

ORIGINAL ARTICLE

What is the potential increase in the heart graft pool by cardiac donation after circulatory death?

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Introduction

One of the most frustrating aspects of transplant surgery is the constant cadaveric organ shortage that the patients and practitioners have to face. For most organs but the heart, grafts retrieved from controlled donors after circulatory death (DCD) are now regularly used in some Western countries to increase the graft pools [1,2]. The results of transplantation of controlled DCD livers or kidneys are confirming the interest of such a policy [3,4]. Spectacular results have been achieved in the domain of DCD lung transplantation, in which organ quality and long-term survival are equivalent to grafts used from

Summary

Heart transplantation remains the only definite treatment option for end-stage heart diseases. The use of hearts procured after donation after circulatory death (DCD) could help decrease the heart graft shortage. The aim of this study was to evaluate the potential increase in heart graft pool by developing DCD heart transplantation. We retrospectively reviewed our local donor database from 2006 to 2011, and screened the complete controlled DCD donor population for potential heart donors, using the same criteria as for donation after brain death (DBD) heart transplantation. Acceptable donation warm ischemic time (DWIT) was limited to 30 min. During this period 177 DBD and 70 DCD were performed. From the 177 DBD, a total of 70 (39.5%) hearts were procured and transplanted. Of the 70 DCD, eight (11%) donors fulfilled the criteria for heart procurement with a DWIT of under 30 min. Within the same period, 82 patients were newly listed for heart transplantation, of which 53 were transplanted, 20 died or were unlisted, and 9 were waiting. It could be estimated that 11% of the DCD might be heart donors, representing a 15% increase in heart transplant activity, as well as potential reduction in the deaths on the waiting list by 40%.

donation after brain death (DBD), without the specific need to change current established protocols [5].

In controlled DCD donation, donor's death is diagnosed on the cessation of heart beating or/and of blood circulation. This absence of efficient cardiac activity may be assessed by electrocardiography, and/or by monitoring of the cardiac function by means of arterial pulses or by invasive arterial pressure monitoring. Until now, DCD heart transplantation (HT) has not reached clinical practice because of concerns regarding the potential deleterious effects of warm ischemia occurring during DCD procurement on heart graft functionality and viability. Even though the first HT performed in 1967 used hearts

retrieved from what would be today considered DCD [6], DCD HT was rapidly abandoned after the definition of brain death. As suitable DBD hearts become more and more scarce [7], the possibility of using heart grafts retrieved from DCD becomes again attractive and could help to reduce the overall mortality on waiting lists. Nonetheless, before DCD HT could be re-introduced, several concerns, especially about the functionality of such grafts, still need to be addressed. Currently, investigations are underway in animal models with promising results [8]. Martin *et al.* published an intriguing article in which successful transplantation of DCD hearts in a pig model was achieved after 30 min of normothermic ischemia [9]. In 1992 [10] and in 1995 [11], Grundy *et al.* published two interesting studies in which DCD heart transplantations were successfully undertaken in a lamb and in a primate model. Of equivalent importance, it is to note that such transplantations have already been successfully been performed in pediatric setting [12], thus pushing the idea forward to explore this concept of DCD heart transplantation.

However, before investing in basic research and in animal models with the goal to develop a successful DCD heart transplantation program, it is important to determine if, by numbers, DCD heart procurement might increase the heart graft donor pool and, as a consequence, decrease the waiting list mortality for HT candidates. The aim of this study was therefore to determine if suitable DCD heart grafts could have been procured and transplanted amongst the pool of DCD donors procured in a group that successfully develop programs of DCD liver and kidney transplantations.

Methods and patients

In 2002, a program of controlled DCD procurement and transplantation was developed at the Department of Abdominal Surgery and Transplantation of the University of Liège, Belgium [13]. The authors retrospectively reviewed the donor data that were prospectively included from January 2006 until December 2011 in the local deceased donor (DD) database. Most information on these donors were recorded according to the Eurotransplant (ET) organization donation form (downloadable at the member ET website at the address: https://members.eurotransplant.org/cms/mediaobject.php?file=et_donor_information_form1.pdf), including donor age, gender, past medical history as diabetes mellitus, hypertension and medication, cause of death, history of cardiac arrest, need of resuscitation, length of intensive care unit (ICU) stay, body mass index (BMI), inotrope use and dosage, and urinary output.

During this 6-year period, 247 effective DD (mean age: 47 years, range: 0–83; gender ratio: 1.5 male/1 female)

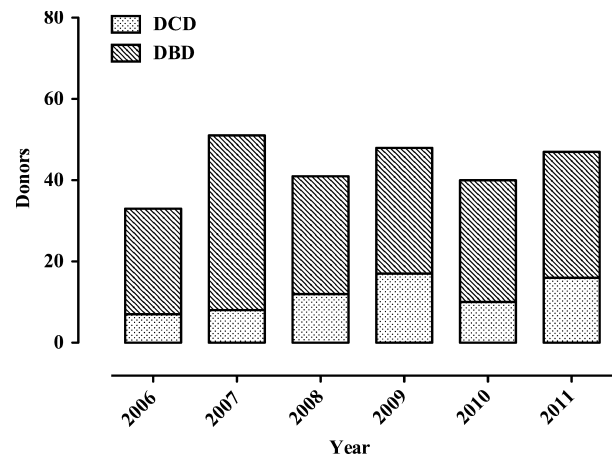


Figure 1 Evolution of the deceased donor procurement activity during the study period.

procedures were performed, allowing procurement of 759 subsequently transplanted organs, including 70 hearts. Among these DD, 177 (72%) were DBD and 70 (28%) were DCD (Fig. 1).

All DCD donations were performed in a controlled manner in the operative room (Maastricht category III) [14]. This DCD program and its protocol were described in previous publications [13,15,16]. In summary, a non-transplant physician performed the withdrawal of life support in the operative room in all cases. The vast majority of the DCD donors received intravenous heparin before cessation of circulation. End-of-life comfort therapy may have been administered before support withdrawal [17]. Invasive femoral arterial pressure was used to diagnose circulatory arrest. Organ recovery started 5 min (stand-off period) after declaration of donor's death on circulatory criteria, using the super rapid technique including rapid midline laparotomy and sternotomy with inferior vena cava decompression in the pericardium, abdominal aortic cannulation, and thoracic aorta clamping, as described [18]. Donation warm ischemic time (DWIT) was defined as the time of life-support withdrawal of the donor to the aortic perfusion with the cold preservation solution. DWIT was divided in two separate phases, the time of support withdrawal to circulatory arrest (withdrawal phase), and the time between circulatory arrest to aortic cannulation (acirculatory phase). The characteristics of the 70 DCD donors are presented in Table 1.

To select the potential heart graft donors within the DCD group, the authors applied the same inclusion criteria as for DBD cardiac donors, with the additional criteria that DWIT must not exceed 30 min (Table 2). This timeframe was selected because of the fact that above-mentioned studies in animal models demonstrated that a 30-min DWIT might be acceptable [9–11], as well as to

allow for a better comparison of our results to previously published articles [19,20]. The characteristics of these potential DCD cardiac donors were compared with the effective 70 DBD cardiac donors procured within the same time period.

In addition, to estimate the rationale of the expansion of the heart donor pool by DCD donation, the number of patients listed for HT, the number of HT candidate deaths while on waiting list or delisting because of clinical deterioration or improvement, the number of HT performed during the same time period, and the number of

patients on the waiting list on December 31st 2011 were retrospectively reviewed. The mean waiting time was also evaluated as the period between listing and transplantation or death.

Statistics

Results are expressed as mean \pm SEM. Significance of differences between groups was measured by unpaired Student's *t*-test or Fisher's exact test, when applicable. All analyses were executed using InStat 3.1 for Mac OS X (GraphPad Software Inc, San Diego, CA, USA). *P*-values <0.05 were considered to be statistically significant.

Table 1. Baseline DCD donors' characteristics.

	Data	Range
Age (years)	54.1	3–83
Female (%)	31.4	
CPR (%)	54	
Causes of death (<i>n</i>)		
Anoxia	35	
Trauma	14	
Cerebrovascular Accident	19	
Other	2	
BMI (kg/m ²)	26.6	17–45
Intensive care stay (days)	6.6	1–23
Urinary output (ml/day)	2,350	900–5,940
Pressors (%)	29.5	
DWIT (min)	20.2	10–35
Withdrawal phase (min)	10.6	0–25
Acirculatory phase (min)	9.4	3–20

DCD, donation after circulatory death; CPR, cardiopulmonary resuscitation; BMI, body mass index; DWIT, donation warm ischemic time.

Table 2. Criteria for DBD and DCD heart donation.

Standard DBD heart donation criteria	
Age between 16 and 65 years	
No diabetes	
No cardiac pathology	
No raised troponins	
Heart rate between 60 and 120 bpm	
Systolic pressure >90 mmHg	
Inotropic support <10 μ g/kg of dobutamine/dopamine	
Inotropic support <1 μ g/kg of norepinephrine	
Cardiac arrest <15 min	
CPR <30 min within the last 24 h	
No episode of severe or prolonged hypotension	
Mechanical ventilation <7 days	
Additional criteria for DCD heart donation	
DWIT < 30 min	
Unperformed test	
Coronary angiography in males >45 years and females >55 years	
Cardiac echography: LVEF >45%	

DBD, donation after brain death; DCD, donation after circulatory death; CPR, cardiopulmonary resuscitation; DWIT, donation warm ischemic time; EFLV, left ventricle ejection fraction.

Results

According to the defined selection criteria for DCD heart donation, eight potential cardiac donors were detected, allowing a potential 11% (8/70) increase in the cardiac graft pool. The general characteristics of the DCD population qualifying for heart donation are summarized in Table 3 and compared with the effective DBD heart donors. With the exception of the use of inotrope treatment, there was no basic significant difference between these two populations. These eight potential DCD heart donors are presented more precisely in the Table 4. They

Table 3. Comparison between effective DBD and potential DCD heart donors in the study period.

	Effective DBD heart donors (<i>n</i> = 70)	Potential DCD heart donors (<i>n</i> = 8)	<i>P</i>
Age (years)	35.6 \pm 1.6	35 \pm 3.4	0.89
Female (%)	31.4	25	0.71
CPR (%)	10	12.5	0.89
Causes of death (%)			
Anoxia	16.5	0	0.2
Trauma	65	50	0.48
CVA	18.5	37.5	0.21
Other (euthanasia)	0	12.5	
BMI (kg/m ²)	23.6 \pm 0.5	22.9 \pm 1.3	0.66
Intensive care stay (days)	3.3 \pm 0.4	4.9 \pm 0.6	0.19
Urinary output (ml/day)	3,817 \pm 207	3,453 \pm 551.6	0.58
Pressors (%)	82.8	25	0.0015
DWIT (min)	NA	15.1 \pm 0.5 (range: 13–17)	
Withdrawal phase (min)	NA	7.0 \pm 0.7 (range: 3–10)	
Acirculatory phase (min)	NA	8.1 \pm 0.6 (range: 5–10)	

DBD, donation after brain death; DCD, donation after circulatory death; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; BMI, body mass index; NA, not available; DWIT, donation warm ischemic time.

Table 4. Characteristics of the eight potential DCD heart donors.

Patient	Year	Gender	Age (years)	COD	Intubation (days)	Norepinephrine	Cardiac arrest	CPR	Hypotension <30 mmHg	DWIT
1	2006	F	43	Euthanasia	0	–	–	–	7 min	17 min
2	2006	M	43	Trauma	4	–	–	–	8 min	17 min
3	2010	M	44	Trauma	3	–	–	–	8 min	15 min
4	2010	F	29	CVA	7	0.7 µg/kg/min	–	–	6 min	16 min
5	2011	M	40	CVA	7	0.1 µg/kg/min	–	–	3 min	13 min
6	2011	M	16	Trauma	6	–	10 min	12 min	7 min	15 min
7	2011	M	28	CVA	4	–	–	–	6 min	13 min
8	2011	M	37	Trauma	3	–	–	–	10 min	15 min

COD, cause of death; DCD, donation after circulatory death; CPR, cardiopulmonary resuscitation; DWIT, donation warm ischemic time; CVA, cerebrovascular accident.

were mostly young males, without inotrope support, and very few cardiac events.

Within the same period of 6 years, 82 patients were listed for HT, among whom 53 were transplanted, 20 died or were delisted (9 died/11 delisted for other reasons), and 9 were still waiting in January 2012. The average time patients remained on the waiting list was 157.1 ± 56.5 days. The effective transplantation of the eight potential DCD heart grafts could have represented a potential maximal 40% reduction in deaths on the waiting list if a suitable recipient was found for all these DCD heart grafts, and a 15% increase in HT activity.

Discussion

In this study, the authors retrospectively analyzed a single-center donor database to identify possible DCD heart donors over a 6-year period. Using the defined inclusion criteria, eight potential heart donors were identified out of 70 DCD donors. This would represent, over the analyzed time span, an increase of 11% (8/70) in heart procurement activity and a potential 40% decrease in waiting list mortality. These figures are situated in between of those published by Singhal *et al.* [19] as well as by Osaki *et al.* [20], which reported an increase of 6% in transplant activity and a 15% increase in the donor pool using DCD for heart donation, respectively.

In the 1960s, the first DD organ procurements were performed after declaration of donor death based on cardiocirculatory arrest criteria, and this was also the case for the Barnard's HT [6]. The concept of brain death was confirmed in 1968 by the Ad Hoc Committee at Harvard Medical School [21]. The wide acceptance of brain death in the Western world, and the better DBD results because of the absence of DWIT, led to the near complete DCD abandonment, but the increasing organ donor shortage has renewed the interest for this particular type of DD. Two different DCD processes may be identified: *uncontrolled DCD* involves organ procurement after unexpected

cardiopulmonary arrest and/or unsuccessful resuscitation [22]. In *controlled DCD*, the cardiocirculatory arrest is the consequence of a planned medical act of withdrawal of ventilatory and organ-perfusion support that can be performed either in the ICU or in the OR. In controlled DCD, procurement WI might be recorded and minimized, as the procurement team is notified of the process and may be ready to start the surgical organ procurement a few minutes after declaration of death. In addition, cold ischemia may also be minimized as the potential organ recipients may be called in hospital before the planned withdrawal of donor's life support. Considering HT, controlled DCD is probably the first, and maybe unique, type of DCD to investigate.

In this study, with the exception of inotrope use, there was no statistical basic difference between the potential DCD heart donors and the DBD donors that actually donated their heart. This finding can mostly be explained by the fact that the used inclusion criteria were identical in both groups, with the sole exception of DWIT. It is also important to note that the sample size is quite small, with eight patients in the potential DCD heart group, rendering statistical analysis difficult. However, the analysis showed a statistical significant difference in the need of inotropic support between potential DCD and effective DBD heart donors. We believe that this observation could be explained by the effects of the catecholamine rush associated with brain death in the DBD group leading to myocardial dysfunction during the time of potential donor assessment and therefore a raised demand of inotropic drugs to maintain correct hemodynamic parameter [23]. However, it remains to be determined if DCD hearts could be of better quality compared with DBD hearts, as they do not have to sustain the massive DBD catecholamine rush that leads to myocardial insult. Because of the critical nature of heart transplantation, it would be preferable to assess the viability and functionality of such grafts in an *ex-vivo* setting before proceeding to implantation, as it is already

done to some extent in kidney [24] and lung transplantation [25]. Studies determining suitable prediction factors for the recovery of DCD hearts in an *ex-vivo* setting have been presented and published [26]. Such protocols will constitute a cornerstone for organ transplantation in the future, especially concerning marginal and/or DCD grafts.

Since the first HT performed by Bernard in 1967, the criteria for heart donation have constantly evolved and been refined becoming more and more rigorous. Combined to an aging population frequently suffering from cardiovascular diseases, this fact leads to a persistent and continuously evolving organ shortage, combined to an increasing demand. As shown in this article, the use of hearts procured from DCD donors could contribute to a real extent to address the growing demand in HT, within a very short time span of investigation.

Beside the small numbers of potential DCD heart donors, one of the limitations of this study is its retrospective nature inducing the lack of certain data points and, as a consequence, the exclusion of some DCD donors from this series, because the authors could not potentially complete all inclusion criteria. In addition, cardiac echography was not performed in this DCD donor series, as they were not considered for potential heart donation. In the setting of DCD HT, it is possible that some of these donors could have been excluded for heart donation because of an abnormal cardiac echography or other cardiac abnormalities that the authors could not retrospectively detect from the medical files. On the other hand, if a clinical DCD HT program would begin, it could be possible to somehow select potential donors with less selective criteria, as longer intubation period or diabetic and older patients. However, performing coronary angiography in potential marginal DCD heart donors could be a matter of ethical debate, but in our view, this could be an acceptable decision as most patients who may eventually become DCD donors are already equipped with a variety of ICU vascular accesses, and the additional access needed for evaluation can easily be implemented in a pain-free and low-risk way in such patients.

Our study showed that roughly 10% of DCD donors might be potential candidates for heart donation. Even though this number may represent a 40% reduction in deaths on our waiting list, this is still insufficient. One could also wonder if the use of DCD donors with extended or enlarged criteria for heart donation can be foreseen. However, DCD HT will require being extremely selective in the early experience. The number of potential DCD heart donors could potentially be higher in an active program, identifying potential donors at an early stage and therefore applying adapted donor man-

agement when withdrawal of care and organ donation is decided.

Authorship

TN: wrote paper, collected data, analyzed data. OD: analyzed data, provided insides into the subject, supervised manuscript. MFH: collected data, analyzed data. DL, JJ, MM: provided insides into the subject. JOD: Supervising professor, provided insides into the subject, supervised manuscript.

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