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Case Reports

Anesthetic Considerations During Heart Transplantation Using Donation After Circulatory Death

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Worldwide, the majority of heart transplant organs are from donation after brain death. However, the shortage of suitable donors places severe limitations on this route. One option to increase the donor pool is to use organs from donation after circulatory death (DCD). Transplant centers for solid organs have been using DCD organs for years. At this time, 40% of solid organ transplantation in the United Kingdom uses organs from DCD. Use of DCD for solid organ transplants in Canada is also rising. Recently, there has been interest in using DCD organs for heart transplantation. The authors will discuss their experience of 4 heart transplants with organs from DCD donors after normothermic regional perfusion (NRP). The authors' first heart transplant using a DCD organ was in January 2020, and the fourth was in March 2020, just before the coronavirus disease 2019 (COVID-19) pandemic.

The authors' protocol using NRP allows adequate evaluation of the donor heart to confidently determine organ acceptance. The co-location of the donor and the recipient in neighboring operating rooms limits ischemic times. Avoidance of an expensive ex vivo organ perfusion machine is an additional benefit for programs that may not have the resources required to purchase and maintain the machine. Some hospitals may not have the resources and space to be able to co-locate both the donor and recipient. Use of cold storage may be an option to transport the procured organ, similar to donation after brain death organs. The authors hope that this technique of NRP in DCD donors can help further increase the donor pool for heart transplantation in the United States.
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Key Words: heart transplant; donation after circulatory death; donation after brain death; normothermic regional perfusion; direct procurement; co-location

THERE ARE more than 3,600 heart transplant candidates in the United States currently on the waiting list for an organ.[1] In 2019, 3,551 heart transplants were performed in the United States.[2] Data from the 2018 Annual Report, from the United Network for Organ Sharing on heart transplants, indicated the median time spent on the waiting list was 6.9 months and 7.2% of patients died within the first year of being listed while waiting for a donor heart.[3]

Worldwide, the majority of heart transplant organs are from donation after brain death (DBD). However, the shortage of suitable donors places severe limitations on this route. One option to increase the donor pool is to use organs from donation after circulatory death (DCD). Transplant centers for solid organs have been using DCD organs for years. At this time, 40% of solid organ transplantation in the United Kingdom uses organs from DCD.[4] Use of DCD for solid organ transplants in Canada also is rising.[5] Recently, there has been interest in using DCD organs for heart transplantation. The authors will discuss their experience of 4 heart transplants with organs from DCD donors after normothermic regional perfusion (NRP). The authors' first heart transplant using a DCD organ was in January 2020, and the fourth was in March 2020, just before the (COVID-19) pandemic.

Description of Cases

All of the authors' cases utilized NRP with a short cold storage time. Donor selection criteria included age between 18 and 49 years, absence of risk factors for coronary artery

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disease including insulin-dependent diabetes, and smoking history >20 pack years. Cardiac evaluation of the donor was limited. Testing most often included transthoracic echocardiography, chest X-ray, electrocardiogram, and chest computed tomography scan. Invasive procedures, such as cardiac catheterization and placement of pulmonary artery catheters, often were not conducted, even after the patient was chosen as a donor.

The screening procedure included a discussion with the donor's physician regarding likelihood of cardiac arrest within 3 hours after withdrawal of support. Once a suitable donor was identified, they were transported to the authors' institution. The local organ procurement organization (LiveOnNY) coordinator discussed organ donation with the family only after the following 3 criteria were met: the decision had been made to withdraw support, organ function was acceptable, and the donor was likely to progress to cardiac arrest within the time allotted after withdrawal of support. Items discussed with the family included the DCD process, the administration of heparin before withdrawal of support, and the possible event that their loved one did not proceed to cardiac arrest. Consent for organ donation was obtained from the family by the heart transplant coordinators who have been previously trained on this protocol.

After the family consented to organ donation, the donor was transported to the operating room (OR). Table 1 summarizes the donor demographics. The anesthesiology, surgery, critical care, perfusion, and nursing teams were all present in the OR to prep the donor for surgery. The sedatives and vasopressors all were continued, and the donor was still intubated and connected to the anesthesia machine and monitors. Care was taken to leave the face and arm exposed after draping. This was for the family to see their loved one and to hold their hand during withdrawal of support.

All teams left the OR except for the critical care team, and the family was brought into the OR. Sterility was maintained, with placement of a sterile surgical drape over the entire surgical field and another drape covering the surgical instruments on the back table. The authors' protocol for withdrawal of life-sustaining therapies includes discontinuation of vasopressors, ensuring an adequate amount of sedatives and analgesics, and extubation. Warm ischemic time began with support withdrawal, and functional ischemic time began when systolic blood pressure decreased below 80 mmHg, and reperfusion marked the end of both ischemic times. The authors' average warm ischemic time was 35 minutes, and the average functional ischemic time was 31.75 minutes (Table 2). The intensivist declared time of death and the family was escorted out of the OR with the transplant coordinator. If, however, cardiac arrest did not occur within 3 hours of withdrawal of support, the donor was to be taken back to their hospital room.

Table 1
Donor Demographics

Case	Donor Age and Gender	Donor Cause of Withdrawal	Organs Donated
1	43 m	Anoxia from liver failure	Heart
2	44 m	Anoxia from drug intoxication	Heart, liver, bilateral kidneys
3	29 m	Anoxia from drug intoxication	Heart, liver, bilateral kidneys
4	26 f	Anoxia from drug intoxication	Heart, liver

Abbreviations: f, female; m, male.

Table 2
Ischemic Times

Case	Warm Ischemic Time* (min)	Functional Ischemic Time† (min)	Incision to CPB Initiation (min)	Cross-clamp Time‡ (min)
1	41	34	12	78
2	28	27	9	71
3	34	31	12	85
4	37	35	12	80

Abbreviation: CPB, cardiopulmonary bypass.

* Warm ischemic time is defined as time of withdrawal of life sustaining therapies until perfusion. † Functional ischemic time is defined as time when systolic blood pressure is below 80 mmHg until perfusion.

‡ Cross-clamp time is defined as time when donor aorta is clamped until recipient aorta is unclamped.

Each of the teams re-entered the OR. The surgeons could not make an incision until after a mandatory 5-minute standoff period. This is to ensure autoresuscitation does not occur, also known as the Lazarus phenomenon, which is spontaneous return of circulation.[6-8]

Once the surgeons performed sternotomy, the aortic arch vessels were clamped to exclude the brain from perfusion. Cardiopulmonary bypass (CPB) was initiated via central cannulation of the ascending aorta and right atrium, and cardiac index >3 L/min/m^2 was maintained. Once the authors ensured that there was no cerebral perfusion, the donor was reintubated and a transesophageal echocardiography probe was placed. Intubation occurred after initiation of CPB because cardiac reperfusion was a priority. Cerebral saturation monitors were placed on the donor to ensure that perfusion to the brain had been excluded to prevent resuscitation after declaration of death. Cerebral oximetry was a means to validate and monitor the lack of cerebral perfusion. Dobutamine was initiated up to 5 μg/kg/min and vasopressors were titrated to maintain mean arterial pressure 70- to- 90mmHg. After reperfusion for 30 minutes, the donor was ventilated and separated from CPB.

Evaluation of hemodynamics and cardiac function was now performed to ensure there were no obvious negative effects from the warm ischemic time. Hemodynamics could be measured by direct needle measurement in the pulmonary artery and left ventricle if a pulmonary artery catheter was not present.

In the authors' experience of 4 cases, the donor heart was acceptable for transplantation after this initial separation from CPB. The authors' protocol includes the provision to re-establish CPB support if the heart function had been poor, for up to 3 hours as needed, with assessment of cardiac function at 30-minute

intervals. The authors will not reject the donor heart based on the level of pressor support; however, a maximum dosage of dobutamine, 5 μg/kg/min can be used for inotropic support. If the contractility is not acceptable on this level of inotropic support within the 3 hours, the heart is rejected for transplantation.

Acceptable parameters from the authors' protocol include mean arterial pressure >60 mmHg, central venous pressure <12 mmHg, pulmonary artery systolic pressure <40 mmHg, pulmonary capillary wedge pressure <12 mmHg, mixed venous saturation >65%, and cardiac index >2.2 L/min/m^2. Protocols from other institutions use very similar parameters to determine organ acceptance.[9-12] Hemodynamic parameters had to remain stable for acceptance. Transesophageal echocardiography parameters for acceptance are left ventricular systolic function ≥50%, normal right ventricular function, and normal biventricular chamber size. The presence of any regional wall motion abnormalities should be determined. Diastolic function is assessed with tissue Doppler, and E' measurement of greater than or equal to 10 cm/sec is acceptable. Valvular regurgitation or stenosis should not be graded more significantly than mild for any of the valves. Interatrial and interventricular septae should be evaluated for defects and shunts. Left atrial appendage should be examined for thrombus. All pulmonary veins should enter the left atrium for ease of excision and transplantation.

Once the heart was accepted for donation, the recipient was induced with general anesthesia and surgery commenced for heart transplantation in the neighboring OR (Fig 1). For recipients with ventricular assist devices or other mechanical circulatory support devices, the time of anesthetic induction was the same as those without prior sternotomy. This is to limit the risk to recipients in the event that the donor heart is rejected for transplantation. During the time period before initiation of CPB in the recipient, the other surgical procurement teams dissected their organ of interest. Once CPB was instituted in the recipient, the donor aorta was cross-clamped, cardioplegia was administered, and the donor heart was excised. It was brought to the recipient OR on ice, and then transplanted into the recipient. Other organs, such as liver and kidney, were harvested from the donors in addition to the heart (Table 1).

The 4 recipients did not require mechanical circulatory support postoperatively. They were all extubated on postoperative day 1. The median hospital discharge was 12.5 days after the transplant (Table 3).

Discussion

DCD organs for heart transplants are Maastricht category III, which is a controlled withdrawal of life-sustaining therapies resulting in observed cardiac arrest.[13] Once donor death has been declared, the heart can be directly procured or reperfused in the donor. Direct procurement (DP) has been utilized in the United Kingdom and Australia.[11,14] Use of the DP technique carries some risk, as it does not allow complete evaluation of the donor heart before transplantation. This is especially true if the donor heart is simply placed in cold storage before transplanting. The effects of the warm ischemic time before death are unpredictable in the organ. Use of an ex vivo organ perfusion machine before transplant allows for limited organ evaluation, with trends of lactate and hemoglobin. It does not allow for visual inspection or echocardiography because the heart is in a resting state and not fully beating while in the perfusion machine.[15] It is also quite expensive, costing $40,000 USD for each use.[16]

The authors' institutional protocol utilizes the NRP technique in DCD donors with cold storage. The heart is evaluated after 30 minutes of reperfusion and separation from CPB. If the donor heart is accepted for transplantation, the donor remains off CPB. Once the donor heart is procured, it is placed on ice. If the donor heart is not deemed acceptable for surgery within the 3 hours of reperfusion, then the whole process for heart donation is stopped. The other organ procurement teams can then harvest if they have accepted their respective organs.

NRP also can be accomplished with use of extracorporeal membrane oxygenation (ECMO) with peripheral cannulation. This has been reported by 2 groups from Denver and Belgium, and the donors were cannulated during the antemortem period.[9,17] At the authors' institution, antemortem intervention is not permitted. The authors' surgeons preferred to use CPB with central cannulation because it is an expedient method to achieve perfusion after the warm ischemic period.

Not every DCD donor progresses to successful transplantation. Reasons include failure of progression to circulatory cessation or poor cardiac function after reperfusion. Two studies analyzed the number of DCD donors who hearts resulted in heart transplants at their respective centers. Messer et al. determined 65% proceeded to successful transplant from potential DCD donors, and Chew et al. determined only 48% proceeded to transplant.[11,14] Another reason that was cited for failure to transplant was machine failure of the ex vivo organ perfusion

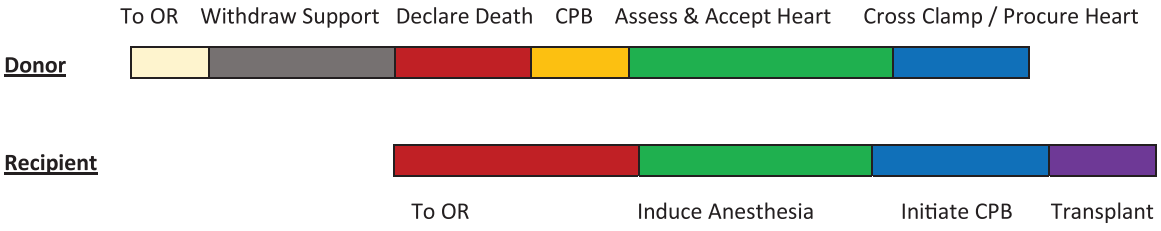

Fig 1. Timeline of events coordinated between donor and recipient. Donor is transported to OR to withdraw support. Once death is declared in donor, recipient is transported to OR. When donor heart is accepted for transplantation, recipient is induced with general anesthesia and surgery begins. When CPB is initiated in recipient, donor heart is procured. Donor heart is transplanted into recipient. Length of bars does not correlate with length of time for each step. CPB, cardiopulmonary bypass; OR, operating room.

Table 3
Recipient Demographics and Outcomes

Case	Recipient Age and Gender	Inotrope and Vasopressor Requirements in OR (μg/kg/min)	Need for Mechanical Support Post Transplant	Extubation (Postoperative Day)	Hospital Discharge (Postoperative Day)
1	50 m	Epinephrine 0.04; milrinone 0.5; dobutamine 7.5	No	1	15
2	45 f	Dobutamine 5, milrinone 0.25	No	1	24
3	50 m	Dobutamine 5; norepinephrine 0.08; epinephrine 0.04	No	1	10
4	59 f	Dobutamine 5	No	1	10

Abbreviations: f, female; m, male; OR, operating room.

machine.[14] The authors' protocol includes co-location of the donor and the recipient. Both the donor and recipient are transferred to the same institution. This requires multiple care teams for the donor and recipient. The authors use an intensivist to withdraw care, a cardiac anesthesiologist and surgeon for the donor, and a separate cardiac anesthesiologist and surgeon for the recipient. As their experience grows, the authors are looking into more efficient use of staff and may not require separate teams of anesthesiologists and surgeons.

To initiate the process, the donor is brought to the OR for withdrawal of life- supporting therapies, and the recipient also is transported to a neighboring OR to await acceptance of the organ and subsequent transplant surgery. Having both the donor and recipient in neighboring ORs reduces ischemic times. Time of warm ischemia is minimized if the donor is in the OR. The transport time from the intensive care unit after circulatory cessation is eliminated. Time of cold storage before transplantation is limited by avoidance of transport to another hospital.

In the authors' experience, mechanical circulatory support was unnecessary during the postoperative period, whereas other institutions required use of postoperative ECMO. The opportunity to fully evaluate the donor heart before acceptance, when the NRP technique was used, may decrease the use of ECMO. Additionally, the shorter ischemic times afforded by co-location of both the donor and recipient may also lead to decreased utilization of ECMO. Chew et al. utilized the DP technique and needed ECMO in 35% of their patients.[14] Messer et al. used a combination of DP and NRP techniques and required ECMO in 12% of the recipients.[11] Neither of these institutions implemented donor withdrawal in the OR nor co-location with the recipient.

Coordination is required to have the donor and recipient located in neighboring ORs. Respect for the emotional states of each family needs to be observed. The authors defined separate paths for the families to take, as well as the timing, to enter and leave the OR. The authors also designated separate areas for the families to grieve or to wait in anticipation of a new heart.

DCD is quite different from DBD for heart transplantation. For DBD, organ perfusion is maintained until the time of organ harvest. DCD organs are exposed to a period of warm ischemic time while waiting until circulatory cessation. Even after the declaration of death, there is also a mandatory standoff period, which is an additional 5 minutes of warm ischemic time. The remaining time of the warm ischemic period is dependent on the technical abilities of the surgeons to open the chest, ligate the aortic arch vessels, cannulate, and initiate CPB. The warm ischemia time is variable and uncontrollable for each donor. Because the organ is exposed to hypoperfusion, hypoxemia, and acidosis, which could all negatively impact the heart, it is essential to re-evaluate the donor heart before accepting it for transplantation. This re-examination is not performed for DBD organs. DBD organs are harvested without reperfusion and reanimation, and DCD hearts can be harvested either before or after reperfusion and reanimation.

Clinical outcomes of DCD and DBD thus far are comparable. Survival, hospital length of stay, and intensive care unit length of stay are not statistically significant.[11,14,17] Rejection episodes also have been similar. At the authors' institution, they have 60-day survival of 100% in the 4 DCD recipients compared with 97% in the DBD group. The authors' patients' median length of hospital stay was 12.5 days for DCD compared with 14 days for DBD heart transplants.

The authors' protocol using NRP allows them to evaluate the donor heart adequately to confidently determine organ acceptance. The co-location of the donor and the recipient in neighboring ORs limits ischemic times. Avoidance of an expensive ex vivo organ perfusion machine is an additional benefit for programs that may not have the resources required to purchase and maintain the machine. Some hospitals may not have the resources and space to be able to co-locate both the donor and recipient. Use of cold storage may be an option to transport the procured organ, similar to DBD organs. The authors hope that this technique of NRP in DCD donors can help further increase the donor pool for heart transplantation in the United States.

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Conflict of Interest

None.

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