

Transplantation of Lungs From Non-Heart-Beating Donors After Functional Assessment Ex Vivo

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Background. If lungs from patients dying of heart attacks are to serve as donor organs in a safe way, their function should be properly assessed before transplantation. The aim of this study was to investigate donor lung function evaluation in a realistic large animal model.

Methods. Twelve 60-kg pigs were used. Five minutes after ventricular fibrillation was induced, cardiopulmonary resuscitation was initiated and maintained for 20 minutes. After a 10-min hands-off period, heparin was administered through a central venous catheter followed by 20 chest compressions. Intrapleural cooling was initiated after 65 minutes of warm ischemia. Cooling proceeded for 6 hours within the cadaver, after which lung function was assessed ex vivo. Recipient pigs underwent left lung transplantation followed by right pneumonectomy, thus making these animals 100% de-

pendent for their survival on the function of the donor lungs.

Results. The assessment showed that all lungs had adequate function to serve as donor lungs. All recipient animals were in good condition during the 24-hour observation period after the operation. The blood gas function did not differ significantly from that in the healthy donor animals before induction of ventricular fibrillation; pulmonary vascular resistance was within normal range.

Conclusions. Lungs from non-heart-beating donors topically cooled in situ for 6 hours after 65 minutes of warm ischemia were assessed ex vivo and found to have normal function. They were then transplanted and retained normal function during a 24-hour observation period.

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About a third of all deaths in the western world are caused by ischemic heart disease. Reported estimate are that 375,000 persons in Europe [1] and 275,000 in the United States [2] undergo sudden cardiac arrest yearly. Out-of-hospital cardiac arrest accounts for about half of all deaths due to cardiovascular disease [2]. If lungs from patients dying after sudden cardiac arrest are to serve as donor organs in a safe way in clinical lung transplantation, their function should be properly assessed before transplantation.

We have previously described how a lung from a non-heart-beating donor was successfully transplanted into a patient with end-stage pulmonary disease [3]. The donor was a 54-year-old man dying of acute myocardial infarction after failed cardiopulmonary resuscitation (CPR). The next of kin gave permission to cool the lungs within the intact body, and intrapleural cooling was started 65 minutes after death. After 3 hours of topical intrapleural cooling, the heart-lung block was excised and the lung function was assessed ex vivo with a modified heart-lung machine. After a cold preservation period of 8 hours, the right lung was successfully transplanted into a 54-year-old woman with chronic obstructive pulmonary disease. The ethics and experiments

making this operation possible have been published elsewhere [3–11].

The aim of the present study was to describe in detail the method used for ex vivo assessment of lung function. To make the study clinically relevant, a large animal model was used, enabling use of exactly the same equipment as in the clinical case. The experiment was designed to simulate a typical situation in which transplantation of a topically cooled lung from a non-heart-beating donor is considered, after first testing its function. If the function is found to be satisfactory, one lung will be transplanted into a recipient animal followed by contralateral pneumonectomy, thereby making the recipient animal 100% dependent for its survival on the function of the donor lung. By comparing the lung function measurements obtained before induction of cardiac arrest in the donor animals with those obtained ex vivo and after transplantation, the function of the same lung can be followed throughout the experiment. Thus we can judge if the ex vivo assessment correctly predicts the posttransplantation function.

Material and Methods

The experimental design is shown in Table 1.

Animals and Anesthesia

Twelve outdoor free-ranging domestic pigs with a mean weight of 63 ± 2 kg (range, 61 to 66 kg) were used (6

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Table 1. Experimental Design

Time	Events
20 min	Baseline values
5 min	Ventricular fibrillation Ventilator disconnected, tracheal tube open to air
20 min	External chest compressions Ventilation with 100% oxygen
10 min	Hands off Ventilator disconnected, tracheal tube open to air Declaration of death
1 min	Heparin 25,000 IU administered by a central venous catheter 20 external chest compressions
45 min	Hands off
10 min	Placement of intercostal tubes Initiation of cold intrapleural Perfadex-infusion
6 h	Intrapleural topical cooling with Perfadex to 12°C
45 min	Excision of the heart-lung block Placement of catheters and cannulas necessary for ex vivo assessment
40 min	Controlled cold reperfusion, gradually warming the lungs to 37°C Perfusion pressure ≤ 20 mm Hg Blood flow ≤ 4.0 L/min
20 min	Assessment of lung function at 37°C
10 min	Core cooling of the lungs to 20°C
3 h	Topical ECMO at 12°C
2 h	Left pneumonectomy, left lung transplantation
30 min	Right pneumonectomy (6 h after transplant)
24 h	Final assessment after 24 hours of reperfusion

ECMO = extracorporeal membrane oxygenation.

donors and 6 recipients). The animals were treated in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication 85-23, revised 1985). The Ethical Committee of the University of Lund approved the study.

All animals received premedication with intramuscular ketamine (Ketalar, Parke-Davis, Morris Plains, NJ), 15 mg/kg body weight and xylasin (Rompun, Bayer, Gothenburg, Sweden) 0.2 mg/kg. For anesthesia induction sodium thiopental (Pentothal; Abbot, North Chicago, IL) 5 mg/kg body weight and atropine (Atropine; Kabi Pharmacia, Uppsala, Sweden) 0.02 mg/kg were given intravenously. Pancuronium (Pavulon, Organon Teknika, Boxel, The Netherlands) was given intravenously before the tracheotomy and introduction of the tracheal tube (Portex #8; Hythe, Kent, England). During the experiment, anesthesia was maintained using a mixture of 8 g ketamine, 30 mg midazolam (Dormicum, Roche, Basel, Switzerland), and 300 mg pancuronium bromide dissolved in 5% glucose to 500 mL as a continuous infusion of 30 mL/h.

Intermittent injections of fentanyl (Leptanal, Lilly, France) 0.02 μ g/kg were also given throughout the experiments. The animals were ventilated with a Siemens Servo ventilator 300 (Siemens-Elema AB, Solna, Sweden). A vol-

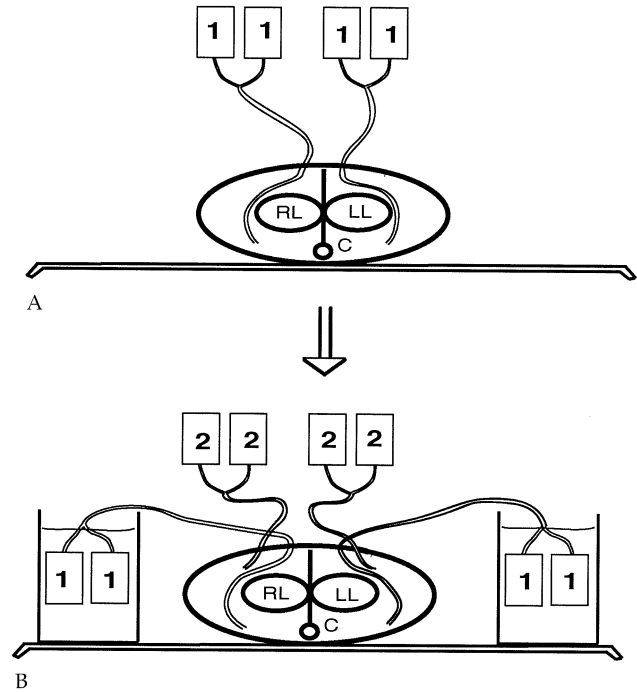


Fig 1. Topical cooling of lungs in situ. (A) After the first pair of Perfadex bags (1) have been emptied into the pleural space on each side, (B) a second pair of bags (2) are infused, while the first pair (1) are immersed in ice water in containers placed so that the water surface is 5 cm higher than the most anterior part of the thorax cavity. By switching every time the infusion bags are empty, an efficient cooling is obtained. It is important that the tracheal tube is open to the air during these procedures. (C = spinal column; LL = left lung; RL = right lung.)

ume-controlled, pressure-regulated ventilation of 10 L/min (20 breaths/min; positive end-expiratory pressure [PEEP], 8 cm H₂O; inspired oxygen fraction, 0.5; max inspiratory pressure, 30 cm H₂O) was used, if not otherwise stated.

A Swan-Ganz catheter was introduced into the pulmonary artery. Catheters were placed in the arch of the aorta through the right carotid artery and in the right atrium through the right internal jugular vein. The pig was kept in a supine position for 20 minutes, and base line hemodynamic values and blood gases were recorded using a data acquisition system (Testpoint; Capital Equipment Corp, Billerica, MA).

Cardiopulmonary Resuscitation of the Donor Pigs

Ventricular fibrillation was induced by electrical stimulation and the ventilator (fraction of inspired O₂ = 0.21) was disconnected. The animal was left untouched with ventricular fibrillation for 5 minutes. Cardiopulmonary resuscitation was then initiated. Two surgeons working in 3-min intervals applied external chest compressions and ventilation was given with 100% oxygen with the ventilator. After 20 minutes, another blood gas sample was taken and the CPR was interrupted. No animal showed signs of return of spontaneous circulation, and after a 10-min hands-off period, the animals were de-

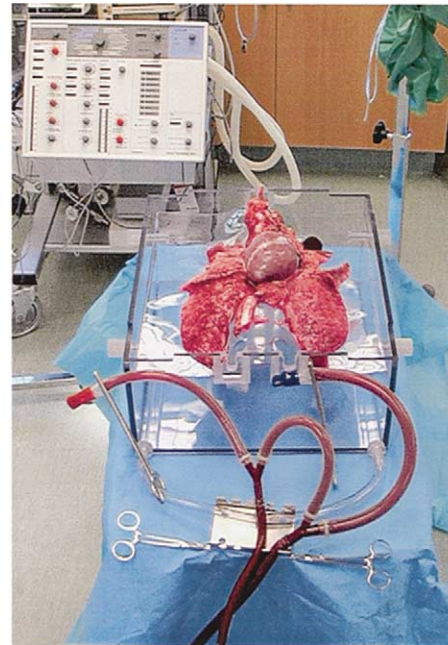
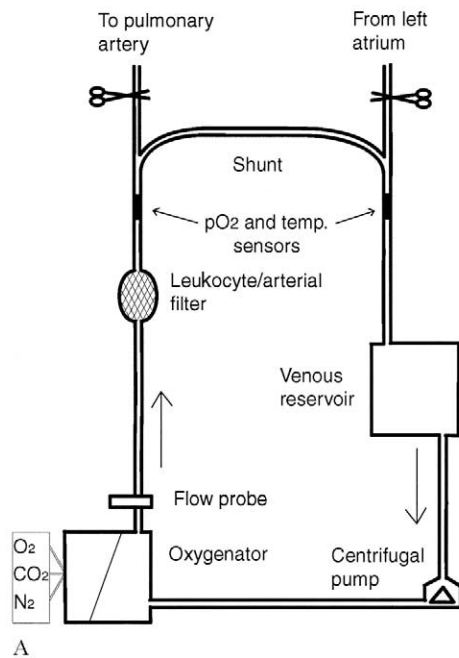


Fig 2. Assessment of lung function *ex vivo*. (A) Schematic of the evaluation system. (temp. = temperature.) (B) The heart-lung block is placed in the evaluation box ready for cannulation.

clared dead. Heparin 25,000 IU was then given through the central venous catheter, followed by 20 external chest compressions. The tracheal tube was disconnected from

the ventilator and exposed to air, a temperature probe was inserted deep into a bronchus through the tracheal tube, and another 45-minute hands-off period was initiated.

Intrapleural Topical Cooling

The thorax was covered with a surgical towel kit used for caesarian section. A 1-inch stab wound was made intercostally on each side, causing bilateral pneumothorax. Infusion of cold buffered Perfadex with added calcium chloride (1 mmol/L) from 2.8-L plastic bags (Vitrolife AB, Gothenburg, Sweden) was initiated 65 minutes after failed resuscitation through an intercostal tube (Portex 28F, Hythe, UK) placed deeply into each pleural space (Fig 1A). The infusion was run until the solution started to flow out of the wound, then a second intercostal tube was introduced superficially into the pleural space on each side through the original stab wound, which was closed by towel clips. The advantage of using towel clips to close the wound is that they can be removed quickly in case of a need to check the position of the intercostal tubes. Two other cold Perfadex bags were connected to the second pair of intercostal tubes, while the two empty Perfadex bags were placed in a container of ice water, situated with the water surface 5 cm higher than the highest point of the thorax of the donor (Fig 1B). This setup ensures that the lungs will be compressed by cold Perfadex from all sides with a pressure of about 5 cm H₂O, transforming the spongy lung tissue into a semisolid tissue, which can be cooled more efficiently. The tracheal tube must be open to the air, so that intrapulmonary air can escape when the

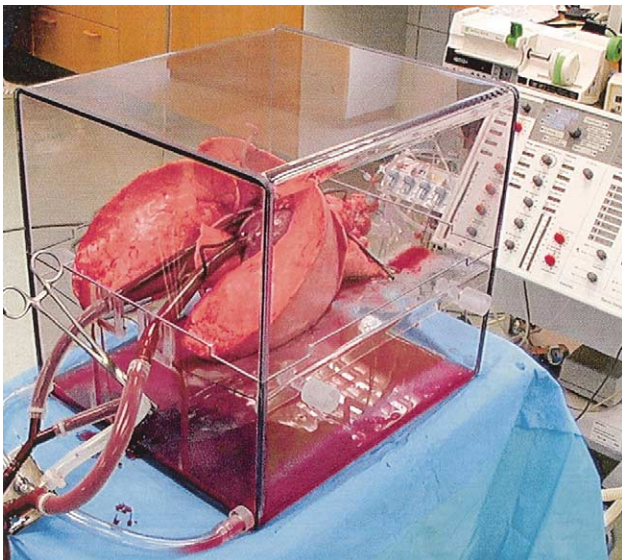


Fig 3. When the temperature of the blood coming out from the lungs is 32°C, ventilation of the lungs is initiated. At 37°C, full flow is run with a maximal mean pulmonary arterial pressure of 20 mm Hg. The lungs are ventilated with an inspired oxygen fraction varying between 0.21 and 1.0, with a respiratory minute volume 2.5 times the perfusion flow, and with a positive end-expiratory pressure of 5 to 8 cm H₂O. After the evaluation, topical extracorporeal membrane oxygenation is performed within the same container.

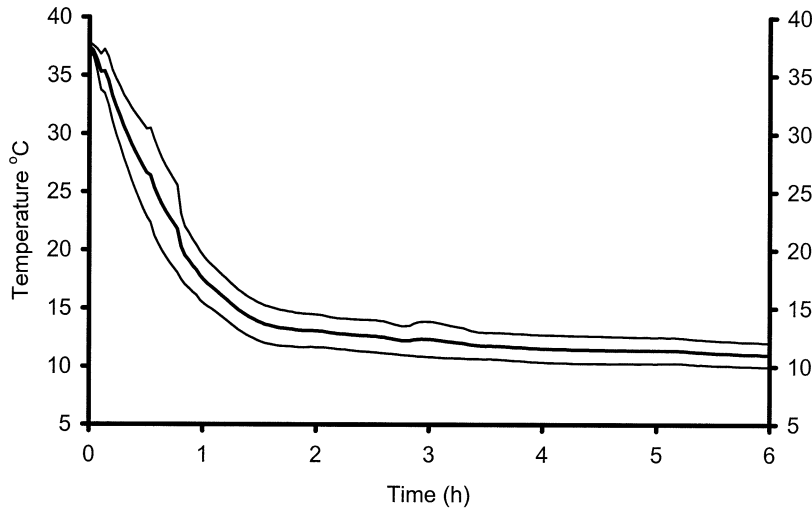


Fig 4. Topical cooling of lungs. The intraluminal bronchial temperature probe was introduced through the tracheal tube deep into the bronchial tree. Mean \pm SEM, n = 6.

lungs are compressed by the cold Perfadex solution. The intratracheal cuff must be well filled, to eliminate the risk of stomach contents flowing over into the bronchi. The caesarian section cover kit effectively eliminates all spilling of Perfadex solution onto the operating table.

Preparation of the Extracorporeal Perfusion Circuit

The ex vivo lung function assessment system (Fig 2A) consists of a hard-shell reservoir (VKH 4201; Jostra AG, Hirrlingen, Germany), a centrifugal pump (Biomedicus, Bio-Console 550; Electromedics Inc, Grand Rapids, MI), a membrane oxygenator with a built in heat-exchanger (Qadrox HMO 1011; Jostra AG), and a leukocyte/arterial filter (LG 6; Pall Newquay, Cornwall, UK). A flow probe (Bio Probe TX50; Electromedics Inc) and pO₂ (Polytrode Oxygen Sensor; Polystan, Værløse, Denmark) and temperature (Space Labs Medical Inc, Redmond, WA) sensors are also included. The system was primed with 1.5 L of the lung evaluation-preservation solution (VT029; Vitrolife AB) mixed with red cells to a hematocrit of 15% \pm 3%. This solution is a buffered, extracellular solution composed to have an optimal colloid osmotic pressure so that physiologic pressure and flow can be maintained without development of pulmonary edema. Separate pigs with the same blood group were used to obtain sequestered red blood cells, which were filtered through a leukocyte filter (PL 100 KLE; Pall Newquay) before being mixed with the solution. Imipenem 0.5 g (Tienam, Merck Sharp & Dohme, Sollentuna, Sweden), insulin 20 IU (Actrapid, Novo Nordisk, Bagsvaerd, Denmark), and heparin 10,000 IU (Leo Pharma, Malmö, Sweden) were also added to the solution. The pH in the mixed solution was adjusted to a physiologic level with isotonic trometamol (Addex-THAM, Kabi, Sweden). Gas was supplied to the membrane oxygenator through two gas mixers, one for oxygen/nitrogen and one for oxygen/carbon dioxide. The flow of the three gases was adjusted until blood gas values resembling a normal mixed venous blood gas were obtained in the evaluation solution, which was recirculated in the system.

Ex Vivo Assessment of Donor Lung Function

After the 6-hour cooling period, a median sternotomy was done and the heart-lung block was excised and placed in a plastic container (Fig 2B). The right ventricle and left atrium were opened widely, and all blood sucked out. The pulmonary artery and left atrium were inspected carefully to determine the presence of coagulated blood. The pulmonary artery was cannulated via the right ventricle through the pulmonary valves with a 28F wire-reinforced cannula, and a tourniquet was placed around the proximal pulmonary artery and tightened around the cannula. The left atrium was cannulated through a stab wound in the apex of the left ventricle with a 36/48F two-stage venous cannula. The narrow cannula tip was cut away and the thick part was positioned with its opening in the middle of the left atrium. A pediatric feeding catheter for pressure measurement was placed in the left atrium, which was closed using a running 4-0

Table 2. Hemodynamics and Gas Exchange Function of Donor Lungs^a

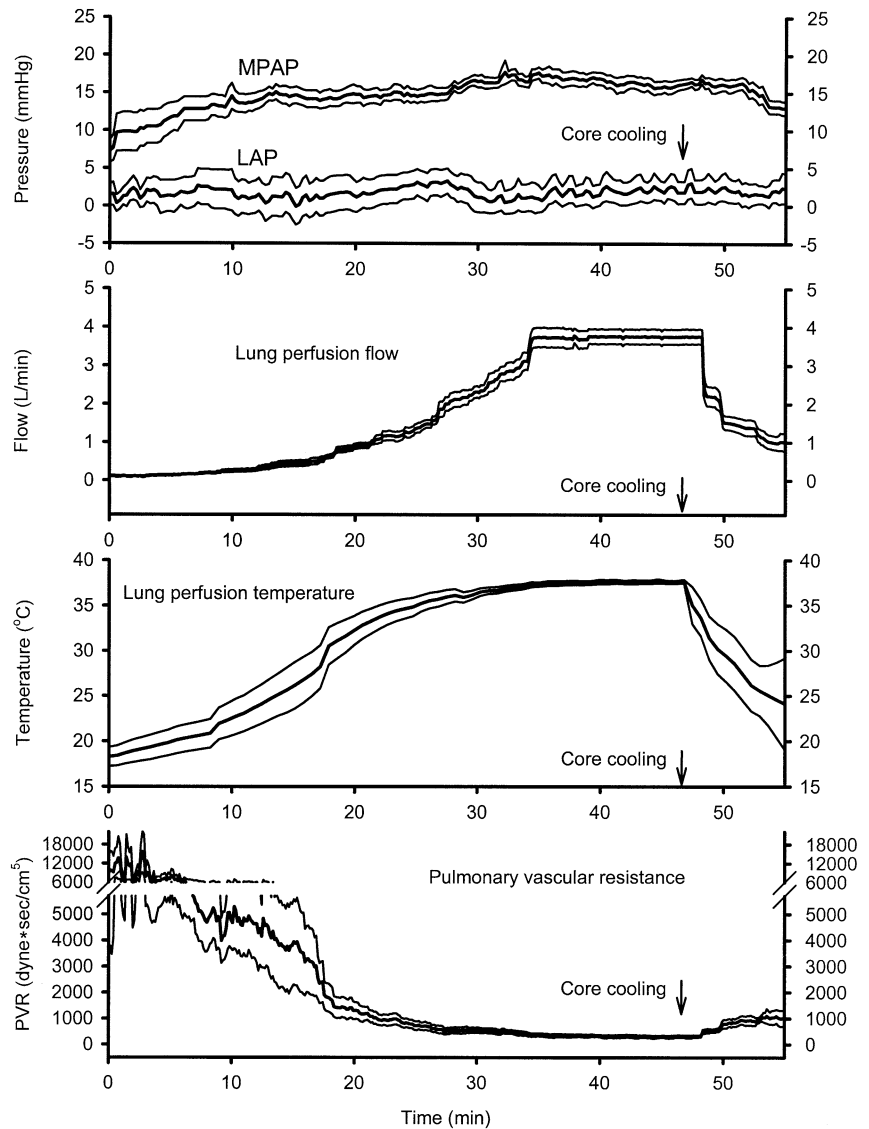
	In Vivo	Ex Vivo	p <
Pulmonary arterial flow (L/min)	4.9 \pm 0.1	3.8 \pm 0.1	0.05
Mean pulmonary arterial pressure (mm Hg)	14 \pm 1	17 \pm 1	
Pulmonary vascular resistance (dynes \cdot s \cdot cm ⁻⁵)	161 \pm 12	310 \pm 15	0.05
Hemoglobin (g/L)	103 \pm 3	53 \pm 5	0.05
Hematocrit (%)	32 \pm 1	15 \pm 2	0.05
PaO ₂ (kPa)	38 \pm 2	41 \pm 5	
Paco ₂ (kpa)	5.0 \pm 0.5	4.4 \pm 0.3	
ETco ₂ (kpa)	4.8 \pm 0.5	4.0 \pm 0.2	
Paco ₂ - ETco ₂	0.2 \pm 0.1	0.4 \pm 0.2	

^a Inspired oxygen fraction = 0.5.

Values are mean \pm SEM, n = 6.

ETco₂ = end tidal carbon dioxide pressure; Paco₂ = arterial carbon dioxide pressure (tension); Pao₂ = arterial oxygen pressure (tension).

Fig 5. Ex vivo assessment of lung hemodynamics. Mean \pm SEM, $n = 6$. (LAP = left arterial pressure; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.)



Prolene (Ethicon, Somerville, NJ) suture; a similar catheter was placed in the pulmonary artery.

The pulmonary artery cannula was connected to the corresponding tube of the extracorporeal circuit, the air was removed, and the shunt of the circuit clamped. A low flow perfusion (100 mL/min) at 25°C was initiated through the lungs. The first 200 mL of blood exiting the cannula in the left atrium was discarded, and then the cannula was connected to the circuit. The lungs were gradually warmed by increasing the temperature of the evaluation solution, and when the temperature of the solution exiting the left atrium was 32°C, ventilation (1 L/min) was started. The pump flow was gradually increased, but the pulmonary artery pressure was never allowed to exceed 20 mm Hg. If a flow of 4 L/min was reached, it was fixed at that rate regardless of the pulmonary artery pressure, if it was less than 20 mm Hg. When the temperature of the solution exiting the left atrium was 37°C, full ventilation was given and the PEEP was

temporarily increased to eliminate atelectases. Then the ventilation rate was fixed at 2.5 times higher than the perfusion flow, with a PEEP of 8 cm H₂O and an inspired oxygen fraction of 0.5 (Fig 3). When a steady state was reached, blood gases and hemodynamics were registered, after which the perfusion flow and ventilation were reduced while core cooling of the lungs to 20°C was accomplished with the heater-cooler unit. Perfusion was then stopped and the cannulas were removed. The left lung was dissected and prepared for transplantation. It was immersed in a semi-inflated state in the evaluation solution diluted by Perfadex to a hematocrit of about 5%. This solution was run continuously (4 L/min) through the oxygenator at 12°C (topical extracorporeal membrane oxygenation [ECMO]).

Recipient Operation

A recipient of similar size and blood group as the donor animal was anesthetized and prepared as described

above. The transplantation was done as described previously [5]. Right pneumonectomy was performed 6 hours after the transplantation. After 24 hours of reperfusion, a final assessment of the lung function was made before the pigs were killed.

Statistics

Values are given as mean \pm standard error of the mean (SEM). Wilcoxon's signed rank test was used, and a *p* value of less than 0.05 was considered as statistically significant.

Results

Circulation During Cardiopulmonary Resuscitation

The end tidal carbon dioxide pressure (ETCO₂) varied between 2.1 and 2.5 kPa during the 20-minute CPR period and the arterial oxygen tension measured at the end of the resuscitation was 58 \pm 9 kPa. The arterial pressure produced by the chest compressions was in the range of 60 to 80 mm Hg.

Intrapleural Topical Cooling

During the first hour, the intrabronchial temperature decreased by about 20°C, ie, by about 0.3°C/min (Fig 4). At the end of the second hour the temperature had decreased to less than 15°C and was maintained around 12°C by adjusting the rate at which the position of the bags was shifted (Fig 1).

In Vivo Versus Ex Vivo Assessment of Lung Function

No significant differences were noted in blood gases when comparing the values obtained in vivo before the induction of ventricular fibrillation with those obtained ex vivo (Table 2). As seen in Figure 5, the peripheral vascular resistance (PVR) was high during the initial cold ex vivo perfusion of the lungs, and warming the lungs to a core temperature of 37°C took 35 minutes.

The PVR was significantly lower in vivo compared with the ex vivo value obtained at normothermia despite the significantly lower hematocrit used during the ex vivo evaluation (Table 2).

Topical Extracorporeal Membrane Oxygenation During Storage Until Transplantation

Maintaining the temperature in the oxygenated solution surrounding the lung at 12°C was easy because of the heater-cooler unit, in accordance with the research protocol design.

Assessment of Lung Function After Transplantation

All animals were in excellent condition throughout the experimental period. The gas exchange function did not differ significantly from base line (Tables 2 and 3, Fig 6). The PVR was around 400 dynes \times s \times cm⁻⁵ (Fig 7), ie, within the normal range for sham-operated animals who had undergone only right pneumonectomy [5].

Table 3. Hemodynamics and Gas Exchange Function 24 Hours After Left Lung Transplantation and Right Pneumonectomy

	Inspired Oxygen Fraction ^a		
	0.5	1.0	0.21
Hematocrit (%)	33 \pm 2	32 \pm 1	33 \pm 2
Pulmonary arterial flow (L/min)	5.4 \pm 0.7	5.3 \pm 0.8	5.4 \pm 0.6
Mean pulmonary arterial pressure (mm hg)	33 \pm 4	34 \pm 4	33 \pm 4
Pulmonary vascular resistance (dynes \cdot s \cdot cm ⁻⁵)	355 \pm 72	351 \pm 73	378 \pm 88
Pao ₂ (kpa)	33.5 \pm 2.2	65.8 \pm 3.0	9.7 \pm 1.2
Pvo ₂ (kpa)	5.6 \pm 0.5	6.2 \pm 0.4	4.7 \pm 0.3
Sao ₂ (%)	100 \pm 0	100 \pm 0	100 \pm 0
Svo ₂ (%)	76 \pm 3	76 \pm 5	64 \pm 7
Pvco ₂ (kpa)	6.5 \pm 0.6	6.8 \pm 0.7	6.6 \pm 0.6
Paco ₂ (kpa)	5.8 \pm 0.6	5.7 \pm 0.6	5.7 \pm 0.3
ETCO ₂ (kpa)	4.8 \pm 0.3	4.6 \pm 0.5	5.0 \pm 0.3

^a Ventilation settings: Tidal volume = 500 mL, frequency 20 breaths/min, positive end-expiratory pressure = 8 cm H₂O.

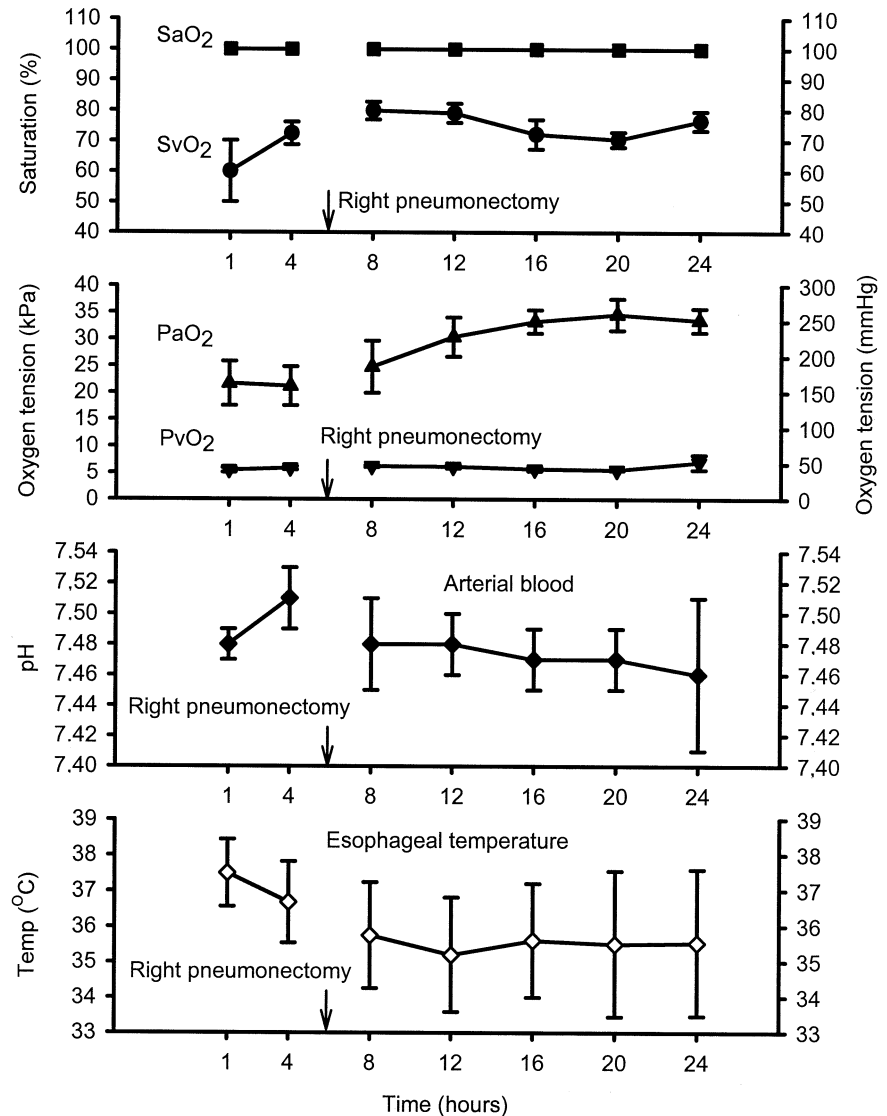
Values are mean \pm SEM, n = 6.

ETCO₂ = end tidal carbon dioxide pressure; Paco₂ = arterial carbon dioxide pressure (tension); Pao₂ = arterial oxygen pressure (tension); Pvco₂ = venous carbon dioxide pressure (tension); Pvo₂ = venous oxygen pressure (tension); Sao₂ = arterial oxygen percent saturation; Svo₂ = mixed venous oxygen percent saturation.

Comment

The method used in this study to evaluate lung function ex vivo was identical to that used when we transplanted the first lung from a patient dying of acute myocardial infarction [3]. With this method, lungs can be evaluated ex vivo without edema formation. The prerequisite is that the perfusion is done at normothermia with an adequate perfusion solution and a perfusion pressure of at most 20 mm Hg. Cold perfusion creates a high PVR and should be used with caution. We have found that a hematocrit of around 15% is optimal; with higher hematocrit values the perfusion pressure needed to get an acceptable flow will be higher. We think the increased PVR seen in the ex vivo perfusion is due mainly to the nonpulsative flow, because the same lungs after transplantation had a normal PVR [5]. If the ex vivo assessment shows that lung function is normal, as in the present study, the evaluation is interrupted, and the perfusion system is used for core cooling of the lungs. The perfusion pressure should be monitored continuously, and kept below 20 mm Hg by reducing the flow as the lung temperature decreases. When 20°C is reached, it is safer, due to the high PVR, to continue the cooling topically. The lung evaluation solution is an excellent preservation solution as well. By keeping the lungs immersed at 8°C by topical ECMO, a new evaluation can be repeated every 24 hours using fresh evaluation solution each time. In this way excellent lung preservation beyond 24 hours is obtained. If the lung transplantation can be completed within a few hours of donor death, as in the present study, we have

Fig 6. Blood gases during the first 24 hours of reperfusion. Right pneumonectomy was done after 6 hours. Inspired oxygen fraction = 0.5. Mean \pm SEM, n = 6. (PaO₂ = arterial oxygen pressure [tension]; PvO₂ = venous oxygen pressure [tension]; SaO₂ = arterial oxygen percent saturation; SvO₂ = mixed venous oxygen percent saturation.)



found that 12°C is an adequate topical ECMO temperature.

Besides the blood gases and PVR, a most valuable measurement to follow during the ex vivo evaluation is the difference between arterial carbon dioxide pressure and ETco₂. With perfect perfusion of the lungs, this difference is close to zero. If the difference is more than 1, the PEEP should be temporarily increased to eliminate possible atelectases and a maximum perfusion flow, creating a perfusion pressure of 20 mm Hg, should be used. If the CO₂ gradient does not decrease to less than 1 under these conditions, suboptimal perfusion, eg, as a result of pulmonary emboli, should be suspected and such lungs should not be transplanted. In this situation, thrombolytic drugs may be added to the evaluation solution to check if the perfusion obstacles thereby are eliminated.

If there is doubt that the lungs can be used for transplantation, the evaluation equipment could be used to perform a test transplantation ex vivo. The potential

recipient is then cannulated percutaneously and perfusion of the donor lungs is initiated by pumping venous blood from the recipient through the donor lungs and then back to the recipient through the oxygenator equipped with a heat exchanger (veno-venous ECMO). By this technique we have revitalized "bad" porcine donor lungs within 6 hours of reperfusion with fresh blood from the potential recipient, and thereafter successfully transplanted one lung.

We performed on the pigs for 20 minutes and administered heparin 10 minutes after we had stopped the resuscitation. During this short period of circulatory arrest we think the risk of blood coagulation within the lungs is minimal; in the present study we did not observe any clots. The low gradient between the arterial CO₂ pressure and ETco₂ values confirmed the lack of any major ventilation-perfusion mismatch. The time period of 10 minutes was chosen to follow the Maastricht guidelines for a clear 10-min interval between cessation of

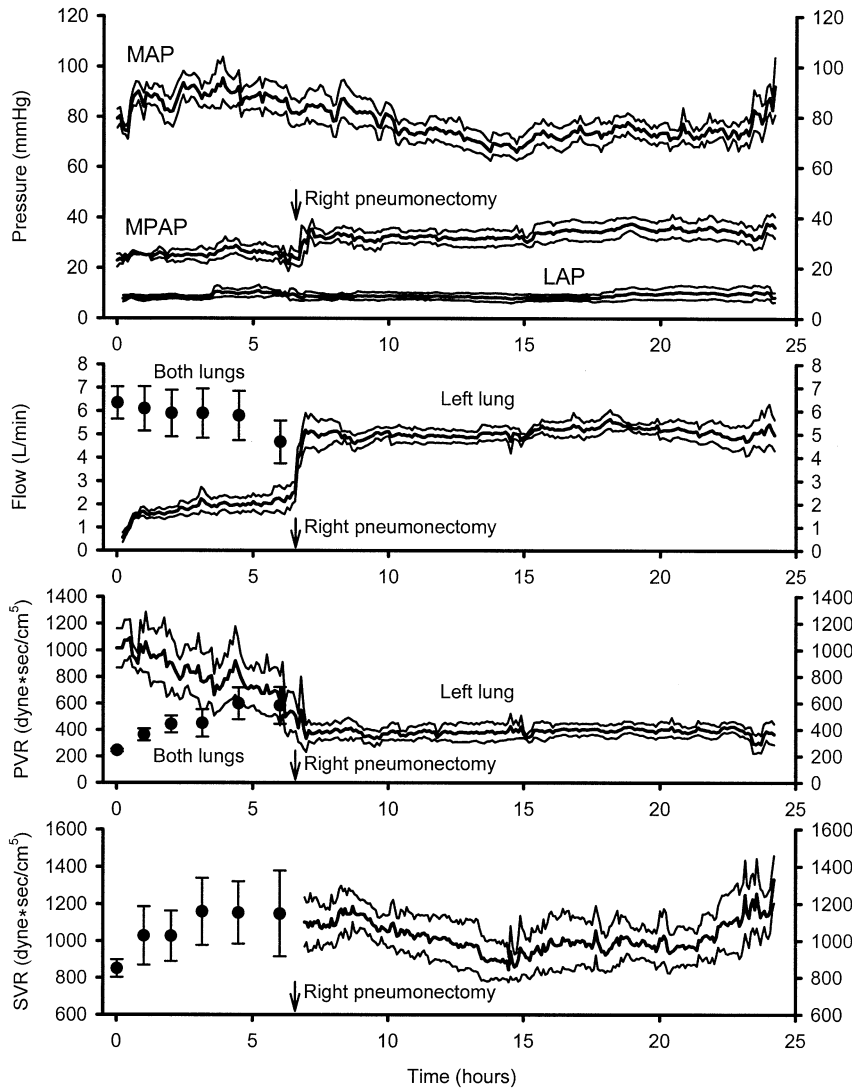


Fig 7. Hemodynamics during the first 24 hours of reperfusion. Thermodilution (Swan-Ganz catheter) was used to calculate cardiac output during the first 6 hours. Right pneumonectomy was done after 6 hours, after which the cardiac output was measured continuously through a flow probe on the left pulmonary artery. Mean \pm SEM, $n = 6$. (LAP = left arterial pressure; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.)

resuscitation and any procedures solely for organ preservation [12].

In our clinical protocol, anticoagulation may be given to the deceased without permission from the next of kin, but nothing else is allowed to facilitate organ donation. Recently, a clinical prospective study was published indicating a better survival of administering thrombolytic therapy combined with heparin to patients with out-of-hospital cardiac arrest when return of spontaneous circulation was not achieved within 15 minutes [13]. Two other clinical studies have been published recently demonstrating the efficacy of therapeutic hypothermia for treating cardiac arrest [1, 14, 15]. Someday, patients who are declared dead after failed resuscitation may be both anticoagulated and cooled. Because of this, more time is obtained to find out if organ donation is suitable.

We are convinced that using lungs from non-heart-beating donors has the potential to eliminate donor shortages if the ethical questions can be solved in full agreement with the general public [3]. The ethical issues that arose in connection with our first clinical case were

recently discussed in an influential American bioethics journal and the concept found to be sound [16].

Ex vivo assessment of donor lungs followed by topical ECMO may transform clinical lung transplantation into a procedure in which only properly evaluated lungs of high quality will be transplanted. Ex vivo assessment and treatment of lungs will also open up the possibility for a second positive judgment of initially rejected donor lungs from beating heart donors.

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INVITED COMMENTARY

Steen and colleagues present a very well documented animal study investigating their group's methods to functionally assess the viability of lungs donated by nonheartbeating donors. The rigorous and meticulous protocol presented and the group's successful use of this technique in a human case support the continued study and possible wide application of these protocols. However, the application of ex vivo testing and preservation of nonheartbeating donor lungs to other institutions and the ability of other institutions to support these services may prove to be more challenging. Many practical obstacles to the wide use of this type of donation may limit the ability of these techniques to significantly close the widening gap between organs donated and the numbers of patients awaiting lung transplantation.

However, lessons already learned in their clinical and experimental studies could immediately improve the ability of multiple institutions to maximize the use of heartbeating donors. The use of lungs that in the past have been considered unacceptable for lung transplantation could be extended if previously defined "poor" quality lungs are found safe for transplant. Many groups are now pushing the previous bounds of the standard criteria of assessing lungs for donation, and the use of these so-called marginal donors could have an immediate effect on alleviating the donor shortfall. The use of such lungs can now be considered, as techniques of lung preservation and controlled leukocyte lung reperfusion appear to be decreasing the immediate dangers of significant acute reperfusion injury. The possible addition of

other techniques, such as topical ECMO for extended preservation and decreased lung inflation during storage (semisolid storage), could further enhance both the supply and function of donor lungs. Presently a working group, identified with the help of the International Society for Heart and Lung Transplant, is developing a lung donor quality score to quantify many aspects of donor lungs. With the cooperative input of multiple transplant centers, this prospective database will be correlated with outcome results and may guide the transplant community to better utilize the potential supply.

The application of ex vivo lung assessment has the potential both to expand the use of heartbeating donors and to develop the practice of lung donation from non-heartbeating donors. Cooperative multi-institutional work to enhance the utilization of heartbeating donors and to further investigate the use of nonheartbeating donors are crucial for the continued growth and development of lung transplantation. To this end, the pioneering work of Dr Steen and his colleagues is an important contribution.

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