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Lung donation after circulatory death

Laurens J. Ceulemans^{a,b,c}, Ilhan Inci^c, and Dirk Van Raemdonck^{a,b}

Purpose of review

The current review presents a concise update on published literature on donation after circulatory death (DCD) and lung transplantation (LTx). Worldwide an increasing need for lungs is evident, however the utilization rate of DCD lung donors is still considerably low. In this summary article, we reviewed both the experimental background and international clinical experience.

Recent findings

Our analysis confirmed satisfactory results for LTx from DCD donors, which equals the results from donation after brain death. Although most studies reported on short-term results, some confirmed these results on the long-term and development of chronic lung allograft dysfunction. Our review summarizes the different DCD categories and underlines the potential of the DCD V category. We analyze the barriers to implement a DCD program, discuss the more recent advances like ex-vivo lung perfusion and describe the future challenges.

Summary

Based on the current short-term and long-term clinical results, we believe that barriers for DCD utilization should be overcome, resulting in a safe implementation of more DCD LTx programs worldwide.

Video abstract

<http://links.lww.com/MOT/A23>

Keywords

donation after circulatory death, lung transplantation, organ donation

INTRODUCTION

Lung transplantation (LTx) activity increases worldwide [1^a,2^a]. Although the number of lungs transplanted per donor reached 0.4, we are still faced with a waiting-list mortality of 10% – according the Organ Procurement and Transplantation Network (OPTN) [1^a–3^a]. Optimization of the donor pool should therefore be granted priority, leading to an increased interest in donation after circulatory death (DCD) [4–6]. It was shown that universal identification of potential DCD donors could increase LTx activity by 50%, which would result in a virtual elimination of the waiting-list [7]. Although countries like the United Kingdom, Australia, Belgium and the Netherlands reached a high percentage of DCD donors, a continuous global underutilization is noticed [5,8,9]. In 2018, the OPTN reported that only 6.6% ($n = 169$) of all LTx ($n = 2542$) came from DCD, within Eurotransplant DCD utilization accounted for 5% ($n = 62$) of all LTx in 2017 ($n = 1233$) [10,11]. The latter could be explained by some countries (e.g. Germany) which have no legal framework to allow DCD [12]. Over the last years, several centers have reported their experience showing equal short-term and long-term outcome following LTx when comparing DCD with

donation after brain death (DBD) [9,13–23,24^a,25,26^a,27,28,29^a].

In this review article, we summarize the historical background, definitions and current evidence for DCD and review the growing clinical experience. We discuss the recent advances in the field and future challenges.

HISTORY OF DONATION AFTER CIRCULATORY DEATH

The first donor used for clinical LTx died from a myocardial infarction and was a DCD donor [30]. Since then, definitions for brain-death were established and only donors who met brain-death criteria

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KEY POINTS

- DCD lung donation cannot be denied in countries with existing legal framework.
- LTx from controlled DCD donors results in the same short-term and mid-term outcome as donation after brain death donors.
- Future research on long-term outcome and a detailed analysis of the agonal phase is needed.

were accepted. In 1991, Egan *et al.* [31] renewed the interest in the potential of DCD donors with a canine model of LTx and in 1995 D'Alessandro *et al.* reported the first modern and successful LTx as part of their institutional DCD program [32,33]. In a landmark publication by Steen *et al.* in 2001 a successful single-LTx was reported from a donor after failed cardiac resuscitation, which is defined as uncontrolled DCD (uDCD) [34], utilizing 17 h of ex-vivo lung perfusion (EVLP) for graft evaluation. Since then several centers have embraced DCD for successful expansion of their donor pool.

THE LUNG IS AN AIRBAG FILLED WITH OXYGEN AND THEREFORE PRIVILEGED TO SUSTAIN ISCHEMIA

The main concern regarding DCD is the warm ischemic time (WIT) between withdrawal of life-sustaining therapy (WLST) and procurement [6,35,36]. However, it has become apparent that the lungs are more robust to ischemia than first suspected. Actually, lung parenchyma is unique among all organs as it depends not solely on blood supply for its oxygenation and lung ischemia does not necessarily equate to tissue hypoxia [37]. In comparison with other organs, the lung has relatively low metabolic needs and is privileged by a local storage of oxygen in the alveoli. This was confirmed in a series of canine single-LTx in which the lung was retrieved at different time points after death and the contralateral pulmonary artery and bronchus were ligated after single-LTx, forcing the animals to survive solely on the transplanted DCD lung [31]. In another series of rat DCD experiments, it was found that lung cell death was delayed by postmortem mechanical ventilation with oxygen [38,39]. In a series of pig experiments, the Leuven group showed that up to 60-min WIT with the lung collapsed was tolerated with a similar graft function as in non-ischemic lungs [40]. They also showed that prevention of alveolar collapse appears to be the critical factor in protecting the warm ischemic lung from

reperfusion injury independent of continuous oxygen supply [41]. Recently, it was shown in pigs that hypoxic cardiac arrest, followed by 60, 90 or 120 min of ischemia and normothermic 4-h EVLP did not result in differences between the groups regarding final oxygenation capacity, lung compliance, histological injury or wet-to-dry ratio, suggesting that longer WIT alone does not predict worse lung function [42]. These findings may lead to an expansion of the acceptable WIT in clinical DCD procedures.

From a biological point of view, it is hypothesized that a brief WIT could even be beneficial due to the phenomenon of preconditioning [43]. Furthermore, DCD donation exclude the detrimental brain-death effect, which results in acute lung injury through a catecholamine storm, hemodynamic instability and systemic inflammation. It is associated with increased organ immunogenicity possibly due to the leukocyte-influx in the allograft [44,45].

DEFINITION OF DONATION AFTER CIRCULATORY DEATH TIMINGS

The length of acceptable WIT is debatable, although most centers agree on 60–90 min [46]. In 2008, Levvey defined WIT as the period between a drop of SBP less than 50 mmHg and pulmonary artery flush. The International Society for Heart and Lung Transplantation (ISHLT) DCD working group recommended in 2015 six crucial time points in the DCD process (Fig. 1) [5,20].

The agonal phase is defined as the period between WLST and death declaration. Most centers accept a maximal period of 60–90 min and up to 180 min in Toronto [20]. Apart from a case report with an agonal phase of 120 min, no clinical research was performed on this topic [47].

Since a recent analysis of the ISHLT DCD registry on 507 DCD LTx did not show a relationship between the duration of WIT or the agonal phase and early survival, the true limits of DCD utilization may not have been reached. That report showed that 84% of DCD organs used for LTx reached asystole within 30 min and 97% within 60 min post WLST [46]. To better understand the impact of these different timings we suggest for future research to focus on the slope of mean arterial pressure and saturation and differentiate among *relative*, *absolute* and *acirculatory* WIT.

DONATION AFTER CIRCULATORY DEATH CLASSIFICATION

Originally, four DCD categories were defined according the Maastricht classification (Table 1) [48].

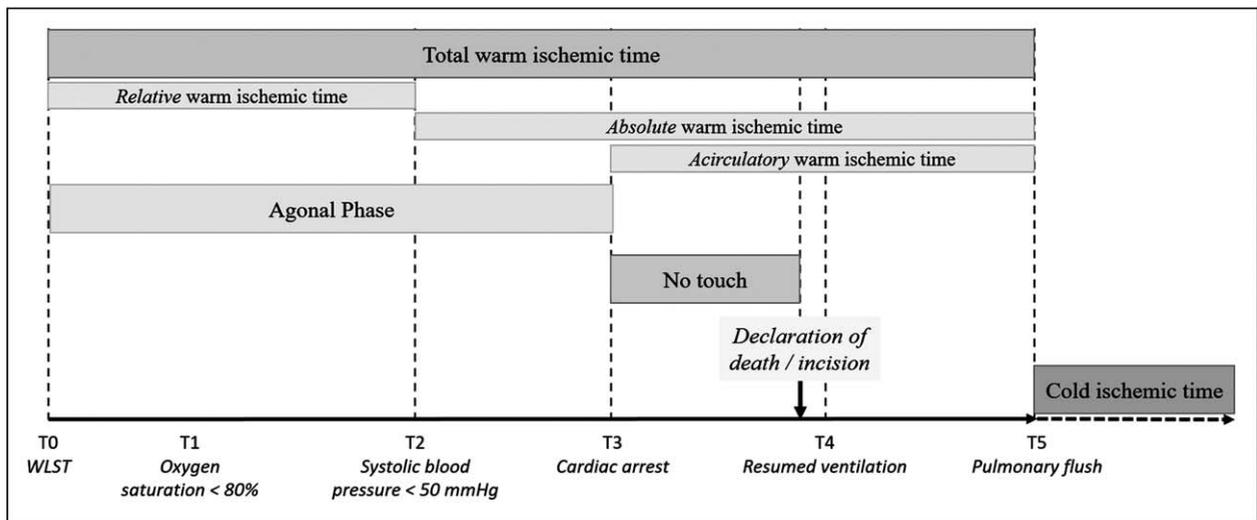


FIGURE 1. Schematic illustration of different time points and intervals related to controlled donation after circulatory death procedure. WLST, withdrawal of life-sustaining therapy.

The first two represent uDCD donors, the third and fourth a controlled type of DCD (cDCD). An uDCD is defined as unexpected death in which the organs could be considered for transplantation if the

relatives are consented in time and the lungs are adequately preserved in the body. In case of cDCD the logistics for procurement, preservation and allocation could be organized in advance [35,36].

Over the years, several subclassifications as well as a category V – donation after euthanasia – were added (Table 2) [49,50]. The section of the European Society for Organ Transplantation focusing on Ethical, Legal and Psychosocial Aspects of organ Transplantation (ELPAT) deceased donation working group defined an alternative uncontrolled category V as ‘unexpected circulatory death in critically ill patients’ [51].

Table 1. Original Maastricht classification of donation after circulatory death [48]

Category	Definition
Uncontrolled	I Death on arrival
	II Unsuccessful resuscitation
Controlled	III Awaiting cardiac arrest
	IV Unexpected cardiac arrest in heart-beating donor

CLINICAL EXPERIENCE

Over the last decade, barriers regarding DCD donation have been overcome by several centers, increasing the worldwide experience.

Table 2. Modified Maastricht classification of donation after circulatory death [50]

Category	Definition	Subclassification
Uncontrolled	I Found dead	Ia Out-of-hospital
		Ib In hospital
	II Witnessed cardiac arrest	IIa Out-of-hospital
		IIb In hospital
Controlled	III Planned WLST/expected circulatory death	IIIa In ICU
		IIIb In OR
	IV Cardiac arrest while brain death prior to organ recovery	IVa Unexpected in ICU
		IVb Expected in OR/ICU
	V Medically assisted circulatory death/euthanasia	Va Out-of-OR
		Vb In OR

ICU, intensive care unit; OR, operating room; WLST, withdrawal of life-sustaining therapy.

Table 3. Standard criteria for lung donation

Age	<65 years
Smoking	<20 pack years
Chest radiograph	clear
Mechanical ventilation	<5 days
Blood transfusion	<5-U red blood cells
Oxygenation	PaO ₂ > 300 mmHg

Barriers to implement donation after circulatory death

It remains surprising that DCD LTx implementation has not found more widespread application. Reasons for this underutilization are multifactorial. The ISHLT DCD working group reported that 85% of the participants mentioned complex logistics and absence of DCD-related protocols as the primary reasons for not using DCD [52]. Other barriers are regulations, fear of public disapproval, lack of surgical expertise, lung quality concerns, declined pre-mortem evaluation, inability to evaluate lungs in a controlled fashion, financial challenges and possibility of aborted procurement [53].

We believe that the procedural complexity should not be overrated; once the ventilation is restored, perfusion, dissection and preservation are the same as for DBD. Aborted DCD procurement – or the so-called dry-run – on the other hand have been reported to be as high as 40% [19,27]. Although scoring systems were developed to predict which patients could potentially become DCD donors, the scoring efficacy lacks scientific accuracy [27].

Donation after circulatory death lung criteria and protocols

For DCD donor selection, most centers apply internationally agreed DBD donor criteria (Table 3).

To further increase the donor pool, centers also accept more extended-criteria donors (ECD). Procedural criteria on the other hand are center-specific and might play a decisive role in whether or not to accept DCD lung allografts. Examples of this are the location of the WLST (ICU versus operating room), the comfort therapy administered by the treating physician, allowed WIT and agonal phase, withdrawal of tracheal tube, time of reventilation, no-touch period and EVLP possibility [4,5,54].

Various ethical frameworks for pre-mortem management are used. In general, it is stated that any intervention that may accelerate death or cause potential harm is considered unacceptable. Administration of heparin is one example. In a DCD pig model Sanchez *et al.* showed that pre-mortem heparin administration did improve EVLP evaluation by

possibly maintaining endothelial homeostasis [55]. In another pig experiment, Keshava *et al.* [56] showed no difference in thrombus formation after flushing of the recovered lungs. To date, no comparative clinical study was performed and centers with or without heparin administration have reported equally good outcome [20].

More important is the appropriate treatment of a patient until death. Therefore, we would recommend continuous protective lung ventilation (tidal volume: 6–8 ml/kg ideal body weight, peak end-expiratory pressure (PEEP): 5–7 cmH₂O), performing adequate bronchoscopy and naso-gastric tube placement to prevent aspiration.

Clinical experience with uncontrolled donation after circulatory death

Experience with uDCD has been limited. Major concerns are that the exact length of postmortem WIT is unknown and that organ function cannot be assessed in advance [5]. Therefore, it is strongly recommended that the lungs should be properly evaluated with EVLP to reduce the risk of primary nonfunction and primary graft dysfunction (PGD) [57].

Currently, Madrid published the largest experience of 29 cases with an overall hospital mortality of 17% and PGD3 of 38% [58].

Clinical experience with controlled type of donation after circulatory death

The advantage of a cDCD setting is that pre-mortem assessment can be performed in the same way as for DBD, that the WIT is known, that the lungs can be inspected in situ and preserved in a standard fashion. If the WLST is performed in the operating room, WIT will remain limited (10–15 min). In general, longer cold ischemic time (CIT) is noticed in DCD compared with DBD donors. This is explained by the fact that DCD lungs are accepted after perfusion, whereas DBD lungs could already be evaluated in situ before cold flush and anesthesia in the recipient can already be induced. A second reason is more particular to Eurotransplant allocation rules, which state that DCD lungs cannot be offered until 4 h before the procedure. This might create logistical problems with no operating room available for the recipient.

Over the last decade, several centers have reported their single-center experience [9,13–23,24,25,26,27,28,29]. In most reports, data were compared with DBD. In general, results were excellent with most studies confirming that outcome after LTx from cDCD is the same as for DBD. We summarize the largest series in Table 4, describing

Table 4. Studies reporting on lung transplantation from controlled donation after circulatory death donor

Reference	Location	Study design	DCD/DBD	PGD		Outcome								
				% DCD/% DBD	Definition	1-year	3-year	5-year	7-year	10-year	3-year	5-year	7-year	
Mason <i>et al.</i> [13]	OPTN, USA	Multicenter retrospective	36/14 903	NR		87/69								
Puri <i>et al.</i> [14]	St. Louis, Missouri, USA	Single-center retrospective	11/282	36/NR	Grade 3, undefined timepoint	82/89								
De Oliveira <i>et al.</i> [15]	Wisconsin, Wisconsin, USA	Single-center retrospective	18/406	33/26	Grade 2 or 3 within 72h	88/88	82/73	82/63				80/75	72/58	
Van De Wauwer <i>et al.</i> [16]	Groningen, The Netherlands	Single-center retrospective	35/77	24/25, 9/16, 3/10 and 6/11	Grade 3 at 0, 24, 48 and 72h	91/91	85/76	73/66 ^a						
De Vleeschauwer <i>et al.</i> [17]	Leuven, Belgium	Single-center retrospective	21/154	55/55 ^a , 12/22 ^b , 10/12 ^b	Grade 3 at 0, 24 and 48h	95/91	71/75					70/82 ^b		
Zych <i>et al.</i> [18]	Harefield, London, UK	Single-center retrospective	26/131	25/12, 4/6, 4/10, 4/6	Grade 3 at 0, 24, 48 and 72h	89/87	82/75					83/81		
Lewey <i>et al.</i> [9]	Melbourne, Brisbane, Perth, Sidney, Australia	Multicenter retrospective	72/503	21/NR and 8/NR	Grade 2 and 3 at 24h	97/90		90/61 ^c						
Mason <i>et al.</i> [19]	Cleveland, Ohio, USA	Single-center retrospective	32/573	3/NR, 3/NR, 6/NR, 6/NR	Grade 3 at 0, 24, 48 and 72h	91/NR	71/NR							
Cypel <i>et al.</i> [20]	ISHLT, DCD registry (10 centers)	Multicenter retrospective	306 ^d /3992	NR		89/88	61/61							
Machuca <i>et al.</i> [21]	Toronto, Canada	Single-center retrospective	55/570	11/NR	Grade 3 at 72h	85/86	54/62							
Sabashnikov <i>et al.</i> [22]	Harefield, London, UK	Single-center retrospective, propensity-matched	60/120	27/11, 9/5, 5/7 and 5/9	Grade 3 at 0, 24, 48 and 72h	86/84	61/77	51/66 ^e				72/88	47/79 ^e	31/59 ^e
Rutens <i>et al.</i> [23]	Leuven, Belgium	Single-center retrospective	59/331	44/47	Grade 3 within 72h	87/91	76/83	71/78				82/85	79/68	
Van Suylen <i>et al.</i> [24]	Groningen, Utrecht, Rotterdam, The Netherlands	Multicenter retrospective, propensity-matched	130/130	8/8 and 8/6	Grade 3 at 48 and 72h	87/82	80/73	69/68				88/88	76/71	
Inci <i>et al.</i> [25]	Zürich, Switzerland	Single-center retrospective	21/130	26/48, 16/10, 16/14 and 15/14	Grade 3 at 0, 24, 48 and 72h	100/85	80/69					68/62		
Villavicencio <i>et al.</i> [26]	OPTN, USA	Multicenter retrospective, propensity-matched	389/20516	NR		86/85	59/55	33/30						
			311/311			87/88	68/71							
	Boston, Massachusetts, USA	Single-center retrospective	15/113	40/9 ^c , 13/11, 20/7 and 10/10	Grade 2 or 3 at 0, 24, 48 and 72h	86/92	86/63							
Costa <i>et al.</i> [27]	New York, New York, USA	Single-center retrospective	46/237	26/19, 20/19 and 13/17	Grade 3 at 24, 48 and 72h	91/91	78/75							
Barbero <i>et al.</i> [28]	Papworth, Cambridge, UK	Single-center retrospective ^f	23/163	26/21 and 17/12	Grade 2 or 3 at 24 and 72h	75/82	51/61					82/78	83/42 ^g	
Van Raemdonck <i>et al.</i> [29 ^h]	ISHLT, DCD registry (23 centers)	Multicenter retrospective	1090/10426	NR		89/88	63/61	59/59	41/39 ^b					

CLAD, chronic lung allograft dysfunction; DBD, donation after brain death; DCD, donation after circulatory death; ISHLT, International Society for Heart and Lung Transplantation; NR, not reported; OPTN, Organ Procurement and Transplantation Network; PGD, primary graft dysfunction.

^aOnly two DCD patients at risk.

^bEstimated from figure.

^cConsidered significant; *P* less than 0.05.

^dIncluding 4% DCD IV and 1% DCD V.

^eFive or less DCD patients at risk.

^fSurvival analysis in subgroup of bilateral lung transplants (14 DCD and 133 DBD).

^gOnly four DCD patients at risk.

PGD ratio, overall survival and chronic lung allograft dysfunction-free survival.

The significant differences between DCD and DBD were 5-year patient survival from the Australian cohort which revealed a 90% survival for the DCD versus 61% for the DBD cohort [9]; the Boston experience only showed worse PGD at time 0 for DCD in comparison with DBD [26[¶]]; and Sabashnikov *et al.* showed a shorter bronchiolitis obliterans-syndrome (BOS)-free survival in the DCD group, although after 4 years post-transplantation only five DCD patients were considered at-risk [22]. Furthermore, a meta-analysis revealed no difference between DBD and DCD LTx in regard to length of stay, acute rejection or airway complications [4]. The first analysis of the ISHLT DCD registry only revealed a 2-day longer stay following DCD LTx ($P=0.016$), which was confirmed in the cohort described by Costa (22 days for DCD versus 18 days for DBD, $P=0.0014$) [20,27]. In 2018, Villavicencio *et al.* performed a multivariable regression analysis of the OPTN data for 25 recipient and donor characteristics, revealing no association between DCD and increased mortality in comparison with DBD [26[¶]]. In 2016, Sabashnikov *et al.* reported the longest follow-up (7 years) comparing DCD with DBD, concluding that DCD lungs had a predisposition for developing BOS [22]. However, at 7-year follow-up only one DCD was included. An update by the ISHLT DCD registry is expected in 2019, comparing 1090 DCD versus 10426 DBD LTx [29^{¶¶}]. Five-year patient and BOS-free survival showed no difference between both groups. In future, more studies analyzing long-term outcome are needed.

Donation after circulatory death V, following euthanasia

After the first case of organ donation following euthanasia in Belgium in 2005, also the Netherlands and Canada created a legal framework for DCD V [59,60]. In general, only patients suffering from a debilitating benign disease like neurological or muscular disorder are considered for organ donation. A clear separation between the euthanasia request, the euthanasia procedure and the procurement is of utmost importance to exclude any conflict of interest between donor and recipient and between the teams involved. This strict separation is also mandatory to maintain public trust [60,61].

The first LTx from a DCD V donor was performed in Leuven in 2007 [59]. Until now, 14 double lungs from DCD V donors have been transplanted in Leuven, representing 12% of the DCD and 2% of the institutional LTx activity. With more LTx from DCD V performed in future it will become

interesting to investigate if there is a difference in outcome between DCD V, DCD III and DBD. Although donors after euthanasia resemble DCD III and their organs suffer a period of inevitable warm ischemia, they are usually not supported on a ventilator and the mode of death is completely different compared with ventilator switch-off awaiting hypoxic cardiac arrest. These donors do not experience an agonal phase prior to circulatory arrest as seen in donors dying from hypoxia or from cardiogenic/hypovolemic shock. There is also no catecholamine storm as observed in DBD donors. These benefits could lead to a better outcome.

A recent perspective article explored the ethical and legal considerations of euthanasia by organ donation for patients who wish to donate their organs as in a 'living organ donation setting' [62[¶]]. This procedure would omit any type of WIT. Currently no ethical or legal framework is available to allow this.

EX-VIVO LUNG PERFUSION

Selective use of EVLP is part of the DCD III program in most centers, however not a prerequisite. In our opinion, EVLP is not necessary in every case since excellent results were obtained without the routine use of EVLP. In the ISHLT 2015 report, only 12% of the DCD cases underwent normothermic EVLP [20]. This low percentage may reflect lack of EVLP-availability at the time of data collection, but also the perception of each center of the benefit of EVLP in assessing cDCD. However, these results have also shown that EVLP is a safe modality with the potential to increase confidence in DCD lungs translating to excellent outcomes. Furthermore, we believe that selective EVLP may help to better assess functionally ECD lungs and may help to safely accept longer agonal phases or expected longer ischemic times. Possible indications for EVLP may be: PaO₂ less than 300 mmHg, edematous lungs, massive blood transfusion (>10U), poor lung compliance, suspicion of aspiration or pulmonary infection.

In 2017, the University of Alberta reported on seven successful DCD LTx that underwent portable normothermic EVLP (OCS Lung, Transmedics, Inc., Andover, Massachusetts, USA) [63[¶]]. In comparison with non-DCD lungs, this EVLP cohort had a significant shorter CIT, a lower PGD grade and higher P:F ratio at 72 h post-transplantation. In 2015, Toronto compared 28 DCD LTx with EVLP (Toronto EVLP-system) versus 27 without EVLP, revealing no difference in survival but a significant shorter hospital stay for the EVLP group [21]. For uDCD, the results remain suboptimal and therefore EVLP is strongly recommended by the ISHLT DCD working group.

Currently the final reports of two prospective multicenter clinical trials involving DCD LTx and EVLP are awaited; first, the aim of the EXPAND Lung Trial (OCS Lung, Transmedics, Inc.) is to assess the short-term clinical outcome of lungs from ECD (including DCD) that were normothermically preserved. 79 ECD were included, of which 33% were DCD LTx [64^{***}]; and second, the NOVEL-extension trial (XVIVO XPS) aims to evaluate the outcome of EVLP in case of DCD LTx. 24 DCD-EVLP LTx were included. In comparison with DBD, there was no difference in PGD and the survival between EVLP recovered DCD, DBD allografts and non-EVLP controls [65^{***}].

These results confirm that EVLP is a safe platform that may further expand the donor pool by assessing questionable DCD lungs. EVLP will also further expand the donor pool as it is an ideal platform for therapeutic intervention (antibiotic, fibrinolytic therapy) and immunomodulation [66^{***}].

NORMOTHERMIC REGIONAL PERFUSION AND DONATION AFTER CIRCULATORY DEATH HEART PROCUREMENT: THE FUTURE CHALLENGES

The application of extracorporeal circulation technology to DCD organ retrieval in the form of thoraco-abdominal normothermic regional perfusion (NRP) is believed to make a significant impact [67^{***}]. In this setting, DCD heart transplantation has been made possible in synergy with technological advances of ex-situ preservation [68^{***}]. NRP enables conversion from a DCD to a DBD-type donor which offers the opportunity for a dynamic organ assessment in situ after death declaration and may lead to expansion of acceptance criteria as well as creating a window of opportunity for early interventions. However, this new logistic challenge should carefully be assessed. Each procurement will require a detailed discussion between the different teams about coordination, timings and preservation strategies.

CONCLUSION

A global implementation of DCD lung donation would significantly decrease the mortality on the waiting-list. Over the last 10 years, several centers and the ISHLT DCD registry reported their experience, showing that LTx from cDCD results in the same short-term and mid-term outcome as from DBD donors. It is advised that EVLP should be used for uDCD. Future research on EVLP, the long-term outcome after DCD and a detailed

analysis of the agonal phase are warranted to further explore the true potential of DCD lung donation.

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Conflicts of interest

There are no conflicts of interest.

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