Lung: living related transplantation

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As with other paired and lobed solid organs, surgical techniques have now evolved to permit safe live donation. Almost all the published experience comes from one centre, with cystic fibrosis recipients receiving right and left lower lobes, typically one from each parent. Donor morbidity has been acceptable, with no known deaths. Early survival, perhaps because patients are only transplanted in extremis, has been less good than can be achieved in cadaver transplantation. Early and late rejection remain at least as common as after conventional transplants, but is nearly always asynchronous, affecting one lung at a time. There remain significant ethical difficulties, and the approach has yet to prove itself.

The discrepancy between donor and recipient numbers, important in all areas of transplantation, is most striking for the lung. For those with cystic fibrosis (CF), now the commonest indication at our own centre, mortality on the waiting list is approaching 50%. The situation is equally bad at other UK centres. To illustrate the problem another way, most of the 200 new patients born each year with this condition will die, as young adults, of respiratory failure. The 150–170 pulmonary transplants performed annually in the UK would not suffice for this population, without even considering all the other indications for transplantation.

The other major clinical problem in pulmonary transplantation, after lack of donor organs, is the very high incidence of late lung injury, characterised histologically as obliterative bronchiolitis (OB) and physiologically as the bronchiolitis obliterans syndrome (BOS)[1]. It affects 30–50% of recipients by 5 years and is responsible for the great majority of late deaths[2]. There is a clear relationship between the frequency of early acute rejection and the incidence of BOS[3]. Finally, the incidence of BOS is much greater in children[4]. There may be more early rejection episodes, or it may just be unrecognised because of difficulties in reporting symptoms and performing investigations.

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These two problems, lack of cadaver donors and frequent late lung injury, particularly in children, come together as the impetus for the development of live, usually related, donor lung transplantation. Donor(s) are available, although with the cost of definite surgical morbidity and some ethical uncertainty. Experience with other solid organ transplants would lead to an expectation of improved results. In

the kidney, for instance, even **unrelated** live donation has a better 3 year survival than cadaver transplantation, despite **worse** HLA matching[5]. This is probably due to less organ damage in the brain-stem dead cadaveric donor, and condition of the donor lungs is known to be a major determinant of outcome after pulmonary transplantation[6]. Long term outcome is definitely better for living **related** kidney donation[7].

Despite these potential advantages, living related lung donation is a very recent development. Although there are now anecdotal reports from a number of centres, almost all of the published results emanate from one group, led by Starnes at the University of Southern California in Los Angeles, USA. The evolution of the technique has very largely been the work of that one group, and much of the current knowledge emanates from them, as is reflected in the references for this review.

Evolution of lobar transplants: surgical alternatives

That the lung is a paired organ, and more usefully, divided into anatomically separable halves—the lobes—was recognised in the earliest days of lung transplantation. An early review, of the first 23 clinical lung transplants, contained descriptions of two lobar transplants, performed in Japan[8]. In both instances, the donated lobe was part of a lung being removed for cancer, and was implanted in the place of a single lobe in a recipient with respiratory failure. Both lobes became oedematous on reperfusion, and never functioned. Both were removed, with subsequent survival of the recipients. The oedema may have been as a result of preservation damage, but is more likely to be as a consequence of the limited amount of tissue transplanted. Most end stage respiratory disease is associated with a degree of pulmonary hypertension, and an elevated vascular resistance in the affected lung. If a normal lung is implanted, with normal vascular resistance, it will be preferentially perfused. If the new vascular bed is large, the fall in overall vascular resistance is enough to eliminate the pulmonary hypertension. A single lung is large enough in this setting, even for severe pulmonary hypertension[9]. However, a single lobe is not large enough. The relatively small vascular bed, probably damaged by some preservation injury, is exposed to a high blood flow, because of preferential perfusion. The pressure remains high because the vascular bed is not large enough to lower the overall vascular resistance, and pulmonary oedema follows. This in turn raises the vascular resistance, worsening the situation. A similar phenomenon is seen if a damaged whole lung is transplanted in pulmonary hypertension, an observation which has lead to some groups advocating only paired lung or heart–lung transplants in this setting.

This difficulty with the size of the donor organ's vascular bed is seen only in the lung (where the whole of the cardiac output has to traverse the pulmonary capillary bed) and there is nothing analogous in renal or lobar liver transplantation.

Once clinical lung transplantation became established, in the mid 1980s, it was accepted that the donor lung should be of approximately the appropriate size for the recipient thorax. This was not a particular problem in adults, and it was realised that a modest oversize could be accommodated in single lung transplantation. But with paediatric recipients, and particularly if a paired transplant was required (for patients with septic lung disease, such as cystic fibrosis), size matching was much more important. One approach was to 'tailor' the lung, either by removing segments (the middle lobe on the right or the lingula on the left) or more gross lung reduction using stapling instruments. These techniques invariably produce a degree of lung injury and should be avoided. They are also limited in the amount of reduction that can easily be accomplished.

The next step is to discard a whole lobe, first described in1992[10]. The remaining lobe represents a small lung, with its appropriate vascular and airway connections. Much was learned about the various anatomical arrangements and how they could be accommodated to the recipient hilum. It became apparent that the lower lobes, particularly on the left, were the most suitable. One attempt to use the right middle lobe of an adult into an infant failed because of pulmonary oedema[11]. This represents a problem of a too small vascular bed, alluded to above. Although having the term 'lobe' the right middle lobe is anatomically a lung segment, sharing its venous drainage with the upper lobe.

Whilst cadaver lobar transplantation is clearly successful, it is wasteful of donor organs, because the unused lobe is discarded. With large numbers of appropriately sized adult donors waiting for transplantation, it is difficult to justify discarding lung tissue for sizing reasons alone. An ingenious approach to this difficulty has been developed by a group in Paris[12]. Two lobes from one lung, usually the left, can be split so as to allow the separate lobes to be implanted as a bilateral lung transplant. The left lower lobe is placed in the left chest and the left upper lobe rotated through 180° and placed on the right. With even greater ingenuity, the same can be done with the right lung! However, the numbers from the whole series are so far very small (7 patients by 1997) and there are no reports from other centres.

Live donor lobar transplantation

The description of lobar transplantation in 1991 included the first mention of a living donor in the modern era of pulmonary allografting[11].

Subsequent published descriptions have all come from the same senior author, now based in Los Angeles. His group described 7 patients in 1994[13], increasing to 38 by 1996[14]. This last paper includes reference (in the Discussion) to a group of six patients transplanted in St Louis, and it is known that other major US centres now have similar limited experience.

Three patients have had lung transplants from living donors in the UK (figures from UKTSSA), but the results are unknown.

Recipient selection

The bulk of the patients in the University of Southern California (USC) series (32 out of 38) had CF, with other diagnoses including pulmonary hypertension, pulmonary fibrosis and retransplantation for post-transplant OB[14]. This aetiological bias is indicative of the very high attrition rate of patients with CF, particularly in its later stages, amongst those waiting for transplantation. They all require bilateral lung transplantation, because of the bilateral lung sepsis, further reducing the donor pool. Ten of the CF patients were children, and the particular problems of finding donors have already been described. The preponderance of CF patients, with many (22) coming from out of the State of California, is also an illustration of the rapid dissemination about new treatments amongst the CF community.

Potential recipients had to fulfil all the usual criteria for cadaver transplantation (Table 1). Colonisation with pan-resistant organisms (particularly *Burkholderia cepacia*) was a contra-indication. Patients were only accepted for living-related transplantation if it was not thought they would survive to receive cadaveric organs. 66% were in hospital and 25% were receiving some form of ventilatory support.

Table 1 Living donor lung transplantation for cystic fibrosis

Recipient indications
Marked weight loss
Increasing hypercapnia or hypoxia
Recurrent life-threatening respiratory tract infections
Ventilator dependence
Contraindications
Colonisation with pan-resistant organisms
Long-term ventilation
Other, irreversible end-organ dysfunction
Cardiac dysfunction

Table 2 Live-donor lung transplantation

Donor Screening
ABO compatibility
Chest X-ray, high resolution chest CT
ECG, echocardiography, ventilation/perfusion scan
Spirometry, blood gases, sputum culture, viral serology

Donor selection

In the early part of the USC series, only parents were considered as donors. Other family members, and eventually unrelated donors were eventually included. Out of the 76 donors (for 38 transplants), 73 were family members. Initial screening was by ABO blood typing, spirometry and chest X-ray. If those were satisfactory, a very rigorous series of investigations was then pursued before donors were deemed acceptable (Table 2). The number of potential donors excluded because of this screening is not stated.

Surgical considerations: the donor

The donor procedure, based on the first 7 transplants in the USC series, has been beautifully described by Cohen[13]. The principles of the operation are to remove adequate tissue to allow a safe anastomosis of vessels and airway, whilst at the same time minimising the risk to the donor.

Bronchoscopy is used to confirm normal anatomy after induction of anaesthesia. The chest is opened through an appropriate lateral thoracotomy, and the fissures opened with staplers to minimise air leak. All the hilar structures are exposed before division. The bronchus is divided obliquely to preserve the middle lobe bronchus for the recipient. Early in the series, the middle lobe was sacrificed in some patients, but

Table 3 Criteria for donor acceptance

Age < 55 years
No significant past medical history
No recent viral infections
Normal chest X-ray, ECG, cardiac echo
FEV1 and FVC > 85% predicted
No previous thoracic surgery on donor side
No significant abnormality on chest CT

(Adapted from Starnes VA, Barr ML, Cohen RG *et al* [14])

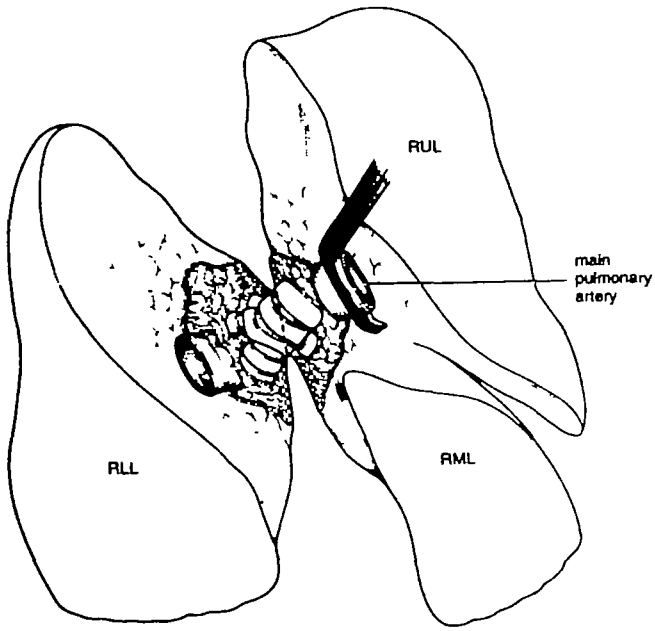

Fig. 1 Dissection and division of the brochuus to the right lower lobe (from Cohen *et al*[13], with permission from *Annals in Thoracic Surgery*)

this makes for considerable donor morbidity from prolonged airleak[15]. Patch repair of the remaining donor's pulmonary artery is sometimes required to maintain perfusion to the posterior segment of the right upper lobe.

On the left, the procedure is a little more straightforward; the structures at the root of the left lower lobe having a similar arrangement to those at the normal left hilum.

Removal of the lobes has to be synchronised with the recipient operation, so as to minimise ischaemic time. After giving heparin and methylprednisolone to the donor, the hilar structures are divided (artery first, to reduce congestion) and the lobe removed. A mixture of antegrade and retrograde flushing of the lung with cold Euro-Collins solution produces complete blanching and uniform cooling.

Care of the donor is along the lines of conventional thoracic surgery. Good analgesia is secured with an opiate epidural, and the drains are removed when air leak ceases.

Surgical considerations: the recipient

Implantation of the two lobes, right lower to right side, left lower to left, is broadly similar to the established bilateral lung transplant[16]. Access to the chest is via a clamshell incision. Cardiopulmonary bypass is used

routinely, partly because one lung anaesthesia is precarious in small patients with end-stage lung disease. Bypass also allows simultaneous reperfusion of the two lungs at the end of the procedure, avoiding the need to pass all the cardiac output through a relatively small, and potentially fragile, vascular bed.

Early postoperative care is similar for that of conventional bilateral lung transplants. The patient is extubated when satisfactory lung performance is attained—usually within 24 h. Appropriate antibiotics can be given on the basis of up-to-date sensitivities (an advantage of a 'planned' transplant). In the USC series, triple drug immunosuppression (cyclosporin, azathioprine and prednisolone) has been used, avoiding cytolytic induction therapy—most of the patients have septic lung conditions and lower rejection rates **might** be expected.

Results

The outcome of this procedure can be judged by several criteria. Simple survival is of importance, as in any form of lung transplantation. Good functional status must be demonstrated, particularly as relatively small units of lung tissue are transplanted. Increased postoperative morbidity, related to space problems as small lungs fail to fill large hemithoraces, might be anticipated.

In the donor, there are considerations of surgical morbidity and late functional loss.

Bilateral lobar transplantation, with organs from two HLA mismatched donors, is a unique immunological model, so rejection rates, and mode of rejection will be of great interest. Finally there are the ethical problems, the balancing of donor morbidity against recipient survival, and the impact of any coercion on family dynamics.

Survival

The current figures from the USC group date from 1996[14]. 38 transplants had been performed on 37 recipients, with 14 deaths over a follow up period of up to 34 months (mean 14 months). The 1 year Kaplan–Meier survival was 68%, extrapolating, with very small numbers to about 50% at 2 years (Fig. 2). Most (12 out of 14) of the deaths were related to sepsis.

These figures are less good than achieved by experienced centres with cadaver transplantation for cystic fibrosis. For instance, Egan and colleagues in the US had a 1 year survival of 85%[17], and a typical

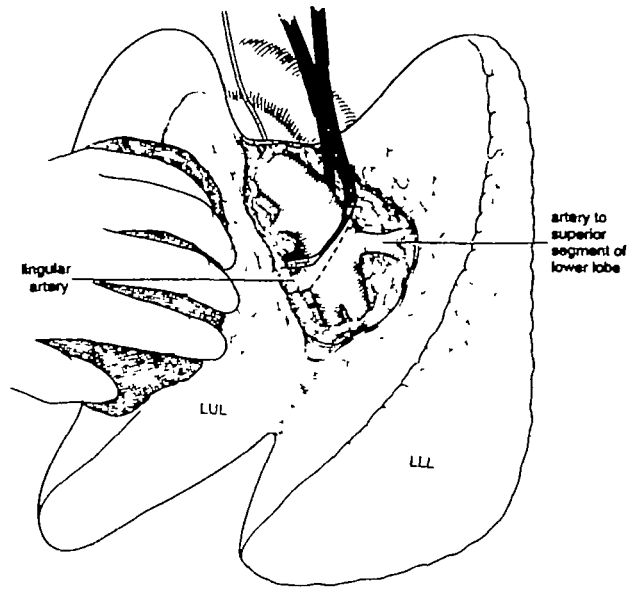

Fig. 2 Dissection and division of the pulmonary artery for donor left lower lobectomy (from Cohen *et al*[13], with permission from *Annals in Thoracic Surgery*)

published figure from a UK centre was 75%[18]. In theory, these living donor recipients should do at least as well as those receiving cadaver organs. They have planned transplants with minimal ischaemic times (means of 65 and 58 min, respectively, on the right and left) and good quality donor organs. Only one death was related to primary organ dysfunction. Patients with pan-resistant organisms were excluded. On the other hand, recipients were in general at the end stages of there disease, and probably represent a more severely affected group than those typically coming to cadaver transplantation. Two-thirds of the

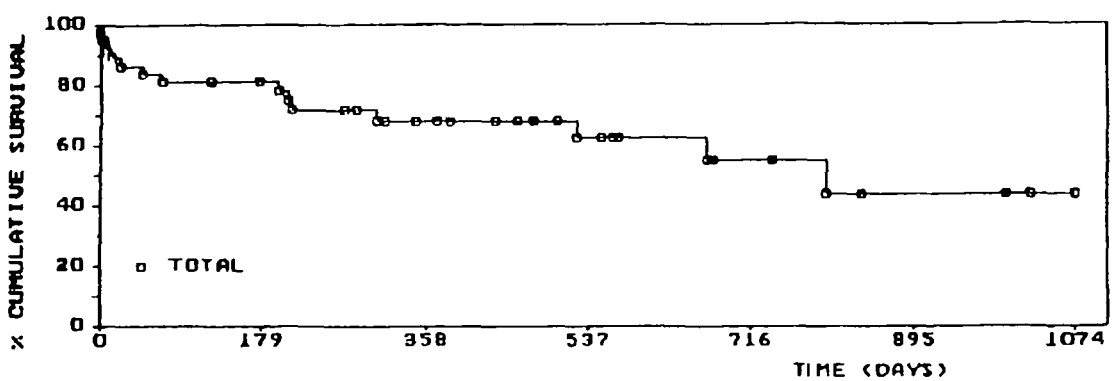

Fig. 3 Kaplan–Meier survival curve after live-donor lobar lung transplantation (from Starnes *et al*[14], with permission from the *Journal of Thoracic and Cardiovascular Surgery*).

operations were done on an urgent basis. An unsupported speculation is that the relatively small volume of lung transplanted renders the recipient less able to survive the pseudomonal respiratory infections that are a feature CF patients after transplantation.

Function

One year after transplantation, surviving patients have excellent spirometry, with results approaching those achieved after cadaver bilateral lung transplant—FEV1 75% of predicted. They have normal pulmonary haemodynamics, as would be predicted from animal models of lobar transplantation[19,20]. There is considerable debate about the long-term function of these lungs. Unlike the lobar liver transplant, the lung will only adapt to the growing thoracic cavity by distension of alveoli. In animal models, and almost certainly in the human analogue, there is no increase in the number of alveoli[21,22]. In the very long term, the 'emphysema' which is a consequence of this overexpansion will cause deteriorating lung function. Given the slow rate of growth of children receiving thoracic organ transplants, overexpansion is unlikely have a major impact on function within the maximum 5–10 year lifetime of a lung graft.

Patterns of rejection

Two important observations have been made from this unique model of a transplant with two different donors in the same *milieu*. Rejection of the lungs is nearly always asynchronous, with one developing an infiltrate and subsequently biopsy proven rejection whilst the other either remains radiologically normal or has no rejection on biopsy. In a preliminary report, this pattern was seen in 10 out of 11 instances[23]. Subsequently, the relationship of HLA matching was explored when at least 28 patients could be followed for at least 6 months. There were more clinically treated rejection episodes in the lungs with 0, 1 or 2 mismatches than in those with 4, 5 or 6 mismatches. Paradoxically, there were fewer biopsy positive rejection episodes in the well matched lungs. The numbers are very small, and these trends did not reach statistical significance, so no firm conclusions can be drawn. It does seem, however, that the degree of HLA mismatch does not predict which one of a pair of lobes is more likely to reject, but that simultaneous rejection of the pair is very unusual.

Donor morbidity

Amongst 76 donors, there were no deaths, and the mean postoperative stay was approximately 10 days. Stay was double (22 days) in the small number where the middle lobe was also removed[15]. Three patients required surgical re-exploration, for bleeding, persistent air leak and suspected empyema. There was a 15–20% reduction in FEV1 and FVC at 6 months, as would be expected from the loss of approximately 20% of the lung parenchyma.

Conclusions: ethical issues and the future

Few firm conclusions can be drawn about live donor lung transplantation when the data come from only a single centre. The technique clearly offers the possibility of transplantation to a group who would otherwise probably have died. However, the results, albeit in a very sick group of recipients, are less good than many achieve with cadaver transplants, and the prospect of reduced acute or chronic rejection has not been realised.

By dint of rigorous selection, donor morbidity has been acceptable, although the impact of a thoracotomy on even a healthy individual should not be underemphasised. The mortality rate for lobectomies to resect cancer is of the order of 2%[25], but these patients are usually elderly and have almost invariably been smokers. The risks of donor lobectomy probably lie midway between live donor nephrectomy, with a mortality risk estimated at 0.03%[26] and live donor liver transplantation where a donor death has been recorded relatively early in the experience[27].

Most of the patients, both in the USC series and elsewhere, were transplanted when in extremis. It is difficult to imagine the absence of an element of coercion within a family under these conditions, particularly if the screening tests (or even blood group incompatibility) exclude the first choice donors. In other forms of live donor transplantation, a 'cooling off' period is often advised, and would be applicable to lobar transplants if recipients and their families could be assessed at an earlier stage.

Living related lobar lung transplantation has yet to find its place in the range of options open to pulmonary transplant surgeons. More results, from more centres, particularly in non-emergency patients are required before general recommendations of acceptability can be made.

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