Transplantation of lungs from a non-heart-beating donor

Stig Steen, Trygve Sjöberg, Leif Pierre, Qiuming Liao, Leif Eriksson, Lars Algotsson

Summary

Background In animals, we have previously done successful lung transplantsations 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. 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.

Results No contraindications to transplantation were found, and the 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.

Introduction

The possibility of transplanting lungs from fresh non-heart-beating cadavers (eg, patients who have had a witnessed cardiac arrest due to ischaemic heart disease) has been the subject of much discussion.1 Experimental studies have shown that the lungs and their vascular function can be safely preserved for up to 24 h;2,3 that the gas-exchange system of the lungs can tolerate 1 h of warm ischaemia after circulatory arrest without significant loss of its functional capacity;4 and that the pulmonary artery can withstand warm ischaemia for 3 h after death without impairment of endothelium-dependent relaxation or vascular smooth-muscle function.5 Furthermore, simple topical cooling of non-ventilated lungs gives excellent preservation for 12–24 h.6

We have previously transplanted animal lungs from non-heart-beating donors in simulated clinical situations in which the lungs were first topically cooled in the non-heart-beating cadaver after failed resuscitation.8–10 However, if lungs from patients dying of acute myocardial infarction are to serve as donor organs in clinical lung transplantation, their function must be properly assessed first. In cooperation with Vitrolife AB (Gothenburg, Sweden), we have developed a lung-function assessment solution which, when mixed with red cells to a packed-cell volume of 10–20%, permits perfusion of lungs ex vivo for several hours without development of oedema (figure 1). By supplying nitrogen, carbon dioxide, and oxygen to the oxygenator, venous blood gases can be simulated in the solution. During ventilation of the lungs with gases of different inspired oxygen fractions, the blood gases analysed in the solution taken from the left atrial cannula will show the gas-exchange capacity of the lungs. Measurement of the endtidal carbon dioxide concentration and comparison of that value with the arterial carbon dioxide concentration, ventilation-perfusion discrepancies (eg, those due to pulmonary emboli) can be detected. By clamping one hilar with a vascular clamp, each lung can be assessed individually. Vascular function can be judged by observing the effect on the pulmonary vascular resistance of a gradual increase in the proportion of nitric oxide in the inhalation gas; the greater the effect of nitric oxide on pulmonary vascular resistance, the more impaired the endothelium-dependent relaxation.11

The results of our animal experiments and studies on ex-vivo assessment of lung function convinced us that it should be possible to transplant lungs from non-heart-beating donors to live recipients, provided an ethically acceptable method of cooling the lungs within 1 h of death could be found. Here we report the methods used to ascertain what constitutes ethical acceptability in these circumstances, and the results of our experience with the first non-heart-beating lung donor and recipient.
Methods

Preliminary investigations

At the beginning of 1997, we started to prepare for a clinical study. We asked doctors, nurses, hospital chaplains, judges, teachers, philosophers, theologians, and ordinary citizens across Sweden about how lungs could be transplanted from a non-heart-beating donor. From this consultation, we learned that any type of surgery on a dead body within 1 h of death was ethically unsound, but that if topical cooling of the lungs could be accomplished without leaving scars, then the planned procedure ought to be acceptable.

We therefore returned to the laboratory and developed an efficient technique for topical cooling of the lungs in animals by puncture-placement of intrapleural cannulae for infusion of a cold (4°C) lung-preservation solution (Perfadex; figure 2). With this technique, the lungs are compressed and are transformed into a semi-solid state, which is more easily cooled.

In September, 1997, we called a meeting with the Chief of Staff of the University Hospital, heads of selected departments (including the emergency and intensive-care units), the Chairman of the Medical Ethical Research Committee, and hospital legal and ethical experts to discuss potential ethical problems with the use of lungs from non-heart-beating donors.

Discussion of ethics

The discussion raised two main concerns. First, what back-up the recipients could be offered if the transplanted lungs should for unexpected reasons fail, and second, whether an extra burden would be added to the next of kin if the question of lung donation was raised within 1 h of death.

The first question could be satisfactorily answered. Our research group had already done extensive research on the treatment of critical respiratory failure.12–15 Total extracorporeal lung assist for 5 weeks had been successfully achieved in the clinic, and when respiratory insufficiency was not total, it could be controlled with hypothermia and buffering. Thus, the risk that the patient could die due to unexpected complications after transplantation with lungs from non-heart-beating donors was deemed to be small. If critical respiratory failure should occur, total extracorporeal lung assist could be started and an urgent call for new donor lungs and retransplantation made.

However, the question about next of kin was deemed to be outside the competence of the participants in the meeting at the University Hospital of Lund, and of the local ethics committee. We agreed that no clinical study should be started before the general public in Sweden had been fully informed. Only after a favourable response from the general public and after consultation with the government’s medical ethics council and the Committee for Ethical Questions of the National Board of Health and Welfare, would it be possible to start a clinical study. Unlike in some European countries, no programme for kidney transplantation from non-heart-beating donors has been ethically accepted in Sweden.

During the end of 1997 and beginning of 1998, the general public in Sweden was informed of the project via all three national television channels, national radio, and major newspapers. The reaction was generally positive and resulted in an invitation to one of us (SS) to attend a hearing at the government’s medical ethics council. The council found the project fully acceptable, but made it clear that the formal decision to undertake a clinical study had to be made by the Ethical Research
Committee of the University of Lund.

Our application to this committee was sent on May 15, 1998, and the study protocol was finally approved on Aug 19. Despite the fact that, in Sweden, preparations for organ donation (but not the operation itself) may be done before the next of kin is informed, the Ethical Research Committee stated that in this case, we were not permitted to do any kind of preparatory procedures on the body before the next of kin had given permission. Thus we had to discuss lung donation and get permission from the next of kin before we could cool the lungs. Furthermore, the potential recipient had to sign a document stating that he or she had been fully informed that this type of transplantation had never been done on a patient before and that unexpected complications could therefore not be excluded. The Committee for Ethical Questions of the National Board of Health and Welfare had no objections to the study.

Transplantation procedure

A potential non-heart–beating donor was defined as any patient younger than 70 years who had died after a failed resuscitation. Direct exclusion criteria were serious lung disease, all types of malignancies except primary brain tumours, and hepatitis and HIV infections. Thorough instructions were given to all personnel who might be involved in the procedure, and a group of hospital chaplains stated their wish to be of help regarding the needs of the next of kin.

The first eligible donor was a 54-year-old man (bodyweight 72 kg, height 171 cm, blood group A positive) who had an acute myocardial infarction and was treated at the cardiac intensive-care unit of our hospital. Cardiac arrest occurred and cardiopulmonary resuscitation was started immediately by means of pneumatic chest compression/decompression apparatus (Jolife AB, Lund, Sweden). After 50 min of unsuccessful resuscitation, the patient was declared dead. 50 000 IU heparin was given via a central venous catheter, and further chest compressions were done to distribute the heparin around the circulatory system. Using a portable computer equipped with a modem, the donation coordinator connected to the donation register of the National Board of Health and Welfare and found that the deceased had not registered his wishes regarding organ or tissue donation. The cardiologist on duty and another senior cardiologist informed the next of kin and asked if they knew whether the deceased had expressed an opinion regarding organ donation. The next of kin stated that the deceased was agreeable to donation, and gave permission to cool the lungs in situ and to use them for transplantation.

<table>
<thead>
<tr>
<th>Time</th>
<th>Treatment</th>
<th>Status</th>
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<tbody>
<tr>
<td>01.25–02.15</td>
<td>Cardiopulmonary resuscitation</td>
<td>Warm ischaemia (1 h 5 min)</td>
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<td>02.15–03.10</td>
<td>Hands off</td>
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<td>03.10–03.20</td>
<td>Pleural cannulae</td>
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<td>03.20–05.30</td>
<td>Topical cooling</td>
<td>Cold ischaemia (3 h)</td>
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<td>05.30–06.20</td>
<td>Viethylene, crossmatching</td>
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<td>08.20–07.25</td>
<td>Functional assessment</td>
<td>Controlled reperfusion</td>
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<td>07.25–14.40</td>
<td>Bronchoscopy, radiography</td>
<td>At 37°C</td>
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<tr>
<td>14.40–15.43</td>
<td>Necropsy</td>
<td>Cold preservation</td>
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<tr>
<td>15.43</td>
<td>Start reperfusion</td>
<td></td>
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Table 1: Schedule for controlled non-heart-beating donor lung transplantation

With the body in the supine position, two pleural catheters (Portex 20F, Hythe, UK) were inserted into the area between the mammilla and the sternum on each side of the chest. Intrapleural topical cooling was started 65 min after declaration of death (table 1). After infusion of 5-6 L cold buffered Perfadex with 1 mmol/L calcium chloride (Vitrolife AB, Gothenburg, Sweden) into each pleural cavity (figure 2), the endotracheal tube was cut short, plugged and hidden within the mouth, with the cuff fully inflated to eliminate bronchial contamination from the stomach. The pleural tubes were clamped and fixed to the thorax, and the body was made ready for the next of kin, who were then given time to be alone with the deceased. When they had left, an additional 2-8 L cold Perfadex was infused into each pleural cavity before transportation to the operating theatre. The heart-lung block was harvested after 3 h, by this time the bronchial temperature of the lungs was 18°C. Bronchoscopy showed some secretions in the trachea and the main bronchi, but the segmental bronchi were clean. After explantation, the body was transported to the Department of Pathology, where an emergency necropsy showed no pathological disorder. At the same time, lung function was assessed ex vivo at 37°C (figure 1), and was found to be excellent (table 2). The lungs were then cooled to a core temperature of 20°C, dissected ready for transplantation, and placed in buffered Perfadex with 1 mmol/L calcium chloride at 8°C. The heart was replaced within the body after investigation. Virological tests were negative for hepatitis A, B, and C viruses, and for HIV.

The recipient was a 54-year-old woman (bodyweight 50 kg, height 168 cm, blood group A positive) with chronic obstructive pulmonary disease. Her lung disease had been symptomatic for about 20 years. She was an ex-smoker, having stopped smoking in 1993 when she became oxygen-dependent. Because of pronounced emphysema, she was assessed for volume-reduction surgery. Bilateral volume reduction was done with a thoracoscopic technique in December, 1997, with initially very good results that permitted discontinuation of the supplemental oxygen therapy. After about a year, however, her symptoms worsened, and in the spring of 2000 she was assessed for lung transplantation. Her vital capacity was then 1·5 L (37% of predicted) and her forced expiratory volume in 1 s...
was 0·4 L (14% of predicted). The pretransplantation assessment showed no contraindications and she was listed for lung transplantation in September, 2000.

Results
A ventilation-perfusion scintigram of the recipient showed no great mismatch; the right lung had 51% and the left lung 49% of the ventilation. Right lung transplantation was done. The phrenic nerve had adhered to the teflon reinforced staple line after the lung-volume reduction surgery, and had to be carefully dissected free. There were also strong adherences between the lung and the diaphragm. Otherwise the transplantation was not difficult, and did not require extracorporeal circulation. The donor lung showed excellent function only 5 min after the start of reperfusion and ventilation, as judged by blood gases and carbon-dioxide curves. The patient was taken to the intensive-care unit 2 h after the start of reperfusion. The fractional concentration of oxygen in inspired gas was 0·3, giving 100% arterial saturation; pulmonary-arterial pressure was normal.

The first 2 weeks after the operation were free of complications. The patient was haemodynamically stable and was weaned from ventilatory support without difficulty on the first day after surgery. The first chest radiograph taken after extubation (18 h after the start of reperfusion) is shown in figure 3. The saturation was good with administration of oxygen at 2–3 L/min through a nasal cannula, and carbon dioxide concentrations in the blood were normal. The patient was mobile the day after the operation, and was transferred to the ward on the third postoperative day. The bacterial culture taken from the donor lung was negative.

During the second week after the operation, the patient recovered well. The chest radiograph 1 week after the transplantation is shown in figure 3. The function of the transplanted lung has been good throughout the first 5 postoperative months despite bile stones, left biliary-duct occlusion, and an abscess in the left hepatic lobe.

Discussion
The lung is unique among the vital organs owing to its tolerance of warm ischaemia. When acute cardiac arrest occurs, the vasculature of the lung is filled with blood saturated with oxygen to 70–100%, and the airways are filled with air (or with 100% oxygen if the person has been resuscitated). Normally the alveolocapillary membrane gets its nutrition by direct diffusion. The lung consists mainly of elastic tissue with a low metabolic requirement and its function is retained for up to an hour after death. If the metabolic rate is reduced by cooling, however, the lung will survive for at least 12 h. The pulmonary vascular endothelium maintains its function several hours after acute circulatory arrest, which prevents, for example, clot formation. In this procedure for transplantation of lungs from a non-heart-beating donor, heparin was given into a central venous catheter 10 min after declaration of death, followed by 20 chest compressions. However, on the basis of experimental observations, we do not think heparin is mandatory, and in four other hospitals where the procedure is now being introduced, administration of heparin is no longer a part of the protocol. The only mandatory procedure is to start cooling within 1 h of a witnessed death or failed resuscitation.

During effective cardiopulmonary resuscitation, the lungs get enough blood flow to survive. The cooling can be accomplished either by repeated intrapleural infusions of cold preservation solution, as in our study, or by recirculation of the preservation solution by means of a small, silent pump incorporated into a closed extracorporeal cooling circuit. This system can be placed under the bed so that it will not disturb the next of kin if they are present.

The ex-vivo lung assessment method described in this study can also be used to assess lungs from marginal heart-beating donors. The medium developed for this procedure is an excellent lung-preservation medium for cold (4ºC) storage of donor lungs. In experiments on adult pigs, we have harvested and assessed lungs with this new system. After the assessment, they were stored at 4ºC for 36 h, before

Figure 3: Chest radiographs of lung-transplant recipient 18 h (top) and 1 week (bottom) after start of reperfusion
transplantation of the left lung was done followed by right pneumonectomy. These lungs produced normal blood gases. With the knowledge gained from this experiment, we did not judge it practical (or necessary) to order air transport for the human recipient in our clinical study. This explained the long period of cold storage (table 1).

The lung function of non-smokers is usually good, even in old age. The pulmonary vascular system is a low-pressure system, and as in the veins, arteriosclerosis does not usually develop. Most patients in Sweden who need new lungs have chronic obstructive pulmonary disease and are 60 years of age or older. 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 who could benefit from a lung transplant.

Contributors
Stig Steen created the experimental models, did the transplantation, and wrote the first version of the paper; Trygve Sjöberg was the non-heart-beating donation coordinator, and was responsible for the education of the medical personnel; Leif Pierre was responsible for perfusion during the ex-vivo lung assessment, and participated in all experiments done in the past 5 years; Qiuming Liao participated in all experiments on the ex-vivo model and was first assistant in the clinical transplantation; Leif Eriksson is the pulmonary physician responsible for the lung transplantation programme at the University Hospital of Lund; and Lars Algòsson was the chief anaesthesiologist in the thoracic intensive-care unit.

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References