ORIGINAL ARTICLE

Utilization of extracorporeal membrane oxygenation in DCD and DBD lung transplants: a 2-year single-center experience

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SUMMARY

Donation after circulatory death (DCD) has the potential to expand the lung donor pool. We aimed to assess whether DCD affected the need for perioperative extracorporeal membrane oxygenation (ECMO) and perioperative outcomes in lung transplantation (LTx) as compared to donation after brain death (DBD). All consecutive LTxs performed between April 2017 and March 2019 at our tertiary center were analyzed. Donor and recipient preoperative characteristics, utilization of ECMO, and perioperative clinical outcomes were compared between DCD and DBD LTx. Multivariate models (frequentist and Bayes) were fitted to evaluate an independent effect of DCD on the intra- and postoperative need for ECMO. Out of 105 enrolled patients, 25 (23.8%) were DCD LTx. Donors' and preoperative recipients' characteristics were comparable between the groups. Intraoperatively, mechanical circulatory support (MCS) was more common in DCD LTx (56.0% vs. 36.2%), but the adjusted difference was minor (RR = 1.16, 95% CI 0.64–2.12; $P = 0.613$). MCS duration, and first and second lung ischemia time were longer in the DCD group. Postoperatively, DCD recipients more commonly required ECMO (32.0% vs. 7.5%) and the difference remained considerable after adjustment for the pre- and intraoperative covariates: RR = 4.11 (95% CI 0.95–17.7), $P = 0.058$, Bayes RR = 4.15 (95% CrI 1.28–13.0). Sensitivity analyses (two DCD-DBD matching procedures) supported a higher risk of postoperative ECMO need in DCD patients. Incidence of delayed chest closure, postoperative chest drainage, and renal replacement therapy was higher in the DCD group. Early postoperative outcomes after DCD LTx appeared generally comparable to those after DBD LTx. DCD was associated with a higher need for postoperative ECMO which could influence clinical outcomes. However, as the DCD group had a significantly higher use of EVLP with more common ECMO preoperatively, this might have contributed to worse outcomes in the DCD group.

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Key words
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Introduction

Lung transplantation (LTx) represents a potentially life-saving therapy for selected patients with end-stage lung disease. However, persistent donor shortage resulting in increased waiting list mortality remains one of the major limitations in LTx [1,2]. Among various strategies to expand the donor pool, the use of lungs from donation after circulatory death (DCD) is becoming established in several countries [3-7]. It is still argued whether LTx using DCD organs is associated with differences in clinical outcomes compared with organs procured following donation after brain death (DBD) [6,8-12]. Concerns of ischemia during the period between discontinuation of life support and organ procurement have limited its application [2]. In our institution, transplantation of the lungs procured from Maastricht category III DCD donors has been an important aspect since 2007 as the proportion has gradually increased from 8% to almost 25% in the last year. Our institution previously reported that the mid-term and long-term survival after DCD LTx is in comparable with the DBD LTx [3,13]; however, at that time, a detailed comparison of extracorporeal membrane oxygenation (ECMO) utilization between the groups was not performed. Several centers reported an intraoperative use of the mechanical circulatory support (MCS) in 20–40% of patients undergoing LTx [14,15]. Nevertheless, there is a growing evidence that the LTx patients requiring intraoperative or post-transplant ECMO have higher risk of bleeding and blood transfusions and have longer duration of mechanical ventilation, intensive care unit (ICU), and hospital stay [16-18].

In the present analysis, we aimed to assess whether DCD LTx in comparison with DBD had an impact on the utilization of perioperative ECMO in our center over a 2-year study period.

Patients and methods

Study design

This study is a retrospective analysis of all consecutive LTx performed at Harefield Hospital between April 2017 and March 2019. The donor data were prospectively collected. Recipients who underwent a redo or single transplantation were excluded. The topic was analyzed in part as a clinical audit performed at Harefield Hospital (reference number 3123). Institutional Ethic Committee approval was obtained. The recipients bridged to transplantation with ECMO were also included in the study.

Data were extracted from the institutional electronic system and from the UK Donor Registry. The predefined objectives were to evaluate potential independent associations of DCD (as opposed to DBD) with the following outcomes: a) the need for intraoperative MSC; b) the need for postoperative ECMO. Data suggested grouping of patients in two clusters based on intraoperative characteristics (*ex vivo* lung perfusion [EVLP], need for MCS, lung ischemia time, and duration of surgery). The effect of DCD on this clustering was therefore also analyzed. As the analysis of the postoperative outcomes also included intraoperative factors that might have affected the outcomes of interest (Fig. 1), mediation analysis was also considered.

Donor selection criteria, assessment, and lung procurement

The selection of donors was based on the current standard ISHLT criteria including extended donor criteria [19]. Donor organ assessment included radiological assessment, fiber-optic bronchoscopy, organ inspection and palpation, assessment of elasticity using deflation test and both systemic and differential blood gas analysis from each pulmonary vein. Recruitment maneuvers were performed prior to the lung retrieval in order to improve

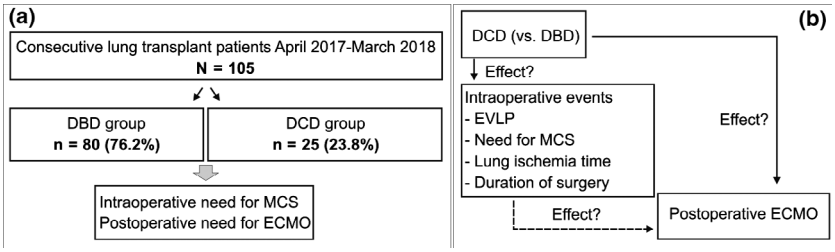

Figure 1 (a) Study outline. (b) The sequence of analyzed associations.

gas exchange. In the case of DBD donors, the ICU is involved in the donor management and optimization before arrival of the cardiothoracic retrieval team.

Particularly, for the DCD group, organs were procured according to the national protocol once donors met standard criteria following withdrawal of life-sustaining therapy (WLST) [20]. DCD lungs were taken into consideration if the time between WLST and cardiac arrest (agonal period) was less than 120 minutes. Death was certified following a 5-minute period of asystole. The total ischemic time was calculated for both lungs and was defined as the time between cardiac arrest in DCD donors (or aortic cross-clamp in DBD donors) and reperfusion of the first and second implanted lung. Surgical technique of the DCD retrieval differs from the standard procedure in several steps and is previously described by our group [3,13].

The standard preservation solution utilized in our institution is low-potassium dextran (Perfadex®, Medisan, Uppsala, Sweden) solution augmented with glyceryl trinitrate 25 mg/L, CaCl2 0.6 mL/L, 3.6% tromethamine (THAM, Hospira, Inc., Lake Forest, IL, USA) and prostacyclin 2.5 ml/L. Lung preservation was described earlier by our group [13]. In 2 DBD and 8 DCD donors, lungs were reconditioned with EVLP. In this case, after returning to our institution, lungs were transferred to the XVIVO Organ Chamber (Vitrolife AB, Göteborg, Sweden) and assessed during *ex vivo* perfusion with Steen solution (Vitrolife AB, Göteborg, Sweden) [21].

ECMO and surgical technique

All patients were listed for transplant after being accepted by multidisciplinary team according to current guidelines. As recommended by our Ethics Committee, all patients on the LTx waiting list were additionally consented for transplantation from DCD donors. Preoperative ECMO was used as a bridge to transplantation in patients who have suffered acute decompensation and continued to deteriorate despite noninvasive or invasive mechanical ventilation. The intraoperative MCS was considered due to severe pulmonary hypertension, inability to tolerate one-lung ventilation, and hemodynamic instability after pulmonary artery clamping. In patients who were bridged to transplantation with ECMO, we considered continuation of the same support during the surgery. Preoperative veno-arterial (VA) ECMO was maintained during the transplantation while veno-venous (VV) ECMO was converted intraoperatively to VA ECMO. Although ECMO was our preferred method of intraoperative support, cardiopulmonary bypass (CPB) has been used depending on the surgeon's preference and particularly in the case of severe hemodynamic instability or uncontrolled intraoperative bleeding.

Recently, sequential anterolateral thoracotomies have been our preferred surgical approach in bilateral sequential single LTx. The clamshell incision was performed in cases with inadequate exposure, increased technical difficulty (previous chest surgery, pleural adhesions) or when it was the transplant surgeon's preference. In these cases, central cannulation of ascending aorta with 18F to 22F EOPA arterial cannula and right atrium with 32F venous Medtronic cannula was preferred. In case of peripheral femoral cannulation, 17F to 21F Bio-Medicus® arterial cannula with 25F Bio-Medicus® multistage venous cannula were inserted using an open technique. If ECMO support needed to be continued postoperatively and there were any concerns with leg ischemia at the end of the transplantation, distal leg perfusion cannula was inserted into the femoral artery.

If CPB was required, full heparinization (300 IU/kg) was provided before initiation of CPB to maintain an activated clotting time (ACT) greater than 400 seconds during the period of CPB. After discontinuation of the CPB, protamine sulfate was administered to reverse the effect of heparin. On the other hand, when ECMO was used, an initial bolus of 5,000 IU intravenous heparin was given and ACT was maintained between 180 and 250 seconds during the period of MCS. In this group, protamine sulfate administration was considered after decannulation in cases of significant bleeding. Postoperatively, we have used VV ECMO to facilitate improved gas exchange when it was required. We have used VA ECMO to provide additional hemodynamic support, or in the case of severe pulmonary hypertension to protect new lungs from hyperperfusion.

Data analysis

Donors' and recipients' characteristics are summarized by donor type. Considering a relatively limited number of patients, univariate comparisons between the two subsets were performed without accounting for multiplicity (hence have no inferential meaning), but were supplemented by standardized differences (d) to illustrate the size of a difference irrespectively of the sample size. Multivariate models were fitted to evaluate independent effect of DCD on the risk of (i) intraoperative need for MCS and (ii) falling into a "worse" intraoperative cluster identified by a fuzzy clustering algorithm

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(more frequent need for EVLP and MCS, longer MCS duration, longer lung ischemia times and surgery duration vs. a "better" cluster). Donors' and preoperative recipients' characteristics were considered as adjustments; (iii) postoperative need for ECMO accounting for the preoperative or for both preoperative and intraoperative adjustments. Both frequentist (log-binomial, two-sided alpha = 0.05) and Bayesian models (link = log, distribution = Poisson, improper Jeffreys priors with 2000 burn-ins, 50000 Monte Carlo samples, Gamerman sampling and thinning = 1) were applied (see Appendix S1 for details on multivariate models). Finally, we implemented a mediation analysis based on logistic models to evaluate whether the association between donor type and postoperative outcomes could be divided into a "direct" and "indirect" one (via its effect on intraoperative events) [22]. For sensitivity analyses, we applied two matching methods [DCD-DBD exact matching on preoperative use of ECMO, implementation of EVLP, and diagnosis of cystic fibrosis; and optimal matching in respect to propensity scores based on overall baseline recipients' characteristics (see Appendix S1)]. We used SAS for Windows 9.4 (SAS Inc., Cary, NC), package rstanarm in R and NCSS software (NCSS, LLC, Kaysville, Utah) for the cluster analysis.

Results

Out of 105 enrolled patients, 25 (23.8%) received lungs procured from DCD donors and 80 (76.2%) received lungs from DBD donors. Except for the higher proportion of men in the DCD group, DBD and DCD donors were similar with respect to many other characteristics (Table 1 and Appendix S1: Table S1). The most common diagnosis leading to LTx in both DBD and DCD recipients was cystic fibrosis and both groups were comparable regarding a number of characteristics. However, DCD recipients appeared slightly younger, more commonly men, and were somewhat more commonly (16.7% vs. 7.5%) bridged to transplant with ECMO (Table 1). Other characteristics, including the underlying diagnosis, size matching, right ventricular failure, pulmonary artery systolic pressure, lung function, estimated glomerular filtration rate and liver function were fairly comparable between the two subsets (Table 1).

More DCD than DBD recipients required intraoperative MCS (56% vs. 36.2%; RR = 1.54, 95% CI 0.95–1.37). ECMO was used in similar proportions of patients (20.0% and 18.8%, respectively), while CPB was more commonly used in DCD recipients (36.0% vs. 17.5%) (Table 2). To reduce dimensionality of the intraoperative data, cluster analysis was performed that identified two clusters of which one ("worse") was characterized by considerably more common use of EVLP, more common utilization and longer duration of MCS, longer lung ischemia time, and surgery duration than the other one ("better") (Table 3). DCD recipients more commonly fell into the "worse" cluster than the DBD recipients (64.0% vs. 38.7%) (Table 3). In multivariate analyses, DCD donation was not independently associated with the risk of intraoperative MCS (RR 1.16, 95% CI: 0.64–2.12, $P = 0.613$; Bayes RR = 1.39, 95% CrI 0.72–0.66) (Table 4), but it was associated with a higher risk of falling into the "worse" cluster (RR 1.58, 95% CI 1.06–2.35, $P = 0.026$; Bayes RR = 1.49, 95% CrI 1.04–2.29) (Table 4).

More DCD than DBD recipients required postoperative ECMO (32.0% vs. 7.5%) (Table 2). In multivariate analyses, DCD donation was independently associated with a higher risk of postoperative ECMO when not accounting for the intraoperative covariates (RR = 4.41, 95% CI 1.21–16.1, $P = 0.025$; Bayes RR = 4.74, 95% CrI 1.59–14.6) (Table 5). However, intraoperative use of MCS and classification into the "worse" cluster were also univariately associated with a probability of postoperative need for ECMO (Appendix S1: Figure S1). When intraoperative use of MCS was accounted for, independent association between DCD and postoperative need for ECMO was slightly weaker (RR = 3.20, 95% CI 0.70–14.7, $P = 0.133$; Bayes RR = 4.22, 95% CrI 1.27–13.4) (Table 6), and it was not much changed when classification into the "worse" intraoperative cluster was considered instead of MCS use (RR = 4.11, 95% CI 0.95–17.7, $P = 0.058$; Bayes RR = 4.15, 95% CrI 1.28–13.0) (Table 7). Analysis of mediation models in which donor type was treated as a predictor, intraoperative MCS or classification into the "worse" intraoperative cluster were treated as mediators and other effects (Tables 6, 7) were considered as covariates, indicated that the "link" between DCD and postoperative need for ECMO was mostly a direct one. In fact, only a minor part of it appeared mediated through its association with the intraoperative need for MCS (28.2% of the total effect is mediated; Appendix S1: Table S2), or, alternatively, through its association with classification into the "worse" intraoperative cluster (23.4% of the total effect is mediated, Appendix S1: Table S3). In sensitivity analyses (19 DCD-DBD pairs exactly matched in respect to preoperative use of ECMO, use of EVLP and diagnosis of CF; or 24 DCD-DBD pairs optimally matched based on propensity scores), proportion of DCD patients requiring postoperative ECMO remained higher

Table 1. Donors' and preoperative recipients' characteristics. Data are count (%) or median (quartiles; range). Standardized differences (*d*) are calculated as DCD-DBD. Appendix S1: Table S1 provides additional data.

	DBD	DCD	*d*	*P*
Number	80	25		
Donors' characteristics				
Age (years)	52 (37–59; 19–74)	49 (32–59; 11–63)	−0.155	0.614
Gender, male	30 (37.5)	16 (64.0)	0.598	0.020
Height (cm)	169 (163–177; 150–201)	174 (165–183; 155–192)	0.343	0.173
Smoking history	41 (51.3)	10 (40.0)	−0.251	0.324
Donor injury: ICH/others	56 (70.0)/24	16 (64.0)/9	−0.150	0.576
Abnormal chest X-ray	22 (27.5)	9 (36.0)	0.217	0.422
Ventilation duration (days)	2.3 (1.9–3.1; 1.0–9.3)	2.4 (1.7–3.8; 1.3–8.6)	0.345	0.898
pO_2/FiO_2 preretrieval	0.58 (0.43–0.64; 0.14–0.74)	0.51 (0.44–0.63; 0.15–0.77)	−0.141	0.598
Cannabis smokers	6 (7.5)	2 (8.0)	0.038	0.935
Recipients' characteristics				
Age (years)	47.5 (33–57; 20–68)	39 (31.5–53.5; 21–61)	−0.297	0.219
Gender, male	38 (47.5)	16 (64.0)	0.372	0.147
Height (cm)	166 (161–173; 146–186)	172 (162–179; 148–190)	0.216	0.341
Body surface area (m^2)	1.7 (1.5–1.8; 1.2–2.3)	1.7 (1.6–1.9; 1.2–2.2)	0.146	0.601
Primary diagnosis				
Cystic fibrosis	37 (46.3)	14 (56.0)	0.216	0.394
Emphysema	22 (27.5)	5 (20.0)		
α1-Antitrypsin deficiency	9 (11.3)	4 (16.0)		
Bronchiectasis	4 (5.0)	0		
Pulmonary fibrosis	3 (3.8)	1 (4.0)		
Hypersensitivity pneumonitis	3 (3.8)	0		
Interstitial lung disease	1 (1.3)	0		
Obliterative bronchiolitis	0	1 (4.0)		
Sarcoidosis	1 (1.3)	0		
FEV1 (L)	0.71 (0.50–0.96; 0.32–3.21)	0.72 (0.58–0.88; 0.37–1.12)	−0.176	0.967
Forced vital capacity (L)	1.82 (1.36–2.46; 0.67–4.24)	1.97 (1.54–2.33; 0.96–3.76)	0.065	0.761
PASP (mmHg)	20 (20–40; 20–90)	26 (20–36; 15–60)	−0.005	0.974
Long-term oxygen therapy	57 (71.2)	17 (68.0)	−0.085	0.757
Noninvasive ventilation	24 (30.0)	6 (24.0)	−0.168	0.557
Preoperative ECMO [VA/VV]	6 (7.5) [1/5]	4 (16.7) [0/4]	0.471	0.230
RV function normal	59 (73.7)	19 (76.0)	0.066	0.821
Impaired [mild/moderate]	21 (26.3) [19/2]	6 (24.0) [5/1]		
eGFR (mL/min/1.73m^2)	90 (90–90; 57–90)	90 (90–90; 64–90)	−0.056	0.940
ALT (IU/L)	16 (12–25; 6–111)	22 (13–34.5; 5–208)	0.264	0.172
Bilirubin (μmol/L)	7 (5–10; 2–25)	7 (4.5–9.5; 3–17)	0.067	0.8352

ALT—alanine aminotransferase, DBD—donation after brain death, DCD—donation after circulatory death, ECMO—extracorporeal membrane oxygenation (VA—veno-arterial, VV—veno-venous), eGFR—estimated glomerular filtration rate, FEV1—forced expiratory volume in 1st second, ICH—intracranial hemorrhage, PASP—pulmonary artery systolic pressure; RV—right ventricle.

compared with DBD patients (31.6% vs. 5.3% or 33.3% vs. 12.5%, respectively) (see Appendix S1: Table S4, Figure S4 for exact matches and Appendix S1: Table S5 and Figure S5 for propensity score-based optimal matches).

A number of postoperative outcomes were more common in DCD patients (Table 2), including delayed chest closure (32.0% vs. 10.0%), respiratory failure (64.0% vs. 43.8%), tracheostomy (44.0% vs. 35.0%), sepsis (24.0% vs. 13.8%), acute kidney injury (32.0% vs. 15.0%), and a need for renal replacement therapy (52.0% vs. 26.2%). DCD patients also experienced higher chest drainage over the first 24 hours (1625 mL vs. 1061 mL), higher peak lactate levels (6.6 vs. 4.9 mmol/L), longer postoperative mechanical ventilation (42.5 vs. 32.8 days), and longer hospital stay (34 vs. 28 days).

Discussion

Since DCD LTx is still confined only to certain countries, there is a limited experience regarding clinical events which are specific for the DCD [2]. Recently,

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Table 2. Intraoperative data and early postoperative outcomes. Data are count (%) or median (quartiles; range). Standardized differences (*d*) are calculated as DCD-DBD. Appendix S1: Table S1 provides additional data.

	DBD	DCD	*d*	*P*
Number	80	25		
Intraoperative				
Clamshell/bilateral anterior thoracotomy	56 (70.0)/24	19 (76.0)/6	0.168	0.557
Use of EVLP	2 (2.5)	8 (32.0)	1.603	<0.001
1st lung ischemia time (min)	400 (308–497; 186–782)	533 (426–629; 267–832)	0.726	0.003
2nd lung ischemia time (min)	528 (458–654; 312–905)	686 (565–811; 350–935)	0.669	0.006
1st lung ischemia—EVLP time	397 (308–495; 186–782)	512 (408–577; 132–715)	0.448	0.023
2nd lung ischemia—EVLP time	528 (458–649; 312–905)	653 (540–725; 224–895)	0.405	0.046
Surgery duration (min)	457 (395–525; 240–860)	450 (395–665; 185–990)	0.306	0.399
Mechanical circulatory support	29 (36.2)	14 (56.0)	0.444	0.082
ECMO/CPB	15 (18.8)/14 (17.5)	5 (20.0)/9 (36)		
ECMO/CPB duration in treated (min)	166 (108–285; 65–474)	332 (124–471; 97–600)	0.693	0.046
Early postoperative				
Mechanical ventilation (hours)	32.8 (19.3–56.8; 2–992)	42.5 (26.8–69.0; 6.5–640)	0.001	0.122
Delayed chest closure	8 (10.0)	8 (32.0)	0.795	0.012
ECMO [VA/VV]	6 (7.5) [4/2]	8 (32.0) [7/1]	0.969	0.004
ECMO duration in treated (hours)	99.5 (13–244; 10–372)	147.5 (98–419; 86–600)	0.393	0.247
Drainage 24h (mL)	1062 (806–1319; 400–5800)	1625 (1037–3275; 400–5900)	0.738	0.001
Red blood cells 72h (units)	3 (1.0–5.8; 0–54)	5 (1.5–16.5; 0–51)	0.458	0.072
Fresh-frozen plasma 72h (units)	2 (0–4; 0–22)	4 (1–9; 0–24)	0.493	0.022
Platelets 72h (units)	1 (0–2; 0–16)	2 (0–5; 0–15)	0.454	0.080
Peak lactates 24h (mmol/L)	4.9 (3.3–6.3; 1.5–14.4)	6.6 (3.9–10.6; 2.3–17.0)	0.561	0.023
Acute kidney injury	12 (15.0)	8 (32.0)	0.540	0.070
Renal replacement therapy	21 (26.2)	13 (52.0)	0.613	0.019
Respiratory failure	35 (43.8)	16 (64.0)	0.455	0.076
Tracheostomy	28 (35.0)	11 (44.0)	0.301	0.420
Pneumonia	32 (40.0)	8 (32.0)	−0.192	0.468
Sepsis	11 (13.8)	6 (24.0)	0.281	0.241
Stroke	6 (7.5)	0	−0.862	0.144
RV failure	1 (1.2)	5 (20.0)	1.643	0.001
ICU length of stay (days)	7.5 (3.8–20.2; 1.4–97.4)	7.5 (3.8–27.0; 2.2–96.1)	0.099	0.632
Hospital length of stay (days)	28 (21–52; 2–163)	34 (18–52; 6–105)	0.170	0.772

CPB—cardiopulmonary bypass, ECMO—extracorporeal membrane oxygenation (VA—veno-arterial, VV—veno-venous), eGFR—estimated glomerular filtration rate, EVLP—ex vivo lung perfusion, ICU—intensive care unit, RV—right ventricle.

ISHLT DCD Registry report [5] showed similar favorable long-term survival in DCD-III and DBD lung recipients (5-year survival 63% vs. 61%). It also included the results from our center. Furthermore, our institution had previously reported comparable mid-term and long-term survival in DCD and DBD LTx [3,13]. In this study, we presented our experience with perioperative utilization of ECMO in DCD and DBD LTx over a 2-year period. Our main finding was that DCD donation was independently associated with a higher risk of postoperative ECMO. When intraoperative use of MCS was accounted for in a multivariate analysis, independent association between DCD and postoperative need for ECMO was still observed although slightly weaker. Furthermore, in sensitivity analyses the proportion of DCD patients requiring postoperative ECMO remained higher when compared to DBD patients. Despite both groups had comparable baseline donor and recipient characteristics, intraoperative MCS was more commonly used in the DCD group. Furthermore, a number of postoperative complications were more common in DCD patients and this could be only partially explained with a higher incidence of postoperative ECMO.

Additional findings of interest were observed in the study. We have observed higher postoperative chest drainage, need for blood transfusions, incidence of delayed chest closure, and need for RRT in the DCD group. EVLP lung assessment was performed in approximately one third of DCD lungs which was significantly

Table 3. Patient clusters identified based on intraoperative data and distribution of DCD and DBD donors across the two clusters. Data are count (%) or median (quartiles; range).

	Cluster 1 ("better")	Cluster 2 ("worse")	*d* Cluster 2 - 1	*P*
Number	58	47		
EVLP	2 (3.4)	8 (17.0)	0.963	0.016
Need for intraoperative MCS	15 (25.9)	28 (59.6)	0.794	<0.001
Duration of intraoperative MCS (min)	0 (0–32.5; 0–474)	105 (0–266; 0–600)	0.620	<0.001
1st lung ischemia time (min)	321 (293–400; 186–488)	570 (492–652; 394–832)	2.686	<0.001
2nd lung ischemia time (min)	478 (409–528; 312–605)	710 (650–833; 527–935)	2.726	<0.001
1st lung ischemia – EVLP time	319 (288–388; 132–459)	547 (487–620; 394–782)	2.816	<0.001
2nd lung ischemia – EVLP time	467 (405–518; 224–599)	691 (631–750; 522–905)	2.713	<0.001
Surgery duration (min)	430 (373–501; 185–860)	500 (420–590; 250–990)	0.698	<0.001
DCD (n = 25)	9/25 (36.0)	16/25 (64.0)		
DBD (n = 80)	49/80 (61.3)	31/80 (38.7)		

Clusters were identified based on the need for EVLP, intraoperative MCS, lung ischemia times, and surgery duration. Options with 2 or 3 clusters were evaluated. Two-cluster option resulted in a more favorable normalized Kaufman coefficient [Dc(U)] (0.161 vs. 0.222) and a more favorable normalized Dunn's coefficient [Fc(U)] (0.512 vs. 0.445) than the three-cluster option. DBD—donation after brain death, DCD—donation after circulatory death, EVLP—Ex vivo lung perfusion, MCS—mechanical circulatory support.

Table 4. Summary of multivariate analysis. Evaluation of independent association of donation after circulatory death (DCD, as opposed to donation after brain death, DBD) and intraoperative outcomes—need for MCS and classification into the "worse" cluster (as identified in Table 3).

	Frequentist		Bayesian	
Intraoperative MCS	RR (95% CI)	*P*	RR (95% HPD CrI)	Probabilities
DCD (vs. DBD)	1.16 (0.64–2.12)	0.613	1.39 (0.72–2.66)	*P* (RR> 1.0)=83.0%
Preoperative ECMO (vs. no)	2.19 (1.06–4.53)	0.034	2.24 (1.03–4.47)	*P* (RR> 1.0)=97.9%
Donor's preretrieval pO_2/FiO_2	0.40 (0.06–2.55)	0.328	0.38 (0.04–3.34)	*P* (RR < 1.0)=80.6%
Recipient's FVC	0.63 (0.41–0.95)	0.029	0.64 (0.40–0.99)	*P* (RR < 1.0)=98.0%
"Worse" intraoperative cluster				
DCD (vs. DBD)	1.58 (1.06–2.35)	0.026	1.49 (1.04–2.29)	*P* (RR> 1.0)=98.3%
Presurgery ECMO (vs. no)	1.08 (0.55–2.12)	0.823	1.05 (0.56–1.50)	*P* (RR> 1.0)=58.0%
Donor's preretrieval pO_2/FiO_2	0.25 (0.05–1.31)	0.100	0.44 (0.15–1.58)	*P* (RR < 1.0)=89.9%
Recipient's FVC	0.93 (0.71–1.22)	0.597	0.96 (0.74–1.21)	*P* (RR < 1.0)=60.6%

See Supplemental Methods for multivariate model building procedure. Appendix S1: Figure S2 contains trace plots showing adequate mixing for all independents in the Bayes models. ECMO—extracorporeal membrane oxygenation, FVC—forced vital capacity, MCS—mechanical circulatory support

more than in the DBD group. In the majority of cases, the main reason was to reassess the lungs retrieved by another center as per surgeon's preference [21,23].

Although we have observed more commonly CPB than ECMO in the DCD group, the choice of intraoperative MCS was at the surgeon's discretion and related to specific indications. Considering the small sample, it is difficult to distinguish between the effects of intraoperative CPB vs. ECMO vs. no intraoperative MCS on postoperative outcomes. Raw data (Appendix S1: Figure S1) indicate that postoperative need for ECMO might be more common if CPB is used intraoperatively rather than ECMO. However, mediation analysis demonstrated that DCD was associated with a higher probability of postoperative ECMO, which was mediated only partially (28.2%) through its association with intraoperative events. ECMO prolongation also bears some risks. Interestingly, duration of intraoperative MCS support, total 1st and 2nd lung ischemia was significantly longer in the DCD group. Lung ischemic times corrected for EVLP time remained significantly longer in DCD LTx.

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Table 5. Evaluation of independent association of donation after circulatory death (DCD, as opposed to donation after brain death, DBD) and postoperative need for ECMO: summary of multivariate analysis *without* taking into account the intraoperative need for MCS or classification into the "worse cluster" (as identified in Table 3).

	Frequentist		Bayesian	
Postoperative ECMO	RR (95% CI)	*P*	RR (95% HPD CrI)	Probabilities
DCD (vs. DBD)	4.41 (1.21–16.1)	0.025	4.74 (1.59–14.6)	*P* (RR> 1.0)=99.6%
Preoperative ECMO (vs. no)	6.24 (1.33–29.2)	0.021	4.33 (1.02–17.8)	*P* (RR> 1.0)=97.4%
Donor's preretrieval pO_2/FiO_2	0.10 (0.01–3.09)	0.186	0.04 (0.00–2.58)	*P* (RR < 1.0)=93.4%
Recipient's FVC	0.17 (0.05–0.62)	0.008	0.21 (0.06–0.62)	*P* (RR < 1.0)=99.9%
Recipient's age	1.06 (1.00–1.13)	0.052	1.04 (0.99–1.10)	*P* (RR> 1.0)=96.2%

See Supplemental Methods for multivariate model building procedure. Appendix S1: Figure S3 contains trace plots showing adequate mixing for all independents in the Bayes model. ECMO—extracorporeal membrane oxygenation, FVC—forced vital capacity, MCS—mechanical circulatory support.

Table 6. Evaluation of independent association of donation after circulatory death (DCD, as opposed to donation after brain death, DBD) and postoperative need for ECMO: summary of multivariate analysis *accounting for* the intraoperative event "use of MCS".

	Frequentist		Bayesian	
Postoperative ECMO	RR (95% CI)	*P*	RR (95% HPD CrI)	Probabilities
Intraoperative MCS (vs. no)	10.1 (1.24–82.4)	0.031	9.19 (1.49–80.0)	*P* (RR> 1.0)=99.8%
DCD (vs. DBD)	3.20 (0.70–14.7)	0.133	4.22 (1.27–13.4)	*P* (RR> 1.0)=99.3%
Preoperative ECMO (vs. no)	3.29 (0.65–16.8)	0.149	2.48 (0.61–10.1)	*P* (RR> 1.0)=90.3%
Donor's preretrieval pO_2/FiO_2	0.32 (0.00–21.9)	0.591	0.18 (0.00–13.8)	*P* (RR < 1.0)=78.7%
Recipient's FVC	0.30 (0.06–1.38)	0.323	0.30 (0.08–0.99)	*P* (RR < 1.0)=98.4%
Recipient's age	1.05 (1.00–1.11)	0.072	1.04 (1.00–1.10)	*P* (RR> 1.0)=97.9%

Intraoperative use of MCS was added to the final model depicted in Table 5. ECMO—extracorporeal membrane oxygenation, FVC—forced vital capacity, MCS—mechanical circulatory support.

Intraoperative use of ECMO has several advantages [14,24]. It can allow lung-protective ventilation strategy, can effectively reduce pulmonary blood flow, and can provide hemodynamic stabilization. However, it carries risk of some adverse effects such as bleeding complications, systemic inflammatory response, acute kidney injury, and thromboembolic complications [10,16,17]. These events can be triggered even more with the use of CPB [15]. In recent reports, postoperative use of ECMO varies from 11% to 55% in patients intraoperatively supported with ECMO and 6–27% if CPB was used [14].

One of the challenges in using DCD lungs is a scarcity of complete information on donor lung assessment. The use of EVLP could be helpful to overcome this limitation. Despite these challenges, many recent studies have demonstrated DCD LTx results to be comparable to those obtained from DBD donation [5-9,25,26]. Recently, we have reported a Kaplan–Meier analysis showing comparable cumulative survival in the DBD and DCD group of 84.2 vs. 86.1% at 1 year, 77.3 vs. 60.9% at 3 years, and 66.4 vs. 50.8% at 7 years, respectively [3,13]. Furthermore, our group has recently demonstrated that DCD recipients have a predisposition for development of bronchiolitis obliterans syndrome in the long-term follow-up [13]. In addition, Vilavicencio *et al.* have recently demonstrated in a propensity-matched analysis that DCD LTx had similar post-transplantation survival when compared with the DBD group [10]. However, they have observed more pulmonary edema on the chest X-ray immediately after LTx and longer mean time to extubation in the DCD group. Similar to our study, they presented comparable baseline characteristics between the DBD and DCD groups along with a higher use of EVLP in the DCD group (53% vs. 7%) and few other differences (recipient age and diagnosis) among the groups [10]. De Vleeschauwer *et al.* [9] also reported comparable survival rates at 6 months, 1 year, and 3 years which were 95%, 95%, and 71% in the DCD group and 96%, 91%, and

Table 7. Evaluation of independent association of donation after circulatory death (DCD, as opposed to donation after brain death, DBD) and postoperative need for ECMO: summary of multivariate analysis *taking into accounting for* classification into the "worse" intraoperative cluster (as identified in Table 3).

	Frequentist		Bayesian	
Postoperative ECMO	RR (95% CI)	*P*	RR (95% HPD CrI)	Probabilities
"Worse" intraoperative cluster (vs. better)	1.70 (0.57–5.11)	0.341	1.87 (0.60–6.90)	*P* (RR> 1.0)=85.5%
DCD (vs. DBD)	4.11 (0.95–17.7)	0.058	4.15 (1.28–13.0)	*P* (RR> 1.0)=99.2%
Preoperative ECMO (vs. no)	5.47 (1.08–27.6)	0.040	4.11 (1.02–19.3)	*P* (RR> 1.0)=97.4%
Donor's preretrieval pO_2/FiO_2	0.26 (0.01–12.0)	0.483	0.08 (0.00–5.80)	*P* (RR < 1.0)=88.7%
Recipient's FVC	0.19 (0.05–0.69)	0.012	0.22 (0.07–0.74)	*P* (RR < 1.0)=99.8%
Recipient's age	1.06 (0.99–1.12)	0.072	1.04 (1.00–1.10)	*P* (RR> 1.0)=96.6%

Variable "cluster" was added to the final model in Table 5. Trace plots in Bayes model were practically identical as for the model in Table 5 (not shown). ECMO—extracorporeal membrane oxygenation, FVC—forced vital capacity.

75% in the DBD group. Still, the period of the warm ischemia remains as one of the concerns about DCD organs. So far, Levvey *et al.* have demonstrated that the duration of donor agonal phase or warm ischemic time up to 60 minutes did not influence negatively early survival in the DCD group [27]. However, out of 465 cases in their study, 84.5% of the DCD donors reached asystole in ≤ 30 minutes after the WLST, and 96.5% in ≤ 60 minutes while only 3.5% reached asystole in> 60 minutes. Therefore, in a multivariable model, donor agonal time and warm ischemia time were not associated with 1-year recipient mortality [27]. Another challenge in LTx using DCD lungs is the lack of complete donor lung assessment when compared to the assessment of DBD lungs. However, the exact role of EVLP for controlled DCD LTx could not be analyzed from the most recent ISHLT DCD Registry report and therefore remains unclear [5].

Several limitations bear review in the discussion of this work. Firstly, the analysis was performed retrospectively in a highly experienced institution and was designed as a single-center study with unmatched cohorts. Furthermore, a relatively small sample size in view of analysis of complications with rare occurrence and short follow-up represents other limitations, although the number of DCD donors is comparable to other experienced centers performing DCD LTx. As the DCD group had a significantly higher use of EVLP, with more common ECMO preoperatively and CPB intraoperatively, this might have contributed to worse outcome in the DCD group and could therefore be a bias. Therefore, we have addressed this concern and, in order to avoid potential bias, we have performed multivariate analyses. The number of patients in the DCD group is relatively small to allow a propensity core matched analysis. In addition, it can be also argued that reasons for intraoperative use of MCS during the first lung implantation could be more recipient-related, but during the second lung implantation can be related to the donor lung characteristics. Furthermore, despite the fact that mean agonal period prior to cardiac arrest in the DCD group was short, our institutional protocol was to reassess with EVLP the lungs retrieved by another center. Also, as the logistics of DBD donation are different, this can be a potential bias when comparing lung ischemic time. As the recipient operation is started as soon as possible after DBD lungs were assessed in the donor hospital, assessment of DCD lungs might be a reason for a small delay before starting the recipient operation. It would be also interesting to expand the research and study primary graft dysfunction in detail. Further studies with long-term follow-up would be useful in order to investigate comparison in survival and occurrence of late complications (bronchiolitis obliterans syndrome).

In conclusion, LTx using controlled DCD donation has increased our lung transplant activity by almost 25% and early postoperative clinical outcomes are in general comparable with those achieved after DBD LTx. However, we have observed a significantly higher need for postoperative ECMO in DCD LTx. ECMO prolongation can also bear some risks. The results of this study add valuable evidence that DCD LTx can be effective strategy to expand the donor pool, although there are some factors that could be associated with adverse events in the perioperative course. Therefore, further studies are required.

Authorship

DS and AVS designed the study. BR, DS, and AVS collected the data. VT, DS, and AVS analyzed the data. DS and AVS wrote the manuscript. PM, US, VT, DGS, BM,

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FDR, and AS performed critical review. All authors have contributed significantly to writing of the manuscript and have approved the final version.

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Conflict of interest

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Supplemental Methods, Results and Sensitivity analysis.

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