ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL PRE-CLINICAL SCIENCE

A simplified preservation method for lungs donated after cardiac death

Andreas Wallinder, MD,[a] Christoffer Hansson, MSc,[b] Stig Steen, MD, PhD,[c] Aziz A. Hussein, MD,[d] Trygve Sjöberg, PhD,[c,e] and Göran Dellgren, MD, PhD[f]

From the Departments of [a]Cardiothoracic Surgery and [b]Cardiothoracic Anaesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg; [c]Department Cardiothoracic Surgery, Lund University Hospital, Lund; Departments of [d]Pathology and Cytology and the [e]Transplant Institute, Sahlgrenska University Hospital, Gothenburg; and [f]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

KEYWORDS:
lung transplantation;
lung preservation;
donation after cardiac death;
ex vivo lung perfusion

Background
The shortage of donor lungs restricts the number of lung transplantations that can be performed. However, extension of the donor pool using organs donated after cardiac death (DCD) could potentially increase the number of patients who undergo transplantation. To establish acceptance among hospital personnel and the donor's next of kin for the uncontrolled DCD procedure we proposed a simplified preservation regime for intrapleural cooling of the donor lungs.

METHODS: In an uncontrolled DCD model, 12 pigs were randomized to intrapleural lung cooling using either a standard method with two bilateral chest tubes and intermittent pleural fluid exchanges, or a simplified, less-invasive method with a single bilateral chest tube and filling of the pleural space without fluid exchange. Lungs were explanted and graft function was assessed during ex vivo lung perfusion (EVLP) and by histologic examination.

RESULTS: Although the mean temperature after 120 minutes of intrapleural cooling was significantly higher in the lungs cooled using the simplified method (25.9°C vs 13.5°C), this did not affect the oxygenation capacity, pulmonary vascular resistance or dynamic compliance of the lungs, as recorded during EVLP. Furthermore, no differences were found between the lungs preserved by the two methods with respect to the wet/dry ratio, levels of myeloperoxidase in bronchoalveolar lavage, or at histologic examination.

CONCLUSIONS: The simplified technique for DCD lung cooling results in a higher preservation temperature but does not affect lung function during EVLP, which implies that this less invasive method can be used in the uncontrolled DCD setting. This is another step forward in the development of a simplified preservation routine for DCD.

J Heart Lung Transplant 2014;33:528–535

Limitations related to the availability of donor lungs restrict the number of lung transplantations that can be performed. Donation after cardiac death (DCD), also referred to as non–heart-beating donation (NHBD), has the potential to increase the pool of organs available for lung transplantation. In uncontrolled DCD, the donor is dead upon arrival at the hospital or has undergone unsuccessful resuscitation in the emergency room. Steen et al introduced lung transplantation from an uncontrolled DCD donor in 2001. The lung function was evaluated during ex vivo

Reprint requests: Andreas Wallinder, MD, Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg SE-413 45, Sweden. Telephone: +46 31 342 89 86. Fax: +46 31 41 79 91.
E-mail address: andreas.wallinder@vgregion.se

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2014.01.854

perfusion before the transplantation.[1] Later, de Antonio et al implemented uncontrolled DCD in clinical practice without ex vivo evaluation before transplantation.[2] In the latter study, lung transplantation after uncontrolled DCD was associated with a higher incidence of graft dysfunction than what could be expected in donation from brain-dead donors.[3] This may have been due to the prolonged period of warm ischemia, the inflicted traumatic lung injury in conjunction with resuscitation, or the fact that the donor history and medical status were partially unknown at the time of transplantation.

Good lung preservation in combination with functional evaluation during ex vivo lung perfusion (EVLP) are of utmost importance in uncontrolled DCD lung transplantation.[4] Legislation in Sweden prohibits intervention in organ preservation before the declaration of death. Intervention after death should be kept at a minimum to facilitate acceptance from next-of-kin for the uncontrolled DCD procedure. A well-educated staff and optimal logistics are essential for counselling the next-of-kin and for limiting the warm ischemic time.[1,2] After cessation of resuscitation, a "hands-off" period of 60 minutes is appropriate, during which death must be declared. An ischemic time of >60 minutes calls for some type of lung preservation.[5–7]

Cold storage of donor lungs in fluid at 8°C has been shown to provide excellent lung preservation for 12 hours in pigs when monitored at 24 hours after lung transplantation. This finding established the possibility of preserving DCD lungs in situ by infusion of cold solution into the pleural cavities.[8] Techniques for intrapleural cooling include intermittent shifting of fluids[4,9] and the use of pumps to circulate the cold fluid.[6] Both methods require professional expertise and may not allow for the next-of-kin to stay with their deceased relative. In a syngeneic DCD rat model, Wierup et al simplified in situ cooling by introducing a single cold (4°C) intrapleural infusion which preserved the lungs at 25°C for 2 hours in situ. The left lung was then transplanted and evaluated after 5 weeks with excellent gas exchange and bronchial healing.[10,11]

The aim of this study was to investigate, in an experimental large-animal model relevant for the clinical situation, if a single intrapleural infusion of cold solution similar to the technique described by Wierup et al can provide adequate lung preservation. If so, this would facilitate the initial handling of the DCD donor and care of the next of kin.

Methods

Animal model

All animals received care in compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and the "Principles of Laboratory Animal Care," formulated by the National Society for Medical Research. The ethics committee of the University of Lund approved the study.

Swedish domestic pigs ($n = 12$) received pre-medication with an intramuscular injection of ketamine at 15 mg/kg body weight (Ketalar Pfizer AB, Sollentuna, Sweden) and xylazine 0.2 mg/kg (Rompun vet Bayer, Leverkusen, Germany) in their stables. An intravenous (IV) catheter was placed in the ear and atropine sulfate 25 μg/kg (Atropin Mylan, Stockholm, Sweden) was given to prevent excessive airway secretion together with pentothal natrium 250 mg (Hospira Enterprises BV, Hoofddorp, The Netherlands). The animal was transferred to the operating room and placed in a supine position. Tracheal intubation was performed after IV administration of 4 mg pancuronium bromide (Pavulon NV Organon, Oss, The Netherlands). Ventilation was maintained in a volume-controlled, pressure-regulated setting at a rate of 20 breaths/min with minute volume 150 ml/kg, maximum inspiratory pressure 30 mm Hg, positive end-expiratory pressure (PEEP) 5 mm Hg and fraction of inspired oxygen (FIO_2) of 0.5, using a servo ventilator (Siemens-Elema AB, Solna, Sweden). Anesthesia was maintained during the experiment with a solution of 8 g ketamine and 240 mg pancuronium bromide mixed in 500 ml of sodium chloride administered at a rate of 10 ml/h. Cut-down in the neck allowed placement of a central venous catheter into the right atrium through the right internal jugular vein and an arterial catheter into the aorta through the right carotid artery. A temperature probe was placed rectally. Baseline values of blood gases (ABL 725; Radiometer, Copenhagen, Denmark) were recorded.

DCD and lung preservation model

The timeline used for the DCD procedure is displayed in Table 1. Ventricular fibrillation (VF) was induced electrically with a needle penetrating the chest wall to the heart surface. The tracheal tube was disconnected from the ventilator when circulatory arrest was confirmed, and the animal was left untouched for 7 minutes. Cardiopulmonary resuscitation (CPR) was started (Lucas 2; Jolife, Lund, Sweden) at a rate of 100 compressions/min. Ventilation at 10 breaths/min was manually performed with a Ruben's bag connected to a tube with 15 liters/min of oxygen. CPR was stopped after 20 minutes. The animals were declared dead after an additional 10-minute "hands-off" period and randomized to either standard (STD) intrapleural cooling through two bilateral pleural chest tubes and intermittent fluid shifts, as described by Steen et al,[12] or by a simplified technique (SIMP). In the SIMP technique, one chest drain was inserted on either side of the thorax and the pleural space was filled with as much cold (6°C) fluid as

Table 1 Timeline for DCD Procedure

Time-point (min)	
0	Ventricular fibrillation
7	External mechanical chest compressions Ventilation with FIO_2 1.0 and respiratory rate 10 breaths/min
27	Hands-off period Tracheal tube disconnected and open to air
37	Declaration of death Randomization to either method of cooling
100	Placement of intercostal tubes and initiation of intrapleural lung cooling
220	Harvesting of lungs after ante- and retrograde flushing with Perfadex
~250	Lungs connected to EVLP machine and start of reconditioning followed by evaluation of lungs