Lung Transplantation for Pulmonary Hypertension: Indications and Outcomes

Maria M. Crespo, MD

Associate Professor of Medicine

Perelman School of Medicine

University of Pennsylvania

Co-Director, Lung Transplant Program

Perelman School of Medicine
University of Pennsylvania

Outline

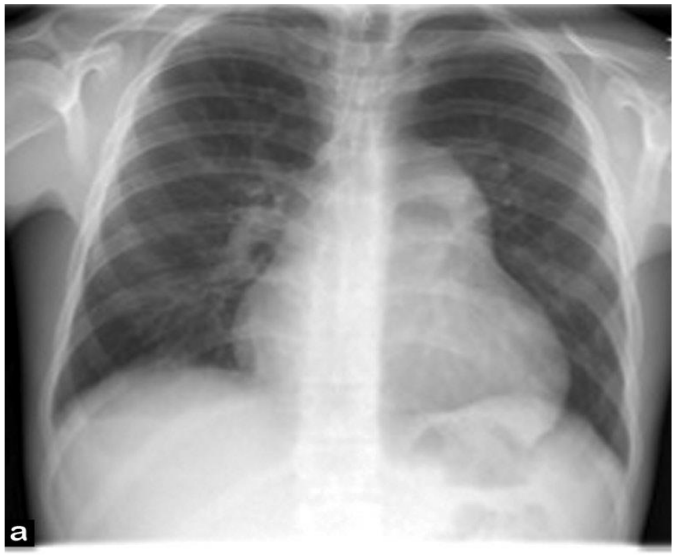
- Background/epidemiology
- Lung Transplantation: *"When and Who"* to refer and list
- Challenges and outcomes of lung transplantation for Pulmonary Hypertension
- Conclusions

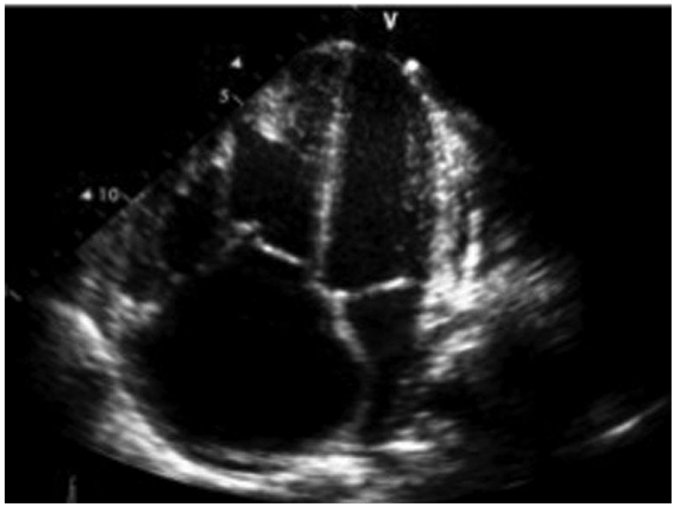
Background

- Pulmonary Hypertension is a rare cause of precapillary pulmonary hypertension
- It affects 15-50 people/million inhabitants
- It used to be called an “orphan disease”
- 5 WSPH. Last 2013 Nice updates definitions and new classification helping distinguish PAH from P-LHD

Background

- Pulmonary hypertension is defined as an elevated mean arterial pressure ≥25 mmHg at rest and normal PAWP ≤15 and PVR >3 Wood units (WSPH)
- It has several etiologies and can be a progressive and fatal disease if untreated
- Although survival of Pulm Hypertension has improved significantly in recent years, it continues to remain a potentially fatal disease with a 1-year mortality ~ 15%.





Classification of Pulmonary Hypertension

- **Group 1 – Pulmonary arterial hypertension (PAH)**
- **Group 2 – PH-HLD due to left heart disease**
- **Group 3 – PH due to chronic lung disease and/or hypoxemia**
- **Group 4 – PH due to chronic thromboembolic pulmonary hypertension (CTEPH)**
- **Group 5 – PH due to unclear multifactorial mechanisms**
- **PAH refers to group 1. PH refers to any of group 2 through group 5 PH, and is also used when referring to all five groups collectively.**

5th WSPH 2013 in Nice
Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62

Classification of Pulmonary Hypertension

- **Group 2: PH due to left heart disease (LHD) is characterized by PH associated with an elevated left atrial pressure (eg, mean LA pressure >14 mmHg) resulting in pulmonary venous hypertension (ie, post-capillary PH)**

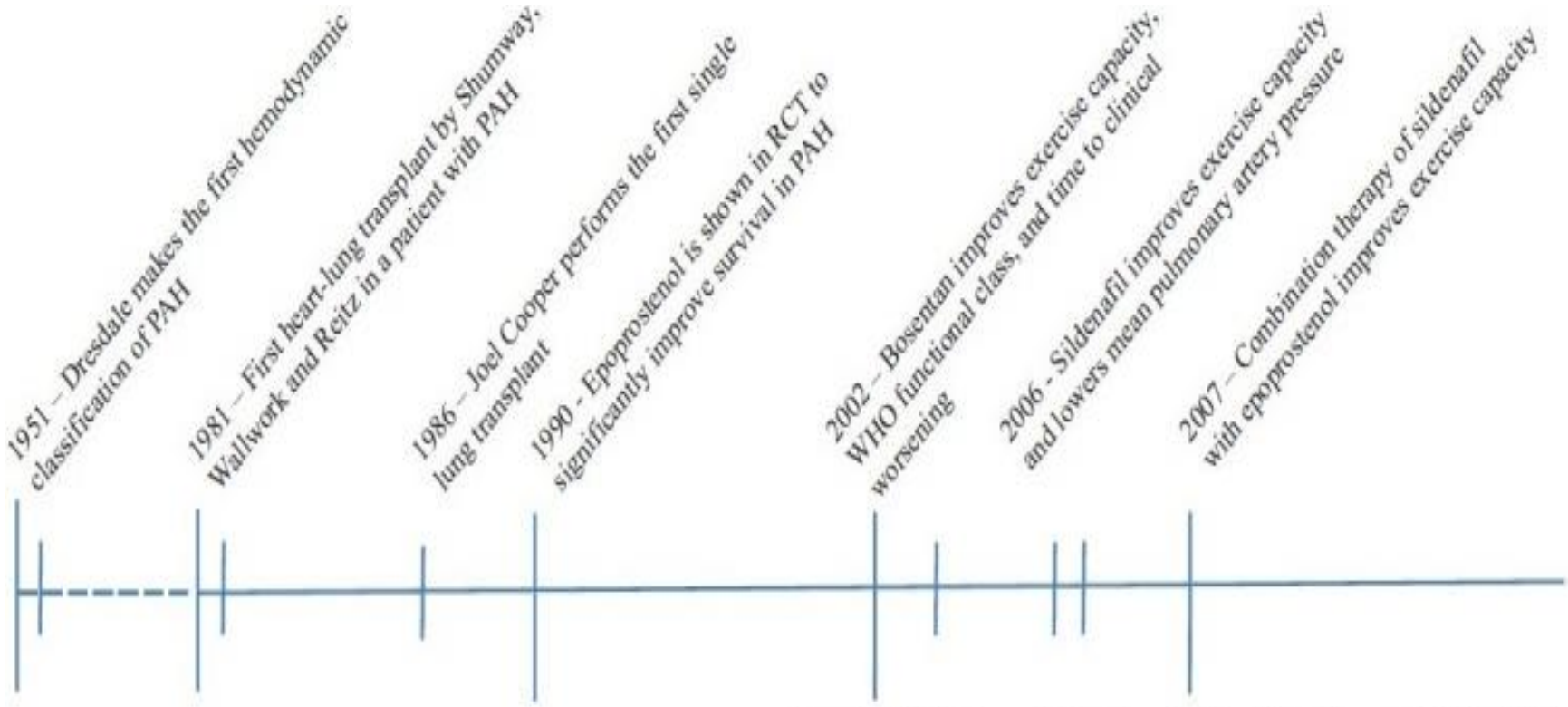
- **Common causes of left atrial hypertension include left ventricular systolic or diastolic dysfunction, and mitral and aortic valve disease**

The WSPH 2013: Borderline PH

- **The term "borderline PH" has been proposed mean PAP 21-24 mmHg but this is of uncertain significance and further epidemiology study is needed to determine prognostic impact and if earlier therapeutic interventions are warranted**
- **Patients with SSc who have a higher prevalence of PH have worse survival compared with IPAH, a mPAP 21-24 mmHg puts them at risk for development of overt PAH within 3 years**

Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62

Timeline of Major Medical and Surgical Developments in the Treatment of Pulmonary Arterial Hypertension



Adult Lung Transplants

Indications (Transplants: January 1995 – June 2015)

Diagnosis	SLT (N=17,213)	BLT (N=32,789)	TOTAL (N=50,002)
COPD	6,999 (40.7%)	8,674 (26.5%)	15,673 (31.3%)
IIP	5,979 (34.7%)	6,264 (19.1%)	12,243 (24.5%)
CF	209 (1.2%)	7,686 (23.4%)	7,895 (15.8%)
ILD-not IIP	977 (5.7%)	1,608 (4.9%)	2,585 (5.2%)
A1ATD	784 (4.6%)	1,784 (5.4%)	2,568 (5.1%)
Re-transplant	874 (5.1%)	1,174 (3.6%)	2,048 (4.1%)
IPAH	87 (0.5%)	1,348 (4.1%)	1,435 (2.9%)
Non CF-bronchiectasis	64 (0.4%)	1,293 (3.9%)	1,357 (2.7%)
Sarcoidosis	307 (1.8%)	941 (2.9%)	1,248 (2.5%)
PH-not IPAH	129 (0.7%)	648 (2.0%)	777 (1.6%)
LAM/tuberous sclerosis	141 (0.8%)	359 (1.1%)	500 (1.0%)
OB	75 (0.4%)	354 (1.1%)	429 (0.9%)
CTD	122 (0.7%)	240 (0.7%)	362 (0.7%)
Cancer	7 (0.0%)	27 (0.1%)	34 (0.1%)
Other	459 (2.7%)	389 (1.2%)	848 (1.7%)

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2016

Perelman School of Medicine University of Pennsylvania

Adult Lung Transplants

Indications (Transplants: January 2004 – June 2015)

Diagnosis	Detailed diagnosis	N (%) (N=36,237)
CF	CYSTIC FIBROSIS	5,593 (15.4%)
Non CF-bronchiectasis	BRONCHIECTASIS	898 (2.5%)
	COMMON VARIABLE IMMUNE DEFICIENCY	7 (<0.05%)
	HYPOGAMMAGLOBULINEMIA	6 (<0.05%)
	KARTAGENER'S SYNDROME	13 (<0.05%)
	PRIMARY CILIARY DYSKINESIA	9 (<0.05%)
IPAH	PULMONARY HYPERTENSION/PULMONARY ARTERIAL HYPERTENSION	897 (2.5%)
PH-not IPAH	CONGENITAL HEART DEFECT - PRIOR SURGERY UNKNOWN	7 (<0.05%)
	CONGENITAL MALFORMATION	1 (<0.05%)
	CONGENITAL: OTHER SPECIFY	5 (<0.05%)
	EISENMENGER'S SYNDROME	55 (0.2%)
	PH-SCLERODERMA/CREST	*176 (0.5%)*
	PH-THROMBOEMBOLIC	20 (0.1%)
	PORTOPULMONARY HYPERTENSION	3 (<0.05%)

2016

Adult Lung Transplants

Indications (Transplants: January 2004 – June 2015)

Diagnosis	Detailed diagnosis	N (%) (N=36,237)
PH-not IPAH (cont'd)	PULMONARY CAPILLARY HEMANGIOMATOSIS	3 (<0.05%)
	PULMONARY TELANGIECTASIA - PULMONARY HYPERTENSION	9 (<0.05%)
	PULMONARY VASCULAR DISEASE	65 (0.2%)
	PULMONARY VENO-OCCLUSIVE DISEASE	43 (0.1%)
	PULMONIC STENOSIS	1 (<0.05%)
	SECONDARY PULMONARY HYPERTENSION	187 (0.5%)
Sarcoidosis	SARCOIDOSIS	934 (2.6%)
Retransplant	BOS/OB	853 (2.4%)
	LUNG RE-TX/GF: ACUTE REJECTION	16 (<0.05%)
	LUNG RE-TX/GF: NON-SPECIFIC	21 (0.1%)
	LUNG RE-TX/GF: OTHER SPECIFY	588 (1.6%)
	LUNG RE-TX/GF: PRIMARY GRAFT FAILURE	127 (0.4%)
	LUNG RE-TX/GF: RESTRICTIVE	14 (<0.05%)

Recommendations for Lung Transplant Referral

- **NYHA functional Class III or IV symptoms during escalating therapy**
- **Rapidly progressive disease**
- **Use of parenteral targeted PAH therapy**
- **Known or suspected PVOD or pulmonary capillary hemangiomatosis (PCH)**

ISHLT 2014 consensus for the selection of lung transplant candidates

Additional Risk Factors for Poor Outcome in PAH

- Hyponatremia
- Hyperbilirubinemia
- Tricuspid annular plane systolic excursion (TAPSE) <1.8 cm
- Syncope
- Underlying connective tissue disease (Scleroderma)
- Chronic obstructive pulmonary disease
- Sarcoidosis
- Pulmonary fibrosis
- Combined emphysema/pulmonary fibrosis and PAH 1-year survival is only 60%

Recommendations for Lung Transplant Listing

- NYHA functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids
- CI < 2 liters/min/m^2
- Mean RA pressure >15mmHg
- 6MWT of <350m
- Development of significant hemoptysis, pericardial effusion or signs of progressive RVF (renal insufficiency, ↑BI, ↑BNP or recurrent ascites
- No significant medical contraindication

ISHLT 2014 consensus for the selection of lung transplant candidates

Recommendations for Lung Transplant Listing

- **High >50% risk of death due to lung disease within 2 years if lung transplantation is not perform**
- **High >80% likelihood of surviving at least 90 days after LTx.**
- **High >80% likelihood of surviving 5 years from a general medical standpoint provided adequate allograft function**

ISHLT 2014 consensus for the selection of lung transplant candidates

Data Elements Used in Determining LAS

Lung Allocation Scoring System 2005

Diagnosis	% predicted FVC
Age	% predicted FVC
NYHA class	6MWT
Assisted ventilation	Serum creatinine
BMI	PA systolic pressure
Diabetes	Pulmonary artery wedge pressure
Supplemental O2 at rest	

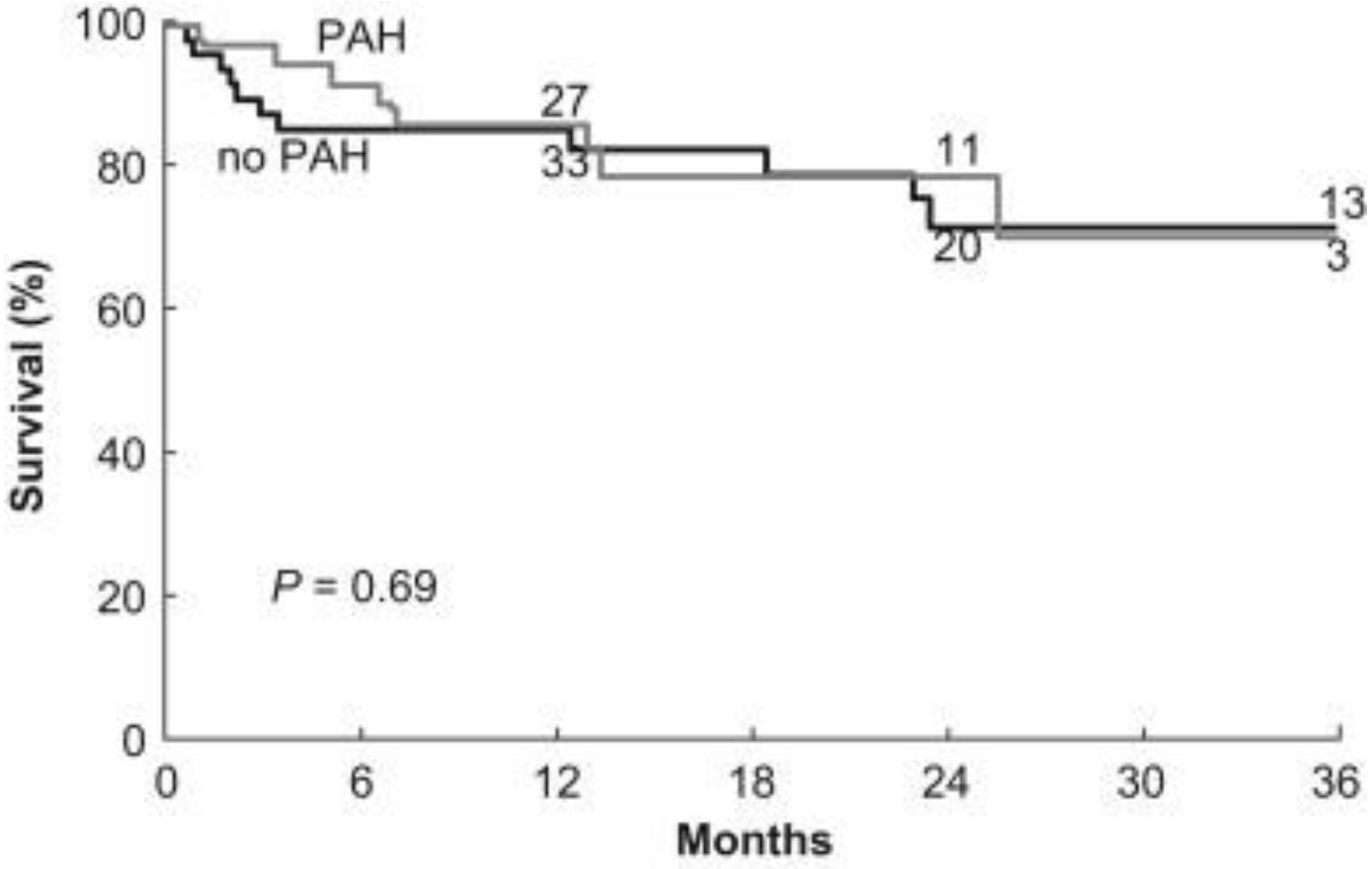
UNOS www.unos.org

Special Challenges Listing PAH Patients

- **Lung Allocation Score (LAS) system –IPAH patients are at a disadvantage compared with other diagnosis**
- **In a multivariable analysis comparing mortality predicted by LAS system to actual mortality in the Revial cohort, two additional variables were independently associated with increased mortality compared to the LAS: Mean RAP ≥14 and 6MWT ≤ 300 m.**
- **Although modification of the LAS system was approved, it has not yet been implemented**
- **UNOS/OPTN continues to use criteria for appeal of an LAS in a patient with IPAH**
- **A patient will be granted a LAS in the 90th percentile of all LAS when:**

1. **Patient deteriorating on optimal medical therapy**
2. **RA pressure > 15 mmHg**
3. **CI <1.8 liters/min/m^2**

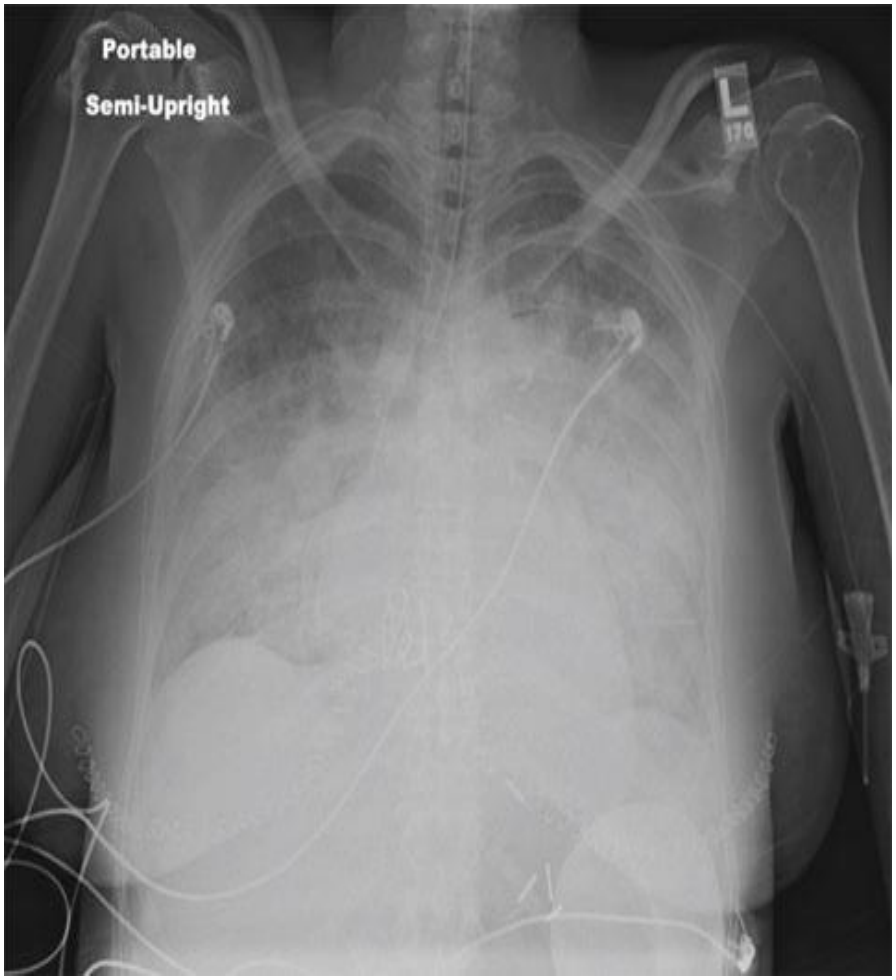
Lung Transplantation: Single vs Double ?



Murthy et al. J Heart Lung Transplant 2013

Lung Transplantation: Single vs Double ?

- **Complexity of peri-operative management needed for SLTx because the majority of the CO (80-90%) perfuses the newly implanted lung. There's a likelihood needing ECMO support due to increase risk for severe PGD in patients with PH**
- **Using DLTx will eliminate the risk of recurrent PH seen occasionally after SLTx**
- **DLTx will decrease the incidence of PGD (LTOG study)**
- **The majority of LTx centers favor DLTx for PAH**
- **Double lung transplant is currently the preferable choice**
- **The use of SLTx have decreased and <5% patients with PAH undergo SLTx (ISHLT 2012)**



2 hrs after lung transplant

Indications For Heart-Lung Transplant

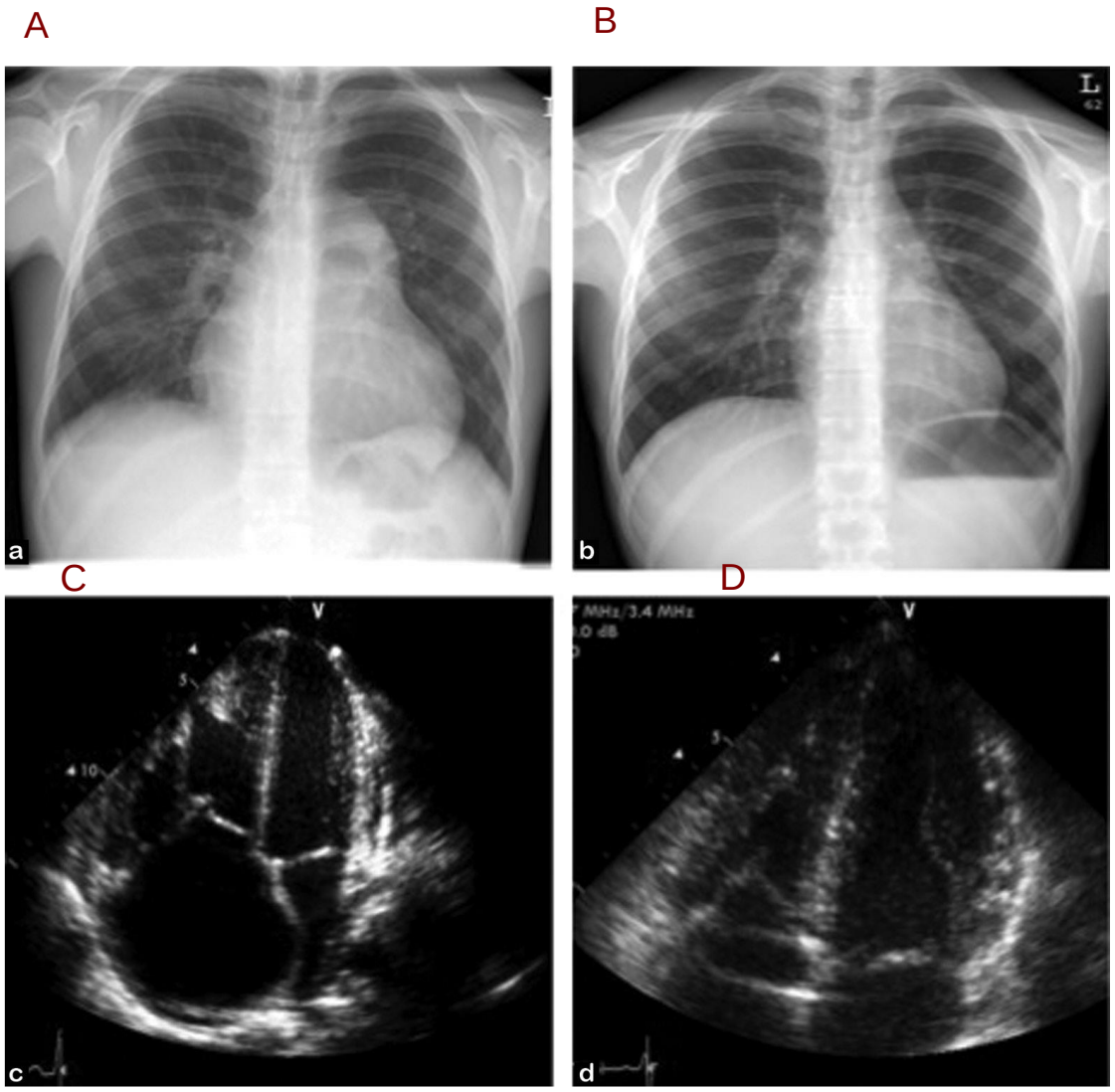
- Patients who have underlying vascular congenital vascular heart disease with complex systemic-to-pulmonary shunt (e.g Eisenmenger syndrome)
- Intra-cardiac lesions that require complex repair (e.g VSD)
- Recommended on patients with severe PA dilation >5 cm
- Severe RV dysfunction and dilation and when LV has also severe dysfunction

Bermudez. .Pulmonary hypertension: Basic Science to clinical Medicine 2016

Post-operative Management

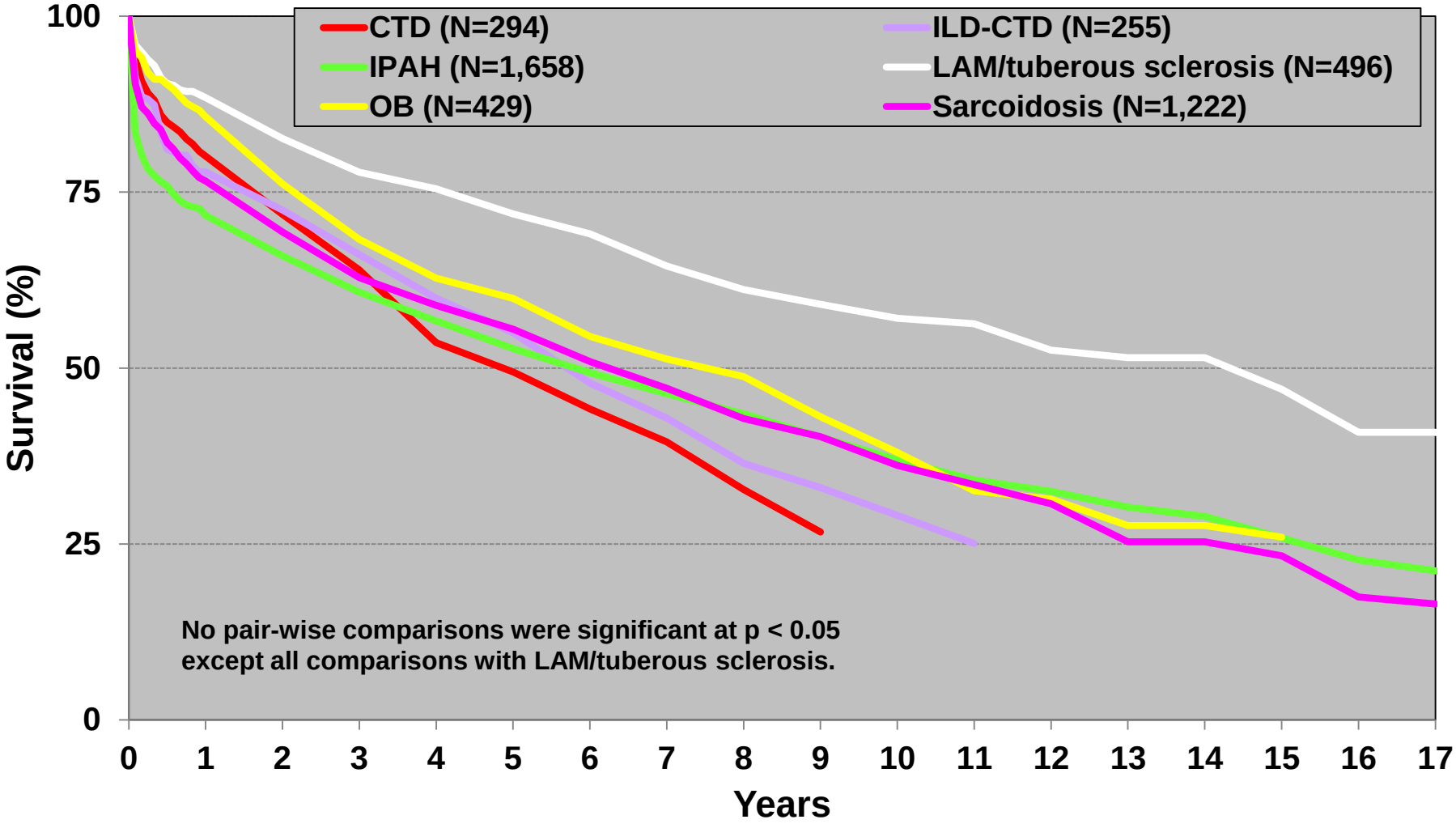
- Is challenging
- Often require temporally inotropes, vasopressor and inhaled nitric oxide support
- They have a higher risk for PGD during the first 72 hrs
- Some centers keep patients on ecmo
- Controlling reperfusion pos- graft implantation with respect to both the pressure and flow through the lungs and the inspired FIO2 has been demonstrated to minimize PGD.
- This is achieved by ventilating with RA and returning volume to the patient so that the mean PA pressures are < 15 for the initial 10-15 minutes.

Outcomes: Physiologic Improvements



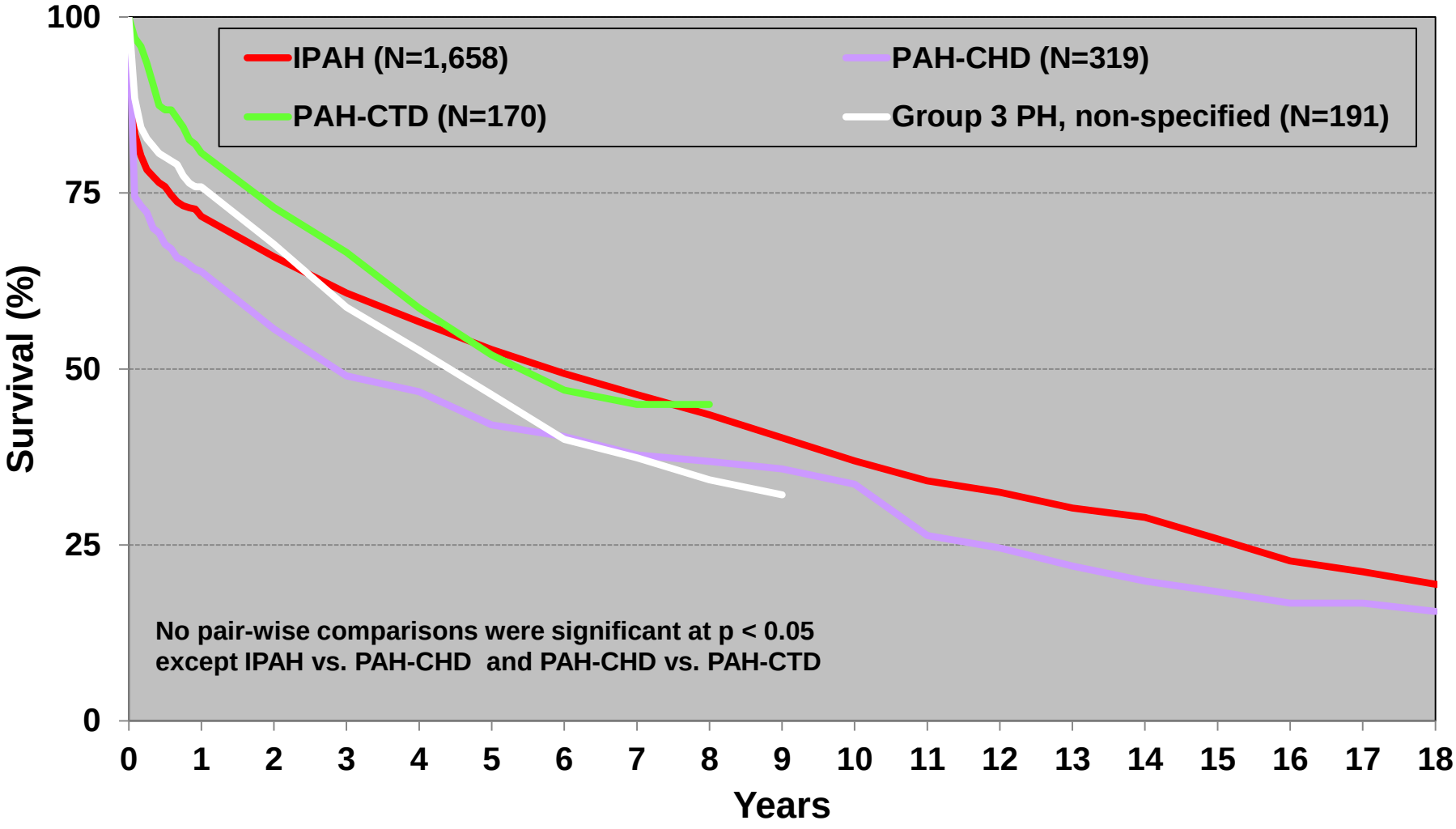
Adult Lung Transplants

Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2014)



Adult Lung Transplants

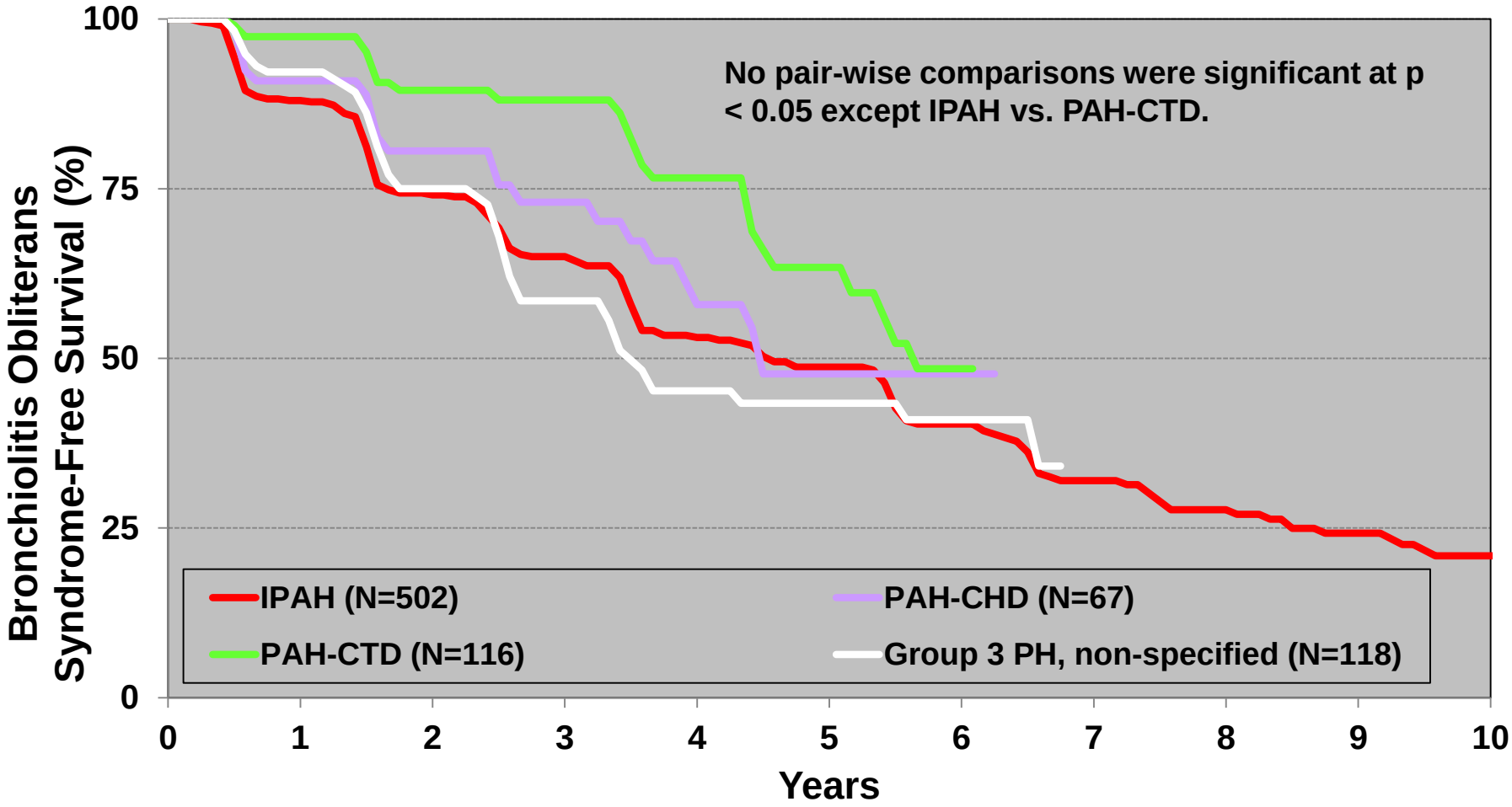
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2014)



Adult Lung Transplants

Bronchiolitis Obliterans Syndrome-Free Survival by Diagnosis Conditional on Survival to 14 days

(Transplants: January 1994 – June 2014)



Adult Lung Transplants

Cause of Death (Deaths: January 1990 – June 2015)
Diagnosis = IPAH

Cause of Death	0-30 Days (N=254)	31 Days - 1 Year (N=181)	>1 Year - 3 Years (N=145)	>3 Years - 5 Years (N=85)	>5 Years - 10 Years (N=115)	>10 Years (N=60)
OB/BOS	0	15 (8.3%)	55 (37.9%)	28 (32.9%)	37 (32.2%)	13 (21.7%)
Acute Rejection	9 (3.5%)	5 (2.8%)	5 (3.4%)	1 (1.2%)	2 (1.7%)	0
Lymphoma	0	1 (0.6%)	2 (1.4%)	1 (1.2%)	1 (0.9%)	2 (3.3%)
Malignancy, Non-Lymphoma	0	0	1 (0.7%)	6 (7.1%)	10 (8.7%)	9 (15.0%)
CMV	0	2 (1.1%)	1 (0.7%)	0	0	0
Infection, Non-CMV	36 (14.2%)	57 (31.5%)	25 (17.2%)	18 (21.2%)	17 (14.8%)	3 (5.0%)
Graft Failure	78 (30.7%)	33 (18.2%)	23 (15.9%)	16 (18.8%)	25 (21.7%)	14 (23.3%)
Cardiovascular	33 (13.0%)	6 (3.3%)	6 (4.1%)	1 (1.2%)	9 (7.8%)	5 (8.3%)
Technical	17 (6.7%)	11 (6.1%)	1 (0.7%)	0	0	0
Multiple Organ Failure	39 (15.4%)	28 (15.5%)	9 (6.2%)	2 (2.4%)	2 (1.7%)	5 (8.3%)
Other	42 (16.5%)	23 (12.7%)	17 (11.7%)	12 (14.1%)	12 (10.4%)	9 (15.0%)

Percentages represent % of deaths in the respective time period.

Conclusions

- Pulmonary arterial hypertension (PAH) accounts for less than 5 percent of lung transplants
- Overall, patients with PAH have the highest 30-day and 3-month mortality following lung transplantation- PGD
- Post-op management is challenging due to hemodynamic issues
- Based on Karnofsky score >80% at 2 and 3 years post-transplant (ISHLT registry 2010)
- Survival conditional on 1-year survival, patients with PAH do very well with a median survival of 10 years

Conclusions

- With the significant medical advances in treatment of PAH, transplantation should be reserved for those patients who have failed pharmacological therapy
- In the subset of patients who do not response to, deteriorate on, or do not tolerate vasodilators, significant improvement in hemodynamics , NYHA functional class, actuarial survival and QOL has been demonstrated with isolated lung transplantation
- Candidate selection and timing of referral to transplant centers is critical for ultimate success, particularly with current LAS


BARCELONA