Initial Experience With Lung Donation After Cardiocirculatory Death in Canada

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Background: Organ donation after cardiac death (DCD) has the potential to alleviate some of the shortage of suitable lungs for transplantation. Only limited data describe outcomes after DCD lung transplantation. This study describes the early and intermediate outcomes after DCD lung transplantation in Canada.

Methods: Data were collected from donors and recipients involved in DCD lung transplantations between June 2006 and December 2008. Described are the lung DCD protocol, donor characteristics, and the occurrence of post-transplant events including primary graft dysfunction (PGD), bronchial complications, acute rejection (AR), bronchiolitis obliterans syndrome (BOS), and survival.

Results: Successful multiorgan controlled DCD increased from 4 donors in 2006 to 26 in 2008**.** Utilization rates of lungs among DCD donors were 0% in 2006, 11% in 2007, and 27% in 2008. The lung transplant team evaluated 13 DCD donors on site, and lungs from 9 donors were ultimately used for 10 recipients. The 30-day mortality was 0%. Severe PGD requiring extracorporeal membrane oxygenation occurred in 1 patient. Median intensive care unit stay was 3.5 days (range, 2–21 days). Hospital stay was 25 days (range, 9–47 days). AR occurred in 2 patients. No early BOS has developed. Nine (90%) patients are alive at a median of 270 days (range, 47–798 days) with good performance status and lung function. One patient died of sepsis 17 months after transplantation.

Conclusion: DCD has steadily increased in Canada since 2006**.** The use of controlled DCD lungs for transplantation is associated with very acceptable early and intermediate clinical outcomes. J Heart Lung Transplant 2009;28:753–8. Copyright © 2009 by the International Society for Heart and Lung Transplantation.

Lung transplantation (LTx) is a lifesaving therapy for patients with end-stage lung disease. However, donor organ availability continues to be a serious problem facing all solid-organ transplant programs and is particularly serious with regard to LTx. The demand for donor lungs exceeds the supply, and patients continue to die while on waiting lists.[1] Because of injuries that occur in the lung during the process of brain death and complications related to the intensive care unit (ICU),[2] only about 15% to 20% of multiorgan donors ultimately have lungs that are considered suitable for LTx.[3]

To overcome this donor shortage, some programs have initiated the use of donors after cardiac arrest (DCD). Controlled DCD (Maastricht category III)[4] includes patients who have dismal prognoses but whose condition does not fulfill the strict definition of brain death. Recent publications of case reports[5,6] and small series[7,8] have shown DCD lung donation from controlled donors to be a safe alternative lung donor pool. Indeed, Mason et al[9] recently reviewed the United States experience with 36 DCD lungs, and the 2-year adjusted recipient survival was slightly better than in recipients who received lungs from donation after brain death.

Organ donations in Canada have traditionally been only from individuals who have died after meeting criteria for brain death.[10] On June 27, 2006, however, The Ottawa Hospital announced organ donation from a patient after cardiac arrest.[11] Six months after this event, we successfully performed our first transplantation using a controlled DCD lung. This report aims to present the early Canadian experience using category III DCD lungs and to provide perspectives that will potentially increase safe utilization from these donors in the near future.

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METHODS

Data were collected from donors and recipients involved in DCD LTx between June 2006 and December 2008. After approval from the Institutional Research Ethics Board and the Ontario Trillium Gift of Life Network, Maastricht category III DCD donors became eligible for LTx. A protocol for DCD organ procurement was then established in our group. Recipients who consented for LTx were informed that they might receive DCD organs, but no specific was required. Decisions about withdrawal of life-sustaining therapies (WLST), management of the dying process, and the determination of death by cardiocirculatory criteria was separate from and independent of the donation/transplant processes.

Donor Lung Selection

Donor lung suitability was determined using the same criteria used for brain-dead donors,[12] which includes history, chest X-ray imaging, arterial blood gases, bronchoscopy, and visual inspection. In addition, extended criteria lungs[13,14] (donor lungs that do not fulfill standard criteria) were also considered for DCD LTx. Ex vivo lung assessment using acellular normothermic lung perfusion[15] was available for donor lungs in which function was considered questionable.

DCD Lung Procedure

The donor was given heparin (30,000 IU) 30 minutes before extubation and WLST. When cardiac arrest occurred, death was certified by 2 physicians of the donor hospital ICU team after a 5-minute period of absent palpable pulses, blood pressure, and respiration. The donor was then transferred to the operating room and reintubation was quickly performed by one of our LTx team members. A flexible bronchoscopy was performed to rule out aspiration of gastric contents during cardiac arrest, presence of mucopurulent secretions, or anatomic abnormalities. Concurrent with the bronchoscopy, another member of the transplant team performed a median sternotomy and cannulation of the pulmonary artery (PA), followed by the standard procurement technique.[16]

Consistent with the preservation protocol used for lung donation after brain death at our institution, 4 liters of antegrade flush through the PA and 1 liter of retrograde flush through the pulmonary veins was performed using cold Perfadex solution (Vitrolife AB, Kungsbacka, Sweden). The decision for utilization of the lungs for LTx and therefore initiation of recipient anesthesia was made only after the lungs were explanted and careful macroscopic evaluation was performed.

Recipient Selection and Care After LTx

Recipient selection, donor/recipient matching, and care after LTx, including fluid management, antibiotic prophylaxis, immunosuppression regimens, and surveillance bronchoscopy were performed according to current standard practice at our institution.[17]

Definitions and Statistics

Successful multiorgan DCD donation was defined as the use of at least 1 organ for transplantation from a DCD donor. The University of Wisconsin (UW) DCD score was a tool developed to assess the respiratory drive of the patient and is used to predict the likelihood of continued spontaneous respirations 1 and 2 hours after extubation.[18] Primary graft dysfunction (PGD) grades after LTx were defined according to recent International Society of Heart an Lung Transplantation (ISHLT) guidelines.[19] Logistic regression was used to correlate the time between WLST and cold flush of the lungs with lung function early after transplantation. Data are expressed as median and ranges.

RESULTS

Between June 2006 and December 2008, 235 LTxs were performed at Toronto General Hospital. During the same period, there were 56 referrals for DCDs. In 9 donors, cardiac arrest did not occur within a period of 2 hours and therefore none of the solid organs were considered for donation. Our lung team evaluated 13 potential DCD lung donors on-site, and organs from 9 were ultimately used for transplantation into 10 recipients, comprising 4 single LTx and 6 bilateral LTxs. Figure 1 shows the distribution of consented DCD donors, successful multiorgan donation, and lung donation since 2006. Reasons for non-use of the lung once the LTx team was on-site included absence of cardiac arrest within a suitable period of time in 3, and pathologic findings during careful inspection after explantation in 1.

In most cases, WLST occurred in the ICU or post-anesthetic care unit, whereas clinical support in 1

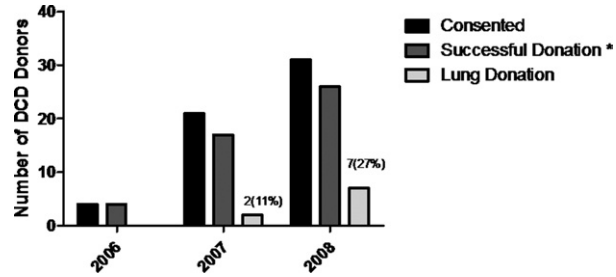

Figure 1. Number of successful donation after cardiac death (DCD) donors in Ontario since 2006. *At least 1 solid organ used for donation. Percentage values represent utilization of lungs among successful multiorgan DCD donation.

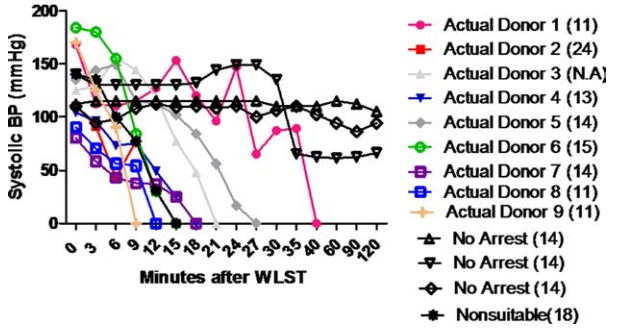

Figure 2. The systolic blood pressure response is documented after withdrawal of life-sustaining therapies (WLST) in 13 potential donation after cardiac death (DCD) lung donors–9 actual (color) and 4 not used (black). University of Wisconsin DCD score is shown in brackets for comparison.

donor was withdrawn in the operating room according to local hospital policy. The blood pressure response after donor extubation in the 13 potential DCD donors paired with the UW DCD score[20] is shown in Figure 2. There was no clear association between the score and the time to cardiocirculatory arrest.

Donor characteristics are reported in Table 1. Three donors met standard criteria, and 6 met extended criteria (i.e., smoking history of 20–40 pack/years or positive results on bronchopulmonary cultures). Donor median age was 43 years (range, 16–56 years), and the last partial pressure of arterial oxygen (Pao_2)/fraction of inspired oxygen (Fio_2) was 425 mm Hg (range, 284–505 mm Hg). Although post-extubation bronchopulmonary aspiration was a concern, no signs of aspiration were observed by the time of reintubation and flexible bronchoscopy in any of the donors.

The demographics and early and intermediate clinically important outcomes of the 10 actual LTx recipients are reported in Tables 2 and 3. No recipients died within 30 days after LTx. Grade 3 primary graft dysfunction[19] after LTx occurred in 1 patient requiring support by extracorporeal membrane oxygenation (ECMO). Values of Pao_2/Fio_2 representing lung function at ICU arrival in correlation with interval WSLT to PA flush are shown in Figure 3. There was an inverse association of interval WLST to PA flush in the donor and immediate recipient lung function after transplantation.

Airway complications occurred in 1 patient who had a small bronchial anastomotic dehiscence associated with invasive bronchial aspergillosis that did not require any surgical or bronchoscopic intervention. Acute rejection (grade 2) occurred in 2 patients, and no patients have yet developed any degree of bronchiolitis obliterans syndrome (BOS). Nine patients (90%) are alive at a median of 270 days (range, 47–798 days) with good performance status and lung function (Table 3). One patient died of sepsis 17 months after LTx after having excellent lung function at his 1-year assessment.

Table 2. Recipient Characteristics

No.	Age, y	Sex	Medical Dx	NYHA class	Ischemia, hours	Procedures
1[a]	59	M	IPF	IV	6	Single LTx
2[a]	70	M	IPF	IV	7.5	Single LTx
3	54	M	Emphysema	III	7	Double LTx
4	63	M	Emphysema	IV	5	Double LTx
5	68	M	Emphysema	III	9	Single LTx
6	49	F	Emphysema	III	6	Double LTx
7	74	F	Emphysema	IV	7	Single LTx EVLP
8	52	F	Emphysema	IV	7.5	Double LTx
9	26	M	CF	IV	9	Double LTx EVLP
10	67	F	Emphysema	IV	7	Double LTx

CF, cystic fibrosis; Dx, diagnosis; EVLP, ex vivo lung perfusion; IPF, idiopathic pulmonary fibrosis; LTx, lung transplantation; NYHA, New York Heart Association.
[a]Same donor.

DISCUSSION

This study shows the results of the first 10 LTx using DCD donation in Canada. The number of successful DCD donors has significantly increased since 2006. Early recipient survival after LTx was excellent, and lengths of ICU and hospital stay are comparable with

Table 1. Donor Characteristics of 9 Lungs Donated after Cardiac Death

No.	Age	Sex	Smoking, pack-years	Cause of death	UW DCD score	WLST to PA flush, min	Pao_2, mm Hg	Chest X-ray	Bronchoscopy	Cultures
1	17	M	0	MVA	11	61	475	Localized	Mucoid	Positive
2	50	F	0	CVA	24	32	427	Normal	Clear	Positive
3	16	M	0	Head trauma	N/A	37	284	Localized	Clear	Negative
4	43	M	27	Anoxia	13	29	466	Normal	Clear	Negative
5	31	M	10	Head trauma	14	40	425	Localized	Mucoid	Negative
6	55	F	30	CVA	15	34	362	Normal	Purulent	Positive
7	56	F	30	CVA	14	34	505	Normal	Clear	Positive
8	49	M	0	CVA	11	23	390	Localized	Clear	Positive
9	20	M	5	MVA	11	30	286	Localized	Purulent	Positive

CVA, cerebrovascular accident; DCD, donation after cardiac death; F, female; M, male; MVA, motor vehicle accident; PA, pulmonary artery; Pao_2, partial pressure of arterial oxygen; WLST, withdrawal of life-saving therapy; UW, University of Wisconsin.

Table 3. Recipient Early and Intermediate Outcomes

No.	PGD, 24-hour grade	ICU stay, days	Airway complications	Re-admit	Highest rejection, grade	FEV_1, %		BOS status	Alive, days
						3 mon	Most recent		
1	3	20	No	No	2	69	75	0	Y-798
2	2	2	No	Pneumonia	0	109	117	0	N-510
3	0–1	4	No	No	1	127	139	0	Y-498
4	0–1	2	No	No	0	58	51	0	Y-348
5	0–1	21	No	No	0	134	149	0	Y-270
6	0–1	2	Dehiscence	ARF	0	73	I13	0	Y-265
7	2	15	No	DVT	0	60	74	0	Y-258
8	0–1	13	No	No	0	75	75	0	Y-120
9	0–1	3	No	Pneumonia	2	NA	68	0	Y-62
10	2	3	No	No	0	NA	84	0	Y-36

ARF, acute renal failure; BOS, bronchiolitis obliterans syndrome; DVT, deep vein thrombosis; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; N, no; PGD, primary graft dysfunction; Y, yes.

our non-DCD population. One patient required ECMO for severe primary graft dysfunction. Interestingly, a contralateral lung from the same donor was transplanted to another recipient who was discharged from the ICU on the second post-operative day. This highlights that not only donor factors but also intraoperative and recipient factors can contribute to early graft function.[21–25]

Our results are comparable with the current reports on controlled DCD lung donation. Early outcomes are very acceptable, the incidence of acute rejection is low, and development of early BOS is rare.[5,7–9] In contrast, use of uncontrolled DCD lungs (Maastricht categories I and II) showed a high early mortality rate of 17%, 1-year survival of only 69%, and an increased incidence of acute rejection episodes, raising concerns of safety.[27] A possible explanation for this adverse outcome is an increased chance of bronchopulmonary aspiration during resuscitation maneuvers in uncontrolled DCD.

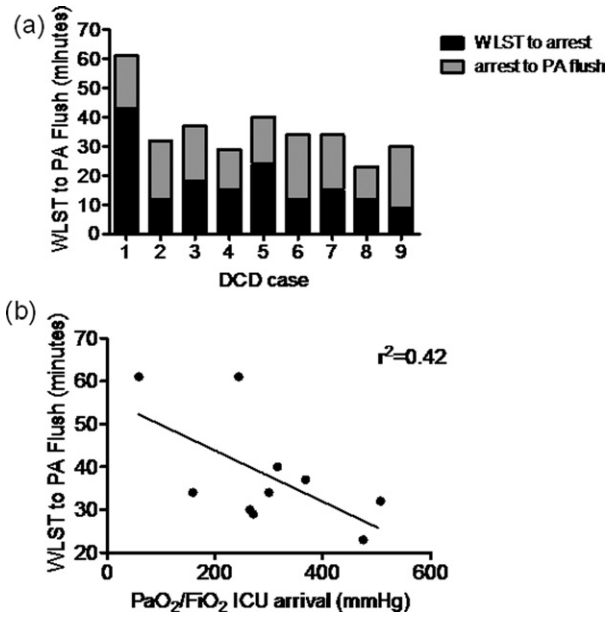

Figure 3. Lung function early after transplantation. (a) Time between withdrawal of life sustaining therapies (WLST) in the donor and pulmonary artery (PA) cold flush. (b) Inverse correlation between recipient partial pressure of arterial oxygen (Pao_2)/fraction of inspired oxygen (Fio_2) and interval between WLST in the donor and PA cold flush. Of note, Patients 1 and 2 received lungs from the same donation after cardiac death (DCD) donor but had different early outcomes after transplantation. ICU, intensive care unit.

In addition, the warm ischemic time in uncontrolled DCD donation is prolonged (mean, 118 minutes).[26] Experimental data have shown a clear association between warm ischemic time in DCD and performance of the lung after transplantation.[27–29] Warm ischemic time longer than 1 hour is also associated with increased release of proinflammatory cytokines, especially interleukin (IL) -1β, early after transplantation.[29,30] The degree of proinflammatory cytokine release after LTx may be important in the interplay of innate and adaptive immune mechanisms that ultimately sustain donor-specific alloimmunity predisposing to BOS.[31] Thus, even in controlled DCD lung donation, warm ischemic time should be an important consideration.

We believe that the time between WLST to cold flush in DCD lungs is a period of risk for lung injury. Once WLST is initiated, the lung is at increased risk from events such as hypotension, warm ischemia (once systolic blood pressure $<$ 50 mm Hg or after cardiac arrest), and aspiration. Our results are similar to Snell et al,[7] in which an inverse association was found between warm ischemic time and Pao_2/Fio_2 ratios after transplantation. The numbers are small in both series; thus, the association between lung function and intervals from WLST to PA flush (including subdivisions of this interval) should be confirmed with larger series.

Because a definitive cutoff cannot currently be established, our current protocol considers donors in which cardiac arrest occurs within 90 minutes after WLST.

Along with the Australian experience, we also found that the UW DCD score[20] was not a powerful tool to predict the time from withdrawal of support to death. Thus, our group no longer uses this score as a decision tool for consideration of whether to send our team for the donor organ retrieval procedure.

A limitation of this study includes the small number of DCD lung donors as well as the short follow-up. However, effect of donor lung quality should be reflected mostly in the early (i.e., primary graft dysfunction or 30-day mortality) and intermediate outcomes (i.e., acute rejection or early BOS). Given the scarce worldwide experience with this process and the lack of large experiences from single centers, we believe reports like ours will help to enhance confidence in LTx teams regarding DCD acceptability.

Although the DCD multiorgan donor pool is becoming substantial, the number of transplanted DCD lungs still remains very low.[32] More accurate evaluation of those organs may increase their use. Functional reevaluation of the lungs using normothermic ex vivo lung perfusion after the DCD procedure may be important in discriminating organ suitability.[5,6,15,33–36]

We have recently developed a reliable and reproducible ex vivo lung perfusion technique (Figure 4) that can maintain donor lungs for at least 12 hours at body temperature with continuous lung function assessment.[15] A clinical trial using this technology to evaluate and improve function of sub-optimal donor lungs is currently being performed at our institution and preliminary results are encouraging. Of note, 2 of our more recent DCD lungs were included in our ex vivo lung perfusion trial to confirm organ function and were transplanted with good recipient outcomes. We currently ex vivo assess all DCD lungs in which the time to donor arrest is longer than 30 minutes, even if they meet standard criteria otherwise.

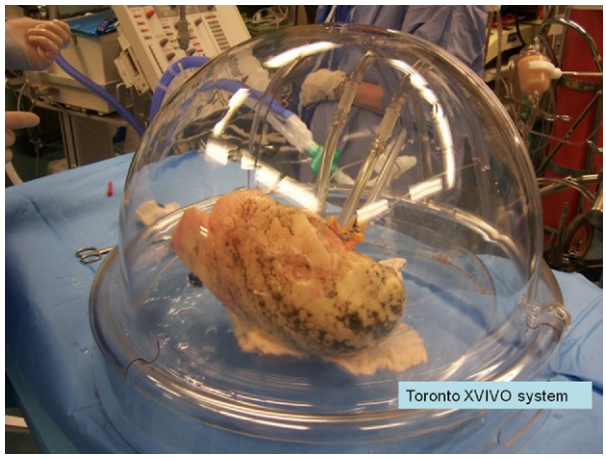

Figure 4. The ex vivo lung perfusion circuit (Toronto XVIVO) is being clinically used to reassess lungs donated after cardiac death ex vivo before transplantation.

Finally, we believe the use of real-time predictive biomarkers in the lung tissue will provide a more accurate reflection of the overall donor lung quality. To that end, we and others have demonstrated that elevated levels of the proinflammatory cytokines IL-6, IL-8, and IL-1β, and low levels of IL-10 in the donor lung tissue can accurately predict increased 30-day mortality due to primary graft dysfunction after LTx in humans.[37–39] Interestingly, some preliminary clinical studies have shown that inflammatory profiles are favorable in lungs from DCDs compared with brain-dead donors[40]; thus, avoidance of the cytokine storm associated with brain death might be an advantage of the DCD lungs.

In conclusion, DCD donation in Canada has steadily increased since 2006. The use of controlled DCD lungs for human LTx is associated with very acceptable early and intermediate clinical outcomes. It is hoped that increased awareness of successful utilization of DCD organs will lead to increased referrals of potential DCD donors to organ procurement organizations. In addition, ex vivo lung reassessment using ex vivo lung perfusion, along with real-time prognostic biomarker testing, may have a significant effect on DCD assessment, leading not only to further expansion of the donor organ pool but also improved outcomes after transplantation.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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