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Yearbook *of* Anesthesiology 12

Indian College of Anaesthesiologists

Editors
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Contents

1. Acute Respiratory Failure: Pathophysiology, Causes, and Diagnosis 1
Roopali Phulli, Praveen Neema

- Pathophysiology of Acute Respiratory Failure in Coronavirus Disease 2019 (COVID-19) *13*
- Diagnosis *15*

2. Noninvasive Ventilation for Acute Respiratory Failure 18
Gautam Gondal, Nishanth Baliga, Sheila Nianan Myatra

- Pathophysiology of AHRF *19*
- Advantages of NIV over IMV *20*
- Role of NIPPV in Acute Respiratory Failure *20*
- Role of HFNO in Acute Respiratory Failure *25*
- NIV in COVID-19 *28*

3. Ventilation Strategies to Prevent Postoperative Pulmonary Infection 34
Mukul Chandra Kapoor

- Postoperative Pulmonary Infections *35*
- Risk Factors for Postoperative Pulmonary Complications *37*
- Role of Mechanical Ventilation in Lung Injury *37*
- Evidence-based Strategies for Intraoperative Lung Protective Ventilation *41*
- Lung Protective Ventilation During Different Stages of General Anesthesia *44*

4. Anesthetic and Intensive Care Management for Lung Transplant 50
Suresh Rao KG, Santosh V, KR Balakrishnan

- Preoperative Assessment *51*
- Intraoperative Management *52*
- Maintenance of Anesthesia *53*
- Mechanical Circulatory Support *54*
- Surgical Consideration and Anastamosis *54*
- Postoperative Analgesia *55*
- ECMO Postlung Transplant *58*
- Weaning of Mechanical Ventilation *58*
- Hemodynamic Management *58*
- Fluid Management *59*
- Infection and Sepsis Management *59*

5. Pediatric Obstructive Sleep Apnea: A Comprehensive Review 62
Arvind Chandrakantan, Adam C Adler

- Pediatric OSA *63*

6. Assessment of Functional Capacity 78
Gautam Khanna

7. Role of Adjuncts for Regional and Neuraxial Anesthesia..... 87
Balavenkata Subramanian Jagannathan, Madhanmohan Chandramohan, Vipin Kumar Goel

- Classification *89*
- Multimodal Perineural Adjuvant *96*

8. Myocardial Injury after Non-cardiac Surgery 102
Alok Kumar, Jayakrishnan S

- Definitions *103*
- Etiopathogenesis *105*
- Risk Factors and Assessment *106*
- Management *108*
- Future Perspectives *111*

9. Anesthesia Management for Carotid Endarterectomy and Stenting 114
Dheeraj Arora, Jitin Narula

- Anatomy *115*
- Carotid Endarterectomy: Surgery *115*
- Anesthesia Management *116*
- Anesthesia Techniques *116*
- Monitoring *119*
- Postoperative Management *120*
- Carotid Artery Stenting *121*

10. Anesthetic Implications in the Intravascular Treatment of Cerebral Aneurysms and Arteriovenous Malformations 127
Anil Parakh, Joanna S Rodriques

- Anesthetic Considerations *128*
- Complications and their Management 131
- Intracranial Aneurysms *132*

11. Anesthetic Considerations for Functional Neurosurgery..... 140
Maria Bustillo

- Functional Neurosurgery *141*
- Deep Brain Stimulation *144*
- Magnetic Resonance Imaging-guided Focused Ultrasound *147*
- Additional Indications for Focused Ultrasound *149*

12. Anesthetic Implications in Pediatric Spinal Neurosurgery 151
Pradeep Sharma, Rahul Yadav

- Common Neurosurgical Entities in the Spinal Region *153*
- Primary Spinal Cord Tumors *155*
- Spinal Cord Injury in Pediatric Age Group *156*
- Craniovertebral Junction Anomalies *156*

- Spinal Deformity *156*
- Spinal Cord Vascular Malformations *157*
- Preoperative Evaluation *157*
- Preoperative Fasting *158*
- Premedication *159*
- Anesthesia Concerns *159*
- Preparation of Operating Room for Surgery *159*
- Induction of General Anesthesia *160*
- Airway Management *161*
- Maintenance of Anesthesia *162*
- Intraoperative Complications *166*
- Emergence and Tracheal Extubation *166*
- Postoperative Management *167*

13. Awake Tracheal Intubation 171
Bindiya Salunke, Jigeeshu V Divatia

- Indications *173*
- Contraindications *173*
- Fasting Guidelines *174*
- Components of Awake Tracheal Intubation *174*
- Failed Awake Intubation Rescue *180*
- Managing Complications *181*
- Tracheal Extubation *181*
- Documentation *181*

14. Anesthesia for Tracheal Reconstruction Surgeries 185
Raj Sahajanandan, Rahul Pillai, Amit Mathew

- Applied Anatomy *186*
- Preoperative Evaluation *186*
- Optimization *189*
- Multidisciplinary Discussion *190*
- Airway Management Strategy *191*
- Anesthetic Management *197*
- Special Considerations *198*
- Evolving Techniques *199*
- Case Scenarios *199*
- Role of ECMO *200*
- Emergence *201*
- Extubation *202*

15. Anesthesia for Pancreas and Islet Cell Transplantation..... 206
Cody Tidwell, Vinh Huu Nguyen, Serjey Ghercuic, Kumar Belani

- Diabetes Mellitus *207*
- Pancreas Anatomy and Physiology *209*
- Patient Selection *210*
- Immunosuppression and Prophylaxis *211*
- Overview of Surgical Technique *211*
- Preoperative Evaluation *213*
- Anesthetic Considerations *213*
- Postoperative Complications *215*

16. Anesthetic Implications in Gastroenterological Interventions Outside the Operating Room 218
Venkatesan Thiruvenkatarajan, Roelof MAW Van Wijk
- Preprocedural Risk Assessment and Optimization *219*
- Monitoring *220*
- Pharmacological Principles of Sedation *221*
- Organizational Logistics of Gastroenterological Procedures in Suites Outside Operating Room *222*
- Oxygen Supplementation and Airway Management Strategies to Mitigate Hypoxemia *224*
- Oxygen Delivery During Gastroenterological Interventions *224*
- Considerations of Capnography Monitoring *232*
- Assessment and Considerations of Aspiration Risk *233*

17. Opioid-free Anesthesia with Friedberg's Triad 239
Barry L Friedberg
- Friedberg's Triad 1.0: Measure the Brain *240*
- Friedberg's Triad 2.0 Preempt the Pain *249*
- Friedberg's Triad 3.0 Emetic Drugs Abstain *252*
- Challenging Cases *253*

18. Environmental and Occupational Considerations of Anesthesia 257
Parli Raghavan Ravi, Rajini Kausalya, Basavaraju Karan
- Earth Atmosphere *258*
- Earth's Energy Expenditure *259*
- Terminology and Definitions *260*
- Montreal Protocol for Ozone Layer *260*
- Kyoto Protocol *260*
- Climate Chemistry and Inhaled Anesthesia Agents *261*
- Global Warming and Inhalation Anesthetic Agents *261*
- Strategies to Reduce Environmental Hazards in Anesthesia *264*
- Waste Prevention: Avoid, Reduce, Reuse, Recycle, and Reprocess *264*
- Education and Advocacy *266*
- Global Consensus Statement from the World Federation of Anesthesiologists on Environmental Protection *266*
- Other Environmental Hazards Exposure to Anesthesiologist *266*
- Substance Use, Abuse, and Addiction *268*
- Radiation *269*
- Surgical Smoke *269*

19. Enhanced Surgical Recovery Programs and Cancer Outcomes 274
Anoushka Afonso, Vijaya Gottumukkala
- Preoperative Preparation *276*
- Intraoperative Management *281*
- Postoperative Care *285*

20. Perioperative Surgical Homes 292
Rashmi Datta
- Traditional Perioperative Management *294*

CHAPTER

4

Anesthetic and Intensive Care Management for Lung Transplant

Suresh Rao KG, Santosh V, KR Balakrishnan

ABSTRACT

Lung transplantation is now an accepted treatment modality for lung failure patients, usually with successful outcomes. A thorough preoperative evaluation with a focus on cardiac status is necessary. Intraoperatively communication between surgeon and anesthesiologist is vital for managing hemodynamic instabilities. Postoperatively primary graft dysfunction should be identified early and managed accordingly. Early extracorporeal support is recommended for primary graft dysfunction.

Keywords: Lung transplant; Extracorporeal membrane oxygenation (ECMO); One-lung ventilation; Right ventricular dysfunction; Primary graft dysfunction; Graft Rejection; End-stage lung disease

KEY POINTS

- A lung transplant is the most challenging transplant among all solid organ transplants because of its unique technical, immunogenic, and infectious aspects and carries higher morbidity and mortality.
- Due attention to steroids and anticoagulants in the preoperative period is required.
- Right heart catheterization is required to rule out left ventricular diastolic dysfunction.
- A coronary angiogram is required in patients above the age of 50 years.
- Transesophageal echo is helpful in monitoring the right ventricular function and evaluating pulmonary artery and venous anastomosis for any narrowing.
- Lung isolation is needed, if a transplant is done without cardiopulmonary bypass.
- Protective ventilation with 4–6 mL/kg body weight, optimal PEEP, and least possible FiO_2 to prevent oxygen toxicity is recommended while reperfusing the graft.
- Due precaution is taken to reduce the usage of fluids and vasoconstrictors.
- Venovenous (VV) ECMO may be required in primary graft dysfunction as a bridge to recovery, and VA ECMO in severe pulmonary hypertension.

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INTRODUCTION

Lung transplantation has become an increasingly important mode of therapy for patients with a variety of end-stage lung diseases. Several lung transplant procedures are generally available, including single and bilateral lung transplantation, cadaveric lobar transplantation, living-donor lobar lung transplantation, and heart-lung transplantation.[1] The number of lung transplant procedures worldwide is increasing despite persistent donor shortages. Lung transplant remains associated with high perioperative morbidity and mortality and the lowest long-term survival of all the solid organ transplants, notably due to the unique technical, immunological and infectious aspects of transplanting human lungs.[2] In this chapter, perioperative management and postoperative care of lung transplantation will be detailed.

PREOPERATIVE ASSESSMENT

Anesthetic management of a patient undergoing lung transplantation is influenced by the planned surgical approach, urgency of the procedure, patient's preoperative pulmonary status, and clinically significant comorbidities.[3] Besides hematologic and biochemical laboratory assessment, focused cardiac and pulmonary assessment is essential.

Pulmonary Function Assessment

Complete pulmonary function testing, including advanced radiographic imaging like computed tomography (CT) and ventilation-perfusion (V/Q) scan, is done to plan surgical and anesthetic management. The focus should be on the etiology of respiratory failure, current clinical status (any deterioration since assessment), and oxygen requirements. Evaluation of other systemic involvement of connective tissue disorders should be done.

Apart from routine preoperative cardiac assessment as per ACC/AHA guidelines,[4] an echocardiogram and coronary angiogram are performed in individuals over 45 years. A right heart hemodynamic study measures cardiac filling pressures and underlying pulmonary hypertension.

Comorbid Illness: Certain comorbid diseases like diabetes mellitus, hypertension, and renal dysfunction may increase the likelihood of peritransplant complications or adversely affect the outcomes.[5] Dysfunction of other vital organs like renal failure, stroke within 30 days, liver cirrhosis with portal hypertension, recent acute coronary syndrome, and untreatable malignancies are absolute contraindications for lung transplantation.

Frailty related to age or chronic end-organ disease is typically identified and treated, if possible (e.g., physical rehabilitation, nutritional optimization)

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Medications: Patients with chronic obstructive pulmonary disease (COPD) and pulmonary arterial hypertension receive regular bronchodilator therapy, inhaled and systemic steroids, and pulmonary vasodilator therapy. It is critically important to continue throughout the perioperative period all chronically administered medications prescribed for pulmonary hypertension.[6] Anticoagulant therapy should be reviewed and modified with drugs with a shorter half life.

Current and historical human leukocyte antigens (HLA) antibody screening tests and the specificity of any preformed HLA antibodies should be reviewed. If the panel reactive antibody titer is high, desensitization should be done.

Adequate blood and blood products should be reserved. Sedative premedication is avoided, especially in those with pulmonary hypertension or supplemental oxygen therapy, and should be administered under strict supervision inside the operating room.

INTRAOPERATIVE MANAGEMENT

The goals of intraoperative management should focus on the preservation of allograft quality, maintenance of cardiovascular stability, and prevention of extrapulmonary complications.[7]

Monitoring and Venous Access

Large bore venous access for rapid volume replacement and invasive monitoring of arterial, central venous, and pulmonary artery pressures via arterial cannula, multilumen central venous line, and pulmonary artery catheter, respectively, is done before induction. Compulsory monitoring includes five-lead electrocardiography, pulse oximetry, urine output, core temperature, capnography, and anesthetic agent gas analysis. Other monitors like depth-of-anesthesia monitoring, cerebral oximetry, arterial blood gas monitoring, continuous cardiac output, and mixed venous oximetry are routinely used during lung transplantation.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is essential for continuous cardiac monitoring. It provides real-time analysis of left and right heart preload, left and right ventricular function, regional wall motion abnormalities, pulmonary artery pressures, and intracardiac air, primarily when used in hemodynamic instability. It can detect patent foramen ovale, intracardiac thrombus, and other unanticipated abnormalities. If unexplained or refractory hypoxemia occurs, intracardiac shunting should be suspected. Detailed examination of the pulmonary vein and arterial anastomosis is done to rule out any narrowing.

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Induction

Induction of anesthesia is one of the most critical periods, and severe hemodynamic instability should be anticipated. The surgeon and perfusionist must be prepared for emergency initiation of cardiopulmonary bypass if a circulatory collapse occurs. Factors that precipitate cardiac instability include severe hypoxia, hypercarbia, acidosis, blunting of endogenous sympathetic drive, anesthetic drugs causing myocardial depression, vasodilatation, and initiation of positive pressure ventilation. The primary hemodynamic goals of induction are to prevent falls in systemic vascular resistance, maintain myocardial contractility, and avoid any increase in pulmonary vascular resistance.

Rapid sequence intubation with scoline or rocuronium is used. Optimization of hemodynamics may need to be achieved by vasopressor and ionotropic support. A double-lumen tube is preferred in most cases as it allows absolute lung isolation and differential ventilation. Single-lumen ETT with bronchial blockers is an alternative. The double-lumen tube is exchanged for a single-lumen ETT at the end of the surgery; tube exchanger is preferred during this.

Broad-spectrum antibiotics are given as prophylaxis before incision. For patients with suppurative lung disease or a current chest infection, the choice of antibiotics is determined by microbiological culture. The microbiological burden of the donor should also be taken into account.

Ventilation

Specific ventilation strategies like low-inspiratory pressures and minimal tidal volume to avoid dynamic hyperinflation, high-airway pressures, and high positive end-expiratory pressure (PEEP) should be employed.[8] One should focus primarily on arterial pH rather than arterial PCO_2 since most patients are adapted to chronic hypercapnia.

MAINTENANCE OF ANESTHESIA

Inhalation anesthesia with sevoflurane/isoflurane is the preferred choice. A total intravenous anesthetic technique has also been described. Inhalational agents have bronchodilatory effects in patients with obstructive airway disease.

One-lung ventilation (OLV) is better tolerated in the lung with greater perfusion. Strategies that decrease the shunt fraction in one lung ventilation should be employed. If severe respiratory acidosis or hypoxemia occurs, mechanical circulatory support should be initiated.

Reduction of pulmonary hypertension and vascular resistance is a principal goal of intraoperative management at every stage of the operation.[9] Vasoactive agents most commonly used are milrinone, noradrenaline, and

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adrenaline. Inhaled pulmonary vasodilators are used to reduce pulmonary vascular resistance (PVR) selectively. Inhaled nitric oxide is the first choice inside the operating room in patients at risk of right ventricular failure.

MECHANICAL CIRCULATORY SUPPORT

Intraoperative extracorporeal membrane oxygenation (ECMO) [Venovenous (VV) or venoarterial (VA)] should be considered in case of refractory hypoxemia, supra-systemic pulmonary artery pressures, and impossible lung protective ventilation strategy. TEE is essential in this decision-making.[10]

Warm beating heart cardiopulmonary bypass (CPB) is also routinely used for lung transplantation based on institutional experience. CPB is also employed when the recipient requires plasmapheresis due to HLA mismatch and HLA antibodies against the donor. Bypass times are often prolonged, so a centrifugal pump offers an advantage over a continuous flow roller pump. An ECMO oxygenator is routinely used.

Venous drainage is generally affected by surgical manipulation of the heart and hilum therefore, strict vigilance is required. Bicaval-cannulation is preferred. The advantages of CPB are hemodynamic stability and allow controlled reperfusion of each graft. Disadvantages of CPB are hemolysis and activation of proinflammatory mediators that can cause lung injury. It also increases the need for blood product transfusion due to haemodilution, coagulopathy, and platelet dysfunction. The use of CPB has been associated with a more extended period of postoperative mechanical ventilation, more pulmonary edema, and increased early morbidity, although this is controversial.

SURGICAL CONSIDERATIONS AND ANASTAMOSIS

In redo surgeries, restrictive or supportive lung disease, extensive pleural adhesions may complicate surgical explantation and need massive blood transfusions.

For bilateral sequential single-lung transplantation performed without CPB, if there is a significant perfusion mismatch between the two lungs, transplantation is done for the lung with lower perfusion. Bronchial anastomosis is initially followed by pulmonary artery and finally pulmonary venous anastomosis. Thorough bronchial toileting using a flexible bronchoscope is done after the bronchial anastomosis. Pulmonary venous anastomosis is done by grafting an island off the donor atrium containing the upper and lower pulmonary veins onto the recipient's left atrium. During this stage, the application of an atrial clamp can cause arrhythmias, decreased left atrial preload, or coronary artery occlusion. Surgical retraction on the heart causes intermittent periods of hypotension and low cardiac output. Hence, regular communication between the anesthetist and surgeon is essential.

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Vasoactive drugs and fluids are required to maintain hemodynamic stability. Caution should be exercised as low-pressure pulmonary edema in the grafts may occur, if an excessive fluid has been given. Before tying the final stitch of the atrial anastomosis, the graft is entirely desired. 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 deair the atrial cuff before the final knot is tied. At this point, hypotension may occur due to several causes.

Sometimes leaks in the vascular anastomosis may need to be controlled by placing additional 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 ischemic 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, limiting initial flows to the vascular bed of the graft, which has been shown to reduce primary graft dysfunction (PGD). To reduce lung injury, initial ventilation to the graft should be with a low FiO_2 tolerated, low-peak inspiratory pressures of 15–20 cmH_2O, and PEEP of 5 cmH_2O. The respiratory rate is initially set to 8–10 breaths per minute. Once the pulmonary artery clamp is fully released, ventilation settings must be adjusted to ensure adequate minute ventilation and CO_2 removal and the FiO_2 titrated to a safe oxygen saturation level.

POSTOPERATIVE ANALGESIA

Multimodal analgesia with intravenous opioids and regional anesthesia techniques are essential in reducing morbidity. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, ketorolac, and other nephrotoxic drugs should be avoided due to their synergistic action with calcineurin inhibitors.

Epidural Analgesia

Adequate postoperative analgesia is essential to facilitate tracheal extubation. Thoracic epidural analgesia (TEA) provides superior analgesia compared with systemic opioids.[11] However, unique risks associated with preoperative epidural catheter placement must be considered in the lung transplant population. First, in the event of a bloody tap, the risk of an epidural hematoma is magnified after full heparinization for CPB. Timely decompression may be delayed due to prolonged surgery and the inability to elicit clinical signs in patients under general anesthesia. Second, the benefit of TEA is shortened or lost, if tracheal

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extubation is delayed due to other complications. An alternative is to insert the epidural postoperatively in an awake or lightly sedated patient before extubation or only if systemic multimodal analgesics are inadequate. For single-sided surgery, paravertebral catheter insertion is an alternative to TEA.

Immunosuppressants

One primary strategy of immunosuppressant induction agents is to suppress the potentially robust T cell immune response to the allograft in the immediate postoperative period after lung transplantation. All lung transplant programs use high-dose steroids like methyl-prednisolone for immunosuppression before implantation of the donor organ. Available induction agents are adjuncts to steroids and deplete existing T cells and/or interrupt T cell activation and proliferation. These induction strategies can be classified into two groups: Monoclonal and polyclonal agents. The decision to use induction therapy and its type must be made based upon comorbidities to balance the effects of immunosuppression on both risks of infection and rejection.

The most common monoclonal induction agent utilized in lung transplantation is basiliximab or alemtuzumab. Induction with alemtuzumab has been associated with greater freedom from developing acute and chronic rejection in lung transplant recipients. Antithymocyte/lymphocyte globulin (ATG) is a polyclonal antibody preparation that nonspecifically binds to antigens on the surface of T cells, resulting in lymphocyte depletion.

The most common complication of these immunosuppressive drugs is acute renal injury. Though transient, renal dysfunction can be exacerbated by associated comorbid illness. Calcineurin inhibitors like cyclosporine and tacrolimus cause vasoconstriction of the renal arteriole, thereby reducing renal blood flow and glomerular filtration rate.

Triple drug maintenance immunosuppression therapy is considered the standard of care after lung transplantation and consists of steroids, calcineurin inhibitors, and antimetabolites. It is not uncommon for patients to require a switch to alternative immunosuppressive regimens based on individual tolerability. These drugs have a narrow therapeutic index, so levels should be frequently monitored. There can also be significant interpatient and intrapatient variability. This variability is due to genetic polymorphisms of cytochrome P450 3A enzymes and the transport protein P-glycoprotein, age, clinical status (time after transplant, liver function, and gut function), disease states (i.e., cystic fibrosis), and presence of interacting medications.

Ventilatory Management

The primary goals of ventilatory strategies are to provide adequate minute ventilation and to avoid ventilator-induced lung injuries like volutrauma,

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barotrauma, and oxygen toxicity.[12] From the time of bronchial anastomosis, lung protective ventilation is initiated [low tidal volume (4–6 mL/kg ideal body weight) and low driving pressures to limit the plateau pressure below 30 cmH_2O].[8] During reperfusion, the lowest acceptable FiO_2 is used to maintain oxygen saturations >92%. A FiO_2 40% is ideal for preventing acute lung injury. No particular ventilation mode is proven beneficial in the early postoperative period, though the pressure control mode with pressure control set below 15 and optimal PEEP is commonly used.[13]

The management should be individualized to achieve set target goals. Sudden deterioration in oxygenation and a decrease in lung compliance are early indicators of graft dysfunction. The differential diagnosis for post-operative hypoxemia includes PGD, anastomotic issues, pneumothorax, atelectasis, fluid overload, cardiac failure, etc. Frequent desaturations may indicate pulmonary hypertensive episodes, which should be managed with inhaled nitric oxide or pulmonary vasodilators, sedation, and muscle relaxation.[14] In many instances, sudden hypoxemia and hypercapnia require emergency bronchoscopic removal of secretions and mucous plugs.

Single-lung transplantation, as for emphysema, pose different challenges. The native and donor lungs will have other respiratory mechanics depending on the native lung disease. In COPD patients, there is a high risk of hyperinflation and auto-PEEP in the native lungs, so lower PEEP is generally employed.

Primary Graft Dysfunction

It is a syndrome of acute severe lung injury, which occurs within 72 hours postlung allograft transplant without any major identifiable cause.[15] It is one of the significant causes of morbidity and mortality in the early postoperative period, with a reported incidence of about 10–25%.[16] It is characterized by progressive hypoxemia, and diffuse alveolar infiltrates in a chest X-ray.

In 2016, the International Society for Heart and Lung Transplantation (ISHLT) consensus statement of the working group on PGD,[17] standardized the definition of PGD **(Table 1)**. Assessment is carried out at specific time points after reperfusion; within the first 6 hours (T0), post 24 hours (T24), 48 hours (T48), and 72 hours (T72). Ideally, the P/F ratio is measured on a FiO_2 of 1.0 and PEEP of 5 cmH_2O.

TABLE 1: Grading of primary graft dysfunction.

Grade	*Pulmonary edema on chest radiograph*	*PaO_2/FiO_2 ratio*
0	No	Any
1	Yes	>300
2	Yes	200–300
3	Yes	<200

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ECMO POSTLUNG TRANSPLANT

Early initiation of ECMO is advised in patients with refractory hypoxemia, ideally within 24 hours after transplantation.[18,19]

Venovenous ECMO with ultra-lung protective ventilation (3 mL/kg) may limit ventilator-induced lung injury and improve graft survival. Oxygen supply to the graft via pulmonary arteries is crucial as bronchial arterial blood supply to the implanted lung is lacking.

Venoarterial ECMO is established in case of severe hemodynamic instability or a severe pulmonary hypertensive crisis. As VA ECMO shunts blood away from the lung, maintaining normal pulmonary artery pressure and pulsatility is essential to prevent graft hypoxia.

In certain situations, VVA ECMO, which combines both VV and VA ECMO techniques, can be utilized to regulate adequate pulmonary perfusion and systemic oxygenation.

WEANING OF MECHANICAL VENTILATION

Chest X-ray is done daily in the initial week. Malposition of invasive lines, diaphragmatic position, atelectasis, and evidence of rejection like infiltrates/opacities, pleural abnormalities, and pneumonia should be examined. Bedside lung ultrasound also is beneficial. In case of unclear findings, CT without contrast is warranted.

Early tracheal extubation is ideal for postlung transplantation. Inhaled nitric oxide at 10–20 PPM, when used to manage pulmonary hypertension post-transplant, is generally weaned in 24–48 hours. PEEP is then weaned, followed by FiO_2 according to serial blood gases and hemodynamics.

Early tracheostomy should be considered in patients requiring prolonged mechanical ventilation. Flexible fiber-optic bronchoscopy is performed in all patients for better trachea bronchial toileting and to evaluate the integrity of the airways. Post-tracheal extubation, aggressive respiratory physiotherapy with incentive spirometry and early mobilization is initiated.

HEMODYNAMIC MANAGEMENT

Invasive cardiovascular monitoring is essential, as early postoperative hemodynamics can be very labile. In high-risk cases like elevated pulmonary arterial pressures at the time of transplant or an underlying diagnosis of pulmonary arterial hypertension, Pulmonary artery catheters with continuous cardiac output and TEE are used to aid management.[20]

An obstruction to the pulmonary vein flow (due to clot, kinking, or narrow anastomosis) may present with hypoxia. TEE becomes a powerful tool in differentiating this condition from other causes, such as acute graft rejection or reperfusion injury. The turbulence of flow, pulmonary vein diameter of <0.5 cm, peak systolic flow velocity >1 m/s, and pulmonary vein-left

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atrial pressure gradient (PVLAG) ≥10–12 mm Hg support the diagnosis of pulmonary vein stenosis.[21]

Hemodynamic goals are to maintain adequate systemic perfusion and oxygen delivery by avoiding hypotension and pulmonary hypertension. Sudden increases in pulmonary vascular resistance can lead to right heart failure and should be monitored continuously. Pulmonary vasodilators like nitric oxide, inhaled prostacyclin, and milrinone reduce the right ventricular afterload and help the right ventricle recover. A cardiac index of 2.2–2.5 is ideal. Vasopressors and ionotropic agents may be required to support hemodynamics.[22] Caution should be used if high-dose vasopressors are used as they may compromise airway mucosal circulation. Serial lactate levels and mixed venous saturations are measured and guided by clinical status.

Arrhythmias, generally supraventricular in origin, are commonly seen, with a reported incidence of 34–74%.[23] Hemodynamically significant arrhythmias should be cardioverted immediately.

FLUID MANAGEMENT

Reperfusion pulmonary edema is common after lung transplantation due to leaky capillaries, and loss of lymphatic drainage should be managed aggressively. Diuretic infusion is required to maintain a total negative balance.

Volume replacement with colloid (5% albumin) rather than crystalloids should be considered. Hematocrit in the range of 25–30% is maintained. Point of care testing of coagulation like thromboelastogram (TEG) should guide blood product replacement.

INFECTION AND SEPSIS MANAGEMENT

Infectious complications contribute substantially to increased postoperative morbidity and mortality following lung transplant. Data suggest that more than 25% of postoperative deaths are due to infectious causes.[24] Postoperative lung complications after lung transplant are listed in **Table 2**.

Lung transplant recipients are uniquely high risk for bacterial and fungal infections. A high level of immunosuppression is maintained. Allograft denervation leads to decreased mucociliary clearance and absent cough reflex. There is also continuous exposure to environmental pathogens and colonizing organisms from the upper respiratory tract.

Bronchoscopy with bronchoalveolar lavage (BAL) is the most sensitive test to rule out infections. Bacterial pneumonia is the most common infection postlung transplant.[25] Viral infections in the early postoperative period are uncommon. Empirical broad-spectrum antibiotics should be initiated intraoperatively before incision, followed by targeted antibiotics for the BAL cultures of the explanted lung from the donor. Antifungal prophylaxis, *Pneumocystis carinii* prophylaxis, and cytomegalovirus prophylaxis are started from postoperative day 2.

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TABLE 2: Postoperative complications after lung transplantation.

Respiratory	*Cardiovascular*	*Surgical*
• Primary graft dysfunction • Pulmonary embolism • Pleural effusions • Transfusion related acute lung injury (TRALI)	• Right heart dysfunction • Arrythmias • Myocardial ischemia	• Bleeding • Pulmonary arterial stenosis • Pulmonary venous thrombosis • Bronchial anastomotic dehiscence
Immunological	***Renal***	***Infectious***
• Hyperacute rejection • Acute rejection • Side effects of drugs	Acute kidney injury	• Bacterial pneumonia • Fungal infections • Viral infections (CMV, EBV)

(CMV: cytomegalovirus; EBV: Epstein-Barr virus)

CONCLUSION

The perioperative and postoperative care of lung transplant recipients requires meticulous attention to detail with a multidisciplinary team approach. Anesthesiologists should have knowledge about transplant immunology, intensive care, TEE, thoracic, and cardiac anesthesia to manage these patients successfully.

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