Review Article

Anaesthesia for patients after lung transplantation

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Purpose: The purpose of this article is to review the literature on post lung transplant patients presenting for surgery and anaesthesia and to provide insight into their perioperative management.

Source: Articles and books were identified via a Medline search and through a review of the bibliographies of these sources.

Principle Findings: Single and double lung transplantation is becoming more common and the period of survival is increasing. As a result, more of these patients are presenting for surgery and anaesthesia. Also, it is increasingly likely that these patients may present, either for emergency or elective surgery, to anaesthetists with limited experience in this field. These patients have considerable medical, physiological and pharmacological problems which need to be understood.

Conclusion: Anaesthesia, local, regional, or general, can be safely delivered to these patients provided that the physiology and pathophysiology of the transplanted lung, the pharmacology of the immunosuppressive agents, and the underlying surgical condition are understood.

Objectif : Cet article vise à réviser les articles publiés sur les transplantés qui se présentent pour une anesthésie et une intervention et de renseigner sur la gestion périopératoire de ces patients.

Source : Les articles et volumes ont été identifiés par une recherche sur Medline à partir d'une revue des bibliographies contenues dans ces publications.

Principales constatations : Les transplantations pulmonaires simples et doubles sont de plus en plus fréquentes et les transplantés survivent plus longtemps. Par conséquent, ces patients se présentent en plus grand nombre pour des interventions urgentes ou programmées à des anesthésistes dont l'expérience est limitée. Il faut donc comprendre que ces patients ont des problèmes médicaux, physiologiques et pharmacologiques particuliers.

Conclusion : L'anesthésie, locale régionale et générale peut être administrée sans danger à ces patients pourvu qu'on tienne compte de la physiologie, de la physiopathologie du poumon transplanté, de la pharmacologie des immunosuppresseurs et de la maladie en cause.

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SINGLE and double lung transplantation has become an accepted method of treatment for a variety of pulmonary diseases. Considerable progress has been made since the first human lung transplant was performed by Hardy in 1963.[1] The first 20 yr were marked by poor outcomes due to poor organ preservation, infection, anastomotic problems, and inadequate immunosuppression. The introduction of cyclosporine in 1981 and the work of groups such as the Toronto Lung Transplant Group began the modern era of lung transplantation.[2] By 1994, the Registry of the International Society for Heart and Lung Transplantation had recorded 1943 single lung transplants from 101 centre and 943 bilateral or double lung transplants from 71 centres. Approximately 500 single lung transplants (SLT) and 300 bilateral/double lung transplants (DLT) were undertaken in 1993.[3] One year survival varies among centres and by the indication for transplantation. Overall survival is reported as 62% for SLT and 71% for DLT with a four year survival of 53% and 62% respectively.[4]

The initial post transplantation period is spent in close proximity to the transplant centre. After four to six weeks the patient returns home and follow up is performed at progressively less frequent intervals. Subsequently, these patients may present for surgery and anaesthesia at a location away from transplant hospital and to anaesthetists who are unfamiliar with the effects of lung transplantation. These patients can present a unique challenge requiring a knowledge of the changes in physiology and pathophysiology, the pharmacology of immunosuppression, the difficulty in differentiating infection from rejection, the avoidance of introducing infection, the management of ventilation, and caring for the underlying condition requiring that the patient be anaesthetized. In addition, the systemic disease for which the lung transplant was needed may have on-going non-pulmonary effects.

Indications and Operative Procedures for Lung Transplantation

The major indications for SLT are: emphysema, alpha-1-antitrypsin deficiency disease, idiopathic pulmonary fibrosis, and primary pulmonary hypertension. Pulmonary infection is a contraindication.[3] The procedure is carried out via a thoracotomy and rarely requires cardiopulmonary bypass. The indications for bilateral/double lung transplantation are similar to those for SLT but pulmonary infection is not a contraindication. The major indication for DLT is cystic fibrosis.[3] (Table I) The procedure is carried out either via a ster-

TABLE 1 Indications for single or double lung transplantation.

Indication	*Single Lung Transplantation (%)*	*Double Lung Transplantation (%)*
Emphysema	41	14.5
Alpha-1-Antitrypsin	16.6	14.7
Idiopathic Pulmonary Fibrosis	17	4.5
Primary Pulmonary Hypertension	10.1	9.3
Cystic Fibrosis	0.4	38.1
Re-transplantation	2.9	3.0
Miscellaneous	11.8	15.8

(Data from: Hosenpud JD, Novick RJ, Breen TJ, Daily OP. The registry of the International Society for Heart and Lung Transplantation: Eleventh Official Report – 1994. J Heart Lung Transplant 1994; 13: 561–70.)

no-bithoracotomy incision or via median sternotomy. Cardiopulmonary bypass is required in about 10% of cases. Most DLTs are carried out as sequential single lung transplants with anastomosis of the bronchus, left atrium and pulmonary artery on each side. In the past, DLTs were carried out en bloc with a tracheal anastomosis. Tracheal dissection may interrupt the sympathetic and parasympathetic nerve pathways resulting, to a varying degree, in a denervated heart.[5] The results is a physiological and pharmacological response similar to the transplanted heart and may have considerable anaesthetic impact. The use of an omental wrap of the bronchial anastomosis to aid healing is no longer needed with the development of the technique of the telescoping bronchial anastomosis and steroid-sparing immunosuppression regimes.

Surgical Disease in Post Lung Transplantation Patients

Surgical intervention may be required for complications related directly to the transplant, complications of immunosuppressive therapy, the underlying condition which necessitated the transplant, or to disease unrelated to the transplant. In the early postoperative period haemorrhage may make re-exploration of the thoracic cavity necessary. Anaesthesia, either local or general, is most commonly needed in these patients for bronchoscopy, biopsy and lavage. This is carried out routinely in the early post-transplant period and then at regular intervals after the patient has been discharged from the hospital. These procedures are also required to differentiate between infection and rejection or to establish a diagnosis of obliterative bronchiolitis.[6–10] Although less common now, due to improved surgical technique and steroid-sparing immunosuppressive regimes, airway obstruction due to stenosis at the site of bronchial anastomosis does occur. Treatment is by dilatation or placement of stents under general anesthesia.[11]

The incidence of surgical complications ranges from 15 to 28% of the transplanted patients with a mortality of 0–40%.[12–14] Merrell *et al.* related their low mortality to corticosteroid sparing immunosuppression and early, aggressive surgical intervention.[14] While there are numerous isolated reports of surgical intervention in lung transplant patients[11,15–17] there is only one study by Smith *et al.* dealing with the a series abdominal complications after lung transplantation.[18] This confirmed the high incidence of abdominal complications (16%) and the associated high mortality (25%). The complications included prolonged ileus, diaphragmatic hernia (related to omentoplasty of the bronchial anastomosis), ischaemic bowel, and cholelithiasis. Other abdominal complications may result from the use of immunosuppressive drugs. Corticosteroids, azathioprine and cyclosporine have been linked to pancreatitis.[19,20,13] Chronic steroid use has been linked to both peptic ulceration and colon perforation.[21,22] Gastric outlet obstruction can occur with cytomegalovirus infection. Cystic fibrosis patients are still at risk for intestinal obstruction as a result of inspissated secretions.[23]

Besides their link to abdominal complications, corticosteroids can cause a number of other surgical complications including aseptic hip joint necrosis, vertebral compression fractures, glaucoma, and cataracts. Neoplasia is also much more common in patients after transplantation and appears to be related to immunosuppression.[24] Occasionally, persistent air leaks occur or hyperinflated bullae that compress the transplanted lung require pneumonectomy or lobectomy of the native lung.[14–16] Trauma or pregnancy are additional reason for transplant recipients might present for surgery.

Physiology of the Transplanted Lung

Disruption of the innervation, lymphatics, and the bronchial circulation occurs when the donor pneumonectomy is performed. This has profound physiological consequences for the transplanted lung and major implications for anaesthesia. Denervation of the heart may also occur in double lung transplantation. Many of the studies on the physiology of the transplanted lung were performed on heart-lung transplant patients, but in general the results can be applied to single or double lung transplants.[25]

In SLT or in DLT carried out as sequential single lung transplants denervation occurs distal to the bronchial anastomosis while in en bloc DLT the denervation includes the carina. In the reimplanted canine lung reinnervation of the transplanted appears to take place. The vagal bronchoconstrictor nerves regenerate in three to six months.[26] Sympathetic reinnervation was demonstrated 45 mo after grafting.[27] In humans, reinnervation is not known to take place.[28]

The major consequence of denervation is the loss of the cough reflex demonstrated by Higenbottam *et al.*[29] They showed that in heart-lung transplantation recipients, the laryngeal mucosa remained sensitive to stimulation but that the consequence of carinal resection was the loss of the cough response to distal airway irritation. This continued up to 36 mo after transplantation confirming that reinnervation does not take place in humans. Where the carina is not resected, the bronchi distal to the anastomosis will not respond to stimulation but the cough reflex of the carina should remain intact. Failure of the cough reflex places the patient at risk for aspiration and infection.

Airway tone is controlled via parasympathetic efferent nerves acting on bronchial smooth muscle. Denervation results in little change in airway tone or function except under specific conditions such as bronchial hyperresponsiveness to inhaled methacholine and histamine.[30] This is a possible manifestation of muscarinic denervation hypersensitivity. However, asthma does not develop.[25] Ipratropium bromide blocks the response to methacholine. Inhaled beta adrenergic blockers have no effect on airway conductance while beta-2 agonists cause bronchodilatation. There is one case report of bronchospasm after heart-lung transplantation which was poorly responsive to isoproterenol, aminophylline, corticosteroids, halothane, and atropine.[31]

Denervation of the lung also results in loss of baroreceptor input from the lung to the medulla. In most animals, vagal block results in slow deep breathing, but bilateral vagal block in humans has been shown to have minimal effect on respiratory rhythm.[32] This was confirmed by Shaw *et al.* who found no effect on respiratory rate or rhythm in bilateral lung transplant patients.[33] Breathing while sleeping is also normal.

Pulmonary blood flow is normal in DLT patients. In SLT patients, 60% to 70% of the perfusion and ventilation goes to the transplanted lung.[34] Denervation does not appear to prevent hypoxic pulmonary vasoconstriction, suggesting that this may be a locally mediated phenomenon.[35] Clinically, this could have an important impact, by shifting pulmonary blood flow from a transplanted lung that is rejecting to a diseased native lung.

Mucociliary clearance is impaired in the early postoperative period and in long-term survivors of heart-lung and DLT.[36,37] Abnormal mucus production is thought to play an important role in this defect. Alveolar macrophage antimicrobial function may also be abnormal.[38] Clinically, the loss of both the cough reflex and impaired mucocillary function plus the use of immunosuppressive agents places the lung transplant patient at increased risk for bacterial bronchitis and pneumonia.[39]

Transection of the trachea or bronchi also severs the lymphatic vessels. In dogs, lymphatic drainage appears to be reestablished between two and four weeks after transplantation.[40] Extravascular lung water volume is increased in the early postoperative period in dogs.[41] Compliance is reduced, while surfactant production appears to be unaffected. Although unproven, it is likely that this also occurs in humans. After transplantation, there is frequently excessive drainage of fluid from the pleural cavity and chest tubes which usually subsides after two weeks.[42] Lung transplant patients are, therefore, at increased risk for developing pulmonary oedema due to fluid overload, particularly in the early postoperative period.

After transplantation for severe chronic obstructive airways disease, hypercapnia and a blunted ventilatory response to CO_2 persist even though pulmonary function tests improve. However, by the 15th to 30th day after transplantation $P_{ET}CO_2$ returns to normal and the response to CO_2 is enhanced.[43] This recovery is explained by a readjustment of the central chemoreceptor regulatory centre since it occurred without alteration of pulmonary function during the test period. Other changes include a reduction in the work of breathing with decreased compliance, improved elastic recoil, and reduced chest wall distention in patients who underwent SLT for emphysema.[44] In these patients diaphragmatic function also appeared to be improved as a result of a more favourable position.[45]

Depending on the underlying disease, after transplantation these patients show improvement in FVC, FEV_1, FEV_1/FVC and FEF_{25-75}. Most patients transplanted for emphysema are New York Heart Association class I or II by six months.[46,47] Near normal lung function tests including arterial blood gas analyses are found in DLT patients while persistent evidence of the underlying restrictive or obstructive lung disease remain in the pulmonary function tests of SLT patients.[48]

Physiology of the Denervated Heart

In DLT performed *en bloc*, dissection around the trachea may disrupt cardiac autonomic nerve supply and result in a denervated heart.[5] While both sympathetic and parasympathetic reinnervation may occur in humans, whether it occurs in these patients and its clinical importance is unknown.[49,50] These patients may show a similar physiology to cardiac transplant patients although this has not been examined in detail. One study demonstrated abnormal responses to carotid sinus pressure, Valsalva manoeuvre, intravenous atropine, and an abnormal response to maximal exercise.[5] These responses are compatible with denervation.

In the absence of vagal tone the denervated heart has a higher resting heart rate (90–100 bpm) and may be more susceptible to arrhythmias.[51] Cardiac output is dependent on intrinsic mechanisms such as the Frank-Starling effect and on circulating catecholamines which will take five to six minutes to act. The heart is preload dependent and increases output by increases in stroke volume initially and only later by compensatory tachycardia. Response to hypovolaemia either as a result of loss of intravascular volume, postural change, or decreased systemic vascular resistance

is exaggerated. Heart rate does not change in response to a variety of agents commonly used in anaesthesia such as pancuronium, anticholinergics, anticholinesterases, phenylephrine, nifedipine, nitroprusside or digoxin. Heart rate increases in response to direct acting beta adrenergic agents such as isoproteronol, ephedrine, and epinephrine.[52,33,53]

Immunosuppression and Rejection in Lung Transplantation

Immunosuppression has made transplantation possible, but it is a double edged sword. The use of these agents has considerable side effects and increases the patients vulnerability to infection. Inadequate immunosuppression raises the danger of rejection while excessive immunosuppression renders the patient susceptible to life-threatening infection. Anaesthesia may be influenced in a number of ways by immunosuppression. Firstly, the side effects of the immunosuppressive agents may influence the choice of anaesthetic agents or their doses. Secondly, immunosuppressive agents may affect the action or duration of drugs used during anesthesia. Thirdly, the therapeutic levels and doses of immunosuppressive agents may be modified by the use of drugs used during anaesthesia. Finally, the blood concentrations, doses, or route of administration of immunosuppressive agents may be altered by intercurrent illness. Anaesthetists should be aware of these possibilities. The lung is unique in that it is one of the largest organs transplanted, its extensive vasculature is exposed to the entire cardiac output, it has its own intrinsic immune apparatus and it is in constant contact with extrinsic inhaled allergens. The local inflammation caused by these allergens may result in activation of T-lymphocytes. For these reason the dose of immunosuppressive agents is higher than for other transplanted organs.

The use of immunosuppressive agents may be divided into three phases. The induction phase is the initiation of immunosuppression. This is the period from transplantation to two to four weeks after transplantation. Since rejection is most likely to occur at this time, intense immunosuppression is administered in the hope of delaying the first episode. Doses are adjusted to keep blood concentrations in the high to supra-therapeutic range. In lung transplantation a triple regimen of cyclosporine, azathioprine, and corticosteroids is usually used. Antisera (Antilymphocyte globulin, OKT3) are added by some programmes. The high level of immunosuppression increases the risk of infection and drug side effects (see Table II). The maintenance phase is the period after induction if there is no episode of acute rejection. Most centres use a triple regimen of cyclosporine, azathioprine, and corticosteroids. This allows a lower dose of each immunosuppressive agent to minimize side effects while maintaining adequate immunosuppression. The acute rejection phase occurs if immunosuppression fails. The threat of acute rejection decreases with time but is always present. During the first three weeks almost all lung transplant patients will experience one episode of acute rejection and 60% of all episodes will occur in the first three months after transplantation.[54] Treatment involves the use of high doses of corticosteroids. The maintenance regimen should also be reviewed and altered if needed. Occasionally, acute rejection will not respond to increases in corticosteroids and the additional agents such as OKT3 may be needed.[55]

The lung is also subject to chronic rejection which manifests as obliterative bronchiolitis (OB). This complication is a major cause of mortality in lung transplantation recipients. Use of a triple regimen may reduce the incidence of OB.[56–58] Severe, frequent, and persistent acute rejection has been linked to the development of chronic rejection and OB as has cytomegalovirus

TABLE II Toxicity and side-effects of the immunosuppressive agents commonly used in lung transplantation

Agent	*Side Effect/Toxicity*
Cyclosporine A	Nephrotoxicity
	Hypertension
	Hepatotoxicity
	Neurotoxicity
	Gastric Atony
	Hyperkalemia
	Hypomagnesemia
Azathioprine	Leukopenia
	Thrombocytopenia
	Anaemia
	Hepatotoxicity
	Pancreatitis
Glucocorticoids	Fluid retention
	Hypertension
	Glucose intolerance
	Adrenal Suppression
	Poor wound healing
	Electrolyte abnormalities
	Peptic ulceration
	Osteoporosis/Aseptic necrosis
	Psychological Disturbance
Antilymphocyte Globulin	Leukopenia
	Thrombocytopenia
	Systemic symptoms
OKT3	Systemic Symptoms
	Non-cardiogenic pulmonary edema
	Aseptic Meningitis/Encephalopathy
FK 506	Nephrotoxicity
	Hypertension
	Neurotoxicity
	Hyperglycaemia

(CMV) infection.[59] Treatment is based on prevention of CMV infection, rapid treatment of acute rejection, and high doses of immunosuppressive agents including cyclosporine, azathioprine, corticosteroids, and anti-lymphocyte globulin.[54]

The Agents

Cyclosporine A: Since its introduction in 1981, cyclosporine (CSA) has changed the outcome of transplantation by reducing the incidence and severity of rejection and is a part of all immunosuppression regimens. It is a cyclic peptide product of a fungus that interferes with the intracellular events that follow T-cell stimulation, by suppressing cytotoxic T-cell development, and B-cell function. It is highly fat soluble and passes easily through cell membranes. Most centres aim for a CSA whole blood concentration of 200-350 $ng \cdot ml^{-1}$. There is considerable variation between the methods used to measure CSA so that it is difficult to compare results between centres.

Nephrotoxicity is the most common and serious side effect of CSA use. The mechanism appears to be a reduction of glomerular filtration rate with decreased renal blood flow. It is dose dependent and corresponds to a high blood trough concentration of CSA. Reducing the dose can alleviate the problem, but CSA has a narrow therapeutic window and dose reduction risks the onset of rejection. Nephrotoxicity may develop within weeks and up to 72% of patients eventually will have renal dysfunction in the years post transplantation. Cyclosporine0 can exacerbate preexisting acute tubular necrosis in the early postoperative period.[60] Other nephrotoxic drugs such as the aminoglycosides, furosemide, amphotericin B, and trimethoprin-sufamethoxasole, have been associated with increased CSA toxicity.[61–63] Nephrotoxicity associated with prolonged use of CSA may not respond to a reduction in dose.[64] Impaired renal function is associated with hypertension, hyperkalaemia, and weight gain.

The second most common side effect of CSA is hypertension which is found in 50–70% of patients. This often responds to sodium restriction since the cause may be the renal defect in sodium excretion.[65] Reduction in CSA dose may also be effective. The hypertension is usually not severe and less than half the patients will require antihypertensive therapy. Cyclosporine can cause dose-related hepatotoxicity which presents with an increasein liver enzymes and/or bilirubin serum concentration. It is rarely of clinical importance. Hand tremors are the most common neurological side effects but more severe problems such as seizures and coma can rarely occur. Differentiating behavioural problems caused by corticosteroids from those caused by CSA can be difficult.

Of more concern to the anaesthetist is gastric atony, which can occur in the first few months postoperatively. Tracheal transection, as performed in en bloc DLT, could be associated with vagally induced gastric atony. However, gastric atony occurred with almost the same frequency in sequential DLT and SLT recipients where the trachea was not transected. The Toronto Lung Transplant Group reported that about one third of patients experienced gastric atony and related this to CSA.[39] The condition responds to metaclopramide. Changes in serum electrolytes: hyperkalaemia has been reported in 10–15% of lung transplant patients but requires little treatment besides dietary restrictions.[39] Hypomagnesaemia (renal wasting) occurs frequently and is often unrecognized.[66] Central nervous system symptoms such as seizures may result. Chronic replacement therapy may be required in 50% of patients. Hypochromic anaemia also develops in patients on CSA. This does not appear to be related to bone marrow depression.[67]

Cyclosporine is metabolized in the liver by the cytochrome P-450 system. Drugs that induce or inhibit this system will affect the concentration of CSA, often quite dramatically (Table III).[68,69] If the use of any of these drugs is contemplated, then blood levels of CSA should be monitored until the effect stabilizes. Metaclopramide may, as a result of its effect on gastric motility, cause a higher and earlier peak in the plasma CSA concentration.[70] If CSA is being given orally then it should be given four to seven hours before surgery to maintain adequate blood levels.[71] Sub-therapeutic cconcentrations occur if CSA is given less than four hours before surgery. General anaesthesia with isoflurane-nitrous oxide dose not effect intravenous cyclosporine pharmacokinetics although this study has only been carried out in rabbits.[72,73]

Occasionally, CSA may be given intravenously intraoperatively and interaction with anaesthetic agents is possible. The intravenous preparation of CSA is dissolved in cremophor which may affect neuromuscular blocking agents: the duration of vecuronium and, to a lesser extent atracurium, was shown to be prolonged by CSA.[74] Sharpe and Gelb showed that the duration of action and intensity of neuromuscular blockade produced by vecuronium was enhanced by the administration of CSA.[75] There have been a number of clinical reports of prolonged neuromuscular blockade in the presence of cyclosporine.[76,77] A study by Sidi *et al.* casts some doubt on the clinical relevance of these results.[78] In this study, five of eight renal transplant patients who had prolonged neuromuscular blockade or respiratory failure had not been given cyclosporine. This underlines the importance of seek-

TABLE III Drug interactions with cyclosporine.

Drugs Increasing Serum Cyclosporine	*Drugs Decreasing Serum Cyclosporine*	*Drugs Potentiating Nephrotoxicity*
Calcium Channel Blockers	Antibiotics	Antibiotics
Verapamil	Nafcillin	Gentamycin
Diltiazem	Rifampin	Tobramycin
Nicardipine		Vancomycin
	Anticonvulsants	Timethoprim-sulphamethoxazole
Antifungals	Phenobarbitone	
Ketoconazole	Phenytoin	
Fluconazole	Carbemazepine	Antineoplastics
Itraconazole		Melaphan
	Other Drugs	
Antibiotics	Octeotride	Antigfungals
Erythromycin	Ticlopidine	Amphotericin B
Clarithromycin		Ketoconazole
Glucocorticoids		Anti-inflammatory Drugs
Methylprednisolone		Azapropazon
		Diclofenac
Other Drugs		
Allopurinol		Gastrointestinal Agents
Metoclopramide		Cimetidine
Bromocriptine		Ranitidine
Danazol		
Immunosuppresives		Tacrolimus

ing other causes for prolonged neuromuscular blockade (electrolyte abnormalities, decreased excretion, etc.) and for monitoring neuromuscular blockade. Cyclosporine was found by Cirella *et al.* to increase, in a dose dependent manner, both the hypnotic effects of the barbiturates and the analgesic effects of fentanyl in mice.[79] They suggested that this change in anaesthetic action may be relevant in humans, but a study by Melendez *et al.* did not reveal any problems.[80]

Azathioprine: Azathioprine is an antimetabolite which exerts its action by blocking DNA/RNA synthesis and prevents the immune cells from responding to an antigenic stimulus. Its action on cells does not differentiate between the immune system and other cells which have a high rate of proliferation. Its action results in bone marrow depression (leukopaenia, thrombocytopaenia, megaloblastic anaemia) and an increased risk of infection. Hepatic dysfunction is another side effect. Dretchen *et al.* suggested that, as a result of azathioprine inhibition of phosphodiesterase at the motor nerve terminal, the duration of succinylcholine neuromuscular blockade may be prolonged, while that of the non depolarizing neuromuscular agents may be prolonged or reversed.[81] This effect appear to be clinically negligible.[82,83]

Corticosteriods: Corticosteriods are commonly used to prevent rejection in lung transplantation either as a maintenance drug or added to the regimen in the face of obliterative bronchiolitis (OB) or acute rejection. Doses are usually rapidly tapered and side effects are therefore minimized. Corticosteriods can cause fluid retention, hypertension, glucose intolerance, osteoporosis, poor wound healing, peptic ulceration, obesity, psychological side effects, and changes in serum electrolytes (hypokalaemia, hypocalcaemia). Adrenal suppression, as a consequence of chronic corticosteroid therapy, may require the administration of supplemental doses perioperatively. In renal transplant patients, one study showed that this was not necessary.[84]

Antilymphocyte Globulin and OKT3: Antilymphocyte globulin and OKT3 are unlikely to be given intraoperatively to post lung transplant recipients but they may be one of the medications in the patients' immunosuppressive regimen. Since both are produced by injecting animals with human lymphocytes, both can produce symptoms of serum sickness, arthralgias, leukopaenia, and thrombocytopenia. The use of OKT3 can also result in aseptic meningitis, nausea, vomiting, hypotension, and non-cardiogenic pulmonary oedema. The more severe side effects can be anticipated with the first dose and may be attenuated by the use of corticosteroids and diphenhydramine. Non-cardiogenic pulmonary oedema may be associated with a pre-existing increased intravascular volume and/or permiability defect.[85] This may be relevant in the early post lung transplant period when lymphatic drainage of the transplanted lung is compromised.

FK 506: FK 506 (Prograf) is a new immunosuppressive agent with a similar mechanism of action to CSA. It has not yet been approved for use in lung transplantation but, given its success in other organ transplantation, it is likely to be used in the future. Also, it appears to useful to reverse ongoing, established rejection.[86,87] In a prospective trial combining azathioprine with either CSA or FK 506, six month graft survival was better in the FK 506 group (86% *vs* 69%) and the percentage of patients rejection free in the FK 506 group was 21% *vs* 3% in the CSA group.[88] As with CSA, blood concentrations are important and should be monitored. Side effects are similar to CSA including nephrotoxicity, but with a lower incidence of hypertension.[89] FK 506 is metabolized by cytochrome P-450 and will be affected in a similar fashion to CSA by drugs that alter this enzymes activity. (Table III)

Preoperative Assessment

Preoperative assessment should focus on five areas: (1) the function of the transplanted lung; (2) possibility of rejection or infection in the transplanted lung; (3) the effect of immunosuppressive therapy on other organs and the effect of organ dysfunction on the transplanted lung; (4) disease in the native lung (SLT); (5) the indication for the surgical procedure and its effect on the lungs. Patients will spend four to six weeks in close proximity to the transplant centre since this is the time rejection and infection are most likely to occur. Following discharge, every patient keeps a diary which will provide valuable information to the anaesthetist regarding respiratory function and immunosuppressive therapy. Contact telephone numbers at the transplant centre are also provided and communication with the transplant group is encouraged.[90] They can give advice with regard immunosuppression management (route of administration and dose may need to be changed), infection, and how to rule out rejection.

Assessment of Graft Function: Immediately after transplantation, pulmonary gas exchange is variable, probably related to graft injury at the time of donor death, the adequacy of organ preservation and the use of cardiopulmonary bypass. Airway pressure during mechanical ventilation is higher than normal due to decreased compliance.[42] Over the next 12 mo, in the absence of infection or rejection, pulmonary function as measured by pulmonary function tests, blood gas analysis, exercise tolerance and subjective dyspnea progressively improves.[48]

In SLT recipients, TLC, FEV_1, VC, DLCO are all markedly improved by nine months. Overall, the tests show a mild restrictive defect with moderate impairment of gas transfer. However, patients transplanted for emphysematous disease, continue to show a moderate obstructive pattern, with FEV_1 of 51 ± 3% *vs* 73 ± 5% in those transplanted for fibrotic lung disease. Blood gas analysis shows normalization of $PaCO_2$ and an improvement in oxygenation. There is a persistent abnormal alveolar-arterial oxygen gradient due to the continued presence of $\dot{V}/\dot{Q}$ mismatch.[91] Exercise tolerance as measured by a six-minute walk test and modified Bruce protocol is improved. Relative pulmonary perfusion of the transplanted lung progressively increases, reaching 69–79% of total pulmonary blood flow. This figure can reach 95–99% in those patients transplanted for primary pulmonary hypertension.[92] In DLT patients, pulmonary function tests are normal at nine months, with only a mildly reduced gas transfer. Arterial blood gases are normal, as is the alveolar-arterial oxygen gradient. As in SLT patients, exercise tolerance is improved.[48] Initial chest x-ray after transplantation shows a reimplantation response which appears to be a type of noncardiogenic pulmonary oedema with perihilar and/or basal intestitial and/or airspace disease. This begins within 48 hr of transplantation and peaks at four days. Changes beginning after five days should be considered due to other causes such as rejection.[93] With time and the absence of complications, the transplanted lung clears.

Evaluation of these patients before surgery includes eliciting a history of increasing dyspnea or need for supplemental oxygen, lung field auscultation (normally clear), pulmonary function tests, review of home spirometry tests from the transplant diary, obtaining arterial blood gas analysis, and a chest x-ray. Rarely, more specialized tests such asd ventilation-perfusion scans may be needed if conditions such as rejection have resulted in shunting of pulmonary blood flow from the transplanted lung. Any deterioration in lung function may be due to a number of problems: rejection, infection, obliterative bronchiolitis, mechanical tamponade of the transplanted lung by an emphysematous native lung, pleural effusion, airway stricture, or pulmonary edema. Differentiation of these problems can be difficult but is important in the anaesthetic management. Mechanical tamponade, pulmonary oedema and pleural effusion are best seen on chest x-ray. Airway stricture is better seen on CT scan or in pulmonary function tests where the flow volume loop may show a biconcave pattern and a decrease in FEF_{25-75}.[93,94]

Obliterative bronchiolitis is a manifestation of chronic rejection and may be related to episodes of acute rejection or multiple viral infections. The onset of OB is often heralded by a cough which is minimally productive of sputum. Dyspnea occurs within months and is followed by a clinical course similar to that of chronic

obstructive pulmonary disease but much more accelerated (months *vs* years). On auscultation, wheezing or fine inspiratory crepitations may be heard. Evidence of severe obstruction is present on pulmonary function testing but total lung capacity is decreased rather than increased. Changes in the lung parenchyma also result in a restrictive defect. Blood gas analysis shows hypoxaemia and an increased (A-a)O_2 gradient. Carbon dioxide retention is rare until late in the disease. Chest radiographs show peribronchial and interstitial infiltrates. Diagnosis is confirmed by transbronchial biopsy. Aggressive corticosteroid therapy and/or antilymphocytic agents may help but ultimately the only treatment for progressive OB is re-transplantation.[56,95]

Infection and Rejection: Both infection and rejection can occur at anytime, but are most common in the first three months after transplantation. Acute rejection presents as cough, fever, dyspnea, adventitious lung sounds, hypoxia, and deterioration in pulmonary function (Table IV). In the first month after transplantation, but rarely after that, rejection manifests as infiltrates on the chest radiograph. In SLT recipients, disease in the native lung has a considerable effect on pulmonary function tests and this decreases the value of spirometry. In SLT recipients the most clinically valuable spirometry results were found in patients transplanted for pulmonary vascular disease while the results were least valuable in those transplanted for obstructive disease.[96] During rejection in SLT recipients transplanted for either restrictive or obstructive disease, perfusion of the transplanted lung decreases markedly with only a mild decrease in ventilation.[97] In contrast, patients undergoing SLT for primary pulmonary hypertension show a marked decrease in ventilation to the transplanted lung with little change in perfusion. This is probably because of the continued high pulmonary artery pressures in the native lung. The consequence of this is a widening of alveolar-arterial oxygen gradient, decreased oxygen saturation and severe dyspnea.[92,98,99] Treatment of rejection includes high dose corticosteriods, and if required, antilymphocyte agents, usually OKT3.

TABLE IV Clinical Criteria for the Diagnosis of Rejection

Temperature: increase >0.5°C above baseline
Oxygenation: $P_aO_2$decrease >10 mm Hg below baseline
Radiograph: New or changing infiltrates
Spirometry: Decrease in FEV_1 >10% below stable baseline
Infection excluded
Response to treatment with methylprednisolone

(From:Trulock EP. Management of lung transplant rejection. Chest 1993; 103: 1566–76.)

Infection must be excluded. Given the non-specific nature of the signs and symptoms of both infection and rejection, this is difficult.[54] Transbronchial biopsy and bronchoalveolar lavage are the procedures of choice in differentiating these two diagnoses.[100] Alternatively, the response to corticosteroids may be used. The common causative organisms of infection are pseudomonas, cytomegalovirus, pneumocystis carinii, candida albicans, and aspergillus.[101] To prevent infection, patients are often placed on a number of prophylactic agents: acyclovir, co-trimoxizole, pentamidine and nystatin. Before proceeding with elective surgery and anaesthesia both rejection and infection should be treated and have resolved. In the emergency situation, surgery should proceed and treatment of these conditions should commence as soon as possible.

Effect of Immunosuppressive Therapy: The side effects of the immunosuppressive agents should be looked for during the preoperative evaluation. Hypertension related to cyclosporine is found in many patients and antihypertensive agents, especially the calcium antagonists, may be used. End organ damage, as a result of hypertension, may occur and an ECG is indicated. Evidence of renal insufficiency, hepatic dysfunction, pancreatitis, glucose intolerance or overt diabetes, electrolyte abnormalities, and bone marrow depression should be sought. Besides suitable pulmonary function tests, the following laboratory tests are appropriate: complete blood count, creatinine, BUN, glucose, electrolytes (including magnesium and calcium), liver function tests, prothrombin time, partial thromboplastin time, amylase, and urinalysis. If any problems are isolated, steps to correct them, including changes in immunosuppressive dose (in consultation with the transplant centre) should be undertaken before elective surgery.

Disease in the Native Lung and Sysyemic Disease: In SLT, the remaining native lung may continue to affect pulmonary function. In lungs transplanted for emphysematous disease, expansion of the bullae or air trapping in the native lung may cause compression of the transplanted lung. Although this has not been as great a problem as expected, a number of cases reqiring pneumonectomy or lobectomy have been reported.[15,16] These recipients with bullous lung disease are also at increased risk for pneumothorax. Fibrotic lung disease in the native lung can result in over expansion of the transplanted lung. These problems may be exacerbated with positive pressure ventilation. These problems do not occur after double lung transplantation. Cardiac denervation is possible if tracheal dissection

and anastomosis were carried out during transplantation. Eliciting a lack of response to a Valsalva manoeuvre may, in the individual patient, provide evidence of cardiac denervation.

The indication for transplantation should also direct attention to aspects of the disease that the lung transplant did not cure. This is particularly true for cystic fibrosis patients. Malnutition may occur as a consequence of intestinal problems. This may affect absorption of oral drugs, including the immunosuppressive agents, so that *iv* administration may be the only way to ensure acceptable blood concentrations. Intravenous administration is often complicated by difficult venous access. Diaphragmatic function may be impaired as a result of muscle weakness making weaning from mechanical ventilation difficult and the monitoring of neuromuscular blockade all the more important. Alpha-1-antitrypsin deficiency disease is associated with hepatic dysfunction and cirrhosis and may be evident on liver function tests.

The Indication for the Surgical Procedure: The nature of the condition requiring surgery may affect the transplanted lung and the planned anaesthetic. Peripheral procedures such as total hip replacement for aseptic hip necrosis will have a direct effect on lung function. The cardiopulmonary effects (hypoxia due to increased shunting, hypotension, increased pulmonary vascular resistance, dysrhythmias, and decreased cardiac output) of bone cement, could occur in lung transplant recipients and are likely to have severe consequences. Both intrathoracic and intra-abdominal complications and surgery may result in diaphragmatic splinting and impaired respiration. The lateral position reqired by some surgical procedures may increase $\dot{V}/\dot{Q}$ problems in SLT recipients (see below). If infection is the indication for surgery, septicaemia or disseminated infection is always possible given the compromised immune status of the patient.

Anaesthetic Management

While there are a number of studies dealing with anaesthesia in the heart or heart-lung transplant patient, this is not the case for lung transplant recipients. There are no prospective or retrospective studies of anaesthesia in this group of patients although the several reports confirm that anesthesia can be safely delivered.[11,15,16,18] Anaesthesia is managed according to basic principles, an understanding of the management of immunosuppressed patients, and a knowledge of the physiology, pharmacology, and complications of lung transplantation.

Preoperative Management and Premedication: It is advisable that the transplant centre be contacted for advice regarding any change in the route of administration or dose of immunosuppressive regimen. Shaw *et al.* recommended that, if possible, the patient should continue to receive all oral agents up to the day of surgery.[33] If oral drugs are precluded (e.g. gastrointestinal surgery) then the drugs should be given intravenously. Table V provides a guide to changes in dosage. Cyclosporine blood concentrations should be monitored. These recommendations extend to the post-operative period.

Although most of these patients are familiar with the hospital environment they are often quite anxious. Premedication with anxiolytics is appropriate provided that pulmonary function is satisfactory. Hypercarbia is common in the early post transplant period and, since the question of possible increased sensitivity to narcotic agents has not been answered, it is prudent to be cautious in their use.[90] Antisialagogues are useful as secretions can be a problem in these patients. Supplemental corticosteroids administration for short or non stressful surgery is probably unnecessary. For longer or more stressful procedures, additional doses of corticosteroids should be considered.[84]

TABLE V Modulation of immunosuppression therapy in transplant patients, undergoing surgery unable to take medication orally.

Before Operation			*After Operation/No Oral Drugs*	
Drug	*Route*	*Drug*	*Route*	*Notes*
Prednisolone	Oral	Methylprednisolone	*iv*	Given in a ratio of 0.8 of the dose of prednisolone
Azathioprine	Oral	Azathioprine	*iv*	Given in same dose as *po* Cyclosporine
	Oral	Cyclosporine	*iv*	Given as 25% of *po* dose over 6 hr twice daily at 08.00 and 20.00. Monitor Blood concentration

(From: Shaw IH, Kirk AJB, Conchaner ID. Anesthesia for patients with transplanted hearts and lungs undergoing non cardiac surgery. Br J Anesth 1991; 67: 772–8)

Avoidance of Infection: A major cause of morbidity and mortality in transplant recipients is infection. The problem of infection is probably more common in lung transplant recipients than other transplant recipients because of the impaired defense mechanisms (lack of cough reflex, poor mucociliary transport), the direct exposure of the transplanted organ to the external environment, and immunosuppression. During the preoperative visit attention should be paid to the state of the patients dentition and elective surgery postponed until any identified infective dental problems are treated. Prophylactic antibiotics should be administered to all patients, preferably no later than 30 min before skin incision, to ensure that adequate tissue concentrations are reached. The choice of antibiotic is dictated by the surgical procedure or known sensitivity of organisms likely to be a problem. Antibiotics should continue into the postoperative period for 24–48 hr. If invasive monitoring is needed, strict sterile technique is necessary. This also applies to obtaining peripheral venous access. Femoral lines should be avoided because of the higher risk of infection and nasal intubation should be avoided because of the increased risk of bacteraemia. Although in the past we have used sterile lanryngoscopes and breathing hoses we no longer do so. Some authors have recommended the routine use air of filters.[90]

Monitoring: The level of perioperative monitoring (besides the standard ECG, BP, temperature, E_TCO_2 and S_pO_2) should be determined by the patient's overall medical condition and nature of surgery. Invasive monitoring should not be undertaken lightly as it carries the risk of infection and other complications (such as pneumothorax) which may compromise the patient or graft function. Given the possibility of increased susceptibility of the transplanted lung to fluid overload and cyclosporine/FK 506 induced renal insufficiency, monitoring of fluid balance is important, particularly when the planned surgery is associated with large fluid shifts. Transoesophageal echocardiography may be useful in these cases, as a monitor of volume status and cardiac funtion (including the right ventricle). Consideration to urinary catheterization and central venous pressure monitoring should given in the appropriate situation. When placing central lines, insertion via the antecubital fossa or internal jugular vein is preferred as the these routes carry a lower risk of pneumothorax than the subclavian approach. In SLT recipients the choice of which internal jugular vein to use can be difficult since the risk of puncturing a native lung bulla is higher in an emphysematous patient. Even so, in most cases, the side of the native lung should be chosen. Pulmonary artery catheters can be safely placed even in the early post transplant period provided that care is exercised with balloon inflation. Arterial catheters should not be placed solely for the purpose of monitoring arterial blood gases since S_pO_2 and E_TCO_2 are usually adequate. If large blood pressure variations, acidosis, hypercarbia, or one lung ventilation are possibilities, use of an arterial catheter is appropriate. If the use of neuromuscular blocking agents is planned, then monitoring of neuromuscular function with a nerve stimulator is essential.

Anaesthesia

As with monitoring, the choice of anaesthesia should be matched to the medical condition, the presence of rejection or infection in the transplanted lung, and the surgical procedure. Local, regional or general anaesthesia can all be used safely if these factors, together with the physiology of the transplanted lung and pharmacology of immunosuppression are taken into account. Prolonged tracheal intubation predisposes to pulmonary infection, therefore one important goal is the recovery of adequate respiratory function and early extubation.

General Anesthesia: All induction agents are safe in lung transplant recipients provided the patient is haemodynamically stable. It has been suggested that propofol is the drug of choice and that benzodiazepines should be avoided given that early extubation is an important goal.[90] For the same reason, high dose opioid techniques for induction or maintenance are undesirable. Volatile agents are well tolerated and, together with adequate pain relief provided by the judicious use of opioids, are the preferred choice for maintaining anesthesia. Nitrous oxide may be used provided there is no other contraindication (pneumothorax, bullous lung disease etc.).

Immunosuppressive agents may interact with neuromuscular blocking agents. The impairment of renal function in some patients may also prolong the action of these agents. Succinylcholine is safe for short procedures such as transbronchial biopsy and may be given by bolus or infusion. If there is evidence of renal insufficiency or failure, the possibility of hyperkalaemia should be considered before succinylcholine administration. Despite their interaction with CSA and azathioprine, atracurium and vecuronium have been used without serious problems in post cardiac transplant patients.[80] There are no studies of the newer agents such as cisatracurium, rocuronium, or mivacurium. Long acting agents such as pancuronium

or doxacurium are best avoided. Residual muscle weakness in the already pulmonary compromised patients a serious problem.

The choice of airway management (mask/laryngeal mask airway *vs* tracheal intubation) rests on the expected duration of surgery, the patients position, and the nature of the surgery itself. Consideration should be given to the fact that these patients have compromised airway protective reflexes, may have gastric atony, and that aspiration pneumonitis would be disastrous. Mask anaesthesia may be used safely for short procedures. The use of a laryngeal mask airway is more controversial given the higher incidence of aspiration.[102] The Trendelenberg position may further compromise pulmonary function and increase the work of breathing. In SLT recipients the effect of the lateral position is unpredictable as both ventilation and perfusion of the transplanted lung are altered. The lithotomy and Trendelenberg positions may predispose to regurgitation and aspiration. Therefore, in all except short procedures in the supine position, tracheal intubation is preferred. The abnormal mucociliary function makes humidification of inspired gases desirable, if tracheal intubation and ventilation are used. A large endotracheal tube facilitates suction of secretions which can be a problem.

When positioning the endotracheal tube, care should be taken to place the endotracheal cuff just beyond the vocal cords to avoid traumatizing the tracheal or bronchial anastomosis. Inadvertent bronchial intubation of the native or transplanted lung could also have dire results. If the surgical procedure requires a double lumen endotracheal tube then this should be place under direct vision with the aid of a fibreoptic laryngoscope. In SLT recipients, it is preferablefor the endobronchial lumen to be placed in the native side.

Positive pressure ventilation is complicated in SLT recipients by the differences in lung compliance between the native and transplanted lungs. In emphysematous lung disease, the more compliant native lung may be preferentially ventilated and compress the transplanted lung. Nitrous oxide and positive end-expiratory pressure should be avoided. In patients transplanted for fibrotic lung disease, the transplanted lung will be preferentially ventilated and overexpand during positive pressure ventilation. In rare instances these differences in lung compliance may require the use of independent lung ventilation via a double lumen tube.[103] These effects are not seen in DLT recipients. In most cases, an ordinary anaesthesia ventilator may be used but changes in lung compliance caused by rejection or infection may result in the need for a more sophisticated, intensive care type ventilator. A low peak inspiratory airway pressure is desirable during positive pressure ventilation to place as little stress as possible on the bronchial or tracheal anastomosis. This is particularly important in the early post transplantation period.

The F_IO_2 must be adjusted to ensure adequate oxygenation. Concern for potential oxygen toxicity with high inspiratory oxygen concentration is unwarranted.[90] Minute ventilation can be adjusted so that P_aCO_2 is maintained at a level similar to the preoperative values for a particular patient. This avoids inducing hypocarbia in those patients who are chronically hypercarbic. A comparison of intraoperative P_aCO_2 with $P_{ET}CO_2$ is useful in those patients where a large difference is likely.

The possibility of cardiac denervation should be borne in mind in those patients who have undergone DLT with tracheal anastomosis. These patients are sensitive to hypovolaemia. Intraoperative bradycardia does not respond to atropine. Direct agents such as isoproterenol, epinephrine and neosynephrine should be available and used if needed.

The action of all muscle relaxants should be reversed as even minimal residual neuromuscular blockade can result in inadequate respiratory effort in this patient population. Careful assessment of respiration before extubation is important. If there is any suspicion of inadequate reversal despite maximal doses of neostigmine then assisted ventilation should continue. The compromised airway reflexes in these patients stress the need for patients to be awake and able to cough effectively before extubation. A brief admission to the intensive care unit for postoperative ventilation may be needed. Extubation should be carried out with the functionally least important lung in the dependent position to protect the better lung from the risk of asperation.[90]

Local and Regional Anaesthesia: Local anaesthetic agents can be used safely in this group of patients.[80] Intercostal nerve blocks, supraclavicular or interscalene plexus blocks, and cervical sympathetic blocks are probably unwise because of the risk of pneumothorax, while deep cervical plexus blocks risk phrenic nerve palsy. Epidural and spinal anaesthesia can be used but caution is needed as intercostal muscle function depression can occur. Fluid preloading may be a risk to a patient with a transplanted lung. Performing any nerve block carries the danger of introducing infection so that sterile technique is important.

Fluid Balance: The duration and long-term severity of obstructed lymphatic drainage and whether other fac-

tors may persist that predispose the transplanted lung to fluid overload is uncertain in humans. It may be a particular problem in the early post-transplant period. The presence of renal insufficiency or failure will complicates the situation. Thus, careful fluid balance is warranted. Monitoring CVP, pulmonary artery pressure, urine output, and the use of transoesophageal echocardiography may be neccessary depending on the clinical situation. This attitude should continue into the postoperative period with careful monitoring of fluid balance.

Postoperative Care

Postoperative care can take place in the recovery unit, the ICU or on the ward depending on the surgery and the patients condition. Isolation is not usually required. The provision of good analgesia is important especially when the surgery may affect pulmonary function (upper abdominal, thoracic). Local anaesthesia, epidural and intrathecal opioids or patient-controlled analgesia can all be used. Care needs to be taken to avoid respiratory depression. Monitoring of oxygen saturation, either in a step-down unit or on the ward, is appropriate. Patients should be encouraged to cough. Physiotherapy and incentive spirometry are important as is postural drainage when indicated.[33] Evidence of infection or rejection should be sought and treated vigorously.

Summary

Anaesthesia, local, regional or general, can be safely delivered to this group of patients provided that the anaesthetist is aware of the physiology and pathophysiology of the transplanted lung and the pharmacology of the immunosuppressive agents. Close contact with the transplant centre is encouraged as they can provide information about the diagnosis and treatment of rejection or infection. Any changes in the immunosuppressive regimen should be carried out in consultation with the transplant centre. Attention to fluid balance is important especially if renal funtion is impaired. Invasive monitoring should be limited to that required to ensure patient safety. Anaesthetic drug interactions with immunosuppressive agents, in most cases, is more theoretical than clinical. The reason for transplantation should be taken into account as it may have considerable impact on pulmonary function or residual systemic disease. One of the primary goals of anaesthesia in these patients is restoration of adequate respiratory function and early extubation of the trachea after anaesthesia. Neuromuscular function should be monitored and long acting muscle relaxants avoided. Similarly, high dose opioid techniques are not indicated. Otherwise, most anaesthetic techniques are well tolerated. Postoperative care is usually routine. Intensive care admission is not needed unless anaesthesia is complicated by inadequate recovery of respiratory function, the surgical condition or the presence of rejection or infection. Continued vigilance and early, aggressive treatment of infection or rejection is mandatory.

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