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VIEWPOINT

Applying the ethical framework for donation after circulatory death to thoracic normothermic regional perfusion procedures

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The novel approach of thoracic normothermic regional perfusion (TA-NRP) for in-situ preservation of organs prior to removal presents a new series of ethical questions about donation after circulatory determination of death (DCD) procedures. This manuscript describes the framework used for the analysis of ethical acceptability of DCD donation and analyzes the specific practice of TA-NRP DCD within that framework to demonstrate that TA-NRP DCD can be performed within the ethical boundaries of DCD donation. We argue that TA-NRP DCD organ procurements meet the ethical standards of informed consent, non-maleficence, adherence to the dead donor rule, and irreversibility, and as such, are ethically acceptable. We also describe the potential benefits of TA-NRP DCD procedures that result from higher organ yields and better recipient outcomes. Finally, we call for open and transparent support of TA-NRP DCD by professional organizations as a necessary cornerstone for the advancement of TA-NRP DCD procedures.

KEYWORDS
donors and donation, donors and donation: donation after circulatory death (DCD), ethics, ethics and public policy, organ procurement and allocation

1 | INTRODUCTION

Donation after the circulatory determination of death (DCD) has been steadily increasing in the United States, and currently accounts for about 15% of deceased donors nationwide. Not only are the numbers increasing, but the transplantable organs from DCD donors have extended beyond kidneys and livers to pancreata, lungs, and, most recently, hearts.[1] While DCD heart donation is possible with rapid recovery and transplantation, wider utilization of these organs in the United States has been facilitated by devices that allow procurement teams to evaluate the function of the heart prior to implantation in the recipient.[2] The ability to utilize DCD hearts for transplantation has led some authors to question whether the threshold for irreversible circulatory function is met in these donors given that the circulatory function of the heart is resumed with machine assistance.[3] Further ethical concern has been expressed regarding thoracic normothermic regional perfusion (TA-NRP) procedures that utilize the donor's body and blood vessels to perfuse the abdominal and thoracic organs because of the perception that the donor is being resuscitated after the declaration of death.[4]

Prior to discussing the ethical concerns about TA-NRP DCD donation, it is essential to describe the similarities and differences between standard and TA-NRP DCD procedures. (Table 1) Both procedures begin after the DCD donor has been declared dead and a hands-off period has been observed during which there is no auto-resuscitation. In standard DCD donation, a sternotomy and laparotomy are performed, the aorta is cannulated, and cold perfusion is initiated along with exsanguination of warm blood. In TA-NRP DCD donation, a sternotomy and laparotomy are performed, the brachiocephalic arteries are occluded to prevent reperfusion of the brain, the right atrium and

Abbreviations: ACP, American College of Physicians; DCD, donation after circulatory determination of death; ECMO, extracorporeal membrane oxygenation; TA-NRP, thoracic normothermic regional perfusion.

aorta are cannulated, and normothermic perfusion using an extracorporeal membrane oxygenation (ECMO) pump is initiated.[1]

In April 2021, the American College of Physicians (ACP) published a statement of ethical concerns with controlled TA-NRP DCD donation.[4] In that statement, the four ethical concerns they raise are: (1) whether the cessation of circulatory and respiratory function is irreversible in TA-NRP DCD donors, (2) if expanding DCD donation will disproportionately affect the "stigmatized population already burdened by the nation's substance abuse epidemic," (3) if donor and recipient family members are not made aware of the full details that this protocol involves, this lack of transparency itself could damage trust in health care and clinical research, and (4) whether the alternative of ex situ machine perfusion is ethically acceptable while TA-NRP DCD is not as "there is a large and ethically significant difference between perfusing an organ versus perfusing an individual." In this manuscript, we describe the ethical framework used for the justification of DCD donation and analyze the specific practice of TA-NRP DCD within that framework. Moreover, we specifically address the TA-NRP DCD related concerns raised by the ACP in our analysis.

2 | ETHICAL FRAMEWORK FOR DCD DONATION

The ethical framework for DCD donation relies on the first principles of respect for persons, nonmaleficence, and beneficence.[5,6] The principle of respect for persons, primarily focusing on autonomy, applies to decisions about organ donation as this promotes the legitimate interest of the individual (or their surrogate) in what is done with their body after death. Respect for autonomy through the process of informed consent also applies to decisions about antemortem interventions for the purpose of organ preservation, which are treated as separate from authorization for donation as these interventions occur prior to death and cannot be assumed to be part of the individual's (or surrogate's) authorization for organ donation.[7,8]

In the context of DCD donation, the principle of non-maleficence is used to determine which pre-mortem interventions are acceptable and how comfort care should be conducted. The threshold for deciding that interventions are harmful in the context of DCD donation is that they intentionally hasten death and therefore violate the principle of double effect.[9] Interventions intended to improve organ viability (e.g., heparin administration) are considered acceptable because they are intended to have the good effect of organ preservation while the potential ill effect of hastening death is not intended but merely foreseen as a possibility and is not the direct cause of the good effect.[10] Following the same principle, the provision of comfort care for DCD donors should be aimed at avoiding pain and suffering and should not intentionally hasten or prolong the dying process.[11]

The principle of non-maleficence is also central to the transition from life to death in DCD donation, in that actions considered harmful to a living person (e.g., burial) are not harmful to a corpse. For the purpose of organ donation, the "dead donor rule" requires that a person must be dead prior to the procurement of vital organs for transplantation, and, while often debated, is currently the ethical standard for determining when vital organs can be procured.[10,12–14] According to the dead donor rule, the act of organ procurement cannot occur prior to the death of the patient. The moment when the individual transitions from alive to dead is therefore very important for DCD procedures because the sooner organs can be procured, the more likely they are to be viable for transplantation.[6] In the United States, the legal definition of death was established by the President's Commission for the Determination of Death in 1981 and enacted in 41 states and the District of Columbia as the Uniform Declaration of Death Act.[15,16] This act states that: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead."[16] The term "irreversible" as defined by the President's Commission specifically relates to the function of the organ within the person: "After an organ has lost the ability to *function* within the organism, electrical and metabolic *activity* at the level of individual cells or even groups of cells may continue for a period of time. Unless this cellular activity is organized and directed, however, it cannot contribute to the operation of the organism as a whole." If the vital organ has irreversibly lost its ability to function within the person, the person is dead regardless of whether cells within the organ are dead or if the organ can function within a different person through the act of transplantation.

If a potential DCD donor meets the ethical threshold of respect for persons, is declared dead by medically accepted criteria, and the principle of non-maleficence is followed, the next ethical principle that must be considered is beneficence, which requires maximizing the benefits and minimizing the risks of medical interventions. In the setting of donation, either living or deceased, the principle of beneficence is generally applied to the recipient(s) of the donation. Interventions that increase the quantity of organs that can be utilized for transplantation or the quality of those organs are in line with the principle of beneficence.

3 | DOES NORMOTHERMIC REGIONAL PERFUSION MEET THE ETHICAL STANDARDS OF DCD DONATION?

3.1 | Respect for persons

In DCD donation, while the decision to donate may have been made by the potential donor, a surrogate must consent to any pre-mortem interventions (e.g., heparin administration, additional testing, additional procedures) that are done for the purpose of organ donation while the potential donor is still alive if no longer competent.[10] TA-NRP DCD does not require any additional pre-mortem interventions beyond those required for standard DCD because central cannulation and machine perfusion are performed after confirmation of the patient's death as part of the organ procurement procedure.

While a different authorization process beyond the standard DCD authorization process is not needed for TA-NRP DCD donation,

TABLE 1 Comparison between TA-NRP DCD and standard DCD procedures

	Standard DCD donation	TA-NRP DCD donation
Authorization and informed consent	Authorization for organ donation can be either first person or surrogate decision Informed consent from a surrogate is needed for ante-mortem interventions	Authorization for organ donation can be either first person or surrogate decision Informed consent from a surrogate is needed for ante-mortem interventions
Disclosure of information about the procurement procedure	After the patient is declared dead and a hands-off period has been observed, the procurement team proceeds with sternotomy and laparotomy, rapid cannulation, cold flush and exsanguination of blood. Cold perfusate is circulated to the organs for the purpose of organ preservation. The heart is restarted on a machine outside of the body	After the patient is declared dead and a hands-off period has been observed, the procurement team proceeds with sternotomy and laparotomy, clamping of brachiocephalic vessels to avoid reperfusion of the brain, rapid cannulation, and initiation of normothermic regional perfusion. Warm oxygenated blood is circulated to the organs and the heart is restarted in the body, all of which is done for the purpose of organ donation and does not resuscitate the person
Declaration of death	Based on cardio-pulmonary criteria and confirmed by the absence of autoresuscitation during the hands-off period	Based on cardio-pulmonary criteria and confirmed by the absence of autoresuscitation during the hands-off period
What happens to the brain	Neuronal hypoxemia and ischemia progress unimpeded as cold perfusion does not reperfuse the brain	Neuronal hypoxemia and ischemia progress unimpeded as clamping the brachiocephalic vessels prevents oxygenated blood from reperfusing the brain
Operative procedure	Laparotomy and sternotomy, rapid cannulation of the aorta, initiation of cold perfusion to the thoracoabdominal organs, exsanguination of warm blood and organ removal	Laparotomy and sternotomy, clamping of the brachiocephalic vessels, rapid cannulation of the aorta, initiation of normothermic perfusion to the thoracoabdominal organs, warm dissection, abdominal cannulation, cold perfusion and organ removal
Cardiac reanimation	The heart is removed from the donor and restarted on a machine that circulates oxygenated blood through a circuit	The heart is restarted in the donor's body with the assistance of the NRP circuit which circulates oxygenated blood to the thoraco-abdominal organs

we agree with the ACP that the plan to pursue TA-NRP DCD should be disclosed and explained as part of the information provided about DCD donation to the donor's family just as the process of rapid cannulation and cooling should be described to the family for a standard DCD donor. Transparency regarding the process is needed to allow the family to decide based on complete disclosure of information as well as to maintain public trust in organ donation.

3.2 | Avoiding harm to persons

The principle of non-maleficence applied to pre-mortem interventions requires that they are not intended to hasten death and that explicit first person or surrogate informed consent has been provided. With respect to pre-mortem management and interventions, the process for TA-NRP DCD is the same as for a standard DCD donor; heparin is administered prior to the withdrawal of life-sustaining treatment, and comfort care is provided per protocol.

3.3 | The dead donor rule, irreversibility, and interventions on a corpse

Because the organ procurement procedure starts immediately after the confirmation of death in DCD donation, either standard or TA-NRP, it is essential that death is accurately diagnosed and confirmed to adhere to the dead donor rule. In the United States, death is determined either by circulatory and respiratory function *or* neurologic criteria, and for the purposes of DCD donation, the determination of death is by the cessation of circulatory and respiratory function. There is no difference in the process for determination of death in standard DCD donation versus TA-NRP DCD donation. Death is determined by a provider who is not a part of the procurement team using accepted medical criteria and confirmed after a pre-defined hands-off period. The purpose of the hands-off period is to confirm that auto-resuscitation does not occur and that cessation of circulatory function is irreversible. At this point, the circulatory and respiratory function of the organs are no longer coordinated to contribute to the organism as a whole, fulfilling the requirement for irreversibility as defined by the President's commission.[15]

In the assessment of TA-NRP DCD by the ACP, the authors state the donor's chest is opened *after the determination of circulatory death* and various techniques are used to prevent cerebral reperfusion and "bring on brain death." As stated above, the donor's chest is opened at the exact same time as a standard DCD donor procurement—after the hand's off period and confirmation of death—so there is no difference in that step of the TA-NRP DCD as compared to standard DCD. This part of the ACP assessment of TA-NRP DCD procurement suggests that circulatory death and brain death are different entities and that one can be declared dead twice in two different ways. This argument is not consistent with the legal definition of death, which is either cardio-respiratory criteria or neurologic criteria. Moreover,

in framing the act of excluding cerebral circulation as "bringing on brain death" the ACP is implying that circulatory death is not death, which brings the entire practice of DCD donation, as well as the legal definition of death in the United States, into question.

The correct characterization of the TA-NRP DCD process is that the donor is dead at the time of procurement, and the exclusion of cerebral perfusion ensures that there is no artificial reanimation of brain function, which some could find ethically problematic.[6] The action of excluding the cerebral circulation occurs after death, and so it cannot not "bring on death." Rather, the purpose is to ensure that the organ procurement procedure does not contravene the wishes of the individual or their surrogate who has chosen to stop all life-sustaining treatments and has put a do-not-resuscitate (DNR) order in place. Clamping the cerebral vessels eliminates any suggestion that artificial resuscitation of the brain is possible with TA-NRP DCD organ procurement and ensures unhindered progression to complete cessation of brain function, which is also what happens after cold perfusion in the standard DCD donor.[2]

The concept of irreversibility for a standard DCD donor is limited to the confirmation of death and assurance that auto-resuscitation does not occur after the initial pronouncement of death. Irreversibility as a condition of DCD organ procurement as well as the declaration of death is intended to ensure that the potential donor does not naturally regain coordinated circulatory and respiratory function. In the analysis of TA-NRP DCD ethics by the ACP, the authors claim that the concept of irreversibility in TA-NRP DCD extends beyond the confirmation of death and into the procurement procedure during which ECMO is initiated to restore perfusion and the circulatory function of the heart. They specifically claim that when the donor is put on NRP, the person is "successfully resuscitated." Restoring the circulatory function of the heart though an ECMO circuit is not auto-resuscitation or even resuscitation of the person. In fact, the position articulated in the ACP statement undermines the donor's specific intention to be a donor and *not* to have his or her life prolonged by artificial means. The ECMO circuit is used in TA-NRP DCD procurements to provide mechanically assisted circulation to maintain perfusion and oxygenation of organs for transplantation. Therefore, to claim that placing the donor on ECMO reverses the cessation of the donor's circulatory function in a way that challenges the principle of irreversibility is false. When a standard cardiac DCD procedure is performed, the heart is removed from the body and put on a machine, restarted and circulates blood and perfusate through the machine. While there is an optical difference between the circulatory function of the heart being restored within the corpse rather than outside of the body, there is no ethical difference. In either a standard or TA-NRP DCD, the heart's circulatory function can be restored for the purpose of donation after the patient's circulation stops, and that restoration is not the result of an auto-resuscitation but rather the result of mechanical assistance that occurs only after the patient is confirmed to be dead.

To summarize, TA-NRP DCD donation meets the necessary ethical thresholds of both the dead donor rule and irreversible cessation of circulatory and respiratory function of the donor. The donor must be declared dead and confirmed dead prior to the procurement operation as with a standard DCD donor, thereby fulfilling the requirements of the dead donor rule. The circulatory and respiratory function of the donor is irreversible by natural means, confirmed by the absence of auto-resuscitation, prior to the commencement of the TA-NRP DCD procurement procedure. The utilization of the donor's blood vessels and an ECMO machine to temporarily provide circulation to maintain the viability of donor organs prior to retrieval is not an act of resuscitation of the donor, but rather an act of organ preservation, which the donor or surrogate intended. More simply stated, NRP does not resuscitate the patient. Clamping and therefore excluding the cerebral circulation avoids the act of resuscitation in a deceased individual with a DNR order.

The ACP concludes their ethical analysis of TA-NRP DCD by stating that there is a "large and ethically significant difference between perfusing an organ and perfusing an individual." We agree and emphasize that TA-NRP DCD perfuses *organs* but not an individual. It perfuses organs using an ECMO circuit that utilizes the blood vessels of a deceased person to circulate machine-oxygenated blood. The alternative action of restarting the heart on a machine located outside of the body does not ethically differentiate TA-NRP DCD from standard cardiac DCD, as there is an external machine in both scenarios and the circulatory function of the heart as an organ is restored for the purpose of transplantation, not resuscitation. In either TA-NRP DCD or standard DCD, perfusion of oxygenated blood to the brain naturally stops at the time of death and is not restored during the procurement procedure. Therefore, we refute the claim that there is an ethical difference between TA-NRP DCD procurement and a standard DCD procurement procedures.

3.4 | Maximizing benefits and minimizing risks

We have demonstrated that TA-NRP DCD organ procurements meet the ethical standards of informed consent/authorization, non-maleficence, adherence to the dead donor rule and irreversibility so they are, at minimum, ethically acceptable. If TA-NRP DCD donation provides an opportunity for the procurement of more, and possibly, better quality donor organs, then the benefit of this type of organ donation is greater and TA-NRP DCD has the possibility of enhancing the benefit of more lives saved from organ donation.[17,18]

The ACP concern that expanding DCD donation with TA-NRP will disproportionately affect the "stigmatized population already burdened by the nation's substance abuse epidemic," while not specific to TA-NRP DCD but rather to DCD donation as a whole, is an important consideration. Because many of the conditions that result in DCD donation are not individually predictable or controllable (e.g., trauma, drug overdose, stroke), the ability of the individual patient to consent to pre-mortem interventions or authorize DCD donation has been lost. Therefore, consent for pre-mortem interventions and authorization for organ donation by family members or surrogates must remain a cornerstone of DCD donation. Second, there need to be policies in place that allow organ procurement organizations

to approach all potential donor families given that organ donation is often seen as something positive that comes from the loss of a loved one. Rather than negatively impacting a stigmatized population, giving more families the option of organ donation using TA-NRP may provide more opportunities for closure and healing in a time of tragedy.

4 | CONCLUSION

After being introduced in the United States, the TA-NRP DCD procedure has come under ethical scrutiny because of the act of initiating ECMO after the donor has died and restoring the circulatory capacity of the heart in the deceased donor's body. In this manuscript, we provide a comprehensive analysis that supports the ethical acceptability of TA-NRP DCD using the standard framework for ethical evaluation of DCD donation. It is essential that the thoracic and abdominal transplant community lead the way in developing statements that confirm the ethical acceptability of TA-NRP DCD so as to openly and transparently support this advancement in organ procurement, giving potential DCD donors a greater opportunity to fulfill their wishes to be organ donors and increasing the number of lives saved through organ transplantation.

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