Heart transplantation following donation after cardiac death: History, current techniques, and future

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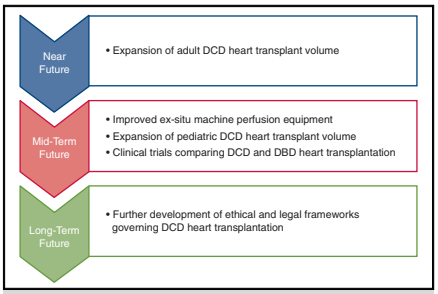
Heart transplantation remains the criterion standard treatment for eligible patients with end-stage heart failure.[1] After heart transplantation, more than 90% of patients are in New York Heart Association functional class I or II at 1 to 3 years. Moreover, the median survival and conditional survival after heart transplantation are 11 and 15 years, respectively.[2] Unfortunately, there are far fewer donor hearts available for transplantation than there are patients who would potentially benefit. Although there are approximately 3500 heart transplants performed in the United States annually, approximately 4500 patients are newly listed for heart transplantation during the same time period.[3] For this reason, extended criteria donor hearts are now routinely considered for transplantation.[2,4] Extended criteria donors are those who would normally be rejected on the basis of such factors as their age, ischemic time, comorbidities, hemodynamic support, or substance abuse. This practice has contributed to an increase in heart transplant volume over the last few years. In spite of this increase, however, there is an ongoing donor organ shortage. A small number of transplant centers have therefore pushed the envelope by pioneering heart transplantation following donation after cardiac death (DCD).[5] DCD involves donors with devastating brain injury who depend on life support but do not meet the legal criteria for brain death.[6] After the withdrawal of life support, death is declared on the basis of cardiac arrest. This practice differs from donation after brain death (DBD), which involves donation of a beating heart.[7] Here, we will consider the history of DCD heart transplantation and the surrounding ethical controversies, outline the different surgical techniques that have been developed, and conclude with a look into the future.



Future directions for donation after cardiac death heart transplantation.

CENTRAL MESSAGE

We consider the history of DCD heart transplantation with the surrounding ethical controversies, outline the surgical techniques that have been developed, and conclude with a look into the future.

PERSPECTIVE

An increasing number of transplant programs use hearts donated after cardiac death. Here we consider the history of donation after cardiac death heart transplantation with the surrounding ethical controversies, outline the different surgical techniques that were developed and conclude with a look into the future.

See Commentaries on pages 1341, 1342, and 1344.

HISTORY OF DCD HEART TRANSPLANTATION

Clinical heart transplantation has its origin in the 1950s and 1960s, when a team led by Norman Shumway developed the theoretic framework and surgical principles underlying orthotopic heart transplantation.[8-11] On the basis of Shumway's team's work, Christiaan Barnard performed the first human heart transplant in 1967.[12] In this first heart transplant, the donor, who had sustained irreversible brain injury in a road traffic accident, was declared dead on the basis of cardiac arrest after the withdrawal of life support in the operating room. After the declaration of death, Christiaan Barnard's team expediently initiated circulatory

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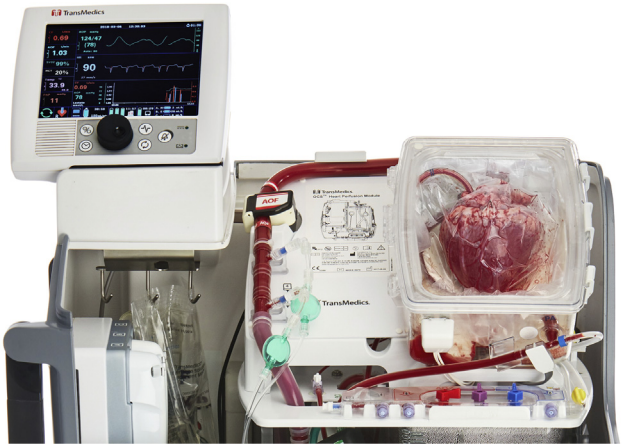

FIGURE 1. The TransMedics OCS Heart device (TransMedics, Inc, Andover, Mass) is a portable extracorporeal perfusion system that was designed to transport donor hearts in a beating and normothermically perfused state.

support to reperfuse and cool the donor heart before recovering it for transplantation. The recipient had been prepared in an adjacent operating room, where Christiaan Barnard proceeded with the operation that would make medical history.[13]

Despite this early experience, DCD heart transplantation was subsequently abandoned in favor of DBD heart transplantation because of concerns regarding warm ischemic injury to the donor heart. Moreover, early efforts at heart transplantation had been marred with ethical and legal controversy surrounding the declaration of death, which resulted in high-profile murder trials of transplant surgeons.[14] Some of the legal issues were resolved with the establishment of the Harvard criteria for brain death in 1968[15] and the Pittsburgh Protocol for Non Heart Beating Donors in 1993.[16] Moreover, large animal experiments also indicated that the risks from ischemic injury to the donor heart are controllable. For example, porcine hearts that had been subjected to hypoxic arrest for 15 minutes followed by reanimation with extracorporeal circulatory support in the donor animal were successfully transplanted into recipient animals and subsequently displayed cardiac function that was not significantly different from that of hearts recovered from donor animals after brain death.[17] Together with the ongoing donor organ shortage, these findings paved the way for a renewed interest in DCD heart transplantation.

Among the earliest human evidence supporting DCD heart transplantation was a retrospective analysis of 25 infant recipients at Loma Linda University, which had excellent outcomes even though 72% of the donors had a history of cardiac arrest requiring cardiopulmonary resuscitation.[18] The relationship between donor cardiac arrest requiring cardiopulmonary resuscitation and recipient outcomes was more formally investigated in a retrospective cohort study that analyzed the outcomes of adult recipients who underwent transplant with hearts that had suffered an episode of cardiac arrest in the donor. Between January 1991 and November 2004 at Royal Papworth Hospital in the United Kingdom, 38 heart donors had been resuscitated for a cardiac arrest lasting a mean 15 $\pm$ 8 minutes before heart transplantation into a recipient a mean 69 $\pm$ 5 hours after the arrest. This study showed that there was no statistically significant difference in 30-day mortality between these recipients and 566 recipients who had received hearts not subjected to an arrest during the same time period.[19]

On the basis of the theoretic framework described here, the first modern DCD heart transplants were carried out by our group at the University of Colorado in 2008. Three infants with mean age of 2.2 months underwent transplant with hearts from donors who were declared dead on the basis of circulatory arrest in an operating room adjacent to that of the prepared recipient. Echocardiographic functional assessment of the hearts and clinical outcomes were not different from those of a cohort of DBD heart transplant controls.[20] This report, however, was marred with ethical controversy. A strong argument was made that DCD heart transplantation violates US criminal homicide rules.[14,21] It was argued that reanimation of the donor heart invalidates the donor declaration of cardiac death, because cardiac death in the United States is defined by irreversible cardiac arrest. The resulting legal ambiguity stifled further pediatric DCD heart transplantation activity in America, and only a modest number of further pediatric DCD heart transplants were performed.[22] By 2017, the total number of pediatric DCD heart transplants reported to the International Society for Heart Lung Transplantation Registry was 21.[23]

A technical innovation available to adult donors only, namely commercialization of the TransMedics OCS Heart device (TransMedics, Inc, Andover, Mass), subsequently paved the way for the first modern adult DCD heart transplantations in Australia. The TransMedics OCS Heart device is a portable extracorporeal perfusion system that was designed to transport donor hearts in a nearly physiologic state—that is, beating and normothermically perfused with blood (Figure 1). Kumud Dhital from St Vincent's Hospital in Sydney used this device to reanimate hearts donated after cardiac death and to evaluate their function before transplantation into recipient patients. All 3 patients in his landmark study had normal cardiac function within a week of transplantation.[24] These breakthroughs catalyzed the establishment of several clinical programs in DCD heart transplantation in America, Europe, and Australia.[5,23,25] By 2019, more than 100 adult DCD heart transplants had been performed globally.[26]

TECHNIQUES FOR HEART TRANSPLANTATION AFTER DCD

The technique for DCD heart procurement varies on the basis of patient size, surgeon preference, and local legal

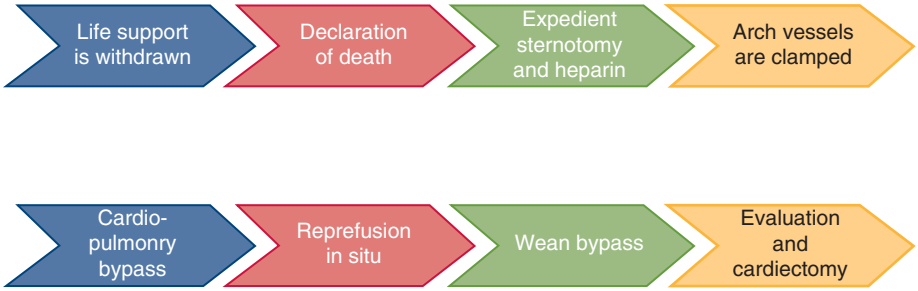

FIGURE 2. Normothermic regional perfusion. This technique is currently used by the Royal Papworth program.[28]

frameworks. Adult DCD heart transplantation is able to use techniques that involve machine perfusion of the DCD hearts either in situ in the donor body with extracorporeal membrane oxygenation or ex vivo with the TransMedics OCS Heart device.[5,27] In contrast, pediatric DCD heart transplantations are carried out with a technique that involves donors and recipients who are colocated in adjacent operating rooms.[20] These techniques for procuring DCD donor hearts are described in more detail here.

Normothermic Regional Perfusion

For DCD heart transplantation with normothermic regional perfusion, life-supporting ventilation is withdrawn from the prepared and draped donor in the operating room, and death is declared on the basis of circulatory arrest. A sternotomy is expediently performed, and the pericardium is opened. Next, heparin is injected into the right atrium and the pulmonary trunk. The donor cerebral circulation is excluded by clamping the arch vessels, eliminating the theoretic recovery of brain activity. This maneuver is facilitated by traction on the ascending aorta. Subsequently, the donor is centrally cannulated for cardiopulmonary bypass. An aortic cannula is inserted into the ascending aorta, a 2-stage venous cannula is inserted in the right atrium, and cardiopulmonary bypass is instituted. Exclusion of the cerebral circulation is confirmed by absent carotid blood flow according to carotid Doppler ultrasonography. Adequate anticoagulation for bypass is confirmed by measuring the activated clotting time. Once the donor heart has been reanimated on cardiopulmonary bypass, the heart rhythm is analyzed and cardioverted if necessary. The donor is also reintubated and ventilated. After a sufficient reperfusion period, the donor is weaned from cardiopulmonary bypass. This effectively converts a heart donated after cardiac death into a beating donor heart. Once the donor has been weaned from cardiopulmonary bypass, the heart is evaluated and retrieved in the familiar fashion (Figure 2).[28]

Ex Situ Reperfusion

For DCD heart transplantation with ex situ reperfusion, life-supporting ventilation is withdrawn in the operating room from the prepared and draped donor, and death is declared on the basis of circulatory arrest. A sternotomy is expediently performed, and the pericardium is opened. Heparin is injected into the right atrium, and a 2-stage venous cannula is inserted into the right atrium to collect donor blood to prime the TransMedics OCS Heart device (Figure 1). A cardioplegia cannula is inserted into the ascending aorta to deliver antegrade cardioplegia to the arrested heart within the donor, which is recovered in the familiar fashion.[28] The explanted heart is attached to the TransMedics OCS Heart device, where it is reanimated by ex vivo perfusion. After return of a cardiac rhythm, the donor heart is evaluated by means of visual inspection, limited hemodynamic assessments, and arterial and biochemical parameters to determine suitability for transplantation (Figure 3).

Modified Conventional Procurement

DCD heart transplantation with modified conventional procurement is ideally suitable for donors and recipients who are located in close proximity, because the ischemic injuries during warm ischemia time and cold ischemia time are additive.[20] Life-supporting ventilation is withdrawn in the operating room from the prepared and draped donor. Heparin is injected and death is declared on the basis of circulatory arrest. While the sternotomy is expediently carried out, cold arterial preservation solution is infused to minimize warm ischemia, and venous blood is withdrawn to avoid distention of the heart.[20] Topical cooling is also provided. The heart is vented and swiftly recovered for transplantation (Figure 4).

FUTURE DIRECTIONS

DCD heart transplantation will continue to evolve in the future (Figure 5). In the near future, we anticipate that the clinical need for donor hearts will result in a continuous expansion of adult DCD heart transplant programs. This would follow a trend that was observed after the introduction of DCD lung transplantation.[29] If widely adopted, heart transplantation after DCD has the potential to increase overall heart transplant volume by more than 20% in the near

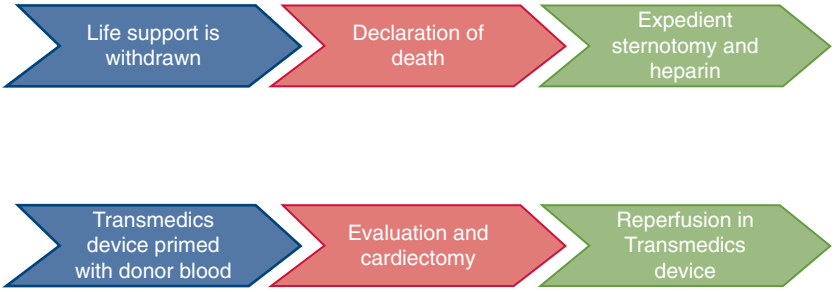

FIGURE 3. Ex situ reperfusion. This technique is currently used by the Sydney, Harefield, and Royal Papworth programs.[24,28,37]

future.[30-32] These forecasts are modeled on donors aged less than 50 years who are not receiving inotropic support and on times from withdrawal of life support to cardiac reperfusion of less than 30 minutes. In contrast, pediatric DCD heart transplant volume will remain modest until appropriate devices for ex situ machine perfusion of pediatric hearts become available.

In the medium-term future, we anticipate that many limitations of the current ex situ perfusion systems will be overcome by industry's development of dedicated equipment tailor-made for DCD heart transplantation. This will include ex situ machine perfusion systems suitable for pediatric hearts, systems for topically cooling the donor heart in vivo, and improved perfusates. Moreover, we expect that improved methods for assessing allograft function on ex situ perfusion systems will become clinically available. For example, ex situ angiography could be used to evaluate older donor hearts for coronary artery disease. In addition, the technical difficulties associated with establishing truly reliable ex situ measures of cardiac hemodynamic function will be overcome. This should allow the application of extended criteria strategies to DCD hearts. Another major limitation of the current ex situ perfusion systems is cost. We anticipate that competition among different suppliers and economies of scale will serve to decrease these costs. This should make DCD heart transplantation available to patients in emerging economies. The increased number of hearts transplanted after cardiac death will also allow the rigorous scientific analysis of the clinical outcomes. This will include trials comparing DCD hearts transplants to DBD heart transplants and trials comparing the different DCD heart procurement strategies with one another. For example, an industry-sponsored randomized and concurrent controlled trial comparing subjects who receive a DCD donor heart transplant with subjects who receive a standard criteria donor heart transplant is currently enrolling patients at several US transplant centers (ClinicalTrials.gov identifier NCT03831048). The resulting insights should result in standardization of DCD heart selection criteria and procurement techniques. It has been suggested that such unified DCD protocols and an algorithm involving national standards for organ assessment would significantly improve transplant numbers and outcomes.[33-35]

For the longer-term future, we anticipate that progressive development of the medical ethics surrounding heart transplantation will lead to changes in the definitions of death and the legal frameworks that govern DCD heart transplantation.[22] The current definition of death, as enshrined in the Uniform Determination of Death Act, relies on either irreversible cessation of circulatory and respiratory function (cardiac death) or irreversible cessation of all functions of the entire brain (brain death). This creates a paradox with regard to DCD heart transplantation, because cardiac function is restored after cardiac death has been declared,

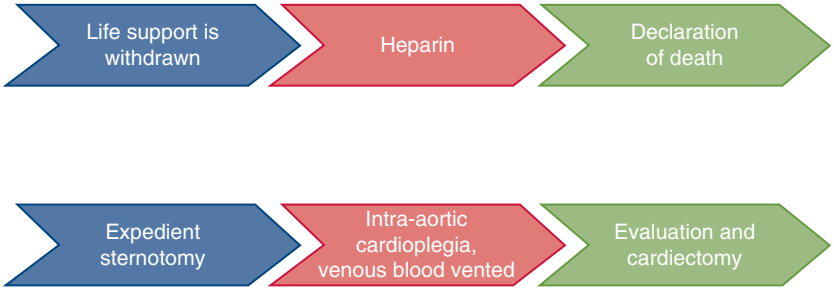

FIGURE 4. Modified conventional procurement. This technique is currently used by the University of Colorado program.[20]

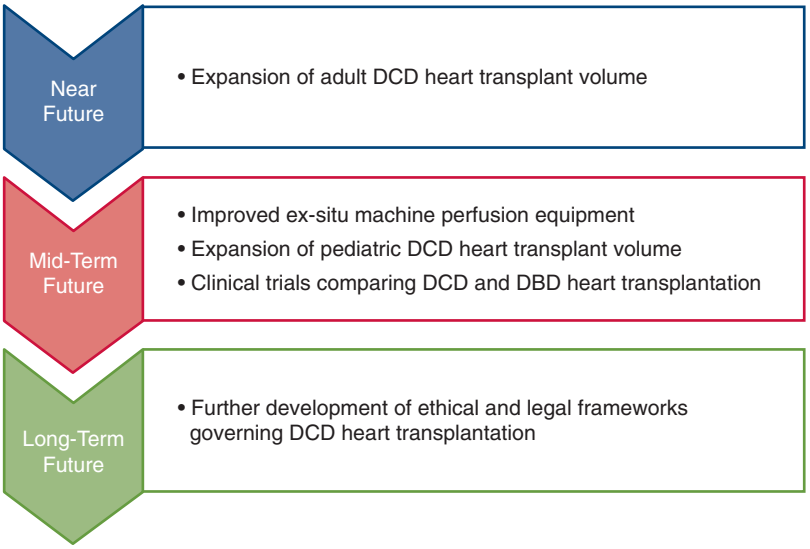

FIGURE 5. Future directions for donation after cardiac death (*DCD*) heart transplantation. *DBD*, Donation after brain death.

potentially invalidating the declaration of cardiac death. Another area of ethical and legal controversy where well-considered judgments differ concerns withdrawal of life support to bring about cardiac death. Here, cultural sensitivities need to be balanced against donor autonomy with regard to the wish to donate the heart, nonmaleficence regarding a humane ending of the donor's life, and beneficence to improve the recipient's health and safety. Eventually, a solution to these controversies may even require abandoning the dead donor rule.[36]

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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