Donation After Cardiac Death: A Necessary Expansion for Heart Transplantation

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The gold standard and sole curative therapy for advanced stage heart failure is cardiac transplantation. As the population ages, the number of patients diagnosed with advanced heart failure and listed for transplant steadily increases annually. However, there remains a paucity of eligible donation after brain death (DBD) donor hearts which severely limits access to cardiac transplantation and leads to increasing wait-list times and avoidable patient mortalities. Though the first human heart transplant in 1967 was performed using a deceased donor heart, the advent of brain death criteria and the ability to avoid long warm ischemic times led donation after cardiac death (DCD) transplantation to fall out of favor. Due the current state of cardiac transplantation, there has been a resurgence in interest in DCD heart transplantation leading to the development of DCD heart transplantation programs in the UK and Australia after positive reports of successful DCD cardiac transplantation in the pediatric literature. These programs have demonstrated favorable post-transplantation outcomes equivalent to matched traditional DBD transplants with current techniques and strict donor criteria. This technique has been proven safe with favorable outcomes and has been demonstrated to significantly increase transplant volumes and decrease patient mortality. Given these outcomes and the high patient benefit to risk ratio, DCD donor heart transplantation is necessary to expand the donor pool and decrease patient mortality and should be developed in high volume experienced cardiac transplant centers.

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Central Message

The paucity of eligible DBD donor hearts limits access to cardiac transplantation. DCD donor heart transplantation is safe and feasible with favorable outcomes and is necessary to expand the donor pool and decrease patient mortality.

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INTRODUCTION

In the treatment of advanced end-stage heart failure, organ transplantation remains the gold standard and sole curative therapy. The number of patients with advanced heart failure who are transplant eligible continues to rise yearly. Despite increases in number of heart transplants, the limited supply of organs severely hampers access to this life-altering treatment, leaving greater numbers of patients enrolled on transplant wait-lists with ever increasing wait-list times and unacceptable wait-list mortalities.

Though the first human heart transplant in 1967 was performed using a deceased donor heart procured after circulatory arrest, the advent of brain death criteria and the ability to avoid long warm ischemic times led donation after cardiac death (DCD) transplantation to fall out of favor. The first resurgence of reports of clinical human DCD heart transplantations appeared in the pediatric literature in 2008. This was later followed by the development of adult DCD heart transplant programs with initial outcome reports in 2015. Data from these programs have demonstrated equivalent outcomes to matched donation after brain death (DBD) transplants in appropriately selected donor hearts in spite of the effects of functional warm ischemic insult, the negative impact of which is absent from DBD transplantation.

Given the ongoing positive DCD outcomes, the paucity of available organs, and high transplant wait-list mortality, DCD heart transplant programs should be developed in current high-volume transplant centers and offered to current transplant-eligible patients.

CURRENT STATE OF OHT

The gold standard definitive treatment for end-stage heart failure is and still remains to be heart transplantation. In the United

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States, there were 3408 heart transplants and 32 heart-lung transplants performed in 2018, yet there were more than 10,700 total deceased donors, when including both DBD and DCD.[1] In the UK, only 27% of DBD hearts are accepted for transplant with approximately 43% of patients on the transplant wait-list experiencing mortality or progression of disease or medical complications making them ineligible for transplant.[2] Approximately 28% of transplant eligible DBD hearts are turned down due to concerns for organ function, 74% of which exhibit a normal EF but had another nonspecified functional concern.[3] As the need for organs increases, the low number of suitable or transplanted hearts from DBD donors further exacerbates the organ shortage.

EXPANSION OF THE DONOR POOL

Expansion of the donor pool to include DCD donors has already occurred in the case of kidney, liver, pancreas, and lung transplantation. Data have shown that expanding the donor pool to include DCD organs for noncardiac transplants has served to increase the number of successful transplants while DBD organ transplants continue to increase in number rather than being supplanted.[4] In an analysis of the New England Organ Bank over a 5-year review, 67% of potential DCDs progressed to become actual DCDs while 16% of those under review transitioned to become DBDs; this led to an additional 276 DBD organ transplants including 24 heart transplants.[5] Thus, consideration of potential DCDs can also lead to an increase in DBD transplants.

DCD lung transplantation in a multicenter analysis was shown to account for 10% of transplantations; furthermore, DCD survival outcomes were shown to be equivalent to DBD results.[6,7] Expansion of kidney transplant programs to include DCD donors has increased the number of transplants performed and improved wait-list outcomes while producing equivalent results compared to DBD donors.[8,9] The same has been demonstrated in DCD pancreas transplants.[10]

In the pediatric literature, expansion to DCD donors is predicted to have an even larger impact in improving wait-list times and decreasing wait-list mortality with projections of reported potential to increase specific institution transplants by 70%.[11] Clinically performed pediatric DCD transplants increased a single institution's yearly transplantation rate by 300% within a single reported study period.[12] This is crucial as pediatric DBD hearts are even more scarce than their adult counterparts and wait-list mortalities in this population are approximately twice as high.

Work by Noterdaeme et al demonstrated a potential for an 11% increase in heart transplants should the DCD hearts that met criteria (DBD criteria + donation withdrawal ischemia time <30 minutes) be transplanted; use of these donor hearts could have reduced this single institution's waiting list death rate by 40%.[13] Performing retrospective chart review of the over 3000 potential DCD donors over a 3-year period using very strict inclusion criteria revealed an estimated potential increase in heart transplantation activity by 30% could be achieved in the UK.[14] When transplantation of DCD hearts was clinically implemented in the UK, the result was a 45% increase in transplant activity.[15] Likewise, in the United States, DCD donor hearts evaluated in retrospective review for suitability of transplant in the University of Wisconsin Database revealed that use of DCD donors could increase regional transplant volume by 17% when implementing DBD criteria alongside limiting the donor age to less than 50 years old and limiting FWIT to less than 30 minutes.[16]

It is likely that in an active DCD program with established guidelines operating inside a successful high-volume heart transplant program, there would be potential for an even greater increase in DCD donor heart utilization.

METHODS OF DCD HEART PROCUREMENT

Procurement of DCD organs may only begin after the withdrawal of life support and subsequent onset of mechanical asystole which serves as the determination of death. After the patient is declared deceased, there are mandatory waiting periods of asystole that must be observed before organ procurement may commence. This period can range from 75 seconds, as in the case of reported pediatric transplants, to 5 minutes, all subject to the national/regional laws and institutional regulations in the location of transplant occurrence. During the mandated wait period, the heart is subject to what is referred to as Warm Ischemic Time (WIT). However, cellular damage does not just occur after the advent of asystole, but rather begins and increases in intensity as diminished whole-body perfusion leads to organ deterioration with the withdrawal of life support. The effects of warm ischemic time inherent to DCD resuscitation and how to limit its impact on cardiac function remain an area of intense study.

DIRECT PROCUREMENT AND PERFUSION

After withdrawal of life support, the onset of subsequent mechanical asystole, and completion of mandated wait time, direct procurement and perfusion (DPP) is performed by cannulation and delivery of cold cardioplegia to induce arrest. Cold ischemic time begins at the time of cross clamp. Prior to delivery of cardioplegia, autologous blood is removed from the donor if ex vivo organ perfusion is to be undertaken.

Unlike in the DBD patient or DCD hearts procured with a normothermic regional perfusion (NRP) technique, this method does not allow for preoperative evaluation of cardiac function. Cardiac function assessment must occur through analysis of the secondary marker, lactate.

NORMOTHERMIC REGIONAL PERFUSION

The NRP method utilized today is reminiscent of the procurement strategy employed in the world's first cardiac transplant performed by Christiaan Barnard in 1967.[17] In order to minimize cold ischemic time, both the donor and recipient were located in neighboring operating suites.

After the mandated postarrest wait period, NRP is performed by placing the donor on ECMO support, with perfusion beginning after the exclusion of circulation to the brain by clamping of aortic arch vessels. Reperfusion using autologous donor blood is speculated to have the potential to minimize reperfusion injury that could be mediated by a fully oxygenated

exogenous blood source. Placing the donor on ECMO allows for intraoperative assessment of cardiac function which can be assessed not only via direct visual assessment but by full TEE analysis.

DONOR ORGAN STORAGE AND TRANSPORT

After procurement with either the DPP or NRP strategy, transportation with either cold storage or ex vivo perfusion has been performed. Ex vivo perfusion with the Transmedics Organ Care System (OCS), the only currently available ex vivo system, is utilized clinically in the current DCD heart transplant programs, when cold storage is not employed.

Prior to its application in DCD donor transplantations, the OCS had been demonstrated to be noninferior with equivalent outcomes in DBD transplants when compared to cold storage in the PROCEED II trial.[18] For hearts procured with the DPP technique, perfusion on OCS represents the only juncture at which analysis of donor heart function can be performed. However, given the heart is perfused ex vivo in an unloaded state, function can only be assessed by following surrogate markers of resuscitation, arterial and venous lactate levels, perfusing pressures, and visual examination; therefore, analysis is limited to metabolic and gross visual surrogates of myocardial function as true structural assessment cannot be performed during ex vivo perfusion with the OCS.

DPP VS NRP

Both methods of donor heart resuscitation described above, DDP and NRP, have been implemented with successful results.[15,19] One study by Messer et al[20] details the outcomes between DCD operations performed with DPP and NRP resuscitation. This data showed comparable survival outcomes with nonsignificant differences between transplants performed with either DCD procurement technique.[21] However, this arm of the study is crippled by its lack of power, owing to low patient numbers.

In the current early dawn of DCD transplants, it is likely that given donor selection criteria is so stringent and that cold ischemic times for DPP perfusion have been very short due to donor colocalization that true differences between the 2 methods may not be observed with such small numbers of patients analyzed. The inability to evaluate donor cardiac function prior to procurement represents an unnecessary risk to the patient. Furthermore, should procurement and resuscitation be begun with ex vivo perfusion and the organ then be deemed functionally ineligible for transplant represents a large preventable financial loss.

This has been confirmed in the literature.[20–22] The assessment of cardiac function during procurement with NRP strategy allows for extended age range of donors (less than 50 years vs less than 40 years) and has had a great conversion to actual transplantation than hearts procured with alternative methods.

CRITERIA FOR DCD HEART TRANSPLANTS

Potential DCD donors can be broken down into 4 categories as part of the Maastricht classification. DCD donors whose organs are used for transplantation fall into Category III; this categorization represents a "controlled" circulatory death in which intentional withdrawal of life support leads to an expected circulatory arrest.[23] A controlled arrest is crucial as it allows for the anticipation and implementation of measures and strategies to decrease functional warm ischemic time.

DCD donor hearts that have been used in transplantation have also been subject to stringent criteria consisting of age limitations (less than 40 or 50 years of age depending on the institution) and strict criteria regarding the allowable functional warm ischemic time or cold ischemic storage time.

CURRENT PROGRAMS AND OUTCOMES OF THE DCD DONOR HEART TRANSPLANTATION

Current data suggest that DCD donor hearts that meet selection criteria and are successfully transplanted lead to outcomes equal to those performed with traditional DBD organs. DCD heart transplantation is being performed only in few established centers worldwide.

Local institution coordinated donor-recipient DCD heart transplant has been performed in children with 100% survival to 6 months compared to 84% for traditional donors and no significant difference in rejection episodes compared to DBD transplants; warm ischemic time (mean of 18 minutes) was very short in these transplants.[12] In an analysis of pediatric DCD transplants in the UNOS database, 40% of patients transplanted were alive with no incidence of rejection at 8 years; 67% of patients who died were on ECMO in the pretransplant period.[24] An ISHLT database study comparing DCD to DBD heart transplants in children demonstrated that children receiving DCD hearts were significantly sicker, with a much higher proportion on preoperative ECMO support (24% vs 6%) and/or inhaled nitric oxide therapy (10% vs 0.6%) in addition to higher incidence of other high-risk recipient factors.[25] As expected in much more ill cohort, mortality was higher in the DCD group for early deaths as compared to traditional DCD recipients; however, mortality differences at 5 years had reached nonsignificance.

In the world of adult heart transplantation, successful clinic DCD transplantation with the DPP procurement and ex vivo perfusion technique in 3 patients was first reported in 2015 from Sydney, Australia.[19] Early concerns were raised regarding the requirement for postoperative ECMO support in 2 of these 3 patients. However, all 3 patients had normal cardiac function within 7 days of transplantation. Donor criteria in this study were strict with donor age limited to up to 40 years of age and cold ischemic time of less than 30 minutes. Since publishing, there have been a total of 12 DCD transplants performed at this center with favorable outcomes of 0% mortality as of April 2017.[26] Since that time postoperative ECMO rates have decreased to 30%. Utilizing appropriately vetted DCD donor hearts, transplant rates were increased by 45%.[15]

Both 90 day and 1-year survival in 28 DCD transplants were found to be equivalent with no significant differences in rejection, graft function, or hospital stay when compared to

matched DBD donor transplants—this included both DPP and NRP DCD donor hearts.[20] This program at Papworth has now performed 39 DCD heart transplants with 91% survival to discharge with only 13% of patients requiring postoperative ECMO.[26] This decrease in postoperative ECMO usage likely represents advancements made in the procurement and resuscitation techniques.

Successful DCD donor transplantation has even been reported in 2 cases of LVAD BTT patients; both patients were reported as alive and well without complications at 290 days.

CONCLUSIONS

Evidence has shown that heart transplantation with DCD donor hearts has been both clinically safe and successful in current DCD transplant programs. The implementation of DCD programs in on wider scale at select high volume heart transplantation centers is essential to expand the heart donor pool and should be presented as an option to transplant eligible patients. As DCD donor experience continues to increase, current methods of procurement and donor organ preservation to transplant will be further refined leading to new innovations that will improve donor heart function. In turn, this will lead to increased organ viability and the ability to even further expand the DCD donor pool, following in the trajectory of DBD transplantations. Just as patients have highly benefited from DCD expansion in other vital organ transplantation programs, the expansion of heart donor criteria will improve patient lives. The primary goal and most vital outcome to be achieved in expanding heart transplantation by including DCD donor hearts will be the increase in number of patients' lives that are saved by reduction of the unacceptable long wait-list times and decrease in the percentage of transplant-eligible patients that experience high and preventable mortality due to limited organ access.

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