Heart transplant donation after circulatory death: current status and implications

Savitri Fedson

Purpose of review
The use of cardiac transplantation following circulatory death (DCD) has been limited worldwide. Concerns about cardiac function after warm ischemia and the potential for decreased graft function have been important considerations in this hesitancy. In addition, ethical and legal questions about the two widely used organ procurement methods have led to discussions and public education in many countries.

Recent findings
Publication of a US randomized trial of cardiac transplantation following DCD has shown that it is both feasible and has similar short-term outcomes compared with cardiac transplantation following brain death (DBD). These data support those from both Australia and the UK who have largest experience to date.

Summary
The adoption of cardiac transplantation following circulatory death has increased overall cardiac transplantation in those transplant centers who have incorporated these donors. Short term outcomes for DCD organ procurement methods are similar to those outcomes using DBD hearts. Continued study and standardization of warm ischemic times will allow for better comparisons of organ procurement techniques and organ optimization. The ethical concerns about procurement methods, in addition to a discussion of procurement costs and feasibility will need to be addressed further in the efforts to expand the organ pool and increase overall cardiac transplantation numbers.

Keywords
bioethics, donation after circulatory death, heart transplantation

INTRODUCTION

Cardiac transplantation has been the final option for end-stage severe heart failure for over fifty years. Although the first cardiac transplant used a heart/organ procured after cardiocirculatory death, cardiac transplantation has long relied on donation after neurologic, or brain death (DBD). The consensus statement from the Harvard Commission on Brain Death (1968) and the addition of neurologic criteria in the Uniform Determination of Death Act (1981) permitted significant advances in transplantation, eliminating the need for co-localizing the recipient and the donor, allowing for greater distances and time between procurement and transplantation, and enabling use of other organs. However, despite the increase in organ donors, the increase in the end-stage heart failure population has outpaced the availability of DBD organs.

The use of organs following donation after circulatory death (DCD) has provided some relief to this pressing need. Death in these circumstances is defined as the irreversible cessation of circulation in the United States and, although endorsed by the World Health Organization, there is no international standard definition or protocol to declare circulatory death for organ donation [1]. The use of DCD organs in the United States has increased fivefold over the past decade, representing 22% of all donors in 2022 primary for abdominal organs [2,3]. There has been simultaneous, but delayed uptake, in the use of DCD organs for cardiac transplantation, led by the transplant groups at the Royal Papworth Hospital in the United Kingdom and St. Vincent's Hospital in Australia, which increased the volume of

Michael E. DeBakey VA Medical Center, Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, Texas, USA

Correspondence to Savitri Fedson, Michael E. DeBakey VA Medical Center, Center for Medical Ethics and Health Policy, Baylor College of Medicine, 2002 Holcombe Blvd mc 111-b, Houston, TX 77098, USA. Tel: +1 713 794 7300; e-mail: fedson@bcm.edu

Curr Opin Cardiol 2024, 39:128–134

DOI:10.1097/HCO.0000000000001109

KEY POINTS

- Donation after circulatory death
- Potential to increase cardiac transplantation by up to 30% in the United States
- Has increased transplantation rates for those waiting at Status 3–6, especially benefiting those with stable durable left ventricular assist devices
- Clinical challenges
- Understand the tolerance for warm ischemia.
- Technical requirements for rapid procurement for DPP
- What perfusate to use to precondition the organ
- Ethical challenges
- Debate surrounding NPR (no uniform international acceptance)
- Pretreatment of the patient-donor.
- Who are best recipients?
- Cost

transplantation 48% over 5 years in the UK and 15% per year in Australia [4]. In recent years in the United States, there have now been slightly more than 1200 cardiac transplants performed using DCD organs. The use of hearts following DCD has been limited in uptake though estimates suggest that use of DCD hearts would increase cardiac transplantation by 30% [5,6] (Fig. 1a and b).

PROCUREMENT DIFFERENCES AND DONOR ORGAN MANAGEMENT

Despite the appeal of broader availability of DCD organs, donation following brain death determination allows a more thorough investigation of organ quality and organ management for all organs. In cardiac transplant, donor brain death permits tests, such as coronary angiography, which allow a functional assessment of organ function while it is still functioning in the donor under physiologic conditions. Clinical decisions to accept an organ have been based on such information. Importantly, organs recovered from DBD are not subjected to warm ischemia. With DCD organs, however, there are legal, ethical and clinical issues which effect the ability to perform testing on the organ. In contrast to DBD donors, the discussion about DCD typically occurs following severe neurologic injury and *after* discussion about withdrawal of life-sustaining therapies (LST) but, importantly, *before* withdrawal is attempted. DCD has replaced the terms 'nonheart beating donors', and 'donation after cardiac death' in recognition that current methods of life support can sustain a patient without cardiac activity, for example in the case of extracorporeal membrane oxygenation (ECMO). To define types of circulatory death further, the Maastricht criteria were developed, based on whether a circulatory death was uncontrolled, or unexpected (Maastricht category I, II, IV) or controlled (cDCD), where there is a planned withdrawal of LST, Maastricht category III). For heart transplantation following DCD it is typically those donors who meet Maastricht III criteria.

One important clinical component of DCD is that any clinical evaluation of organ function needs to be performed on a patient, rather than an organ in a deceased donor. While the discussion about organ donation happens after and independent of the decision to withdraw LST, the initial assessment of cardiac function occurs before withdrawal of LST. Therefore, these assessments are performed on a patient rather than a donor. There are important ethical and medical obligations to the patient can impede thorough organ evaluation. These are tied to the principles of nonmaleficence, of not harming the patient, and the principle that a patient should not be a means to an end. Therefore, antemortem therapy, or interventions such as the placement of catheters to potentially decrease warm ischemic time, cannot routinely be performed on a patient prior to declaration of death.

The main physiologic difference between DCD and DBD organs is the warm ischemic time that takes place during the withdrawal of LST but before circulatory death is declared. During this time, the processes of ischemia, hypoxia, and catecholamine release can deleteriously affect organ function, in particular, cardiac function, which leads to myocardial edema, which can appear as left ventricular hypertrophy on echocardiography.

At present, there are three common methods for the controlled procurement of organs after DCD: direct procurement using machine perfusion (DP-MP), or procurement after thoraco-abdominal-normothermic regional perfusion (TA-NRP) using either MP (NRP-MP) or traditional cold static storage (NRP-CS). For TA-NRP ECMO is initiated in the donor after declaration of death to perfuse the organs *in situ*. In the rare instance where the donor and recipient are in the same center, direct procurement with cold storage can be used. Following withdrawal of LST, and the subsequent circulatory arrest, there is a mandatory stand off period (which varies by country) [7,8] during which time the donor heart experiences functional warm ischemia (fWIT) which then ends when

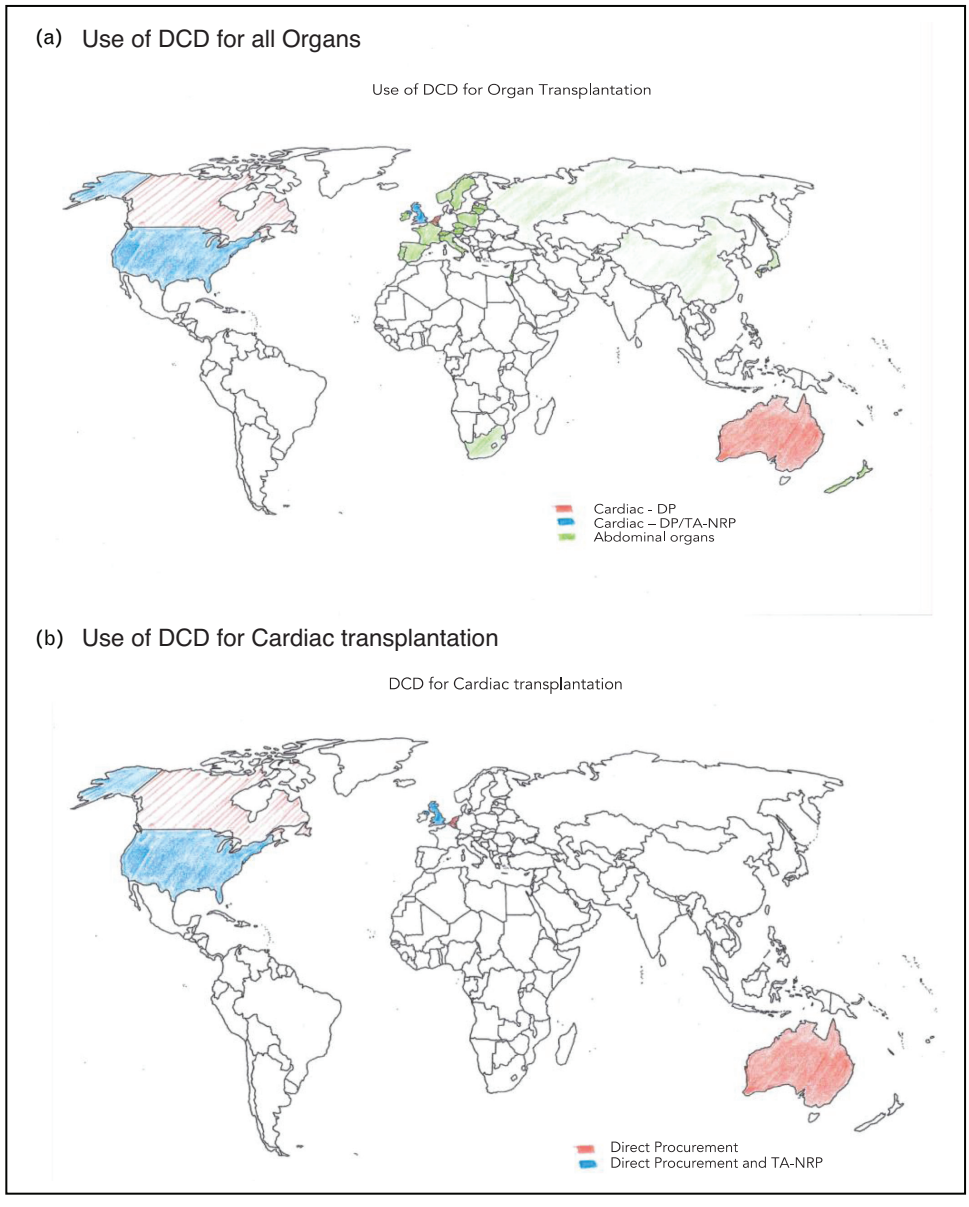

FIGURE 1. (a) Use of DCD for all organs. (b) Use of DCD for cardiac transplantation. DCD, donation after circulatory death.

the heart is either flushed during DP or has re-perfusion with NRP. This interval has been the focus of both scientific study as well as ethical conversation and is unique to DCD organ procurement.

Noninvasive evaluation of the organ can occur before declaration of death. Testing such as an EKG or echocardiogram or serum laboratories confer minimal risk or discomfort to the patient. Increasingly many families give consent for invasive procedures, such as coronary angiography, which are nonbeneficial to the patient-to-be-donor but are beneficial for the organ recipients. This consent is not standard nor mandatory (personal communication). There are also legal protections for the patient-donor and variable practices regarding antemortem interventions, such as placement of cannula for NPR, and administration of medications.

One of the major differences in the potential quality variance between hearts recovered following donation after DCD, compared to DCD, is the warm ischemic time. The definition of what comprises functional warm ischemic time (fWIT) has differed in the published reports, for example, sustained systolic blood pressure less than 90mmHg or less than 50mmHg with systemic saturations of less than 70%. This variability in warm ischemic time does make comparisons across centers using different procurement strategies challenging (Table 1). The appraisal of donor organ function occurs after this WIT, which is the period when the donor organ is most vulnerable.

Table 1. Method of cDCD-heart recovery

	Direct perfusion-machine perfusion (DP-MP)	Thoraco-abdominal normothermic regional perfusion (TA-NRP)	
		MP	CS
Where	All centers Not permissible in stand-alone organ recovery institutions	Only where port-mortem restarting of circulation is permitted	
Organ assessment	Visible assessment of unloaded heart Can support prolonged travel time	Physiologic assessment in-situ Can support prolonged travel time	
Cost	40 000 USD (OCS) Requirement for donor blood – may affect abdominal organs	40 000 USD(OCS) Personnel, equipment for ECMO and OR services Requirement for donor blood – may affect abdominal organ	5000 USD (NRP)

cDCD, controlled donation following circulatory death; CS, cold storage; DP, direct procurement; ECMO, extracorporeal membrane oxygenation; MP, machine perfusion; OCS, organ care system; TA-NPR, thoracoabdominal normothermic regional perfusion.

Assessment of cardiac function, while using normothermic MP following either DP or NRP, currently relies on visual assessment of cardiac performance in an unloaded state. Parameters such as heart rate and rhythm, in addition to aortic pressures, coronary flow and measurement of lactate, are also available [9▪▪]. A few centers have performed angiography on the Organ Care System (OCS) (TransMedics; Andover, MA, USA) [4,10,11]. but this is not standard practice. Use of MP also requires the use of 1.5–2L of donor blood which can affect the quality of abdominal organs [2]. Procurement using NRP allows for a visual judgment of organ function in a loaded, or physiologic condition, in addition to any biochemical testing, which may more closely predict organ function once fully re-perfused in the recipient. In part because of the uncertainties of cardiac function after transplantation that the use of DCD for cardiac transplantation lagged behind other organs.

CLINICAL OUTCOMES

In 2008, the Pediatric Heart Transplant Group at Denver Children's Hospital [12] reported successful outcomes for three children receiving transplanted organs from donors who had died from circulatory causes [13]. Their achievements reinvigorated contemporary interest in using DCD organs for transplantation. The use of DCD for cardiac transplantation began in earnest in both the UK and Australia in the mid-2010s. The rates of primary graft dysfunction vary between varied between 2.3% and 28%, and use of extracorporeal membrane oxygenation (ECMO) between 11% and 35% [14,15]. The 5-year results from the Royal Papworth Hospital in the UK showed that 100 of 128 potential DCD donors progressed to cardiac arrest within 4 h of withdrawal of LST. Of these 100 patients, 75 underwent DP and 25 with TA-NRP [16] the transplant rate was 76% for DP compared to 88% for TA-NRP. They compared the outcomes of DCD recipients to their propensity-matched DBD, with no significant difference in 1 year survival (91% for DCD, compared to 89% for DBD, $P = 0.72$). The use of postoperative MCS was not statistically different, but was 15% in the DCD group. Messer *et al.* [16] found that the use of TA-NRP allowed them to use donors older than 50 years because of their ability to perform functional assessments of cardiac function. The 5 year survival for the 22 patients with TA-NRP was 100%; for DP 1 year survival was 86%.

Similar data have been presented from St. Vincent's Hospital. Chew *et al.* [17] presented results of 23 patients transplanted using DP-MP with the OCS system. Of 48 potential donors, who gave 33 organs for transplantation; 23 were ultimately transplanted. Thirty-five percentage of patients receiving these organs required postoperative ECMO, one patient died early with primary graft dysfunction, and they report a 91% 1-year survival. Use of DCD donation increased their transplant activity by 15%.

The first US trial of DCD cardiac donation was published in 2023. Schroder *et al.* [18] presented outcomes from 180 patients, randomized in a 3 : 1 ratio to receive either a DCD using DP-MP with the OCS or DBD organ. The risk adjusted 6-month survival for recipients from a DCD heart was 94%, compared to 90% for hearts from DBD donation. Donor age was limited to those <50 years. There was a 15% incidence of severe ISHLT primary graft

function in the DCD recipients. Based on current US data, the use of DCD organs has increased organ availability for those awaiting at lower urgency status, such as those status 3–6. Most notably of patients with stable durable LVADs, those with ABO blood group O received these organs. From all reports the survival at 6 months is comparable to survival following traditional DBD at 91–95% [19–22]. Although there are trends to early right ventricular dysfunction and increased need for temporary MCS [14].

CHALLENGES FOR DONATION AFTER CIRCULATORY DEATH

There are still significant social as well as complex biologic challenges to overcome with heart recovery following DCD donation.

The biological challenges of DCD include developing a better understanding of what comprises fWIT. Hypoxia induces is pulmonary vasoconstriction, increase in systemic catecholamines, right ventricular distension, and worsening myocardial ischemia [23]. These are the clinical targets for interventions to limit warm ischemia; fWIT should be certainly less than 60 min, with a goal of less than 30 min. From a technical perspective, there remain areas for continued improvement and refinement, and there is a learning curve to these procedures. While procurement teams have managed to decrease the WIT for both DP and for the establishment of NRP, questions about how this WIT might be mitigated are under investigation, including whether pretreatment of the patient-donor before or during organ recovery, might mitigate some of the ischemia-reperfusion injury [9▪▪,24]. There are cold, asanguineous machine perfusion platforms which, in the future, might decrease such injury in simultaneously recovered abdominal organs.

There remain substantial social challenges for broader acceptance of DCD for cardiac transplant which stem from debates surrounding procurement methods and whether the use of TA-NRP violates the 'Dead Donor Rule' (DDR). This rule is not a legal standard, but rather the ethical premise of transplantation requires dissociating the death of a person from the procurement of organs and, more specifically, requires that a person must be declared dead before organ recovery/harvest, and stipulates that the removal of vital organs for transplantation will not cause the death of the patient. For declaration of death following circulatory arrest, or cardiac death in some countries even when organ procurement is not a concern, there is a mandatory standoff period ranging from 2–5 min to ensure that neurologic death has also occurred [1,25] (Table 2). This period of standoff does occur with current accepted DCD procurement methods, which satisfies death criteria. Some countries have suggest using formal tests to determine neurologic death after circulatory death, which present challenges themselves as these testing methods were not created for patients supported by ECMO [26].

ETHICAL IMPLICATIONS FOR DONATION AFTER CIRCULATORY DEATH

The controversy surrounding DCD is most acutely felt when the heart is procured for transplantation. In cases of is direct procurement the heart and other organs are removed from the donor body. The ongoing debate about the use of TA-NRP, however, is grounded on the fact that the heart remains in-situ, in the body of the donor. This then brings into discussion different interpretations of the definition and meaning of circulatory death, of whether mechanical circulation within the donor following death nullifies circulatory death, and whether brain necrosis or mortification is a necessary constituent. With TA-NRP, the supra-aortic trunk vessels are clamped prior to the initiation of circulation using an ECMO circuit. The isolation of the cerebral circulation from the perfusion of the rest of the donor has been variably interpreted and is controversial. One stance is that the isolation of these vessels prevents the influx of catecholamines and other vasoactive substances that are released during cerebral ischemia and the Cushing's response; isolation

Table 2. Variations in determination of death in 3 counties using cardiac DCD organs

	Circulatory death		Neurologic death
Australian	Irreversible cessation of circulation of blood in the body of a person		Irreversible cessation of all functions of the brain of a person
United Kingdom	No statutory definition	Requires stand off to ensure neurologic death	
United States	Irreversible cessation of circulatory and respiratory functions		Irreversible cessation of all functions of the entire brain, including the brain stem

DD, donation after circulatory death.

of the cerebral circulation therefore is beneficial for donor organ quality. More commonly, the discussion focuses on whether the prevention cerebral blood flow is a deliberate intent to cause neurologic death, and therefore violates the DDR. Due these concerns, the use of TA-NRP is not globally accepted [27,28▪].

The heart as an organ does not necessarily die with the death of the patient; much of the early discussion about the use of DCD hearts with direct procurement was focused on the restoration of cardiac function in the recipient and whether this 'reanimation' implied that the criteria for circulatory death for the donor was invalid. The role of donor autonomy, and the right to informed refusal of LST, was critical in these early conversations. The intent for the patient was to be a donor, thus withdrawing their LST, while simultaneously hoping that their organs would still be physiologically intact and would function in a recipient. This would be true for thoracic as well as abdominal organs. However, currently, the discussion has focused on the method of organ procurement and with TA-NRP in particularly, whether the reanimation of the heart in the donor negates their circulatory death. Further concerns have been raised about the potential for inequities in both donor and recipient access to these technologies. The publication of the US randomized trial showed that the beneficiaries of DCD organs were more likely to be Black, and their donors, white. This may reassure some over concerns that organ recovery after DCD would further emphasize existing health inequalities however, this is most likely related to the epidemic and demographics of opiate overdoses. Nonetheless, this does highlight the challenges and limitations of the current 2018 UNOS allocation policy and the use of durable versus temporary mechanical circulatory support. As there appear to be clinical similarities in outcomes for DCD, when compared to DBD recipients, the consequences for the heart recipients are reassuring. Whether there are differences in heart recipient survival based on the procurement methods are still to be illuminated. However, the geographic variability of DCD transplantation does create potential inequities. DCD organ procurement cannot occur in free-standing organ procurement facilities as these cannot provide care for patients unlike DBD procurement where the donor has been declared dead prior to transfer to one of these centers.

Additional questions surrounding the method of procurement in the US includes the relative costs of the two most standard methods. Use of NRP has a cost of approximately USD 5000 whereas the use of MP with the OCS system costs approximately USD 38 000. These costs are significant and the question about who will pay for these and whether these options will be equitably available for all potential recipients remains. As the new continuous distribution model for heart allograft allocation is developed, it is unclear whether access to DCD will be included in the algorithm. Patients listed at larger centers, or those with existing abdominal programs that have adopted DCD use will have increased options for listing criteria. Insurance coverage in the US may affect access not only to transplantation in general, but to potential donors.

CONCLUSION

The 1- and 5-year outcomes for recipients of heart recovered from DCD appear to be equivalent to those from DBD [29]. The incorporation of DCD into current programs has certainly increased transplantation rates. As the global experience increases, the ideal donor characteristics and limitations will become clearer. Transplantation as a field relies on public trust and education. It is primarily through the act of anonymous charitable donation that organs become available. Now that there are different methods of organ procurement, is there an obligation to meet the standards of informed consent from family members, or should the discussion with family be an authorization to proceed, governed by different ethical standards? The decision to incorporate DCD organs into a transplant program is complex and is intertwined with factors such as the program size, local or regional views about DCD and DBD and matters of cost, and the interplay between clinical practice, science and medical ethics.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Dhanani S, Hornby L, Ward R, Shemie S. Variability in the determination of death after cardiac arrest: a review of guidelines and statements. J Intensive Care Med 2012; 27:238–252.
2. Thiessen C, Wisel SA, Roll GR. Simultaneous thoracic and abdominal donation after circulatory death organ recovery: the abdominal surgeon's perspective. Curr Opin Organ Transplant 2023; 28:139–144.

3. UNOS data. Available at: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
4. Messer SJ, Axell RG, Colah S, *et al.* Functional assessment and transplantation of the donor heart after circulatory death. J Heart Lung Transplant 2016; 35:1443–1452.
5. Farr M, Truby LK, Lindower J, *et al.* Potential for donation after circulatory death heart transplantation in the United States: retrospective analysis of a limited UNOS dataset. Am J Transplant 2020; 20:525–529.
6. Suarez-Pierre A, Iguidbashian J, Stuart C, *et al.* Appraisal of donation after circulatory death: how far could we expand the heart donor pool? Ann Thorac Surg 2022; 114:676–682.
7. Bernat JL, D'Alessandro AM, Port FK, *et al.* Report of a national conference on donation after cardiac death. Am J Transplant 2006; 6:281–291.
8. Page A, Messer S, Large SR. Heart transplantation from donation after circulatory determined death. Ann Cardiothorac Surg 2018; 7:75–81.
9. Niederberger P, Farine E, Raillard M, *et al.* Heart transplantation with donation
■■ after circulatory death. Circ Heart Fail 2019; 12:e005517.

This paper provides a thorough review of the animal and prelinical studies to improve graft function during warm ischemia.

10. Meredith T, Scheuer S, Hoffman M, *et al.* Coronary angiography of the ex-situ beating donor heart in a portable organ care system. Catheter Cardiovasc Interv 2022; 100:1252–1260.
11. Anthony C, Michel J, Christofi M, *et al.* Ex vivo coronary angiographic evaluation of a beating donor heart. Circulation 2014; 130:e341–e343.
12. Thomas J, Chen Q, Roach A, *et al.* Donation after circulatory death heart procurement strategy impacts utilization and outcomes of concurrently procured abdominal organs. J Heart Lung Transplant 2023; 42:993–1001.
13. Boucek MM, Mashburn C, Dunn SM, *et al.* Pediatric heart transplantation after declaration of cardiocirculatory death. N Engl J Med 2008; 359:709–714.
14. D'Alessandro DA, Wolfe SB, Osho AA, *et al.* Hemodynamic and clinical performance of hearts donated after circulatory death. J Am Coll Cardiol 2022; 80:1314–1326.
15. Kobashigawa J, Zuckermann A, Macdonald P, *et al.* Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant 2014; 33:327–340.
16. Messer S, Cernic S, Page A, *et al.* A 5-year single-center early experience of heart transplantation from donation after circulatory-determined death donors. J Heart Lung Transplant 2020; 39:1463–1475.
17. Chew HC, Iyer A, Connellan M, *et al.* Outcomes of donation after circulatory death heart transplantation in Australia. J Am Coll Cardiol 2019; 73:1447–1459.
18. Schroder JN, Patel CB, DeVore AD, *et al.* Transplantation outcomes with donor hearts after circulatory death. N Engl J Med 2023; 388:2121–2131.
19. Chen Q, Emerson D, Megna D, *et al.* Heart transplantation using donation after circulatory death in the United States. J Thorac Cardiovasc Surg 2023; 165:1849–160; e6.
20. Urban M, Moody M, Lyden E, *et al.* Impact of donation after circulatory death heart transplantation on waitlist outcomes and transplantation activity. Clin Transplant 2023; 37:e14942.
21. Koscik R, Ngai J. Donation after circulatory death: expanding heart transplants. J Cardiothorac Vasc Anesth 2022; 36:3867–3876.
22. Smith DE, Kon ZN, Carillo JA, *et al.* Early experience with donation after circulatory death heart transplantation using normothermic regional perfusion in the United States. J Thorac Cardiovasc Surg 2022; 164:557–568; e1.
23. Dhital KK, Chew HC, Macdonald PS. Donation after circulatory death heart transplantation. Curr Opin Organ Transplant 2017; 22:189–197.
24. Quader M, Toldo S, Chen QH, *et al.* Heart transplantation from donation after circulatory death donors: present and future. J Card Surg 2020; 35:875–885.
25. Bollen JAM, Shaw D, de Wert G, *et al.* Euthanasia through living organ donation: ethical, legal, and medical challenges. J Heart Lung Transplant 2019; 38:111–113.
26. Dalle Ave AL, Shaw DM, Bernat JL. Ethical issues in the use of extracorporeal membrane oxygenation in controlled donation after circulatory determination of death. Am J Transplant 2016; 16:2293–2299.
27. DiChiacchio L, Goodwin ML, Kagawa H, *et al.* Heart transplant and donors after circulatory death: a clinical-preclinical systematic review. J Surg Res 2023; 292:222–233.
28. Kaffka Genaamd Dengler SE, Vervoorn MT, Brouwer M, *et al.* Dilemmas
■ concerning heart procurement in controlled donation after circulatory death. Front Cardiovasc Med 2023; 10:1225543.

This paper provides an international perspective on societal debates and ethical concerns at the center of the DCD discussion.

29. Madan S, Saeed O, Forest SJ, Goldstein DJ, *et al.* Feasibility and potential impact of heart transplantation from adult donors after circulatory death. J Am Coll Cardiol 2022; 79:148–162.