic agents,

including beta-blockers, should be avoided [94]. Respiratory factors include pre-existing or novel pulmonary venous embolism with poor anticoagulant compliance is associated with increasing poor outcomes [95]. Finally, infectious triggers include secondary central venous catheter insertion affecting right ventricular function and systemic inflammatory response syndromes (SIRS) mediating left ventricular dysfunction are associated with poor outcomes [88].

A lack of consensus guidelines underpinning management has caused significant challenge even within specialist centres [96]. Management has two aspects, improved oxygenation by attenuating hypoxic pulmonary vasoconstriction, thus normalisation of acid-base balance and reversal of RV dysfunction.

Acute management principles can be split into general measures and pharmacological therapies. General principles include identifying possible causes for acute deterioration and cardiovascular management, including fluid optimisation and measures to maintain sinus rhythm. Moreover, respiratory optimisation to reduce PVR includes, increasing the fraction of inspired oxygen, hyperventilation and muscle relaxation. Severe acidosis can be transiently improved by plasma alkalisation with bicarbonate infusion. Pharmacological interventions include, preferred first-line agents to increase systemic blood pressure above mean pulmonary pressure incorporate vasopressor (low dose noradrenaline, and vasopressin) and inotropic agents (dobutamine and milrinone). The use of vasopressin, which mediates systemic vasoconstriction and pulmonary vasodilatation following nitric oxide release is increasingly used [97]. In refractory disease despite optimal management, inappropriate candidates rescue therapies include urgent transplantation with supportive extracorporeal life support.

## ■ THORACIC SURGERY AND PH

PH is an important risk factor associated with significant morbidity and mortality in patients undergoing thoracic procedures [63,98]. Patients should undergo a full perioperative assessment with intraoperative planning before significant events, including one-lung ventilation (OLV) and pulmonary artery ligation. OLV can elevate carbon dioxide and PA pressures from high ventilatory pressures which may lead to acute RV failure. Transthoracic echocardiography and PAC are prerequisites to assess RV filling and ventricular function

[99]. A multidisciplinary approach which includes thoracic anaesthetist and PH specialist underpins successful management.

## ■ POST-OPERATIVE CARE

Patients with PH should have a robust multidisciplinary post-operative care plan provided in a level two or three care setting within a specialist centre. This must include a balanced analgesic approach, including regional anaesthesia to reduce opioid requirements.

Cardiovascular control; Firstly, sinus rhythm aiming for a SBP >90mmHg and MAP >65mmHg [72,100]. However, in specific patients with longstanding PH, perfusion can be maintained at a lower MAP. Atrial arrhythmias should be treated with amiodarone or flecainide [101]. Atrial rate control can be achieved with cardiac glycosides, including digoxin, whilst avoiding beta-blockade [102]. Secondly, fluid balance should be carefully optimised. Right ventricular preload is essential to maintain pulmonary perfusion and cardiac output. Reduced preload from hypovolaemia from sepsis, gastrointestinal losses or over diuresis can lead to a reduced right ventricular stroke volume, impaired pulmonary perfusion, impaired left ventricular stroke volume, and cardiac output.

Conversely, overhydration decreases right ventricular stroke volume leading to reduced ventricular contractility and intraventricular septum displacement, impairing cardiac output [103]. Reduced RV afterload can be achieved by a range of measures described in intraoperative management; however, there are ongoing risks of excessive hypotension, ventilation-perfusion mismatch and medication specific side effects. Thirdly, cardiac contractility and myocardial perfusion pressure are fundamental to maintain cardiac output whilst preventing myocardial ischaemia. Inotropic agents enhance contractility, ensuring myocardial perfusion pressure with additional augmentation of peripheral hypotension by decreased peripheral vascular resistance with vasopressor agents.

Respiratory control, over-oxygenation with a high fraction of inspired oxygen (FIO<sub>2</sub>) aiming for a saturation >94% to prevent hypoxic pulmonary vasoconstriction, mild hyperventilation to avoid acidosis, recruitment manoeuvres to prevent ventilation-perfusion mismatch, low maximum inspiratory pressures and positive end-expiratory pressure and finally, lung-protective ventilation with tidal volumes between 6-8ml/kg.

## ■ POST-OPERATIVE COMPLICATIONS

Pulmonary hypertension is a predictor of poor outcome concerning general and specific complications resulting in delayed extubation, prolonged hospital stay, higher readmissions rates and in-patient mortality [61,104,105].

General complications include sepsis, bleeding, delirium, electrolyte disturbance and pulmonary embolus [61,62]. Specific considerations are pulmonary complications affecting up to 30% of patients, mainly occur during the first 24 hours, including acute respiratory depression, respiratory distress and pneumothorax [106,107]. Cardiovascular complications, increasing weight gain from 24-48 hours secondary to third space fluid movement should be predicted by symptoms and clinical assessment, allowing dose adjustment of diuretics, higher incidence of cardiovascular instability and arrhythmias. Acute elevations in PA pressure, most commonly at 48 hours, leads to irreversible bi-ventricular failure, myocardial ischaemia, renal impairment and death [62].

## ■ CONCLUSION

Pulmonary hypertension is a complex progressive disease with multiple aetiologies. A holistic understanding of the disease pathology and physiology is fundamental for anaesthetists to deliver safe, effective anaesthetic care. Investigation of a patient's degree of disease is crucial to aid risk stratification and perioperative prognosis.

## ■ CONFLICT OF INTEREST

None to declare.

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