Functional evaluation of human donation after cardiac death donor hearts using a continuous isolated myocardial perfusion technique: Potential for expansion of the cardiac donor population

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Objective: To investigate the resuscitation potential and contractile function in adult human donation after cardiac death (DCD) hearts by ex vivo perfusion.

Methods: With institutional review board approval and under the DCD protocol at the University of Wisconsin (UW) Organ Procurement Organization, 5 brain dead (BD) and 5 DCD donor hearts were evaluated. All BD hearts were declined for clinical transplantation because of coronary artery disease, advanced age, or social history. All hearts were preserved by flushing and cold storage with UW solution. By using our ex vivo perfusion system, the left ventricular end systolic pressure-volume relationship (LV-ESPVR) was assessed for 2 hours of oxygenated blood reperfusion.

Results: All BD (n = 5) and 4 DCD hearts were successfully resuscitated. One DCD heart was unable to be resuscitated due to prolonged warm ischemic time (WIT; 174 minutes). Mean WIT for resuscitated DCD hearts (from extubation to flushing with cold UW solution) was 34 ± 3 minutes (range, 26 to 40 minutes); mean cold ischemic time for BD donors was 211 ± 31 minutes compared with 177 ± 64 minutes for DCD donors. The calculated LV-ESPVRs for BD hearts after 1 and 2 hours of reperfusion were 6.9 ± 0.7 and 5.7 ± 1.0 mm Hg/mL, respectively; LV-ESPVRs for DCD hearts after 1 and 2 hours of reperfusion were 5.6 ± 1.5 ($P = .45$) and 3.0 ± 0.7 mm Hg/mL ($P = .07$), respectively.

Conclusions: We successfully resuscitated and measured ex vivo cardiac function in human DCD and BD donor hearts. Resuscitation potential in DCD hearts was achieved when the WIT was less than 40 minutes. Contractile performance in DCD hearts tended to be lower compared with BD hearts. Further investigation with longer reperfusion periods seems warranted. (J Thorac Cardiovasc Surg 2014;148:1123-30)

Heart transplantation is an established and effective treatment for patients with end-stage heart failure; however, the shortage of donor organs is the most critical problem. The Organ Procurement and Transplantation Network (OPTN) reports indicate that the number of registrations on the heart waiting list is approximately 3000 in a recent 3-year period and 15% of patients die within 1 year while awaiting a donor heart (http://optn.transplant.hrsa.gov/). To maintain or increase the present transplantation rate, donation after cardiac death (DCD) donors have been proposed as another donor source. The concept of heart transplantation using DCD donors existed in the 1960s before brain death became legally accepted and the first successful clinical human heart transplantation in an adult was performed using a DCD heart allograft in 1967 by Christiaan Barnard.[1] In the current era, Boucek and collegues[2] reported the short-term results of 3 infants undergoing successful orthotopic heart transplantation from DCD donors. For noncardiac organ transplantation, clinical studies from several institutions show that DCD donors are reliable donor sources for organs such as kidney[3] and liver.[4] The OPTN data show a progressive increase in the rate of organ recovery from DCD donors (1089 DCDs in 2012, compared with 189 in 2002) and that these donors accounted for 12% of all deceased donors in 2012 (http://optn.transplant.hrsa.gov/). In particular, at several Organ Procurement Organization programs, DCD donors accounted for more than 20% of all deceased donors. Although the use of DCD donors for noncardiac organ transplant has been increasing, the potential for heart transplantation from DCD donors remains unrealized, because of potentially severe myocardial damage due to unavoidable warm ischemia (from the withdrawal of life support to flushing with cold preservative solution).

According to the 1995 Maastricht categories,[5] DCD donors are classified as uncontrolled or controlled donors.

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Abbreviations and Acronyms

BD	= brain dead
CIT	= cold ischemic time
DCD	= donation after cardiac death
LV-EDP	= left ventricular end diastolic pressure
LV-ESP	= left ventricular end systolic pressure
LV-EDPVR	= left ventricular end diastolic pressure-volume relationship
LV-ESPVR	= left ventricular end systolic pressure-volume relationship
LV dP/dt max	= left ventricular maximum of first derivative of pressure
LV dP/dt min	= left ventricular minimum of first derivative of pressure
LVP	= left ventricular pressure
OPTN	= Organ Procurement and Transplantation Network
UW	= University of Wisconsin
UWHC-OPO	= University of Wisconsin Hospital and Clinics-Organ Procurement Organization
WIT	= warm ischemic time

Uncontrolled donors are dead on arrival (category I) or had an unsuccessful resuscitation (category II). Controlled donors have an awaited cardiac arrest (category III) or develop cardiac arrest while brain dead (category IV). The so-called Maastricht category III, withdrawal of donor treatment (usually in the intensive care unit or operating room), is a controlled DCD technique and the only one presently in use in the United States, including our institution. This category III DCD donor could potentially be used for clinical heart transplantation.

Over the past decades, many animal experiments have been undertaken to evaluate the feasibility of heart transplantation from DCD donors, using various reperfusion strategies and animal DCD models. Some researchers indicated excellent results in animal DCD heart transplant experiments. Shirakura and colleagues[6] reported satisfactory functional recovery of canine hearts after a 24-hour period of preservation in a 30-minute warm ischemic DCD transplant model, and Gundry and colleagues[7] achieved long-term survival of baboons receiving transplantation of hearts harvested from 30-minute warm ischemic DCD donors. However, these successful experimental outcomes are largely attributable to the application of multiple pretreatments, which, in humans, would be ethically unacceptable. In our previous animal studies,[8,9] we evaluated acute posttransplant graft function using a 30-minute warm ischemic pig DCD model without any cardioprotective pretreatments except for heparin, and this graft functional recovery rate was approximately 80% of the pretransplant (normal) value. These animal studies support the potential acceptability of 30-minute warm ischemic DCD cardiac grafts. However, the acceptability of warm ischemic time (WIT) for human adult DCD hearts is still unknown because resuscitation potential and functional recovery after warm ischemia have not yet been elucidated.

The purpose of this study was to evaluate the resuscitation potential and contractile function in adult human DCD hearts using an ex vivo perfusion system and investigate functional recovery for human DCD hearts compared with human brain dead (BD) hearts.

MATERIALS AND METHODS

DCD and BD Donors

Five BD and 5 DCD donor hearts were evaluated in this study, with institutional review board approval and using the deceased donor (BD and DCD) protocol in the University of Wisconsin Hospital and Clinics-Organ Procurement Organization (UWHC-OPO).[10]

All DCD donor hearts were obtained from donors eligible for other organ transplant protocols in the UWHC-OPO, who agreed to donate the heart for research purposes. Each organ was checked separately on the consent form. All DCD donors in this study were brought to the operating room before the withdrawal of life support. While the patient was fully supported, 30,000 units of heparin were given intravenously to facilitate subsequent organ flushing. The patient's physician of record withdrew life support by stopping intravenous medications and extubation. The organ recovery procedure commenced only after an additional 5 minutes elapsed after the declaration of death, as described in the 1997 Institute of Medicine Guidelines.[11] Five minutes after the declaration of death, median sternotomy and a midline abdominal incision were made and the inferior vena cava was dissected immediately to decompress the heart. All DCD hearts were asystolic when they were explanted. After organ recovery for clinical transplantation, the ascending aorta was cannulated and approximately 2 L of UW solution was infused in situ. Then the heart was removed en bloc, stored in UW solution at 4°C, and transported to our research laboratory.

All BD hearts were obtained from donors who were ineligible for our BD heart transplant protocol, and who agreed to donate the heart for research purposes. Each organ was checked separately on the consent form. All BD hearts were preserved using our institutional method of BD heart recovery. After administration of 30,000 units of heparin, the ascending aorta was clamped and approximately 2 L of UW solution was infused through the aortic cannula. The inferior vena cava was divided immediately to decompress the heart. The heart was removed en bloc and stored in UW solution at 4°C.

WIT was defined as the interval between withdrawal of life support and cold flush of UW solution; cold ischemic time (CIT) was defined as the interval between cold flush and oxygenated blood reperfusion of the graft.

Ex Vivo Myocardial Perfusion System

The perfusion circuit was an open system and the reperfusion protocol was similar to that previously described (Figure 1).[9] The system consisted of a Terumo pediatric membrane oxygenator with the reservoir containing a filter (Terumo Cardiovascular Systems, Ann Arbor, Mich), a circulating water bath, a hemofilter, a roller head pump, a temperature meter, a leukocyte-depletion filter (Pall, Glen Cove, NY), and 6.4-mm (0.25-inch) connective tubing. A new circuit was used for each procedure in a semisterile manner. The total circuit volume was 600 mL. Coronary venous