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Review Article

Pulmonary hypertension and its management in patients undergoing non-cardiac surgery

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Summary

Pulmonary hypertension is a complex disorder of the pulmonary vasculature that leads to increased peri-operative morbidity and mortality. Non-cardiac surgery constitutes a significant risk in patients with pulmonary hypertension. The management of right ventricular failure is inherently challenging and fraught with life-threatening consequences. A thorough understanding of the pathophysiology, the severity of the disease and its treatment modalities is required to deliver optimal peri-operative care. This review provides an evidence-based overview of the definition, classification, pathophysiology, diagnosis and treatment of pulmonary hypertension and focuses on the peri-operative management and treatment of pulmonary hypertensive crises in a non-cardiac setting.

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Introduction

Pulmonary hypertension (PH) is a serious condition and, despite advances in treatment, prognosis remains poor [1]. Patients with PH may present for anaesthesia and non-cardiac surgery and there are very few retrospective studies reporting outcome, with postoperative mortality rates varying between 1% and 18% [2–6]. This disparity reflects the wide variation in the methods used to diagnose PH, the severity of the disease and whether or not a control population was included. Peri-operative morbidity appears to be in the range of 14–42% and includes respiratory failure, heart failure, dysrhythmias, sepsis, renal insufficiency and myocardial infarction [2–6]. Although it is clear that PH represents an independent risk factor for peri-operative complications and postoperative death, the actual incidence of these complications is still unknown. In this article, we aim to review studies published in the last decade with emphasis on pre-operative recognition and peri-operative management of adults with PH.

Methods

A comprehensive literature search was performed on MEDLINE and EMBASE using the National Health Service health database, advanced search interface, assessing articles from 2003 to 2014. To achieve maximum sensitivity of the search, the following key words were applied: 'pulmonary hypertension'; 'surgical procedures'; 'cardiac surgical procedures'; 'anesthesia'; 'anesthetics'; 'noncardiac'; 'non cardiac'; 'anesthe'; 'anaesthe'. The search results included English, Spanish, French, German, Russian and Japanese studies. A total

of 169 articles were initially identified. We excluded cardiac surgery, paediatric surgery, transplantation surgery and adults with congenital heart disease. Foreign language papers except Spanish articles were excluded. Individual case reports and non-systematic reviews were also excluded. A total of 44 articles were included following the initial search. In addition, articles were retrieved on scanning bibliographies. The three authors examined and graded the articles based on their clinical relevance and methodology. Due to the scarce number of randomised controlled trials, available case series and recommendations based on expert opinion were included. Where the evidence found on a particular section was considered unsatisfactory, a more specific search was performed and older evidence revisited. Epidemiological data and information on changing demographics and survival were obtained from PH registries [1, 7]. The current prevalence and survival data in the UK were obtained from the National Audit of Pulmonary Hypertension 2012 [8].

Definition and classification

PH is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg measured by right heart catheterisation at rest [9, 10]. There are multiple aetiologies for elevated pressure in the pulmonary circulation and PH could be defined as a haemodynamic state rather than a single disease entity. A recently updated World Health Organization (WHO) clinical classification from the Fifth World Symposium 2013 can be found in Table 1 [11]. A distinction between pre-capillary and post-capillary PH is fundamental to understanding the vascular and haemodynamic changes present in patients with PH. Throughout this article, pulmonary arterial hypertension (PAH) will be used when referring to WHO group 1 in particular, whilst PH will be used for pulmonary hypertension in general. The characterisation of the different haemodynamic profiles is summarised in Table 2.

Table 1 World Health Organization clinical classification of pulmonary hypertension [11].

1. Pulmonary arterial hypertension (PAH)
    - 1.1. Idiopathic PAH
    - 1.2. Heritable
        - 1.2.1. BMPR2
        - 1.2.2. ALK1, endoglin,SMAD9,CAV1, KCNK3
        - 1.2.3. Unknown
    - 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 haemangiomatosis

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 diseases 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

5. Pulmonary hypertension with unclear multifactorial mechanisms
    - 5.1. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
    - 5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
    - 5.3. Metabolic disorders: glycogen storage disease, Gauchers disease, thyroid disorders
    - 5.4. Others: tumour obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

BMPR2, bone morphogenetic protein receptor type 2; ALK1, activin receptor-like kinase type 1; SMAD, SMAD group of intracellular proteins; CAV1, Caveolin-1; KCNK, Potassium channel subfamily K; HIV, human immunodeficiency virus.

Prevalence

There are no reliable data on the prevalence or aetiology of pulmonary hypertension, but an estimation can be made by examining individual groups of patients. In a major study in France, a prevalence of 15 per million inhabitants was observed for PAH between 2002 and 2003 [13]. The data from the National Pulmonary Hypertension Audit, UK 2013, showed that designated centres saw 124 patients per million population in Great Britain between 2012 and 2013 [8]. The most common diagnosis, was PAH in 45% of patients, followed by chronic thromboembolic pulmonary

Table 2 Haemodynamic definition of pulmonary hypertension [9, 10, 12].

Definition	Characteristics (all values at rest)	WHO clinical groups
Pulmonary hypertension (PH)	mPAP ≥ 25 mmHg	All
1) Pre-capillary PH	mPAP ≥ 25 mmHg PAWP ≤ 15 mmHg PVR > 3 WU CO normal/reduced/high	Pulmonary arterial hypertension PH due to lung disease CTEPH PH with unclear and/or multifactorial mechanisms
2) Post-capillary PH	mPAP ≥ 25 mmHg, PAWP > 15 mmHg CO normal/reduced/high	PH due to left heart disease
2a) Isolated post-capillary PH*	PAWP > 15 mmHg	PH due to left heart disease
2b) Post-capillary PH with pre-capillary component*	DPAP-PAWP < 7 mmHg PAWP > 15 mmHg DPAP-PAWP ≥ 7 mmHg	PH due to left heart disease

mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units; CTEPH, Chronic thromboembolic pulmonary hypertension; CO, cardiac output; High cardiac output can be present in cases of hyperkinetic conditions such as systemic to pulmonary shunts (pulmonary circulation only), anaemia, hyperthyroidism, portal hypertension, sepsis etc.; DPAP, Diastolic pulmonary artery pressure.
*Proposed definition by Vachiéry et al.

hypertension (CTEPH) in 19%. Both left heart disease and lung disease contributed 7% each. Survival of PAH patients in the current treatment era has improved from a median of 2.8 years in the US National Institutes of Health (NIH) registry in 1980, to a 49% survival at seven years from diagnosis reported by the US REVEAL (The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) published in 2012 [7, 14, 15].

Pathogenesis

Although the factors responsible for disease initiation are different depending on the subcategories of PH, various interrelated processes result in endothelial dysfunction favouring vasoconstriction, vascular remodelling with excessive cell proliferation in the presence of reduced cell apoptosis and thrombosis [16, 17] (Fig. 1).

In PAH, levels of prostacyclin (PGI_2) are reduced and thromboxane synthesis is increased [17]. Prostacyclin is a potent vasodilator that inhibits platelet aggregation and smooth muscle cell proliferation [18]. Thromboxane A_2 stimulates vasoconstriction and platelet aggregation.

Nitric oxide (NO) acts via cyclic GMP (cGMP), causes vasodilatation and has antiproliferative properties [17]. All forms of PH are believed to result in a state of reduced NO bioavailability [19, 20]. Phosphodiesterase-5 (PDE-5) breaks down cGMP into inactive 5GMP. There is increased expression of PDE-5 both in the endothelial smooth muscle cells and in the right ventricle [16].

There is also an association between PAH and increased production in the pulmonary vasculature of endothelin-1 (ET-1), which is a potent vasoconstrictor and stimulates smooth muscle cell proliferation [21]. Structural remodelling is seen in PAH and the term 'mitochondrial remodelling' is used to describe the metabolic changes that occur in the vascular endothelial cells [22]. There is also a genetic component: mutation of bone morphogenetic protein receptor-2 (BMPR2) leads to loss of inhibitory action of bone morphogenetic protein on growth of vascular endothelial and smooth muscle cells [23]. Ultimately, chronically elevated afterload results in hypertrophy and dilatation of the right ventricle, and a metabolic shift from oxidative mitochondrial metabolism to the less energy efficient glycolytic pathway, which is related to cardiac ischaemia [24].

Diagnosis and treatment

Transthoracic echocardiogram (TTE) remains the method of choice for screening and assessing the likelihood of PH when clinically suspected. Right heart

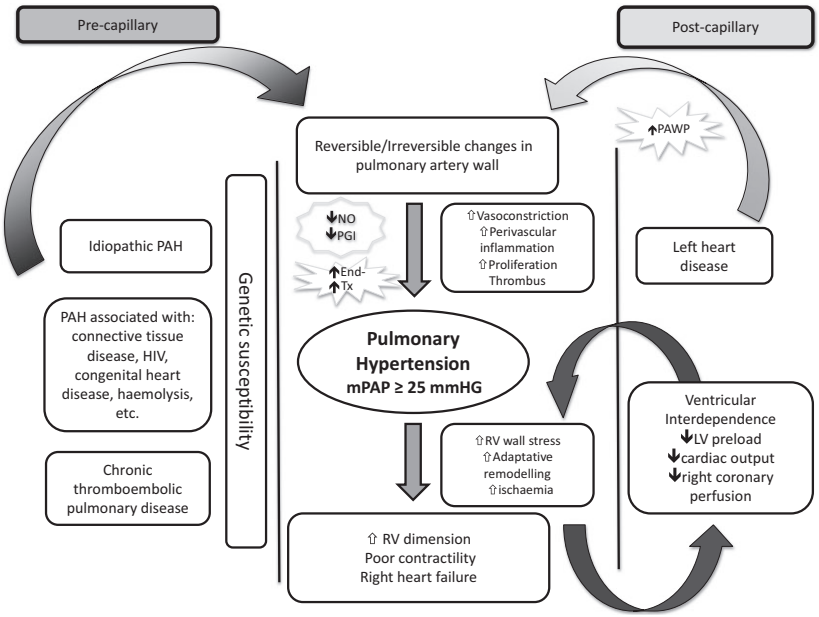

Figure 1 Schematic representation of the pathophysiology of pulmonary hypertension and its progression. Sustained pulmonary pressure has a negative impact on the right ventricular performance, causing remodelling and susceptibility to endocardial ischaemia. The left heart is affected by the persistent left shift of the interventricular septum and imbalance in the ventricular interdependence reduces pre-load, decreasing cardiac output and compromising right coronary artery blood flow. PAH, pulmonary arterial hypertension; HIV, Human immunodeficiency virus; NO, nitric oxide; PGI, prostacyclin; End, endothelin; Tx, thromboxane; mPAP, mean pulmonary artery pressure; RV, right ventricle; PAWP, pulmonary artery wedge pressure.

catheterisation is the gold standard to confirm the diagnosis and establish the severity of PH [9]. Once the diagnosis is confirmed, other diagnostic tools assist in establishing the underlying aetiology and clinical group to which the patient belongs (Table 3).

There is a complex pathophysiology of PAH such that, despite advances in treatment over the last decade, it remains incurable. Treatment with PH-targeted drug therapy is only licensed for patients in WHO group 1. In the UK, drug prescribing is restricted to national PH centres (Fig. 2).

General measures include advice on physical activity and supervised rehabilitation, psychological support, infection control, birth control and pregnancy. Supportive measures include advice on anticoagulation, diuretics and oxygen therapy. For almost 30 years, anticoagulation has been recommended for patients with idiopathic PAH based on pathological findings of thrombotic arteriopathy. The COMPERA registry data showed that the survival improvement at three years remained statistically significant in patients with

Table 3 Diagnostic tests to establish the aetiology of pulmonary hypertension [9].

Diagnosis	Associated condition
Echocardiography	Left ventricular systolic and diastolic dysfunction Left-sided valvular heart disease CHD with systemic to pulmonary shunt
X-ray chest, PFT	COPD, sarcoidosis Interstitial pulmonary fibrosis
V̇/Q̇ scan, CTPA	Chronic thromboembolic pulmonary disease
Sleep study	Obstructive sleep apnoea
Serological test (ANA, HIV)	Lupus, scleroderma, HIV
Liver ultrasound	Portopulmonary hypertension
Right heart catheterisation	CHD with systemic to pulmonary shunt Postcapillary PH due to left heart disease
Cardiac MRI	CHD, cardiomyopathies

CHD, congenital heart disease; PFT, pulmonary function tests; COPD, chronic obstructive pulmonary disease; V̇/Q̇, ventilation/perfusion; CTPA, contrast CT angiography of the pulmonary artery; ANA, antinuclear antibody; HIV, human immunodeficiency virus.

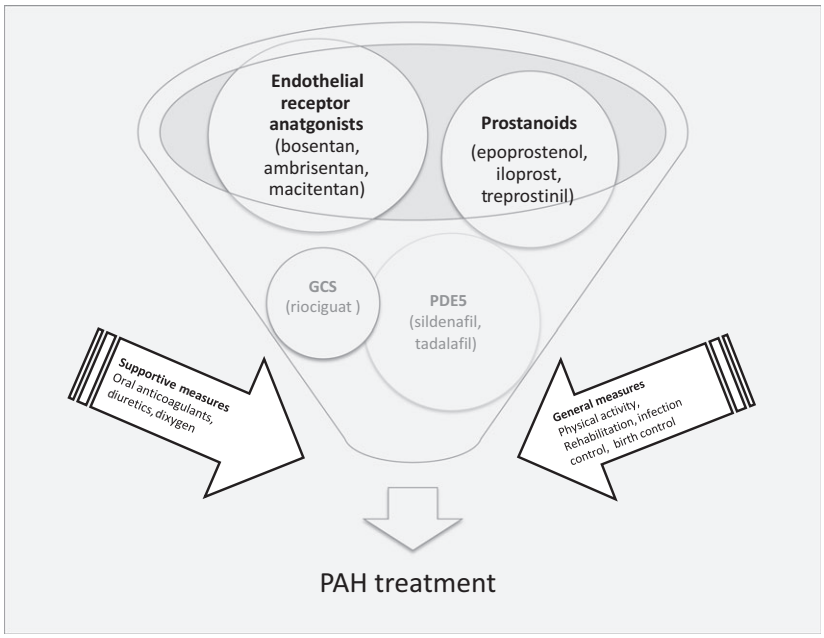

Figure 2 Diagram summarising PAH target therapy as well as general and supportive treatment measures. PDE5, phospodiesterase-5 inhibitors; GCS, guanylate cyclase stimulator.

idiopathic PAH. In contrast, the use of anticoagulants was not associated with a survival benefit in patients with other forms of PAH [25]. Decompensated right heart failure leads to fluid retention and although there are no randomised controlled trials comparing diuretics in PAH, clinical experience shows clear symptomatic benefit in fluid-overloaded patients [9]. Oxygen administration has been demonstrated to reduce pulmonary vascular resistance in patients with PAH, but there are no data to confirm that long-term oxygen therapy is beneficial. Guidance is based on evidence of its benefit in patients with chronic obstructive pulmonary disease [26].

Specific drug therapy includes calcium channel blockers that have traditionally been used in the treatment of idiopathic PAH. It has been increasingly recognised that only a small number of patients (< 10%) demonstrate a favourable response to acute vasodilator testing at the time of right heart catheterisation, and their use in non-responders can be associated with deleterious effects [27]. Synthetic prostacyclin analogues, such as epoprostenol, iloprost and treprostinil, have shown efficacy in patients with idiopathic PAH. Epoprostenol has a short half-life and is stable at room temperature for only 8 h; hence, it needs to be administered continuously by means of an infusion pump and a permanent tunnelled catheter. It improves exercise capacity and is the only treatment shown to improve survival in idiopathic PAH in a randomised study [28]. Iloprost is available for intravenous, oral, and aerosol administration. Inhaled iloprost in patients with PAH and CTEPH showed an improvement in symptoms and clinical events [29]. Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature and has shown clinical and haemodynamic improvement in PAH patients [30]. Another group of drugs, endothelin receptor antagonists, which include bosentan, ambrisentan and macitentan, are effective in the treatment of PAH. Bosentan is an orally active, dual endothelin-A and endothelin-B receptor antagonist and has been evaluated in PAH. Patient have shown improvement in functional class, haemodynamics and time to clinical worsening [31]. Ambrisentan is an oral selective endothelin-A receptor antagonist that has been shown to improve exercise capacity in PAH patients [32]. Macitentan is a new, orally active drug that has been tested in a large prospective study in PAH patients. A decrease in a composite endpoint has been shown that included worsening PH and death [33]. Phosphodiesterase-5 inhibitors, such as sildenafil and tadalafil, are orally active, potent, and selective inhibitors of the PDE-5 enzyme and have been shown to improve exercise

capacity, symptoms and haemodynamics in PAH patients [34, 35]. Riociguat is a new drug that stimulates soluble guanylate cyclase, leading to an increase in cyclic GMP, and has proven to be efficacious in PAH and CTEPH patients [36]. The incidence of transplantation has increased and both heart–lung transplantation and double-lung transplantation improve survival in transplantation candidates with idiopathic PAH [37].

Group 4 CTEPH patients should be referred for consideration of pulmonary endarterectomy. Specific drug therapy is also used in CTEPH patients who are not suitable for surgical treatment or those with residual PH after pulmonary endarterectomy as an unlicensed indication.

In general, treatment of patients in WHO groups 2, 3 and 5 should be focused on the underlying condition.

Pre-operative risk assessment

The peri-operative management of patients with PH should involve a multidisciplinary team. Patients need to be explicitly informed of the possibility of serious complications that can lead to prolonged hospitalisation or even death. The mortality associated with non-cardiac surgery is influenced by the severity of PH and type of surgery. Table 4 summarises the studies in PH patients undergoing non-cardiac surgery. In a 2005 study by Ramakrishna et al., which included 145 surgical patients with PH of varying aetiology, the peri-operative mortality rate was 7% [5]. A year later, in a smaller case series of 21 patients with moderate to severe PH, Minai et al. showed an 18% mortality rate [6]. However, both these studies were retrospective in design and included patients treated until 2003, before modern therapies for PAH had evolved. Also, almost 75% of patients in Ramakrishna et al.'s study were in New York Heart Association (NYHA) functional class 1–2 (Table 5) and only 13% of the patients were taking a prostanoid or endothelin antagonist. In contrast, Minai et al. had larger proportions of patients in NYHA class 2–4 and more patients were on PH-targeted therapy. Nevertheless, in both series, right ventricular failure was the contributing cause of death in 50% of the patients [5, 6].

In a case–control study of PH patients undergoing non-cardiac, intermediate- and high-risk surgery, Kaw et al. included 96 patients with PH confirmed with pulmonary artery catheter and compared them with a similar group without PH [2]. The PH group had a higher complication rate (25% vs 2.5%), but mortality was low (1%). Importantly, this study included mainly patients with PH related to left heart failure [2]. Lai et al. found a 9.7% mortality rate in PH patients undergoing non-cardiac surgery; however, PH diagnosis was based on echocardiography [3] and the

Table 4 Summary of studies showing morbidity and mortality associated with pulmonary hypertension (PH) in patients undergoing non-cardiac surgery [2–6, 38]. Values are proportion.

	Ramakrishna et al. (2005) (n = 145)	Minai et al. (2006) (n = 21)	Lai et al. (2007) (n = 62)	Price et al. (2010) (n = 28)	Memtsoudis et al. (2010) (n = 3543)	Kaw et al. (2011) (n = 96)
Country	USA	USA	Taiwan	France	USA	USA
PH due to left heart disease	No	No	Yes	No	No	Yes
General anaesthesia	100%	79%	58%	50%	Data unavailable	100%
Major surgery	79%	86%	58%	57%	THR/TKR	100%
Mortality	7%	18%	9.7%	7%	2.4/0.9%	1%
Morbidity	42%	14%	24%	29%	_	28%
Study type/ limitations	Retrospective No control ECHO criteria to define PH	Retrospective No control Severe PH	Retrospective Contolled Doppler ECHO criteria	Retrospective No control RHC criteria Mild-to-moderate disease	NIS database Matched samples. Immediate postoperative period only	Retrospective Controlled RHC criteria

ECHO, echocardiography; RHC, right heart catheterisation; THR/TKR, total hip/knee replacement; NIS, National Inpatient Sample.

Table 5 Functional classification of pulmonary hypertension (modified after the New York Heart Association (NYHA) functional classification according to the WHO 1998) [9].

Class 1	Pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class 2	Pulmonary hypertension resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class 3	Pulmonary hypertension resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class 4	Pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

increased mortality could be due to selection bias by the inclusion of patients with untreated severe PAH. There were no right heart catheterisation data and the contribution of left sided disease could not be accurately assessed.

More recently, Price et al. studied 28 PH patients having surgery under general or regional anaesthesia. At the time of surgery, 75% of patients were in NYHA functional class 1–2. Deaths occurred in 7% of patients and peri-operative complications, all related to PH, occurred in 29% of patients [4]. Risk factors associated with complications were emergency surgery ($p < 0.001$), major surgery ($p = 0.008$) and a long operative time (193 vs 112 min; $p = 0.003$) [4]. Memtsoudis et al. matched 3302 PH patients who underwent total hip or knee arthroplasty with non-PH controls from the national database. The PH group showed a 4 to 4.5-fold increase in the adjusted risk of mortality after hip or knee arthroplasty compared with patients without PH, and that the PAH subgroup had the highest mortality. The overall mortality was lower compared with previous studies, possibly due to spanning only the immediate peri-operative period [38].

With regard to patients undergoing pre-operative evaluation, a distinction should be made between those patients with an established diagnosis of pulmonary hypertension and those who have not been formally assessed. Patients 'suspected' of having PH with an uncertain underlying cause and ungraded severity are subject to poorer pre-operative optimisation and are exposed to a higher risk of peri-operative complications. In these circumstances, elective surgery must be postponed and the patient referred to a specialised PH service before surgery.

The pre-operative evaluation of a patient with established pulmonary hypertension should be based on a risk assessment that takes into account their functional state, severity of the disease and type of surgery proposed. A detailed history and physical examination should be complemented with relevant investigations. Patients' symptoms range from general fatigue, dyspnoea and chest pain on exertion to syncope in advanced PAH. Syncope is an ominous sign and, in most cases, is related to the inability to increase cardiac output on exertion and places the patient in the advanced functional class [39]. NYHA functional class at diagnosis is an important predictor of survival in patients with PAH and improvement from functional class 3/4 to 1/2 with treatment is associated with a better prognosis [14]. The six-minute walking distance (6MWD) is used to assess exercise capacity in patients with PH and a reduced total distance is associated with a higher mortality [40].

Pre-operative investigations include laboratory tests, electrocardiography, echocardiography, chest radiography and a recent right heart catheterisation. Blood tests to assess haemoglobin level and renal function and to measure pro-brain natriuretic peptide (pro BNP) and/or its terminal fraction are requested. Although a high BNP level is an independent predictor for postoperative cardiac mortality in patients undergoing non-cardiac surgery, its use in stratifying postoperative risk has not been established in PH patients [41]. Transthoracic echocardiography is non-invasive and readily available to evaluate right ventricular function in patients with PH. Echocardiographic predictors of poor prognosis in patients with PAH are right atrial enlargement, reduced tricuspid annular plane systolic excursion (TAPSE) and pericardial effusion [42]. Right

heart catheterisation establishes the diagnosis and type of PH and provides essential information regarding the severity of the disease and right heart function [43]. It also allows differentiation between pre- and post-capillary PH, which is particularly relevant in patients with risk factors for left heart disease [44].

Before surgery, medications should be reviewed and altered depending on recent investigation results. Examples include: initiation or augmentation of PAH-specific therapies for patients in WHO Group 1; diuretics and systemic vasodilators and appropriate heart failure therapies for patients in WHO group 2; administration of oxygen, bronchodilators, antibiotics and steroids in patients with chronic obstructive pulmonary disease; and use of bi-level positive airway pressure for obstructive sleep apnoea [45]. Established PAH therapies should be continued in the peri-operative period and when oral formulations cannot be used, temporary administration of inhaled (NO, nebulised prostacyclin) or intravenous (prostacyclin, sildenafil) therapy should be considered. Warfarin should be discontinued before the procedure without the need for bridging with heparin unless there is another indication (e.g. pulmonary embolism, CTEPH, mechanical heart valve). Patients should receive prophylactic anticoagulation to prevent deep vein thrombosis and pulmonary thromboembolism.

The type of surgery is also relevant in the pre-operative risk assessment. High-risk surgery includes that associated with major blood loss, significant peri-operative systemic inflammatory response, venous air, carbon dioxide, fat or cement embolism, and loss of lung blood vessels [45]. Table 6 summarises patient and surgical risk factors that are associated with increased morbidity and mortality in patients with PH.

Table 6 Patient and surgical risk factors associated with increased morbidity and mortality in patients with pulmonary hypertension [2–6].

Patient factors	Surgical factors
NYHA/WHO functional class ≥ 2	Emergency surgery
6MWD < 300 m	Intermediate-/high-risk surgery
History of coronary artery disease	ASA physical status > 2
History of pulmonary embolism	Duration of anaesthesia > 3 h
History of chronic renal insufficiency	Intra-operative use of vasopressors
RVH with severe systolic dysfunction	
Higher mean pulmonary artery pressure	

NYHA, New York Heart Association; WHO, World Health Organization; 6MWD, six-minutes walking distance; RVH, right ventricular hypertrophy.

Principles of anaesthetic management

Prevention of PH crisis and right ventricular failure relies on the optimal mechanical matching of the right ventricle and pulmonary circulation. A variety of intra-operative events, both surgical and anaesthetic, can affect the right ventricular oxygen supply–demand relationship.

The transition from spontaneous breathing to intermittent positive pressure ventilation, addition of positive end-expiratory pressure (PEEP), patient positioning, pneumoperitoneum or diaphragmatic compression can significantly increase right ventricular afterload and precipitate a pulmonary hypertensive crisis. In addition to the pulmonary vascular effects of hypoxia and hypercarbia, patients may also be subjected to venous emboli arising from air, thrombi or particulate matter forced into the circulation.

Right ventricular contractility in PH patients can range from normal through varying degrees of systolic dysfunction. Ventricular wall hypertrophy and chamber dilatation are common, the latter being more significant in the advanced stages of PH. Right ventricular contractility can be affected directly or indirectly by either depression from anaesthetic drugs or acute changes in the sympathetic/parasympathetic balance. Table 7 shows the effect of various anaesthetic agents on right ventricular contractility and afterload. Inhaled anaesthetics such as isoflurane and desflurane have a marked dose-dependent effect in reducing right ventricular contractility and some negative impact on right ventricular afterload; hence, they significantly impair right ventricle pulmonary artery coupling [46, 47]. Sevoflurane causes significant depression of global right ventricular function associated with a qualitatively different effect on inflow and outflow tracts, without any modification of pulmonary vascular

Table 7 Effect of anaesthetic agents on right ventricular (RV) contractility and pulmonary vascular resistance [46–57].

Anaesthetic Agent	Isoflurane Desflurane	Sevoflurane	Nitrous oxide	Thiopental	Etomidate	Ketamine	Propofol	Opioids
RV contractility	↓↓	↓↓	↓	↓	–	↓	↓↓	↔
Pulmonary vascular resistance	↑	↔	↑↑	↔	–	↑adult ↔ child	↓	↔

↓↓-marked decrease; ↑↑-marked increase; ↑-increase; ↓-decrease; ↔ no change; – not known.

resistance [48]. The use of nitrous oxide should be restricted because it increases pulmonary vascular resistance [49].

With regard to intravenous anaesthetic agents, thiopental reduces right ventricular contractility and systemic vascular resistance, but does not affect pulmonary vascular resistance [50]. Etomidate has been advocated as the induction agent of choice in patients with right ventricular dysfunction, although there are no comparative data [51]. Ketamine increases pulmonary vascular resistance in adults [52], although this has not been observed in children [53]. Propofol sedation in patients with acute respiratory failure or neurological disease receiving critical care was found to decrease right ventricular contractility and this effect was reversed by dobutamine [54]. Interestingly, in a comparison study of propofol and isoflurane in patients undergoing one-lung ventilation, there was a greater reduction in the mean cardiac index and right ventricular ejection fraction with propofol, but propofol was not associated with a significant increase in shunt fraction, whereas isoflurane was associated with a three-fold increase in shunt fraction [55]. Fentanyl and sufentanil have minimal effects on pulmonary haemodynamics [56]. Remifentanil produces minor pulmonary vasodilatation, which is mediated by histamine release [57].

Although central neuraxial blockade has been used safely in patients with PH, blocking cardiac sympathetic fibres in the upper thoracic region disrupts right ventricular homeometric autoregulation [58]. Homeometric autoregulation is an adaptive mechanism that allows the right ventricle to tolerate acute increases in afterload but preserves the mechanical coupling between right ventricle and the pulmonary circulation. When inhibited (e.g. by central neuraxial blockade), it can lead to a critical reduction in cardiac output and right heart failure that is not due to impaired right ventricular coronary flow dynamics or systemic vasodilation [58].

The balance between myocardial oxygen supply and demand is affected by several events that occur during anaesthesia and surgery. The altered pattern of increased right ventricular pressures and systolic wall tension with limited coronary blood flow occurring mainly in diastole has a greater impact on right ventricular perfusion during systemic hypotension [59].

Intra-operative anaesthetic management

There is a lack of evidence-based guidelines on the peri-operative management of patients with PH, and the recommendations in this section are based on literature review and the authors' experience.

All patients should be given supplementary oxygen. In addition to preventing hypoxia, oxygen is a direct pulmonary vasodilator. It is good practice to remove air from intravenous syringes and lines. Hypothermia can cause pulmonary vasoconstriction and $\dot{V}/\dot{Q}$ mismatch and it should be prevented by using forced air-warming blankets, heat and moisture exchangers and warmed intravenous fluids.

Airway and ventilation

When using conscious sedation techniques, it is vital to ensure a patent airway and easy access to it, in case ventilation becomes compromised. During induction of general anaesthesia, there is a period of susceptibility until the airway is secured and ventilation controlled. An adequate depth of anaesthesia should be ensured before attempting laryngoscopy and tracheal intubation, as sympathetic stimulation has deleterious

effects on right ventricular afterload. Hypercarbia, acidosis, high inspiratory pressures and high levels of PEEP should also be avoided.

Monitoring

There is no strong evidence to suggest that any specific type of monitoring has an influence on patient morbidity and mortality. Nonetheless, invasive arterial monitoring before anaesthetic induction can facilitate early recognition of haemodynamic instability and allows intermittent arterial blood gas sampling to check adequacy of ventilation. Right atrial pressure measurement reflects the relationship of blood volume to the capacity of the venous system and also reflects the functional capacity of the right ventricle. Intra-operative monitoring with transoesophageal echocardiography (TOE) and/or a pulmonary artery catheter should be considered in all patients with severe PH or mild-to-moderate PH with existing right-sided heart failure [60]. Monitoring with TOE allows continuous measurement of systolic pulmonary artery pressure, valuable information on right ventricular performance and guidance for fluid management [61]. Studies have shown that the use of TOE triggered a change in the overall therapeutic management in between 30% and 50% of high-risk patients undergoing non-cardiac surgery [62, 63]. However, several factors limit the routine use of TOE; the image acquisition and interpretation of findings are dependent on the operator's training and personal experience, and the probe is not well tolerated in awake patients undergoing regional anaesthesia [62].

The intra-operative use of a pulmonary artery catheter is controversial. Many studies have failed to demonstrate any benefit in its use for intra-operative monitoring; however, in most of the studies, a pulmonary artery catheter was used for measurement and guiding optimisation of cardiac output and left ventricular end-diastolic pressure [64]. Despite there being no robust data for the use of pulmonary artery catheter monitoring in patients with PH undergoing non-cardiac surgery, its use in the peri-operative setting provides unique direct, consistent and continuous measurement of pulmonary artery pressure, pulmonary vascular resistance and dynamic changes that occur in response to fluid administration, drug therapy or unexpected events that raise pulmonary artery pressure [9]. All authors point out that the insertion of a pulmonary artery catheter is associated with certain risks, which must be considered before insertion is attempted [65].

Circulation

In general, patients with PH have low systemic arterial pressures as a result of both their disease and specific medical therapy, rendering them susceptible to decompensation. The goal is to maintain the pre-anaesthetic haemodynamic condition. Therefore, invasive monitoring before induction is often required. Permissive hypotension is not applicable to high-risk PH patients; in contrast, the use of a low dose of vasoconstrictor to compensate for the reduction in systemic vascular resistance caused by anaesthetic drugs is a safe and effective approach. Blaise et al. recommended intra-operative management that allows the mean pulmonary artery pressure to fluctuate in the range of 15% of the initial value [66]. However, a pulmonary artery catheter is not always placed before induction of anaesthesia and placement whilst awake is distressing for the patient and can negatively impact the pulmonary vascular resistance. A practical approach would include siting an arterial line awake followed by a balanced anaesthetic induction that aims to maintain the baseline blood pressure; See Table 8 for proposed haemodynamic goals. Intra-operative fluid therapy should be relatively restricted and in a targeted manner based on the central venous pressure.

Vasoconstrictors, inotropes and inodilators

Maintaining the gradient between aorta and right ventricle is achieved by using sympathomimetic and non-sympathomimetic vasopressors. Noradrenaline and vasopressin improve perfusion of the right coronary artery, reduce the pulmonary/systemic vascular resistance ratio, enhance right ventricular performance and marginally improve cardiac output [67, 68]. However, the evidence of their impact on mortality related to right heart failure is weak [69]. Inotropes that enhance right ventricular performance, such as adrenaline, dobutamine and levosimendan are effective in treating right-sided heart failure. The

Table 8 Peri-operative haemodynamic goals.

Systolic blood pressure ≥ 90 mmHg and/or 40 mmHg above sPAP
MAP ≥ 65 and/or 20 mmHg above mPAP
mPAP < 35 mmHg or 25 mmHg lower than MAP
PVR/SVR ratio < 0.5 or aim for pre-operative PVR/SVR ratio
RAP the lowest possible that maintains MAP > 65 mmHg
Cardiac index ≥ 2.2 $l.min^{-1}.m^2$

sPAP, systolic pulmonary artery pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PVR/SVR ratio, pulmonary vascular resistance/systemic vascular resistance ratio; RAP, right atrial pressure.

use of inotropes has a modest impact in reducing the overall mortality related to PH, and their wide availability and ease of administration make this group of drugs very attractive for use in the peri-operative setting. Inodilators, such as the phosphodiesterase-3 inhibitors milrinone and enoximone, have been shown to be beneficial when compared with conventional inotropic support only [69]. It appears that the influence of phosphodiesterase-3 inhibitors on reducing pulmonary vascular resistance is more pronounced than the reduction in systemic vascular resistance. However, reduction in systemic vascular resistance can compromise right coronary artery blood flow in patients with severe PH and therefore they should be administered cautiously.

Vasodilators

In 2010, sildenafil was approved for intravenous therapy of PAH and it may be an attractive option for the peri-operative management of patients already taking oral sildenafil [70]. Selective pulmonary vasodilator therapy by the inhaled route has the advantage of minimal effect on the systemic circulation; the drugs improve oxygenation by decreasing the pulmonary shunt, which is important in patients who suffer PH associated with acute lung injury. Inhaled NO is effective, but, despite rapid metabolism, the use of NO over a prolonged period is associated with rebound phenomena and direct toxicity to the lung [71]. Prostacyclin and its analogues offer a good alternative to NO and there are several reports of the use of inhaled epoprostenol in the peri-operative setting. A study that included 35 patients with PH showed successful use of inhaled prostacyclin in the operating theatre and intensive care unit [72]. Iloprost has a longer half-life than prostacyclin and is less likely to cause rebound phenomena after discontinuation. It can be administered peri-operatively via both controlled and spontaneous ventilation. Evidence with iloprost in patients undergoing non-cardiac surgery is scarce and limited to case reports [73]. Inhaled treprostinil is stable at room temperature and has been shown to benefit patients with PAH, but its use peri-operatively is also limited to a few case reports [74]. Table 9 outlines the management of a pulmonary hypertensive crisis.

Postoperative management

Patients with PH should be fully monitored in the intensive care unit postoperatively. There should be a robust plan for pain management, including regional blocks and non-opioid medications. Postoperative clinical deterioration and death are due to fluid shifts, pulmonary vasoconstriction, arrhythmias and pulmonary thromboembolism. Respiratory failure (60%) and right ventricular failure (50%) are the most frequent contributing causes to death [5]. Atrial tachyarrhythmias are associated with right ventricular failure and death [75]. Beta-blockers should be avoided as they are poorly tolerated in these patients [76] and amiodarone would be the drug of choice, although dronedarone or flecanide should be considered if amiodarone is contraindicated or not tolerated [75]. In patients in whom sinus rhythm cannot be restored, digoxin should be considered for rate control [75]. Post-surgical complications such as bleeding and infection must be promptly controlled and treated. Right ventricular function in PH is 'preload-dependent' but at the same time, fluid overloading is detrimental. Maintenance of systemic pressures with vasopressors and inotropes, along with replacement of blood volume when necessary, is of paramount importance. Vasodilator therapies that were started intraoperatively must be continued and slowly transitioned back to the patient's pre-operative regimen.

Pregnancy

Historically, it is well known that pregnancy poses an immense risk to women with PAH. Avoidance of pregnancy is still strongly advocated and early termi-

Table 9 Treatment of pulmonary hypertensive crisis.

General principles
Avoid hypoxic pulmonary vasoconstriction
Avoid hypercarbia, acidosis and hypothermia
Avoid high airway pressures
Optimise right ventricular preload
Reduce right ventricular afterload
Maintain coronary blood flow
Maintain sinus rhythm
Maintain arterial blood pressure and cardiac output
Vasopressors– noradrenaline; vasopressin
Inotropes– adrenaline; dobutamine
Inodilators– milrinone; enoximone
Intravenous vasodilators (caution if low systolic blood pressure)
Milrinone (25–50 μg.kg^{-1} bolus, followed by 0.5–0.75 μg.kg^{-1}.min^{-1} continuous infusion)
Prostacyclin (4–10 ng.kg^{-1}.min^{-1} continuous infusion)
Iloprost (1–3 ng.kg^{-1}.min^{-1} continuous infusion)
Sildenafil (10 mg bolus three times a day)
Selective pulmonary vasodilation
Iloprost (5–10 μg diluted in 10 ml saline, nebulised over 10 min, repeated every 2–4 h)
Prostacyclin (25–50 μg diluted in 50 ml saline, nebulised over 15 min, repeated every hour)
Nitric oxide (5–40 ppm continuously)

nation is recommended for PAH patients. With regards to the specific medical management of PAH, endothelin receptor antagonists are contraindicated during pregnancy due to their teratogenic effect, but epoprostenol, trepostinil, nebulised iloprost, sildenafil and inhaled nitric oxide can be used [77]. Calcium channel blockers are recommended for responders to the vasodilatory testing.

Weiss et al. reported a mortality rate of 30% in patients with idiopathic PAH and 56% in patients with PH associated with other conditions [78]. A more recent systematic review concluded that mortality was reduced to 17% in idiopathic PAH and 33% in PH associated with other conditions [79]. Vaginal delivery is associated with less blood loss and a lower risk of maternal infection; however, labour without effective analgesia is associated with stress, pain and increased sympathetic tone, which are deleterious in patients with severe PH. Elective caesarean section allows for better planning, a multidisciplinary team approach and optimal pain control. Although the majority of leading centres favour elective caesarean section over vaginal delivery, the optimal anaesthetic technique remains controversial. In two recently published series, elective caesarean section was the mode of delivery in more than 95% of cases. In Jaïs et al.'s. series [80], 80% of patients received regional anaesthesia, while in Rosengarten et al.'s. series, up to 80% of caesarean sections were performed under general anaesthesia [81]. Interestingly, the maternal mortality rate was similar in both cohorts (20% and 22%, respectively). In a retrospective review, Bedard et al. found that general anaesthesia was associated with a four-fold increase in maternal mortality; however, it could be possible that patients who underwent emergency caesarean section, and those who received general anaesthesia, had more severe disease [79]. The majority of deaths in pregnant patients with PAH occur in the peripartum period, mainly due to right heart failure and pulmonary thromboembolism. The practice of thromboprophylaxsis in pregnant patients with PH is not standardised. Most case reports describing pregnant patients with PH placed patients on thromboprophylaxis during pregnancy and through the postpartum period with only a brief interruption around the time of delivery. Exceptions are for those who had a history of thromboembolic disease and idiopathic PAH where higher levels of anticoagulation may be required [77, 79].

Conclusions

Recent advances in our understanding of PH and the availability of new treatment modalities have resulted in improved survival. There are an increasing number of patients presenting for non-cardiac surgery. Their successful management requires a multidisciplinary team approach and thorough pre-operative risk assessment. Correct diagnosis, optimisation of the patient's functional status and haemodynamics and management of co-morbidities are vital. Anaesthetic management is dependent on an understanding of pathophysiology and avoidance of a pulmonary hypertensive crisis. The presence of an experienced anaesthetist and surgeon in a specialist centre is advocated. Further studies on patients with PH undergoing non-cardiac surgery are required to provide guidance on the optimal management of this rare and complex disease.

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