



Lung transplantation for pulmonary hypertension

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Abstract: From its identification as a distinct disease entity, understanding and management of pulmonary hypertension has continuously evolved. Diagnostic and therapeutic interventions have greatly improved the prognostic implications of this devastating disease, previously rapidly and uniformly fatal to one chronically managed by multi-disciplinary teams. Improved diagnostic algorithms and active research into biochemical signatures of pulmonary hypertension (PH) have led to earlier diagnosis of PH. Medical therapy has moved from upfront use of continuous intravenous prostaglandins to administration of combinations of oral medications targeting multiple pathways underlying this disease process. In addition to improved medical therapies, recently introduced interventions such as pulmonary endarterectomy and pulmonary artery balloon angioplasty for chronic thromboembolic pulmonary hypertension (CTEPH) give patients an increasing array of treatment options. Despite these many advances, lung transplantation remains the definitive treatment for patients with disease refractory to or progressing on best medical therapy. As our understanding of medical therapy has advanced, so to have best practices for lung transplantation. Recipient selection and approach to organ transplantation techniques have continuously evolved. Mechanical circulatory support has become increasingly employed to bridge patients through lung transplantation in the immediate post transplantation recovery. In this review, we give a history of lung transplantation for PH, an overview of PH, discuss current best practices and look to the future for insights into the care of these patients.

Keywords: Pulmonary hypertension (PH); lung transplantation; pulmonary artery hypertension

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Introduction and background

Pulmonary hypertension (PH) is a complex and heterogeneous set of disease processes that significantly affect patients' lives. Though the true incidence is unknown, ranges vary from 2–15 individuals per million population. Part of the reason for this wide range is the heterogeneity of the disease processes that comprise PH, variations in management and the clinical expression of the PH disease process, which can be a confounder to other pathophysiology.

To facilitate a standard nomenclature, and potentially diagnosis and management of patients with PH, the World Health Organization has grouped PH in to the following five categories:

- (I) Pulmonary artery hypertension (PAH)—an intrinsic pulmonary vascular process;
- (II) PH secondary to left heart disease—including myocardial dysfunction and valvular diseases;
- (III) PH secondary to lung disease and/or hypoxia—a secondary process such as that from pulmonary fibrosis or sleep disordered breathing;

- (IV) PH secondary to pulmonary arterial obstructions—including chronic thromboembolic pulmonary hypertension (CTEPH);
- (V) PH secondary to unclear and/or multifactorial mechanisms—including blood dyscrasis and sarcoidosis.

Over the past 20 years, the medical management of group 1, true PAH, has evolved. A management strategy for patients with refractory PAH is (bilateral) lung transplantation. The contribution of lung transplantation to the management of PAH (group 1) is the focus of this review.

Historical perspective

The term “primary pulmonary hypertension” has been well described in the literature since 1951 (1). Simultaneous to the evolving understanding of this newly minted disease, techniques for and management of lung transplantation were being refined throughout the 1960s and 1970s. In 1968, a major milestone was achieved for patient survival after lung transplant when a patient survived 10 months following a single lung transplant (2). As work with immunosuppressive regimens advanced—including the clinical use of the calcineurin inhibitor cyclosporine—surgeons at Stanford translated the laboratory work of Doctors Shumway, Wallwork, and Reitz into clinical practice by performing the first heart-lung transplant in 1981 for a 45-year-old female patient with end stage primary PH (3). Since the 1980s, almost 20 years after the first lung transplant in 1963 by Hardy and associates, lung transplant has been an accepted treatment for PH (4).

Due to scarcity of organ blocks for heart-lung transplants, the transplant community has transitioned towards lung transplantation alone for those suffering from PH. This is evident in the 2019 International Thoracic Organ Transplant Registry that reported data from 69,200 adult lung and 4,128 adult heart-lung transplants through June 2018 (5). In part, this transition was due to the recognition that the primary pathophysiology in this disease is within the pulmonary vasculature and is not due to intrinsic right ventricular issues. Indeed, the right ventricle demonstrates a remarkable ability to recover to a physiologic state over time after the removal of the high resistance pulmonary vasculature (6).

In specific patient populations like PH, bilateral lung transplant (BLT) has found increasing popularity. A review article in *Annals of Surgery* in 1993 noted two key reasons

for BLT preference, including minimizing early post-operative issues with PH crisis and an improved tolerance of bronchiolitis obliterans (7). As the trend toward BLT for PH has continued in the early 2000s, Brouckaert and colleagues conducted a large single-center retrospective study comparing BLT to HLT over 24 years (8). In the absence of a prospective, randomized trial, this work found no significant difference in early mortality and overall graft survival between the two transplant options. Therefore, consensus statements since the 2010s support BLTs as the preferred surgical treatment in PH (9).

Pre-transplant management

Pulmonary arterial hypertension (PAH) is a complex disease with heterogeneous etiologies and varying clinical course (10,11). The unique needs of this patient population necessitate a high quality, specialized, multi-disciplinary approach to diagnosis and management (12). Patients require close monitoring for progression of symptoms and response to therapies. Following the initial diagnosis of PAH, referral to an expert center is imperative (10). Appropriate classification of disease directly affects patient care, as clinical management of differing etiologies may differ greatly. The importance of properly diagnosing the etiology of a patient’s PH is underscored by remarkable incongruences in care provided across centers. One program found that of 140 patients referred to their center, 72 patients (51%) had a change in diagnosis following appropriate evaluation. Of 42 patients in this group started on therapy for PH prior to referral, 23 (57%) patients were found to be on inappropriate medications (13). Risk stratification using validated criteria guides initial therapies and defines risk for mortality (12,14,15). Patient’s clinical and hemodynamic response to initial therapy has crucial prognostic value (16,17). Of 383 patients with group 1 PH, those who remained in or improved to a low risk profile at one year had better survival at 1, 3 and 5 years than those remaining in, or worsening to an intermediate or high-risk profile (18).

Upfront multidrug therapy has become the standard of care for patients with significant disease (19–22). Patients with severe hemodynamic compromise may need to be initiated on parenteral therapies urgently. As hemodynamics worsen and the right heart fails, patients may suffer from profound volume overload, hepatic congestion, cardiac cachexia and renal failure, among other co-morbidities (23). Referral for lung transplantation is indicated in patients

with progressive disease despite maximal appropriate medical therapy, and for those patients requiring parenteral therapy. Additionally, patients with phenotypes known to respond poorly to medical therapy, such as pulmonary veno-occlusive disease (PVOD), should be referred promptly (9). Ideally, early referral allows time for patients to consider transplantation, and for the transplant teams to fully evaluate patient candidacy, while working to mitigate any potential risks (24).

Consideration of transplant listing should be made when a patient demonstrates high risk of short-term mortality, despite optimized medical therapy. Validated risk stratification tools (14,15) bring objectivity to this decision. Patients stratified as high risk have a one-year mortality risk well in excess of 10%. Since the 1-year mortality following lung transplantation is approximately 10% (5) there is a mortality benefit to offering transplantation in this high-risk cohort. Time on the waitlist is influenced by many factors, including the patient's lung allocation score (LAS), history of sensitization, blood group and size. Patients with PH on the lung transplant wait listing have higher rates of mortality than peers without PH (25,26) and it has been observed that the LAS disadvantages patients with PH (27). Revisions to the LAS have sought to appropriately capture illness severity, though in some countries, an exception score may be requested from a local review board when the transplant team feels that the calculated LAS does not adequately reflect the severity of patient illness.

Patients with PH and decompensated right heart failure are at high risk for mortality and should be managed at expert centers by experienced teams capable of providing high quality intensive care. Teams should have the ability to implement invasive therapies including extracorporeal support devices when the clinical situation remains dire despite maximal medical therapy. Goals of such interventions are to decompress the overloaded right heart, decrease flow and resistance through the pulmonary circulation, and provide adequately oxygenated blood to the systemic circulation. Prior to implementing such a strategy, it is imperative to clearly delineate goals of therapy, whether they are palliative in nature, as a bridge to recovery or a bridge to transplantation.

Atrial septostomy allows right to left shunting of deoxygenated blood. Though arterial desaturation is expected, this procedure augments cardiac output and increases overall systemic delivery of oxygen. In specialized centers, a more likely approach would be the use of extracorporeal life support (ECLS) devices. Venoarterial

(VA) extracorporeal membrane oxygenation (ECMO) decompresses the right heart and pulmonary circulation via venous outflow cannulas. Blood is directed through a membrane oxygenator and subsequently pumped into the systemic circulation, where the now well-oxygenated blood perfuses tissue beds. Though less commonly utilized, venovenous (VV) configurations of ECMO may be considered in appropriate situations. This form of mechanical support withdraws vena caval blood, directs it through a membrane oxygenator, and then reintroduces this well oxygenated blood into the right sided circulation. The downside of VV ECMO (when isolated as pure ECMO) is that no right ventricular support is provided and the cardiac and pulmonary circulation is reliant on intrinsic cardiac function. Alternative to this pure VV ECMO approach is utilizing a single site, percutaneous cannula such as the ProtekDuo (LinaNova, Boston, MA) (28).

The pure VV ECMO configuration may be best employed in patients with atrial septal defects or a patent foramen ovale allowing direct instillation of oxygenated blood into the systemic circulation (29). In mechanically ventilated patients, VV-ECMO may allow for the use of ultra-protective ventilator settings, limiting applied pulmonary arterial pressures (30). A final form of extracorporeal oxygenation is performed by placement of a membrane oxygenator directly between the pulmonary artery and left atrium. In patients with PH, blood can flow through this low resistance oxygenator driven by native high right sided pressures, simultaneously offloading the right sided circulation and providing oxygenated blood to the systemic circulation (31,32).

Considerations when employing ECLS devices include anticipated time to transplantation, and complications related to ECLS devices, such as coagulopathy, cerebral vascular accidents, venous thrombosis, bleeding and infection (33). With increasing experience with ECLS, complication rates have decreased over time.

ECMO techniques have been increasingly deployed as a bridge to transplantation (31,34-37), and patients can be maintained on ECLS for long periods of time (35), though ongoing mobilization and conditioning are important when choosing vascular access sites. When choosing access sites, risks and benefits of central versus peripheral cannulation must be considered. Peripheral femoral cannulation techniques are easiest to deploy, but limit patient mobility. In bi-femoral VA-ECMO, it is important to consider the mixing point between the retrograde flow of oxygenated post membrane-oxygenator blood and the deoxygenated

blood ejected antegrade from the left ventricle. Patients may have poorly oxygenated blood supplied to their coronary or cerebral vasculature and this must be closely monitored. Large caliber arterial femoral cannulas may obstruct antegrade flow to the distal limb, placing the limb at risk for ischemic complications. A distal perfusion cannula may be deployed if necessary. Central cannulation via sternotomy or thoracotomy obviates concerns related to limited mobility, limb ischemia and distal mixing points but requires an invasive implantation procedure. Peripheral cannulation with venous access via the superior vena cava, and arterial return via the ipsilateral subclavian artery allows for reinfusion of oxygenated blood directly into the proximal aortic arch, thus mitigating concerns regarding lower extremity ischemia and decreased mobility seen in bi-femoral access, while removing the need for central cannulation (38).

Subtypes of pulmonary arterial hypertension require special attention to management. Rapid progression of PH may occur in connective tissue diseases (CTD-PAH), especially systemic sclerosis (SSc), and requires close screening (10,39). Immunosuppressive agents may lead to clinical improvement in some forms of CTD-PAH, though this has not been demonstrated in SSc-PAH (40). A higher mortality rate in CTD-PAH has been shown compared to idiopathic PAH. In one registry of 651 PAH patients, despite less severe hemodynamics, the median survival for patients with SSc-PAH was 3 years, compared to 7.8 years seen in idiopathic PAH (41). One, three- and five-year post transplant mortality was lower in SSc patients with PAH compared to those with SSc related interstitial lung disease with or without PH (42).

Pulmonary venous obstructive disease is typically refractory to pulmonary vasodilators, which may induce pulmonary edema and precipitate rapid clinical worsening. Referral for lung transplantation should be made at the time of diagnosis, as PVOD is frequently rapidly progressive. An analysis of the United Network for Organ Sharing (UNOS) database showed that at 6 months, 22% of patients with PVOD had died on the lung transplant waiting list, compared to 11% with PAH, despite similar a similar LAS (43).

CTEPH is currently the only potentially curable form of PH. Pulmonary endarterectomy (PEA) may reverse a patient's hemodynamic derangements and offers an excellent long-term survival benefit, with ten-year survival in excess of 70% reported (44). In patients with CTEPH, PEA offers a 63% relative risk reduction of death compared to those who do not undergo PEA (45). In up to one-third of

patients, those with distal disease or otherwise non-operable cases, pulmonary balloon angioplasty is a viable treatment option, durably lowering pulmonary vascular resistance and improving exercise capacity and offering excellent 5-year survival rates of up to 98.4% (46).

Transplantation

As a patient's medical therapy has been optimized and they have undergone appropriate institutional transplant evaluation, the timing and choice of transplant become key branch points in the patient's care plan. There are limited true contraindications to lung transplant from a surgical perspective although a history of previous chest surgery, presence of conditions exacerbated by cardiopulmonary bypass (CPB) (e.g., bleeding disorders, cerebrovascular disease, and renal disease), and age of patient at time of transplantation should be given special consideration. The technically challenging situation of reoperative thoracic surgery can adversely affect outcomes such as increased bleeding, nerve injury, renal insufficiency and respiratory complications (47). Choice of surgical incision may vary per surgeon and institutional preference from median sternotomy to a bilateral clamshell approach. In cases with prior chest surgery, alternative cannulation sites for ECLS and CPB should be considered regardless of the higher risk of limb ischemia and vein thrombosis (48).

Right heart function and ability to tolerate single lung ventilation must be considered in planning for circulatory support in BLTs, particularly in the patient with end-stage PH. Many surgeons continue to utilize CPB in the setting of high pulmonary pressures and in otherwise high-risk patient populations (49). Despite this, newer studies support the transition to ECLS as CPB has been identified as an independent risk factor for primary graft dysfunction (50-52). Asimakopoulos and colleagues showed worsening of pulmonary function and significant inflammatory response with the use of CPB culminating in acute lung injury and therefore favor ECLS when performing lung transplantation (53). A 2018 retrospective study compared central and peripheral ECMO in BLT and found long-term survival and in-hospital mortality were unaffected on the basis of cannulation sites (54).

As surgical planning is needed for optimal outcomes, anesthesia is a key player in the operating room's multidisciplinary approach. Airway management with bronchial blockers (BB) or double-lumen endotracheal tubes (DLTs) each offer differing advantages and disadvantages.

In a 2015 meta-analysis in thoracic surgery cases, BBs were shown to have lower incidence of airway injury, though DLTs could be placed with higher reliability and speed (55). Induction of anesthesia in PH patient with right heart dysfunction is difficult to manage and the anesthesia team must combat the ill effects of systemic vasodilation and subsequent reduction in right ventricular preload (56). Pre-induction initiation, or preparation of peripheral ECLS cannulation sites can expedite initiation of circulatory support, thereby avoiding acute right heart failure.

Postoperative care of PH transplant patients poses a new set of challenges unlike those issues encountered in the operating room. As lung physiology normalizes with the immediate reduction of pulmonary vascular resistance, the left ventricular filling pressure and cardiac output increase and can unmask left sided dysfunction (57). A strategy of post-operative continuation of ECLS to allow controlled normalization of global cardiac hemodynamics has been shown to greatly decrease both the incidence of PGD and incidence of early (within 3 months) mortality (58). The prolonged ECLS approach has recently been expanded to prevention to primary graft dysfunction (59).

Future

Pulmonary arterial hypertension remains an incurable disease and will likely remain so for the foreseeable future, however remarkable progress has been made over the last two decades. An improved understanding of the pathophysiology of pulmonary arterial hypertension has helped to identify the prostaglandin, nitric oxide and endothelin pathways as important therapeutic targets. Ongoing research has led to an improved understanding of pathways underlying the cellular dysfunction leading to PAH, opening new potential therapeutic and diagnostic avenues. Mutations in bone morphogenetic protein receptor type 2 (BMP2) have been demonstrated in 80% of families with PAH and in 20% of idiopathic PAH cases (60). Elucidation of the signaling pathways and associated proteins has led to trials repurposing existing medications, as well as a number of potential new therapies, currently in various stages of clinical research (61). In experimental PAH models, perivascular infiltrates of inflammatory cells have been seen preceding structural vascular changes, leading to an immunity driven hypothesis of PAH, and the investigation of inflammatory modulators for this disease (62). Mutations in the recently discovered gene

EIF2AK4 can accurately diagnose the rare PAH variants PVOD and pulmonary capillary hemangiomatosis (PCH) without the need for tissue biopsy (61). An ever-expanding population of genes and mutant proteins has been found in familial and sporadic forms of PH and are ongoing topics of investigation (11,61,62). In addition to new medications, emerging techniques such as nanoparticle delivery provide the opportunity to improve on the pharmacokinetic profiles of established therapies (63).

Advances in mechanical interventions for management of PH also hold great promise. Recently described success in prolonged post-lung transplant ECMO support—allowing for cardiac accommodation to a newly low resistance pulmonary circulation—mitigates primary graft dysfunction and decreases the high early mortality rates seen in this population (33,35,58). If widely accepted, this practice may lead to great improvements in long-term mortality in patients with PAH. As the number of centers performing both pulmonary endarterectomy and pulmonary balloon angioplasty increases, patients with CTEPH will increasingly be able to avoid transplantation. Finally, new interventions are finding their way into clinical care. Pulmonary artery denervation has shown promise in improving hemodynamic parameters and six-minute walk distance in patients with PAH in patients with disease refractory to maximal medical therapy (64). If ongoing trials prove successful, clinicians will have a new tool in combatting this devastating disease (65,66).

The disease process of pulmonary arterial hypertension is an exemplar of how basic science research and a fundamental understanding of physiology can directly affect clinical care and profoundly improve disease outcomes. This once uniformly fatal disease can now regularly be managed with oral therapies. When disease becomes severe, the expanding, and ever improving armamentarium of therapeutic interventions, including lung transplantation offers realistic hope for improved quality and quantity of life. PH remains an area of active research. As of this writing, well in excess of 200 studies evaluating diagnostic, new and existing pharmacologic agents and therapeutic modalities are currently enrolling PAH patients. The future of PH has never looked brighter.

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