The perioperative management of lung transplantation

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This article is dedicated to my lovely Mam, Pamela Johnstone, who lost her battle to cancer just prior to the article's inception.

Edited by Associate Professor Matt Doane

INTRODUCTION

Lung transplantation is an established standard of care to treat end-stage lung disease. Since the first successful lung transplant 30 years ago, advances in lung preservation, surgical technique and immunosuppression regimens have allowed lung transplantation to become a destination therapy for a diverse spectrum of lung disorders. In a carefully selected patient group, where all medical treatments have been exhausted, it represents an opportunity to regain quality of life and longevity.

This review article aims to give the reader an overview of lung transplantation and its evolution. It will detail current indications for lung transplants and considerations in the preassessment process.

Delivery of anaesthesia for lung transplantation is universally challenging. Inherent in the challenges is the opportunity for the cardiac anaesthetist to utilise every one of their specific skill sets. If they can execute these skills to a high standard, they have the potential to directly and significantly impact perioperative morbidity and mortality.

TIMELINE OF LUNG TRANSPLANT

1946. The first lung transplant in the Soviet Union was a single lung transplant in a dog.[1] Ultimately, this was unsuccessful due to bronchial anastomotic dehiscence.

1963. Haglin demonstrates reimplanted lungs in a primate that can maintain function post-operatively despite denervation.[2] The same year, Hardy and his team reported the first human lung transplant. The patient was deceased by day 18 post-surgery.[3]

1971. Derom's team is regarded as reporting the first real survivor of lung transplantation, although survival was only 10 months duration.[4] In the early days of lung transplantation, the overriding themes of failure were secondary to inadequate immunosuppression and difficulties with bronchial anastomoses.

The development of the immunosuppressant drug cyclosporine and demonstrable improvements in survival following liver and kidney transplantation led to renewed interest in cardiothoracic transplant.

1982. The first successful combined heart-lung transplant was performed.[5]

1983. The Toronto group showed that corticosteroid use appeared to be a significant factor in the weakness of bronchial anastomosis. By using the calcineurin inhibitor cyclosporine, corticosteroid use could be reduced, and bronchial healing could be improved.

1986. The Toronto Lung Transplant Programme performed the first successful single lung transplantation in two patients with pulmonary fibrosis.[6] This team also performed the first successful double-lung transplant using a tracheal anastomosis. They are credited with developing our standard technique today, which involves bilateral sequential transplantation. (This has the benefit of avoiding cardiopulmonary bypass).[7] In this same year, Australasia's first heart-lung transplant was performed at Sydney's St Vincent's Hospital in Dr Victor Chang's unit.

1990. The first isolated lung transplant was performed in Australia in 1990, also at St Vincent's Hospital, Sydney.[8]

LUNG TRANSPLANTATION: THE CURRENT CLIMATE

The number of adult lung transplants performed worldwide is almost 70,000.[9] In 2022, the NHS Blood and Transplant published its annual report. The report detailed the indications for lung transplantation (and their respective contributions to the overall total) as fibrotic (53%), obstructive (26%), vascular lung disease (9%) and septic (8%).[53] The leading indication for lung transplantation globally is Chronic Obstructive Pulmonary Disease. This breakdown in prevalence has remained static in Europe, but in North America and elsewhere, there have been an increasing number of transplants performed for idiopathic pulmonary fibrosis.[9]

In Australasia, five centres perform lung transplants: The Alfred (Melbourne), St Vincent's (Sydney), the Prince Charles (Brisbane), and the Fiona Stanley (Perth). In New Zealand, lung transplants are performed via the New Zealand Heart and Lung Transplant Service at Auckland City Hospital.

In 2021, there were 197 lung transplant recipients in Australia and New Zealand.[10] This breaks down to 6.5 transplant recipients per million of the population (pmp) in Australia (an increase of 16% on the previous year) and 5.8 pmp in New Zealand (a rise of 57.9% on the last year). The number of patients being put forward for lung transplantation is ever-increasing.

The landscape for donation has changed somewhat with the acceptance of donations after circulatory death (DCD), which has increased the pool of potential donors. The Australian Donation and Transplant Activity Report 2022 saw a 122% increase in deceased donation rates over the past 10 years.[11]

Last year, DCD transplantation represented 23% of total activity in the UK.[53] In donations after brainstem death (DBD), donor optimisation has increased the number of hearts and lungs retrieved from DBD donors. This increased success comes from a bundle of care involving a trained cardiothoracic retrieval team member attending to the donor before the rest of the team to assist with optimisation.

The COVID-19 pandemic significantly impacted this increased donation trend, and lung transplant rates have declined from pre-pandemic levels across most states. In 2022, 142 lung transplants were performed in Australia, 29 fewer than in 2021, when there were 171.[11]

Pre-transplantation considerations

Lung transplantation represents a conflicting paradigm; it offers the possibility of returning a severely debilitated patient to an acceptable quality of life. Conversely, the high-risk nature of the perioperative journey means it has the potential to cause the patient not only significant morbidity but even premature death.

In the first year, 20% of patients will die from primary graft dysfunction or infection with or without multi-organ failure.[12] Survival is 60% at five years, and 40% at 10 years.[13,14] These high stakes of the operation itself, combined with the comorbid state of most transplant recipients (poor respiratory reserve, often significant cardiac disease, and chronic infection), make delivery of anaesthesia for this patient group an extreme challenge.

Eligibility of recipients

Lung transplantation is recommended based on a balance of benefits, risks, and alternatives.[15] Donor lungs remain a scarce commodity, and a critical determinant of outcomes is the appropriate selection of recipients in the first instance. This is based on the patient's clinical need and capacity to benefit. Every transplant unit is responsible for maximising overall benefit by ensuring optimal organ allocation. Early referral is essential, allowing robust patient assessment and thorough education of patients and their families.

Lung transplantation is considered for adults with advanced lung disease, on maximal medical therapy. They must meet the following general criteria[16]:

- There is a high (50%) risk of death from lung disease within two years if lung transplantation is not performed.
- High (80%) likelihood of surviving at least 90 days after lung transplantation.
- High (80%) likelihood of 5-year post-transplant survival from a general medical perspective, provided there is adequate graft function.

Pre-transplant listing

A multi-disciplinary team decides to list a patient. The process encompasses four distinct phases:

- Referral.
- Pre-assessment in an outpatient or inpatient setting.
- Listing decision (via a multi-disciplinary team).
- Follow-up on the waiting list.

Given the rapidly progressive nature of some lung disorders, such as interstitial lung disease (ILD), and the unpredictable course of others, such as pulmonary arterial hypertension (PAH), early referral is critical. This gives the transplant team time to assess the patient and allows the patient time to prepare psychologically and get their affairs in order. Mortality on the waiting list remains high, and an essential component of proactive MDT planning is early referral and liaison with palliative care services at the time of listing. Data from the United States in 2019 placed the mortality rate on the waiting list at 14.6%.[17] The NHSBT data collected between 2017 and 2019 showed that three years after being placed on the transplant list, 45% of people had received a transplant, and 18% had died.[53]

Referral

Transplant teams use detailed inclusion and exclusion criteria to list or delist a patient for lung transplantation. The International Society for Heart and Lung Transplantation (ISHLT) provides disease-specific thresholds for listing a patient for transplant.[18–20]

In Australia, transplant lists are nationally coordinated systems. In 2009, the Commonwealth Government created the National Organ and Tissue Authority. This group works alongside all Australian states and territories to improve organ and tissue donation.

In Australasia, lungs are offered to the jurisdiction's home state first. If there is no lung transplant centre in the state, the organ is put forward according to the specific ADTCA/TSANZ Organ Allocation Rotation. When there are urgent listings, a recipient in the donor's state is offered the organ before offering it to the transplant unit of the urgent listing.[47]

There is no specific national priority urgent lung listing category in Australasia. However, to increase a person's chance of being allocated donor lungs, a lung transplant wait list patient from one state may be notified to another state's lung transplant program. This is termed national notification and is at the discretion of the lung transplant unit director.[47]

Given the diversity of lung diseases, recipient eligibility criteria are disease-specific, as summarised in Tables 1-4.[21]

Table 1. Diffuse parenchymal lung disease referral criteria

Diffuse parenchymal lung disease	Referral criteria
Includes lung fibrosis of any aetiology, chronic hypersensitivity pneumonitis and sarcoidosis	Decline in forced vital capacity (FVC) of 10% or more and in diffusing capacity of the lungs for carbon monoxide (DLCO) of 10% or more within the prior 6 months Development of pulmonary hypertension Hospitalisation because of respiratory decline, acute exacerbation, or pneumothorax Significant exercise-associated desaturation or requirement for oxygen

Table 2. Obstructive lung disease referral criteria

Obstructive lung diseases	Referral criteria
Includes smoking-related COPD, alpha 1 antitrypsin deficiency, obliterative bronchiolitis and chronic asthma	Forced expiratory volume in one second (FEV_1) <20% of predicted Body-mass, airflow obstruction, dyspnoea, and exercise (BODE) index >7 Severe exacerbation with hypercapnic respiratory failure or recurrent exacerbations Moderate to severe pulmonary hypertension PCO_2 >50 mmHg and/or PO_2 <60 mmHg

Table 3. Pulmonary vascular lung disease referral criteria

Pulmonary vascular disease	Referral criteria
Includes idiopathic PAH or that associated with connective tissue disease, complex congenital heart disease with Eisenmenger's syndrome, chronic thromboembolic pulmonary hypertension	NYHA Functional class III or IV despite escalation of pulmonary vasodilator therapy Refractory or progressive right heart failure

Table 4. Suppurative lung disease referral criteria

Suppurative lung disease	CF referral criteria
Includes Cystic Fibrosis (CF) and non-CF bronchiectasis	Frequent hospitalisation FEV_1 <30% of predicted especially if a rapid downward trajectory is observed Increasing antibiotic dependence or resistance Life threatening haemoptysis or pneumothorax Requirement for non-invasive ventilation Development of pulmonary hypertension PCO_2 >50 mmHg and/or PO_2 <60 mmHg

Considerations for exclusion from the transplant list

Not all patients who meet transplantation criteria are suitable. Careful evaluation of extra-pulmonary medical comorbidities, mental health and social circumstances are undertaken to ascertain the prospect of post-transplant success and survival. Absolute contraindications include malignancy within the last 5 years, BMI>35 kg/m^2 and untreatable advanced dysfunction of another organ system.

Medical conditions that have not resulted in end-organ damage should be optimised before transplant, such as gastroesophageal reflux disease (GORD) or systemic hypertension. HIV is a relative contraindication, and patients with viral Hepatitis B and C may be considered, provided there is no active disease or viral replication. Table 5 describes absolute exclusion criteria for lung transplantation.[15,20]

Table 5. Exclusion criteria for lung transplantation

ABSOLUTE contraindications

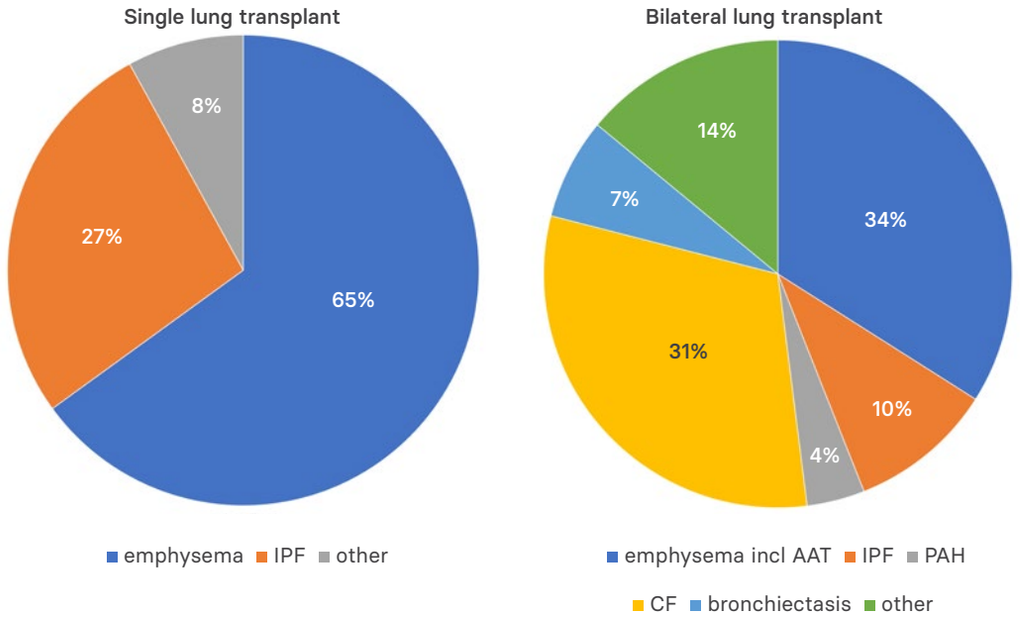
- Active malignancy
- BMI >35 kg/m^2
- Advanced dysfunction in another body system that impacts perioperative survival or 5-year survival
- Unstable critical condition (e.g., sepsis)
- Significant chest wall or spinal deformity causing restrictive lung disease
- Uncontrolled extrapulmonary manifestations of systemic disease
- Substance addiction or abuse
- Documented nonadherence to medical therapy
- Mental health conditions that fail to respond to treatment and are associated with poor quality of life and compliance to medical therapy
- Absence of reliable social support

Single and bilateral transplants

Generally, lung transplantations are bilateral. During the initial suitability assessment, a decision is made whether single lung transplantation is an option. Occasionally, a single lung transplant will be opted for where the primary disease process is COPD or ILD and only in an older patient demographic. Suppurative lung disease or pulmonary hypertension are contraindications to single lung transplantation.[22]

Figure 1 describes the prevalence of indications for single and bilateral lung transplantation in Australia.[23]

Figure 1. Indications for single and bilateral lung transplantation in Australia



Alpha-1 Antitrypsin Disease (AAT) Idiopathic Pulmonary Fibrosis (IPF)

Consent

Consent for transplantation is robust. It includes a discussion of the surgical and anaesthetic risks and benefits and a donor acceptance form. In this form, the recipient consents to the criteria for selecting their organ. This includes, for example, whether they would be happy to receive lungs from smoking donors.

Specific prospective recipients are placed at much higher risk for adverse events, and at the time of listing, they should be counselled about this. Higher-risk patients include those who have:

- Pre-transplant extracorporeal membrane oxygenation (ECMO)
- Oxygen requirement > 5L/min
- Severe PAH
- Chronic steroid use
- Donor-to-recipient weight ratio <0.7
- Cytomegalovirus (CMV) mismatch

Objectives of pre-listing assessment

Assessing the appropriateness of listing for lung transplantation encompasses clinical, social, and psychological suitability. Table 6 delineates these considerations in more detail.

Clinical urgency is graded by the required support level and evidence of rapid deterioration from the underlying indication for transplant.

Table 6. Potential clinical investigations before listing for lung transplantation

Blood tests haematology, biochemistry, serology, immunology	blood group, antibody screen, FBC, APTT PT, INR, fibrinogen urea and electrolytes, creatinine, uric acid, calcium, phosphate, liver function tests, thyroid function tests, fasting blood glucose, fasting blood lipids, alpha 1-antitrypsin (if indicated) HIV, hepatitis B and C, syphilis, rubella, toxoplasma, Epstein Barr Virus, varicella- auto-immune screen, aspergillus serology, human leucocyte antigen (HLA) typing and antibody screen zoster, herpes simplex, CMV
Pulmonary assessment	LFT: Flow volume loop, lung volumes, gas diffusion, plethysmography 6-minute walk test (6MWT) with oximetry Arterial blood gas Respiratory muscle function tests VQ scan Thoracic CT: exclude malignancy, assess pulmonary vasculature and collaterals
Cardiac high likelihood of concomitant cardiovascular disease in patients with end stage pulmonary disease, means high risk patients warrant assessment by a cardiologist	ECG TTE: RV function and pulmonary arterial (PA) pressures Cardiac catheterisation Right heart catheterisation
Microbiology	Sputum culture and sensitivity (C & S) Midstream urine: urinalysis (C & S)
DEXA bone scan	To assess for severe or symptomatic osteoporosis (defined as bone mineral density > 2 SD less than predicted for the patient's age)

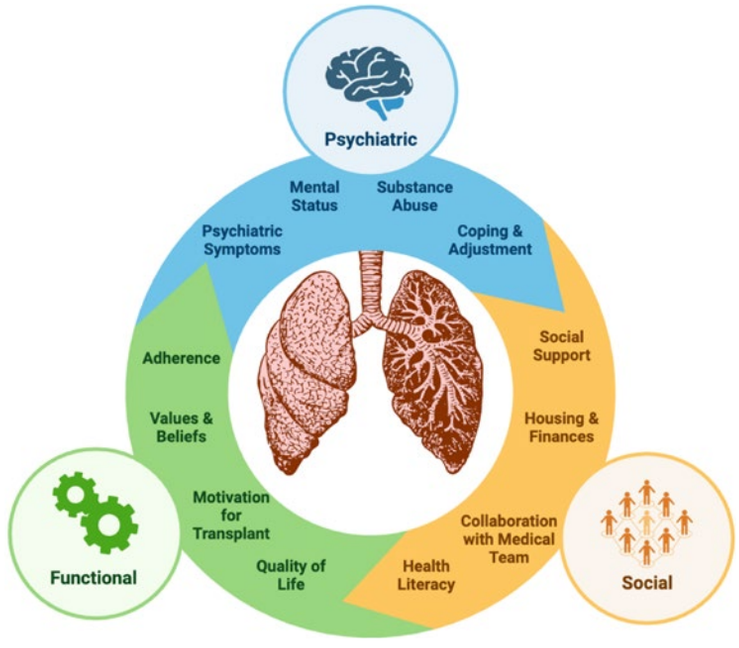
Psychosocial evaluation

To live with a lung transplant is a life-long commitment to medical follow-up and compliance. Nonadherence to even one dose of immunosuppressant can have catastrophic consequences for the recipient.

Psychiatric assessment focuses on previous history and current stability, coping mechanisms, and recent and past substance abuse. Social assessment examines health literacy, the ability to collaborate with the medical team, and the quality of social support and housing. Functional evaluation reviews individual values and beliefs. Ensuring potential recipients understand the responsibilities of receiving a transplant and their motivation is essential for long-term success.[48]

Figure 2 describes key elements of a lung transplant candidate's psychosocial and functional assessment.[48]

Figure 2. The psychological functional assessment of the lung transplant candidate



Other considerations

Candidates for lung transplantation are approaching their physiological reserve. The underlying lung disorder has often altered their respiratory mechanics, causing a pathological breathing pattern:

- Increased breathing effort due to chronic hyperinflation and unfavourable diaphragmatic position
- Increased airway resistance and decreased lung compliance
- Impairment of secretion clearance and mucociliary transport.

Lack of respiratory reserve often renders these patients inactive, with consecutive deconditioning in strength, endurance, and cardiopulmonary performance. This is usually compounded by reduced trunk mobility (for example, in emphysema), leading to shortening of the respiratory muscles and steroid-induced myopathy.

Enrolment in a pulmonary rehabilitation program is mandatory. For those patients on long-term corticosteroid therapy, there is a gradual reduction in their dosing, ideally tapering entirely off.

Prehabilitation encompasses aerobic load training to optimise body composition, intending to increase muscle mass while reducing body fat. It includes improving posture, chest, and joint mobility. The overall goal is to optimise the functional capacity of the transplant candidate despite the existing terminal underlying disease and maintain this until transplantation.

Follow up on the waitlist

All patients on the list are regularly reviewed by their respiratory physician to ensure their condition still meets transplantation criteria. Fundamental investigations are updated, and ongoing pulmonary rehabilitation continues.

Extracorporeal life support in lung transplantation

Extracorporeal life support (ECLS) describes a spectrum of mechanical support that oxygenates, removes CO_2 and/or improves haemodynamic stability. It includes extracorporeal membrane oxygenation (ECMO) and interventional lung assist devices such as the Novalung (trademark Fresenius Medical Care North America). ECMO is the only form of ECLS for both the heart and lungs. It can be utilised at each discrete stage of the lung transplantation process. The indications for ECMO in lung transplantation are listed in Table 7.

Table 7. Perioperative indications for ECMO in lung transplantation

Bridge to lung transplantation (BTT)
Intraoperative cardiopulmonary support
Bridge to recovery post-operatively

Broadly speaking, ECMO can be veno-arterial (V-A) or veno-venous (V-V). The type of ECMO support is determined by the configuration of the cannulation and is tailored to the patient's clinical needs.

In V-A ECMO, blood is removed from the body via a venous cannula, oxygenated, and returned to an artery from where it is circulated around the body, reducing the stress on the heart and lungs. In V-V ECMO, there is no direct support for the heart. Blood is taken from a vein, oxygen is added, CO2 is removed, and blood is returned via a vein from where the patient's heart can pump oxygen-rich blood around the body. It allows the lungs to rest.

Table 8 describes what cardiorespiratory support can be supplied by various ECMO configurations, highlighting the indications for use in lung transplantation.[24] Intraoperatively, central V-A (right atrium to aorta) is most common as it negates Harlequin Syndrome.[1]

Table 8. ECMO configurations in lung transplantation

ECMO configuration	Support	Indication	Use in lung transplant
V-V: peripheral cannula in superior vena cava (SVC), internal jugular (IJV) or femoral vein	respiratory	hypoxaemia	BTT post-op respiratory support
V-A: can be peripheral, (femoral and subclavian arteries) or central (right atrium to aorta).	respiratory and circulatory	hypoxaemia and cardiac failure	BTT intraoperative mechanical support
VV-A as per V-V plus an additional cannula in the subclavian or femoral artery	respiratory and circulatory	severe right heart dysfunction with hypoxaemia	BTT intraoperative mechanical support is possible but unusual post-op respiratory support

ECMO pre-surgery: A bridge to transplant

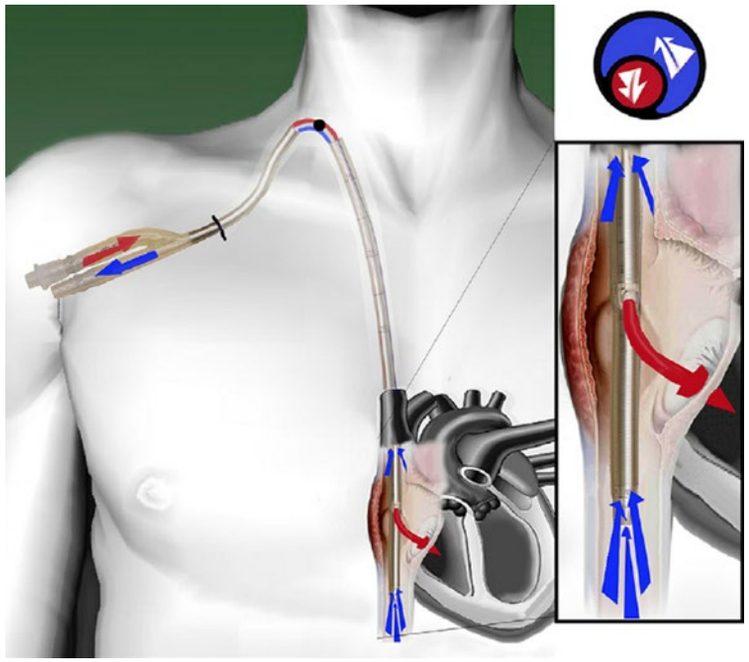
Traditionally, mechanical ventilation and sedation were the only options to bridge a patient in terminal respiratory failure to transplant. Prolonged sedation and artificial ventilation render the patient bed-bound, leading to profound deconditioning. Mechanical ventilation is associated with significant risks such as airway complications, pneumonia, and sepsis, all of which impact post-transplant outcomes and result in a decreasing probability of successful transplantation. Today, in a select group of patients, ECMO can be utilised as a BTT to improve pre-transplant stability whilst a suitable donor is found. ECMO as a BTT should only be considered for those patients who have acutely decompensated and have otherwise good rehabilitation potential. This usually means they have had a short duration of severe illness.

V-V ECMO is the method of choice as a BTT for isolated respiratory failure.[52] Indications for V-A ECMO in BTT are severe pulmonary hypertension, right ventricular dysfunction, and those decompensating on V-V ECMO. These individuals have worse outcomes following lung transplant than patients with other indications,[52] as V-A ECMO is more invasive and carries higher risk. The outflow cannula being directly in the arterial circulation means the patient requires an increased amount of heparin for anticoagulation, and there is a higher rate of embolic events, stroke, and limb complications. In comparison, V-V ECMO has a lower rate of vascular and neurological complications.[24]

V-V ECMO can be in a femoral-femoral configuration, or most recently, it has been deployed using a single-site veno-venous device. The Avalon cannula is a bi-caval, dual-lumen catheter with a single insertion site in the IJV. Deoxygenated venous blood is simultaneously drained from the SVC and inferior vena cava (IVC), and oxygenated blood is returned to the heart via a delivery port in the right atrium.

Figure 3 demonstrates the Avalon cannula in-situ. Inflow to the ECMO circuit is from the tip of the cannula, located in the IVC, along with fenestrations in the middle of the cannula at the SVC-right atrial junction. The outflow is directed towards the tricuspid valve.

Figure 3. Positioning of an Avalon bi-caval dual-lumen catheter



This system has only a single insertion point in the IJV. It simulates normal physiological blood flow by removing deoxygenated blood from both the SVC and IVC and returning oxygenated blood to the right atrium.

Regardless of the configuration, the key to ultimate success in ECMO as a BTT is to have a patient established on ECMO, awake and not intubated, who is mobilising, thus preventing deconditioning. While the upper-extremity-only circuit spares the need to access a patient's femoral vessels,[25] physiotherapy and prehabilitation are well-established practices in patients with femoral cannulation. The means to prevent deconditioning while a patient waits for their donor lungs has allowed a successful lung transplant to be performed after a patient has been on ECMO, in some cases for several months.[52]

Transplantation: Preoperative considerations

Once a donor has been identified, two distinct teams are mobilised. The first team will assess the donor lungs for suitability. Team two will remain at the transplant centre, where they will contact the potential recipient and prepare them for imminent surgery.

Donor evaluation: Explanation assessment

Evaluation of the donor lung can begin many hours or days before the explant process. After confirmation of consent, verification of brainstem death (in DBD), and assessment of ABO compatibility, a comprehensive history is taken from the donor's family.

Fibreoptic bronchoscopy is performed on the donor,[21] allowing inspection of the airway anatomy and the extent of secretions. The proceduralist will also acquire bronchial washings to guide the perioperative antimicrobial regimen. On surgical explantation, the lungs are assessed for their ability to be recruited.

Donor evaluation: Explantation and dissection

If the donor is DCD, the chest is rapidly opened after bronchoscopy, and the cross-clamp is applied to the

aorta and SVC.

If donation is via DBD, once the chest is opened a deflation test is performed followed by full recruitment. The FiO_2 is increased to 1, and arterial blood gases are taken. Lung protective ventilation is commenced with a FiO_2 approximating 0.5 and PEEP 5-8cmH_20. The gases are communicated to the implant centre, and once the implant team accepts the lungs, a decision is made as to when to apply the cross-clamp. The lungs are re-recruited before being transported (inflated) and on ice.

Ex-vivo lung perfusion

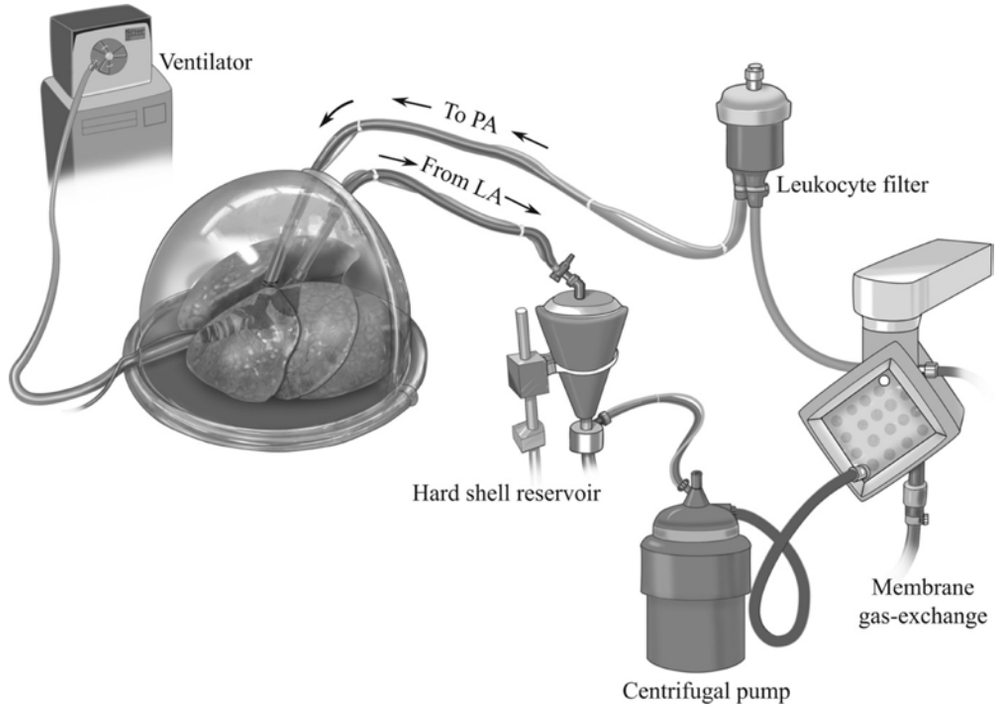
The lungs are one of the most precarious organs during the transplantation process. Events surrounding brain death subject the lungs to various mechanisms of injury, including ventilator-acquired pneumonia, neurogenic or hydrostatic pulmonary oedema, and barotrauma. Unfortunately, this means that many potential donor lungs are rejected. Data from the 2019 Organ Procurement and Transplantation Network (OPTN) reports that 6.4% of lungs recovered for transplant were not transplanted.[17] Consequently, recent strategies to optimise the viability of potential donor organs have gained much traction.

Ex-vivo lung perfusion (EVLP)[26] has made the expansion of the donor pool possible. EVLP has emerged as a modern preservation technique that allows more accurate lung assessment and improves lung function. An example is presented in Figure 4.

EVLP involves 4-6 hours of reconditioning via perfusion and ventilation of the lungs under an EVLP dome. There are four distinct phases encapsulated with EVLP[27]:

1. gradual rewarming to a state of normothermia
2. gradual increase in vascular flow as the lungs are rewarmed, targeting 40% of the donor-predicted cardiac output (CO)
3. protective lung ventilation
4. acellular perfusate with increased colloid osmotic pressure.

Figure 4. Lungs awaiting transplantation, in steady state under an EVLP dome[55]



Donor and recipient compatibility

The two most crucial features in matching a donor to a recipient are ABO blood group compatibility and size compatibility.[51] The latter can be fraught and is mainly based on comparing the donor and recipient heights and estimating lung volumes. The underlying condition of the recipient also affects the size of the lungs they require. Emphysematous lungs have larger thoracic cavities, while ILD is associated with smaller thoracic cavities.

AB blood group recipients are more likely to be matched, whereas patients with the O blood group remain on the wait list for much longer. Data from the NHSBT between 2018 and 2021 calculated the median time for AB and O at 345 days and 1177 days, respectively.[53] Table 9 demonstrates the criteria for allocation of donor lungs to recipients.

Table 9. Patient allocation criteria for lung transplantation

1. ABO compatibility
2. Size compatibility based on CXR measurements and total lung capacity values
3. Absence of a positive T-cell crossmatch and acceptable anti-HLA antibody profile on Luminex testing
Where more than one potential recipient meets the above criteria, the first choice will be determined by the following process
4. Clinical urgency and logistics
5. Long-term outcome/benefit
6. CMV status of donor and recipient
7. Recipient waiting time (if all other factors are equal)

Preoperative anaesthesia assessment

By the time the recipient arrives on their surgery day, they have undergone extensive anaesthetic review. On arrival, the case anaesthetist performs a targeted assessment, ascertains the need for premedication, and constructs a robust airway strategy. This is especially necessary for patients whose primary condition may render their airway more challenging to manage, such as those with connective tissue disease.

The presence of right ventricular impairment and/or pulmonary hypertension should be reviewed to allow the anaesthetist to risk stratify the potential for perioperative cardiac decompensation. Given the need to protect central veins if ECMO cannulation is required, a strategy for vascular access should be carefully considered.

Transplantation: Intraoperative management

The retrieval team will provide an estimated time of arrival for the donor lungs, at which point the anaesthetist and transplant coordinator will liaise to ensure meticulous timing of arrival of the recipient into the operating theatre. Initiation of anaesthesia must only be commenced after the call to confirm the donor lungs are officially accepted. This ensures graft ischaemic time is minimised. It also limits unnecessary time under anaesthesia for the recipient who, once intubated, may be very difficult, if impossible, to extubate given the extent of their end-stage lung disease.

Ischaemic time

The total ischaemic time is the difference between the donor cross-clamp and recipient reperfusion. By convention, the limit of acceptable ischaemic time for lungs was six hours. Data from ISHLT show that ischaemic times carry much less significance provided the lungs are preserved at 4 degrees centigrade on ice. Today, lung allografts with ischaemic times of 8-10 hours are associated with acceptable perioperative outcomes and post-transplant survival.[28]

Anaesthetic management

Typically, 1 hour is allocated for anaesthesia and 1 hour for preimplantation surgery. Full monitoring,

including a right-sided radial arterial line, is applied, and large IV access is established. Anaesthesia is induced and maintained with either volatile anaesthesia or total intravenous anaesthesia (TIVA) if ECMO is being utilised.

Induction of anaesthesia can be fraught in this patient demographic with profound hypotension or complete cardiovascular collapse. Having the surgeon and perfusionist in the OT during induction is prudent.

Meticulous essential airway management is paramount. Avoid aggressive bag-mask ventilation but ensure adequate ventilation to avoid hypoxaemia or hypercarbia both of which will increase pulmonary vascular resistance. Avoid aggressive bag-mask ventilation but ensure adequate ventilation to avoid hypoxaemia or hypercarbia, which will increase pulmonary vascular resistance (PVR). The convention is to place a left sided double lumen tube (DLT) if the transplant is off-pump or on ECMO and a single-lumen ETT if on CPB. The convention is to place a left-sided double-lumen tube (DLT) if the transplant is off-pump or ECMO and a single-lumen ETT if on CPB.

A quad lumen central line and vascular sheath are sited, and ideally, a pulmonary artery catheter (PAC) is floated. The tip of the PAC is withdrawn to the proximal PA before pneumonectomy of the recipient's native, diseased lungs to avoid it being included in the suture line. The position is confirmed using transoesophageal echo (TOE).

Cerebral monitoring, often consisting of processed EEG and/or cerebral oximetry, is more commonly used as a marker of brain oxygenation.

Meticulous attention should be paid to maintaining normothermia through a forced air patient warming device and fluid warmer, especially if the operation is carried out on ECMO or without CPB.

Patient blood management

Blood products should be readily available at the time of incision. These include packed red blood cells and fresh frozen plasma. Cell savers are utilised from the start. A rapid volume transfuser, such as a level 1, should be available from the beginning. Patient blood management (PBM) also includes point-of-care testing to guide the judicious use of blood products through TEG or ROTEM.

Immunological considerations

Antibiotics are delivered 30 minutes before skin incision. The regimen is based on the institution's antimicrobial policy and the patient's pre-existing colonisation. A dose of 10mg/kg of methylprednisolone is delivered before reperfusion and three doses post-operatively in the intensive care unit (ICU). However, institutional practice may vary and should be clarified at each new location.

Transoesophageal Echo (TOE)

TOE is utilised throughout the surgery for haemodynamic monitoring, including RV and pulmonary venous and pulmonary artery anastomosis assessments. The TOE also guides the vasculature de-airing during the anastomoses' final stages.

Transplant surgical access

Bilateral lung transplantation can be performed via clamshell incision, sternotomy, or bilateral anterior thoracotomies. The latter is more prevalent in off-pump techniques.

Circulation strategies for lung transplantation

Lung transplantation can be performed off-pump, via sequential one-lung ventilation, or using ECLS via CPB or ECMO. The circulation strategy employed may influence lung transplantation outcomes including the development of one of the most feared outcomes: Primary Graft Dysfunction (PGD). PGD is a particular type of acute respiratory distress syndrome (ARDS), primarily due to ischaemia-reperfusion syndrome.

Retrospective data analysis from the international ECLS registry demonstrates that severe PGD at 48-72hours is greater when lung transplantation is performed using CPB (43%) when compared to V-A ECMO (29%) and off-pump techniques (12%).[29]

While there are indications that off-pump techniques may be associated with better outcomes; it is only

sometimes feasible to utilise this approach. The growing global trend is towards intraoperative ECMO for lung transplantation, which allows extension of ECLS into the postoperative period, if it is required.[30] For those patients where off-pump surgery is instituted in the first instance, there must be a robust strategy in place to evaluate the need for intraoperative ECMO during the clamping of each PA as a backup strategy. Table 10 describes each strategy's key advantages and disadvantages.[31]

Table 10. Comparison of strategies for intraoperative mechanical circulatory support for lung transplantation

Modality	Advantages	Disadvantages
Off-pump	no anticoagulation, minimal bleeding, shorter operation times, minimal inflammatory cascade	cardiac compression can cause haemodynamic instability, operative visualisation less optimum
CPB	use of pump sucker, open heart anastomosis is possible, cardiac decompression with less hemodynamic instability	full heparinization, higher bleeding risk and more blood products transfused, greater inflammatory cascade
ECMO	less heparinisation less bleeding and less requirement for blood product replacement stable oxygenation and removal of carbon dioxide, decreased pulmonary hypertension stable haemodynamics with cardiac compression	risks of air embolism risks of vascular complications associated with cannulation

Off-pump lung transplant surgery

In bilateral sequential lung transplants, the first newly implanted lung supports the body, while the second lung is implanted. If both lungs are adequate, implanting the right lung first is preferable because it provides a larger vascular bed to receive the total cardiac output immediately after implantation. Also, the left lung is usually implanted faster.

If there is a discrepancy in function between the lungs, then the least functional lung is usually dissected first, and a trial of PA clamping is performed. This is a critical time for the anaesthetist, during which the patient's haemodynamic and respiratory function are continuously monitored clinically and using TOE. Cardiopulmonary conditions must be optimised during this brief but compromised timeframe. Indication for emergent ECMO is assessed using the following criteria:[30]

1. Hypercapnia
2. Decrease in arterial saturation to <90%
3. Cardiac index of <2 litre/min/m^2
4. Increase in PA pressure to supra-systemic values.

Hypoxia or acidosis is very concerning and may herald the need for emergent V-A ECMO.

Once the surgical anastomoses are completed, the lung can be re-perfused. Before releasing the PA clamp, the anaesthetist must inspect the lung using bronchoscopy. Bronchoscopy allows direct assessment of the bronchial anastomoses and meticulous suctioning of secretions.

The PA clamp should be released very slowly as the reperfusion time is extremely high risk and may result in profound hypotension. Pulmonary oedema heralds allograft injury. This is a critical time for the anaesthetist, who must deploy strategies for ventilation and circulation with meticulous precision.

From the ventilation perspective, the FiO2 is set at 0.21 at the time of reperfusion, and protective ventilation is targeted with low tidal volume, low minute ventilation, and the application of positive end-expiratory pressure (PEEP). The PAC is utilised throughout to monitor and assess mean pulmonary artery pressure. When performed off-pump or when weaning from ECLS, full protective ventilation is employed on low FiO_2.[54]

Before removing the cross-clamp, vasoactive infusions are increased.

At this point in the process, blood pressure is supported with boluses of intravenous fluid, 5-10 microgram boluses of adrenaline, and intravenous calcium administration.

On-pump lung transplant surgery

On-pump surgery utilises a traditional CPB circuit, which carries a higher risk than ECMO. Firstly, CPB is an independent risk factor for PGD.[31] Unlike ECMO, CPB is an open system that requires full heparinisation, exposing the patient to significant bleeding complications. The blood-circuit interface causes the induction of inflammatory mediators, which can contribute to coagulopathy.

ECMO for lung transplant surgery

The global trend is to perform lung transplantation on V-A ECMO. V-V ECMO can be used intraoperatively but provides no haemodynamic support. It is prudent to ensure that anaesthetic monitoring includes temperature and cerebral oximetry. Defibrillator pads should be attached from the start. Total intravenous anaesthesia is utilised when on ECMO.

Once surgical dissection is satisfactory, heparin is given to maintain an ACT between 180-220 seconds. Cannulation in a V-A configuration is performed, ideally intraoperatively.

The anaesthetic goals of maintaining a patient on V-A ECMO for lung transplantation are:

1. Maintain heart contractility, promoting blood flow into the lungs
2. Maintain a MAP of 60-65mmHg for coronary perfusion
3. Monitor cerebral oximetry as a marker of brain perfusion
4. Maintain a temperature of >36 degrees Celsius using a forced air patient warming device, warmed fluids, and the heater/cooler on the ECMO circuit
5. Manage significant fluid shifts with the careful administration of intravenous fluid (there are no pump suckers or reservoir, making volume management, maintenance of ECMO flow and haemodynamics very challenging).

While ECMO has a more favourable risk profile in many senses, one of its major drawbacks is that there is no safety margin for air embolus.

Numerous specific targets for ECMO management exist. ECMO is established with a flow of 50% of the cardiac output. Flow is adjusted according to haemodynamic demands and gas exchange and confirmed as pulsatile flow over the PA. Systolic PA pressures should be maintained below 40mmHg. The transplanted lung is re-perfused and reinflated, and perfusion is confirmed with an $etCO_2$ over 20mmHg. Lung perfusion may be associated with a drop in ECMO flow, requiring vasoconstrictor administration to support the blood pressure.

Meticulous bronchoscopy and lavage are performed. Once the lung is fully inflated, a PA systolic pressure of 10 – 15mmHg is targeted. This ensures good pulmonary blood flow. The TOE is used to confirm good flow from the pulmonary veins.

Once the second lung has been implanted, the ECMO flow can be reduced to 1L, and the arterial and venous lines cross-clamped. The lungs are assessed, and provided the set criteria are met, the ECMO cannulae can be removed.

Criteria for weaning from ECMO:

1. PaO_2:FiO_2>100mmHg
2. mPAP/mSAP <2/3
3. stable cardiopulmonary conditions between the measurements.

If these criteria are not met, ECMO is continued in the ICU in the post-operative phase, although the configuration of the cannulation may be changed depending on the circumstances.

Transplantation: Post-operative management

The immediate post-operative phase is crucial in determining short- and long-term survival.

Immunosuppression

Acute rejection complicates 50% of lung transplants and is a risk factor for chronic allograft dysfunction.[32] The acute post-transplant immunosuppression regimen varies between centres and should be tailored to individual patients. It may consist of induction therapy (such as alemtuzumab) and triple drug immunosuppression consisting of a calcineurin inhibitor (cyclosporine or tacrolimus), a cell inhibitor (azathioprine or mycophenolate mofetil), and a corticosteroid.[33]

Commencement of the nephrotoxic drug cyclosporine often complicates the postoperative period with acute kidney injury (AKI), especially in those recipients who are older or have pre-existing kidney injury. Cyclosporine-induced acute nephrotoxicity is caused by constriction of the afferent arterioles,[34] and the associated AKI significantly hampers post-operative recovery, with higher incidences of ventilated days, more tracheostomies, and administration of vasoactive medication for more extended periods compared to those without.[35]

Infection

Post-operative infections are common. They contribute to accelerated graft failure. Infection risk is assessed in terms of risk posed by the donor (having any pre-existing infections/colonisation) and risk posed by bacterial presence in the pre-transplant recipient, as well as post-operative hospital-acquired infections in the recipient post-transplant. Broncho-alveolar lavage samples are sent for C&S for both the donor and the recipient. In the immediate postoperative period, donor-derived pathogens account for most infections and empirical antibiotic prophylaxis reflects this with cover for broad-spectrum microbes such as methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas, and Enterobacter.[36]

Bacterial infections can present as pneumonia, parapneumonic effusions and empyema, mediastinitis, anastomotic leaks, and surgical wound dehiscence. Pneumonia being the most common bacterial infection, recipients are often commenced on prophylaxis with trimethoprim-sulfamethoxazole, given the risk of pneumocystis jirovecji and its potential to cause life-threatening lung infection.[37] Multi-drug resistant infections are usually an issue in this patient demographic, and knowledge of the recipient's pre-transplant cultures helps to tailor the appropriate antimicrobial therapy.

CMV status of the donor and recipient must be known. Lung transplantation recipients who are CMV-negative and receive CMV-positive donor lungs have the highest risk of developing severe life-threatening diseases.[38] Prophylaxis should be started immediately in all lung transplant recipients and generally consists of intravenous ganciclovir followed by oral valganciclovir or acyclovir.

Invasive fungal infections in lung transplantation are associated with high morbidity and mortality.[39] The most common organisms are Aspergillus and Candida. Risk factors include fungal colonisation, idiopathic pulmonary fibrosis, advancing age, increased BMI, airway ischaemia, and (interestingly) the presence of significant construction projects around the transplant centre.[39]

Post-operative complications

Potential complications following a lung transplant are summarised in Table 11. The most significant being PGD.

Table 11. Summary of post-transplant complications

Causes of respiratory failure
PGD
donor associated pneumonia
ventilator associated pneumonia
acute rejection
cardiogenic pulmonary oedema
pulmonary embolus
pulmonary vein anastomotic obstruction from thrombosis or dissection
transposition of the donor vessel
lung or lobar torsion
phrenic nerve injury leading to diaphragmatic injury
haemothorax
Airway complications
bronchial stenosis
bronchial anastomotic dehiscence
exophytic excessive granulation tissue formation
tracheobronchomalacia
bronchial fistulas
Other
bleeding
cardiogenic shock
tamponade
infection and or sepsis
arrhythmias
pericarditis
GORD
bowel ischaemia
immunosuppression side effects
CNS complications
critical illness myopathy

Primary graft dysfunction

PGD can be seen immediately on allograft perfusion. It occurs in 20-30% of recipients and is a type of ARDS precipitated by prolonged ischaemia time, reperfusion injury, and innate immune responses.

The ISHLT proposed a validated grading system to quantify PGD based on the onset of changes in partial pressure of oxygen (PaO_2:FiO_2) and chest radiography at specific epochs of time after reperfusion (0, 24, 48 and 72 hours).[40] Oedema is a crucial hallmark of the onset of PGD, with progressively declining PaO_2:FiO_2 ratios delineating the proportional severity of dysfunction. The grading classification is described in Table 12.

Grade 3 PGD is associated with morbidity in both the short and long term and can carry mortality as high as 50%.[41]

Table 12. ISHLT grading system of PGD

Grade	CXR findings	PaO_2:FiO_2
PGD 0	No oedema	Any
PGD 1	Oedema	>300
PGD 2	Oedema	200-300
PGD 3	Oedema	<200

Risk factors for PGD

The anatomical functionality of the lungs is not entirely restored after transplantation. Donor lungs lack bronchial circulation, which may affect parenchymal oxygen delivery. The bronchial anastomosis lacks innervation, leading to abnormal cough reflexes or hypoxic pulmonary vasoconstriction (HPV). Disruption of lymphatics also impairs the drainage of interstitial fluid.

The type of lung donor is associated with varying physiological challenges. Lungs retrieved via DBD are exposed to a substantial inflammatory response; in DCD, the donor may have had a prolonged period of mechanical ventilation.

The physical size of the donor lungs is also an important consideration, which can create mismatches with the recipient and varying associated issues. Donor lungs that are small relative to the recipient can create reduced pulmonary vasculature that may lead to pulmonary hypertension. Lungs larger than the recipient's chest cavity can lead to restrictive lung function patterns.

Recipient comorbidities, specifically obese recipients and those with sarcoidosis, IPF, or pulmonary hypertension,[33] are associated with a greater risk of PGD.

Intraoperative factors, such as CPB use, fat embolism or venous thrombosis, prolonged ischaemia time, a large volume of blood transfusions, or high FiO_2, all increase the incidence of PGD.[42] Aside from the radiological and gas exchange findings, which are used as diagnostic criteria for PGD, physiologically, PGD is characterised by increased PVR, decreased pulmonary compliance, and intrapulmonary shunts. The management of PGD is mainly supportive. However, post-transplant ECMO has been shown to improve survival if instituted early on, with a one-year survival of 64%.[41,33]

Transplantation: ICU management

A comprehensive discussion of post-op ICU management is outside the scope of this article, but mechanical ventilation and haemodynamic management will be considered.

Ventilatory considerations

The goals in the immediate post-operative phase are:

- adequate gas exchange
- monitoring lung allograft function
- early weaning of mechanical ventilation to minimise ventilator-induced lung injury to the graft.

Protective lung ventilation is instituted with targets of[43]:

- tidal volume 6ml/kg of *donor* predicted body weight
- plateau pressure <30cmH_2O
- pH>7.25
- oxygen sats > 90% and PaO2> 60mmHg (8kPa).

Tidal volume targets are based on donor rather than recipient body weight.[44] Inspired oxygen is minimised to reduce oxidative stress.[45] Once gas exchange is adequate (aligned with a pH>7.25 and PaO_2:FiO_2>200mmHg), mechanical ventilation and sedation can be weaned.

Mobilisation and chest physio are crucial to facilitate bronchial hygiene and avoid atelectasis. This is particularly important in transplanted lungs, where normal lung innervation and bronchial circulation are disrupted.[33]

Uncontrolled pain after lung transplantation inhibits coughing, reduces pulmonary toilet, and compromises graft expansion. Thoracic epidural analgesia (TEA) is commonly employed as part of a multimodal analgesia regime, but the exact timing of placement remains contentious.[49]

Given the risk of vertebral canal haematoma associated with preoperative placement and subsequent anticoagulation for intraoperative mechanical circulatory support, post-operative placement is more commonplace. A case series of over 100 lung transplant patients who had post-operative TEA demonstrated optimum analgesia with minimal complication rate.[50] Bilateral thoracic paravertebral block catheters are considered a good alternative that is increasingly utilised. Sternotomies usually won't need either.

Most transplanted lungs will incur uncomplicated pleural effusions, which mostly resolve within two weeks. Pleural complications include haemothorax, chylothorax, pneumothorax, and empyema. Air leaks complicate up to 35% of lung transplants.[45] Risk factors include donor-recipient size mismatch, bronchopleural fistulas, dehiscence of bronchial anastomoses, infection, rejection and/or ischaemia.

Diaphragmatic function can be compromised secondary to injury of the phrenic nerve either mechanically during surgery or because of myelin dysfunction associated with the transplant processes. Both mechanisms are associated with an increased incidence of PGD and mortality.[38]

Haemodynamic considerations

The goals in the immediate postoperative phase focus on maintaining adequate end-organ perfusion using the lowest possible CO to reduce the risk of exacerbating lung oedema from reperfusion injury.

End organ perfusion is monitored using surrogates such as lactate, urine output, and mixed venous oxygen saturations.

A PA catheter guides haemodynamic management by allowing assessment of cardiac preload (CVP and wedge pressure), systemic and PA pressure, systemic and peripheral vascular resistance, CO and mixed venous saturations.[33] Neutral fluid balance is targeted as sedation is weaned, and CO and lung perfusion increase. Any decline in the graft function, such as deterioration in gas exchange or lung compliance, may signal the development of PGD and prompt the weaning process to be slowed down. After that, early postoperative CXR and daily CXRs are part of PGD monitoring and diagnosis.

Typical haemodynamic targets are:

- CVP<7mmHg
- MAP 65-75 mmHg
- CI 2.2-2.5L · min^{-1} · m^{-2}

Cardiovascular complications include dysrhythmias, with atrial fibrillation (AF), supraventricular tachycardias, and atrial flutter, presenting an incidence of 25-35%.[38] Risk factors for AF include pre-transplant IPF, left atrial enlargement, diastolic dysfunction, and pre-existing coronary artery disease.

CONCLUSIONS

The perioperative care for lung transplantation is complex. It requires an MDT approach that commences long before the day of surgery and extends well into the post-operative phase. Intraoperative anaesthetic management is both highly challenging and extremely rewarding. For the anaesthetist, it allows execution of a highly honed skill set to a meticulous standard. For the lung transplant recipient, it represents the potential to regain quantity and quality of life.

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