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International Society for Heart and Lung Transplantation Donation After Circulatory Death Registry Report

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KEYWORDS:
lung transplantation;
donation after circulatory death;
donor lungs allograft;
survival;
allograft ischemic time;
mortality risk factors

BACKGROUND: The objective of this study was to review the international experience in lung transplantation using lung donation after circulatory death (DCD).

METHODS: In this retrospective study, data from the International Society for Heart and Lung Transplantation (ISHLT) DCD Registry were analyzed. The study cohort included DCD lung transplants performed between January 2003 and June 2013, and reported to the ISHLT DCD Registry as of April 2014. The participating institutions included 10 centers in North America, Europe and Australia. The control group was a cohort of lung recipients transplanted using brain-dead donors (DBDs) during the same study period. The primary end-point was survival after lung transplantation.

RESULTS: There were 306 transplants performed using DCD donors and 3,992 transplants using DBD donors during the study period. Of the DCD transplants, 94.8% were Maastricht Category III, whereas 4% were Category IV and 1.2% Category V (euthanasia). Heparin was given in 54% of the cases, donor extubation occurred in 90% of the cases, and normothermic ex vivo lung perfusion (EVLP) was used in 12%. The median time from withdrawal of life support therapy (WLST) to cardiac arrest was 15 minutes (5th to 95th percentiles of 5 to 55 minutes), and from WLST to cold flush was 33 minutes (5th to 95th percentiles of 19.5 to 79.5 minutes). Recipient age and medical diagnosis were similar in DCD and DBD groups (p = not significant [NS]). Median hospital length of stay was 18 days in DCD lung transplants and 16 days in DBD transplants ($p = 0.016$). Thirty-day survival was 96% in the DCD group and 97% in the DBD group. One-year survival was 89% in the DCD group and 88% in the DBD group (p = NS). Five-year survival was 61% in both groups (p = NS). The mechanism of donor death within the DCD group seemed to influence recipient early survival. The survival rates through 30 days were significantly different by donor mechanism of death ($p = 0.0152$). There was no significant correlation between the interval of WLST to pulmonary flush with survival ($p = 0.11$).

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CONCLUSION: This large study of international, multi-center experience demonstrates excellent survival after lung transplantation using DCD donors. It should be further evaluated whether the mechanism of donor death influences survival after DCD transplant.
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Two decades have passed since the initial successful report on the use of donation after circulatory death donors (DCDs) for lung transplantation,[1] but only recently the use of these donors became more widely applied. Several series from individual institutions and national organizations have been reported and, in general, outcomes in controlled DCD lung transplantation have been comparable with standard brain-dead donor (DBD) transplantation.[2–10] Only a few reports have demonstrated worse outcomes with respect to primary graft dysfunction (PGD) and bronchiolitis obliterans syndrome (BOS).[5,11] However, despite a significant growth in DCD multi-organ donation in many countries, lung transplantation rates using DCD donors is still fairly limited. As an example, in the United States, DCD accounts for <5% of lung transplant activity and utilization of potential DCD donors remains very poor.[12,13]

In 2011, a DCD working group initiated the DCD Registry within the International Society for Heart and Lung Transplantation (ISHLT). Members were invited to participate based on their clinical experience with DCD lung transplantation and previous academic work in the area. The goals of this working group were to: (1) establish and standardize definitions of the different time intervals related to the DCD donation process; (2) determine survival outcomes in DCD lung transplants as compared with DBD transplants; and (3) determine donor, recipient and process characteristics in DCD transplant that could relate to outcomes. The large number of patients in our study group was expected to allow for identification of meaningful and generalizable prognostic factors, which was not possible previously due to the relatively small number of cases in the previously reported studies.

Methods

Study design

This was a retrospective study using data collected in the ISHLT DCD Registry. The study cohort included all DCD lung transplants performed between January 2003 and June 2013, and reported to the ISHLT DCD database as of April 7, 2014. The participating centers in North America, Europe and Australia included: St. Vincent's Hospital, Sydney, NSW, Australia; The Prince Charles Hospital, Brisbane, Queensland, Australia; The Alfred Hospital, Melbourne, Victoria, Australia; The Toronto General Hospital, Toronto, Ontario, Canada; The Hospital for Sick Children, Toronto, Ontario, Canada; UZ Gasthuisberg Leuven, Leuven, Belgium; Universitair Medisch Centrum Groningen, Groningen, The Netherlands; University of Minnesota Medical Center, Minneapolis, Minnesota, USA; Barnes-Jewish Hospital, St. Louis, Missouri, USA; and the Cleveland Clinic, Cleveland, Ohio, USA. The control group was identified within the main ISHLT Transplant Registry as a cohort of lung recipients transplanted using DBD and transplanted during the same study period within the centers listed. Patients bridged to transplant with extracorporeal life support therapy (ECLS) were excluded. The primary end-point was survival after lung transplantation.

Definitions

To standardize the definitions around important times in the DCD process, the following time-points were identified:

T0: withdrawal of life-sustaining therapies OR euthanasia.
T1: oxygen saturation <80%.
T2: systolic blood pressure <50 mm Hg.
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) were then calculated and survival stratification was performed based on the lengths of these intervals.

Variables

Several categorical variables were collected to establish current DCD practices. Donor characteristics included: donor age; mechanism of death; Maastricht category[14]; use of heparin; use of steroids; use of fibrinolytics; extubation during WLST; use of nasogastric tube; use of bronchoscopy; and ex vivo lung perfusion (EVLP) for assessment of the lungs. Recipient characteristics included age, medical diagnosis and transplant type (single vs bilateral). Hospital length of stay was also recorded.

Statistical analysis

Comparisons were made using the Mann–Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. For comparisons between DCD and DBD, the DCD cohort was limited to transplants involving a DCD Maastricht Category III (controlled donation).[14] Survival rates were computed with the Kaplan–Meier method. Survival curves were compared using the log-rank test statistic; survival rates at a specified time-point were compared using a complementary log-log transformation test.[15]

Results

Donor and transplant process characteristics

During the study period, 306 lung transplants were performed using DCD donors and 3,992 transplants using DBD donors. Among the DCD transplants, 94.8% were

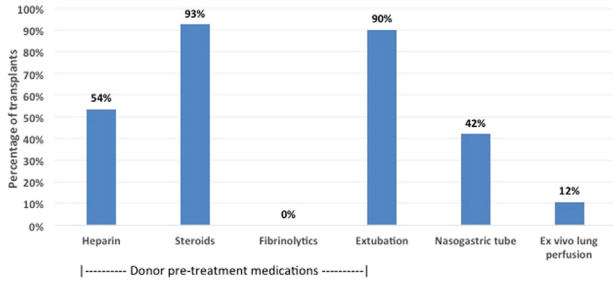

Figure 1 Variables of the DCD process. Use of drugs, bronchoscopy, extubation or insertion of nasogastric tube before withdrawal of life support therapies, and the use of normothermic ex vivo lung perfusion (EVLP) after graft retrieval.

Maastricht Category III, 4% were Category IV and 1.2% Category V (euthanasia). Median DCD donor age was 44 (16 to 62) years compared with 40 (15 and 64) years in DBD donors ($p = 0.0021$). Practices related to the DCD process, such as use of drugs before WLST, extubation and use of EVLP, are shown in Figure 1. Heparin was used in 54% of cases, and EVLP was performed in only 12%. Table 1 presents the current characteristics of the DCD process practiced at each center participating in this report.

The distribution of time intervals in the DCD process is shown in Figure 2. No differences in 1-year survival were observed for the different lengths of Intervals 1 and 2 (<10 minutes vs 10 to 20 minutes vs >20 minutes; $p = 0.36$ and $p = 0.83$ for Intervals 1 and 2, respectively). Similarly, no differences in survival were observed for Interval 3 duration (<30 minutes vs 30 to 45 minutes vs >45 minutes; $p = 0.11$).

Recipient characteristics

The distributions of recipient age and medical diagnoses of lung disease in the DCD and DBD groups are demonstrated in Figure 3. There were no significant differences among these characteristics between the 2 patient groups.

Post-transplant outcomes

There were no significant differences in survival between the DCD and DBD groups within the first year post-transplant (Figure 4). 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 ($p = 0.59$; Figure 4a). Five-year survival was 61% in both groups ($p = 0.87$; Figure 4b). Median hospital stay after transplant was 18 days in the DCD group and 16 days in the DBD group ($p = 0.016$).

In the DCD group, donor age did not influence recipient outcomes ($p = 0.92$; Figure 5a). However, the mechanism of death within the DCD group seemed to influence short-term recipient survival. Of the 11 deaths within 30 days of transplant, 6 involved donors with head trauma. The survival rates through 30 days were significantly different by donor mechanism of death ($p = 0.0152$). Survival rates at 1 year were 90% in recipients of organs from DCD donors whose deaths were related to anoxic brain injury, 92% in deaths related to cerebrovascular events, and 85% in head trauma. However, the survival rates through 1 year were not significantly different by donor mechanism of death ($p = 0.28$; Figure 5b).

Discussion

This multi-center, international study is the largest report to date evaluating survival of recipients receiving lung transplantation from DCD donors. The results of this experience corroborate previous single-center findings and demonstrate excellent results, including survival and hospital length of stay in recipients of DCD donor lung transplants, comparable with DBD donors.

As DCD lung transplant practices expand, we considered it important to establish standardized definitions related to the time when WLST occurs, so that data may be properly compared among different centers. Earlier attempts to define these intervals were described by Levvey and colleagues.[16] At inception of data collection, a consensus among the investigators in this study (participants in the ISHLT DCD working group) established major time-points in the DCD process (T0 to T5) that we believed may influence organ quality and thus recipient outcomes. In this report, no correlation between intervals of these times and recipient outcomes was seen. We believe it is important to re-examine this issue once the Registry expands further, especially with

Table 1 Characteristics of DCD Practices in Participating Centers

Center	Transplants 2012 to 2014 (n)	Percentage of Transplants from DCD (%)	Use of heparin pre-mortem	Use of Bronchoscopy Pre-mortem	Selective use of EVLP	Stand-off period	Maximum time allowed for WLS T to arrest
Toronto	352	15	Yes	Yes	Yes	5 min	180 min
Sydney	139	23	No	No	Yes	2 min	90 min
Melbourne	214	23	Yes[a]	Yes	No	2 to 5 min	90 min
Brisbane	93	15	No	No	Yes	5 min	90 min
Leuven	199	14	Yes	No	Yes	5 min	120 min
Groningen	112	32	No	Yes	Yes	5 min	90 min
Minnesota	126	7	Yes	Yes	Yes	5 min	90 min
St. Louis	191	<1	Yes	Yes	No	5 min	30 min
Cleveland	302	8	Yes	Yes	No	5 min	60 min

DCD, donation after circulatory death donor; EVLP, ex vivo lung perfusion; WLST, withdrawal of life support therapy.
[a]When allowed by donor hospital.

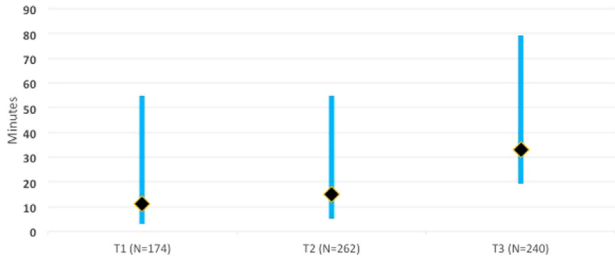

Figure 2 The distribution of time intervals in the DCD process. Interval 1 = time from WLST to agonal phase (determined by systolic blood pressure <50 mm Hg); Interval 2 = time from WLST to cessation of cardiac output/asystole; Interval 3 = time from WLST to start of cold flush perfusion. Diamond = median; bars = 5th to 95th percentile.

regard to number of transplants and length of recipient follow-up. In addition, all cases reported here had relatively short intervals from WLST to cold flush perfusion (95th percentile for Interval 3 = 79.5 minutes), and some centers are now accepting Interval 3 cases of up to 180 minutes. Thus, data obtained in those circumstances will be very valuable. If we can confirm that even longer intervals from WLST to arrest result in favorable post-transplant outcomes, it may further expand the current DCD donor pool. In addition, the pattern of blood pressure drop (sudden vs gradual) during the agonal period may have an impact in organ quality.

Additional findings of interest were observed in this study. First, we found that the donors were pre-treated with heparin in only 54% of cases. Thus, in accordance with previous single-center publications,[8] the absence of anti-coagulation did not adversely impact outcomes. Second, only 12% of the DCD cases underwent normothermic EVLP.[17] This low percentage may reflect lack of availability of the EVLP technology and expertise at the time these data were collected, but also the perception of each center of the real need or benefit of EVLP in assessing

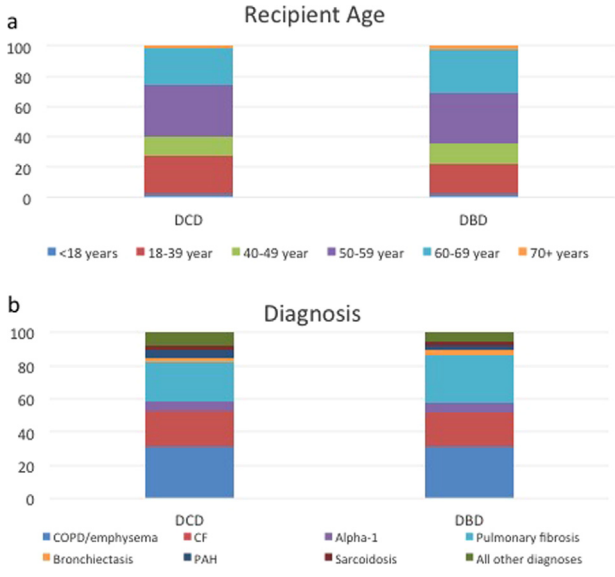

Figure 3 Distribution of recipient age (a) and medical diagnosis of recipient lung disease in the DCD and DBD groups (b).

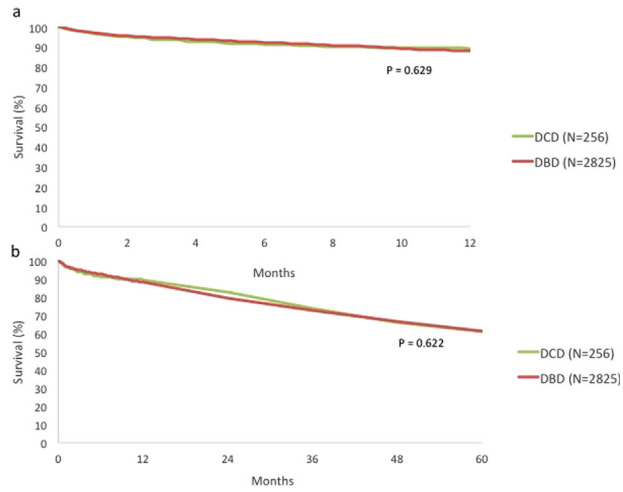

Figure 4 One-year (a) and 5-year (b) post-transplant survival in the DCD vs DBD groups. Asterisk indicates that only transplants performed between January 2006 and December 2012 used for survival calculations.

Category III DCD donors. In contrast to uncontrolled DCD lung transplantation when the outcomes were sub-optimal without EVLP,[18] the data provided herein demonstrate the safety of controlled DCD lung transplantation without EVLP. However, EVLP could increase utilization of extended-criteria DCD donors, and would seem necessary in Categories I and II. A recent report demonstrated improved recipient outcomes when selective EVLP was used in extended-criteria Category III DCD donors.[19]

A third unique observation was the influence of the mechanism of injury leading to donor death on recipient outcomes. Recipients receiving lung transplants from donors with head trauma had worse early outcomes compared with patients receiving donor lungs from donors with hypoxemic injury or a spontaneous cerebrovascular

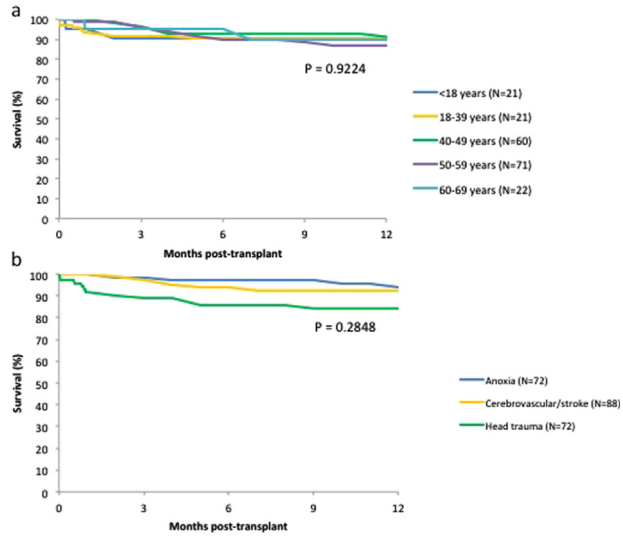

Figure 5 One-year survival stratified by DCD donor age (a) and mechanism of donor injury (b). Asterisk indicates only transplants performed between January 2006 and December 2012 used for survival calculations.

event. Whereas a causal relationship cannot be established, one of the possibilities is the presence of unrecognized aspiration of gastric contents in patients with trauma.

Although this cohort is the largest to date, our study has limitations. First, the centers reporting data to the ISHLT DCD Registry are highly committed to DCD lung transplantation with well-established DCD protocols, trained personnel and overall very good outcomes. Thus, these excellent results may not be immediately generalizable if DCD was expanded to less experienced centers. Second, some important data that could reflect donor lung quality and be related to recipient outcomes may not be captured in the Registry—for example, data on primary graft dysfunction in the first 72 hours after transplantation, length of mechanical ventilation and chronic graft dysfunction rates were not available in the current Registry. Finally, we acknowledge the limitation of not having data from Maastricht Category I and II DCD donors. This is clearly a priority for the DCD Registry.

In conclusion, short- and long-term outcomes after lung transplantation using controlled DCD donation yields excellent outcomes that are comparable to results achieved using DBD donors. It should be further evaluated whether the mechanism of donor death influences survival after DCD transplant. We hope this report will further increase awareness of the potential of DCD lung donation to increase lung transplantation, and that it will catalyze adoption of DCD practices in additional lung transplant centers. The definitions of the critical time-points in the DCD donation process will facilitate more accurate comparisons of outcomes between centers in the future.

Disclosure statement

The authors have no conflicts of interest to disclose. The DCD Registry has been funded by the ISHLT.

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