Anaesthetic management for lung transplantation

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Preparation

Patient assessment

The broad categories of end stage lung disease requiring lung transplantation are suppurative, obstructive, restrictive and pulmonary vascular. They each lend themselves to different potential complications during anaesthesia, and thus require slightly different management strategies (1). The nature of transplantation surgery is that it is unpredictable and emergent. Hence the preoperative workup of transplant recipients must be thoroughly performed in advance with appropriate updating of clinical data and investigations whilst on the waiting list. Specific information required include patients height and current weight, results from latest pulmonary function test, transthoracic echocardiography, left heart catheterization if appropriate, lung perfusion scan which gives information on which lung will better tolerate OLV, presence of antibodies to the donor, and current bloodwork. In addition to the usual anaesthetic issues of aspiration risk, airway assessment, co-morbidities, medications and adverse reactions, assessment on the day of surgery focuses on the current illness state and amount of deterioration since investigations were performed as the patient's physical state may be significantly worse than investigations may suggest.

Premedication

Normal medications that need to be continued include bronchodilators, antibiotics, and pulmonary vasodilators. If the patient is receiving intravenous prostaglandins, it is continued until CPB is initiated. Immunosuppression regimes commence pretransplantation and vary between institutions. Broad spectrum antibiotics are given for prophylaxis, but for patients with suppurative lung disease or a current chest infection, the choice of antibiotics will be determined by the actual or suspected microbiological burden. The microbiological burden of the donor is also taken into account. Due to the lack of respiratory reserve, sedation outside of the operating room is not recommended and should only be given with extreme caution, as it may easily precipitate a cardiorespiratory arrest due to hypoxaemia, hypercarbia or increased pulmonary vascular resistance resulting in acute right ventricular failure.

Thoracic epidural analgesia

Adequate post operative analgesia is important to facilitate extubation. Thoracic epidural analgesia (TEA) provides superior analgesia compared with systemic opioids. However special problems and risks with preoperative epidural insertion need to be considered in the lung transplant population. Firstly, in the event of a bloody tap, the risk of a epidural haematoma is magnified with subsequent full heparinization for cardiopulmonary bypass. Timely decompression may be delayed due to prolonged surgery and inability to elicit clinical signs in the sedated and intubated patient. Secondly, the benefit of TEA is shortened or lost if extubation is delayed due to other complications. Therefore patients should be selected carefully based on risk and benefit discussions. Alternatives are to have the epidural inserted postoperatively in an awake or lightly sedated patient prior to extubation or only if systemic multimodal

analgesics are inadequate. For single sided surgery, paravertebral catheter insertion is an alternative to TEA.

Monitoring and vascular access

Vascular access comprises a large peripheral intravenous cannula, a pulmonary artery catheter sheath with side port, a multi-lumen central line and an arterial cannula.

Mandatory monitoring includes 5 lead electrocardiography, pulse oximetry, invasive measurement of arterial, central venous and pulmonary artery pressures, urinary output via an indwelling catheter, temperature, capnography, spirometry and anaesthetic agent gas analysis.

Other options include depth-of-anaesthesia monitoring, cerebral oximetry using transcutaneous near infrared spectroscopy, continuous arterial blood gas monitoring, continuous cardiac output and mixed venous oximetry.

Transoesophageal echocardiography

There is no consensus about routine use of intraoperative transoesophageal echocardiography during lung transplantation for assessing surgical anastomotic sites. It is a class 2b indication in the ACC/AHA/ASE guideline update of 2003 meaning its usefulness or efficacy is not well established by evidence or opinion. However, more established indications include evaluation of pulmonary hypertension, right ventricular dysfunction, and suspicion of a patent foramen ovale. It provides useful information about left and right sided preload, left and right ventricular function, regional wall motion abnormalities, and intracardiac air, especially when used in situations of haemodynamic instability (2). It may also identify intracardiac thrombus and other unexpected abnormalities. In the case of unexplained or refractory hypoxaemia, it can detect the presence of intracardiac shunting.

Induction

The induction of anaesthesia is one of the most critical periods, and the surgeon and perfusionist must be present and prepared to urgently perform sternotomy and initiation of cardiopulmonary bypass in the event of severe cardiorespiratory instability. In the patient with little or no cardiorespiratory reserve, cardiovascular collapse can be precipitated by many factors. These include hypoxia, hypercarbia, the reduction of endogenous sympathetic drive, drugs causing myocardial depression or vasodilatation, and the commencement of positive pressure ventilation causing reduction of systemic venous return and increased right ventricular afterload.

Therefore, the haemodynamic goals of induction are to preserve systemic vascular resistance, myocardial contractility, and avoidance of any increase in pulmonary vascular resistance (3). This can usually be achieved with a titrated narcotic based induction consisting of 0.05-0.1 mg$\cdot$kg^{-1} of midazolam, 5-10 mcg$\cdot$kg^{-1} of fentanyl and judicious doses of propofol followed by a muscle relaxant. Other induction regimes have also been described. In patients with high aspiration risk, gastric acid lowering premedication and cricoid pressure during induction with suxamethonium or high dose rocuronium is used. A non-titrated rapid sequence induction is rarely justifiable due to the risk of haemodynamic collapse. Ketamine is an alternative and ideal choice of induction agent in patients with severe pulmonary hypertension. Optimization of haemodynamics may need to be achieved by commencing β_1 and α_1 agonist infusions and pulmonary vasodilators before induction.

With the exception of an on-pump single lung transplant where a single lumen tube may suffice, a left sided double lumen tube is preferred for all other cases. Use of a bronchial blocker through a single lumen

tube is an alternative but a double lumen tube allows increased surgical flexibility, irrigation of the divided bronchus, differential ventilation after the graft is reperfused, and faster lung isolation. The double lumen tube is changed to a single lumen tube at the end of surgery before leaving the operating room. Doing this under direct vision or preferably using a tube exchange catheter is recommended, as airway oedema and swelling can occur during the course of the operation. Loss of the airway in this situation has occurred with disastrous outcomes.

Anaesthetic considerations specific to recipient pulmonary pathology (see Table 1)

Obstructive lung disease

This group includes patients with COPD and alpha-1 antitripsin deficiency and bronchiolitis obliterans syndrome presenting for re-transplantation. Patients with obstructive lung disease may undergo a single or bilateral lung transplant. The majority of this group will have smoking related emphysema, so may have co-existing cardiovascular disease. A pre-induction ABG is required for baseline $PaCO_2$. There is an increased risk of pneumothorax with positive pressure ventilation and central line insertion. Cor pulmonale may exist with increased pulmonary vascular resistance, elevated pulmonary artery pressure, and right heart dysfunction. These patients already have a reduced venous return to the left heart with reduced left ventricular end diastolic volume, reduced stoke volume and cardiac output compared with normal patients. A longer expiratory time is required to prevent dynamic hyperinflation, further reduction in venous return and circulatory collapse. Disconnecting the ETT and allowing lung deflation will allow venous return to the heart and restore blood pressure if this is the cause of hypotension. These patients have a high level of intrinsic PEEP and external PEEP is usually not required and may in fact cause hyperinflation, increase shunt and reduce PaO_2. A large alveolar dead space makes the end tidal CO_2 underestimate the $PaCO_2$ by an unpredictable amount. Frequent correlation to arterial blood gases is required. It is appropriate to ventilate the patient to their baseline $PaCO_2$.

Table 1: Disease-specific intraoperative anesthetic considerations

Recipient Pathology	Intra-operative Complications
Emphysema (COPD, Alpha-1 Antitrypsin deficiency)	Hypotension with positive-pressure ventilation due to auto-PEEP.
Cystic Fibrosis	Profuse thick secretions. Difficult to maintain baseline $PaCO_2$ with positive pressure ventilation. Small stature, often difficult access in chest for surgeon
Idiopathic Pulmonary Fibrosis	May have associated diseases (e.g. scleroderma). Often older with coronary artery disease. May have severe pulmonary hypertension. May not tolerate one-lung ventilation and may require CPB.
Primary Pulmonary Hypertension	Cardiovascular collapse secondary to hypotension on induction. Always require CPB.
Broncho-alveolar Carcinoma	Profuse watery secretions

Restrictive lung disease

This group includes patients with idiopathic pulmonary fibrosis, connective tissue disease, and drug or radiation induced parenchymal lung disease. Ventilating these patients can be difficult. To obtain adequate tidal volumes, peak inspiratory pressures exceeding 40 cm H_2O may be required. This is tolerated especially if bilateral sequential single-lung transplantation (BSSLT) is planned. Volume controlled ventilation allows better control of tidal volumes and some ventilators may not allow pressure control ventilation mode to exceed 40 cm H_2O. These patients benefit with some PEEP. An ICU level ventilator may be required if the ventilator on the anaesthesia delivery unit is not adequate. Pulmonary hypertension is common and can be severe. Elderly patients with end-stage restrictive lung disease are one subgroup where the long-term outcomes from single-lung transplantation are equivalent to those from BSSLT.

Suppurative lung disease

The majority of these patients have cystic fibrosis (CF), but may also include patients with non CF bronchietasis. At induction, a single lumen tube is inserted to allow a bronchoscope with a large working channel to perform adequate pulmonary toilet. The working channel of the sub 4 mm bronchoscopes used in double lumen tubes is too small for the thick purulent secretions encountered. The single lumen tube is then changed to a double lumen tube. Aggressive airway toileting is required during surgery as lung manipulation can squeeze purulent alveolar secretions into the large conducting airways. After pneumonectomy, it is our institution's practice to irrigate the open main bronchus by pouring dilute povo-iodine solution (1:5 dilution in saline) down the appropriate lumen of the double lumen tube. An approximate volume of 50-100 ml of this solution is flushed down the ipsilateral lumen of the DLT and simultaneously aspirated from the open distal bronchus by the surgeon. This is followed with a saline flush until clear.

Intra-operative ventilation of CF patients can be extremely difficult and may require high airway pressures and relatively large volumes to maintain the patient's preoperative $PaCO_2$. For chronically hypercapnic patients, if CPB is required, we try to maintain the $PaCO_2$ during CPB at the patient's normal pre-induction baseline.

Due to multiresistant organisms, some CF patients require consultation with infectious diseases or microbiology to determine appropriate antibiotic cover. Some centres would consider patients colonised with *Burkholderia cepacia* complex a contraindication to transplantation as they provide a unique challenge with higher short and medium term post-operative mortality due to pneumonia, sepsis and bronchiolitis obliterans.

Pulmonary hypertension

In the context of patients with pulmonary hypertension presenting for lung transplantation, the cause may be (1) idiopathic, (2) associated with lung disease or hypoxia (pulmonary fibrosis, COPD), or less commonly, (3) associated with connective tissue disease, and (4) intracardiac shunt with Eisenmenger's physiology. It may also be seen post transplantation in primary graft dysfunction.

In patients with severe pulmonary hypertension and right heart failure, it is advisable to have central venous access and the pulmonary artery catheter floated into position prior to induction because these patient often becomes haemodynamically compromised with induction of anaesthesia and need inotropic or vasopressor support (4) Preinduction femoral cannulation under local anaesthesia for cardiopulmonary bypass should be considered for very high risk patients.

Maintenance of anaesthesia

Patients undergoing lung transplantation feature prominantly in studies of intraoperative awareness. Care must be taken to ensure that these high risk patients receive adequate amounts of anaesthetic agents. Maintenance of anaesthesia by propofol infusion, inhalational anaesthetic agent or both have been described. Nitrous oxide is avoided due to its deleterious effect on pulmonary vascular resistance. The advantage of a total intravenous technique is less inhibition of hypoxic pulmonary vasoconstriction although this does not translate to a clinically significant increase in PaO_2 when less than 1.0 MAC of inhalational anaesthetic is used. There is also less myocardial depression, and smoother transition to cardiopulmonary bypass (CPB) if required. The advantage of an inhalational technique is bronchodilatation, especially in patients with reversible obstructive airways disease. A disadvantage is the slower wash-in of the anaesthetic due to the limited minute volume encountered in some of these patients.

One lung ventilation (OLV) is better tolerated in the lung with greater perfusion. The shunt fraction is greater compared with OLV in the decubitus position due to the lack of benefit of gravity. The strategies of managing hypoxia on OLV are listed in table 2. Severe respiratory acidosis (pH <7.2) can be problematic and strategies employed to increase alveolar minute volume may ultimately be unsuccessful, therefore requiring cardiopulmonary bypass.

Temperature monitoring and active warming is required as hypothermia worsens pulmonary hypertension, coagulopathy and risk of arrhythmias. We routinely use both upper- and lower-body forced-air heating blankets. Magnesium sulphate (2 grams) is infused to try to prevent arrhythmias.

Repeated hilar manipulation and cardiac compression lead to reduced cardiac output and hypotension. Vasopressor support is invariably required to maintain adequate perfusion pressure. Optimizing fluid status is im-portant but excessive fluid therapy is to be avoided as the graft is susceptible to pulmonary oedema. Finding evidence to recommend one type of fluid over another is difficult due to multiple confounding factors and small series of patients. However the volume of intraoperative gelatin based colloid given has been associated with worse post operative oxygenation and delayed extubation.

Single vs. bilateral lung transplantation

Most patients with end-stage parenchymal lung disease can get symptomatic improvement with a single-lung transplant. Suppurative lung disease is a contraindication for single-lung transplantation. Although single-lung transplants allows more patients to be transplanted by splitting pair of lungs between two patients, case controlled studies have shown bilateral lung transplantation(BLT) to be an independent factor in improved long term survival. Potential therapeutic benefits of BLT include a reduction in alveolar damage during reperfusion, improved pulmonary compliance and mechanics, and the avoidance of native lung pathology. Previous double-lung tranplantation (DLT) featured en bloc tracheal anastomosis but without bronchial artery anastomosis. This led to airway ischaemia and donor tracheal necrosis, dehiscience and fibrotic stenosis. This problem was obviated with telescoping bronchial anastomoses with mediastinal coverage so now the procedure is performed and referred to as bilateral sequential single lung transplantation (BSSLT).

Surgery for a SLT can be via a postero-lateral or antero-lateral approach. For BSSLT bilateral anterolateral clam shell incision with or without transverse sternotomy is used.

Cardiopulmonary bypass

In institutions that do not use CPB routinely, planned CPB is used when patients have se-

vere pulmonary hypertension, require a concomitant cardiac procedure such as repair of intracardiac shunt, or require plasmapheresis due to human leukocyte antigen (HLA) mismatch and presence of HLA antibodies against the donor. In unplanned cases, the decision to use CPB is made if the patient (1) does not tolerate one lung ventilation (either hypoxia or refractory hypercarbia), (2) does not tolerate clamping of a pulmonary artery (right ventricular failure), or (3) has other refractory haemodynamic instability. If high pulmonary artery pressures do not fall after the first side is reperfused, cardiopulmonary bypass may also be commenced to protect the graft from pulmonary hypertension which can contribute to primary graft dysfunction. Cardiopulmonary bypass is required if the patient already is dependant on extracorporeal support (ECMO or the Novalung interventional lung assist device) although some centres consider this a contraindication to lung transplantation due to potentially poorer outcomes. In our centre's adult practice, two-thirds of cases are done without CPB. In the cases where CPB is used, two-thirds are elective, and one-third is for specific intraoperative problems, most commonly haemodynamic instability.

Warm (37 degrees), beating heart CPB is routine unless a concomitant cardiac procedure is also performed. Bypass times are often prolonged so a centrifugal pump offers some advantage over a continuous flow roller pump. Venous drainage may often be impaired by severe surgical manipulation of the heart and hilum therefore vigilance is required, and flows may often need to be temporarily reduced to prevent complete emptying of the reservoir. Bicaval cannulation provides less interruption of venous return than single two stage atrial cannulation.

Reperfusion and ventilation of the first side commences whilst still on CPB to limit the warm ischaemic time of the graft.

Major coagulopathy is invariably present after coming off prolonged cardiopulmonary bypass, so platelets and fresh frozen plasma should be ready to be given after reversal of

heparinisation. An antifibrinolytic agent is used. Our current protocol is tranexamic acid 30 mg kg^{-1} bolus prior to CPB then an infusion of 16 mg kg^{-1} hr^{-1} until the end of CPB. The advantages of CPB are haemodynamically stabilty and that it allows controlled reperfusion of grafts. Disadvantages of CPB are that prolonged pump runs cause haemolysis and activation of proinflammatory cascades that increase the risk of lung injury. It also increases the need for transfusion of blood products due to haemodilution, coagulopathy, and platelet dysfunction. Use of CPB has been associated with a longer period of postoperative mechanical ventilation, more pulmonary oedema, and increased early mortality although this is controversial.

Right ventricular failure

Failure in the at-risk right ventricular (RV) can be precipitated by an acute increase in afterload, or ischaemia due to either prolonged hypotension or air embolism. This is encountered at induction, after commencing OLV, during manipulation of the hila, at pulmonary artery clamping, after reperfusion and with severe early graft dysfunction. A failing RV dilates, flattens out the interventricular septum and impinges on left ventricular filling, the interventricular dependance phenomenon.

RV afterload reduction is the primary treatment goal. Also important are preserving coronary perfusion and biventricular inotropic support. Basic things such as correcting acidosis, hypoxia, hypercarbia, hypothermia, minimizing ventilation pressures and undoing the precipitating event (if possible) should not be overlooked. Inotropics most commonly used are milrinone, noradrenaline and adrenaline. Milrinone causes systemic as well as pulmonary vasodilatation so often requires a vasopressor to support the blood pressure. Inhaled pulmonary vasodilators are used to selectively reduce PVR. Our first choice in the operating room is nitric oxide (see below). Inhaled milrinone has been used in cardiac surgery and heart transplant patients,

but little has been reported in the lung transplant population.

Stages of surgery

Dissection and removal of native lung

This may be difficult and prolonged if extensive pleural adhesions are present. This is more likely in patients with previous thoracic surgery, restrictive or suppurative lung disease. Significant blood loss may occur. For BSSLT performed off pump, if there is a significant perfusion asymmetry, the lung with the lower perfusion is transplanted first.
Testing the haemodynamic consequences of dividing the pulmonary artery by pinching it off temporarily is advised as the right ventricle can acutely fail.

Anastomosis of donor lung

A cooling jacket with ice cold saline being circulated through it is placed in the thoracic cavity to minimise warm ischaemic injury to the graft during this stage. This jacket can contribute to patient hypothermia.
The bronchial anastomosis is completed first. After this is complete, bronchoscopic toileting of the graft may be performed. The pulmonary artery anastomosis is next followed by the venous anastomosis, which is done by grafting an island of donor atrium containing the upper and lower pulmonary veins on to the recipient's left atrium. An atrial clamp is required, and its application may cause arrhythmias, impede left ventricular filling or obstruct a coronary artery. Surgical access to the hilum and atrium requires retraction on the heart causing intermittent periods of hypotension and low cardiac output Communication between anaesthetist and surgeon is critical. The circulation usually requires support with vasopressors. Some degree of fluid expansion may be required to optimize preload, although caution should be exercised

as low pressure pulmonary oedema in the grafts may occur if excessive fluid has been given.

Reperfusion of graft

This is a busy period which often requires an extra set of hands to deal with differential lung ventilation and cardiovascular emergencies at the same time.
Before tying the final stitch of the atrial anastomosis, the graft is de-aired through an opening in the atrial anastomosis. This is done by inflating the lung to a sustained pressure of 15-20 cmH_2O and partially releasing the pulmonary artery clamp. The atrial clamp is then released to de-air the atrial cuff before the final knot is tied. At this point, hypotension may occur due to several causes. There are sometimes leaks in the vascular anastomosis which need to be controlled by placing further sutures. A significant amount of blood loss may rapidly occur in the interim requiring prompt intravascular volume replacement. Temporary myocardial stunning occurs as the initial venous return to the left atrium is cold, contains ischaemic metabolites and is acellular. Treatment with a small bolus of adrenaline or calcium is often required to improve myocardial contractility. Coronary artery air embolism may also occur. This is usually seen in the right coronary artery as it is uppermost in the supine position. ST depression or elevation may be seen in the inferior leads and if treated with vasopressors, is usually transient.
The pulmonary artery clamp is slowly released over a ten minute period, limiting initial flows to the vascular bed of the graft which has been shown to reduce primary graft dysfunction. To reduce lung injury, initial ventilation to the graft should be with a low FiO_2, low peak inspiratory pressures of 15-20 cmH_2O and a positive end expiratory pressure of 5 cmH_2O. The respiratory rate is initially set to 8-10 breaths per minute. The other lung requires 100% oxygen, most easily given via a self inflating bag. Once the pul-

monary artery clamp is fully released, ventilation settings need to be adjusted to ensure adequate minute ventilation and CO_2 removal, and the FiO_2 titrated to a safe level of oxygen saturation. For the first side of a off-pump BSSLT, the new graft needs to support the ventilatory requirements of the patient whilst the contralateral side is operated on. For patients on CPB, ventilation is continued on the initial settings and restriction of venous cannula drainage by partial clamping allows some right ventricular ejection to perfuse the graft. This is titrated to a pulmonary artery pressure of 10-15 mm Hg.

Primary graft dysfunction

This devastating complication is akin to acute lung injury (ALI) due to the transplantation process. It has been reported to occur up to 25% of lung transplantations and increases both short and long term mortality (5). It may manifest immediately following reperfusion and therefore intra-operative management is considered here. It can occupy a spectrum of mild self-limiting disease to fulminant respiratory failure. The hallmark of PGD is poor oxygenation and severity grading is based on PaO_2/FiO_2 ratios similar to acute lung injury. Other features encountered in the operating room are poor respiratory compliance, high pulmonary vascular resistance, and pulmonary oedema.

As in ALI or ARDS, initial management is to ensure that a protective ventilation strategy is employed to limit volutrauma and barotrauma. Differential synchronous lung ventilation may need to be employed if the lungs vary significantly in compliance as may be encountered after single lung transplantation. Pharmacological management is with selective pulmonary vasodilators and right ventricular support. These pharmacotherapies may improve lung function sufficiently, but in severe cases, extracorporeal support may be required. Severe PGD is associated with haemodynamic and multiorgan failure and is the leading cause of early post operative mortality.

Nitric oxide

Inhaled nitric oxide (iNO) in the range of 10 to 40 ppm is used in established PGD to treat severe hypoxia or elevated pulmonary artery pressures. NO increase cyclic guanosine monophosphate which relaxes smooth muscle. It improves ventilation/perfusion matching and decreases pulmonary artery pressures by selectively vasodilating pulmonary vasculature in ventilated portions of the lung. The effect is transient with rebound pulmonary hypertension seen during weaning, and survival benefit has not been shown, but its use may help stabilize the patient sufficiently during this turbulent period. Prophylactic use of iNO has not been shown to prevent PGD. Disadvantages of iNO include the potential for methaemoglobinaemia and cytotoxicity from free radical production. NO oxidises to nitrogen dioxide, and other higher oxides which are pulmonary toxic. Therefore specialized monitoring and delivery systems need to be used which contributes to its very high cost.

Prostaglandins

Inhaled aerosolized prostacyclin (PGI_2) is an alternative to inhaled nitric oxide. It is less expensive and does not require a bulky delivery system. Commercial PGI_2 „Epoprostenol" is reconstituted in sterile glycine, diluted with normal saline according to body weight and aerosolized via a „low-flow" nebuliser that delivers 8 ml/hr of solution with a driving flow rate of 2 L/min to give a typical dose of 50 ng kg^{-1} min^{-1}. Relatively large doses are required due to the inefficiency of aerosolised particles reaching the alveoli. A continuous nebuliser is required due to the short half life of epoprostenol. A small amount of literature in the use of PGI_2 for primary graft dysfunction shows equivalence in lowering pul-

monary artery pressures, improving oxygenation and lack of systemic side effects compared with inhaled nitric oxide. There are no studies which show long term outcome in this setting.

Intravenous prostaglandins are rarely used in the acute setting due to their systemic effects causing hypotension and non-selective pulmonary vasodilation that may worsen intrapulmonary shunt and oxygenation.

Summary

An over-simplification of the anaesthetic management for lung transplantation is to consider it as a cardiac anaesthetic with a double-lumen tube and a noradrenaline infusion. However, the spectrum of intra-operative complications which have to be dealt with vary tremendously depending on the recipient's underlying pathology (see Table 1).

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