Severe pulmonary arterial hypertension: treatment options and the bridge to transplantation

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ABSTRACT Pulmonary arterial hypertension (PAH) is a rare disease leading to right heart failure and death. Prognosis remains poor, particularly for patients with severe disease, *i.e.* World Health Organization functional class IV. There have been significant improvements in treatment options. Several agents are available that target the three main established PAH disease pathways, and can be combined sequentially or upfront. Strong scientific evidence supports the use of intravenous epoprostenol in severe PAH; however, despite recommendations, many patients do not receive parenteral prostanoids and there is a lack of evidence from randomised clinical trials supporting the value of other PAH medications alone in severe PAH.

Lung transplantation is an important option in patients with severe PAH who have not responded sufficiently to therapy, or who have worsened despite maximal treatment. Bridging techniques are available for patients who worsen while awaiting transplantation. The type of bridging technique used depends on various factors including patient illness severity, physician experience and the anticipated waiting time for transplantation. With the aim to facilitate the treatment decision-making process, herein we review the medical treatment options available for patients with severe PAH, and the bridging techniques that may be used to sustain patients awaiting transplantation.

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Introduction

Pulmonary arterial hypertension (PAH) is a rare disease in which remodelling of the pulmonary vasculature progressively leads to increased pulmonary vascular resistance, right ventricular failure and ultimately death [1]. Severity of disease is determined according to World Health Organization (WHO) functional class. Severe PAH (WHO functional class IV) may encompass patients: 1) presenting in functional class IV (the French PAH registry reported 12% of patients as presenting in functional class IV [2]); 2) not responding adequately and/or not meeting treatment goals; and 3) who progress or deteriorate on maximal therapy. Patients in functional class IV have lower exercise capacity (as measured by the 6-min walking distance (6MWD)), higher right atrial pressure (RAP), lower cardiac index, increased pulmonary vascular resistance index and lower peak oxygen consumption compared with patients in functional class I–III [2, 3]. The prognosis for patients with severe PAH is poor. The French registry (82.6% of patients in functional class III/IV) found that patients in functional class IV at enrolment had a 3-year survival of 38% compared with 80% and 60% for WHO

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functional class I/II and III, respectively [4]. Similarly, a study from the UK (14% of patients in functional class IV) found that, compared with patients in functional class IV, patients in functional class I/II and III had a significantly reduced risk of death (HR 0.3, p=0.007 and HR 0.5, p=0.01, respectively) [5].

The available treatment options for PAH have significantly improved over time, targeting the three main currently established biological signalling pathways in PAH: the endothelin, nitric oxide and prostacyclin pathways [6]. The PAH-specific drug classes include the endothelin receptor antagonists, phosphodiesterase type-5 inhibitors (PDE-5i) or soluble guanylate cyclase stimulators and prostanoids. The updated PAH treatment algorithm following the 5th World Symposium on Pulmonary Hypertension (Nice, France) recommends that when initial monotherapy or upfront combination therapy with PDE-5i, endothelin receptor antagonists, soluble guanylate cyclase stimulators or prostanoids fail, sequential combination therapy, in which there is a stepwise addition of drugs to a patient's current medication regimen, is initiated (I–A). At the same time, eligibility for lung transplantation should be assessed for those patients who remain in functional class III or IV [7]. Assessment for lung transplantation takes several factors into account, including the patient's physical status, organ function and comorbidities [8, 9]. The waiting time for lung transplantation can be lengthy, and patients may suffer acute decompensation while on the waiting list, becoming too ill to withstand the procedure. However, a number of bridging techniques are available to support patients awaiting transplantation.

Overall, the advances in available PAH-specific drug therapies, together with physical therapy, other supportive therapies and advancement of surgical techniques, have improved the prognosis of PAH patients. Data from a number of large registries indicate that survival has improved over time [10]. However, PAH remains a progressive illness, and patients in functional class III who progress to functional class IV have significantly worse survival than those who remain in functional class III or improve to functional class I/II [11]. A study of long-term epoprostenol treatment found that 3-year survival was 47% *versus* 71% for patients in functional class IV compared with functional class III [12]. Here, we review the treatment options in patients with severe PAH, the assessment and selection of suitable patients for lung transplantation and the various bridging techniques available.

Treatment options for patients with severe PAH

Therapeutic strategies: the present and the future

The recently updated PAH treatment algorithm (fig. 1) assigns intravenous epoprostenol the highest grade of recommendation and level of evidence (I–A or B) in functional class IV PAH [7]. The only treatment to show a survival benefit in a landmark short-term randomised controlled trial (RCT) was *i.v.* epoprostenol. A prospective study of 81 patients with idiopathic PAH (IPAH) randomised to receive either *i.v.* epoprostenol in addition to conventional therapy (n=41) or conventional therapy alone (n=40) showed that patients who received epoprostenol had significantly improved survival over 12 weeks (p=0.003) [13]. A meta-analysis of the three RCTs evaluating epoprostenol found that epoprostenol was associated with a 68–70% relative risk reduction for mortality [7].

Other recommended treatments in functional class IV PAH include ambrisentan, bosentan, macitentan, riociguat, sildenafil, tadalafil and the thermostable prostacyclin analogues treprostinil (subcutaneous, intravenous and inhaled) and iloprost (inhaled and intravenous). However, these treatments all have a lower strength of recommendation compared with *i.v.* epoprostenol based on the limited evidence available (IIa–C). Small numbers of functional class IV patients were included in the RCTs investigating these treatments [7]. In general, the proportion included ranged from 1% to 9% (average 3%) [14–22], with the exception of a study of inhaled iloprost (84 (41%) out of 203 in functional class IV) [23].

Combination therapy, in which two or more drugs are used simultaneously to target different pathological signalling pathways, is supported by the PAH treatment algorithm for initial use in functional class IV patients, although with a lower level of recommendation compared with monotherapy (IIB–C). There have been conflicting results from some RCTs evaluating sequential combination therapy. However, goal-oriented treatment with sequential combination therapy has been shown to increase survival [24], and sequential combination therapy has a class I–A recommendation [7]. Addition of imatinib mesylate to the therapy regimen of patients with PAH was recently evaluated in the IMPRES study (Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study) [25]; however, its development has been interrupted due to its poor efficacy/tolerability profile.

Experience with the use of upfront combination therapy is growing [26], and although promising results have been observed with upfront triple-combination therapy in patients in WHO functional class IV and in patients in WHO funtional class III with severe haemodynamic impairment [27, 28], more data are needed.

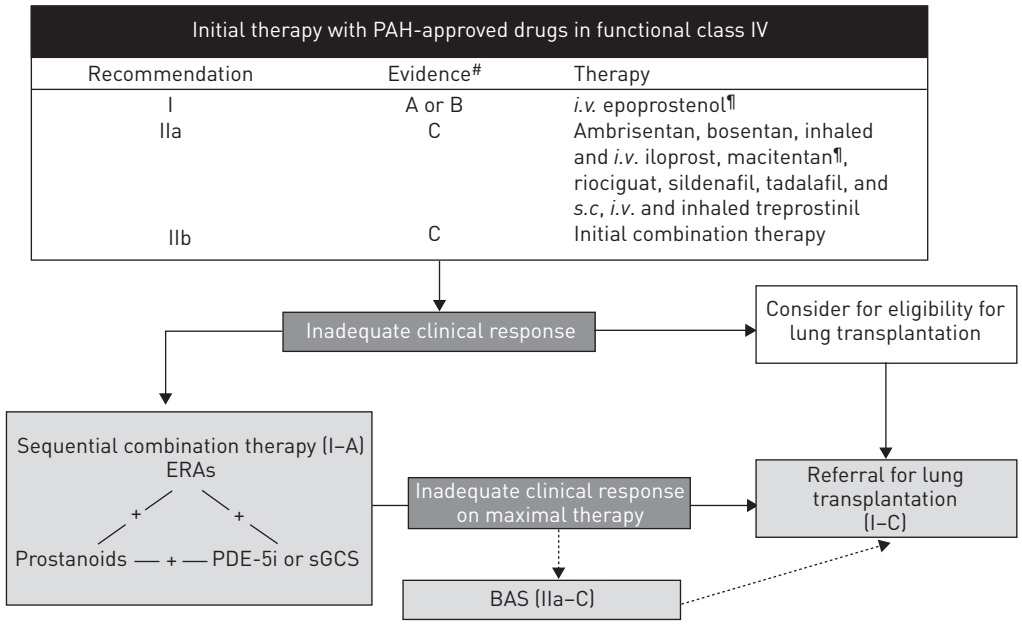

FIGURE 1 Updated treatment algorithm for patients with pulmonary arterial hypertension (PAH) in World Health Organization (WHO) functional class IV. ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase type-5 inhibitor; sGCS: soluble guanylate cyclase stimulators; BAS: balloon atrial septostomy. #: based on the WHO functional class of the majority of patients in the studies; ¶: morbidity and mortality were the primary end-point in a randomised controlled study or reduction in all-cause mortality (prospectively defined). Reproduced from [7] with permission from the publisher.

Improving drug delivery: a way to improve adequacy with treatment algorithms?

An initiative that aimed to identify and help implement evidence-based practices in the management of PAH patients in a real-world setting, the PAH-Quality Enhancement Research Initiative, analysed data provided by physicians on the diagnosis, management and outcomes of patients with PAH [29]. This study found that only half of functional class IV patients were receiving prostacyclin or prostacyclin analogues at enrolment (55%), although this increased to 71% at 2 years of follow-up [29]. Additionally, data from the US-based REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) registry found that among 530 patients whose functional class was assessed <6 months prior to all-cause mortality, 36% were in functional class IV [30]. Of these patients, 41% were not receiving a parenteral prostanoid at the time of death (fig. 2). Additionally, only half of patients (52%) who were assessed as having worsened to functional class IV and surviving to 90 days following the assessment were receiving *i.v.* prostacyclin. Epoprostenol is the only PAH-specific therapy recommended as first-line therapy in WHO functional class IV patients, with the strongest level of recommendation, but these real-world data show that its use is not ubiquitous. There are challenges associated with continuous *i.v.* epoprostenol (synthetic prostacyclin) infusion that may account for the disparity between its recommended use in functional class IV patients and its real-world use. Infrequent patient follow-up may result in patients progressing and potentially dying before functional class assessment [30]. Administration of *i.v.* epoprostenol may be inconvenient for patients [29]. Due to its short half-life, it must be administered continuously using an infusion pump and permanent central *i.v.* catheter, it is unstable in aqueous solutions and requires reconstitution and regular cassette changes (every 8–12 h or 24 h with use of an ice pack) [31, 32], thus impacting on the patient's freedom to carry out everyday activities. In addition, the permanent *i.v.* catheter means that bloodstream infection and sepsis are common [31]. A recent study reported an incidence of 0.118 episodes per 1000 treatment days [33]. Infections associated with long-term catheterisation may be fatal in certain cases [22].

A room temperature stable epoprostenol, Veletri (Actelion Pharmaceuticals US, Inc., San Francisco, CA, USA), has been approved in some countries. Reconstituted solutions can be used at room temperature for up to 72 h and no ice packs are required [34]. The effect of transitioning patients (n=41, functional class I–III) from epoprostenol requiring ice pack use to room temperature stable epoprostenol was assessed and demonstrated that patients receiving the latter reported increased treatment convenience, while clinical efficacy measures (including haemodynamics and functional class status) and safety profile remained

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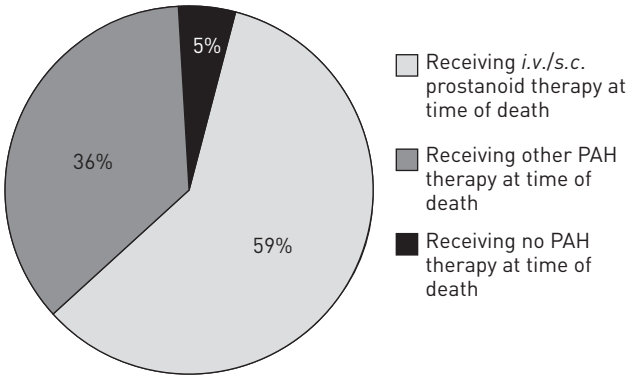

FIGURE 2 Use of parenteral prostanoids in 192 patients with pulmonary arterial hypertension (PAH) in functional class IV at the time of all-cause mortality. Results from the US REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) registry. Data from [30].

consistent [35]. Three patients reported device-/catheter-related infections, all of which were local infections with no evidence of bacteraemia.

An oral therapy targeting the prostacyclin receptor could offer improved convenience over current *i.v.* therapy and might encourage greater clinical use. The FREEDOM trials (NCT00325403 [36], NCT00325442 [37] and NCT00887978 [38]) evaluated the efficacy and safety of oral treprostinil, a prostanoid recently approved by the US Food and Drug Administration, in patients with or without background PAH-specific therapy; however, the proportion of functional class IV patients was low (<4% per treatment group). Selexipag, an investigational oral, selective prostacyclin receptor agonist, is currently being investigated in >1000 patients with PAH in a multicentre, double-blind, phase III, long-term, event-driven study (NCT01106014) [39].

PAH and lung transplantation

Patients who undergo lung transplantation may receive heart–lung, double-lung or single-lung transplants. The International Society for Heart and Lung Transplantation recently reported that between 1995 and 2012, most patients with IPAH who underwent transplantation received a double-lung transplant [40].

It is recommended that a patient's eligibility for lung transplantation is assessed immediately following an inadequate response to PAH monotherapy or upfront combination therapy, and in parallel to initiation of sequential combination therapy. Potential eligibility for transplantation should be considered in all patients presenting in WHO functional class IV. Following an inadequate response to maximal sequential combination therapy, patients should be referred for transplantation [7]. Timely referral is essential, as any delay in referral, together with the waiting period for available donors, increases waiting list mortality and may also adversely impact on the patient's condition at the time of transplantation [7].

The low availability of donor lungs increases the time spent on the waiting list for transplantation. The quality of donor lungs needs to be high and relaxing the selection criteria for lung donors (*e.g.* to include smokers and patients aged >55 years), has been successful in increasing the number of available lungs. However, in some cases (*e.g.* in brain dead donors) the lungs may become oedematous due to prolonged infusion and, therefore, unsuitable for transplantation [41]. Lung "reconditioning" by *ex vivo* lung perfusion (EVLP) is now possible, leading to an increase in the number and quality of the available donor pool [42]. A recent prospective study compared the outcome of lung transplantation in patients who received lungs at high risk for non-use (due to meeting certain criteria including poor lung deflation or inflation, presence of oedema or donated following cardiac death) that had undergone EVLP (n=20) *versus* those that did not require EVLP (n=116) [43]. No significant differences were found in terms of primary graft dysfunction at 72 h (15% *versus* 30%), length of intensive care unit (ICU) stay (4 days *versus* 4 days), length of hospital stay (23 days *versus* 27 days) or survival at 1-year (80% *versus* 84%) in patients receiving lungs with EVLP *versus* no EVLP, respectively.

Fewer IPAH patients undergo lung transplantation compared with other lung diseases, such as chronic obstructive pulmonary disease, interstitial lung disease and bronchiectasis in association with cystic fibrosis [8, 40]. In addition, IPAH patients have higher waiting list mortality than other lung diseases, even when adjusting for patient demographics and transplantation type (HR 3.1 for chronic obstructive pulmonary disease compared with 1.8 for cystic fibrosis) [44].

The lung allocation score (LAS) was introduced in the USA in May 2005 and takes into account the patient's functional status, exercise capacity, lung function, haemodynamics and any requirement for oxygen and ventilator support [45]; a similar LAS was implemented in Germany in 2011 [8]. Previously, the urgency of need for lung transplantation was based on time spent on the waiting list [44]; however, using the LAS, priority is determined by predictive models that weigh medical urgency (risk of death on the waiting list) against expected outcome (post-transplantation 1-year survival). Like the previous listing of "highly urgent/urgent", the LAS listing reflects the urgency of the transplantation need, yet it is a more transparent system as it is calculated by a programme that may be accessed *via* the Internet by both the doctor and patient. However, while waiting list mortality in the USA has decreased for other lung diseases following the introduction of the LAS, it has remained unchanged for IPAH, and post-transplantation survival has also not improved [44]. Recent reports have suggested that the LAS system does not accurately reflect the urgency of transplantation need for patients with PAH [46], and that including alternative thresholds for 6MWD, functional class and mean RAP would provide better discrimination of urgency than the current LAS [47].

Identifying patients most likely to benefit from lung transplantation

Bridging patients with severe PAH to lung transplantation is now possible and the available techniques have improved over time. However, the most appropriate patients for this strategy remain to be determined. Not all patients with severe PAH will be suitable for transplantation, and it is important to bridge those patients who are likely to benefit. Evaluation of patients for lung transplantation is a thorough, multidisciplinary process, which may include evaluation of patient risk factors (age, weight and psychosocial aspects), haemodynamics, laboratory variables and clinical examination [48–50]. Conditions that may impact on the likelihood of a patient benefiting from lung transplantation include comorbidities, infection and organ failure [9]. Absolute contraindications for lung transplantation include severe organ dysfunction, chronic non-curable infection and recent malignancy (with the exception of certain skin cancers) [9]. Selection of patients for transplantation referral is also influenced by the underlying aetiology of PAH [51]. For instance, patients with PAH associated with connective tissue disease tend to have a worse prognosis than patients with IPAH [52–55], and may benefit from an earlier referral. Similarly, patients diagnosed with pulmonary veno-occlusive disease (PVOD), a severe condition that is clinically similar to PAH [56], and pulmonary capillary haemangiomatosis have the worst prognosis and should be referred for transplantation at diagnosis [7].

With careful management, the use of *i.v.* epoprostenol has been shown to be an option for bridging patients with PVOD to transplantation, despite observations of pulmonary oedema [56, 57]. A study from the French Reference Centre for Pulmonary Hypertension reported that 12 PVOD patients in functional class III/IV awaiting lung transplantation who received continuous low-dose *i.v.* epoprostenol infusion and high-dose diuretics demonstrated significant improvements in functional class (although not to functional class I/II) and in haemodynamics following 3–4 months of treatment [56]. Nine out of the 12 patients received a lung transplantation (heart–lung: n=5; double-lung: n=4) and the authors suggested that cautious epoprostenol therapy had potential use as a bridge to lung transplantation in PVOD patients.

Physicians must, therefore, consider a multitude of factors in order to identify the patients with severe PAH not only most in need, but also most suitable for bridging to lung transplantation. Patients who are ultimately listed for transplantation may be refined over time through clinical experience [58].

PAH and lung transplantation: bridging the gap

There are a number of bridging techniques available for physicians to prepare patients with severe PAH for lung transplantation. The decision-making process to choose a particular bridging technique is complex, and may be based on the severity of the patient's illness and the anticipated wait between bridging and transplantation.

Atrial septostomy

In patients with severe PAH, creation of an inter-atrial right-to-left shunt can decompress the right heart chambers and significantly increase left ventricle pre-load and cardiac output. A study of 15 patients who underwent graded balloon dilation atrial septostomy found a significant decrease in right ventricular end-diastolic pressure and an increase in cardiac index ($p<0.05$) [59]. The procedure also significantly improved exercise capacity (as measured by 6MWD) shortly after the procedure, as well as in the longer term [59]. Atrial septostomy has been shown to improve haemodynamics in PAH patients (table 1) [63]. A review of 177 published cases of atrial septostomy found significant improvements in RAP and cardiac index following the procedure (unpublished observations). Furthermore, a study of 50 procedures performed in 34 patients who had undergone balloon dilation atrial septostomy found significant improvements in haemodynamics,

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TABLE 1 Atrial septostomy improves haemodynamics in patients with pulmonary arterial hypertension

First author [ref.]	Patients n	Initial RAP mmHg	RAP change	LAP change	Cardiac index change	SOT change
Rich [60]	6	17	41	NC	58	27
Nihill [61]	14	12	NC		36	9
Kerstein [62]	15	11	11	55	15	5
Sandoval [59]	15	15	29	55	35	22
Rothman [63]	12	23	22	20	24	18

Data are presented as %, unless otherwise stated. RAP: right atrial pressure; LAP: left atrial pressure; SOT: systemic organ transplant; NC: no change. Reproduced from [63] with permission from the publisher.

functional class and exercise capacity post-procedure (all $p<0.01$) [64]. Improvements in functional class were observed in patients who received PAH-specific drugs in combination with atrial septostomy compared with those who received atrial septostomy alone (functional class post-atrial septostomy 1.9 *versus* 2.3, respectively, $p=0.01$). In addition, higher functional class post-procedure was associated with increased risk of death (HR 2.7, $p=0.03$), while higher arterial oxygen saturation (SaO_2) (HR 0.92, $p=0.02$), exercise endurance (HR 0.99, $p=0.01$) and use of PAH-specific therapy post-procedure (HR 0.31, $p=0.02$) were associated with reduced risk of death.

However, atrial septostomy has inherent risks and should only be carried out in centres with substantial experience in the technique [65]. SaO_2 has been reported to decrease following the procedure [66], and this may affect prognosis if SaO_2 drops to <75% as reported by Rich and Lam [67]. Recent recommendations state that the procedure should be avoided in end-stage patients with baseline mean RAP >20 mmHg and SaO_2 <85% on room air at rest; while the use of a thorough pre-procedure risk assessment may reduce mortality [7]. When carried out in an expert centre, this procedure has the potential to be used not only as a bridge to transplantation but also as a possible useful adjunct to therapy.

Interventional lung assist devices

The interventional lung assist device (Novalung GmbH, Heilbronn, Germany) is a pumpless extracorporeal lung-assist device that provides an oxygenating shunt from the pulmonary artery to the left atrium providing pressure decompression and gas exchange, thus facilitating the recovery of right ventricular function [51]. It is associated with reduced inotrope support, improved gas exchange parameters, optimisation of ventilatory support requirements and, in selected cases, extubation [51]. In the first reported study of interventional lung-assist devices in PAH, a prospective observational study, 10 out of 12 patients were successfully bridged to transplantation and the 1-year post-transplantation survival for these patients was 80% [68]. One additional benefit of interventional lung-assist therapy is that patients are able to maintain exercise and receive physiotherapy while on shunt, thus maintaining rehabilitation to maintain peripheral muscle mass [69].

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is a temporary invasive method of providing partial or total support of cardiopulmonary function in order to maintain adequate oxygenation and ventilation as a bridge to transplantation [70]; however, its use is normally limited to 2 weeks [71]. Patients should be monitored for exclusion criteria for lung transplantation while on ECMO, including multi-organ failure, sepsis and non-stabilisation or non-improvement [72]. A long-term study of 20 patients who underwent ECMO as a bridge to lung transplantation found that 1-year survival for transplanted patients was 75%; however, the authors emphasised the importance of selecting patients who were likely to benefit from the procedure [58]. The upper body configuration of veno–arterial ECMO, an alternative extubated, non-sedated system in which blood is drained through a cannula in the right internal jugular vein and re-infused *via* the right subclavian artery, allows for ambulation and performance of physical therapy [73]. Other techniques of non-intubated awake ECMO for severely deteriorating patients have also shown therapeutic benefit [72, 74, 75] and permit ambulation and improvement of physical condition prior to transplantation [76]. Patient management is complex and must take into account anticoagulation, blood transfusion, physical therapy, ventilation and nutrition; an integrated ECMO team, transplantation unit and ICU are essential for successful bridging to transplantation [72].

Transcatheter Potts shunt

Transcatheter Potts shunt creation, in which a side-to-side anastomosis from the left pulmonary artery to the descending aorta is created, is another potential bridging technique based on the knowledge that PAH patients with Eisenmenger's syndrome or patent foramen ovale survive longer than patients with IPAH [50]. The presence of a right-to-left shunt in these patients prevents development of suprasystemic right ventricular pressure, and allows for maintenance of right ventricle function [77]. However, there are insufficient data in the literature to describe its use in PAH. A single case report of creation of a Potts shunt in a child with end-stage PAH after late closure of a ventricular septal defect reported clinical improvement post-procedure [77].

There are now some clinical data on a transcatheter Potts shunt in which percutaneous catheter placement is used to connect the left pulmonary artery to the descending aorta. A recent study described the creation of a transcatheter Potts shunt using fluoroscopically guided retrograde needle perforation of the descending aorta at the site of apposition to the left pulmonary artery [78]. Seven patients were considered for this technique and it was attempted in four patients. Of the three patients who underwent successful transcatheter Potts shunt creation, two patients demonstrated improvement in symptoms with no late complications with a follow-up of 10 and 4 months, respectively; one patient died due to comorbidities.

Summary

Decisions regarding which bridging technique to use are usually based on the physician's experience and may be influenced by the urgency of transplantation need. For instance, while the Novalung may be beneficial in patients with long waiting times, ECMO may be preferred for emergency cases [79]. There are strengths and weaknesses to each approach. Unfortunately, as yet, there is a lack of clinical trial evidence from which to draw guidance for determining the appropriate strategy for a particular patient with severe PAH.

Outcomes following lung transplantation

The response of the right ventricle to lung transplantation is immediate. While patients are often admitted for surgery on combination vasodilator therapy, they may be able to stop these medications post-operatively [48]. Haemodynamic improvements are also evidenced instantly and significant improvements in mean pulmonary artery pressure have been demonstrated directly following lung transplantation [80].

Early complications after lung transplantation may include primary graft dysfunction, pneumonia, acute cellular rejection, problems with anastomoses and antibody-mediated hyperacute rejection [8]. Most rejections of transplanted lungs occur within the first 6 months [81]. Other complications following transplantation include infection, airway complications, renal failure, cardiovascular complications and cancer [8].

Lung transplantation is associated with good longer term survival in patients with PAH; 10-year survival in 1-year survivors post-transplantation is reported to be 45% [51]. However, a recent study reported higher early mortality in patients with PAH having undergone lung transplantation compared with other diseases [82]. In addition, the outcome can vary depending on the underlying aetiology. A single-centre study found that 123 patients with IPAH undergoing lung transplantation had worse 10-year survival compared with patients with other categories of PAH including connective tissue disease-PAH (n=102), congenital heart disease-associated PAH (n=77) and chronic thromboembolic pulmonary hypertension (n=14) (42% *versus* 70%, p=0.01) [83]. However, survival of patients with PAH undergoing lung transplantation is improving with 5- and 10-year survival rates of 50–75% and 43–66%, respectively, being reported [83–85]. A long-term US study of 89 IPAH patients undergoing lung transplantation between 1982 and 2006 reported 5- and 10-year survival rates of 40% and 33%, respectively, in patients who underwent combined heart–lung transplants [84]. No significant difference in survival was observed between patients receiving heart–lung, single-lung or double-lung transplants [84]. This study also found that, in patients transplanted in recent years (1994–2006), survival was significantly improved compared with patients in the prior cohort (1982–1993) (p=0.004). A recent publication from the International Society for Heart and Lung Transplantation reported that the median long-term survival rates of adults who underwent lung transplantation for various indications between 1994 and 2011 were 53% and 31% at 5 and 10 years; similar rates were observed in patients with IPAH (n=1400) [40]. These rates were similar to other reports [83–85]. However, when only patients with IPAH who survived to 1 year were included (n=921), the survival rates were higher (~70% and ~50% at 5 and 10 years, respectively).

Conclusion

For patients with severe PAH, those patients who present with functional class IV disease or who progress and deteriorate while on therapy, the proceedings of the 5th World Symposium on Pulmonary

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Hypertension recommend first-line *i.v.* epoprostenol therapy, based on the highest level of evidence. Other PAH medications (ambrisentan, bosentan, iloprost, macitentan, riociguat, sildenafil, tadalafil and treprostinil) as monotherapy, or initial combination therapy are recommended with lower evidence. Sequential combination therapy is advised for patients with severe PAH who do not adequately respond or deteriorate. Despite the evidence available for *i.v.* epoprostenol use in functional class IV patients, it has been shown that many patients die without having received epoprostenol therapy. Development of therapies that offer improved convenience may improve its use in daily practice.

Lung transplantation remains an important treatment option for patients with severe PAH who do not respond to or who deteriorate while on maximal PAH drug therapy. Treatment decisions made at this time are influenced by the following factors: 1) there is a shortage of suitable lung donors; 2) waiting times are long; and 3) patients with severe PAH show an increased risk of dying while waiting for lung transplantation. While the LAS is a transparent system to rank a patient's urgency, it does not seem to capture the critical nature of patients with PAH, and more patients with IPAH tend to die while on the waiting list compared with other diseases. As such there is a need for good bridging techniques in order to support patients with PAH while they await transplant. It is important to assess and identify patients who are most likely to benefit from transplant, and to decide which bridging technique(s) are most suited to an individual patient, in order to achieve the best outcome.

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