

NON-HEART BEATING LUNG DONATION: ASPECTS FOR THE FUTURE

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Introductory article

Transplantation of lungs from a non-heart-beating donor

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Background: In animals we have previously done successful lung transplantation using organs from non-heart-beating donors. We have also developed an ex-vivo system of assessing the function of such organs before transplantation. The next stage was to try the technique in human beings. Bearing in mind the sensitive ethical issues involved, our first aim was to find out what procedures would be acceptable, and to use the results to guide a clinical lung transplantation from a non-heart-beating donor. **Methods:** The ethical acceptability of the study was gauged from the results of a broad information programme directed at the general public in Sweden, and from discussions with professionals including doctors, nurses, hospital chaplains and judges. The donor was a patient dying of acute myocardial infarction in a cardiac intensive care unit after failed cardiopulmonary resuscitation. The next of kin gave permission to cool the lungs within the intact body, and intrapleural cooling was started 65 min after death. Blood samples were sent for virological testing and cross matching. The next of kin then had time to be alone with the deceased. After 3 h the body was transported to the operating theatre and the heart-lung block removed. The lungs were assessed ex vivo, and the body was transported to the pathology department for necropsy. **Results:** No contraindications to transplantation were found, and the right lung was transplanted successfully into a 54 year old woman with chronic obstructive pulmonary disease. The donor lung showed excellent function only 5 min after reperfusion and ventilation, and during the first 5 months of follow up the function of the transplanted lung has been good. **Interpretation:** About half the deaths in Sweden are caused by cardiac and cerebrovascular disease. This group could be a potential source of lung donors. When all hospitals and ambulance personnel in Sweden have received training in non-heart-beating lung donation, we hope that there will be enough donor lungs of good quality for all patients needing a lung transplant. (*Lancet* 2001;357:825–9)

The Introductory article by Steen *et al*¹ had been eagerly anticipated by the lung transplantation community and the *Lancet* chose to commission an editorial to accompany it in the same journal. This editorial commented that lung transplantation remains an experimental procedure, but this seems unjustified given the substantial evidence supporting improved health status following transplantation and current rates of survival of 80–85% at 1 year and up to 65% at 5 years in a group of patients estimated to have a survival of less than 18 months.

Lung transplantation is thus a well accepted treatment for advanced pulmonary disease of many causes, but its major failing is that it does not meet the required demand. The number of lung transplantations performed is falling, and the UK waiting list currently outnumbers the annual transplantation figures by a factor of almost two.²

STRATEGIES FOR INCREASING DONOR LUNGS

As a consequence, there has been much discussion over the current criteria defining the suitability of lungs from brain stem dead donors. Mounting evidence supports the view that lungs no longer conforming to long standing criteria (called marginal lungs) can be successfully used. Currently, lungs positive on Gram staining for bacteria or from a donor with an arterial oxygen tension (Pao₂) on 100% oxygen of 300 mm Hg (40 kPa) or more are now regularly used. Despite this, there remains a large discrepancy between numbers of potential recipients and actual donors. Consideration therefore has been given to alternative sources of organs for transplantation. Living lobar transplantation has been performed in a few carefully selected

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patients, but is currently only practical in the small patient with bilateral disease.³ Xenotransplantation may offer hope for the future but it is not available at present. Attention has therefore been focused on the organs of donors who have suffered cardiac arrest—the so-called “non-heart beating donor” (NHBD).⁴ The first reported clinical lung transplantation performed by Hardy *et al*⁵ in 1963 used a lung from a donor following cardiac arrest and there are other anecdotal reports of successful lung transplantation from NHBDs.⁶ Several successful European schemes offer renal transplantation from NHBDs including those in Maastricht,⁷ Leicester,⁸ and Newcastle.⁹ Long term results of renal transplants performed from NHBDs are acceptable, but delayed function requiring renal support is a problem in over 60% of cases.¹⁰

Background

The lung may be more amenable to non-heart beating donation than the kidney by virtue of its structure. Lung parenchyma cells are immediately adjacent to alveolar spaces and a source of oxygen. Tissue levels of high energy nucleotide phosphates remain near normal for up to 4 hours after the cessation of circulation providing the lung remains inflated.¹¹ Work with different animal models has consistently shown that lungs transplanted after 1–2 hours of warm ischaemia perform satisfactorily.^{12–14} Inflation with or without ventilation with either oxygen or air for a period of a few hours provides optimal storage conditions.^{15, 16}

The selection of suitable lungs for transplantation remains a problem; currently only 20–25% of brain stem dead multiple organ donors have lungs suitable for transplantation due to trauma, infection, or inflammatory change.⁴ The donor pulmonary venous oxygen tension remains the best practical marker for the prediction of satisfactory initial function after transplantation.¹⁷ Fisher *et al*¹⁸ have demonstrated the value of donor lavage interleukin (IL)-8 levels in the prediction of lung vascular injury after transplantation and a correlation between IL-8 and P_{aO_2} /inspired oxygen fraction (F_{iO_2}) ratios. Despite this, poor function after transplantation remains a major problem with function being significantly impaired in 10–15%.¹⁹

Many studies have been undertaken in animal models to test the hypothesis that lungs from NHBDs would work satisfactorily. The first important issue to determine was whether lungs or hearts taken from donors who developed cardiac arrest following hypoxia could be potentially used. Mauney *et al*²⁰ using a rabbit model determined the effects of pre-arrest hypoxia and post-arrest warm ischaemia on the function of both cardiac and pulmonary allografts procured from NHBDs undergoing hypoxic arrest. Rabbit hearts and lungs were procured after hypoxic arrest from separate donors and placed on isolated blood perfusion circuits to allow functional analysis. Control heart and lungs were excised and perfused without prior hypoxic arrest. Hearts from the hypoxic arrest animals mimicking NHBDs were then placed on the isolated blood perfusion circuit and a functional analysis performed with or without a further 20 minutes or 30 minutes of post-arrest warm ischaemia. Two groups of lungs were studied using similar hypoxic perfusion after 20 and 30 minutes of post-arrest warm ischaemia. Pre-arrest hypoxic perfusion clearly caused significant dysfunction of hearts compared with non-ischaemic controls. Pre-arrest hypoxic perfusion combined with post-arrest ischaemia resulted in an additive degree of dysfunction, more severe than a similar period of warm ischaemia alone. Both groups of experimental lungs, however, displayed function

similar to that of non-ischaemic controls in terms of pulmonary haemodynamics, airway resistance, and oxygenation. The authors concluded that pre-arrest hypoxic perfusion significantly contributed to the dysfunction of potential cardiac allografts. Potential pulmonary allograft function was not affected, however, leading to the conclusion that the use of NHBD lungs was feasible.

Using a pig model, Steen and colleagues²¹ transplanted pig lungs that had been topically cooled in a non-heart beating donor for 6 hours using the most challenging evaluation method possible—namely, single lung transplantation followed by immediate contralateral pneumonectomy. Domestic pigs (six donors and six recipients) with a mean (SD) body weight of 59 (3) kg were used. Ventricular fibrillation was induced and after 1 minute cardiac massage was started and then heparin (5 mg/kg body weight) was given by a central venous catheter. Cardiac massage was continued for 10 minutes during which the pig was ventilated with 50% oxygen. The pleural cavities were opened and the tracheal tube disconnected from the ventilator with the result that both lungs deflated. Saline slush was placed in both pleural cavities so that it completely covered the lungs. Within 40 minutes the lung core temperature was less than 10°C and it was kept around 8°C for 6 hours by adjusting the amount of iced slush. The left lung was then harvested and transplanted into a prepared recipient, followed by right pneumonectomy within 46 (4) minutes, thus making the recipient pig totally dependent on the transplanted cadaver lung. The mean ischaemic time for the cadaver lungs was 8 hours and 2 minutes (range 7 hours 25 minutes to 8 hours 59 minutes). All animals remained in excellent condition throughout the 24 hour observation period, with P_{aO_2} approximately 225 mm Hg (30 kPa) and an inspired oxygen fraction of 50%. Steen *et al* concluded that lungs from non-heart beating donors may be used for transplantation if heparinisation and topical cooling could be initiated within minutes of irreversible cardiac arrest.

Continuing with a pig model, Steen *et al*²² then demonstrated the viability of extended preservation of lungs using a low potassium dextran pulmonary perfusate. The function of six porcine left lung allografts were studied after pulmonary, bronchial, and artery perfusion with Perfadex (Kabi Pharmacia, Uppsala, Sweden) at room temperature followed by 24 hour storage of the lungs in an atelectatic state in 6–8°C Perfadex, a low potassium dextran solution. Left lung transplantation was performed followed by right pneumonectomy, thereby making all the animals totally dependent for their survival on the transplanted lungs. The pigs were ventilated with a volume control ventilator at 20 breaths/min with 500 ml tidal volume, 8 cm H_2O positive end expiratory pressure, and an inspired oxygen fraction of 50%. All the transplanted animals were in good condition throughout the 24 hour observation period with P_{aO_2} 188 mm Hg (25 kPa) and P_{aCO_2} 38 mm Hg (5 kPa). The mean pulmonary arterial pressure was 30 mm Hg and pulmonary vascular resistance was 500 dyn.s.cm⁻⁵. After 24 hours the inspired oxygen fraction was increased to 100% and P_{aO_2} increased to 325 (38) mm Hg (43.3 (5) kPa).

Clinical programme

These and other experiments led Steen and colleagues in 2001 to consider a human programme of transplantation using NHBD. They had carried out further work in the animal laboratory and developed a refinement in pulmonary perfusate using cold buffered Perfadex with 1 mmol/l calcium chloride (Vitrolife AB, Gotenburg, Sweden). Bearing

Learning points

- ▶ The shortfall in suitable donor lungs for patients awaiting lung transplantation remains one of the most important problems in this field
- ▶ Over the last 5 years the concept of using kidneys from NHBDs has developed into clinical reality
- ▶ There is a large volume of experimental work supporting the successful use of lungs for transplantation harvested from NHBDs
- ▶ It is to be hoped that this first clinical report of successful lung transplantation using a lung from an NHBD will stimulate other groups to develop similar clinical programmes in this area

in mind the sensitive ethical issues regarding human transplantation from NHBD, the first aim was to find out what the public at large would find acceptable. The ethical acceptability of lung transplantation from NHBD was gauged from the results of a broad information programme directed at the general public in Sweden, and from discussions with professionals including doctors, nurses, hospital chaplains, and judges. The favourable response led the Swedish Government Medical Ethics Council to grant permission providing the Ethical Research Committee in Lund also gave approval for the procedure to be carried out in a human. The protocol was approved. The first donor was a patient who died following acute myocardial infarction on the cardiac intensive care unit after failed cardiopulmonary resuscitation. The next of kin gave permission to cool the lungs within the intact body, and intrapleural cooling was started 65 minutes after death. Blood samples were sent for virological testing and cross matching. The next of kin then had time to be alone with the deceased. Three hours later the body was transported to the operating theatre and the heart-lung block removed. The lungs were assessed ex vivo and the body was transported to the pathology department for post mortem examination. No contraindications for transplantation were found, and the right lung was then transplanted successfully into a 54 year old woman with advanced chronic obstructive pulmonary disease. The donor lung showed excellent function 5 minutes after perfusion and ventilation and during the first 5 months of follow up the function of the transplanted lung was good.

Despite this early success no further NHBD lungs have been procured in Sweden, raising concerns over the general applicability of the procedure. A number of groups including our own in Newcastle have established successful experimental programmes in animals and are poised to enter the clinical arena. The potential of NHBD is to yield enough donor lungs of good quality for all patients requiring a lung transplant, and groups active in this area should be encouraged to continue with their important work.

Conclusions

The paper by Steen *et al*¹ raises a number of important issues. The first relates to consensus on the ethics of procedure. Steen's group consulted widely in Sweden and obtained agreement. Can the consensus that Steen obtained be expected from other societies? Although NHBD kidney and liver programmes exist, would the UK be supportive given the current distrust of doctors fuelled by a sensationalist media?

A second issue relates to functional assessment of the organ ex vivo to ensure that transplantation is safe. This has been addressed by several groups in addition to Steen's, all of which have presented convincing evidence that detailed assessment is possible within the necessary time constraints. Groups active in this area should be encouraged and supported to develop their own clinical programmes.

The shortfall in suitable donor organs remains one of the most important problems facing lung transplantation and the concept of using lungs taken from NHBDs represents an exciting and very important prospect for hundreds of patients with advanced lung disease on active waiting lists.

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