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Case Report

Successful Transplantation of Lungs From an Uncontrolled Donor After Circulatory Death Preserved *In Situ* by Alveolar Recruitment Maneuvers and Assessed by *Ex Vivo* Lung Perfusion

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We developed a protocol to procure lungs from uncontrolled donors after circulatory determination of death (NCT02061462). Subjects with cardiovascular collapse, treated on scene by a resuscitation team and transferred to the emergency room, are considered potential donors once declared dead. Exclusion criteria include unwitnessed collapse, no-flow period of >15 min and low flow >60 min. After death, lung preservation with recruitment maneuvers, continuous positive airway pressure, and protective mechanical ventilation is applied to the donor. After procurement, *ex vivo* lung perfusion (EVLP) is performed. From November 2014, 10 subjects were considered potential donors; one of these underwent the full process of procurement, EVLP, and transplantation. The donor was a 46-year-old male who died because of thoracic aortic dissection. Lungs were procured 4 h and 48 min after death, and deemed suitable for transplantation after EVLP. Lungs were then offered to a rapidly deteriorating recipient with cystic fibrosis (lung allocation score [LAS] 46) who consented to the transplant in this experimental setting. Six months after transplantation, the recipient is in good condition (forced expiratory volume in 1 s 85%) with no signs of rejection. This protocol allowed procurement of lungs from an uncontrolled donor after circulatory determination of death following an extended period of warm ischemia.

Abbreviations: CPAP, continuous positive airway pressure; CPR, cardiopulmonary resuscitation; DCDD, circulatory determination of death; EVLP, *ex vivo* lung perfusion; PEEP, positive end-expiratory pressure; uDCDD, uncontrolled DCDD

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Introduction

As a measure to increase the number of organs available for transplantation, many countries worldwide have adopted organ procurement from donors after circulatory death (1–3). The majority of organs so far have been procured from controlled donors, according to the Maastricht definition (4,5), mainly in Belgium, The Netherlands, the United Kingdom, Australia, and the United States. However, despite being an indisputable source of organs, as emphasized by the World Health Organization (6), this procedure has been considered with caution. Indeed, the possibility that a number of potential donors after brain death (DBD) turn into donors after circulatory determination of death (DCDD) within the controlled category of donors has caused skepticism (7). If true, this

would eventually lead to a lesser number of organs procured, since the numbers of organs procured from DCDD are significantly lower than those procured from DBD (8). Conversely, recovery of organs from uncontrolled DCDD (uDCDD) would increase the pool of organs available for transplantation (9). However, donation from this category adds logistical, ethical, and legal complexity to the donation process in many countries (10). In fact, far fewer organs have been recovered from uncontrolled donors, mainly in France and Spain (11).

Preclinical data show that lungs have the potential to better tolerate warm ischemia relative to other solid organs (12–15). This could make the uDCDD process safer in the lungs compared to other solid organs. However, although deceased donors are considered a valuable strategy to procure lungs (16), there are few reports on lung donation from uDCDD (17–19).

We are currently investigating the safety/efficacy of a clinical protocol designed to procure lungs from uncontrolled donors after determination of death with circulatory criteria. In this report, we present the first case recruited, and discuss some peculiarities of our protocol.

Materials and Methods

The trial was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda and of the San Gerardo Hospital (NCT02061462).

Subjects with cardiovascular collapse, treated by an advanced life support crew on scene first, then transferred to the emergency room (San Gerardo Hospital, Monza), are considered to be potential donors if declared dead after advanced cardiac life support attempts failed. Unwitnessed collapse, no-flow period of >15 min, or low flow >60 min are among exclusion criteria. After clinical diagnosis of death (5 min of no touch), a recruitment maneuver (RM) is performed (RM: positive end-expiratory pressure, PEEP 5; inspiratory/expiratory [I/E] ratio 1:1; respiratory rate, RR 10/min; Pressure controlled + 25 ×2, PC + 30 ×2, PC + 35 ×4) and continuous positive end-expiratory pressure (CPAP 10 cmH_2O, 100% FiO_2) is applied until death is confirmed according to circulatory criteria (20 min of flat electrocardiogram in our country). After next of kin consent to donation is obtained, heparin is given (10 000 U endovenous push, followed by 3 min of cardiopulmonary resuscitation, CPR), a new RM is performed and ventilation is started (respiratory rate 4/min, tidal volume 6 mL/kg, PEEP 8 cmH_2O, fraction of inspired oxygen [FiO_2] 100%, I/E ratio 1:1). If chest radiograph is negative, the subject is transferred to the operating room. If bronchoscope evaluation is negative, lungs are perfused *in situ* with a fibrinolytic agent (15 mg recombinant tissue plasminogen activator [rTPA]), flushed with preservation solution (Perfadex® [XVIVO Perfusion AB, Göteborg, Sweden], 60 mL/kg antegrade, 250 ×4 mL retrograde) and cold stored on ice. Once transferred to the Fondazione Ca' Granda (25 km away from Monza), lung function is evaluated after *ex vivo* lung perfusion (EVLP), run with a low-flow, open atrium and low hematocrit technique, as previously described (20).

An overview of the protocol flow is shown in Figure 1.

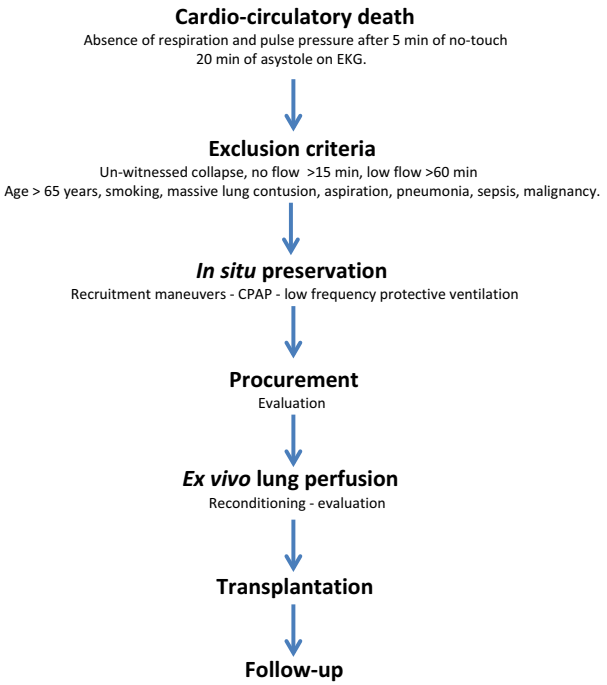

Figure 1: Lung-DCDD protocol flow. DCDD, circulatory determination of death.

Results

A pilot phase of potential donor's recruitment active from 8 am to 4 pm, 7 days a week started on May 12, 2014. Recruitment was interrupted for logistical reasons during the summer (from August 1, 2014 to September 15). During this first period, five subjects aged <65 years were treated because of cardiocirculatory arrest and transferred to the emergency room of the San Gerardo Hospital. However, all of them arrived beyond recruitment time and were not considered potential lung donors. On November 1, 2014 recruitment was activated on a 24-h-a-day, 7-days-a-week basis. Since then, the potential donor recruitment system has been activated for 10 subjects. Details are shown in Table 1.

Subject number 1 in Table 1 was the only one with lungs procured that had EVLP. These lungs were transplanted. He was a 46-year-old male who had thoracic pain and, soon after arrival of the emergency team, collapsed. CPR was started immediately (0 min no flow); a first return of spontaneous circulation revealed ST-elevated myocardial infarction, but pulseless electrical activity developed soon after. The subject was transferred to the emergency room while automated chest compression (LUCAS™, Jolife AB/Physio-Control, Lund, Sweden) was ongoing. After the diagnosis of aortic dissection, the possibility of receiving extracorporeal life support (VA-ECMO) was excluded and the medical team decided to withdraw

further treatment. The subject was declared dead after a total low-flow time of 45 min. Recruitment maneuvers and CPAP were applied and death was confirmed. Chest radiograph showed reduced lung volumes and a wide mediastinum consistent with the diagnosis of dissection (Figure 2). Consent for donation was obtained 2 h after death. At that time, heparin was given and ventilation started. The donor was then transferred to the operating room where lungs were procured (4 h and 48 min after death) and cold stored on ice. Upon arrival to the Fondazione Ca' Granda, EVLP was run for a total of 6 h, after which lungs were deemed suitable for transplantation (Table 2) and cooled down. Time flow of the donation process is shown in Table 3. Lungs were offered to a rapidly deteriorating recipient with cystic fibrosis (LAS 46) who had been hospitalized for 4 months. The patient was on noninvasive ventilation 24 h a day and consented to the transplant in this experimental setting. Surgery was complicated by cardiogenic shock and need of VA-ECMO support with massive bleeding. Intensive care unit stay (19 days) was initially characterized by distributive-hypovolemic shock. Primary graft dysfunction at 72 h was grade 2; lung function was proper throughout the following days. Weaning from mechanical ventilation was difficult because of muscle fatigue due to preoperative deconditioning. Hospital length of stay was 39 days. Six months after transplantation, the recipient is at home, in good condition (forced expiratory volume in 1 s 85%). Three- and 6-month surveillance lung biopsy were both negative.

Discussion

The present case report confirms that lung procurement from uDCDD is feasible. The protocol implemented allowed procurement of lungs even after an extended period of warm ischemia.

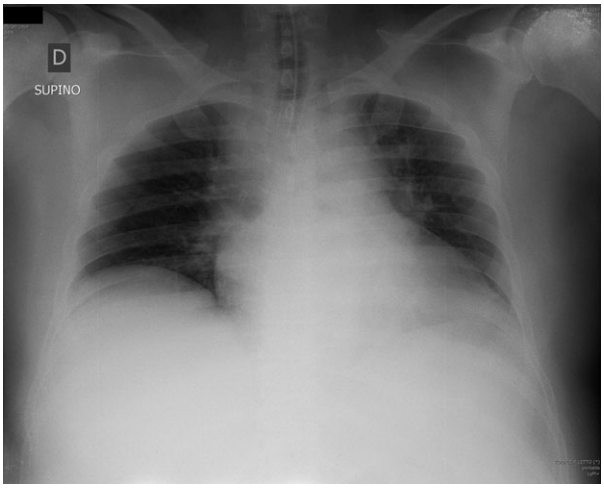

Figure 2: Chest radiograph of the donor.

Preclinical investigations show that lungs may be preserved in the non-heart-beating donor with lung inflation and ventilation (13,15). Lungs are anatomically open to air and can receive oxygen through diffusion. Consequently, they better tolerate the absence of blood. Moreover, as many as 60 min of total warm ischemia time is considered clinically safe according to UK criteria for DCDD organ procurement (7). Taking advantage of this background, and after preclinical investigations, we developed an *in situ* preservation strategy to procure lungs from uDCDD. The procedure consisted of lung recruitment maneuvers, CPAP, and protective mechanical ventilation.

Lung recruitment maneuvers are of crucial importance to fully open up the lung at the beginning of *in situ* preservation in order to facilitate oxygen diffusion to distal alveoli. Recruitment maneuvers, together with chest radiograph (Figure 2), can also provide important information on lung function at early stages of the donation process. As keeping the lung open over time is imperative, in our protocol CPAP is applied at the outset. This maintains the lung fully open during the 20-min ECG recordings required by Italian legislation, time possibly needed in other countries to procure organs. Thereafter, low tidal volume–high PEEP ventilation is applied with a low respiratory rate to avoid the harm of hypocapnia (21). Using this strategy, in our donor respiratory mechanics were stable over 4 h (Figure 3).

The preservation strategy we adopted differs from that described by Steen et al. (22). Indeed, whereas they applied a technique of topical lung cooling via chest tubes, we used *in situ* preservation with lung recruitment maneuvers, CPAP, and mechanical ventilation between declaration of death and cold flush and storage. It is possible that topical cooling allows longer *in situ* preservation time (23,24), relative to our strategy, aimed at gaining time for procurement. However, this case report indicates that lungs recovered from uDCDDs can be suitable for transplant after >4 h of total warm ischemic time, in line with results obtained from preclinical investigations (15). The recipient's postoperative course, likely caused by massive blood loss that required intraoperative ECMO, might have also been related to the use of uDCDD lungs. However, the 6-month clinical outcome proves the feasibility of this preservation strategy.

The validity of machine perfusion when solid organs are procured from uDCDD donors has been suggested (25,26). Because of the impossibility to obtain PaO_2/FiO_2 for lung evaluation after cardiac arrest, we decided to include EVLP in our protocol as Steen mentions in his seminal article (22).

During EVLP, pulmonary vascular resistances were higher than in DBD donors, as previously shown (27). Assessment of vascular resistance is of great relevance

Table 1: Potential lung donors

Subject	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	M	M	M	M	M	M
Birth	September 01, 1968	June 07, 1981	November 30, 1969	October 24, 1957	July 29, 1965	February 20, 1965	October 11, 1957	October 16, 1949	April 15, 1966	March 15, 1983
Age	46	33	45	57	49	49	57	65	48	32
Clinical events										
Date	November 1, 2014	November 18, 2014	December 11, 2014	December 12, 2014	December 25, 2014	January 15, 2015	January 31, 2015	February 19, 2015	March 22, 2015	May 14, 2015
CCA	10:15	–	15:20	17:50	15:53	9:13	11:38	18:45	17:48	22:10
CPR	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
BLS	10:15	16:19	15:32	18:15	16:00	9:23	11:53	18:56	17:58	22:25
Rhythm	PEA	Asystole	Asystole	PEA	PEA	VF	Asystole	VF	Asystole	Asystole
ALS	10:15	–	15:35	18:17	16:05	9:29	11:53	18:56	18:04	22:32
ER	10:50	16:56	16:06	19:07	17:06	10:18	12:48	19:47	18:48	23:15
Exitus	11:00	17:07	16:23	19:08	17:30	10:38	13:29	19:55	19:00	23:24
Exclusion criteria										
Witness	Y	N	N	Y	Y	Y	Y	Y	Y	Y
No Flow	0:00	–	0:12	0:25	0:07	0:10	0:15	0:11	0:10	0:15
Low Flow	0:45	0:48	0:51	0:53	1:30	1:15	01:36	00:59	01:02	00:59
Other	–	–	Smoking	LMA	Smoking	Aspiration	–	Smoking	Aspiration	–
Consent	Y	–	Y	–	Y	N	–	–	–	N

CCA, cardiocirculatory arrest; CPR, cardiopulmonary resuscitation; BLS, basic life support; PEA, pulseless electrical activity; VF, ventricular fibrillation; ALS, advanced life support; ER, emergency room; Smoking, active smoking of >20 cigarettes/day or history of >20 packs/year; LMA, laryngeal mask airway.

Table 2: Functional data during *ex vivo* lung perfusion (EVLP)

	60 min	120 min	180 min	240 min	Evaluation
LA temp (°C)	37.1	36.2	36.4	36.4	36.2
Perfusate flow (L/min)	2.45	2.42	2.43	2.4	2.4
PAP_m (cmH_2O)	17	18	19	18	19
PVR (dine*s/cm^5)	489	528	559	533	566
Vt (mL/kg)	5.6	5.4	5.6	5.6	5.6
Paw_m (cmH_2O)	6	6	6	6	6
Paw_{peak} (cmH_2O)	13	11	11	13	12
Cpl_{dyn} (mL/cmH_2O)	70	90	93	70	80
Gas mix	CO_2/air	CO_2/air	CO_2/air	CO_2/air	CO_2/N_2
FiO_2 ventilator	0.21	0.4	0.4	0.4	1
PCO_2 IN (mmHg)	39	36	31	28	–
PCO_2 OUT (mmHg)	31	31	26	–	–
PCO_2 OUT_{left} (mmHg)	–	–	–	28	32
PCO_2 OUT_{right} (mmHg)	–	–	–	22	28
PO_2 IN (mmHg)	146	154	154	161	75
PO_2 OUT (mmHg)	146	249	243	–	–
PO_2 OUT_{left} (mmHg)	–	–	–	239	490
PO_2 OUT_{right} (mmHg)	–	–	–	221	436

EVLP was run as previously described (20). Briefly, during the first 40 min of the procedure blood flow was gradually increased up to a target perfusate flow of 40% of the estimated cardiac output, and temperature of the perfusate gradually increased from 25°C to a left atrium target temperature of 37°C. Once the lung outflow temperature exceeded 32°C, a gas mix of air and 5% CO_2 was connected to the circuit oxygenator and mechanical ventilation was started. After 4 h from the start of the procedure, ventilator FiO_2 was set at 1 and circuit oxygenator gas mix changed to N_2/CO_2. Twenty minutes later, measures were taken to evaluate lung suitability. At this time the decision was made to offer the lung to the recipient; EVLP continued during this time so that normothermic perfusion lasted a total of 320 min. Data are presented as mean ± standard deviation. LA temp, left atrium temperature (ºC).
Vt, tidal volume (mL/kg donor weight); PAP_m, mean pulmonary arterial pressure (mmHg); PVR, pulmonary vascular resistance (dine*s/cm^5); PVR was calculated considering wedge pressure 2 mmHg, as measured at the end of the procedure in the pulmonary veins with a pressure probe; Paw_m, mean airways pressure (cmH_2O); Paw_{peak}, peak airways pressure (cmH_2O); Cpl_{dyn}, dynamic lung compliance (mL/cmH_2O); FiO_2, fraction of inspired oxygen; PCO_2 and PO_2 IN, partial pressure of CO_2 and O_2 measured on a sample of perfusate taken from the pulmonary artery cannula (mmHg); PCO_2 and PO_2 OUT, partial pressure of CO_2 and of O_2 measured on a sample of perfusate taken from lung outflow (mmHg); PCO_2 and PO_2 $OUT_{right/left}$, partial pressure of CO_2 and of O_2 measured on samples of perfusate taken from right/left pulmonary vein, respectively.

when dealing with DCDD lungs to exclude clot formation after circulation has stopped. In our protocol, heparin was added only after consent to donation was obtained, but lungs were treated with rTPA before flushing with the preservation solution. In fact, fibrinolytic treatment improves the quality of DCDD when applied during EVLP (27). Importantly, at this time of the process, response of the lung to vasculature flushing is used to decide whether to proceed with EVLP or not (see Figure 1, procurement). Indeed, in a rat model the time to flush the lungs with a constant volume of preservation solution correlates with the development of lung edema (28).

This first "successful case" supports the validity of our protocol. However, while it allows the assumption that lung procurement is feasible even after an extended warm ischemia time, efficacy and safety remain to be more extensively proven. Nevertheless, our case may add to the discussion on the relevance of lungs procurement from uDCDD. In fact, the present protocol has a number of potential advantages. There are virtually no costs; indeed, most of the subjects are intubated at the time of death after CPR withdrawal, and only a ventilator is needed to preserve the lungs. Procedures are not invasive: at the time of donor's death, relatives face an intact body, apart from endotracheal intubation. Clearly, impossibility to procure organs other than the lungs is a major weakness of the present protocol. However, tissues may be procured. Moreover, as the lung preservation strategy is simple, if proven safe and efficacious, many emergency rooms that do not have the possibility of setting up ECMO technology might be actively involved in lung and tissue procurement in a hub-and-spoke model as the one we have described.

As recently pointed out by Egan and Reqaurd, a number of ethical issues come with uDCDD programs (19). A clear separation of treatment from procurement is one of these. For this reason, the regional (AREU 118) and local (San Gerardo Hospital) emergency teams treated the subject until death diagnosis. Thereafter, a separate team of neuro-intensivists (San Gerardo Hospital), eager in the process of donation, took the responsibility upon the arrival of the procurement team (Fondazione Ca' Granda). As in the protocol of Egan et al (19), we are committed to build a multidisciplinary team. Moreover, a continuous program of medical and paramedical staff education is active.

Table 3: Timing of lung procurement

Clinical events		
CCA	10:15 am	No flow, 0 h:0 min
ROSC	10:38	
CCA	10:43	
Diagnosis of death (hands off)	11:00	Low flow, 0 h:45 min
In situ preservation		
RM + CPAP	11:05	
Confirmation of death (ECG, 20 min)	11:25	
Consent to donation	01:25 pm	
Heparin + CPR	01:33	
RM + ventilation	01:40	
Surgery for procurement	02:36	
rTPA + 1st cooling	03:48	*In situ* preservation, 4 h:48 min
Ex vivo lung perfusion		
Start of EVLP procedure	08:16	
2nd Cooling	02:26 am	EVLP, 6 h:10 min
Transplantation		
Reperfusion 1st lung	09:18	Death to reperfusion, 22 h:18 min
Reperfusion 2nd lung	12:34	Death to reperfusion, 25 h:34 min

CCA, cardiocirculatory arrest; ROSC, return of spontaneous circulation; RM, recruitment maneuver; CPAP, continuous positive end-expiratory pressure; ECG, electrocardiogram; CPR, cardiopulmonary resuscitation, rTPA, recombinant tissue plasminogen activator; EVLP, *ex vivo* lung perfusion.

During the first 6 months of activity, there were two denials of consent out of five requests. In a situation such as sudden death, this can be expected, particularly if, as in Egan's protocol (19), witness to the cardiac arrest is not necessarily the next of kin. In this regard, the possibility to extend the time from death to organ consent offered by the *in situ* preservation strategy is of great interest.

Lung preservation procedures, including heparin, ventilation, and bronchoscopy, were all applied postmortem. Only blood was withdrawn just before hands-off. This decision might be considered a weakness of our protocol, particularly in countries where, unlike Italy, there is a general education about this kind of donation. We elected to use this strategy to make this novel donation process easier to accept.

In conclusion, we have confirmed previous findings on the feasibility of lung donation from uDCDD. We also provided evidence that *in situ* lung preservation with recruitment maneuvers, CPAP, and protective ventilation followed by EVLP after procurement allows lung transplantation after extended periods of warm ischemia.

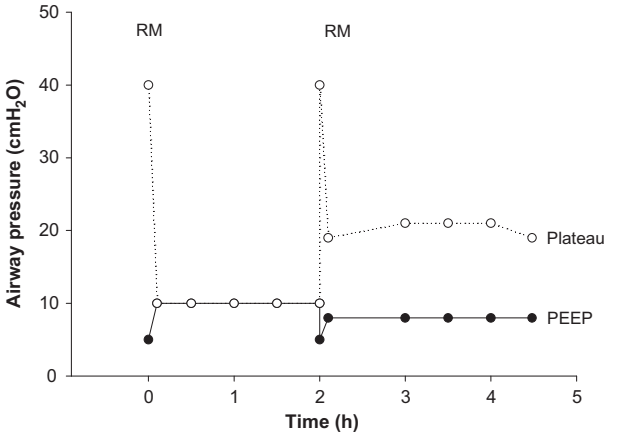

Figure 3: The figure shows airway pressure measured during the open-lung preservation strategy. A first recruitment maneuver (RM, PEEP 5, I:E 1:1, RR 10, Pressure controlled + 25 ×2, PC + 30 ×2, PC + 35 ×4), was followed by continuous positive airway pressure (CPAP 10 cmH_2O, 100% FiO_2). Consent to donation was obtained 2 h later. Thereafter, a new recruitment maneuver was performed, and low frequency–low tidal volume–high PEEP ventilation started (respiratory rate: 4/min, tidal volume: 6 mL/kg, PEEP: 8 cm H_2O, FiO_2: 100%, inspiratory/expiratory ratio: 1:1). PEEP, positive end-expiratory pressure.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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