

Original
Article

Lung Transplantation with Controlled Donation after Circulatory Death Donors

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Purpose: Utilization of donation after circulatory death (DCD) donors has the potential to decrease donor shortage in lung transplantation (LTx). This study reviews the long-term outcome of LTx from DCD donors.

Methods: We included all consecutive DCD (Maastricht Category III) and all donations after brain death (DBD) donor lung transplants at our Center performed between January 2012 and February 2017. Data were analyzed comparing the two groups in regard of survival after LTx as primary outcome.

Results: Median withdrawal to cardiac arrest time was 17 min (interquartile range [IQR]: 11.5–20.5). Median cardiac arrest to cold perfusion was 32 min (IQR: 24.5–36.5). Primary graft dysfunction (PGD) grade 3 at T72 occurred in three recipients. Chronic lung allograft dysfunction (CLAD) led to death in two cases. In DCD group, there was no 90-day mortality. In DCD, group 1- and 3-year survival rates were 100% and 80%. In DBD group, 1- and 3-year survival rates were 85% and 69% ($p = 0.4$).

Conclusions: Our report confirmed the comparable outcome from DCD donors compared with DBD donors. Utility of DCD donors is a safe option to overcome donor shortage.

Keywords: donation after cardiac death, controlled DCD, lung transplantation, survival

Introduction

Donor shortage is still a major obstacle for lung transplantation (LTx). Lung procurement rate is lower than that of other solid organs, such as liver or kidney. The reason for this low retrieval rate is related to susceptibility of the lung tissue.¹⁾ Neurogenic pulmonary edema is

one of the consequences of brain death, which also leads to upregulation of inflammatory mediators.²⁾

Aspiration of gastric contents, pulmonary infections, contusion, and ventilation-associated lung injury are other reasons for low retrieval rate¹⁾ leading to dying on waiting list, which could be as high as 13.2%.³⁾ First clinical LTx donors were actually from donation after circulatory death (DCD) donors^{4,5)} before donation after brain death (DBD) widely used.⁶⁾ After reintroduction of DCD concept experimentally,⁷⁾ clinical application of this donor type increased. Currently, DCD donors are a valid option to increase donor pool worldwide.^{8–11)}

The Swiss Academy of Medical Sciences launched a new guideline interpreting the law in a way that DCD procedures are compatible with the new law. At our center, we discussed possibilities to start the program with lawyers and our clinical ethics committee and other experienced colleagues. Afterwards, we started transplantation from Category 3 DCD donors in our center.

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The implementation of this concept required a committed multidisciplinary team effort.

Following Swiss Academy of Medical Sciences guidelines, the utilization of DCD (Category III) donors is re-started in Switzerland (as of September 1st 2011). The “Swiss Transplant Working Group on DCD Donation” held multiple meetings to establish best medical and ethical practice. The Zurich University Hospital constituted interdisciplinary working group for a multi-organ DCD retrieval program. Following approval by our local committee (DCD Working Group) in Zurich, we decided to restart the program by performing the first three DCD category III donors only for kidneys, fourth and fifth donors for liver, followed by lung retrieval. It is important to mention that our center had the experience with DCD kidney transplantation that started in 1985.¹²⁾ We performed the first lung DCD LTx in February 2012.

In this study, we present our single-center experience with 21 DCD transplantations performed over the last 5 years.

Materials and Methods

We included Maastricht category III DCD lung transplants and all DBD lung transplants performed between January 2012 and February 2017 at our center. There were 21 transplants performed from DCD donors and 130 from DBD donors. Transplantations performed from DBD during the same study period served as controls.

Donor assessment

DCD donor assessment included University of Wisconsin DCD Evaluation Tool.¹³⁾ All donors except one were in our hospital. At our center, the age limit is 70 years. We also accept “extended criteria” donors such as smoking history of >20 pack/years, intensive care unit (ICU) stay >5 days, PaO₂/FiO₂ <400 mmHg, and abnormal chest X-ray are also accepted.

Recipient selection

Recipient selection is done according to current international guidelines.¹⁴⁾ As recommended by our Ethics Committee, we consent all the recipients on the waiting list for DCD donor LTx and ex vivo lung perfusion (EVLV). Prospective cross-match was performed in all recipients.

Lung procurement, preservation, and transplantation

If the family of a potential DCD donor or the donor him- or herself has consented to donation including all

necessary procedures, the withdrawal of life-sustaining therapy (WLST) under palliative sedation, confirmation of brain death and procurement of organs are done in the operation room. WLST normally begins at 08:30 am. However, if there is a special wish from family members, the transplant coordination arranges the timing for WLST. Before WLST, all of the procurement surgeons should be ready in the operating room area waiting in a different room. The family of the potential donor is accompanied by a team member of our Donor Care Association for final farewell in the operating room. Only physicians and other team members in charge of the donor are present. For WLST, the patient is extubated, all inotropic medications are stopped and palliative sedation for symptom control continued. Prior to extubation, suction of nasogastric tube is performed to prevent gastric aspiration. Intravenous heparin of 5000 IU is injected when mean arterial pressure is less than 50 mmHg. If the potential DCD donor does not die in a certain acceptable time period (Agonal phase: 60 min window), the patient is returned to the ICU. Following cardiac death approval, which is performed with Echocardiogram, a 10 min of stand-off period begins. After this stand-off period, confirmation of brain death has to be undertaken due to legal regulations and according to the protocol of the Swiss Academy of Medical Sciences. Then, the patient is re-intubated and ventilation is started.

The patient is draped for multi-organ retrieval. Following reintubation, bronchoscopy is performed to rule out aspiration of gastric content in the airways. Following crash laparotomy by the abdominal organ transplant team and cannulation, a rapid sternotomy is performed. Pulmonary artery is cannulated. Pleural cavities are opened. The lungs are inspected and examined manually. Lung preservation is done with antegrade Perfadex (Vitrolife, Goteburg, Sweden) infusion. We apply the same volume of Perfadex in DCD and DBD donors. We perfuse 2.8 L antegrade, and at the back table 1 L retrograde. But if we think the output is not clear enough then we use another 1 L of Perfadex either during antegrade or retrograde perfusion.

During the cold perfusion, the lungs are topically cooled with saline. If the lungs seem suitable for transplantation, the anesthesia team is informed to intubate the recipient who is waiting in another operating room. Subsequently, lung recovery is performed according to our standard practice.¹⁵⁾ At the time of LTx, a retrograde pulmonary flush is performed through the pulmonary veins on the back table. If a size reduction (i.e., lobar

transplant) is planned, anatomical resection or split of the lungs is also performed on the back table.¹⁶⁾

The indications of intraoperative extracorporeal membrane oxygenation (ECMO) implantation were primary pulmonary artery hypertension, pulmonary artery pressure more than 40 mmHg after occluding the pulmonary artery, deteriorated gas exchange following one-lung ventilation. In addition, if we observe graft dysfunction after the implantation of the first side, we go on the ECMO.

To be sure about the lung quality and function, selective EVLP (normothermic, acellular) is performed. We perform selective use of EVLP in our program, as we believe that this technology provides us the comfort to evaluate the graft before implantation. The indications are not different than from other centers. Briefly, PaO₂ less than 300 mmHg, heavy lungs during palpation, massive blood transfusion (>10 units), poor lung compliance, suspicion of aspiration, and high C-reactive protein (CRP) suggesting pulmonary infection which might be treated during EVLP with antibiotics.

Definitions

In DCD donation, warm ischemic time (WIT) is defined as the time between cardiac arrest and cold perfusion. At our center, maximum acceptable WIT is 60 min. In our database, all time points to calculate the time intervals that are recommended by the International Society for Heart and Lung Transplantation (ISHLT) DCD Working Group are also recorded. Acceptable time at our center for agonal period is defined, as the time between WLST and cardiac arrest is 60 min. Early surgical complication is defined as a complication that occurs during the posttransplant hospitalization period.

Statistics

All data were analyzed using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, Version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Data are presented as continuous or categorical variables. To check the normality of continuous data, we performed the one-sample Kolmogorov–Smirnov test. If the patients' continuous variables are normally distributed, we used mean \pm standard deviation. We used median and interquartile range (IQR) if these variables are not normally distributed. Categorical variables are shown as total number and percentages. Continuous variables were tested either with unpaired t-test or Mann–Whitney test. Categorical variables are tested with Pearson's χ^2 . Survival

analysis and freedom from chronic lung allograft dysfunction (CLAD) are performed with Kaplan–Meier method and compared with log-rank test.

Results

In the study period, lungs were offered from 56 potential DCD donors. Only 23 of those were considered suitable for LTx. In two donors, cardiac arrest did not occur within the 60 min period. The utility rate was 37.5% (21/56).

At least one of these marginal donor criteria (age \geq 55 years, smoking history \geq 20 pack-years, abnormal chest X-ray, abnormal bronchoscopy, and PaO₂/FiO₂ \leq 300 mmHg) was present in 34% of DBD and in 53% of DCD donors. In 16% of DBD donors and in 35% of DCD donors, there were two or more of these criteria. Three or more criteria were present in 5% of DBD and in 17% of DCD donors.

During the study period, transplantations from DCD donors constituted 14% (21/151) of our LTx activity. Median agonal phase (withdrawal–cardiac arrest) was 17 min (IQR: 11.5–20.5 min). Median WIT (cardiac arrest–cold perfusion) was 31 min (IQR: 24.5–36.5 min) (**Table 1**).

In two DCD donors, normothermic EVLP was done before organ implantation. The indication for EVLP was edematous lung with low PaO₂/FiO₂ in one donor and high CRP level with positive blood culture in another donor. All DCD transplants were bilateral. Donor and recipient characteristics are shown in **Table 1**. In DBD, the LTx rate with intraoperative ECMO use was 59% and in DCD 43% (**Table 1**).

In three recipients within the DCD group, primary graft dysfunction (PGD) grade 3 at T72 occurred. PGD grade was comparable between DBD and DCD groups (**Fig. 1**).

The rate of any early surgical complication (during the post-transplant inpatient stay) was 33% in DCD versus 45% in the DBD group, respectively ($p = 0.3$). In one patient of DBD group, an early airway complication following bilateral lobar LTx required revision. On the left side, cartilage broke occluding the bronchial lumen, this was solved successfully by early revision (<24 h). As late airway complications (one patient in each group), we observed late bronchial stump failure in the follow-up period. These recipients underwent bilateral lobar LTx with stapled lower lobe bronchus. Both recipients were managed successfully with omentum flap interposition after staged management of empyema.

Table 1 Donor and recipient characteristics

Donor characteristics	DBD	DCD	p value
Age	48.5 (34–59)	49 ± 16.3	0.7
Female, N (%)	45 (35)	9 (43)	0.4
Height (cm)	175 (170–180)	172 ± 9.7	0.2
Weight (kg)	76 (65–85)	72 ± 11.7	0.2
PaO ₂ /FiO ₂	48.4 ± 13.1	48.4 ± 9	0.9
Use of EVLP	5 (4)	2 (10)	
Cause of death (N)			0.2
Anoxia	25	5	
Vascular	75	12	
Trauma	25	4	
Suicide	4	–	
Other	1	–	
WLST-CA (min)	–	17 (11.5–20.5)	
CA-ColdPerf (min)	–	31 (24.5–36.5)	
WLST-ColdPerf (min)	–	42 (37–52.5)	
SaO ₂ 70%-ColdPerf (min)	–	40 (33–46.5)	
sBP <50 mmHg-ColdPerf (min)	–	37 (31–42)	
Start Ventilation-ColdPerf (min)	–	13 (11.5–17.5)	
Recipient characteristics			
Age	49.5 (30; 59)	49 (32; 58.5)	0.8
Female, N (%)	58 (45)	9 (43)	0.8
Height (cm)	168 ± 11.5	167 ± 10.7	0.8
Weight (kg)	60 (48–75)	61 ± 19.1	0.5
BMI (kg/m ²)	20.8 (18–25)	21 ± 4.8	0.8
Time on waiting list (d)	220 (82–419)	262 (170–583)	0.09
Diagnosis, N (%)			0.3
CF	44 (34)	10 (48)	
PPH	8 (6)	–	
EMP	43 (33)	6 (29)	
IPF	26 (20)	2 (9)	
OTH	9 (7)	3 (14)	
Pretx. FEV1 (L)	0.8 (0.6–1.2)	0.79 (0.6–1.2)	0.9
Pretx. FEV1 (%)	28 (20–37)	28 (21–34)	0.8
Pretx. ECLS	21 (16)	2 (9.5)	0.5
Intraoperative ECLS	77 (59)	9 (43)	0.2
Type of LTx, N (%)			
Unilateral	4 (3)	–	
Bilateral	126 (97)	21 (100)	1
Down-sizing, N (%)			
Bilateral Lobar LTx	29 (22)	3 (14)	0.6
Unilateral Lobar LTx	16 (12)	3 (14)	0.6
Re-LTx, N (%)	8 (6)	–	
Ischemia (right) min	257 (212–316)	292 (258–380)	0.01
Ischemia (left) min	354 (305–405)	438 (329–472)	0.02
Intubation time (d)	1 (1–3)	1 (1–2)	0.3
ICU stay (d)	3 (2–10)	3 (2; 6)	0.3
30-day mortality, N (%)	4 (3)	–	
Posttx. FEV1 (l)	2.3 ± 0.7	2.3 ± 0.9	0.7
Posttx. FEV1 (%)	71 ± 20.6	70 ± 24	0.9

Values are given as median (IQR) or mean ± standard deviation. WLST: withdrawal of life-sustaining therapy; CA: cardiac arrest; ColdPerf: cold perfusion; sBP: systolic blood pressure; LTx: lung transplantation; Posttx: post-transplantation; Pretx: pre-transplantation; FEV1: forced expiratory volume in 1 s; ICU: intensive care unit; d: day; ECLS: extracorporeal life support; BMI: body mass index; CF: cystic fibrosis; PPH: primary pulmonary hypertension; EMP: emphysema; IPF: idiopathic pulmonary fibrosis; OTH: other

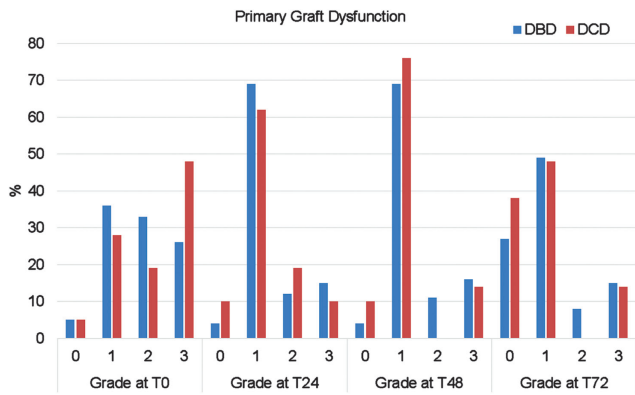


Fig. 1 PGD. Proportions of the different PGD grades at 0, 24, 48, and 72 h after transplantation in DCD and DBD recipients. The number of patients is given on the bars. No significant difference was found. PGD: primary graft dysfunction; DCD: donation after circulatory death; DBD: donation after brain death

The correlation of different three time intervals for WIT (cardiac arrest–cold perfusion, WLST–cold perfusion, and sBP<50 mmHg–cold perfusion) with PGD grade 3 at T72 is shown in **Fig. 2**. There is no correlation between the incidence of PGD3 at T0/T24/T48 and the time intervals. No significant correlation for three time intervals and occurrence of PGD grade 3 at T72 was detected (**Fig. 2**).

In five DCD donor LTX recipients, CLAD occurred (CLAD 3, N = 3; CLAD 1, N = 2). In the DCD group, two recipients died due to CLAD. CLAD-free survival was comparable between the groups (**Fig. 3**). The 90-day mortality in the DCD group was 0%. Actuarial survival rates at 1 year and 3 years were 100% and 80% for DCD and 85% and 69% for the DBD group, respectively (p = 0.5) (**Fig. 4**).

Discussion

Our data demonstrated comparable rate of PGD, complications, freedom from CLAD, and survival between DCD and DBD donor LTx. In addition, different WIT definitions did not correlate with PGD grade 3 at T72. One of the main limitations of this report is the small number of cases in DCD group compared to DBD group.

There is still not a consensus for how to define WIT for DCD donors.¹⁷ Experimental studies showed that the lung function remains stable up to 90 min after cardiac arrest.^{1,17}

Evaluation of the DCD donor lung in EVLP is still controversial.¹⁸ EVLP has been used to assess an uncontrolled DCD donor lungs before implantation.¹⁹

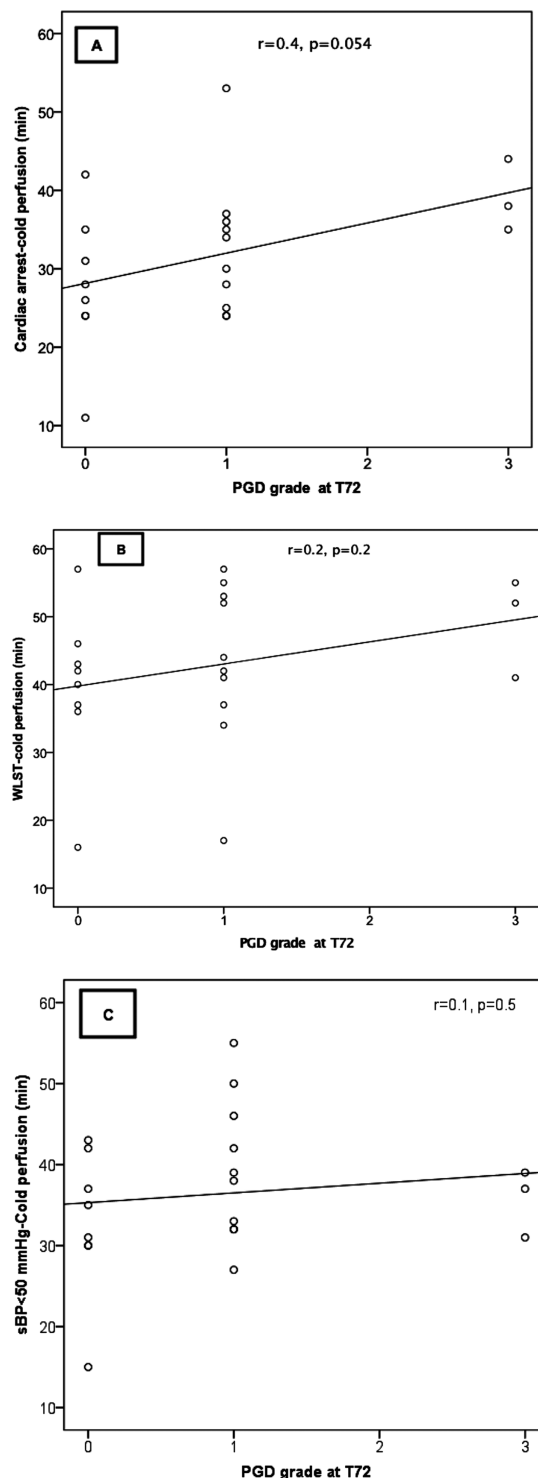


Fig. 2 The correlation of different three time intervals for WIT (cardiac arrest–cold perfusion (A), WLST–cold perfusion (B), and sBP <50 mmHg–cold perfusion (C)) with PGD grade 3 at T72. No significant correlation for three time intervals and occurrence of PGD grade 3 at T72 was detected. sBP: systolic blood pressure; WLST: withdrawal of life-sustaining therapy; WIT: warm ischemic time; PGD: primary graft dysfunction

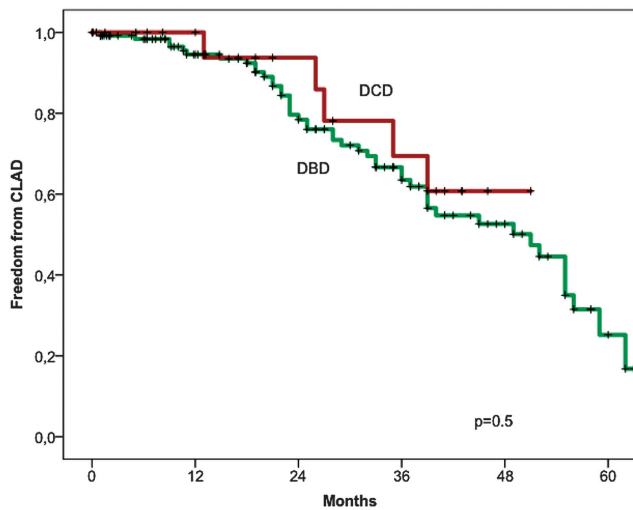


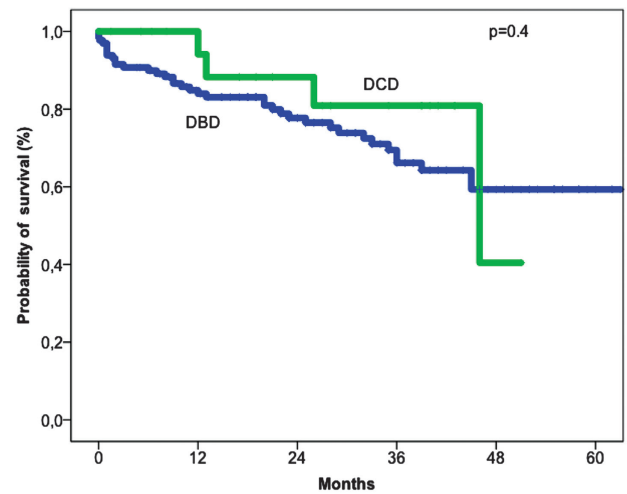
Fig. 3 CLAD-free survival in DCD and DBD groups. CLAD-free survival was comparable between the groups. CLAD: chronic lung allograft dysfunction; DCD: donation after circulatory death; DBD: donation after brain death

We and other centers currently use EVLP as an adjunct method to evaluate DCD donors before transplantation.^{9,20–22} Contrary to this, good outcomes have been reported without utilizing EVLP.⁸

In our LTx Program, we prospectively record all important time points and intervals for future evaluation and correlation with graft function. Our WIT is comparable with the internationally published series.^{8,10,20,21,23}

In spite of the findings on the protective effect of ventilation on lung tissue^{7,17,24–26} graft survival in LTx depends on long-term function of the airways and the vasculature^{25,27} The rate of airway complications in our cohort was comparable between DCD and DBD transplants.^{8,11,20,28} De Oliveira et al.²⁹ reported higher incidence of airway complications was in their group of DCD donor LTx group.

Melbourne group reported 90% 5-year survival rate in DCD group.⁸ At 24 h, the incidence of PGD grade 3 was 8.5%. Overall, the incidence of grade 3 chronic rejections was 5%. In the Melbourne series, the association between the WIT and the PaO₂/FiO₂ ratio derived on return to ICU showed a weak correlation between systolic blood pressure <50 mmHg to pulmonary arterial flush time and graft oxygenation at 24h; however, this appeared to be less obvious by 24 h post-LTx.⁸ In our cohort, we did not find any correlation between different time intervals of WIT and PGD grade 3 at T72. ISHLT DCD Registry demonstrated comparable 1- and 5-year survival between DCD and DBD donors.²³ Although most of the groups report superior or at least comparable



Number at risk						
Months	0	12	24	36	48	60
DBD	130	94	66	40	21	3
DCD	21	16	12	8	1	0

Fig. 4 Post-transplant survival in DCD and DBD groups. Actuarial survival rates were comparable between the two groups. DCD: donation after circulatory death; DBD: donation after brain death

outcomes, the St. Louis group showed that early outcomes after LTx using DCD donors were somewhat inferior to those of series from other centers.³⁰ The hospital mortality in the St. Louis' series for DCD recipients was 18%, with an overall mortality of 36%.

Conclusion

In conclusion, our results also strengthen the comparable outcomes from LTx using DCD donors. Such a DCD program can be implemented successfully if a committed multi-disciplinary team is working well together using a standardized and commonly agreed upon protocol. The ideal definition of WIT and acceptable agonal phase would become clearer with prospective data collection on all potential DCD lung donors.

Disclosure Statement

No conflicts of interest to disclose for any authors.

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