

Lung Transplant Consideration: Anesthesiologist Perspective

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Abstract

Lung transplant has seen a significant progress since 1963 till this era. Worldwide lung transplant indications have broadened with time. Alpha 1 antitrypsin deficiency used to be the most common reason for transplant but now conditions like idiopathic pulmonary fibrosis, Cystic fibrosis, Non Cystic fibrosis bronchiectasis, lymphangioleiomyomatosis have become leading indications towards lung transplant. Relaxation of donor selection criteria management protocol preserving and optimizing lung function with development ex vivo perfusion techniques to recondition suboptimal lung has improved lung transplantation success. Post-transplant survival still poses challenge as median survival stands low around five years.

Keywords: Lung transplant; Donor criteria; Ex vivo; Post-transplant

Introduction

Organ Transplantation in India under aegis of National Organization Tissue Transplantation Organization (NOTTO) setup under Directorate General of Health Services established to oversee all donation and transplantation activities. In this regard, the entire

country is having the following setup at National, Regional and State Level (Table 1 & 2). Lung transplant be considered for adults with chronic end stage lung disease meeting all of the following general criteria [5].

Table 1: History of lung transplant.

National Level	(NOTTO)				
Regional Level (ROTTO)	PGIMER Chandigarh	KEM Hospital Mumbai	IPGME & R Kolkata	RGGGH Chennai	Guwahati Medical College
State Level (SOTTO)					

Table 2: Anesthesia for Lung Transplant.

Vladimir P Demikhov	1 st experimental lung transplant 1940 [1,2]
James Hardy	1 st human lung transplant attempted in 1963 [3]
Bruce Reitz and Norman Shumway	1 st successful combined heart lung transplant [4]
Joel Cooper	Two successful human single lung transplants [6]
Starnes and co-workers	1 st living lobar donor lung transplant in child with cystic fibrosis [8].

- a. High (>50%) risk of death from lung disease within 2 years if lung transplant is not performed.
- b. High (>80%) likelihood of survival at least 90 days after lung transplant.
- c. High (>80%) likelihood of five years posttransplant survival from a general medical perspective provided there is adequate graft junction (Table 3).

Table 3: Lung transplant is complex procedure consideration for transplant.

Absolute Contraindication	Absolute Contraindication
<ol style="list-style-type: none"> 1. Recent Malignancy 2. Untreatable significant dysfunction unless combined organ transplant be done 3. Uncorrected atherosclerotic disease with suspected or confirmed end organ ischemia/dysfunction 4. Acute Medical instability not limited to acute sepsis, liver failure, myocardial infarction. 5. Uncorrectable bleeding diathesis 6. Chronic infection with highly, virulent, or resistant microbes poorly controlled pre-transplant. 7. Active tuberculosis infection. 8. Significant chest wall/spinal deformity expected to cause severe restriction after transplant. 9. Class II/III obesity. 10. Nonadherence to medical therapy or prolonged episodes of nonadherence to medical therapy. 11. Psychiatric/psychological condition associated with inability to cooperate with medical/ allied health care team. 12. Absence of adequate social support. 13. Severely limited functional status with poor rehabilitation potential. 14. Substance abuse of dependence (alcohol, tobacco, marijuana). 	<ol style="list-style-type: none"> 1. Age> 65 years, low physiological reserve. 2. Class I obesity. 3. Progressive/severe malnutrition. 4. Severe symptomatic osteoporosis. 5. Extensive prior chest surgery with lung resection. 6. Mechanical ventilation or Extracorporeal life support. 7. Colonization or infection with highly resistant or virulent bacteria, fungi, Mycobacterium bacilli. 8. Infection with Hepatitis B, C consider transplant without significant clinical, radiological, or biochemical signs of cirrhosis/Portal hypertension stable on therapy. 9. HIV, lung transplant for ones with controlled disease undetectable HIV RNA compliant on combined ART therapy. 10. Infection with Burkholderia gladioli, cenocepacia and multidrug resistant Mycobacterium abscesses if infection treated preoperatively and reasonable control postoperatively. 11. Atherosclerotic disease burden sufficient to cause end organ disease after lung transplant. Consideration to PCI/CABG and transplant. 12. Medical condition be optimized like Type2 Diabetes Mellitus, Hypertension, Epilepsy, Central venous obstruction, Gastroesophageal reflux disease.

Table 4: Factors as per lung allocation score also highlight waitlist and transplant survival.

Waitlist survival	Transplant survival
Forced vital capacity	Forced Vital Capacity (B, D)
Pulmonary artery diastolic pressure (A, C, D)	Pulmonary capillary wedge pressure(D)
Oxygen requirement at rest (A, C, D)	Mechanical ventilation
Age	Age
Body Mass Index	Serum Creatinine
T2 Diabetes Mellitus Insulin dependent	Functional Status of patient
6 Minute Walk test	Diagnosis
Mechanical ventilation	
Diagnosis by group (A, B, C, D)	

Diseases Specific Candidate Selection

Patient selection needs to be meticulous use of Lung allocation Score since 2005 prioritizes patients on the basis of risk of death on waiting list(urgency) and chance of surviving one year after transplant(utility) [7].

Interstitial Lung Disease

Timing of referral

Histological/radiographic evidence of Usual Interstitial Pneumonitis (UIP) or fibrosing Non-specific Interstitial Pneumonitis (NSIP) regardless of lung function.

Abnormal lung function

- I. FVC<80% predicted
- II. DLCO<40% predicted

Dyspnea/functional limitation attributable to lung disease. Oxygen requirement even if only during exertion. Interstitial lung disease with failure to improve dyspnea.

Timing of listing

Decline in FVC>10% during 6 months follow up. Decline in DLCO>15% during 6 months follow up. Desaturation <88% or distance <250m on 6 minute walk test or >50m decline over 6 months. Pulmonary hypertension on right heart catheterization or 2D echo. Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.

Cystic fibrosis

Timing for referral

FEV1<_30% with rapidly falling FEV1 despite optimal therapy.

6 Minute walk distance < 400m

Pulmonary hypertension in absence of hypoxic exacerbation. Increased frequency of exacerbation associated with episode of acute respiratory failure requiring noninvasive ventilation. Increasing antibiotic resistance and poor clinical recovery from exacerbation. Worsening nutritional status despite supplementation. Pneumothorax Life threatening hemoptysis despite bronchial embolization

Timing for listing

Chronic respiratory failure associated with hypoxia (PaO₂<60mmHg/8kpa), hypercapnia PaCO₂>50mmHg/6.6kpa). Long-term non-invasive ventilation, pulmonary hypertension frequent hospitalization, rapid decline in lung function and WHO functional class IV.

COPD

Timing for referral

Progressive disease despite maximal treatment including medication, oxygen therapy and pulmonary rehabilitation. Patient not candidate for endoscopic or surgical lung volume reduction surgery. Bode index 5 to 6 with presence of hypercapnia PaCO₂>50mmHg/6.6kPa and hypoxia with PaO₂<60mmHg/8kPa with associated FEV1 below 25% of predicted value.

Timing of listing (presence of one criteria is sufficient)

BODE index ≥7 or FEV1 <15% to 20% predicted. Three or more severe exacerbation during preceding year. One severe exacerbation with acute hypercapnic respiratory failure. Moderate to severe pulmonary hypertension

Pulmonary vascular disease

Timing of referral

NYHA Class III/IV symptoms during escalating therapy, rapidly progressive disease, and parenteral targeted pulmonary hypertension therapy regardless of NYHA functional class. Known/suspected pulmonary vaso-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.

Timing for listing

NYHA Class III/IV despite trial of 3 months of combination therapy including proteinoids. Cardiac Index below 2 L/min/m² or mean right atrial pressure more than 15mmHg. The six minute walk test less than 350m and development of significant hemoptysis, pericardial effusion with signs of progressive right heart failure.

Removal from waiting list

Monitor patients for change in clinical status specially for Bridge to mechanical ventilation/Extracorporeal life support system. Presence of absolute/relative contraindications as listed above. Group A Mostly emphysema, Group B Pulmonary hypertension,

Idiopathic and congenital heart disease, Group C Septic lung disease like Cystic fibrosis, Group D Interstitial lung disease mostly Idiopathic pulmonary fibrosis (Table 4).

Anesthetic Concerns

Broad categories & indications for lung transplant once satisfied requires thorough pre-operative assessment as highlighted by findings in timing and listing characteristics above.

Pre-operative workup shall include [10-14]

Preanesthetic workup covering patient disease history and physical examination along with latest pulmonary function test. Effort tolerance as assessed by six minute walk test or in case of exercise intolerance by Dobutamine stress echo. The latest transthoracic echocardiogram (2D) with or without right heart catheterization ± coronary angiography depending on trans thoracic Echocardiography findings.

Antibiotic and immunosuppressant with possible need in selective cases for lung V/Q scan to assess lung tolerance for one lung ventilation.

Premedication

Preoperatively consideration to continuing the ongoing bronchodilator therapy, antibiotics and pulmonary vasodilator be considered. Patients on intravenous prostaglandins to continue till cardiopulmonary bypass (CPB) is initiated. Immunosuppression pre-transplant be considered as per institutional protocol. Sedation is avoided preoperatively as it can precipitate cardiorespiratory compromise. Post-operative analgesia by utilizing thoracic epidural analgesia or paravertebral block be decided preoperatively.

Intraoperative Monitoring and Induction

Essential monitors

Routine ASA standard intraoperative monitoring utilizing five lead electrocardiography system, pulse oximetry, quantitative waveform capnography, volatile anesthetic agent, core body temperature with invasive blood pressure, central venous pressure and consideration in presence of pre-existing pulmonary hypertension to pulmonary artery pressure pressure and transesophageal echocardiography monitoring be done alongside with the hourly urine output monitoring with indwelling Foley catheter and spirometric lung volume analysis be considered.

Additional monitors as per institutional protocol can be

BIS guided anesthetic depth, transcutaneous cerebral oximetry, near infra- red spectrophotometry, mixed venous blood oximetry, continuous cardiac output monitoring and continuous ABG monitoring

Role of Tee [11]

ASA/Society of Cardiovascular Anesthesiology Statement (2010) recommends TEE be used when planned surgery or patient

cardiovascular pathology might result in severe hemodynamic, pulmonary, or neurologic compromise. Role of TEE in an End stage

lung disease with Pulmonary artery hypertension due to lung pathology TEE evaluates during transplant [12-20] (Figure 1).

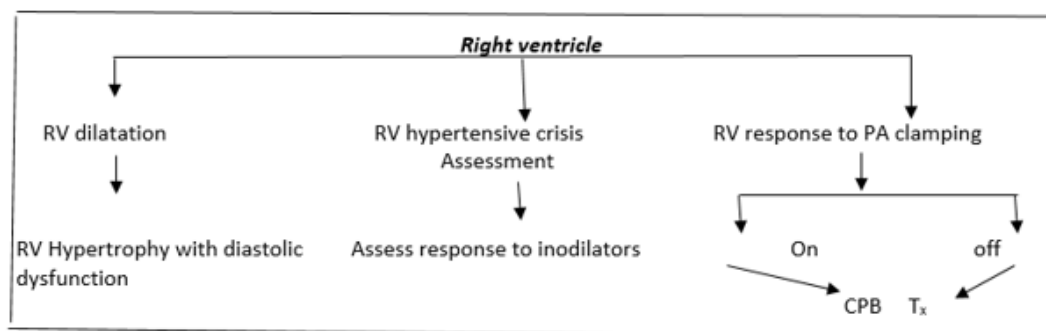


Figure 1

Preoperative screening for patent foramen ovale as it presents in 15-20% of patient population requiring intraoperative surgical closure [18]. Consideration for mechanical support requiring either cardiopulmonary bypass or ECMO [18]. Lung transplant candidates with suprasystemic pulmonary artery hypertension and gas exchange issues are ECMO supported preoperatively. Cannulation for ECMO can be guided by transesophageal echocardiography. Assessment for Pulmonary Venous Stenosis [19] with vessel diameter below 0.5cm, flow velocity more than 1m/sec, left atrial to pulmonary vein pressure gradient more than 10 to 12mmHg are suggestive criteria for Pulmonary venous stenosis.

Induction of Anesthesia

Risk for cardio-respiratory collapse is high so surgeon/perfusionist must be present for urgent sternotomy and cardiopulmonary bypass initiation. Hemodynamic goals are to preserve systemic vascular resistance and myocardial contractility, avoid increase in pulmonary vascular resistance by controlling factors like hypercarbia, pain, hypothermia, hypoxia, and hypovolemia. Narcotic based induction remains cornerstone involving 5-10mcg/kg fentanyl with 0.05-0.1mg/kg midazolam. Judicious dose of propofol followed by muscle relaxant and double lumen tube placed preferably left sided or single lumen tube for on pump single lung transplant can be considered. Double lumen tube provides increased surgical flexibility, irrigation of divided bronchus and differential ventilation after graft reperfusion with faster lung isolation.

Anesthesia Concerns Specific to Disease [5,17]

Obstructive lung disease

COPD/Alpha-one antitrypsin deficiency/ Bronchiolitis obliterans causative for smoking related emphysema entails pre-induction arterial blood gas analysis. The risk of pneumothorax during positive pressure ventilation/central venous access be kept in mind. Dynamic hyperinflation and cardiovascular collapse can occur so expiratory time for ventilation be increased. The quantitative ETCO₂ measurement can underestimate the PaCO₂

due to increased alveolar dead space.

Restrictive lung disease

IPF/scleroderma/Drug or radiation induced lung disease can lead to high peak airway pressures requiring ICU ventilators in place of routine anesthesia ventilators as they may not be able to deliver sufficient flows. The risk for pulmonary hypertension is increased so risk of rising pulmonary vascular resistance.

Suppurative lung disease

Cystic Fibrosis/Non Cystic fibrosis bronchiectasis needs aggressive pulmonary toileting due to increased purulent alveolar secretions into large conducting airways. Risk of multidrug resistant infection be considered prior to surgery.

Pulmonary vascular disease

Pulmonary arterial hypertension candidate consideration to CVC/PA catheter prior to induction be considered due to high risk of hemodynamic instability. Pre-induction femoral cannulation for CPB be considered in high risk patients.

Stages of Surgery

- a) Dissection of native lung
- b) Donor lung anastomosis (Figure 2)
- c) Graft Reperfusion

Deairing of graft through an opening in atrial anastomosis is done followed by lung inflation to sustained pressure of 15-20cmH₂O with partial release of pulmonary artery clamp. Atrial clamp is decamped to de-air the cuff before final knot is tied. Look out for hypotension now (Figure 3) Management is small boluses of adrenaline/calcium.

Coronary artery embolism

Usual in RCA as its position is uppermost in supine position. PA clamp is released slowly over 10 minutes limiting initial graft flow has shown to reduce primary graft dysfunction.

Ventilation Strategy

Maintain lowest FiO_2 maintaining adequate oxygenation with low peak inspiratory pressure of 15-20cm H₂O with PEEP 5 cm H₂O and respiratory rate of 8-10 breaths per minute.

Complication

Primary graft dysfunction

Graft removal leads to warm and cold ischemia with subsequent reperfusion injury leading to primary graft dysfunction [21,22]. Features of Primary graft dysfunction Poor oxygenation with

severity graded—on basis of PaO_2/FiO_2 ratio. Poor respiratory compliance with high pulmonary vascular resistance and pulmonary edema.

Management

Lung protective ventilation strategy as per ARDS protocol
Differentials synchronous lung ventilation if lung

compliance varies significantly. Selective pulmonary vasodilator Inhaled Nitric Oxide 10-40 ppm treat severe hypoxia and elevated pulmonary artery pressure (Figure 4 & 5).

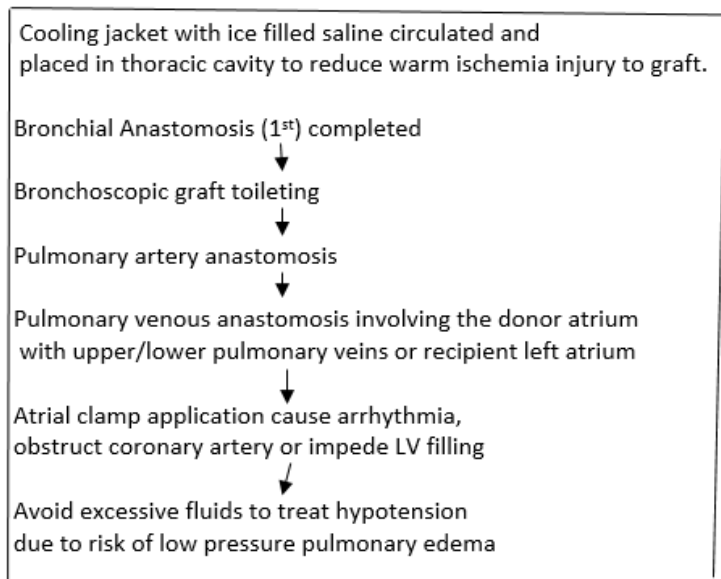


Figure 2

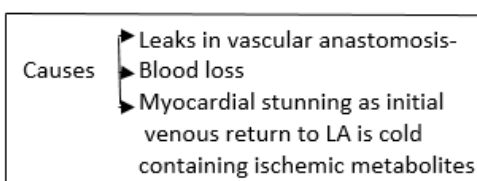


Figure 3

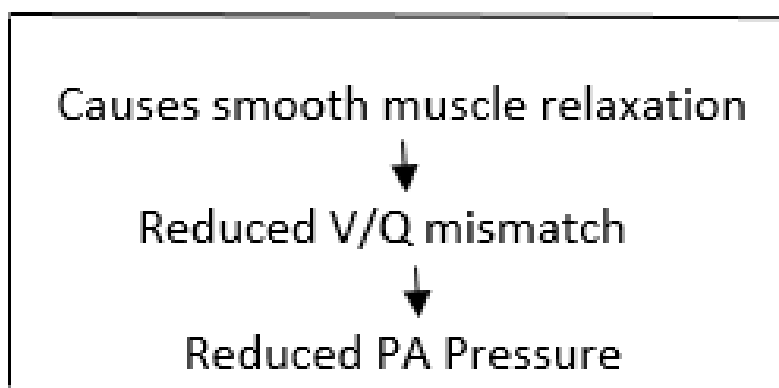


Figure 4

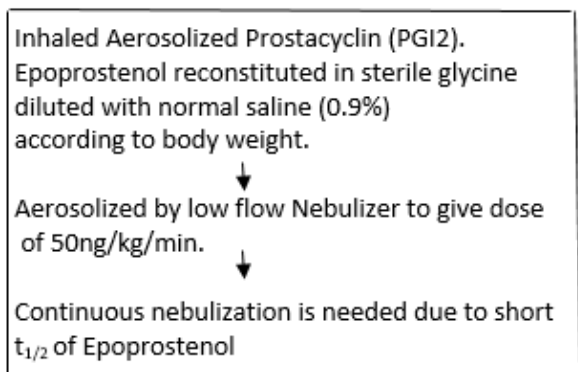


Figure 5: Prostaglandins.

Acute Cellular Rejection [23-29]

It occurs in upto 90% of patients in first postoperative year. It responds readily to simple augmentation of immunosuppressant with corticosteroids. Treatment reported in 40 to 50% patients during first year. Bronchoscopic transbronchial biopsy with histology showing perivascular and interstitial lymphocytic infiltrates. Based on the extent of lymphocytic infiltrates severity is grade. Reduced spirometry values measured at home can be used as standard daily monitoring. Severe acute cellular rejection with increased incidence of bronchiolitis obliterans syndrome has clinical hallmark of chronic allograft rejection.

Chronic Rejection of Lung allograft [24-33]

Leading cause for long term morbidity mortality pathologically shows obliterative bronchiolitis. Clinically seen as progressive airflow obstruction associated dyspnea and cough. Augmentation immunosuppressants, lymphoid irradiation and photopheresis are effective treatment. Bronchiolitis obliterans syndrome is seen in 64% of post-transplant candidates with 20% drop in FEV1 from baseline. Oral azithromycin recently has shown to improve lung function bronchiolitis obliterans syndrome.

Infection [34]

Transplanted lung is prone to various infections Bacterial, fungal, viral and parasitic as denervated lung with poor cough reflex and abnormal mucosal function limits removal of foreign material from Lungs. Maurer and colleagues found bacterial infection more common than viral and fungal infection [34].

Airway compromise

Donor bronchus depends on retrograde blood flow through low pressure pulmonary venous to bronchial vascular collaterals thus placing airway at risk of ischemic injury.

Newer Development in lung transplant [35-37]

Ex vivo perfusion system to condition lungs Hyperoncotic perfusate draws fluid out of extravascular space and causes dehydration of edematous lungs. Improved oxygenation permits

successful lung transplant initially deemed unsuitable.

Coupling Gene therapy technology

In ex vivo technique Cypel and colleagues demonstrated that transfer of IL-10 gene to perfused lung improved oxygenation reduced pulmonary vascular resistance reduced proinflammatory cytokine production with recovery of alveolar epithelial cell tight junction.

Acknowledgement

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Conflict of Interest

No conflict of interest.

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