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Lung Transplantation from Donation after Circulatory Determination of Death: A Contemporary Review

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Abstract

During the last decade many strategies are developed in order to expand the donor pool. One of the strategies that bring more attention is the use of grafts from donors after circulatory death (DCD), also frequently referred to as nonheart-beating donors (NHBD). Here we offer a short and compressible, state of the art review of lung transplantation from DCD.

Introduction

Lung transplantation (LTx) represents a life-saving therapy for patients with end-stage lung disease. Since the first successful LTx, 50 years ago [1], the number of patients listed for transplant has been steadily increasing. However, that increase has been constantly challenged by a donor shortage. Of the available organ donors, only 20% are typically acceptable for lung donation. Although the selection process may vary between institutions, there are common criteria for ideal donors (Table 1) [2,3]. Donation after brain death (DBD) constituted the primary source for LTx. Multiple approaches have been developed to overcome the shortage of grafts for LTx, such as living lobar donation, use of extended criteria donors, *ex vivo* lung perfusion (EVLP), and donation after cardiac death, also known as donation after circulatory death (DCD) [4,5]. This article reviews DCDLTx and its value in increasing the LTx donor pool.

After the first report of successful LTx with DCD by Hardy in 1963 [1] the use of DCD donor went hold apart until begins of 1990s, when Thomas Egan and colleagues revisited the possibility of using lungs from DCDs, reopening the door for others to investigate the viability of these grafts related to warm ischemia and best preservation [6]. During the late 90s and early 2000s, experimental evidence came to light, determining warm ischemic time longer than 90 minutes might be extreme, confirming topical cooling as the best way to preserve lungs in situ for DCD, the importance of retrograde perfusion in these donors, and *ex vivo* evaluation as a potential tool to improve graft quality [3-8]. During de presents years the use of DCD lungs has grown internationally with DCD lungs accounting for 2% of lung transplants in the United States, 5% in Canada, 4.4% in Europe, 13.3% in the United Kingdom, and 22.5% in Australia [7].

Classification

The first international workshop for DCD was held in Maastricht in the Netherlands in 1995 to characterize potential donors after cardiac (modified in 2003), defining DCD categories according to the circumstances of the donor's death [8,9] (Table 2). Category I (dead on arrival), II (unsuccessful resuscitation) and V (in hospital patient) were considered to be uncontrolled donors (uDCD) does patient who suffer from unexpected cardiac arrest and/or unsuccessful cardiopulmonary resuscitation. In these scenarios, evaluation of graft function a priori is not feasible. Whereas category III (awaiting cardiac arrest) and IV (cardiac arrest in a brain-dead donor) were considered to be controlled donors (cDCD) scenario entails withdrawal of life-support measures in the intensive care unit (ICU) or operating room. Benefits of DCD donation include the ability to allocate the organ in advance, relative ability to predict cardiac arrest, and opportunity to evaluate graft function.

Controlled DCD

The cDCD are the perfect scenario for scheduling the procedure, assess graft viability extensible controlled recipient selection and careful communication with the donor's relatives. Potential donors for cDCD are typically patients with irreversible cerebral injury, high spinal cord injury, or end-stage musculoskeletal disorders that are expected to die within 60 mins following withdrawal of life-support (WLS). Most centers use the same donor criteria for as for DBD donation (Table 1).

Recently, some countries (Belgium, Holland) have started to consider donation after euthanasia.

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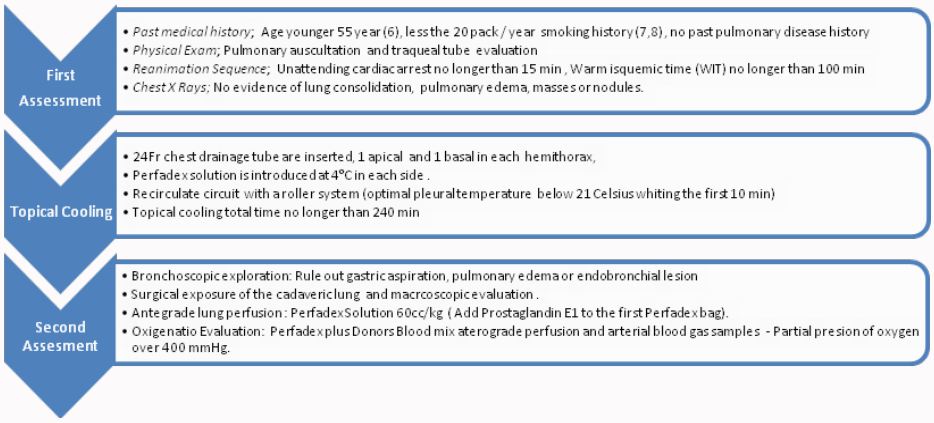

Figure 1:

Table 1: Criteria for ideal and extend donors.

• Age younger than 55 years
• Lungs from donors older than 55 years have been successfully transplanted
• Increased age is associated with borderline risk for increased 5-year mortality, increased 10-year mortality, and increased risk of bronchiolitis obliterans syndrome
• Less than 20 pack-years smoking history
• No study has evaluated number of pack-years that would preclude lungs from being transplanted
• More than 20 pack-years is associated with longer time spent by recipient in intensive care, impaired early oxygenation and ventilation, but no difference in late outcomes
• Recent study showed increased 3-year mortality associated with smoking donors compared with non-smoking donors, and an increased incidence of bronchiolitis obliterans syndrome
• Crucial factor is assessment of lungs for evidence of emphysematous changes and malignancy
• Appropriate size matching with prospective recipient
• Oversized lungs can undergo lung-reduction surgery to prevent thoracic compartment syndrome
• Total donor lung capacity 75–125% of recipient capacity was not associated with clinical problems
• Ratio of pulmonary arterial oxygen to fraction of inspired oxygen (PF ratio) higher than 300 mm Hg*
•Recruitment maneuvers to resolve atelectasis.
Consider ex-vivo lung perfusion in borderline grafts with PF ratios 300 mm Hg or lower
• No evidence of pulmonary infection, absence of purulent secretions on bronchoscopy, and absence of organisms on sputum Gram stain
• 50% of donors are colonized with organisms; however, this should not present as purulence
• Routine prophylaxis of every recipient with broad spectrum antimicrobials
• Blood-type compatibility, absence of chest trauma, no prior cardiopulmonary surgeries

Donor manegment and lung preservation for lung trasplant. **Munshi L, Keshavjee S, Cypel M.** Lacent respiratory medicine. 2013; 1: 318-328.

Table 2: (Categories of donation after circulatory death) [61].

Category I. Dead on arrival.
Category II. Unsuccessful resuscitation (CPR). (Uncontrolled)
Category III. Awaiting cardiac arrest followingwithdrawal of care. (Controlled)
Category IV. Cardiac arrest after brain death.
Category V. Cardiac arrest in a hospital patient.

CPR cardiopulmonary resuscitation.

These donors are included in Maastricht III category.

In all cases, donation is completely independent from the decision of WLST. Only when a certain patient is considered for lung donation, a Transplant Coordinator contacts the potential donor's relatives for consent.

In addition to standard criteria, specific procedural criteria play an important role in determining whether to accept the controlled cDCD lung or not; first the likelihood of death following WLS: Several algorithms have been developed in order to predict the expiration of potential cDCD donors based on patient clinical status. (Wisconsin Algorithm, UNOS Algorithm) [10-12]. Use of these predictive tools has further improved the ability to define eligibility for lung donation in the cDCD setting. Second important criteria is the time frame of each step in the cDCD, recently, the International Society for Heart and Lung Transplantation (ISHLT) DCDD Registry proposed a time-point; T0: withdrawal of life-sustaining therapies (WLST) OR euthanasia. T1: oxygen saturation o80%. T2: systolic blood pressure of 50 mmHg. T3: cessation of cardiac output/asystole. T4: resumed lung inflation/ventilation. T5: start of pulmonary flush. The intervals of times for T0 to T2 (Interval 1), T0 to T3 (Interval 2), T0 to T5 (Interval 3) and T2 to T5 (Interval 4) [13].

Donor management

Once the decision has been made based on Hospital protocol and family wishes, the potential donor is carried out by the ICU personnel in the operating room (OR) or stays in the ICU, closely monitored: Invasive arterial pressure (systolic, diastolic and mean). Heart rate and rhythm, respiratory rate, O_2 saturation and diuresis. Then WLST (mechanical ventilation, ECLS, IV drug) starts until cardiac arrest. A time limit of two hours to cardiac arrest is accepted, after which the patient is returned to the ICU.

After cardiac arrest a period of no-touch from 2 to 20 mins (depending on local protocols) is observed [14,15]. Most programs adopted a 5 min no-touch period to confirm death.

Some controversy surrounds the criteria for declaration of death, but most groups accept death declared by the ICU staff, independent

Table 3: (Outcomes reported to date for lung transplant onuDCD).

Study	N	Mean WIT	PGD 2,3	BOS	Suvival (Discharge, 1y and 3y)
Gomez de Antonio 2002-2009	29	114 min	17%, 38%	1y 11%, 3y35%, 5y 45%	83% 78% 68%
Gamez 2012	3	152	No PGD	UD	UD
Marques de Valdecilla (2013)	17	UD	14%	UD	83%, UD

N: Number of Patient, WIT: Warm Ischemic Time; PGD: Primary Graft Dysfunction (2 and 3 grade base on X-ray and PF findings); BOS: Bronchiolitis Obliterans; UD: Indeterminate; y: Years.

of the transplant team, based on cardiopulmonary criteria, defined as irreversible or permanent cessation of respiration and circulation after a certain period of time [16,17]. Signs of death are determined via absence of heart sounds, pulse, and lack of spontaneous respiration during a no touch period of 5 mins using the Institute of Medicine recommendations, providing there is no hypothermia, drowning, penetrating trauma or suspected intoxication [18].

During the period between withdrawal of support and actual cardiac arrest, there have been described some events that correlate with quality of the organs. The agonal phase (AP) is defined as the period of time between limitation and declaration of death (Interval 2). Some research has suggested an inverse correlation between the length of the AP and graft viability and function [19-22]. Warm ischemic time (WIT) defined by The American Society of Transplant Surgeons (ASTS) as the period of time between withdrawal of life-sustaining therapies and graft cold perfusion (Interval 3). However, these guidelines also define a 'true warm ischemic time', which is the interval between significant ischemic insult and initiation of cold perfusion, considering that the real ischemic damage starts when mean arterial pressure (mAP) drops below 60 mmHg [15] (Interval 4). As in AP some research link prolong WIT with lower PaO_2/FiO_2 ratio and longer ICU stay after transplant 40 [21,23-25]. Today most groups accept WIT of 60 to 90 mins of WIT, depending on the definitions.

The procurement process is similar to a brain death donor in terms of evaluation and surgical technique, there are two crucial aspect that differ; First, after determination of death by the ICU staff the donor is quickly reintubated and ventilation restarted as donor is transferred to the OR (if the WLST was on the ICU). The airway is checked by bronchoscopy in order to rule out aspiration during the agonal phase. Simultaneously, fast opening of the chest and flush perfusion through the pulmonary artery is performed [26,27].

Uncontrolled DCD

In contrast to the controlled DCD, the uncontrolled DCD donation represents a complicate scenario were neither time nor circumstances of death are known, so the success of the procedure depends on a really organized network of pre-hospital and hospital emergency services, and transplant coordinator skills and motivation to request consent for organ donation. For this reason, only fourteen years after Steen´s report, only the Madrid group is reporting a consistent number of lung transplantations from uDCD [28].

Donor Management

The uDCD program includes a medical and surgical multidisciplinary team on site upon arrival of the potential donor. This team includes surgeons, anesthesiologists, perfusionist and nurses. Also essential are the out-of-hospital emergency teams, trained to provide high quality basic and advanced life support [29].

A potential uDCD is considered after a witnessed cardiac arrest, when emergency unit's starts basic and advanced resuscitation maneuvers within 15 mins and after 30 mins of advanced CPR there is no recovery of spontaneous circulation. The patient is then transported to the emergency department under advanced CPR. In the ER death is declared by the ICU staff independent of the transplant team based on cardiopulmonary criteria, defined as describe before [16-18].

Once legal permission for preservation is obtained, heparin (3 to 5 mg/kg) is given to the potential donor to reduce the risk of pulmonary thromboembolism [30-33] cold Perfadex® at 4°C (Medisan, Uppsala, Sweden) is instilled through chest drains into both pleural cavities to bring lung temperature below 21°C [28,34,35] and veno-arterial extracorporeal membrane oxygenation is implemented for abdominal organ preservation, with insertion of a Fogarty catheter supra-diaphragmatically to prevent abdominal solutions entering the chest [36,29] accepting a maximum warm ischemic time period (from absence of circulation until effective topical cooling of 90 mins.

After topical cooling the procurement process is similar to cDCD in term of evaluation and surgical technique, there are two crucial aspects that differ;

1.-There is a period of time between topical cooling and definitive intravascular preservation (flush), that should not exceed 240 mins [10,11,16].

2.-There is no way to evaluate these grafts before arrest, so after the initial solution flush (60 ml/kg of cool Perfadex), additional 300 ml of donor blood are passed through the system and gas analysis from the left atrium and each pulmonary vein is done with temperature correction, seeking a partial pressure of oxygen greater than 400 mm Hg [28,37-46] (Figure 1).

Results

Controlled DCD

Two decades have passed since initial successful cDCDLTx [47]. Several series from individual institutions and national organizations have been reported [48-52] (Table 4A,4B).

Today these donors represent about 10% of average transplant volume worldwide. Only a few reports have showed worse outcomes with respect to primary graft dysfunction (PGD) and bronchiolitis obliterans syndrome (BOS) [50,53]. A growing international multicenter registry reported outcomes comparable to DBD in terms of early and intermediate survival [54,55] More recently ISHLT DCD registry published the biggest multicenter series[13] with 306 LTx with no differences in DCD and DBD in survival. Thirty-day survival was 96% in the DCD group and 97% in the DBD group, and 1-year survival was 89% in the DCD group and 88% in the DBD group. Five year survival was 61% in both groups. Median hospital stay after transplant was 18 days in the DCD group and 16 days in the DBD group. Very interesting in this report is the finding that the mechanism of death within the DCD group seemed to influence short-term recipient survival. Of the 11 deaths within 30 days of

Table 4a: Outcomes reported for lung transplant o cDCD.

Author and Year	N	PGD 3 (%)	ICU/Hospital days	Survival 1y /3y /5y	BOS free (%) 5y
Mason 2008	36	NR	NR/17	94/78/NR	NR
Puri 2009	11	36	NR	82/NR	NR
De Olivera 2010	27	33	4/17	88/82/82	72
Hernandez-Alejandro 2011	20	NR	NR	70	NR
Van De Wauwer 2011	35	6	4/32	91/85/73	87
Pilarczyk 2011	22	NR	16/32	89/66/32	54
De Vleeschauwer 2011	41	20	7/29	93/74/74	65
Mason 2012	32	6	4/14	91/71/NR	84
Levvey 2012	133	8	5/20	97/NR/90	93
Zych 2012	26	4	5/35	89/82	83

N: Number of Patient; WIT: Warm Ischemic Time; PGD: Primary Graft Dysfunction (2 and 3 grade base on X-ray and PF findings); BOS: Bronchiolitis Obliterans; NR: No Report; ICU: Intensive Care Unite; Y: Years.
(Campo-Cañaveral de la Cruz JL, 2015).

Table 4b: Outcomes reported to date for lung transplant cDCDcompere DBD).

					Survival				
	N		PGD		1Y	3Y	5Y	BOS free % 5y	
Author and year	DCD	DBD	DCD	DBD	DCD/DBD	DCD/DBD	DCD/DBD	DCD	DBD
De Olivera 2010	27	406	33	26	88/88	83/73	82/63	72	58
De Vleeschauwer 2011	41	266	20	20	93/92	74/85	74/84	65	83
Levvey 2012	133	905	8	NR	97/90	NR	90/61	93	NR
Pilarczyk 2011	22	164	NR	NR	84/89	66/70	37/52	54	58
Van De Wauwer 2011	35	77	6	11	91/91	85/76	73/66	87	85
Zych 2012	26	131	4	6	87/87	82/75	NR	83	81

N: Number of Patient; WIT: Warm Ischemic Time; PGD: Primary Graft Dysfunction; BOS: Bronchiolitis Obliterans; NR: No Report; DBD: Death Brain Donor; DCD: Death Cardiac Donor; Y: Years.

transplant, 6 involved donors with head trauma.

Ex vivo lung perfusion (EVLP) in cDCD

Ex vivo lung perfusion has become a potentially useful tool to reassess, preserve or recover grafts, thus expanding the donor pool. The Toronto group reported in 2012 fifty lung transplants following EVLP, 22 of which were from cDCD, with similar outcomes when compared to the control group (no EVLP perfusion) [56]. They advocate the use of EVLP in cDCD grafts due to concerns regarding the incidence of primary graft dysfunction. With this strategy, they have increased to 2 hours the acceptable time between withdrawal of life-support and cardiac arrest. More recently the same group reported the results of 28 EVLP with no differences on survival compared to a cohort of DBDLTx (1 and 5 year 85% and 54% vs. 86% and 62%). They also found that DCD plus EVLP group showed shorter hospital stay (media 18 days vs. 24 days, respectably) and a trend toward shorter length of mechanical ventilation (2 vs. 3 days) [57].

Successful outcomes in the cDCD situation have been reported without EVLP by other groups [20,49]. In fact, only 13% of all transplants reported form cDCD donors in the ISHLT DCD registry in 2013 and 2015, were performed after EVLP assessment [45]. It seems that EVLP may well prove to be a valuable tool to improve utilization of these donor lungs, especially when extended donor criteria are used however further studies are necessary to better define the role of EVLP in this context.

Uncontrolled DCD

Results published from LTx utilizing uDCD is scarce, even though the interest on this kind of donors is growing in the lasts years, only a few reports of successful uDCD around the world have been published [45]. The most active programs are in Spain. In our experience, approximately 5% of all potential uDCD become effective lung donors. The primary reasons for rejection of a donor include lack of family consent and prolonged ischemic times. After preservation of potentially suitable organs, the main reasons for not implanting lungs are gastric aspiration, pulmonary contusion, or suspected pulmonary embolism.

As for May 2015, we have performed 49 lung transplants from uDCD .We found an incidence of grade 3 PGD of 37%, and 30 day mortality 16%. One, 3 and 5 years survival rates were 70, 62 and 54% respectively [58]. Chronic allograft rejection rates at 3 and 5 years are 23% and 54% respectively, comparable to those reported in the international registry [59-63]. After many year working with uDCD we found that young donor who are close to the ischemia conservative times, a faster cool down of those grafts and short topical cooling period are the most reliable factors for viable LTx.

EVLP and uDCD

The first successful lung transplantation form uDCD published by Steen and co-workers [64] was done with the use of an *ex vivo* lung perfusion system. From 2009 to 2014 we adopted EVLP as an additional tool to evaluate certain grafts prior to implantation. In that period have been able to perform 11 uDCD lung transplants after

EVLP evaluation (7 with EVLP following Toronto protocol and 4 with Organ Care portable system), with inconsistent results in terms of PGD (5 patients developed grade 3 PGD) [65].

While EVLP is hoped to improve graft function and reduce PGD, it appears that with uDCD PGD is still a major concern. Current EVLP systems focus on preservation solutions specifically designed to dry the lungs, which is a crucial factor after brain death and in some cases of cDCD. In uDCD, the principal foe is warm ischemia, leading to immediate cell death and architectural damage ending in pulmonary edema. We speculate that the mode of vascular injury increases the risk of PGD despite extra vascular water extraction and excellent performance *ex vivo*.

Conclusion

DCD LTx has become a valuable and reliable approach to expand the donor pool and in some scenarios even superior to DBD donors, It is seems that the avoidance of inflammatory mediators resulting from brain death may prove to favor DCDLTx compared with DBD. Concerns regarding assessment of uDCD lungs before transplantation may be mitigated by EVLP, especially in the future when introduction of novel pharmacologic or biologic therapies using EVLP may lead to improved graft function. Our experience with DCDLTx using standardized selection, procurement, and implantation techniques has been good. The education of transplant coordinators, physicians, and surgeons will be critical in expanding the usefulness of this promising source of donor organs.

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