Evaluation of Techniques for Lung Transplantation Following Donation After Cardiac Death

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Background. **Lung transplantation using "donation after cardiac death" donors is a potential means to alleviate the shortage of suitable donor lungs for transplantation, but the practicality and utility of the various possible techniques need to be clarified.**

Methods. **Using a dog model, we explored seven variations of standoff (ischemic) time (50 to 240 minutes), topical cooling (60 to 120 minutes), and flush cooling and cold storage (30 to 140 minutes) to mimic different human donor lung retrieval scenarios that can follow donation after cardiac death. The functional status of donation after cardiac death donor lungs was assessed initially with a 250 mL pulmonary arterial blood flush while ventilating with 100% oxygen and then on an ex-vivo perfusion rig for 120 minutes after retrieval.**

Results. **All lungs achieved an excellent pO_2/FiO_2 ratio ranging from 472 to 586 with stable pulmonary artery pressures and pulmonary vascular resistance and no net weight gain (952 ± 221 g versus 1,006 ± 235 g) during the 120-minute evaluation period. Initial blood flush correlated well with measured perfusion rig pO_2 at 30 minutes ($R^2 = 0.63$).**

Conclusions. **This canine study suggests that lungs donated after cardiac death are reproducibly useable for transplantation with ischemic times of as long as 60 minutes. Although more study is needed, a blood flush evaluation is simple and may have a role as a secondary allograft assessment tool. The existing techniques of donor lung evaluation and preservation after donation following cardiac death thus appear both feasible and practical.**

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Lung transplantation as a therapy for the management of end-stage lung disease is limited in its applicability by a lack of donor organs. Lung transplantation utilizing donation after cardiac death (DCD) donors has the potential to provide a previously untapped source of lungs for transplantation [1, 2]. As well as increasing overall numbers, DCD transplantation would allow organ donation from a pool of persons who have expressed a wish to donate their organs, facilitating lung donation from outside the intensive care unit, and potentially providing organs less damaged by the catecholamine and endocrine storm that characterizes brain death [3].

Until now, very few human DCD donor lung transplantation procedures have been performed around the world [4]. Historically, the techniques for the assessment, preservation, and retrieval of DCD lungs have been characterized by the Maastricht category descriptor of the donor (Table 1) [5]. Nunez and colleagues [6] describe a technique that has been utilized for Maastricht category I retrievals; Steen and colleagues [7], a single category II retrieval; and Love and coworkers [8], category III retrievals. These different strategies have evolved in response to local legal and donor pool circumstances (ie, prior existence of a local renal DCD program). Notwithstanding how they have been previously utilized, the variations in technique have different strengths and weaknesses that need to be carefully considered for the wider clinical application of DCD lung transplantation.

Additionally, to maximize the overall potential for organ transplantation through the use of DCD donors, the retrieval of DCD lungs should also be compatible with the existing techniques to retrieve other DCD donor organs such as kidneys and livers. Clearly, the more organs available and utilized per multiorgan DCD donor, the greater the cost/benefit ratio of extending the existing traditional heart-beating donor referral and assessment system to routinely incorporate DCD donors.

This study aimed to use an animal model to critically review and apply all existing DCD lung assessment, preservation, and surgical techniques to a range of scenarios that would cover all four Maastricht category DCD donors. The primary outcome will be the assessment of the potential allograft on an ex-vivo perfusion circuit [7, 9], utilized as a surrogate for transplantation. The studies aim to mimic the real-world clinical context of local and distant donation, and the issue of a DCD lung transplantation as part of a DCD donor multiorgan procurement.

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Table 1. Donation After Cardiac Death Donors

Maastricht Workshop Categories (1995) [5]
I Dead on arrival
II Unsuccessful resuscitation
III Awaiting cardiac arrest/cessation of futile treatment
IV Cardiac arrest in brain dead donor

Material and Methods

Animals and Anesthesia

Seven greyhound dogs weighing 28 to 34 kg were used for seven DCD lung experiments (including one combination lung, liver, and renal procedure). The experiments were structured to explore the practicality and relative efficacy of different permutations of warm ischemic time, cold preservation technique (topical cooling versus pulmonary artery flush cooling), and graft assessment technique (blood flush versus ex-vivo perfusion rig). The experimental protocols are detailed in Table 2. Experiment 1 was a negative control experiment without standoff time (ST) but as might be seen for in-house category III or IV DCD donors. Experiments 2 through 4 added 60 minutes of ST, mimicking an in-house category I through IV donor and varied the preservation technique. Experiment 5 mimicked a typical distant category I or II donor scenario with the need for graft assessment and retrieval. Experiment 6 was proposed as a positive control experiment of the effects of prolonged warm ischemia and ST. Experiment 7 represented a typical in-house category III or IV DCD donor multiorgan retrieval scenario.

During the planned ST (0 to 4 hours), the chest remained closed without ventilation, and the cadaver temperature was not artificially controlled. All animals received humane care in accordance with the "Australian Code of Practice for the Care and Use of Animals for Scientific Purposes" under approval from the Alfred Medical Research and Education Precinct Animal Ethics Committee.

All animals received premedication with subcutaneous 0.1 mg/kg acetylpromazine and intramuscular 0.05 mg/kg atropine and 0.2 mg/kg morphine. For the induction of anesthesia, 6 mg/kg propofol and 10 mg morphine were given intravenously. An infusion of propofol 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ followed to maintain anesthesia. A cuffed tracheal tube was introduced, and lungs were ventilated 10 mL/kg on air at 20 breaths per minute through a volume cycle ventilator. Heparin sodium 10,000 IU was administered intravenously for anticoagulation. Three hundred milliliters to 500 mL blood was removed and leucocyte filtered (R-500N, Sepacell; Asahi Medical, Tokyo, Japan) for use in the perfusate and lung evaluation bolus flush, while 0.9% saline was infused to maintain arterial blood pressure. Ventricular fibrillation was induced by electrical stimulation using a needle electrode, and the ventilator was then disconnected.

The onset of ventricular fibrillation defined the onset of the warm ischemic time (WIT). Procedure time represented dissection and organ manipulation time, and may have resulted in slow cooling or warming of the organs depending on the circumstance. Cold ischemic time (CIT) was measured from the onset of the infusion of cold fluid.

Lung Preservation

Topical lung cooling was achieved by infusing 2.8 L 4°C Perfadex solution (Vitrolife, Gothenberg, Sweden) into each pleural space through 16F intercostal catheters (Trocar, Argyle, Ireland), as previously described [7, 9–11]. Pulmonary artery flush cooling was achieved by infusing 50 mL/kg 4°C Perfadex solution through a 24F catheter (DLP, Grand Rapids, Michigan), as previously described [7, 9–11]. The left atrial appendage was incised for venting and blood gas sampling (see below). Subsequently the catheter was removed, and the heart-lung block excised and stored at 4°C.

Table 2. Experimental Design

Number	Description	Detail	Maastricht Category[a] Applicability and Other Techniques Tested
1	Control experiment	120-minute ex vivo rig	III, IV + potential multiorgan retrieval
2	60-minute ST	60-minute ST + 120-minute rig	I, II, III, IV
3	60-minute ST + topical cooling	60-minute ST + 120-minute topical cooling + 120-minute rig	I, II, III, IV
4	60-minute ST + flush cooling	60-minute ST + 120-minute flush cooling + 120-minute rig	I, II, III, IV + blood flush evaluation
5	120-minute ST + topical cooling + flush cooling	120-minute ST + 120-minute topical cooling + 120-minute flush cooling + 120-minute rig	I, II, III, IV + blood flush evaluation + potential distant donor
6	240-minute ST + flush cooling	240-minute ST + 30-minute flush cooling + 120-minute rig	I, II, III, IV + blood flush evaluation
7	Multiorgan	30-minute ST + 120-minute flush cooling + 120-minute rig	I, II, III, IV + blood flush evaluation + multiorgan retrieval

[a] See Table 1 and Koostra et al [5].

ST = standoff time (no ventilation or temperature regulation).