Improving donor lung evaluation: a new approach to increase organ supply for lung transplantation

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Major technical and pharmacological advances mean that lung transplantation now offers a realistic opportunity for long term survival in selected patients with end stage pulmonary disease.[1 2] Unfortunately up to 50% of patients identified as suitable candidates to undergo lung transplantation will die from their underlying lung disease before an organ becomes available.[3 4] The severe shortage of donor lungs is now the major limitation to the use of the procedure as a widely available therapeutic option. The current method of donor lung evaluation excludes the vast majority of potential lung donors. New objective indices of donor lung injury may help to rationalise the selection process. This would enable many of the previously excluded organs to be accepted, addressing the current problem of organ shortage.

Donor lungs originate from ventilated brain dead patients whose relatives have given consent for organ donation. Multiple strategies have been adopted by the transplant community to increase the number of donor organs for all types of solid organ transplantation. Attempts at raising awareness in medical staff to identify potential brain dead donors and in the general public to encourage consent when approached have failed to dramatically increase the number of organs available for transplantation. Despite 25% of the public carrying a donor card, both emotional and cultural reasons within families have prevented this leading to a significant increase in donors. In other countries legislation requiring medical staff to approach all potential donor families and the introduction of opt-out rather than opt-in systems of donation have not resulted in a major increase in the donor pool.[5] To date the attempts at increasing numbers of potential donors have been disappointing and transplant teams have turned to other possible ways of addressing the shortage of donor lungs.

Lung transplantation using lobes from living family members has proved a useful procedure in selected cases, especially in teenagers,[6] and results are equivalent to that achieved with cadaveric organs. There are, however, both medical and ethical reservations to its widespread use[7] and it is therefore unlikely to be a viable option for the majority of patients on the lung transplant waiting list.

Patients who die suddenly and are not maintained on life support have not previously been considered potential lung donors; however, their kidneys have been used successfully[8] and animal models suggest that "non-heart beating donors" may provide an opportunity to increase the donor lung pool.[9] This approach requires much more extensive evaluation before it could be used in clinical transplantation.

The concept of xenotransplantation might appear to be the solution to organ shortage but, in reality, many major obstacles remain before animal lungs could be used routinely.[10] As well as the ethical considerations, there are serious medical concerns including the spread of zoonoses such as endogenous porcine retroviruses.[11]

These new approaches offer some hope for the future, yet the need for any new approach to be extensively evaluated and the severity of the current problem has led to growing interest in re-examining the existing donor pool. In the UK the lungs from only 60% of multi-organ donors will be offered for consideration and only 25% of these lungs are deemed suitable for use in transplantation.[4]

Most potential donor lungs are not accepted because they fail to meet the predetermined clinical selection criteria.[4] Briefly, criteria used to assess a potential donor lung are based on (a) the arterial blood gas tensions as measured on standard ventilator settings as a measure of organ function; (b) the appearance of the chest radiograph to identify disease and infection; (c) the physical examination of the organ by the surgeon at the time of retrieval to assess organ injury and viability; and (d) the reported appearance of any airway secretions via endotracheal suctioning, including gram staining.[12] These criteria attempt to determine the function and viability of the lung while still in the donor but there is no evidence that they provide a useful guide to how the organ will function after implantation. There has been concern that the use of lungs which do not satisfy current selection criteria might be associated with greater early morbidity and mortality in recipients. However, there is increasing evidence that the use of such "marginal or non-ideal" lungs has no detrimental effect on early outcome.[13 14] As a result, significant numbers of donor lungs deemed unsuitable for transplantation by current criteria may have been viable postoperatively and could potentially have been used.[15]

Re-evaluation and relaxation of the current selection criteria, in conjunction with better ways of assessing a donor lung after brain death, would appear to be the most effective way of addressing the shortage.[16] Even if the total number of donors remains unchanged, an increase in the use of offered lungs by 20% would double the number of lung transplantations performed in the UK each year.

Currently the decision to use a non-ideal organ is subjective and those undertaking the responsibility have limited time and resources available to help. The decision would be considerably easier if objective indices were available to help to establish viability and potential function of the lung. Furthermore, if reversible causes of dysfunction could be identified, early intervention with supportive therapy may render such organs acceptable. A study of potential heart donors has shown increased acceptance of marginal hearts following the adoption of supportive donor management techniques.[17] Management aimed at optimising donor lung function prior to retrieval must become as important as care after transplantation if adequate numbers of useable organs are to be achieved.

To identify indices which will provide valuable objective information about non-ideal lungs and their function in the recipient it is necessary to consider potential abnormalities that can develop in brain dead donors. Donors originate from two main groups: fatal traumatic head injuries and spontaneous intracranial events. Early outcome after transplantation has been shown to be the same using donors from either group.[18] Both these groups have multiple risk factors for the development of lung injury. The majority will have been unconscious prior to intubation and are thus at increased risk of aspiration. Donors may undergo emergency surgery and blood transfusion before brain death and are all ventilated for a varying period of

time in the intensive care environment. All these features contribute to an increased risk of sepsis[19] which, in turn, leads to increased risk of lung injury. Finally, the changes in brain death itself may mimic the physiology of the systemic inflammatory response syndrome (SIRS) and could contribute to the development of significant lung injury in the donor.

Brain stem death causes pathophysiological changes which are poorly understood. Studies using animal models have demonstrated changes in homeostatic regulation in donors after brain death. There is disturbance in the neuroendocrine axis producing acute autonomic dysfunction.[20] This produces peripheral vasodilatation and a sudden fall in thyroid hormone levels causing a change in the organ's ability to replenish its energy stores.[21] Further evidence of the importance of these changes in brain death is demonstrated by the use of T_3 hormone replacement to treat borderline heart donors with a dramatic improvement in cardiac function.[22] There is evidence of systemic cytokine activation with serum IL-6 levels significantly increased compared with non-brain dead controls.[23] The pulmonary blood flow characteristics, together with the cardiopulmonary haemodynamics, change considerably to produce oedema and possible pulmonary endothelial damage as a result of increased hydrostatic pressure in the lung.[24] These features suggest that the pathophysiological changes in brain death could produce significant lung injury and significantly increase the risk of subsequent acute respiratory distress syndrome (ARDS).

It is important that any new indices used in the selection process can quantify the degree of lung injury in the donor and the likelihood of it progressing in the recipient. Assessment of lung injury and the prognostic significance of the degree of injury has been extensively studied in both patients with and those at risk of ARDS.[25] Potential lung donors are at risk of developing progressive lung injury and the identification of those non-ideal donors, who appear to have a high risk of subsequent ARDS, would certainly help to rationalise the selection process. Obtaining material directly from the donor lung via bronchoscopy and bronchoalveolar lavage provides a means of examining the pulmonary microenvironment in situ. Bronchoscopy itself adds important information about pathology within the donor lung which may have been missed using current selection criteria.[26] Sampling performed by this method could allow the degree of pulmonary endothelial, pneumocyte, and airway epithelial cell activation and injury to be investigated. It also has the advantage of providing data specific to the lung. Plasma measurements may also be useful but provide information about systemic rather than lung condition.

The integrity of the pulmonary endothelium and the endothelial-alveolar barrier is essential for effective function of the lung. In lung injury the endothelium plays an important part in mediating inflammatory cell adhesion and migration from the vascular compartment. It also controls permeability leading to capillary leakage and subsequent alveolar flooding. Finally, it has a role in releasing powerful inflammatory mediators which activate the inflammatory cascade.

Identification of increased numbers and concentration of neutrophil polymorphs in the air spaces will confirm the presence of inflammatory activation due to both infective and non-infective causes. Assessment of protein leakage into the alveolar space will quantify the increase in microvascular permeability and may give some estimate of endothelial integrity. Endothelial activation and injury in the lung has been assessed in many previous studies.[27 28] Von Willebrand factor in serum has been measured in several studies and may correlate current endothelial activation with the subsequent development of lung injury.[29] Measurement of soluble selectin molecules, adhesion molecules necessary for leucocyte interaction with the endothelium, may provide an indication of developing lung injury.[30] Progression of lung injury results from uncontrolled activation of the inflammatory cascade and the identification of an imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines in the lung may be a predictor of more severe progressive injury.[31] The powerful neutrophil chemokine IL-8 is believed to play an integral part in neutrophil recruitment in lung injury and has shown promise in being able to predict the subsequent development of significant lung injury.[32]

Epithelial cell integrity at an alveolar level is essential for the good function of the potential donor lung. Epithelial injury has been investigated by measuring surfactant protein concentrations in bronchoalveolar lavage fluid and low levels have been associated with more severe injury.[33]

Extending the boundaries of donor lung acceptability would appear to offer the best chance of dealing with the immediate donor shortage. The challenge for the future will be to identify the best markers of lung injury in the donor which help to predict function subsequently in the entirely different environment of the recipient. The ability to quantify injury at a cellular level in the donor and then to determine its effect on function and early mortality in the recipient requires urgent evaluation before marginal lungs become routinely accepted as suitable organs for lung transplantation.

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1 Dark JH, Corris PA. Current state of lung transplantation. *Thorax* 1989;**44**:689–92.
2 Theodore J, Lewiston N. Lung transplantation comes of age. *N Engl J Med* 1990;**322**:772–4.
3 Ryan PJ, Stableforth DE. Referral for lung transplantation: experience of a Birmingham Adult Cystic Fibrosis Centre between 1987 and 1994. *Thorax* 1996;**51**:302–5.
4 UKTSSA. Cardiothoracic Organ Transplant Audit 1985–1995. UKTSSA, 1997.
5 Mozes M, Bolden A, Hayes R, *et al*. Impediments to successful organ procurement in the "required request" era: an urban centre experience. *Transplant Proc* 1991;**23**:2545.
6 Kramer MR, Sprung CL. Living related donation in lung transplantation. *Arch Intern Med* 1995;**155**:1734–8.
7 Dark JH. Lung: living related transplantation. *Br Med Bull* 1997;**53**:892–903.
8 Kootstra G. Expanding the donor pool: the challenge of non-heart beating donor kidneys. *Transplant Proc* 1997;**29**:3620.
9 Egan TM, Lambert CJ, Reddick R, *et al*. A stratergy to increase the donor pool: use of cadaver lungs for transplantation. *Ann Thorac Surg* 1991;**52**:1113–21.
10 Starzl T, Rao A, Murase N, *et al*. Will xenotransplantation ever be feasible. *J Am Coll Surg* 1998;**186**:383–7.
11 Michaels M. Infectious concerns of cross-species transplantation: xenozoonoses. *World J Surg* 1997;**21**:968–74.
12 Sundaresan S, Trachiotis G, Aoe M, *et al*. Donor lung procurement: assessment and operative technique. *Ann Thorac Surg* 1993;**56**:1409–13.
13 Sundaresan S, Semenkovich J, Ochoa L, *et al*. Successful outcome of lung transplantation is not compromised by the use of marginal donor lungs. *J Thorac Cardiovasc Surg* 1995;**109**:1075–9; discussion 1079–80.
14 Kron IL, Tribble CG, Kern JA, *et al*. Successful transplantation of marginally acceptable thoracic organs. *Ann Surg* 1993;**217**:518–22; discussion 522–4.
15 Wheeldon DR, Potter CD, Jonas M, *et al*. Transplantation of "unsuitable" organs? *Transplant Proc* 1993;**25**:3104–5.
16 Shumway SJ, Hertz MI, Petty MG, *et al*. Liberalization of donor criteria in lung and heart-lung transplantation. *Ann Thorac Surg* 1994;**57**:92–5.

17 Wheeldon D, Potter C, Oduro A, *et al*. Transforming the "unacceptable" donor: outcomes from the adoption of a standardised donor management technique. *J Heart Lung Transplant* 1995;**14**:734–42.
18 Waller DA, AM T, Wrightson N, *et al.* Does the mode of donor death influence the early outcome of lung transplantation? A review of lung transplantation from donors involved in major trauma. *J Heart Lung Transplant* 1995;**14**:318–21.
19 Hsieh A-H, Bishop J, Kublis P. Pneumonia following closed head injury. *Am Rev Respir Dis* 1992;**146**:290–4.
20 Chiolero R, Berger M. Endocrine response to brain injury. *New Horizons* 1994;**2**:432–42.
21 Cooper D, Novitzky D, Wicomb W. The pathphysiological effects of brain-death on potential donor organs, with particular reference to the heart. *Ann R Coll Surg Engl* 1989;**71**:261–6.
22 Howard T. Selection and management of the brain-dead cadaver donor. *Curr Opin Organ Transplant* 1997;**2**:139–45.
23 Amado J, Lopez-Espadas F, Vazquez-Barquero A, *et al*. Blood levels of cytokines in brain-dead patients: relationship with circulating hormones and acute-phase reactants. *Metabolism* 1995;**44**:812–6.
24 Bittner H, Kendall S, Chen E, *et al*. The effects of brain death on cardiopulmonary haemodynamics and pulmonary blood flow characteristics. *Chest* 1995;**108**:1358–63.
25 Meduri GU, Kohler G, Headley S, *et al*. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. *Chest* 1995;**108**:1303–14.
26 Riou B, Guesde R, Jacquens Y, *et al*. Fibreoptic bronchoscopy in brain-dead organ donors. *Am J Respir Crit Care Med* 1994;**150**:558–60.
27 Sakamaki F, Ishizaka A, Handa M, *et al*. Soluble form of P-selectin in plasma is elevated in acute lung injury. *Am J Respir Crit Care Med* 1995;**151**:1821–6.
28 Sinclair DG, Braude S, Haslam PL, *et al*. Pulmonary endothelial permeability in patients with severe lung injury. Clinical correlates and natural history. *Chest* 1994;**106**:535–9.
29 Rubin D, Wiener-Kronish J, Murray J, *et al*. Elevated von Willebrand factor antigen is an early plasma predictor of acute lung injury in nonpulmonary sepsis syndrome. *J Clin Invest* 1990;**86**:474–80.
30 Donnelly SC, Haslett C, Dransfield I, *et al*. Role of selectins in development of the adult respiratory distress sydrome. *Lancet* 1994;**344**:215–9.
31 Donnelly SC, Stieter RM, Reid PT, *et al*. The association between mortality rates and decreased concentrations of interleukin-10 and interleukin-1 receptor antagonist in the lung fluid of patients with the adult respiratory distress syndrome. *Ann Intern Med* 1996;**125**:191–6.
32 Reid P, Donnelly S. Predicting ARDS and early intra-pulmonary inflammation. *Br J Hosp Med* 1996;**55**:499–502.
33 Gregory TJ, Longmore WJ, Moxley MA, *et al*. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest* 1991;**88**:1976–81.