Impact of donor time to cardiac arrest in lung donation after circulatory death

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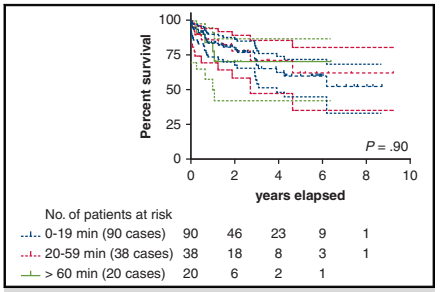
ABSTRACT

Objective: Acceptance of lungs from donation after circulatory determination of death has been generally restricted to donors who have cardiac arrest within 60 minutes after withdrawal of life-sustaining therapies. We aimed to determine the effect of the interval between withdrawal of life-sustaining therapies to arrest and recipient outcomes. Second, we aimed to compare outcomes between donation after circulatory determination of death transplants and donation after neurologic determination of death transplants.

Methods: A single-center, retrospective review was performed analyzing the clinical outcomes of transplant recipients who received donation after circulatory determination of death lungs and those who received donation after neurologic determination of death lungs. Donation after circulatory determination of death cases were then grouped on the basis of the interval between withdrawal of life-sustaining therapies and asystole: 0 to 19 minutes (rapid), 20 to 59 minutes (intermediate), and more than 60 minutes (long). Recipient outcomes from each of these groups were compared.

Results: A total of 180 cases of donation after circulatory determination of death and 1088 cases of donation after neurologic determination of death were reviewed between 2007 and 2017. There were no significant differences in the 2 groups in terms of age, gender, recipient diagnosis, and type of transplant (bilateral vs single). Ex vivo lung perfusion was used in 118 of 180 (65.6%) donation after circulatory determination of death cases and 149 of 1088 (13.7%) donation after neurologic determination of death cases before transplantation. The median survivals of recipients who received donation after circulatory determination of death lungs versus donation after neurologic determination of death lungs were 8.0 and 6.9 years, respectively. Time between withdrawal of life-sustaining therapies and asystole was available for 148 of 180 donors (82.2%) from the donation after circulatory determination of death group. Mean and median time from withdrawal of life-sustaining therapies to asystole were 28.6 minutes and 16 minutes, respectively. Twenty donors required more than 60 minutes to experience cardiac arrest, with the longest duration being 154 minutes before asystole was recorded. Recipients of donation after circulatory determination of death lungs who had cardiac



Recipient survival stratified according to the interval between WLST and asystole.

CENTRAL MESSAGE

Donors who had cardiac arrest at more than 60 minutes were not associated with recipient outcomes as demonstrated by similar ICU length of stay, mechanical ventilation days, PGD 2 and 3 (72 hours), and survival.

PERSPECTIVE

We evaluate the effect of time to donor cardiac arrest. Donors who had cardiac arrest at more than 60 minutes were not associated with recipient outcomes or survival. This report may encourage other lung transplant programs with appropriate lung evaluation tools and experience to expand their donor pool even if the agonal phase extends to more than 60 minutes.

See Commentaries on pages 1556, 1559, and 1560.

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Abbreviations and Acronyms

CI = confidence interval
DCDD = donation after circulatory determination of death
DNDD = donation after neurologic determination of death
EVLP = ex vivo lung perfusion
ICU = intensive care unit
ISHLT = International Society for Heart and Lung Transplantation
IQR = interquartile range
LTx = lung transplantation
PA = pulmonary artery
PGD = primary graft dysfunction
WLST = withdrawal of life-sustaining therapies

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arrest at 0 to 19 minutes (90 donors), 20 to 59 minutes (38 donors), and more than 60 minutes (20 donors) did not demonstrate any significant differences in terms of short- and long-term survivals, primary graft dysfunction 2 and 3, intensive care unit stay, mechanical ventilation days, or total hospital stay.

Conclusions: Short- and long-term outcomes in recipients who received donation after neurologic determination of death versus donation after circulatory determination of death lungs are similar. Different withdrawals of life-sustaining therapies to arrest intervals were not associated with recipient outcomes. The maximum acceptable duration of this interval has yet to be established. (J Thorac Cardiovasc Surg 2021;161:1546-55)

A large number of patients with end-stage lung diseases are currently listed for lung transplantation (LTx).[1] Of 100 eligible donors in the United States, the use rate for lungs is only 18.5 compared with 64.7 and 67 for livers and kidneys, respectively.[2] This discrepancy can be partly explained by the direct and indirect injuries lungs experience secondary to the supportive measures that critically ill patients require. Furthermore, critically ill mechanically ventilated patients have the inherent risk of ventilator-induced lung injury and aspiration injury, both of which may preclude the use of lungs for transplantation.

Although the number of LTxs performed increases each year, the number of patients being listed for LTx still far outweighs the availability of suitable lung donors.[3,4] Attempts to reduce the gap between listed patients and available donors have included expanding the donor criteria to include lungs from donation after circulatory determination of death (DCDD) and implementing ex vivo lung perfusion (EVLP) to better evaluate and treat injured donor lungs. DCDD lungs are subject to perimortem and postmortem insults that include protracted warm ischemia after cardiac arrest and an elevated aspiration risk during the interval between withdrawal of life-sustaining therapies (WLST) and organ procurement.[5] Despite the higher potential for injury to DCDD lungs, multiple retrospective series have demonstrated similar short-term outcomes comparable to those from recipients who received lungs from donation after neurologic determination of death (DNDD).[5-9] A recent meta-analysis included a comprehensive review of 271 recipients of DCDD lungs from 6 retrospective observational cohort studies and revealed similar early and intermediate survival after LTx when compared with recipients with DNDD lungs.[10] Despite this evidence, a low proportion of potential DCDDs are used for LTx, one of the reasons being a prolonged interval between WLST and cardiac arrest, also called the "agonal period."[11-13] It remains to be determined whether the time length between WLST and cardiac arrest has an effect on recipient outcomes. It is also evident that most centers would not accept a lung if that interval exceeds 60 minutes.[14] Therefore, the primary aim of this study was to determine if the length of time between WLST and asystole had any influence on recipient short- and long-term outcomes after DCDD LTx.

Second, we revisited a single-center DCDD LTx experience comparing short- and long-term outcomes in recipients who receive DCDD lungs with those who receive DNDD lungs.

MATERIALS AND METHODS

This was a retrospective review of a prospectively collected database that included all LTxs performed at the Toronto General Hospital between January 2007 and December 2017 inclusive with follow-up until March 2018. The study was approved by the University Health Network research ethics board. The EVLP case data and DCDD/DNDD transplant databases are prospectively maintained by research staff at University Health Network, and the donor hemodynamic data and duration of time between WLST and asystole are maintained by the Trillium Gift of Life Network (Organ Procurement Organization in Ontario, Canada).

Donor selection and indications for EVLP have been described.[15-17] All LTx recipients on our wait-list were eligible to receive DCDD lungs without the need for special consent. Donor procurement and logistics surrounding DCDD lung use, intensive care unit (ICU), and operating room time courses have been described by Machuca and colleagues.[17] Briefly, the duration of time between WLST and asystole, that is T0 to T3, defined

by the International Society for Heart and Lung Transplantation (ISHLT) working group,[14] was recorded during the agonal phase. Hemodynamic data were recorded every 2 to 5 minutes for this duration until asystole was recorded. The patients underwent a 5-minute no touch period before which the donor was taken to the operating room and reintubated before procurement. Further evaluation of the lungs is then performed via bronchoscopy assessing for signs of aspiration or airway injury while a second surgeon performs the sternotomy in preparation for standard lung procurement with cold Perfadex (Xvivo Perfusion, Göteborg, Sweden) flush. Procedural and operative details have been reported by our group.[17]

All DCDD donors reported in this article were Maastricht category III (controlled, awaiting cardiac arrest). DCDD donors were then grouped on the basis of their interval between WLST and asystole: 0 to 19 minutes (rapid), 20 to 59 minutes (intermediate), and more than 60 minutes (long). Intervals were chosen as described to maximize the number of transplants in each interval that would make the most robust and useful statistical comparison. The majority of donors became asystolic within the first 20 minutes. Our aim for dividing the donors into the described intervals was predominately based on attempting to balance donor numbers as best as possible in consideration of the wide variability observed among WLST to asystole intervals that the donors displayed. Recipient outcomes such as survival, ICU length of stay, and primary graft dysfunction (PGD) from each of these groups were compared. PGD grades were assigned on the basis of the ISHLT criteria published in the consensus statement.[18]

Statistical analysis was performed using Prism 8 (GraphPad Software, San Diego, Calif) and SAS/STAT Software (SAS Institute Inc, Cary, NC). Survival curves were plotted using the Kaplan–Meier method and analyzed using log-rank (Mantel–Cox) tests. Patients were censored in March 2018. Parametric continuous variables were compared with the Student *t* test, and nonparametric data sets were analyzed using Mann–Whitney tests and Kruskal–Wallis where appropriate. Categoric variables were compared with the chi-square test. Cox proportional hazards regression modeling was used to model survival by DCDD versus DNDD adjusting for covariates. Sensitivity analyses were performed to account for missing WLST to asystole data in the DCDD transplant cohort.

RESULTS

Study Population

Between 2007 and 2017, we performed 1088 DNDD and 180 DCDD LTxs. Baseline demographics and other operative variables such as type of transplant (bilateral vs single) are listed in Table 1.

Survival and Ex Vivo Lung Perfusion: Donation After Neurologic Determination of Death Versus Donation After Circulatory Determination of Death

Median survival of recipients who received DNDD versus DCDD donor lungs was similar: 6.9 and 8.0 years, respectively (Figure 1) ($P = .79$; 95% confidence interval [CI],

TABLE 1. Donor and recipient demographics for donation after neurologic determination of death and donation after circulatory determination of death lung transplants

Variable	DNDD (n = 1088)	DCDD (n = 180)	*P* value
Donor variables			
Age (y)	45.20 ± 17.94	46.73 ± 16.06	.34
Gender (male)	579 (53%)	98 (54%)	.77
Cause of brain injury			<.01
Anoxia/cardiac arrest	170 (16%)	55 (31%)	
Cerebrovascular/stroke	583 (54%)	72 (40%)	
Head trauma/motor vehicle accident	251 (21%)	42 (23%)	
Other	84 (7.7%)	11 (6.1%)	
BMI	26.18 ± 5.75	27.20 ± 7.338	.32
P/F ratio at ICU arrival	356.3 ± 161	303.4 ± 161	<.01
EVLP	149 (14%)	118 (65.5%)	<.01
Recipient variables			
Age (y)	50.35 ± 15.60	51.96 ± 15.25	.15
Gender (male)	624 (57%)	104 (58%)	.92
Diagnosis			.95
IPF	421 (39%)	71 (39%)	
Emphysema	215 (20%)	41 (23%)	
Cystic fibrosis	167 (15%)	25 (14%)	
Retransplant	48 (4.4%)	6 (3.3%)	
PPH	42 (3.9%)	7 (3.9%)	
Scleroderma	38 (3.5%)	6 (3.3%)	
Alpha-1 antitrypsin deficiency	34 (3.1%)	7 (3.9%)	
Other	123 (11%)	17 (9.4%)	
Type of transplant (bilateral)			.24
Bilateral	895 (82%)	151 (84%)	
Right single	94 (8.6%)	11 (6.1%)	
Left single	86 (7.9%)	18 (10%)	
Heart and lung	13 (1.2%)		

Mean ± standard deviation is illustrated, and other variables are listed as absolute numbers with percentage in parentheses. *DNDD*, Donation after neurologic determination of death; *DCDD*, donation after circulatory determination of death; *BMI*, body mass index; *P/F ratio*, PaO_2/FiO_2 ratio (mm Hg); *ICU*, intensive care unit; *EVLP*, ex vivo lung perfusion; *IPF*, idiopathic pulmonary fibrosis; *PPH*, primary pulmonary hypertension.

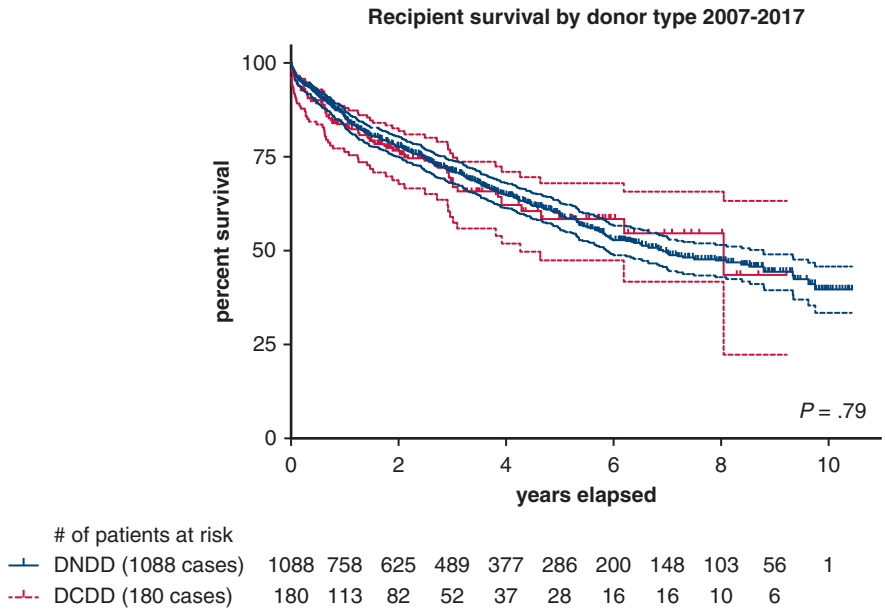

FIGURE 1. Kaplan–Meier survival plot comparing median survival between recipients who received lungs from DNDD and DCDD between 2007 and 2017 inclusive. Log-rank (Mantel-Cox) was used to calculate the *P* value. Median survival for DNDD LTxs was 6.9 years and 8.1 years for DCDD LTxs. Confidence limits are shown as error bars above and below each survival curve in the same smaller font color. Number of patients at risk is tabulated below the time axis. *DNDD*, Donation after neurologic determination of death; *DCDD*, donation after circulatory determination of death.

0.64-1.15). EVLP was used in 149 of 1088 (13.7%) of DNDD and 118 of 180 (65.6%) of DCDD lung donors before transplantation. Within the DNDD and DCDD groups, no significant differences in recipient survival was found in those who received lungs who underwent EVLP versus those who did not (Figure 2) ($P = .93$ for DNDD, 95% CI, 0.76-1.45 and $P = .44$ for DCDD 95% CI, 0.71-2.22).

Primary Lung Graft Dysfunction and Early Outcomes

For DNDD transplants, the incidence of PGD 2 and 3 at 72 hours was 17.2% (187/1088) and 9.0% (98/1088), respectively, and for DCDD transplants, the incidence was 15% (27/180) and 13.9% (25/180), respectively ($P = .37$; 95% CI, 0.55-4.90). Median number of days on mechanical ventilation was 2 (interquartile range [IQR], 4.75; 95% CI, 6.16-8.91) and 2 (IQR, 4.25; 95% CI, 4.7-8.5) for recipients of DNDD and DCDD lungs, respectively ($P = .89$) (Figure 3, *A*). Median post-transplantation ICU stay was 4 days (IQR, 12; 95% CI, 10.27-13.0) and 4.5 days (IQR, 12.75; 95% CI, 8.91-15.42) for recipients of DNDD and DCDD lungs, respectively ($P = .79$) (Figure 3, *B*). Median total hospital length of stay was not significantly different between the 2 groups, DNDD: 25 days (IQR, 30; 95% CI, 38.13-43.31) and DCDD: 23 days (IQR, 27; 95% CI, 35.71-52.1) ($P = .63$).

Impact of Withdrawal of Life-Sustaining Therapies to Asystole Interval on Post-Transplant Outcomes

Time between WLST and asystole (T0-T3) was available for 148 of 180 donors (82%) from the DCDD group. Mean and median time from WLST to asystole were 28.6 minutes and 16 minutes, respectively. Twenty donors required more than 60 minutes to arrest, with the longest duration being 154 minutes before asystole was recorded. All of these donors (>60 minutes) were evaluated on EVLP before transplant.

The mean interval ± standard deviation between WLST and an oxygen saturation less than 80% (T0-T1) was 2.6 ± 1.9 minutes, 4.7 ± 5.2 minutes, and 16.7 ± 29 minutes for the 3 groups, respectively. The mean interval ± standard deviation between WLST and a systolic blood pressure less than 50 mm Hg (T0-T2) for the donor groups with rapid (0-19 minutes), intermediate (20-59 minutes), and long (>60 minutes) was 8.7 ± 4.1 minutes, 22.7 ± 13.1 minutes, and 91.1 ± 35 minutes, respectively. The difference in time between the first recorded systolic blood pressure less than 50 mm Hg (T2) and asystole (T3) was also calculated for each specified T0-T3 interval and were 3.7 ± 3.8 minutes, 7.5 ± 7.7 minutes, and 8.1 ± 11.8 minutes, respectively. There was no significant difference when the T2-T3 interval was compared among the 3 T0-T3 intervals analyzed (rapid, intermediate, and long) ($P = .06$ by Kruskal–Wallis).

The incidence of PGD 2 and 3 at 72 hours was not different among the 3 groups: 12% (11/90) and 15.5% (14/90), 21% (8/38) and 13.1%(5/38), and 20% (4/20) and 15% (3/20) for recipients of lung donors with rapid (0-19 minutes), intermediate (20-59 minutes), and long (>60 minutes) intervals between WLST and asystole, respectively ($P = .39$).

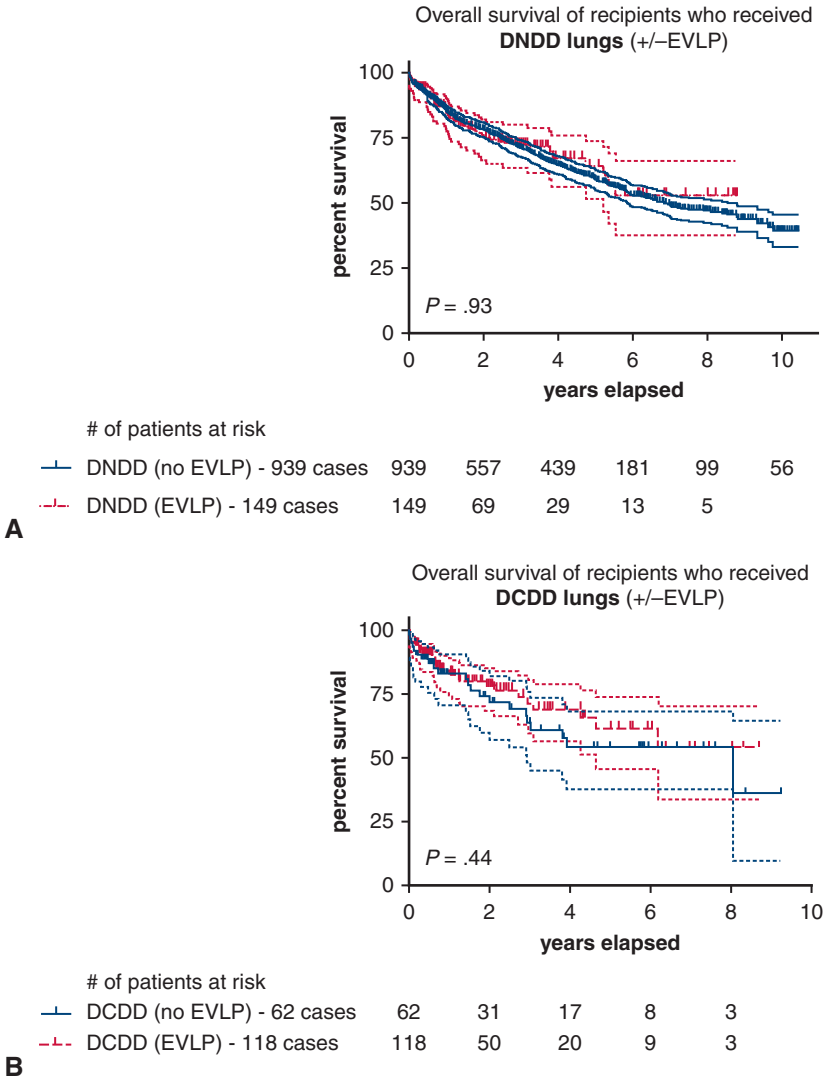

FIGURE 2. Overall median survival of transplant recipients who received lungs from DNDD (A) and DCDD (B) and further stratified by whether or not donor lungs received EVLP between 2007 and 2017 inclusive. Log-rank (Mantel-Cox) was used to calculated *P* value. Confidence limits are shown as error bars above and below each survival curve in the same smaller font color. Number of patients at risk is tabulated below the time axis. *DNDD*, Donation after neurologic determination of death; *EVLP*, ex vivo lung perfusion; *DCDD*, donation after circulatory determination of death.

Recipient mechanical ventilation days (Figure 4, *A*, $P = .52$), postoperative ICU stay (Figure 4, *B*, $P = .88$), and total hospital stay ($P = .25$) were similar among all 3 groups. Recipients of DCDD lung donors who had cardiac arrest at 0 to 19 minutes (90 donors), 20 to 59 minutes (38 donors), and more than 60 minutes (20 donors) did not demonstrate any significant differences in terms of overall survival (Figure 5, $P = .90$).

Ex Vivo Lung Perfusion Use During Donation After Circulatory Determination of Death Transplantation

EVLP was used in all of the donors who had cardiac arrest after 60 minutes (100%). In donors who had cardiac arrest between 20 and 59 minutes and 0 and 19 minutes, EVLP was used in 66% and 63% of donors, respectively. As discussed, the decision to use EVLP was based on previously established criteria16-18 for donors in whom arrests occurred in less than 60 minutes. EVLP was used in 118 of 180 (65.6%) of DCDD. In those donors who underwent EVLP, baseline (measured at the first hour) EVLP parameters including pulmonary vascular resistance (left atrial pressure [mm Hg] minus pulmonary artery [PA] pressure [mm Hg]/PA flow [L/min] dynes·seconds·cm^{-5}), delta PO_2 (left atrial PO_2 minus PA PO_2), peak inspiratory pressure (cmH_2O), static (Cstat), and dynamic (Cdyn) lung compliance (mL/cmH_2O) were compared. Baseline EVLP data were not available for 7, 7, and 2 donors from each WLST to asystole group (0-19, 20-59, and >60 minutes),

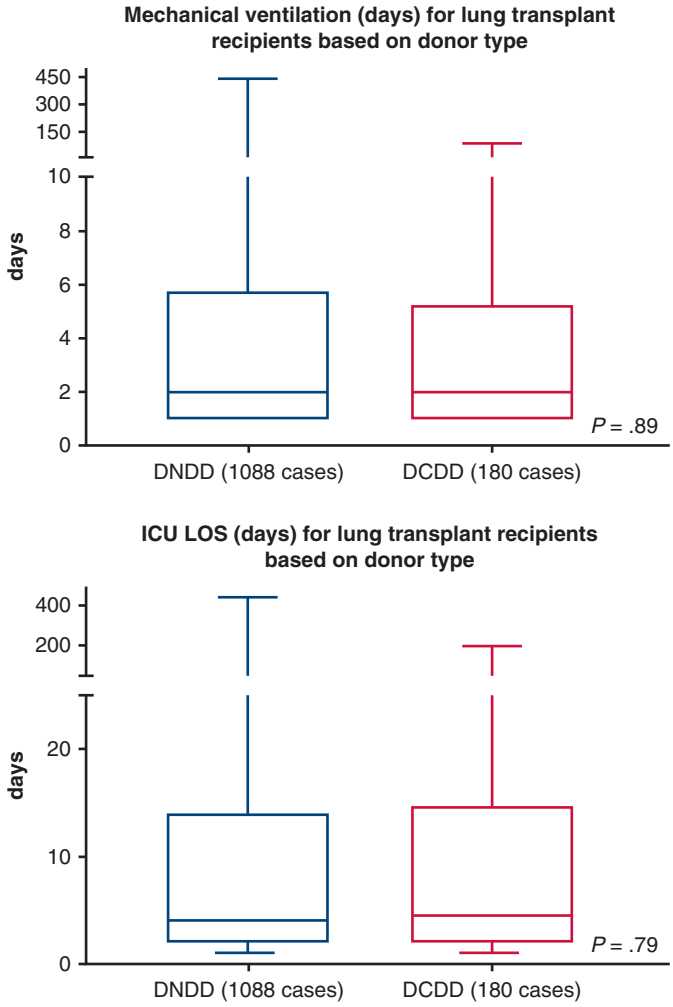

FIGURE 3. Box-and-whisker plot of (A) mechanical ventilation (days) and (B) ICU length of stay (days) in LTx recipients based on donor type: DNDD versus DCDD. *Upper* and *lower limit* of *boxes* represent 75th and 25th percentile, respectively, *whiskers* represent max and min values, and *horizontal line* within box represents median value. Mann–Whitney test was used to calculate the *P* value in each figure. *DNDD*, Donation after neurologic determination of death; *DCDD*, donation after circulatory determination of death; *ICU*, intensive care unit; *LOS*, length of stay.

respectively. There was no statistically significant difference in these baseline measurements, pulmonary vascular resistance ($P = .75$), delta PO_2 ($P = .6$) peak inspiratory pressure, Cstat ($P = .69$), and Cdyn ($P = .39$) from DCDD in the 0 to 19 minutes, 20 to 59 minutes, and more than 60 minutes WLST to systole categories.

Further Statistical Analysis

Cox proportional hazards regression modeling was used to model recipient survival based on transplant type DCDD versus DNDD and adjusting for covariates that included whether the transplant was single or bilateral, use of EVLP, donor cause of death, cigarette use in the donor, recipient and donor age, recipient diagnosis, and P/F ratio. Adjusting for these covariates, there was no difference in survival between DCDD and DNDD LTxs ($P = .12$; hazard ratio, 1.16; CI, 0.97-1.35) (Table E1).

DISCUSSION

To our knowledge, this comparative analysis represents one of the largest single-center cohorts of DCDD LTxs. The results presented demonstrate that the interval between WLST and cardiac arrest was not associated with recipient outcomes. Furthermore, we report that long-term outcomes do not differ among LTx recipients of DCDD and DNDD organs as demonstrated by the recent international experience.[9]

The practice of using DCDD lungs differs geographically. For example, less than 2% of all LTxs in the United States use DCDD donors, whereas in some European LTx centers, DCDD donors comprise up to 40% of their donor pool.[4,19] In Ontario, DCDD donors currently account for 35% of all donors. The results of this study and others referenced in this article may encourage LTx programs with the appropriate resources to augment their donor

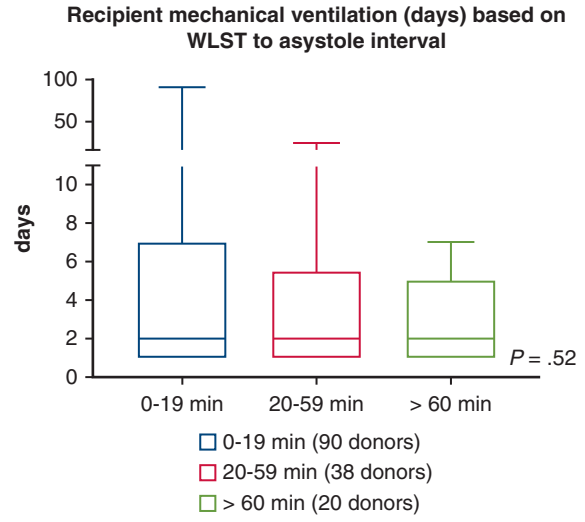

FIGURE 4. Box-and-whisker plot of (A) recipient mechanical ventilation (days) and (B) recipient ICU length of stay (days) based on DCDD who underwent rapid (0-19 minutes), intermediate (20-59 minutes), and long (>60 minutes) interval between WLST and asystole. *Upper* and *lower limit* of *boxes* represent 75th and 25th percentile, respectively, *whiskers* represent maximum and minimum values, and *horizontal line* within box represents median value. Kruskal–Wallis statistical test was used to calculate *P* value in each of the graphs. *WLST*, Withdrawal of life-sustaining therapies; *ICU*, intensive care unit; *LOS*, length of stay.

pool in hopes of decreasing wait-list times for patients awaiting LTx.

Our publication is novel in that we evaluated the effect of time to donor cardiac arrest including 20 donors who had an interval between WLST and asystole greater than 60 minutes. The longest period recorded was 154 minutes. The time to asystole in donors who had cardiac arrest at more than 60 minutes, although the smallest number of donors within the DCDD group, was not associated with recipient outcomes as demonstrated by similar ICU length of stay, mechanical ventilation duration, PGD 2 and 3 (at 72 hours), and survival. Our results suggest that the length of ISHLT T0-T3 interval may not be predictive in and of itself of graft function. There are likely other donor factors that have yet to be elucidated that may assist in providing LTx surgeons more predictive tools in helping improve DCDD use. To that end, EVLP seemed to be a critical tool to ensure organ viability after a prolonged agonal period in DCDD and perhaps was the contributing factor leading to similar outcomes in the 3 groups. The authors also recognize that our institution's extensive experience with EVLP may be an unaccountable factor that may have contributed to similar outcomes across each group. EVLP use at our institution is approximately 65% in DCDD LTx. Currently, the use of EVLP in controlled DCDD is selective based on other donor risk factors.[15-17]

We believe further research into this area of LTx is needed. Evaluation of not only the "duration of time" to arrest but also the "pattern of vital signs" during that period may ultimately influence organ quality. It has been our observational experience that some donors exhibit a long, stable decline of hemodynamic parameters, whereas others demonstrate more erratic, unpredictable hemodynamic derangements before asystole. Intervals defined by the ISHLT working group were evaluated, and no impact was observed when compared in the 3 defined cohorts. Further, characterization of donor hemodynamic patterns in a larger cohort of patients may be used to compare DCDD donor and recipient data and may perhaps assist in improving EVLP and DCDD use.

Study Limitations

The conclusions of the current study are limited to the retrospective nature of this study. Approximately 32 DCDD included in this study did not have complete data, that is, we did not have the precise duration of WLST to asystole because the donors were out of the province or country. In light of this large subset of donors who did not have WLST to asystole data, a sensitivity analysis was performed (Online Supplement) to evaluate whether there were differences in recipient or donor variables in those transplants in which the interval data were missing. Among the cases in whom the WLST to asystole interval data were not available, donor and recipient age, P/F ratio at ICU arrival, bilateral versus single LTxs, cause of death in donor, and recipient diagnosis did not demonstrate differences. However, EVLP use was higher in the missing data group ($P = .0495$), and there was more unknown cigarette use among those missing the time data between WLST and asystole ($P = .03$).

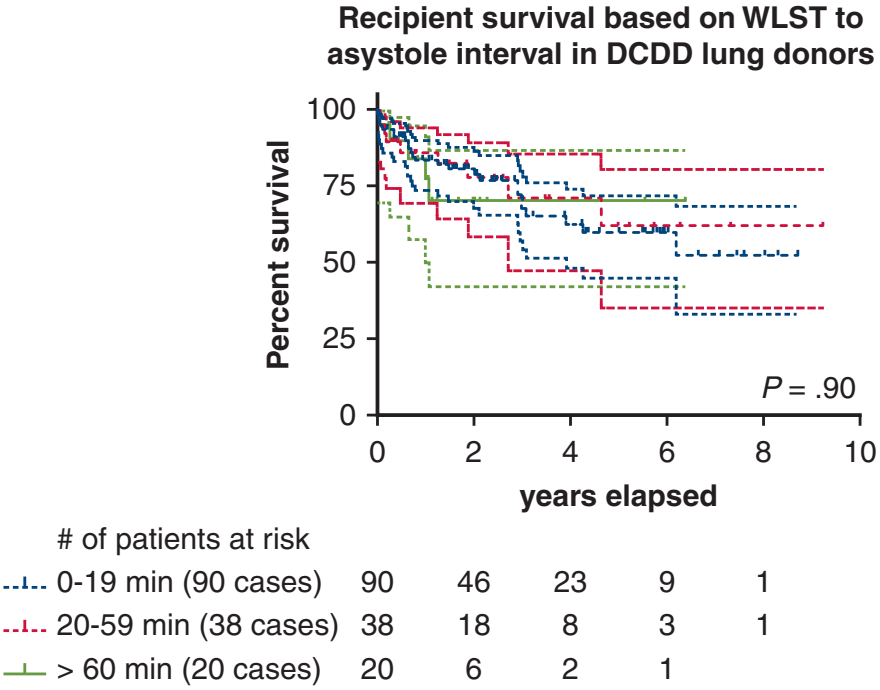

FIGURE 5. Recipient survival stratified on the basis of the interval between WLST and asystole in DCDD. Survival curves for recipients who received lungs from donors with a rapid (0-19 minutes), intermediate (20-59 minutes), and long (>60 minutes) duration between WLST and asystole were compared using log-rank (Mantel-Cox) statistical test. Confidence limits are shown as error bars above and below each survival curve in the same smaller font color. Number of patients at risk is tabulated below the time axis. *WLST*, Withdrawal of life-sustaining therapies; *DCDD*, donation after circulatory determination of death.

Second, we only evaluated the impact of duration of the T0-T3 interval (WLST to asystole) and not the effect of other intervals in the DCDD process, such as time from death declaration to cold flush (warm ischemic time) or functional warm ischemic time.[20] This time frame is defined by a hypoperfused state in which the systolic blood pressure is less than 50 to 60 mm Hg. This time frame and its impact on outcome were not directly evaluated in this cohort of patients, although we did not observe differences in this time frame among the 3 interval subgroups analyzed. Last, although a clinically significant number of transplants were performed in the group that had WLST to asystole that was greater than 60 minutes, the small numbers may have weakened our statistical analysis.

CONCLUSIONS

The length of time between WLST and asystole was not significantly associated with recipient outcomes, including ICU length of stay, mechanical ventilation days, and overall mortality. Although practices regarding DCDD use vary geographically, this report may encourage other LTx programs with appropriate lung evaluation tools to expand their donor pool even if the agonal phase extends more than 60 minutes. Our institution currently considers a WLST to asystole interval up to 180 minutes for all DCDD. The maximum acceptable duration of this interval has yet to be established.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/18Apr29/25ABC General Thoracic SS/S53/S53_3_webcast_034748250.mp4.

Conflict of Interest Statement

Drs Waddell, Keshavjee, and Cypel are consultants for Lung Bioengineering/United Therapeutics, founders for Perfusix Canada and XOR Labs Toronto. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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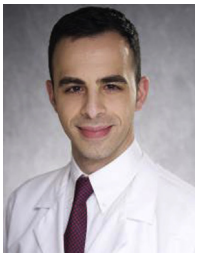
Key Words: lung transplantation, donation after circulatory determination of death, donation after cardiac death, donation after neurologic determination of death, ex vivo lung perfusion, primary graft dysfunction

Discussion

Presenter: Dr Robert Qaqish

Dr Sudish Murthy *(Cleveland, Ohio)*. Dr Qaqish and colleagues have reviewed their vast experience in LTx and found a significant number of patients who recently received DCDD organs. They've tried to address whether the seemingly artificial limits placed on time from extubation to organ harvest, which is 60 minutes for most centers, is reasonable. They leveraged some heterogeneity within their own practice to find patients at extremes of the interval from extubation to circulatory arrest and reviewed their outcomes. This is an important study given the paucity of organs and vanishingly small amount of data from which to craft reasonable guidelines for use of this unique organ source. The principle finding is that the interval doesn't seem to affect outcome post-transplant given their own institutional-specific pattern of organ use.

Is this a study on the use of DCDD organs or EVLP? The use of EVLP in the DCDD group is approximately 5 times higher than in the general DNDD group. What do you think about that?



Dr Robert Qaqish *(Iowa City, Iowa)*. I think it's a poignant analysis and a good question. You are right to point out that our EVLP use was higher, although there are reasons for that. There are inherent reasons why DCDD use is so low in the United States, and they are multifactorial. For example, there are complex logistics, and there is an unpredictability that underlies whether or not a donor will progress to circulatory death. Just as there are extended-criteria donors, there are extended-criteria features that sometimes will discourage LTx programs from using DCDD. What EVLP allows us to do specifically for the

DCDD population is that it allows us to evaluate the organs before transplantation. Yes, the use was higher, but all for good reasons. As it relates to our institution, the decision to put lungs on EVLP relates to the donor. For example, if a donor is evaluated and there are no previous clinical concerns, the P/F ratio is greater than 100, and the time to circulatory arrest is short, we leave it up to the discretion of the surgeon on call. Some surgeons are more aggressive than others in their implementation of EVLP. When we have a donor with suspected aspiration, a borderline P/F ratio, and the time to arrest is greater than 60 minutes, it is mandatory that those lungs get placed on EVLP for safety reasons and for evaluation.

Dr Murthy. Perhaps in your article you should consider suggesting that "EVLP may be uncoupling any potential negative impact from delayed extubation to circulatory arrest interval," just to get that message that you are now relaying here to the reader.

Does your time of EVLP then vary based on the time to circulatory arrest in these patients with extended circulatory arrest? And might that EVLP time be based on some objective data of gas exchange or compliance on the circuit? Have you guys thought about that or what do you think about that?

Dr Qaqish. Yes, we have thought about it. We have published protocols in terms of our acceptance criteria. In general, all lungs are evaluated on EVLP for approximately 4 to 6 hours. We have regimented, strict assessments that we perform every hour as they relate to hemodynamics, as well as compliance of the lungs. At least 2 assessments are required: radiographic at 1 and 3 hours, as well as bronchoscopy at 1 and 3 hours—and the decision is made as early as 3 hours whether or not the lungs are accepted for transplantation. We use these criteria for every single lung that gets placed on EVLP, regardless of the reasons why they were placed on EVLP.

Dr Murthy. Do the standard parameters and descriptors of donor and recipient affect the receipt of an organ in this extended circulatory arrest cohort? In other words, are the donors younger never-smokers or the recipients unable to wait for another chance at an organ? Could this be a potential bias or was it all based on gas-exchange and compliance on the EVLP circuit as the dominant clinical driver to use the organs?

Dr Qaqish. If I understand your question correctly, all of our potential recipients have an equal opportunity to receive brain-death donor lungs or DCDD lungs. We do not select.

Dr Murthy. This is an important study. We don't have real guidelines on these types of organs until perhaps now, and this is a valuable resource in a situation where the organ shortage is critical. As you have demonstrated with your use of EVLP, you are ramping up your transplants and almost certainly reducing wait times and death before transplant. This may add at least 20% more organs I suspect and unlocks a new source of organs that was simply discarded before. I congratulate you and your group.

Dr Dirk E. M. Van Raemdonck *(Leuven, Belgium).* Your definition of the agonal phase was the ratio between extubation and circulatory arrest. However, the agonal phase does not start until the patient becomes hypotensive or hypoxic. Do you have an idea of the interval between the hypotensive start and the circulatory arrest? Especially in those 20 donors with a long interval.

Dr Qaqish. I think that is an important point that was brought up. We have those data. For the purposes of this analysis, they were not used. In terms of our organ procurement, we do have those data for the majority of those. As you well know, there is sometimes an erratic derangement in hemodynamics in some lung-transplant donors versus more of a stable decline. So to answer your question, yes, we do have those data. We did not consider those decreases in hemodynamics, namely, systolic blood pressure less than 50, and then start the time at that point. It is something that we can go back and look at and supplement our analysis with.

Dr Matthew P. Fox *(Louisville, Ky).* My question is in the denominator, from how many of the patients who went over 60 minutes from withdrawal of life support to asystole did you actually procure the lungs? Of those patients who were put on EVLP, how many did you decline? I think from a smaller-volume program standpoint, it is kind of hard for us to wait around for 2 or 3 hours for a patient who might not die. It would be interesting to me to know the rate of acceptance. You would think the rate of aspiration would go up. I think this study shows that EVLP works, and if the lungs do good on EVLP, they would do great on the patient. I think from a resource perspective it would be interesting to know.

Dr Marcelo Cypel *(Toronto, Ontario, Canada).* I think I can help answer that. Approximately 30% to 40% of our DCDD donors do not arrest within 3 hours. That's a higher number than observed in Europe. From the lungs we take and put on EVLP, approximately 60% to 70% we end up using for transplant. So, there is still a 30% decline from the time of EVLP.

TABLE E1. Results of Cox proportional hazards regression modeling used to model survival by donation after circulatory determination of death versus donation after neurologic determination of death adjusting for covariates: analysis of maximum likelihood estimates

Parameter		DF	Parameter estimate	Standard error	Chi-square	Pr > Chi-square	Hazard ratio
Type	DCDD	1	0.15062	0.09708	2.4071	0.1208	1.163
TX	BLT	1	0.09826	0.08458	1.3496	0.2453	1.103
EVLP	Y	1	0.40735	0.08362	23.7339	<0.0001	1.503
COD_D	Anoxia/cardiac arrest	1	0.32092	0.51071	0.3949	0.5298	1.378
COD_D	Cerebrovascular/stroke	1	0.02805	0.50548	0.0031	0.9558	1.028
COD_D	Head trauma	1	0.21408	0.50968	0.1764	0.6745	1.239
COD_D	Motor vehicle accident	1	−0.60577	0.77602	0.6094	0.435	0.546
COD_D	Other	1	0.38871	0.52311	0.5522	0.4574	1.475
COD_D	Primary CNS tumor	1	0.11464	0.61889	0.0343	0.853	1.121
Cigarette use	Y	1	−0.05501	0.06231	0.7795	0.3773	0.946
Cigarette use	U	1	0.08924	0.12331	0.5237	0.4693	1.093
P_Disease	Alpha-1 antitrypsin deficiency	1	0.14778	0.22519	0.4307	0.5117	1.159
P_Disease	BO	1	0.07838	0.25236	0.0965	0.7561	1.082
P_Disease	Bronchiectasis	1	−0.0066	0.23304	0.0008	0.9774	0.993
P_Disease	CA	1	−0.01817	0.52645	0.0012	0.9725	0.982
P_Disease	COPD/emphysema	1	−0.18518	0.16831	1.2105	0.2712	0.831
P_Disease	Cystic fibrosis	1	0.05008	0.18215	0.0756	0.7834	1.051
P_Disease	Eisenmenger's syndrome	1	0.02202	0.34905	0.004	0.9497	1.022
P_Disease	Hypersensitivity pneumonitis	1	1.05541	0.35788	8.6971	0.0032	2.873
P_Disease	LAM	1	0.52573	0.44113	1.4203	0.2334	1.692
P_Disease	Langerhans cell histiocytosis	1	0.32336	0.52449	0.3801	0.5375	1.382
P_Disease	Other	1	−0.11243	0.36893	0.0929	0.7606	0.894
P_Disease	PPH	1	0.12526	0.21899	0.3272	0.5673	1.133
P_Disease	Proteinosis	1	0.61024	1.08162	0.3183	0.5726	1.841
P_Disease	Pulmonary fibrosis	1	0.02855	0.16184	0.0311	0.86	1.029
P_Disease	PvenoOD	1	0.21973	0.60641	0.1313	0.7171	1.246
P_Disease	Retransplant	1	0.50413	0.21482	5.5071	0.0189	1.656
P_Disease	Sarcoidosis	1	0.05975	0.25683	0.0541	0.816	1.062
Age_D		1	0.00771	0.00197	15.2906	<0.0001	1.008
AGE_R		1	0.01176	0.00298	15.5198	<0.0001	1.012
P_F_Ratio_a		1	−0.00432	0.000203	4.5275	0.0334	1

DF, Degrees of freedom; *DCDD*, donation after circulatory determination of death; *TX*, transplantation; *BLT*, bilateral lung transplant; *COD*, cause of death; *EVLP*, ex vivo lung perfusion; *CNS*, central nervous system; *BO*, bronchiolitis obliterans; *CA*, cancer; *COPD*, chronic obstructive pulmonary disease; *LAM*, lymphangioleiomyomatosis; *PPH*, primary pulmonary hypertension; *PvenoOD*, pulmonary veno-occlusive disease.