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EDITORIAL COMMENT

Use of Heart Donors Following Circulatory Death

A Viable Addition to the Heart Donor Pool*

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Despite significant advances in medical management and availability of durable mechanical circulatory support (MCS) devices to treat end-stage heart disease, no therapy to date has provided the survival benefit afforded by heart transplantation (1). For an adult patient who received a heart transplant worldwide between 2002 to 2008, median survival following heart transplantation now extends to 12.2 years (2). Heart transplantation has been chronically plagued by donor shortages that have limited the overall epidemiological benefit of this therapy. Even with the significant increase in the number of heart transplant procedures performed in the United States (3,244 heart transplants performed in 2017 in the United States) (3) as a result of the expansion of acceptable donor criteria (e.g., use of donors with Hepatitis C in uninfected recipients) (4) and the opioid epidemic (5), substantially more patients could benefit from heart transplantation each year.

Recently, there has been a growing interest in utilizing heart organs obtained from donors following circulatory death (i.e., donation after circulatory death [DCD]) to expand the heart donor pool (6). The DCD heart donor paradigm has the potential to increase heart transplantation volume by an estimated 20% (7,8). Current established practices in heart transplantation utilize hearts from donors meeting brain death criteria (i.e., donation after brain death [DBD]) that were established by an ad hoc committee at the Harvard Medical School in 1968 and subsequently enacted by the Uniform Determination of Death Act in 1981 (9,10). In contrast to DBD donation, DCD donors are declared dead on the basis of irreversible cardiac arrest rather than irreversible loss of all brain function (11). Due to unique ethical and legal concerns that arise from the surgical techniques for DCD heart procurement and clinical concerns for the potential of ischemic injury, clinical adoption of DCD heart transplantation in the United States has not occurred with any significance. However, utilization of DCD organ donors for tissue and organs other than the heart has been readily adopted in the United States, reflected by the mandate by the Joint Commission to require all accredited hospitals to have a DCD policy (12).

There are essentially 3 techniques for procurement of DCD heart organs: normothermic regional perfusion, direct procurement and perfusion, and direct procurement from a colocated donor (6). A common requirement for all techniques is that cardiac death must be declared within minutes of withdrawal of life support to minimize warm ischemic time and prevent significant ischemic injury to the donor heart organ. The technique of normothermic regional perfusion utilizes cardiopulmonary bypass to reanimate the heart in vivo following circulatory death. To ensure absence of brain activity during the donation process, the technique of normothermic regional perfusion requires interruption of the cerebral circulation by clamping the head vessels arising from the aortic arch (i.e., the innominate, carotid, and subclavian arteries) prior to institution of regional perfusion. An advantage of normothermic reperfusion is that after return of a cardiac rhythm, ventilator support can be reestablished and cardiopulmonary bypass support can be weaned, thus permitting heart evaluation for

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transplantation and retrieval in a fashion similar to DBD organ donation. With direct procurement and perfusion, the heart is retrieved from the donor and connected to an ex vivo perfusion system for reanimation (6,8,13). After return of a cardiac rhythm, the heart is evaluated for transplantation using biochemical assessments of lactate metabolism. The technique of colocation using direct organ procurement utilizes direct procurement with cold preservation and immediate transplantation into the recipient in an adjacent operating room with subsequent reperfusion and reanimation in vivo in the recipient using cardiopulmonary bypass (6).

Over 50 years ago, the world's first adult heart transplant, performed in 1967 by Dr. Christian Barnard at the Groote Schuur Hospital, Cape Town, South Africa, was obtained from a DCD donor as brain death was not legally recognized at the time. DCD heart donation was performed using a colocation technique as the only available option (14). More modern-day feasibility of DCD heart transplantation was demonstrated over a decade ago in the United States, with the successful transplantation of DCD hearts in 3 infants at Children's Hospital Colorado (15,16). Recent successful adult non-U.S. experiences, first performed in Australia in 2014 and subsequently in the United Kingdom in 2015, have revived the debate of use of DCD heart donors in the United States (8,17).

SEE PAGE 1447

In this issue of the *Journal*, Chew et al. (18) report on the Australian experience of DCD heart transplantation utilizing the technique of direct procurement and reanimation of the heart using ex-vivo machine perfusion. Of 45 eligible DCD donors, 12 donors did not progress to circulatory arrest within the pre-specified time frame (i.e., limitation of the warm ischemic time to 30 min) and were not utilized for donation (12 of 45; 26.7%). Of the remaining 33 hearts procured, 8 (8 of 33; 24.2%) hearts failed to meet viability criteria during normothermic machine perfusion and 2 (2 of 33; 6.1%) hearts were declined due to machine malfunction resulting in transplantation of 23 hearts (23 of 33; 69.9% of heart procured and 23 of 45; 51.1% of acceptable DCD heart donors). All recipients had successful implantation, with post-transplant MCS utilized in 9 cases for primary graft dysfunction (PGD) (8 cases of extracorporeal membrane oxygenation (ECMO) and 1 case of intra-aortic balloon counterpulsation. One case requiring ECMO subsequently died on the sixth postoperative day, representing a mortality of 4.4% over 4 years with a total follow-up period of 15,500 days for the entire cohort. All surviving recipients had normal cardiac function on echocardiogram and no evidence of acute rejection on discharge. All surviving patients remain in NYHA functional class I with normal biventricular function.

The report by Chew et al. (18) represents a significant advancement in the use of DCD heart organs to expand the heart donor pool. The experience of Chew et al. (18) demonstrates feasibility of the DCD donor process and provides data that DCD heart donors can achieve excellent post-transplant survival despite a high incidence of PGD. These data add to the growing experience of DCD heart donation that should provide a stimulus for such efforts in the United States.

While the use of DCD donors has the potential for significantly increasing the donor heart pool in the United States, significant efforts should be directed to resolve important issues to foster greater clinical adoption. First, the use of DCD donors currently requires a significant increase in resources that will appreciably increase the cost and resource utilization associated with heart transplantation. In the Australian experience, 2 surgeons, a perfusionist, an anesthesiologist, and a transplant coordinator traveled to the donor hospital, and the current protocol of direct procurement and perfusion utilized by Chew et al. (18) uses the OCS Heart System (TransMedics, Andover, Massachusetts) for donor organ resuscitation and evaluation. This protocol adds significant cost and resource utilization to the current donation process. In the United States, such costs and utilization of resources will likely initially limit DCD heart donation to larger medical centers capable of absorbing such costs that may inadvertently lead to greater regional disparities in access to heart transplantation in the United States. Second, the optimal DCD donor and recipient characteristics to minimize resource utilization and maximize transplant survival are currently unknown but will likely evolve with greater experience. In the report by Chew et al. (18), there was a significantly higher rate of PGD requiring post-transplant ECMO use in recipients on MCS at the time of heart transplantation (5 of 8; 62.5%). Whether pre-existing MCS represents a relative contraindication during the initial stages of clinical development of DCD heart donation remains an important question. Third, the time interval from asystole to cardioplegia time was significantly longer in the recipients requiring ECMO, suggesting that processes during the DCD donation process could be further optimized or acceptance criteria modified. The technique of DCD heart donor procurement using a direct procurement and perfusion strategy limits functional assessment of the donor following cardiac arrest. Current methodology of the OCS Heart System

utilizes biochemical assessment of lactate metabolism (19). This suggests a need for further development of perfusion systems permitting mechanical evaluation of heart function and the need to continue to evaluate multiple techniques for DCD procurement, such as normothermic regional perfusion, to identify optimal ways to assess DCD donor function.

Despite a robust experience with DCD transplantation of lungs, livers, and kidneys in the United States, DCD heart transplantation carries inherent clinical challenges. A significant ethical and clinical framework for DCD heart donation in the United States has been made by groundbreaking efforts in Australia and the United Kingdom. Because of the dire need for donor hearts, it is clinically necessary to resolve these controversies and challenges to expand the current heart donor pool in the United States.

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