Perioperative management of pulmonary hypertension during lung transplantation (a lesson for other anaesthesia settings)☆

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Abstract Patients with pulmonary hypertension are some of the most challenging for an anaesthesiologist to manage. Pulmonary hypertension in patients undergoing surgical procedures is associated with high morbidity and mortality due to right ventricular failure, arrhythmias and ischaemia leading to haemodynamic instability. Lung transplantation is the only therapeutic option for end-stage lung disease. Patients undergoing lung transplantation present a variety of challenges for anaesthesia team, but pulmonary hypertension remains the most important. The purpose of this article is to review the anaesthetic management of pulmonary hypertension during lung transplantation, with particular emphasis on the choice of anaesthesia, pulmonary vasodilator therapy, inotropic and vasopressor therapy, and the most recent intraoperative monitoring recommendations to optimize patient care.

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Manejo perioperatorio de la hipertensión pulmonar durante el trasplante pulmonar
(Una lección para otros escenarios anestésicos)

Resumen La presencia de hipertensión pulmonar en el paciente quirúrgico constituye un reto para el anestesiólogo, dado que se asocia con una elevada morbilidad y mortalidad debido a lo frecuente del fallo del ventrículo derecho y colapso circulatorio. El trasplante pulmonar es la última opción terapéutica en los pacientes con insuficiencia respiratoria terminal. Estos pacientes representan un reto para el anestesiólogo siendo la hipertensión pulmonar el más importante. El propósito de esta artículo es la revisión del manejo anestésico de la hipertensión pulmonar durante el trasplante de pulmón, con especial énfasis en la elección del tipo de

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Introduction

Lung transplantation is the only option for mid-term and long-term survival in patients with terminal respiratory failure. Survival rates vary according to the reason for transplantation, but the rate usually exceeds 80% one year and 50% five years after transplantation. Pulmonary hypertension (PH) is a common complication associated with almost all the causes of chronic respiratory failure that are indications for transplantation (emphysema, interstitial pulmonary disease, chronic obstructive pulmonary disease, sarcoidosis, etc.). Idiopathic PH is also an indication for transplantation when vasodilator treatment (calcium channel blockers, endothelin receptor antagonists, phosphodiesterase inhibitors, prostanooids) fails. The overall incidence of severe PH in patients on the lung transplant waiting list has been estimated to be 25–45%.

During the surgical procedure for lung transplantation, PH becomes more evident after clamping of the pulmonary artery for removal of the native lung since all the cardiac output (CO) must circulate through the pulmonary vascular bed of the remaining lung. This may result in right ventricular (RV) failure and the need to initiate cardiopulmonary bypass (CPB), which entails a longer surgical time, greater transfusion requirements, the release of inflammatory mediators, a longer time on postoperative mechanical ventilation, a longer hospital stay, a higher primary graft dysfunction rate and, for some authors, a higher mortality rate. A literature review focused on the perioperative management for lung transplantation, and pathophysiology and treatment of PH. For this, a search was performed in PubMed/Medline using the terms: "anaesthesia and lung transplantation" "pathophysiology of pulmonary hypertension" "pulmonary hypertension therapy" "right ventricle failure" "iloprost" "prostacyclin"

Defining pulmonary hypertension

Pulmonary hypertension has been defined as an increase in mean pulmonary arterial pressure (mPAP) to 25 mmHg or greater at rest assessed by right heart catheterization. Table 1 gives different haemodynamic definitions according to various combinations of values of pulmonary wedge pressure (PWP), pulmonary vascular resistance (PVR), and CO. During preoperative assessment, it is important to establish the transpulmonary gradient (TPG) (mPAP-mPWP). A TPG equal to or greater than 12 mmHg implies a disproportionate increase in post-capillary or reactive PVR, and fixed structural obstructive remodelling of the pulmonary artery resistance vessels. It is important to bear this in mind when indicating single or double lung transplantation, since in single lung transplantation there will be no improvement in PH after the procedure. The World Health Organization classification for PH is shown in Table 2

Surgical times in lung transplantation

Onset times for PH in the course of transplant surgery are well-defined, but the time of onset will vary according to the disease and the individual patient. Patients with pulmonary arterial hypertension (PAH), will by definition present with PH, since this is the indication for transplantation. In these cases, most specialists will indicate initiation of CPB from the start and, although lung transplantation can be performed without this support, the risk of acute RV failure and/or postoperative multiple organ dysfunction secondary to a sustained low CO makes initiation of CPB mandatory. The presence of severe PH in the other groups indicated
Table 2  The World Health Organization Classification of PH.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PAH</td>
<td>Idiopathic. Heritable</td>
</tr>
<tr>
<td>1’</td>
<td>Pulmonary veno-occlusive disease/haemangiomatosis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PH due left heart disease</td>
<td>Sist/Diastolic/Valvular Disease</td>
</tr>
<tr>
<td>3</td>
<td>PH due lung disease</td>
<td>Obstructive/Interstitial Disease</td>
</tr>
<tr>
<td>4</td>
<td>Chronic thromboembolic PH</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PH with unclear/multifactorial mechanism</td>
<td>Sarcoidosis</td>
</tr>
</tbody>
</table>

PAH, pulmonary arterial hypertension; PAH, arterial pulmonary hypertension; PH, pulmonary hypertension.

for transplantation varies, but the highest incidence corresponds to patients with interstitial disease and some group 5 patients. However, patients with mild-moderate PH may experience severe increase in PAP during different phases of surgery.

One lung ventilation (OLV)

Initiation of OLV increases PAP due to lung collapse and the activation of hypoxic pulmonary vasoconstriction (HPV). Hypoxaemia and a significant increase in PVR will develop if the shunt is refractory to therapeutic measures such as high fraction of inspired oxygen (FiO₂), continuous positive airway pressure (CPAP) in the non-dependent lung.

Pulmonary artery (PA) clamping

Ligation or clamping of the PA improves oxygenation during OLV but increases PAP, which can lead to acute RV failure. This is less likely to occur in patients with mild-moderate PH, particularly if they have a degree of RV hypertrophy. Patients with severe PH cannot tolerate PA clamping and in most cases will require CPB. Prior to PA ligation, a 5-min clamping test is necessary to predict haemodynamic response. The presence of one or more of these variables: hypotension (>90mmHg), low CO (Cl < 2L/min/m²), low SvO₂ (<60%), oliguria (>20ml/h), hypoxaemia (Sat O₂ < 90%), and/or acidosis (pH < 7.2), will force to enter in CPB.

Left atrial clamping

During lung implantation, the left atrium must be clamped in order to suture both donor and recipient atrial cuffs. This will cause a decrease in atrial volume and lead in a retrograde manner to an increase in pulmonary venous pressure, pulmonary capillary pressure, and pulmonary arterial pressure.

Lung reperfusion

In patients with pre-existing PH, lung transplantation usually results in a significant decrease in PAP. However, development of primary graft dysfunction leads to hypoxaemia and increased PVR. Each of these phases will require decisions to be taken in order to reduce the PVR and to optimize gas exchange, CO and systemic perfusion pressure.

Anaesthetic management

Anaesthetic management during lung transplantation is a challenge for the anaesthesia team, especially in patients with PH. Rapid and constant decision-making are determined by clamping and unclamping of the large vessels, ventilatory difficulties and their gasometric consequences, and the compression of the large vessels and heart chambers by the surgeon’s hands. In PH patients, several mechanisms are implicated in right-side heart failure.

Induction of anaesthesia

Anaesthesia induction in patients with PH is a high risk procedure. These patients have a fixed systolic volume (SV), and high systemic vascular resistances (SVRs) to maintain normal blood pressure. Most intravenous anaesthetic agents have myocardial depressant properties and reduce arterial and venous resistances, which leads to a decrease in RV preload, systemic arterial pressure and coronary perfusion. Because hypoxia and hypercapnia increase PVR, ventilation and oxygenation should be controlled at all times. If the appropriate measures are not taken, anaesthetic induction could result in a catastrophic event (systemic hypotension, low CO, RV ischaemia and failure, and cardiac arrest). Preoxygenation is required for at least 5 min to optimize oxygen saturation prior to induction of anaesthesia. Some patients will not comply with fasting (full stomach) and will require rapid sequence induction. There is no clear evidence showing that any agent is preferable for induction, even drugs without myocardial-depressant or systemic effects may be poorly tolerated by PH patients. Among i.v agents, etomidate is an ideal agent for its minimal haemodynamic effects. Our team uses etomidate (0.2mg/kg) with low doses of midazolam (0.1mg/kg), and fentanyl (150–200µg). Prior to induction, we always administer a crystalloids overload (250–300ml). However, approximately 10–20% of patients will develop reversible hypotension, which usually responds well to vasopressor therapy (phenylephrine, nor-epinephrine).

Induction of anaesthesia should not commence in patients with severe PH without a surgeon being present in the operating room. If severe hypotension or cardiovascular
arrest develops, attending surgeons could be required to institute emergency CPB via femoral cannulation.

Anaesthetic maintenance

After anaesthesia induction and double lumen orotracheal intubation, mechanical ventilation is started. We use always left double lumen tubes to avoid right upper lobe bronchus obstruction. Mechanical ventilation induces changes in intrapleural or intrathoracic pressure and lung volume, which can independently affect the key determinants of cardiovascular performance: atrial filling or preload, impedance to venicular emptying or afterload, heart rate, and myocardial contractility. Changes in intrathoracic pressure are transmitted to the intrathoracic structures: namely, the heart, pericardium, and the great arteries and veins. Intermittent positive pressure ventilation produces an increase in intrathoracic pressure during inspiration and, therefore, in right atrial pressure and, if a positive end expiratory pressure (PEEP) is added, these pressures will remain greater than atmospheric pressure throughout the respiratory cycle. In PH patients, these changes can be critical, and it is important to select the appropriate respiratory settings (obstructive or restrictive pattern).

Balanced general anaesthesia is the choice in lung transplantation. Total intravenous anaesthesia (propofol) is not indicated by effects on SVR and contractility. Volatile agents can lead to a dose-dependent depression of cardiac contractility and a reduction in SVRs that may be problematic. Desflurane (but not sevoflurane) inhibits endothelium-dependent relaxation by inhibiting adenosine triphosphate sensitive potassium channels and appears to antagonize the pulmonary vasodilatory effects of other medications and should be therefore avoid. Although all volatile anaesthetics reduce PVRs and SVRs, sevoflurane causes a larger decrease in mPAP than isoflurane with similar myocardial depression. Nitrous oxide (N2O) has minimal effects on haemodynamics but can still depress myocardial contractility. In adults, N2O increases PVRs, especially after CPB surgery. Interestingly, in children, the PVRs did not increase even in the presence of PH. In any case, the use of N2O limits FI02 and should not be used in lung transplant surgery. As an important component of a balanced anaesthesia, all kinds of opiates can be used (fentanyl, sufentanil, alfentanil, remifentanil), and titration is more important than opiate type.

Monitoring

Routine monitoring for pulmonary transplantation includes pulse oximetry, electrocardiography, invasive arterial blood and central venous pressure (CVP) and pulmonary artery pressures. Following tracheal intubation, capnography, inhalation agent monitoring, respiratory monitoring (airway pressures, respiratory volumes, static and dynamic elastances, etc.) and central temperature monitoring are started. We usually cannulate the left radial and femoral arteries: the radial artery for intermittent blood gas samples and the femoral artery for blood pressure. Pulmonary artery catheter (PAC) monitoring is an essential tool during lung transplantation. Continuous monitoring of PAP is essential for intraoperative therapy. In addition to continuous measurement of mPAP, SVRs and PVRs and CO may act as useful indicators for controlling volume replacement and the administration of vasodilating or inotropic medication. The CVP waveforms allow rapid diagnosis of tricuspid regurgitation (tall “v” waves). Oxygen mixed venous saturation (SvO2) can be used as a reliable marker of global tissue perfusion.

A decrease in SvO2 may be caused by (a) a decrease in oxygen saturation (SaO2), (b) a decrease in CO, (c) a decrease in haemoglobin level, and (d) an increase in oxygen consumption. If SaO2, haemoglobin, and oxygen consumption do not change, there will be a direct relationship between SvO2 and CO. Since PWP loses nearly all of its value in patients with severe lung disease during mechanical ventilation, we use a continuous CO catheter equipped with fast-response termistor (around 50 ms). This type of PAC allows semicontinuous measurement of RV ejection fraction (RVEF), RV end-diastolic volume (RVEDV), and RV end-systolic volume (RVESV).

Fluid management of PH patients is often difficult, as both hypovolemia and hypervolemia can have detrimental effects on RV function, blood pressure, organ perfusion, and graft failure. Dynamic variables like pulse pressure variation and stroke volume variation do not predict volume responsiveness in this context (open thorax, RV failure, high alveolar pressures). Then we have to use static variables (PVC, PWP, RVEDV) and TEE to RV preload optimization.

Transoesophageal echocardiography (TEE) is an essential tool during lung transplantation for patients in the late stages of the disease and with existing right-sided heart failure. Pulmonary artery catheterization and TEE are the methods for appropriate intraoperative monitoring of right-heart function and visualization of the therapy effects if this is required. There is a strong consensus that TEE should be used during lung transplantation. Benefits of TEE during lung transplantation include real-time visualization of cardiac function and structure, early identification of RV failure, immediate evaluation of pharmacologic interventions, exclusion of significant air emboli and assessment of pulmonary vascular anastomosis and foramen ovale patency (PFO). It may be extremely useful in determining the urgent need for CPB.

In the presence of PH, TEE allows optimization of preload and inotropic support by continuous monitoring of RV function. Enlargement of the RV with an underfilled left ventricle, a paradoxical leftward shift of the septum, right-to-left shunt across a PFO, severe tricuspid regurgitation and decreased tricuspid annular plane systolic excursion (TAPSE) are some of the echocardiographic signs of severe RV deterioration in the perioperative setting. An important issue in lung transplantation that is frequently overlooked is whether or not the patient has a PFO. Such patients are at risk of right-left shunt, leading to hypoxia and systemic embolism. The factors determining the clinical significance of PFO include its size, the pressure gradient between the right atrium and left atrium, and the direction of inferior vena cava flow. After transplantation, an unexplained poor gas exchange or pulmonary oedema might be due to limited pulmonary venous drainage at the anastomosis site. Evaluation by TEE and prompt detection can result in a
surgical solution before the patient leaves the operating theatre.

Pulmonary hypertension crisis

The most important requirement for intraoperative management and maintenance of anaesthesia is to avoid anything that could increase RV afterload or decrease RV contractility, as both factors will ultimately lead to ischaemia and right-sided heart failure. As one of the strongest inducers of pulmonary vasoconstriction is hypoxia, inspiratory oxygen administration should be set to a sufficiently high level (FiO₂ 0.6–1.0) to minimize the risk of oxygen desaturation. This treatment can be supported by carefully performed recruitment manoeuvres to largely eliminate inadequate ventilation-perfusion ratios. Intraoperative low-tidal-volume ventilation (6–8 ml/kg) offers benefits over “conventional” pressure-controlled ventilation with a “high-tidal-volume” (10–12 ml/kg), but it is important to avoid alveolar over-inflation in PH patients. This is important in patients with obstructive lung disease or emphysema, in whom a high tidal-volume and a high respiratory rate lead to dynamic hyperinflation (auto-PEEP) and the aggravation of pre-existing PH. As with hyperinflation, atelectasis lung induces increases of RV afterload. So we must try to place the lung near to functional residual capacity in order to reduce PVR. Normocapnia must be a goal since, in addition to hypoxia and acidosis, hypercapnia worsens PH. Usually this goal is difficult to obtain in patients with terminal lung disease.

Intraoperative management should ensure that depth of anaesthesia and analgesia is always sufficient, as stress and pain during awareness may contribute to pulmonary vasoconstriction. Furthermore, intraoperative “standard measures” also include adequate temperature management, since hypothermia and shivering can considerably increase pulmonary pressure and should, therefore, be strictly avoided. Intraoperative fluid therapy should also be carried out rather restrictively and in a targeted manner, with adequate haemodynamic monitoring to optimize RV preload. In general, PH patients should be considered to have low arterial pressure as a result of their disease and the specific therapy, and the possibilities for compensation are limited by right-sided heart failure. If an increase in PAP occurs in the intra- or post-operative period and cannot be controlled by the standard measures, specific medication should be initiated immediately to reduce RV afterload and thus the risk of right-sided heart failure. Pulmonary hypertension crisis is a critical situation since a sudden increase in PVR may lead to severe RV failure, systemic hypotension, low RV coronary perfusion, and circulatory shock with a high risk of cardiac arrest (Fig. 1).

The normal pulmonary circulation is a high-flow low-pressure system. Unlike the left ventricle (LV), the thin-walled RV tolerates acute increases in afterload poorly, which may lead to acute distension, with a resulting increase in oxygen consumption and a reduction in contractility. The dilated RV, together with paradoxic intraventricular septal movement, leads to a reduction in LV filling, CO, and oxygen delivery. The principle of ventricular interdependence is important in order to explain the decreased LV CO seen during increased RV pressure or volume overload. Also, because of RV/LV interactions, LV filling may depend on atrial contraction to a significant extent so that the LV may tolerate atrial fibrillation and vasodilating therapy poorly. Perfusion of the right coronary artery is usually dependent on a pressure gradient between the aorta and RV, which, in the setting of increased RV afterload and decreased coronary blood flow, may result in RV ischaemia, with further severe haemodynamic decomposition. In acute-chronic RV pressure overload (as in patients during lung transplantation), the already hypertrophied RV tolerates much higher pressures before decomposition, although the ability of the RV to increase CO in chronic PH may be restricted by its relatively “fixed” afterload. During lung transplantation, the commonest cause of increased RV afterload is an increase in PVR. Specialists learning lung transplantation management should bear in mind the PVR formula, PVR = 80 × (mPAP – PWP)/CO. In patients with a “fixed” PVR, the PAP value is mainly dependent on CO. In these cases, a decrease in PAP does not always derive from an improvement in PVR but from a reduction in CO. In any case, it is vital to avoid a PAP value greater than the systemic pressure because, if this occurs, cardiovascular collapse is imminent.

General management of PH (Table 3)

In the management of PH patients, a series of factors should be borne in mind that can increase PAP and which, either as preventive measures or as therapeutic tools, constitute the cornerstones of the general management of PH patients in the perioperative period of lung transplantation.

<table>
<thead>
<tr>
<th>Table 3 Basic principles in pulmonary hypertension therapy.</th>
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<tbody>
<tr>
<td>Moderate hyperventilation (PCO₂ target 30–35 mmHg)</td>
</tr>
<tr>
<td>Normothermia</td>
</tr>
<tr>
<td>“Luxury Oxygenation” (High FiO₂)</td>
</tr>
<tr>
<td>High transfusion threshold</td>
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<tr>
<td>Avoidance bradyarrhythmias and tachyarrhythmias</td>
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<tr>
<td>Avoidance of systemic hypotension</td>
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<tr>
<td>Treatment of metabolic Acidosis (pH &gt; 7.4)</td>
</tr>
<tr>
<td>Avoidance hypovolemia, “goal-directed” fluid and volume therapy with haemodynamic monitoring</td>
</tr>
<tr>
<td>Lung near to Functional Residual Capacity (non atelectasis, non hyperinflation)</td>
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</table>

Hypoxaemia

As mentioned earlier, hypoxaemia, results in a significant increase in PAP by inducing HPV. The increase in PVRs is not linear, but exponential when partial PaO₂ falls below 60 mmHg. In contrast, hyperoxia is a notable pulmonary vasodilator.

Hypercapnia

Hypocapnia is a potent pulmonary vasoconstrictor. Its mechanism is twofold: on the one hand, it induces
respiratory acidosis, which itself raises PVRs, and on the other, induces a hyper adrenergic state by releasing endogenous catecholamines that stimulate pulmonary vasocostriction. One goal in the management of PH patients is to achieve normocapnia, which is sometimes difficult given the limited functional respiratory reserve of the patients. In contrast, hypocapnia has beneficial effects on PVRs and moderate hyperventilation (pCO2 30–35 mmHg) is a valuable therapeutic goal.

Acidosis

Whether respiratory or metabolic, is a potent stimulant of pulmonary vasculature, raising PVR and PAP. Administration of bicarbonate or tromethamine (THAM) should be considered with the therapeutic aim of achieving a pH of 7.4–7.45.

Balanced anaesthesia

Pain or superficial anaesthesia may lead to a severe increase in PAP. On the other hand, an excessively deep anaesthesia may have catastrophic consequences both through a decrease in SVRs and through depression of myocardial contractility.21

Haemoglobin (Hb)

Anaemia is poorly tolerated in PH patients because their limited CO prevents the compensation necessary to maintain adequate oxygen transport by increasing CO. During lung transplantation our team proceeds to transfusion when the Hb level falls below 9–10 g/dl.

Cardiac rhythm

During lung transplant surgery, especially during manipulation of the left atrium and pulmonary veins, the patient may go into atrial fibrillation. Usually the loss of atrial contraction on ventricular filling causes a 20% reduction in CO. This arrhythmia is very poorly tolerated by patients with RV dysfunction, and electrical or chemical cardioversion should be achieved as quickly as possible. Patients with severe PH have a fixed stroke volume with the result that bradyarrhythmias are generally poorly tolerated.

Systemic vascular resistances

The existence of a more or less fixed stroke volume means that the PH patient maintains arterial pressure at the expense of high SVRs. A decrease in SVRs (vasodilators) will result in a lowering of arterial pressure with potential catastrophic consequences. The fall in arterial pressure reduces coronary perfusion (remember that the RV, as a low pressure chamber, is perfused both in systole and in diastole) resulting in ischaemia, especially in a hypertrophic RV (chronic PH). Similarly, the decrease in SVRs results in reduced LV afterload, with a consequent fall in LV end diastolic pressure, is favoured by the displacement of the septum (ventricular interdependence) in the presence of high RV end diastolic pressures.22,23

Temperature

Hypothermia is a factor with well-known vasoconstriction effects on pulmonary vasculature though the adrenergic pathway. It is important to maintain normothermia throughout the procedure.
Inotropic and vasopressor therapy

Sympathomimetic inotropes (Dopamine, Dobutamine)

Desirable cardiac β₁ effects at lower doses may be offset by chronotropic effects precipitating tachyarrhythmias, as well as worsening pulmonary vasoconstriction at higher doses through α-agonism. Arterial hypotension may result from adrenergic agents and also with phosphodiesterase (PDE) inhibitors. Dobutamine also tends to increase the heart rate and CO, has a better profile than dopamine, and does not increase PVR at doses up to 10 μg/kg/min. At doses between 5 and 10 μg/kg/min it can decrease PVR and increase CO in a dose-dependent manner. It has a synergistic effect with NO in PH patients. Its effects on heart rate (tachycardia), myocardial oxygen consumption, SVR, limit its utility in RV dysfunction and associated vasopressor therapy is usually required. Dopamine increases CO, although it causes mild tachycardia and can increase PVR/SVR ratio. Therefore, it is not the ideal inotrope in the PH setting.

Isoproterenol is primarily a β₁ and β₂-adrenergic agonist that has historically been used to treat PH during surgery. Because it is a stronger chronotropic agent than dobutamine, its use has been limited by the induction of arrhythmias and the lack of effect on PAP.

Type III phosphodiesterase inhibitors PDEIII (inodilators)

Although dobutamine can be considered an inodilator because it increases myocardial contractility simultaneously causing systemic and pulmonary vasodilation, this term is reserved for PDE III inhibitors. PDE III inhibitors usually activate intracellular cyclic adenosine monophosphate (cAMP) and, therefore, increase cAMP and augment myocardial contractility (and CO) while dilating the vasculature. Several selective PDE III inhibitors are known: enoximone, milrinone, and amrinone. Milrinone is the most frequently used and has been shown to reduce PAP and augment RV function in PH patients. The influence of milrinone on PVR appears to be more pronounced than the reduction in SVR, which, together with a positive impact on myocardial contractility, makes it suitable for administration even in unstable circulatory situations. Mild tachycardia and arterial hypotension are the most deleterious effects. In our experience, tachycardia and atrial fibrillation are less frequent with milrinone than with dobutamine in the lung transplantation setting. We do not use the bolus dose of milrinone and start with infusion in order to avoid the systemic effects.

Levosimendan

Is considered another inodilator. Levosimendan sensitizes tropon-C to calcium and selectively inhibits PDE III, improving diastolic function and myocardial contractility without increasing oxygen consumption. It also acts as a vasodilator through calcium desensitization, potassium opening, and PDE III inhibition. Levosimendan leads to a rapid improvement in haemodynamics, including reduced PVR in patients with decompensated heart failure, resulting in a beneficial effect on RV efficiency. Although levosimendan has shown good results in biventricular failure, with an improvement in RV-PA coupling, its role in acute RV failure needs to be clarified.

Epinephrine

Although commonly used to improve CO and to increase SVR in hypotensive patients in the ICU, epinephrine, a potent α- and β-adrenergic agent, has not been studied in the setting of PH. However it is considered a rescue agent in acute RV failure, and could be interesting drug at low doses (0.05–0.4 μg/kg/min).

Norepinephrine (NE)

An essential goal in PH management is to maintain systemic blood pressure above pulmonary arterial pressures, thereby preserving right coronary blood flow. Unlike left coronary artery perfusion, which occurs only during diastole (as aortic pressure exceeds LV pressure only during this period), right coronary artery perfusion usually occurs throughout the cardiac cycle, predominating in systole. It is understood that, as PVR approaches SVR, coronary perfusion will decrease, and if PVR exceeds SVR, coronary filling will occur only in diastole (in this situation diastolic perfusion can also be affected by the increase of end-diastolic pressure). By increasing aortic root pressure through use of vasopressors in the setting of increased RV afterload, RV ischaemia can be reversed. Vasopressors will, however, inevitably have direct effects on the pulmonary circulation as well as myocardial effects. When used in animal and human studies of both acute and chronic PH, NE has been shown to increase mPAP and PVR (stimulation α₁- and α₂-adrenergic receptors), although the potential adverse effects on PVR are likely to occur only at high doses (NE at doses less than 0.5 μg/kg/min do not increase PVR). However, unlike phenylephrine, NE maintained or improved CO in patients with PH. Importantly, NE is positively inotropic through β-1 receptor agonism, thus improving RV/PA coupling, CO, and RV performance. Selective infusion of NE into the left atrium, combined with prostaglandin E1 administration into the right atrium, has been useful in weaning patients with acute PH from CPB. There is no evidence that such selective infusion is beneficial in other patient populations. In patients with chronic PH, NE reduces the PVR/SVR ratio, although it may not improve CO, which may relate to the “fixed” PVR elevation.

Phenylephrine (Ph)

Is an α₁-adrenergic agent and a powerful arteriolar vasoconstrictor that can improve RV coronary perfusion. However, phenylephrine increases mPAP and PVR and decreases CO, thus worsening RV pressure overload in patients with chronic PH.
Vasopressin (VP)

Is a weak nonadrenergic vasopressor (via the vasopressinergic (V1) receptor) that is believed to be a systemic vasoconstrictor and a selective pulmonary vasodilator, a property that manifests clinically as a reduction in PVR/SVR ratio. Vasopressin has a diuretic effect in vasodilatory shock, reduces the heart rate, and induces fewer tachyarrhythmias than NE. Vasopressin may cause dose-related adverse myocardial effects at infusion rates exceeding 0.4 U/min, or even above 0.08 U/min in cardiogenic shock, which is probably related to direct myocardial effects, including coronary vasoconstriction. Some groups use vasopressin routinely during lung transplantation at doses up to 0.02–0.03 U/min. 35

Extracorporeal support

In unplanned cases, the decision to use CPB is made if the patient (1) does not tolerate one lung ventilation (either hypoxia or refractory hypercarbia), (2) does not tolerate clamping of a pulmonary artery (right ventricular failure), or (3) has other refractory haemodynamic instability. In bilateral lung transplantation, if high pulmonary artery pressures do not fall after the first side is reperfused, CPB also be commenced to protect the graft from pulmonary hypertension which can contribute to primary graft dysfunction. Lately many centres (including ours) have now adopted ECMO when CPB is required during transplantation procedure instead of full CPB. Some of the advantages of ECMO over CPB include a simpler set-up, significantly lower anticoagulation requirements (usual activated clotting times of 180–220 s), decreased transfusion requirements, less proinflammatory activation, and the possibility to continue ECMO into the post-operative period to protect the graft in patients with PH for example. One recent study compared ECMO with CPB in lung transplantation and demonstrated significantly less complications and better survival for the ECMO group.

Venovenous ECMO becomes the device of choice in respiratory failure refractory to mechanical ventilation, but this device not support circulatory status. Arteriovenous ECMO allow not only respiratory but also circulatory support, this is of importance when lung failure is present with PH and RV failure. Arteriovenous ECMO is the most common extracorporeal support for lung transplantation surgery refractory to standard medical therapy. Cannulation can be peripheral, the most common (artery and femoral vein) or central (right atrial/pulmonary artery and aorta). 31,32

Vasodilator therapy in PH

The RV is usually unable to generate a mPAP greater than 40–50 mmHg in the setting of acute severe high PVR. In contrast, in severe chronic PH, the RV dilates and hypertrophies with gradual RV dysfunction. Treatment of pulmonary afterload with pulmonary vasodilators includes a wide array of drugs classes, which mainly exert their effects on pulmonary vasculature in one of three ways. 31–39 (Table 4)

- Direct cAMP-dependent mechanism: the agent occupies the receptor coupled to adenylate cyclase leading to cAMP production, thus resulting in the activation of cAMP-dependent protein kinase, which, in turn, promotes smooth muscle relaxation. Drugs that increase cAMP by stimulating adenylyl cyclase include β-adrenergic agonists (e.g. isoproterenol, dobutamine), nitrovasodilators (e.g. nitroglycerin, nitroprusside), prostanoids and calcium channel blockers.

- Indirect or cyclic guanosine 3′–5′ monophosphate (cGMP) dependent mechanism: these drugs exert their pulmonary vasodilator effects through activation of cytoplasmatic guanylate cyclase, leading to an increase in cGMP. This further activates a family of cGMP-dependent protein kinases, resulting in relaxation of the vascular smooth muscle. NO is the classical drug that stimulates cGMP. Other drugs include the PDE III derivatives and PDE type V such as sildenafil or tadalafil. PDEs also increase levels of cAMP by inhibiting its breakdown.

- Endothelin receptor antagonists (ERAs). Endothelin causes vasoconstriction and cell proliferation via receptors on smooth muscle cells. Endothelin receptor A (ETA) promotes vasoconstriction and cell proliferation, whereas receptor B (ETB) is involved in clearance of endothelin as well as NO release from the endothelium. Bosantan blocks ETA and ETB receptors, whereas ambrisentan and sitaxsentan are selective ETA antagonists.

Some vasodilator drugs have limitations, especially in intravenous use: (a) systemic hypotension is due a non-selective pulmonary vasodilator effect, and arterial vasodilator effect mostly occurring at doses that do not produce adequate pulmonary vasodilation, (b) decreased contractility due to hypotension or negative inotropic effects, (c) hypoxaemia due to attenuation of HPV by vasodilation both injured and intact pulmonary vessels, thereby altering ventilation-perfusion ratio.

Intravenous nitropridilators (nitroglycerin, nitroprusside)

They are traditionally non-selective and non-specific pulmonary vasodilators. Both agents decrease PVR, but the concomitant and very often dramatic decrease in SVR limits their clinical use. Both agents also inhibit HPV, resulting in an increase in venous admixture and a reduction in PaO₂. 35,36

Inhaled nitropridilators

NO donors can be inhaled in order to avoid the systemic effects. Inhaled nebulized nitroprusside produces a selective reduction of hypoxia-induced PH in piglets, but has a slower onset than NO. Inhaled nitroglycerin (2.5 μg/kg/min during 10 min, 250 μg/ml NaCl 0.9%) cause pulmonary vasodilation via NO metabolism. In children with PH related to congenital heart disease, inhaled nitroglycerin decreases PAP and PVR, without significant changes in heart rate, PWP, or systemic arterial pressure. Additionally, inhaled nitroglycerin has been shown to be more beneficial than iv nitroglycerin for PH management. Citrulline, an NO precursor, also represents a possible future treatment for PH. 39
Table 4  Vasodilator therapy for use in pulmonary hypertension.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>50 μg/kg bolus (optional), followed by 0.25–0.5 μg/kg BW/min</td>
<td>Can induce hypotension</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2–5 μg/kg/min</td>
<td>Tachycardia, arrhythmias</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>4–10 ng/kg/min</td>
<td>Hypotension, antiplatelet</td>
</tr>
<tr>
<td>Nitropresside</td>
<td>0.2–0.3 μg/kg/min</td>
<td>Severe Hypotension, hypoxaemia</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>2–10 μg/kg/min</td>
<td>Severe hypotension, hypoxaemia</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>10–20 mg over 10 min (80 mg over 40 min)</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Per Os</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>20–40 mg/4–6 h</td>
<td>No association NO donors</td>
</tr>
<tr>
<td>Inhaled (Pulmonary selective vasodilators)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>10–50 ng/kg/min</td>
<td>Headache, facial flushing</td>
</tr>
<tr>
<td>Milrinone</td>
<td>2–4 mg (diluted 10–15 ml NaCl 0.9%) for 10 min</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>2.5 μg/kg/min (10 min) (250 μg/ml NaCl 0.9%)</td>
<td></td>
</tr>
<tr>
<td>Iloprost</td>
<td>10–20 μg diluted 2 ml for 10–15 min (ultrasonic nebulizer)</td>
<td></td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>20–40 ppm continuously</td>
<td>Methemoglobinemia, nitric dioxide production, PH rebound, economic cost</td>
</tr>
</tbody>
</table>

Common drugs for intra- and postoperative therapy in pulmonary hypertension Reduction of right-ventricular afterload Intravenous vasodilators

Inhaled nitric oxide (NO)

Inhaled NO (endothelial-derived relaxing factor) is a selective vasodilator, which reduces PVR in proportion to the level of initial vascular tone. When delivered as a gas, exogenous NO diffuses into the adjacent vascular smooth muscle resulting in relaxation. After diffusing into the intravascular space, NO rapidly binds to haemoglobin forming nitrosyl haemoglobin, which is rapidly oxidized to methaemoglobin and subsequently excreted by the kidneys. Inhaled NO is particularly attractive when the goal is to dilate the pulmonary arterial bed without lowering systemic blood pressure because it is selective for the pulmonary vascular bed when delivered as a rapidly acting gas. NO is generated from L-arginine and oxygen through the activity of specific NO synthases; its effects include not only vasodilation but also bronchodilation, anti-inflammation, and anti-proliferation. Long-term use of inhaled NO is limited by a very short half-life (NO has a plasma half-life of less than 12 seconds), risk of methaemoglobinemia, and rebound PH with planned or inadvertent discontinuation. Moreover, the interaction of NO and high concentrations of oxygen produces NO2, a significant oxidant. It is very important to monitor NO2 and limit the production to 2 ppm. The maximum increase in CO and lowering of CVP, TPG, and mPAP occur at approximately 20 ppm. In contrast to many inhibitors of HVP, gas exchange is preserved during NO inhalation. PaO2 and HVP may be unchanged or even increased as pulmonary venous admixture is reduced after NO inhalation. The role of NO in cardiac surgery has received considerable attention in recent years. There is a loss of endogenous NO production on CPB, and NO can be considered a replacement therapy that may ameliorate postoperative PH. NO has proved high efficacy in PH treatment in cardiac surgery, neonatal respiratory syndrome, adult distress respiratory syndrome, and heart and lung transplantation.

In lung transplantation, some authors have reported the beneficial effects of NO on ischaemia-reperfusion injury, and speculated a protective effect on primary graft dysfunction. However, this has not been confirmed and others observed no relevant effect of NO on pulmonary oedema, PaO2 or other important pathophysiologic parameters in the postoperative course of lung transplantation.40–43

Prostanoids (eicosanoids)

Clinically used substances commonly referred to as "prostanoids" are, from a chemical standpoint, actually eicosanoids. Eicosanoids include all of the converted products resulting from cyclooxygenases (prostaglandins, thromboxane A2 and prostacyclin) as well as those from lipoxygenases (leukotriene). Prostacyclin, as well as its synthetic derivates mainly exert antithrombotic, vasodilatory, cytoprotective and immunomodulatory effects. Their effects on the vascular system are triggered by the increase of "second messenger" cAMP within the muscle cells; calcium pumps are activated, thereby catalyzing the outward flow of calcium from cytoplasm. The resulting overall situation is one vasorelaxation in the presence of reduced arterial resistance.44

Several prostacyclin analogues have been developed for PH, including epoprostenol (iv), iloprost (iv, inhaled), treprostinil (iv, subcutaneous, inhaled). The agents have differing pharmacokinetic properties and require different drug delivery mechanism, but appear to have similar
pharmacodynamic effects. For PH treatment during perioperative lung transplantation, three drugs are relevant: prostacyclin, epoprostenol and iloprost.45

Prostacyclin (PGI2)

In PH it reduces PVR, increases CO and improves clinical outcome. Potential adverse effects are similar to those of other prostanoids: systemic hypotension, worsening oxygenation, antplatelet effect, headache, flushing, jaw pain, nausea, and diarrhea. Arterial hypotension is the first and most dangerous adverse effect and limits the use of PGI2 in the perioperative period. Intravenous PGI2 may cause marked desaturation in patients with lung disease. However, inhaled PGI2 rapidly improves pulmonary haemodynamics after acute PH. Inhaled PGI2 improves PH with minimal effects on SVR, and can improve oxygenation. This method of administration has been shown to be effective after cardiac surgery (CPB), heart transplantation, adult respiratory distress syndrome, and lung transplantation. Inhaled PGI2 can be administered at increasing doses (2.5, 5, 10, 20, 30 μg/ml via nebulizer) into the ventilator circuit through the inspiratory limb (30–40 ng/kg/min).44–46

Iloprost (IL)

Iloprost is a stable carbacycline analogue of prostacyclin at room temperature, has an elimination half-life of 20–30 min, and can be used at physiological pH levels. It inhibits thrombocyte aggregation and brings about vascular dilatation. No toxic metabolites have been observed during or after IL therapy.47 As with other prostanoids, IV administration is accompanied by various important systemic effects (a lack of pulmonary selectivity).

A controlled study performed in Greece showed that, during the perioperative period after weaning from CPB, inhaled IL (9–20 μg) brought about a reduction in the TPG, and a significant decrease in both the mPAP to systemic arterial ratio and the PVR to SVR ratio while an improvement in RV function was observed on echocardiography.48 During heart transplantation, weaning from CPB may be laborious in the PH and RV dysfunction setting. Inhaled IL can reduce PAP, mPAP to systemic artery pressure ratio, and PVR to SVR ratio, improving RV function. Thus, episodes of PH during heart transplantation can be treated successfully with inhaled IL without side effects or systemic deleterious impact.49 Similar results were found after mitral repair surgery.50 The efficacy of inhaled IL has also been shown during pulmonary thromboendarterectomy and during RV failure after support with LV assistance device.51,52

In lung transplantation, inhaled IL has been used successfully for PH, with studies reporting an improvement in CO, venous and arterial oxygenation, pulmonary pressure, and RV function without systemic hypotension. This approach can allow lung transplantation to be performed without CPB, as is often required in patients with severe PH. Administration of nebulized IL reduced pulmonary pressure and increased CO in treated patients, with no effects on systemic pressure, thus indicating a selective action on pulmonary vasculature. In the past, the short duration of the effect of IL was considered a limitation. However, recent pharmacokinetic and pharmacodynamic studies have shown a remarkable bioavailability for inhaled IL, with plasma levels similar to those attained by the iv route. Although plasma levels decrease 5 min after administration and return to baseline levels after 30 min, the clinical effects on PVR persist up to 40–60 min. This means that a clinically relevant difference exists between the pharmacokinetics and pharmacodynamics. It has been shown that this is due to the fact that most inhaled particles are deposited in the respiratory tract, while only a small percentage is exhaled. Indeed, IL particles retained in the pulmonary perivascular tissue, interstitial spaces and pulmonary artery cells have a longer half-life than systemic IL.53

It is essential that the aerosolized particles should be small enough (median aerodynamic diameter, 3–5 μm) to ensure alveolar deposition. For this reason, IL inhalation requires the use of a special ultrasonic nebulizer. The Aeroneb-Pro (Aerogen, Galway, Ireland) is the device most frequently used in the operating theatre and ICU when the patient is on mechanical ventilation. The dose is usually between 5 and 10 μg in 2–3 ml of nebulized distilled water for 15–30 min and the therapeutic effect lasts 45–60 min.54

Epoprostenol (E)

Is a synthetic prostacyclin and was the first medication approved by the US Food and Drug Administration for PH in 1996. Several controlled and uncontrolled studies have demonstrated the benefit of epoprostenol in idiopathic, congenital heart disease, portal hypertension, HIV, chronic thromboembolic disease, and PH.

Phosphodiesterase-5 inhibitor (PDE-5)

Sildenafil, a potent inhibitor of PDE-5 used for erectile dysfunction, is an effective treatment option for PH. PDE-5 inhibition increases intracellular cGMP and prolong NO vasodilator effects. When sildenafil is used in combination with NO, it has been shown to increase and prolong the haemodynamic effects and prevents rebound vasocostriction when NO is discontinued. Its ability to augment and prolong the haemodynamic effects of other pulmonary vasodilators has been used successfully to minimize rebound PH after inhaled NO discontinuation, weaning from iv vasodilators in patients after cardiac surgery, as well as in chronic PH therapy.

Clinical experience suggests that sildenafil is safe and effective in combination with prostacyclin. The usefulness of sildenafil has been demonstrated in chronic and acute arterial PH, post-cardiotomy PH, LV failure, congestive heart failure, and heart and lung transplantation. In 2010, sildenafil was approved for iv therapy of PH and may, therefore, be an attractive option for the perioperative management of patients who are treated with oral sildenafil. Its effect starts after 10–15 min and lasts 4–6 h.56,57

Combination therapies

As in patients with chronic PH, in surgical patients, several authors have investigated varying combinations of drugs
that act via different pathways. Inhaled IL has been combined with either NO or sildenafil. NO and PGII act via different signalling pathways: NO via guanylyl cyclase and PGII by increasing intracellular cAMP levels. PDE inhibitors, like sildenafil, specifically inhibit PDE-5 and induce pulmonary vasodilation by increasing cGMP levels. NO is the agent most often used for treatment of PH during lung transplantation. Our lung transplantation team always uses sildenafil 40 mg po 20-30 min before anaesthesia induction, and 20 ppm of NO after tracheal intubation and initiation of mechanical ventilation. If PAP during the procedure is not controlled, we add inhaled IL. This association results in a significant decrease in PVR and in PAP, and an improvement of CO and SvO2. In agreement with other authors, we believe that this therapy can avoid CPB-ECMO in lung transplantation and its deleterious effects (bleeding, graft dysfunction, and prolonged intensive care and hospital stay, etc.). However in PAH patients surgery under CPB or ECMO is mandatory.\textsuperscript{50,58-61}

Conclusions

Failure in the at-risk right ventricular can be precipitated by an acute increase in afterload, or ischaemia due to either prolonged hypotension or air embolism. This is encountered during all parts of surgery (induction, after starting OLV, during manipulation of the heart, at pulmonary artery clamping, after reperfusion and with severe early graft dysfunction). RV afterload reduction is the primary treatment goal, vasodilator therapy with NO, or intravenous/inhaled prostanoids are mandatory. Also important are preserving coronary perfusion and biventricular inotropic support. Basic things such as correcting acidosis, hypoxia, hypercarbia, hypothermia, minimizing ventilation pressures can improve pulmonary resistances.

Conflict of interest

The authors declare no conflicts of interest.

References

4. Nakayama M, Kondo U, Murray PA. Pulmonary vasodilator response to adenosine triphosphate-sensitive potassium channel activation is attenuated during desflurane but preserved during sevoflurane anesthesia compared with the conscious state. Anesthesiology. 1998;88:1023-35.