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REVIEW ARTICLE
Diseases of pulmonary circulation

Pulmonary arterial hypertension: management in specific medical conditions (RCD code: II-1A.1)

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Abstract

Pulmonary arterial hypertension (PAH) is a severe and progressive disease. Due to the narrowing of the blood vessels in the lungs, pulmonary vascular resistance and pulmonary pressures increase. This results in reduced cardiac output, right heart failure and ultimately in death. Pulmonary hypertension, particularly PAH, is an independent risk factor for both peri-operative complications and post-operative mortality. The peri-operative management of patients with PAH is particularly challenging and requires a multidisciplinary approach**.** Appropriate patient preparation requires an accurate assessment of the severity of pulmonary hypertension, comorbidities and the type of surgery to be performed. Additionally, patients with PAH are more likely to develop an infection, particularly of the respiratory system. Infection**s** are important risk factors for disease exacerbation, often affecting prognosis. For this reason, there is a need for effective prophylactic, diagnostic and rapid therapeutic strategies in PAH patients admitted with suspected infection. While pregnancy is not considered a disease, it is associated with a significant mortality and morbidity risk in patients with PAH and therefore it is contraindicated in this group. Thus, the proper education of patients and effective contraception are necessary in order to minimize health risks. If a woman decides to maintain her pregnancy, careful monitoring, specific treatment optimization and close co-operation with an obstetrician are needed. The proper assessment of the severity of PAH and the optimization of specific treatments are crucial to improve the prognosis of PAH patients in all high-risk conditions. Additionally, the early diagnosis of high-risk conditions allows for early intensive treatment or control, which should be performed at a PAH treatment referral centre. JRCD 2018; 3 (6): 193–197

Key words: rare disease, pulmonary arterial hypertension, surgery, infections, pregnancy

Introduction

Pulmonary hypertension (PH) is a haemodynamic condition defined as a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg at rest, measured by right heart catheterization (RHC). A comprehensive clinical classification from the 2015 European Society of Cardiology/ European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and treatment of PH can be found in Table 1 [1]. Pulmonary arterial hypertension (PAH) is a form of PH with a pulmonary capillary wedge pressure of ≤15 mm Hg or normal left ventricular end-diastolic pressure with no left heart disease, lung disease or hypoxia. Before diagnosing PAH, chronic thromboembolic PH and other causes of pulmonary artery obstruction should be excluded. PAH is a progressive disease characterized by endothelial dysfunction favouring vasoconstriction, proliferation and remodelling of smooth muscle cells. Due to progressive narrowing of the blood vessels, pulmonary vascular resistance (PVR) and pulmonary pressures increase. This results in reduced cardiac output, right heart failure (HF), and ultimately in death. Over the years, modern drug therapies have reduced short- and long-term mortality as well as clinical deterioration [2,3], and showed improvement in patient symptomatic status [4,5]. Nevertheless, PAH remains a chronic disease with no cure. In addition, PAH exacerbates patients' existing symptoms and increases both morbidity and mortality in many other diseases. This review focuses on the most common non-cardiac events affecting patients with PAH and their particular implications.

Surgical procedure

Thanks to modern medicine, patients with PAH live longer and have a higher overall quality of life. Consequently, they are more likely to require elective non-cardiac surgery procedures (NCS).

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Table 1. Clinical Classification of Pulmonary Hypertension

Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
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′.1 Idiopathic PAH
1′.2 Heritable PAH
1′.2.1 BMPR2 mutation
1′.2.2 Other mutations
1′.3 Drug, toxin and radiation induced
1′.4 Associated with:
1′.4.1 Connective tissue disease
1′.4.2 HIV infection
1″. Persistent pulmonary hypertension of the newborn (PPHN)
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
2.5. Congenital/acquired pulmonary veins stenosis
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 lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions
4.1. Chronic thromboembolic pulmonary hypertension
4.2. Other pulmonary artery obstructions
4.2.1. Angiosarcoma
4.2.2. Other intravascular tumors
4.2.3. Arteritis
4.2.4. Congenital pulmonary arteritis stenoses
4.2.5. Parasites (hydatidosis)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Pulmonary hypertension, in particular PAH, may affect the prognosis in patients requiring anaesthesia and major surgery [6,7], including heart and lung transplantation [8,9], liver transplantation [10–13] and pneumonectomy. PH is an independent risk factor for peri-operative complications and postoperative mortality. The most common complications of the peri-operative period are a systemic inflammatory response, sepsis, profound hypoxemia, renal insufficiency, deterioration of PH and right HF [14]. Additionally, there is an increased risk of bleeding due to pre-treatment with anticoagulants and prostacyclin analogues. The peri-operative management of patients with PAH is particularly challenging and requires a multidisciplinary team which consists of a surgeon, an anaesthesiologist and a cardiologist from a PH centre.

In the pre-operative period, the patient should be advised about the increased operational risk and possible complications, including death. The morbidity and mortality are influenced by the severity of PH before surgery, co-morbidities and the type of surgery. Therefore, a detailed medical history as well as a thorough physical examination should be supplemented by laboratory tests, particularly the serum concentrations of brain natriuretic peptides in order to adequately prepare a surgery [15]. Cardiac examinations should include electrocardiography, echocardiography with particular attention paid to the right atrial area and the presence of pericardial effusions, chest radiography, as well as the six-minute walking distance (6MWD) to estimate exercise capacity. The RHC is necessary to confirm the diagnosis and type of PH, if this data was not obtained before. Furthermore, RHC is also used to assess the effectiveness of therapy and eventually to determine scope of treatment prior to surgery.

Pilkington et al. provided an evidence-based overview of the studies published in the last decade focusing on the peri-operative management of adults with PH. Analysis of this data revealed, that peri-operative morbidity was 14–42% [6,7]. Postoperative mortality rates varied between 1% to 18% [16–18]. This large discrepancy **is** mainly due to a wide variety of methods used to diagnose PH. In some studies, the diagnosis of PH was based exclusively on echocardiography without RHC confirmation. Additionally, disease severity seems to vary in particular studies.

According to recent studies, right ventricular failure (RVF) was a contributing cause of death in 50% of patients at various stages of PAH, undergoing surgery [17,18]. Kaw et al. conducted a case-control study of PH patients undergoing non-cardiac, intermediate and high-risk surgery [6]. Compared to the post-capillary PH group, patients with PAH had a higher risk of peri-operative complications, 16% vs. 41%, respectively. The results of a case series reported by Minai et al. showed an increased incidence of post-operative complications in patients with PAH who underwent intra-operative pulmonary artery catheterization or were not on vasoactive therapy during surgery [18]. These findings, however, were not statistically significant and require further investigation. Meyer et al., who conducted a prospective study, including 114 patients with PAH from 11 PH centres, reported a morbidity and mortality rates of 6.1% (7 patients) and 3.5% (4 patients), respectively [19]. Forty three percent of the study population was categorized in the New York Heart Association (NYHA) **as** class III/IV. The mortality rate significantly differed for patients who required emergency (15%) or nonemergency surgery (2%). The majority of patients were operated under general anaesthesia (82%, n = 93), and the remaining group under spinal (18%, n = 21). Three out of four (75%) fatal interventions were performed under general anaesthesia. The PH medications were continued throughout the peri-operative period

in almost all cases, and 20 patients (18%) had one or more PAH medications added in this period. In **a** univariate analysis, factors such as: a 6MWD <399 m and a right atrial pressure >7 mm Hg before the surgery, intra- or postoperative need for vasopressors, emergency surgery, all increased the risk of major postoperative complications. Of particular note, 75% of all surgical procedures and 57% of emergency interventions were performed in PH centres, what may influence the prognosis.

Current ESC/ERS guidelines only address the management of PH patients undergoing surgery in a limited degree [1]. Epidural anaesthesia should be prioritised over general anaesthesia according to guidelines, although the data is inconclusive and the preferred method is not always feasible. In addition, the guidelines stress the possible need for a transition from oral therapy to intravenous or inhaled therapy during the peri-operative period.

The practical guidelines for management of PH patients undergoing surgery were summarized in six points by Jean-Luc Vachiery at the ESC Congress in Rome [20]. In general, it is important to continue PH therapy. When the oral mode cannot be used, volatile (nitroxide, prostacyclin) or parenteral (prostacyclin, sildenafil) agents should be considered. In addition, effective pain control is required for any procedure to be performed**.** This prevents excessive sympathetic activation, which has a negative effect on the cardiovascular system and overall homeostasis. Pain-driven catecholamine release, may cause an increase in blood viscosity, blood pressure and heart rate. Platelet aggregation is accelerated, which reduces fibrinolytic activity and promotes thrombosis. Additionally, this ultimately increases oxygen consumption by the heart muscle and consequently reduces its supply. This painful experience may also trigger HF decomposition. Opioids, midazolam and etomidate agents should be opted for during anaesthesia. There is no clear evidence of a negative effect of etomidate on the right ventricular systolic function and pulmonary resistance. In addition, some studies confirm the safety of muscle relaxants and volatile agents [21].

Regarding intubation, it is recommended to use a rapid sequence intubation technique (RSI). This method is designed to minimize the chance of pulmonary aspiration. The patient must be adequately pre-oxygenated to prevent desaturation during the period of apnoea after the paralytic agent has been administered (to minimize the risk of gastric content aspiration). The RSI consists of administering an induction agent, establishing the ability to mask ventilate, administrating a neuromuscular blocking agent, and endotracheal intubation once paralysis has been achieved [21, 22].

It is necessary to be prepared for hypotension occurring due to preload dependence during surgery. In order to achieve the proper perfusion and function of the right ventricle, it is recommended to maintain sinus rhythm and blood pressure with vasopressors, avoid systemic vasodilators and correct hypoxemia and acidosis. The use of low dose vasoconstrictors to compensate for the effects of anaesthetic drugs is considered safe and effective [23]. Hemodynamic goals include: a systolic systemic arterial pressure of >90 mm Hg and/or 40 mm Hg above systolic pulmonary arterial pressure (sPAP), a mean systemic arterial pressure of >65 mm Hg and/or 20 mm Hg above the mPAP and cardiac index (CI) of >2.2 l/min/m^2.

Recommendations for mechanical ventilation primarily focus on minimizing pulmonary parenchymal injury. The strategy for lung protection is based on a low tidal volume (5 ml/kg) and plateau pressure of <30 cm H_2O. Optimizing oxygenation involves increasing the fraction of inspired oxygen and avoiding positive end-expiratory pressure, as this increases pulmonary resistance. Positive-pressure ventilation limits the filling of the right ventricle because the elevated intrathoracic pressure restricts venous flow into the thorax and consequently reduces cardiac output [21]. The use of intra-operative pulmonary catheter monitoring in patients with PH undergoing NCS is not recommended. In patients with severe PH, an arterial line should be used to monitor blood pressure [24].

In summary, the primary prerequisite factor for safe surgical operation of patients with PAH is the maintenance of an adequate systemic perfusion pressure of >65 mm Hg, which can be achieved by providing a suitable preload (central venous pressure of about 10 mm Hg) or by using norepinephrine as required [25, 26]. Another important aspect is the rapid identification and treatment of coexisting conditions such as electrolyte disturbances, anaemia, and arrhythmias. Arrhythmias can be treated relatively safely with amiodarone or electrical cardioversion. It is recommended to avoid β-blockers, class I antiarrhythmics and ivabradine [27, 28]. Finally, in order to avoid RVF, it is necessary to prevent hypotension and acidosis, maintain stable blood pressure and volume and provide appropriate treatment for PH.

Infections

Patients with PAH are more likely to develop an infection, especially of the respiratory system. Pneumonia is particularly dangerous. It is associated with a 7% risk of death. Despite the lack of controlled studies, annual influenza vaccinations and pneumococcal vaccinations are recommended to be performed every 5 years. Sztrymf et al. evaluated prognostic factors of acute HF in patients with PAH [29]. The results showed, that simple clinical and biological parameters can be valuable in evaluating the prognosis in the setting of PAH. The occurrence of an infection during hospitalization was associated with poorer outcomes. Infections were significantly more common in patients who died during hospitalization. Another recent retrospective study of patients with PAH showed that infections accounted for 27% of decompensated RVFs [30]. In addition, the overall mortality was high, especially in patients with infection-related episodes (50%) and in "cold-dry" hemodynamic profiles (at 100%).

Moreover, a recent study has demonstrated the role of C-reactive protein (CRP) in predicting the outcome and response to therapy in stable PAH [31]. It is worth noting that in the study by Sztrymf, CRP serum levels were also slightly elevated in patients without an identified infection on admission.

An infection significantly worsens prognosis in patients with PAH and acute HF. In sepsis, dysfunction and damage affect both the right and left ventricles [32]. Due to this poor prognosis, there is a need for efficient preventive, diagnostic and rapid treatment strategies in PAH patients admitted with a suspected infection.

Pregnancy

While pregnancy cannot be considered a disease, pregnancy in patients with PAH is associated with a significantly increased risk of morbidity and mortality. The most common cause of death is right HF and stroke due to intracardiac shunting [33]. Right ventricular insufficiency is largely due to peripartum hemodynamic stress, bleeding complications and the use of general anaesthesia [34,35]. A systematic review of the literature by Pieper et al. on the use of targeted PAH during pregnancy indicates a significant reduction in mortality since the previous review in 1998 (16% vs. 38%) and a further negligible decline in mortality from the 2009 review (16% vs. 25%) [36]. Nevertheless, the current ESC/ERS guidelines recommend, that women with PAH avoided pregnancy [1]. The recommended form of contraception is preparations containing only progesterone. Patients treated with bosentan and on a progestogen-only pill should use additional barrier contraception methods, because as studies show, bosentan may reduce the effects of progesterone [1, 37, 38]. In addition, injectable progestin should be used with great caution, as one meta-analysis showed a two-fold increase in the risk of venous thromboembolism (VTE) in patients using them [39]. Oestrogen containing contraceptives can be considered only in women taking anticoagulation agents due to an increased risk of VTE. Barrier methods should be used as an additional method of contraception [1].

Due to the improved overall quality of life and prognosis, patients with PAH are more likely to become pregnant despite advice to the contrary. Pregnant women should be advised of the high risk involved in the pregnancy and the possibility of abortion should be discussed. Patients who decide to terminate their pregnancy need to have this procedure performed by the 22nd week of gestation. Patient care should be based on the close co-operation of PH specialists with obstetricians, critical care specialists and neonatologists. In addition, regular close follow-up appointments at a PAH centre is recommended. Patients with well-controlled PAH, including specific treatment optimization and a low PVR, have a lower risk pregnancy compared to patients with uncontrolled PAH [40]. Patients who decide to continue their pregnancy should be treated with PAH-specific therapies [1], which are considered safe and effective [34,40,41,42], with the exception of endothelin receptor antagonists (ERA) [37,43–45]. ERAs are contraindicated due to their teratogenic effect [43,45,46]. Currently, there are no clear guidelines on the time and method of delivery for pregnant patients with PAH. Nevertheless, labour on a due date is of crucial importance.

Outcome of pregnancies in 26 patients with PAH were analysed in a multicentre, prospective registry [40]. The data showed an improved prognosis, particularly in well controlled PAH, when compared to previous studies. 16 (62%) pregnancies were successful, wherein 8 of them were long-term recipients of calcium channel blockers. Three women died (12%), while one (4%) required a transplant due to acute RVF.

In another study, mPAP before and in during the early stage of pregnancy was considered a significant prognostic factor for pregnancy outcomes in patients with PAH [47]. Of the 42 women enrolled in the study, 18 decided to terminate their pregnancy. PAH was qualified as severe when the mPAP was >40 mm Hg by RHC or when estimated sPAP was >50 mm Hg on echocardiography. In the group of severe patients, 1 patient died. The severity of symptoms according to the NYHA classification was significantly higher in patients with severe PH. In addition, the women with severe PAH delivered earlier (35.4 vs. 31.5 weeks, $p < 0.005$) and had higher rates of small-for-gestational age infants. A case series on short-term outcomes of three women with PAH, who were treated with pulmonary vasodilator therapy during pregnancy showed, that this specific treatment can be used safely over the course of pregnancy and may improve maternal and fetal prognosis [48]. Patients received intravenous prostacyclin and 5-phosphodiesterase inhibitor. Pregnancies ended with caesarean sections between 28 and 30 weeks of gestation. All patients and their children survived. The birth weight of the children ranged from 1027 to 1300 g. According to the latest ESC registry of pregnant women with PH, which currently includes 151 patients, the majority belongs to left heart disease PH (112 patients). PAH affects 39 patients [49]. The highest rate of mortality is observed in the group with idiopathic PAH (IPAH) (3/7, 43%).

In conclusion, pregnancy in patients with PH is contraindicated as the mortality rate of pregnant women is still high (10–15%), especially in patients with IPAH (43%), despite the progress in PH treatment. Therefore, the proper education of the patient and effective contraception are necessary [50]. If a woman decides to continue her pregnancy, careful monitoring, specific treatment optimization, and close co-operation with an obstetrician are required.

Summary

In order to improve prognosis of PAH patients in all high-risk conditions it is necessary to reliably assess the severity of the disease and optimize specific treatment. It is very important to avoid conditions, that worsen the prognosis of patients with PAH by preventing infections, sensibly considering all indications for surgery and advocating for effective contraception. Early diagnosis of other high-risk conditions is also of crucial importance. Close cooperation with PAH centres is recommended.

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