Transplantation of the lung

T. Higenbottam, B.A. Otulana, J. Wallwork

ABSTRACT: The introduction of cyclosporine as a highly effective immunosuppressive agent and the development of new techniques for heart-lung and lung transplantation have led to a new treatment for a wide range of fatal cardiopulmonary diseases. Indications for surgery are now becoming clear, together with major contra-indications. Suppurative lung disease, such as cystic fibrosis, can be effectively treated by heart-lung transplant (HLT). A whole new field of pulmonary medicine is emerging to provide the physiological monitoring and diagnostic techniques for major complications such as opportunistic lung infection and pulmonary rejection. Obliterative bronchiolitis, a consequence of frequent and severe rejection, still provides a major challenge to the immunologists and respiratory physician. Lung transplantation, by disrupting the vascular supply and innervation of the lung, is raising major questions about the generally accepted beliefs of regulation of breathing and pulmonary mechanics. Finally, as the survival rate improves beyond the current 50% at 3 yrs, lung transplantation will perhaps present further challenges to our understanding of the pathogenesis of various diseases such as asthma and cystic fibrosis.


The surgical techniques

With the clinical success of renal and cardiac transplantation tremendous interest developed in the possibility of lung and heart-lung transplantation for end-stage cardiopulmonary and lung disease. Early animal studies confirmed the technical feasibility of lung transplantation, but concern remained about long-term survival, particularly in the absence of vagal innervation of the lung [1]. Non-primate mammals appear unable to sustain ventilation without pulmonary vagal innervation but, fortunately, primates [2] including man sustain normal ventilation despite loss of pulmonary vagal innervation [3].

Early experience of clinical lung transplantation was not promising, long-term survivors being rare [4]. One of the main problems encountered by early workers involved the healing of the airway anastomosis [5]. Two scientific developments, however, provided a solution. In 1976, Borel et al. discovered the powerful immunosuppressive, cyclosporine (previously called cyclosporin A) which inhibits T lymphocyte helper cells, probably by binding to a specific protein receptor, called cyclophilin [7]. High dose steroids could be avoided, particularly during the early post-operative period, by use of cyclosporine, with clear benefits to wound healing. Using an earlier report of a similar surgical technique, Ritz et al. in Stanford [8] developed the “en bloc” heart-lung transplant (HLT) operation in a primate model in combination with cyclosporine to achieve long-term survival. The healing of the tracheal anastomosis, with the “en bloc” technique, is aided by collateral blood supply arising from the mediastinum, principally the coronary arteries which supply the lower trachea and carina [9].

Widespread use of HLT is limited by availability of suitable donors, particularly as cardiac transplantation is so successful [10]. Single lung transplantation offers a solution by enabling lungs and heart to be used for separate recipients. The introduction of the “omentum wrap” [11] mobilizing the omentum and wrapping it around the bronchial anastomosis has contributed to clinically successful single lung transplantation [12]. Double lung transplantation, without the heart has also been described [13] but tracheal anastomosis healing is poorer than in HLT presumably because of the loss of mediastinal collaterals. Alternatively bilateral bronchial anastomosis with “omenta wraps” may offer a solution to enable double lung transplantation [14]. But as HLT appears so successful, to enhance the availability of donor organs the “domino” operation has been devised where the heart of the HLT recipient is donated to another cardiac recipient.

Medical after care

Early experience of lung transplantation identified two major problems in aftercare. The first was a high incidence of primary graft failure, so called
post-implantation syndrome which closely resembles adult respiratory distress syndrome [15]. The second was the inability to detect graft rejection and distinguish rejection from pulmonary infection; lung rejection in a chronic form contributing to long-term graft failure [16].

Preservation of the donor lung

It is essential that after lung transplantation, the new graft function immediately. There is no equivalent to haemodialysis, which is used in renal transplantation to ensure the patient's survival until the graft begins to function. During the donor operation and with subsequent transportation to the recipient the lungs experience prolonged ischaemia. To reduce ischaemic injury solid organs are cooled [17]. Colloidal solutions seem better vehicles to cool the lungs than crystalloid solutions [18]. Also, it is probably better to keep the lungs inflated than deflated [19] in preserving function. Using these principles the early HLT surgery involved transporting the donor to the recipient hospital, the donor and recipient operations being performed in adjoining operating theatres to reduce to a minimum the ischaemic time. Obvious practical and ethical problems ensued from moving donors, which limited availability, a method for long-term preservation was therefore needed.

Recently a number of methods have been described to extend ischaemic times to enable procurement of organs from distant hospitals. One such method involves a mechanical system which perfuses the heat-lung block during transportation [20]. Another was using cardiopulmonary bypass to cool the lungs before harvesting. Perhaps the simplest method uses intravenous prostacyclin (PGI2) to vasodilate the donor's pulmonary vascular bed, before infusion of a single flush colloidal based preservation solution [21, 22]. This method achieves ischaemic times up to 5.5 h and excellent immediate graft function (fig. 1). Only one primary graft failure occurred in 61 HLT patients where most were extubated within 24 h of surgery (table 1). At present the main limit to the ischaemic time in HLT is probably the inability to preserve cardiac function.

No matter how effective the long-term preservation system, careful selection of the donor organs is important (table 2) to lessen the risks of using injured or damaged lungs and to avoid obviously infected organs.

Diagnosis of lung rejection

Lung rejection was a major problem in the early experience of transplantation. Repeated untreated acute rejection is now thought to have contributed to the disabling and fatal airways obstruction seen in up to 50% of HLT patients [20, 23]. With HLT it had been thought that endomyocardial biopsy (EMB), a method established to diagnose rejection in cardiac transplantation [24], could be used to monitor rejection. However, both experimental [25] and clinical [26] studies suggest that the lungs undergo rejection before the heart. Indeed we have now abandoned the use of EMB in HLT patients as cardiac rejection is rare if the lung rejection is controlled [27].

Table 1. - Causes of early surgical death in eight heart-lung transplant (HLT) recipients in the immediate post-operative period

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular event</td>
<td>2</td>
</tr>
<tr>
<td>Tracheal dehiscence</td>
<td>1</td>
</tr>
<tr>
<td>Inflamed/ruptured aorta</td>
<td>1</td>
</tr>
<tr>
<td>Small bowel infarction/SLE</td>
<td>1</td>
</tr>
<tr>
<td>ARDS/hepatic dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Early graft failure</td>
<td>1</td>
</tr>
</tbody>
</table>

Total 7 out of 61 operations

ARDS: adult respiratory distress syndrome.

<table>
<thead>
<tr>
<th>Table 2. - Criteria for donor selection</th>
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</thead>
<tbody>
<tr>
<td>1. Age below 40 yrs.</td>
</tr>
<tr>
<td>2. No major thoracic trauma.</td>
</tr>
<tr>
<td>3. No past history of pulmonary disease, including asthma.</td>
</tr>
<tr>
<td>5. No systemic or pulmonary infections.</td>
</tr>
<tr>
<td>7. Normal lung compliance with peak inspiratory pressure &lt;20 mmHg, tidal volume of &lt;15 ml/kg and respiratory rate 10–14 br·min⁻¹.</td>
</tr>
<tr>
<td>8. Normal gas exchange, arterial oxygen tension (Pao₂) &lt;15 kPa with fractional inspiratory oxygen (Fio₂) 30%.</td>
</tr>
<tr>
<td>9. Inotropic requirement &lt;10 μg·kg⁻¹·min⁻¹ of dopamine or dobutamine.</td>
</tr>
<tr>
<td>10. Normal electrocardiogram (ECG).</td>
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</tbody>
</table>

Fig. 1. - Alveolar-arterial oxygen gradient (A-aO₂) for near and distant procurement groups at various times post-operatively.
Additionally, HLT patients commonly experience pulmonary infections [20]; the same is true for single lung transplant patients [12].

Transbronchial lung biopsy (TBB) through a fiberoptic bronchoscope provides a sensitive means for diagnosing lung rejection [28] and enables distinction from pulmonary infection [29]. The technique has now been extended to child HLT patients [30].

With a clear histological diagnosis it has proved possible to demonstrate the clinical features of rejection and infection. For example, the chest radiograph is commonly normal during acute rejection episodes (table 3) [31] but spirometric volumes and total lung capacity fall (table 4 and fig. 2) [32]. Indeed, patients can monitor lung function daily using a battery operated pocket spirometer, providing and early indication for TBB [33].

The use of a simple preservation system, close monitoring of pulmonary function and TBB have been associated with improved survival figures [34].

Table 3. - Prevalence of abnormal chest radiograph in histologically diagnosed acute heart-lung transplant patients

<table>
<thead>
<tr>
<th>Rejection</th>
<th>Within 1 month of surgery</th>
<th>After 1 month of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CXR</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

Radiographs taken in the first month post-transplant are compared with those taken thereafter. CXR: chest X-ray.

Table 4. - Mean values of lung function measurements before, during and after acute lung rejection

<table>
<thead>
<tr>
<th></th>
<th>FEV₁ (l)</th>
<th>VC (l)</th>
<th>TLC (l)</th>
<th>Tlco (mmol·kPa⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 3 months (n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>2.5</td>
<td>2.8</td>
<td>4.7</td>
<td>6.0</td>
</tr>
<tr>
<td>During</td>
<td>1.7</td>
<td>1.9</td>
<td>3.8</td>
<td>4.3</td>
</tr>
<tr>
<td>After</td>
<td>2.2</td>
<td>2.3</td>
<td>4.6</td>
<td>5.4</td>
</tr>
<tr>
<td>LSD</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Subsequent months (n=16)

<table>
<thead>
<tr>
<th></th>
<th>FEV₁ (l)</th>
<th>VC (l)</th>
<th>TLC (l)</th>
<th>Tlco (mmol·kPa⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>2.8</td>
<td>3.4</td>
<td>5.9</td>
<td>6.0</td>
</tr>
<tr>
<td>During</td>
<td>2.3</td>
<td>3.1</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>After</td>
<td>3.0</td>
<td>3.7</td>
<td>5.8</td>
<td>6.1</td>
</tr>
<tr>
<td>LSD</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Changes in lung function with 30 episodes of histologically diagnosed lung rejection and after treatment with augmented immunosuppression in heart-lung transplant (HLT) patients. Rejection is generally more severe in the first three months post-transplant. FEV₁: forced expiratory volume in one second; VC: vital capacity; TLC: total lung capacity; Tlco: transfer factor of the lung for carbon monoxide; LSD: least significant difference comparing pairs of means at p=0.05.

Fig. 2. - Changes in FEV₁ and Tlco on development of histologically-proven lung rejection and following treatment. Values are expressed as percentage predicted based on recipients' sex, age and height. B: before; D: during; A: after, lung rejection; FEV₁: forced expiratory volume in one second; Tlco: transfer factor of the lung for carbon monoxide.

Indications for lung and heart-lung transplantation

Heart-lung transplantation

Combined HLT was first introduced as a treatment for end-stage pulmonary vascular disease, Eisenmenger's syndrome and primary pulmonary hypertension [35]. It has since been extended to chronic lung disease [36] including cystic fibrosis [37].
Eisenmenger's syndrome

Secondary pulmonary hypertension developing as a result of congenital cardiac right to left shunts, commonly ventricular septal defects or patent ductus arteriosus, causes considerable restriction of life style and is ultimately fatal. The development of right ventricular decompensation with fluid retention is a poor prognostic sign, but it is difficult to predict the survival chances of an individual patient. For this reason patient selection remains imprecise.

Primary pulmonary hypertension (PPH)

This is a rare condition afflicting young adults, although children and older patients can develop the disease [38]. Women are more often affected than men. Without a clear idea of the mechanism by which the disease develops the division of the condition according to the predominant histopathological abnormality is not helpful in deciding on prognosis. Three predominate types are seen [39], namely plexogenic pulmonary arteriopathy, peripheral thrombotic and veno-occlusive disease. Commonly the first two forms occur together in the same patient [40].

The natural history of the disease is however becoming clear. From a retrospective study of 120 patients at the Mayo Clinic [41] patients with a mixed venous oxygen saturation (Svo2), measured from a pulmonary arterial blood sample, of <65% have only a 17% chance of surviving 3 yrs. Up to 55% of patients with Svo2>63% may survive three yrs. The Svo2 % reflects the low cardiac index in PPH patients, which is a result of the marked obstruction and obliteration of the small pulmonary arteries causing the rise in pulmonary vascular resistance.

After diagnostic right heart catheterization patients for HLT can be selected according to the Svo2 % or cardiac output. However, as prolonged delays are likely until a suitable donor can be found, many patients can be expected to die before HLT is possible. Vasodilator treatment may be effective in improving patients haemodynamics and lessening symptoms [42-44] although survival may not be affected [45]. Continuous long-term infusion of prostacyclin (PGI2) by a subclavian line has been used successfully to “by time” before transplantation in severely afflicted patients [44].

Chronic lung disease

Following the success of HLT for pulmonary vascular disease, its use was extended to treat chronic lung disease [36]. A wide range of diseases have been treated successfully (table 5) including emphysema, lung fibrosis and bronchiectasis. Patients are selected according to degree of respiratory failure, severity of ventilatory dysfunction and evidence of cor pulmonale (table 6), the latter feature providing a powerful guide to prognosis [46].

Cystic fibrosis (CF) is the most common fatal inherited disease in Caucasians [47]. Since the location of the CF gene upon human chromosome 7cen-q22 [48-50] the quest is to provide a pre-natal diagnosis but until then medical care is directed to limiting the consequences of the disease. Despite many advances patients die in early adulthood, usually from respiratory failure from chronic suppurrative lung disease, the cause of which remains unknown but is putatively linked to abnormal chloride ion transport across the epithelium [51]. Heart-lung transplantation now offers a chance of survival to such patients [37]. Furthermore, after lung transplantation, the donor lung retains normal ionic transport across the respiratory epithelium [52]. In other words, epithelial abnormality does not recur within the transplanted lung.

Table 5.—Diseases treated by lung and heart-lung transplantation

<table>
<thead>
<tr>
<th>Lung transplantation</th>
<th>Heart-lung transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>Good results</td>
</tr>
<tr>
<td>Fibrosing alveolitis</td>
<td>Single lung good results</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>No reports</td>
</tr>
<tr>
<td>Sarcoid</td>
<td>No reports</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Good results</td>
</tr>
</tbody>
</table>

Table 6.—Indications for lung transplantation and heart-lung transplantation

<table>
<thead>
<tr>
<th>Chronic lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FEV1 &lt;25%</td>
</tr>
<tr>
<td>2. Tlco &lt;50%</td>
</tr>
<tr>
<td>3. Hypoxic respiratory failure with or without hypercapnia</td>
</tr>
<tr>
<td>4. Evidence of cor pulmonale</td>
</tr>
<tr>
<td>a) Right axis deviation on ECG</td>
</tr>
<tr>
<td>b) Raised mean pulmonary artery pressure on Doppler echocardiogram</td>
</tr>
<tr>
<td>c) Fluid retention despite diuretics</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in one second; Tlco: transfer factor of the lungs for carbon monoxide; ECG: electrocardiogram

Contra-indications to heart-lung transplantation

A patient for HLT must have a stable social background and a positive attitude towards life. Previous thoracic and cardiovascular surgery are no longer absolute contraindications, this includes pulmonary lobectomy or previous corrective cardiac surgery. However, pleurectomy and pleurodesis for recurrent pneumothorax remains a contraindication because of enhanced risks of chest wall bleeding after surgery.

Localized pulmonary infection, which will be removed at surgery, is not a contraindication. But pulmonary aspergillus fumigatus infections, particularly mycetoma, are excluded due to fears that pleural disease will not be eradicated by surgery.
Multi-organ disease is becoming less of a problem, e.g. severe liver disease can be treated by simultaneous liver and heart-lung transplantation [53]. Insulin dependent diabetes mellitus is no longer a contraindication.

However, transplantation of critically sick patients on life support systems remains an absolute contraindication because survival results are so poor in such patients. It represents, therefore, an inappropriate use of resources.

**Lung Transplantation**

The shortage of suitable donors for HLT together with the competing needs for cardiac transplantations have led to alternative approaches to lung transplantation of which single and double lung transplants are most recently described.

**Single lung transplantation**

This was first introduced, after the introduction of cyclosporine, for the treatment of cryptogenic fibrosing alveolitis [12], with good long-term results. The patients so treated were in respiratory failure with severe ventilatory and gas diffusion abnormalities.

Early experience of single lung transplantation, before the cyclosporine era, suggested that single lung transplantation could not be used in emphysema or primary pulmonary hypertension, due to the post-operative imbalance of distribution of ventilation and perfusion. However, improved surgical techniques and better organ preservation now make single lung transplantation suitable for emphysema and pulmonary hypertension (A. Patterson, personal communication).

**Double lung transplantation**

Introduced to enable the use of the donor heart for another recipient, double lung transplantation is still at an innovative stage, perhaps reflecting the concern about the healing of tracheal anastomosis. As a new development bilateral bronchial anastomosis and double lung transplantation has been attempted, long-term results are awaited.

The main area where double lung transplantation may be of value is in CF [13]. Suppurative lung disease precludes single lung transplantation due to fears that the infection of the remaining lung will spill over into the new transplanted lung.

**Long-term function of the lungs after transplantation**

The pulmonary function improves after single lung [12], double lung [13] and heart-lung transplantation [36, 37] for chronic lung disease. In HLT the total lung capacity (TLC) and spirometric values, forced expiratory volume in one second (FEV₁) and vital capacity (VC), fall initially after surgery. This fall is comparable with the change in function after median sternotomy for coronary artery surgery [54] and probably reflects a change in configuration of the chest wall and ribs [55]. Subsequently the TLC returns to pre-operative values (fig. 3). The final value appears uninfluenced by the donor lung size and seems to be determined by the recipient's chest wall size [56].

![Fig. 3. - The change in individual values for total lung capacity (TLC) in 14 heart-lung transplant (HLT) patients followed up for 12 months after transplantation. In most cases, the TLC returned to the pre-transplant level at 1 yr, after the initial fall at 1 month.](image)

The effect of recipient's thoracic dimensions on transplanted lung size

Most methods for matching the donor lung size to the recipient's thoracic cavity volumes depend upon measurements from radiographs [21, 22]. These methods simply offer an assessment of height [56]. As recipients have a wide range of lung disease, causing their thoracic cavities to be larger than predicted, e.g. as in emphysema, or smaller as in cryptogenic fibrosing alveolitis, matching donor and recipient height leads to patients receiving donor lungs up to 4 l too small or up to 2 l too large (fig. 4) [56]. Despite these disparities in size, the final TLC of the recipient is close to their pre-operative value (fig. 3), suggesting that the chest wall in adults provides the major volumetric constraint for lung volume. From these considerations a simple guideline to matching donor and recipients lung size is to use the recipients' TLC measured before surgery and the donor's predicted TLC obtained from height, age and sex [56].
Fig. 4. — A plot of the difference in total lung capacity (TLC) between donor and recipients of heart-lung transplant (HLT) against the recipients’ measured TLC. There is a trend towards less difference at larger volume of recipients’ lung.

Indices of airflow in the transplanted lung

It has been noted in several studies that early after surgery, HLT patients have low values for airways resistance [57, 58] and forced expiratory flow volume curve analysis reveals that expiratory flow instead of declining linearly with volume, shows a plateau followed by a “knee” and then a decline. As yet there is no explanation for this observation, although it is similar to that seen in studies of dog lung and excised human lungs and this has been attributed to increased longitudinal tracheal tension [59]. Perhaps the tracheal anastomosis renders the trachea more rigid. Denervation seems an unlikely explanation, as there is little evidence of re-innervation (see below) but airflow obstruction can develop [58].

Lung rejection on lung function

With acute lung rejection, diagnosed by histology of TBB, it has been shown that TLC, FEV₁, and VC decline. This is also true with pulmonary infection. Use can be made of spirometry to monitor graft function to provide an early indication for TBB. Changes in single-breath transfer factor for carbon monoxide (Tl.co) are more variable in acute rejection. These volumetric changes with acute rejection and infection [32] are different from chronic lung rejection, so called obliterative bronchiolitis (OB) [58, 60], where airflow obstruction dominates the pathophysiological picture. Here the flow-volume curve becomes curvilinear, FEV₁ falling by a greater degree than VC.

Gas diffusion in lung transplantation

In lung transplantation, single lung [12], double lung [13] and heart-lung [56] transplantation the Tl.co tends to be lower than normal. In part this reflects the anaemia in the immunosuppressed patient but a complete explanation is not yet available [32].

Control of ventilation after lung transplantation

Pulmonary proprioceptive vagal afferent nerves, probably from slowly adapting stretch receptors, are responsible for the Hering-Breuer inflation reflex [1]. In anaesthetized animals this reflex contributes to the regulation of the breathing pattern [1]. This contribution causes termination of inspiration and prolongation of expiration.

In man there is doubt as to the existence of the Hering-Breuer inflation reflex at rest [61, 62]. Although it has been argued that such afferent information may be important at higher levels of ventilation, early work depended upon relatively nonspecific reversible neural blockade.

There is evidence that, at least up to 36 months after surgery, there is no afferent re-innervation of the lungs with HLT [63]. Immunohistochemical studies of lung tissue from HLT patients at death or re-transplantation revealed no afferent re-innervation (J. Polak, personal communication). This is in parallel with in vivo re-implantation studies, where only very limited evidence of afferent re-innervation can be found [64].
Studies of breathing pattern at rest in HLT patients show the same variation of tidal volume (Vt) and breathing frequency (f) as normals both asleep and awake [65]. Also, augmented breaths, “sighs” occurred at the same frequency as normals. During hyperventilation, which occurs with carbon dioxide rebreathing, HLT patients show the same pattern of change in Vt and duration of inspiration (Ti) as normals [66]. With exercise HLT patients, like heart transplant (HT) patients, appear to hyperventilate [67, 68], i.e. the level of ventilation (Ve) is excessive compared with oxygen uptake. This does not appear, therefore, to simply reflect denervation of the lungs because both HT and HLT patients show similar patterns compared to normals [67, 68] which probably reflects cardiac denervation. As a result, although normal arterial gas tensions and pH, with the exception of arterial carbon dioxide tension lower (Paco2), the mixed venous blood shows a marked fall in PVO2 and pH and rise in PCO2 [69] (fig. 5). This disparity between normal arterial gases and markedly altered mixed venous blood gases provides support for the possible existence of chemoreceptors in the central veins and right atria [70].

Control of airway function after HLT and lung transplantation

Lung transplantation and heart-lung transplantation acutely disrupts neural and vascular elements of the lung. Reinnervation of the lungs may occur. Experimentally, re-implantation of canine single lungs show signs of efferent lung function but no convincing evidence that afferent nerves re-innervate the lungs [64]. In man, after HLT, the cough response to ultrasonically nebulized distilled water (USNDW) is absent up to 36 months after surgery [63]. The cough response to USNDW is probably a result of stimulation of airway rapidly adapting stretch receptors [71, 72]. This can, therefore, be taken as evidence that at least there is no afferent re-innervation after HLT.

Fig. 5. Changes in arterial and mixed venous oxygen saturation (Sao2, SVO2); CO2 tension (Paco2, PVo2), and hydrogen ion concentration ([H]) in 6 HLT patients from rest (R) to exercise (E) of 50 W supine cycling. More striking changes occurred in the mixed venous than in the arterial blood in association with the exercise hyperventilation. HLT: heart-lung transplant.

Fig. 6. Cough frequency during one minute inhalation of ultrasonically nebulized distilled water in 15 heart-lung transplant (HLT) patients compared with 15 matched controls. There was a significant reduction in cough response in the HLT patients.
In HLT the bronchial arterial supply to the lung is interrupted. The tracheal anastomosis is probably perfused by the collateral blood supply from the mediastinum, in particular the coronary artery supply [9]. Evidence is now emerging that after transplantation the intrapulmonary bronchi are perfused by retrograde flow along the bronchial arteries, pulmonary to bronchial arteries being responsible [73].

Following HLT and lung transplantation, many patients show bronchial hyperresponsiveness to methacholine as in asthma, [74, 75]. This responsiveness is not associated with acute rejection [76]. It may reflect denervation hypersensitivity of airway smooth muscle muscarinic receptors. In contrast to methacholine responsiveness, HLT patients respond with bronchoconstriction to USNDW only in the presence of rejection [76]. Bronchial responsiveness in HLT illustrates separate mechanisms of pharmacological challenge and physical challenge. It is possible that airway responses to distilled water may depend upon a pathophysiological bronchial artery response [76].

The present challenges presented by lung transplantation

The two greatest challenges facing lung transplantation are the development of airways disease, obliterative bronchiolitis and pulmonary infection [20]. These two complications currently limit long-term survival.

Obliterative bronchiolitis in HLT

Unlike cardiac rejection in heart transplants, HLT patients do not experience acute life-threatening lung rejection [77]. However, 30–50% develop severe obstructive airways disease, an obliterative bronchiolitis (OB), which insidiously leads to morbidity and fatalities [20, 23]. Early clinical studies failed to demonstrate any correlation between the frequency of acute rejection and development of OB [78]. However, TBB by providing a more accurate means of diagnosing rejection and distinguishing it from pulmonary infections [29] has enabled a correlation to be found. Those patients who develop OB experience more frequent acute lung rejection and more severe rejection than those patients who remain well [79, 80]. The pattern is of frequent and severe acute lung rejection occurring within a few months of surgery. This association between acute rejection and OB is similar to experimental studies [81] and emphasizes the immunological basis for the airways disease.

Single lung transplantation is associated with OB (A. Patterson and J. Dark, personal communication) but as yet its incidence is unknown and little investigation has been undertaken in these patients.

Much attention has been focused on the possibility that OB was the result of an immunological process directed against airway epithelial cells [82]. Indeed, HLT patients show enhanced expression of certain class II major histocompatibility antigens (MHC) on airway epithelial cells [83]. However, this may not be specific to transplanted organs.

Alternatively, it has been argued that OB is the end result of vascular arteriosclerosis [84]. Certainly, coronary arterial vascular sclerosis is observed at autopsy in HLT patients dying from OB and similar changes are seen in pulmonary arteries. In this context it is important to remember that the obliterative bronchiolitis in HLT is a disease of the intrapulmonary airways, that is those parts of the graft dependent on retrograde blood flow from the pulmonary arteries [73]. The bronchi and bronchioles could be considered at risk from ischaemia if the pulmonary blood flow were to be impeded as in acute rejection [29]. Typically the major airways become bronchiectatic whilst the small airways become fibrosed (fig. 7).

Whatever the mechanism, the close association between frequency and severity of acute lung rejection and the later development of OB enables recognition of patients at risk at an early stage, when augmented immunosuppressive treatment may prevent the disease [80].

![Fig. 7. - A photograph of a transplanted lung at post-mortem 3 yrs after heart-lung transplantation. The cut surface shows fibrous obliteration of the airways.](image-url)

Table 7. - Immunosuppressive regime for heart-lung transplant patients

<table>
<thead>
<tr>
<th></th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>Peri-operative</td>
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<tr>
<td>Cyclosporine (4–6 mg·kg(^{-1}))</td>
<td>Cyclosporine (6–10 mg·kg(^{-1}) per day</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>1 g + 125 mg for 3 days) Azathioprine adjusted to keep WBC &lt;6000·mm(^3)</td>
</tr>
<tr>
<td>Murine ATG x 3 days</td>
<td></td>
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<tr>
<td>Azathioprine 3 mg·kg(^{-1}) per day</td>
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</table>

WBC: white cell count.
Patients are managed on cyclosporine and azathioprine (table 7). With acute rejection, immunosuppression is augmented with three days of methylprednisolone, 0.5–1.0 g per day, followed by oral prednisolone, 1 mg·kg⁻¹ per day, decreasing to around 10 mg per day over a 10 day period. Repeated TBB are then performed. If they have not cleared then a further “pulse” of augmented immunosuppression is given. This approach may have contributed to the reduced incidence of OB in our series [80].

There is still much to be learned about the mechanisms of OB but careful monitoring of lung function and active management of acute lung rejection diagnosed by TBB can influence outcome.

Pulmonary infection in lung transplant patients

Pulmonary infections are common in lung transplant patients [85]. Diagnosis proved difficult until the introduction of TBB, the clinical signs and symptoms of lung rejection and infection being similar [86].

Bacterial, viral and fungal infections can be diagnosed by culture of TBB or bronchoalveolar lavage specimens. Standard cytology can be used to diagnose cytomegalovirus (CMV) and Pneumocystis carinii (PC) pneumonia. Precision and sensitivity can now be increased by using monoclonal antibody techniques, immunochemistry particularly for the early antigen of CMV and for PC.

Histological examination of TBBs is essential to exclude acute lung rejection. It is important to appreciate that both infection and rejection can co-exist in the lungs of the same patients, up to 25% in one study [87]. In addition, characteristic “owls eye” intracellular inclusions of CMV can be observed in TBB from patients with CMV pneumonia and these are associated with an alveolaric appearance [88]. Herpes simplex (HSV) pneumonia also shows a characteristic intra-cellular inclusion on TBB [89]. In PC pneumonia, a foamy intra-alveolar infiltrate is seen, the trophozoites being seen with a silver stain method. Invasive aspergillus infections can be similarly demonstrated using silver stains on TBB section. The mycelia can be seen extending into the lung tissue.

Many of these infections can be avoided. Primary CMV pneumonia occurs commonly in HL T recipients who, before surgery, have negative serology but receive organs from a CMV positive donor [88]. By avoiding such a mismatch serious pneumonia may be reduced in frequency. Prophylactic acyclovir at times when immunosuppressive treatment is augmented can reduce frequency of HSV pneumonia [89]. This may also be true for CMV. CMV pneumonia is, however successfully treated with gancyclovir [86, 88] together with hyper-immune globulin if it is a primary infection. HSV pneumonia can be effectively treated with intro-venous acyclovir [89].

A prophylactic co-trimoxazole at times of augmented immunosuppression can reduce the incidence of PCP. We have favoured the use of intravenous sulphadimidine and trimethoprim for active PCP [90]. But it is important to note that many antibiotics interfere with cyclosporine [90].

Invasive Aspergillus fumigatus infections of the lung should still be treated with intravenous amphotericin. A total accumulative dose of 2 g should be achieved with daily doses of 0.75 mg·kg⁻¹. The major concern is the added nephrotoxicity of amphotericin and cyclosporine.

It has been argued that pulmonary infections cause OB, particularly CMV pneumonia [20]. However, OB patients have no more frequent infection of the lung than patients who have normal lungs [80]. An immunological mechanism for OB seems more likely.

The future of lung and heart-lung transplantation

Much has been learnt about this new field of transplantation over the last eight years. The surgical techniques are well established but further prolongation of the organ preservation time is needed to increase availability of organs. Much depends however on the establishment of a European-wide organization for donor organs. But even with such developments, lung transplantation will remain a limited activity.

The major obstacle to success is the problem of obliterative bronchiolitis. However, because of accessibility of the lung to biopsy and to obtaining immunologically active cells by means of bronchoalveolar lavage, it is likely that new insights into the mechanisms of acute rejection will be identified.

Perhaps we are now able to consider heart-lung and lung transplantation in the same light as cardiac transplantation, having moved from experimental to clinical treatment.

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**Translation**