Pulmonary Hypertension
The Role of Lung Transplantation

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KEYWORDS

• Idiopathic pulmonary arterial hypertension • Lung transplantation • Heart-lung transplant
• Extracorporeal lung support • Lung allocation score

KEY POINTS

- Bilateral lung transplant is preferred over single lung transplant for severe and refractory pulmonary hypertension.
- Heart-lung transplant is reserved for a specific subset of individuals with concomitant left ventricular dysfunction or complex congenital heart defects.
- Criteria for transplant referral and listing for pulmonary hypertension continue to evolve given variable combinations of medical therapeutic agents balanced by prolonged wait list times.

INTRODUCTION

In the early 1990s, epoprostenol was initially introduced as a therapeutic bridge to transplantation, eventually confirming a survival advantage for idiopathic pulmonary hypertension (iPAH) and had comparable results to heart-lung transplantation (HLTx).[1,2] However, the addition of multiple additional medical therapeutic agents, as well as the impact of the new lung allocation score (LAS) in 2005, increased waiting list mortality for iPAH.[3] In the new millennium, the balance between the available medical therapy and treatment combinations, the relative disadvantage of the LAS regarding the diagnosis of PAH, donor organ shortages, and the limitations and risks of lung transplantation (LTx) and HLTx will be critical to optimizing patient outcomes (**Table 1**).

HEART-LUNG TRANSPLANTATION

HLTx emerged in the 1980s as the primary curative procedure for patients with severe pulmonary vascular disease inclusive of complex congenital heart disease (CHD). In 1981, the first iPAH HLTx was successfully performed at Stanford, and an additional 22 HLTx cases followed over next 5 years, with a 3-year survival of 60%. However, the past decade has noted a dramatic shift in favor of LTx since the early 2000s, while two-thirds of the indications for HLTx remain CHD (34.9%) and iPAH (27.2%).[4,5]

The median survival of HLTx from 2004 to 2014 has improved to 5.8 years versus 3 years in prior decades.[5] Compared to LTx, HLTx patients have a more pronounced early mortality, however, those who survived 1 year, had a low mortality rate with a survival conditional half-life of greater

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Table 1
Prognostic markers: suggested listing criteria for transplantation/pulmonary hypertension

Clinical Domains	Prognostic Markers	Outcomes[a]
Serology and markers of right heart failure	NT-pro-BNP (Δ500 pg/mL) Bilirubin >1.2 Renal insufficiency	↑ mortality [HR 1.13][13] ↑ mortality [HR = 13.3][14] ↑ mortality [HR 1.2–3.3][15]
Symptoms/physical examination (associated with RHF)	Hemoptysis Recurrent ascites	↑ mortality[16] [17]
Functionality	6MWD <150 m NYHA II-IV	1-y survival 68.4%[18] 3-y survival 29%–66%[19]
Hemodynamics	mRA >15 mm Hg CI <2.5 L/min/m^2	↑mortality [HR 2.28][20] ↑mortality [HR 3.89][21]
Noninvasive imaging	Echocardiogram TAPSE <15 mm MRI RVEF <35% MRI RVEDV >84 mL/m^2	↑ mortality [HR = 3.17][22] ↑ mortality[23] ↑ mortality[24]

Abbreviations: 6MWD, 6-minute walk distance; CI, cardiac index; eRAP, echocardiogram right atrial pressure; HR, hazard ratio; LTx, lung transplant; mRA, mean right atrial pressure; NT- pro-BNP, brain naturetic peptide; RHF, right heart failure; RV, right ventricle; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular planar systolic excursion.
[a] All hazard ratios, $P<.05$.

than 10-year.[5] **Table 2** describes the indications for HLTx versus LTx.

LUNG TRANSPLANTATION

The surgical procedure of choice for iPAH and secondary PH (primarily represented by parenchymal lung disease) is LTx.[6] Most centers favor bilateral LTx (BLTx); however, single LTx (SLTx) has several advantages including improved operative risk profile and donor utilization, shorter cardiopulmonary bypass time, and noninferior outcomes (see **Table 2**). Immediate peri- and postoperative care for iPAH may involve inhaled nitric oxide, and vasopressor and/or inotropic support for the right ventricle during recovery. Post-transplant

Table 2
Transplant options for pulmonary hypertension

Transplant Type	Pulmonary Hypertension Indications	Risk and Benefits	Overall Median Survival	Postoperative Physiology
Single lung	• WHO 3	↓ Bypass time ↓ Functional reserve	3.5 y[25]	↑ V/Q mismatch ↑ Pao_2/Fio_2 ratio ↓ mPA(early) ↑ RV function ↑ PVR
Bilateral lung (±intracardiac repair)	• ASD • VSD • AP Window • Eisenmengers-PDA • WHO 1 & 3	↑ Bypass time ↑Ischemic time ↑Functional reserve	6 y[25]	↓ Pao_2/Fio_2 (early) ↑ mPA
Heart-Lung	• Uncorrectable congenital cardiac lesions • Single-ventricle anatomy/physiology • WHO 2	↑ Bypass time ↑ Ischemic time ↑Functional reserve ↑Waitlist Time	4.4 y[26]	↑ mPA (early)

Abbreviations: AP window, aortopulmonary window; ASD, atrial septal defect; mPA, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PDA, patent ductas arteriosus; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle; V/Q, ventilation perfusion; VSD, ventricular septal defect; WHO, world health organization.