

Toward Transparency and Trust: Assessing and Addressing Key Ethical Concerns in Normothermic Regional Perfusion

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Abstract: Normothermic Regional Perfusion, or NRP, is a method of donated organ reperfusion using cardiopulmonary bypass or a modified extracorporeal membrane oxygenation (ECMO) circuit after circulatory death while leaving organs in the dead donor's corpse. Despite its potential, several key ethical issues remain unaddressed by this technology.

In a landscape where demand for transplantable organs far exceeds the supply, novel technologies, expanded donor criteria, and innovative procedures inevitably emerge. Donations after circulatory death (DCD), and not just after brain death, require machine perfusion technology to support donated organs outside of the body prior to implantation in the recipient. More recently, normothermic regional perfusion (NRP) has been proposed and piloted to further expand the capacity for DCD transplants. The literature provides examples of successful NRP use and commentary on the permissibility of such

protocols, yet significant operational and ethical questions remain.¹ In order for NRP to not erode transparency and trust in the US transplant system, additional ethical analysis is needed, and additional study and process protections need to be instituted. Here, we briefly review existing NRP experience outcomes and key ethical and policy concerns that must be considered when developing and implementing NRP policies and procedures. Table 1 outlines key terminology crucial for discussing ethical and policy dimensions of the technology.

NRP and its Potential?

When a prospective organ donor suffers a severe injury short of brain death, and families or decision makers decide to discontinue life sustaining interventions, organ donation must follow a structured protocol referred to as “controlled donation after circulatory death (cDCD),” a recent and widely accepted means of organ donation. In standard practice of cDCD, organ procurement teams wait a fixed observational period after cardiac arrest to ensure cessation of circulation and confirmation of circulatory death. Then, surgeons carefully remove donatable organs from the donor's body and stabilize until implantation into a recipient.

NRP minimizes organ damage associated with prolonged explant-

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tation by instead maintaining the donated organ within the dead donor's body and connecting to oxygenating bypass machines. It can be applied to the entire thoraco-abdominal region (TA-NRP) or restricted

applications.⁴ Nevertheless, in Spain, Italy, and France, NRP remains limited to abdominal organs. In contrast, TA-NRP has been utilized in the UK, where, for instance, Royal Papworth Hospital reported a 48% increase in

cerebral perfusion blocking efficacy. If blood flow were not completely ceased, the death determination would be in question. In response, some are attempting to refine protocols to ensure permanence of neurological death.⁸ Others have proposed implementing a brief neurological evaluation to confirm that the patient is dead by both cardiac and neurological criteria, which would establish a new "doubly dead" standard. Thus, despite initial promising outcomes, TA-NRP remains especially controversial, with many programs opting to use alternative procurement methods, avoiding reperfusion of the heart, or NRP altogether, and opting for ex-situ machine perfusion after cDCD.

Below, we outline several key ethical considerations that must be addressed if transplant-capable institutions intend to implement NRP routinely. Without answers to these critical questions, transparency and trust in the US transplant system could easily erode.

The Importance of Words

Prior to addressing the content of key ethical considerations in NRP, it is essential to first attend to the language surrounding it. For instance, what might the term "reanimation," a common term to describe NRP, imply that may differ from, say, "in situ tissue perfusion?" The first is

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to the abdominal region (A-NRP). In either case, blood flow to cerebral arteries is intentionally obstructed. Thus, by retaining prior circulatory systems, NRP minimizes transplantable organ ischemia, thereby improving tissue viability.²

In France and Italy, NRP emerged in response to post-DCD-death observation periods closer to 20 minutes, much longer than the US's typical 5-minute rule.³ As NRP grew, experience from Spain demonstrated the ability to use more livers from older DCD donors with fewer com-

heart transplant activity. Their 5-year study demonstrated outcomes with DCD/TA-NRP comparable to brain-death donations, overcoming prior DCD ischemic complications.⁵ US studies have shown similar results, with success in both A-NRP and TA-NRP.⁶

In the UK, TA-NRP's permissibility hinges on the assumption that there is no restoration of cerebral perfusion.⁷ Yet, concern about that specific provision prompted officials in the UK to temporarily pause, pending further investigation into

Table 1

Key Terminology in the Ethics of Normothermic Regional Perfusion

NRP, Normothermic Regional Perfusion	The reperfusion of organs while still inside the donor body
DCD, Donation after Circulatory Death	Organ donation occurring after the donor succumbs to severe injury resulting in irreversible cessation of circulatory or respiratory function
cDCD, Controlled Donation after Circulatory Death	Donation after circulatory death occurring after the controlled withdrawal of life sustaining therapy
DBD, Donation after Brain Death	Organ donation after the donor is pronounced dead by neurological criteria
OPO, Organ Procurement Organization	Not-for-profit organizations responsible for recovering organs from deceased donors for transplantation in the U.S.
ORC, Organ Recovery Center	A non-hospital center for transplant management and practice
DDR, Dead Donor Rule	States that organs may only be donated after the donor is dead and the procurement team may not hasten the death of the donor
UDDA, Uniform Determination of Death Act	Defines the conditions for a death determination to be made, in both DBD and DCD cases

imprecise and suggests something almost miraculous, while the second seems like technical jargon intended to obfuscate. That same attentiveness is crucial in a range of discussions in the transplant landscape. For instance, while some might equate “death by neurological criteria” as “brain death,” the latter is oversimplified, and implies it is a unique form of “death.” The modifiers “artificial” or “mechanical” or “harvest” or “recover” similarly inflect a certain mood that can too easily smuggle in value judgments about a specific behavior or technology without defining or stipulating terms. For example, when discussing NRP, one should avoid referring to it as a therapy since it supports organ retrieval, not the donor’s recovery. At the same time, such conversations must include the specifics of procedures as part of the donation consent process.

The struggle to use words to advance greater understanding and not just advance one’s own position speaks to the importance of investing in high-quality deliberation about the ethical issues raised by NRP. Such a commitment must acknowledge NRP’s potential to accelerate transplant capacity, while also acknowledging that just because we *can* does not mean we *should*. In this setting, the emergence of NRP places a moral responsibility on institutions to discuss, engage in, and address lingering ethical questions across a range of issues, which we outline below.

Key Ethical Considerations

Stewardship of Donor Bodies in cDCD and NRP

Donor bodies deserve respect, a respect derivative of the principle of respect for persons. And at the same time, all of transplantation necessarily focusses on transplantability considerations, including pragmatic ethical considerations intended to be utility-maximizing. This respect-utility tension plays out with the bodies of those declared dead by neurological criteria (brain death) and persists until the donated organ(s) leave the donor’s body. The longer transplantable organs exist in a body declared dead, the longer that respect-utility

tension hovers over the transplant process. NRP heightens an existing tension already present in transplantation — between respecting donor bodies and maximizing transplantability, particularly when transferring a living patient out of the hospital setting contemplated for the sole purpose of cDCD with NRP.

The emergence of Organ Recovery Centers (ORC) highlights that tension. These free-standing centers exist to facilitate efficiency in and availability of transplantation, a move supported by a recent National Academies recommendation that each Organ Procurement Organization (OPO) establish their own organ recovery centers. Transferring a dying or deceased patient for the sole purpose of efficient organ donation creates its own unique, ethical challenges. What safeguards will guide the care of bodies to ensure they are managed with respect? Will there be consent for transfer? This may be critical, as transferring a potential organ donor to a separate facility can have implications for the donor’s family and loved ones. Are the ethics of transfer different for cDCD, cDCD with NRP, or Donation after Brain-Death (DBD)? Will there be transparency with respect to clinical outcomes of ORCs? Will organ donors or their surrogates have agency in determining where the organ procurement will take place, particularly if there are differences in outcomes between ORCs? This ethical tension between respect and utility cannot be ignored and must be addressed proactively and robustly.

Professional Norms Regarding Hastening Death and Maintaining Bodies of the Dead

The active role of surgeons and other healthcare professionals is central to high-integrity healthcare and no less so in transplant. However, NRP challenges the scope of professional norms by expanding surgeon, nurse, and perfusionist involvement in how they engage a dead person’s body. For example, when organ procurement surgeons block blood flow to the brain, they intentionally occlude cerebral perfusion. In doing so, they

are actively engaging in keeping a dead person (declared so by cDCD) neurologically dead. This “keeping dead” role introduces questions about the moral agency of procurement surgeons that seem at odds with a fundamental distinction between hastening death and letting die that is central to medicine’s morals.

Animal research suggests this is not a trivial concern. A study addressing the effect of clamping aortic arch vessels for NRP in porcine models suggests that reperfusion of the brain following circulatory death leads to brain activity, but clamping the arch vessels ensures permanent cessation of brain function, burdening the surgeon with an obligation to actively maintain brain death.⁹ The procuring surgeon’s role in preventing cerebral reperfusion raises questions about the surgeon’s complicity with the death of the donor’s brain, which may not be irreversibly damaged at the time of cardiac arrest.

This expansion of traditional notions of professional norms extends into the roles of nurses and perfusionists who would be called upon to “care for” bodies of dead donors to provide resources for organ recipients, not to heal the body in front of them. Thus, logistical aspects of NRP test the professional norms of healthcare providers and challenge protections implied in the Uniform Declaration of Death Act, including the Dead Donor Rule.

Uncertainties of Death Determination

Determinations of death, even under cDCD, can be complicated. Families can be very invested in their choice to donate. But unlike brain death, DCD requires that a donor’s heart stops spontaneously. And at times, families can wait up to 90 minutes for their loved one to die. And if then life does not end, they must ask, “What’s next?” creating a situation in which families may suffer more.

The ethical permissibility of organ transplantation relies on agreed upon norms included in the Uniform Determination of Death Act (UDDA), especially the Dead Donor Rule (DDR). The DDR commits to

not harvest organs from a living person. That agreed upon protection limits what can be done to a donor before the time of death even for the sake of saving another life. This safeguard, aimed at limiting the use of human beings as mere means, protects still living patients from the utility-promoting ends of transplant teams and society. NRP introduces uncertainty in death determination by mechanically reversing part of the very circulatory system that, minutes earlier, was determined to be “irreversibly” ended (cDCD). These uncertainties relate to what we mean by irreversibility.

Central to the DDR is the concept of irreversibility. We take organs from the corpses of dead people only when we are sure they are clinically dead. The President’s Commission on Death Determination defined circulatory death as “irreversible absence of circulation and respiration” and the UDDA adds that “a determination of death must be made in accordance with accepted medical standards.”¹⁰ The American Society of Anesthesiologists recently defined irreversibility as “persistent cessation of function during an appropriate period of observation” which occurs when “respiration and circulation has ceased, and cardiopulmonary function *will not resume spontaneously*.” This interpretation of irreversibility is a way to be more confident that a cardiorespiratory death is “permanent.”¹¹ Equating irreversibility and permanence, then, the 5-minute observation period after cardiac arrest in cDCD is crucial also for NRP acceptability under the DDR. But NRP does reverse regional circulation, undermining any reasonable claim to permanence.

In practice, irreversibility is both important and imprecise as a criterion. If we decided to move forward with NRP and preserve the DDR, significant thought and care would need to go into whether and how to preserve some notion of “irreversibility.” Without it, the DDR may not survive, and the safeguards it intends to establish would erode. Without further work on defining irreversibility and revisiting “accepted medical

standards” outlined in the UDDA, a fragile public consensus on the permissible conditions for organ donation may crumble and mistrust will propagate.

Economic Priorities and Distributive Justice

None of this discussion can avoid economic realities and concerns for distributive justice. Utilizing NRP will result in the expansion of transplant program capacity and staffing. While NRP may cost less than machine perfusion, establishing it requires significant institutional and personnel resources to sustain.¹² How would an organization determine if further investment in this kind of transplant programming might be prudent to pursue? Is there a mathematical limit on the extent of resources institutions ought to devote to transplantation versus other worthy causes, such as prevention of end stage disease in the community? Moreover, in a time of staffing shortages, how many perfusionists and nurses ought to be deployed to care for dead bodies when the living need care? Does the analysis change when one considers how many potential organ recipients might benefit from this effort? These questions may not have clear answers, but we should at least be willing to assess the impact of NRP on these real economic and distributive justice considerations.

Cultural Assumptions and Biases Surrounding Death Determination

Deep life-and-death cultural assumptions surround transplantation. Many cultures see the heart as central to the person and their identity. Others locate the seat of the person in the psyche or brain. TA-NRP may be avoided to reduce harm to those who view the heart as central to an individual and are distressed by the cultural significance of a beating heart, but this does not begin to address the broader cultural and philosophical implications of implementing NRP. Notions of human nature are as varied as the cultures of the world. What if NRP applied only to the abdominal region somehow privileged or revitalized the life of a person whose culture

located the seat of their identity in the gut, kidneys, liver, or pancreas? For such groups, normalizing of NRP, even in the limited scope of A-NRP, would constitute a kind of reversal of death. Though such a concern seems hypothetical, it raises the possibility that we might bring our cultural biases to different determinations in the DCD/NRP process that could be morally problematic and inattentive to the depths of moral diversity in transplantation. In a way, NRP, as currently practiced, codifies the Western-centric notion of brain and/or heart as the life-and-person-defining center of the embodied person. Implicitly imposing this bias on patients and families from other cultural traditions could be problematic.

Trust and the Role of Community Voices

With these ethical considerations swirling around NRP and DCD, it is no wonder that maintaining trust in the transplant system and engaging community voices in doing so becomes so important.

Maintaining and bolstering trust requires transparency. Thus, how clinical teams speak about NRP is crucial, reemphasizing the need for non-pejorative descriptive language for family members including not describing NRP as therapy or care.¹³ NRP is only worth exploring if long-term trust in a high-integrity transplant system can be ensured.

While NRP addresses a need for additional organs, that need cannot trump respect for donor lives and the diverse community voices from which donors come. Without community perspectives, it is not possible to understand how implementation of the practice might cause harm to already grieving families, or whether donors would authorize such a procurement procedure in the first place. On the other hand, widespread acknowledgement of promising transplant outcomes following NRP could lead to special requests for the procedure out of a desire to make the greatest impact possible as a donor. Adopting NRP as an option for DCD organ procurement raises questions about the validity and significance of

advance authorization, the involvement of surrogates in the decision-making process, and broadly, who gets to decide the appropriateness of procurement procedures. Even still, these concerns only address the donor's perspective. A recipient of an NRP-procured organ may have their own concerns about equitable allocation of such organs and moral qualms about the acquisition procedure. Attending to community voices and developing policies and procedures that are responsive to voiced concerns should engender high-integrity transplant systems and engender trust.

Toward Transparency and Trust: Caution, Self-Assessment, Due Process, and Safeguards

NRP program implementation requires due process, principally through policies and procedures that aim to minimize risk, improve quality, foster trust, and encourage safeguards in the presence of uncertainty. NRP implementation attempts without transparent policies, ongoing monitoring, and evaluation pose significant risk. These alone will not eliminate the hard ethical tensions described here, but will, at a minimum, position institutions to self-assess in a rigorous and prospective manner. That entails national policy efforts to devise and implement a definition of irreversibility that is meaningful and trust-promoting and limiting NRP transplants to IRB-approved research protocols that offer independent review and provide ample time to further assess local and regional community perspectives, monitor for harms, and confirm putative clinical transplant benefits. Additionally, assessing the impact of NRP implementation on moral distress and staffing will be crucial.

Exploring the genuine promise of NRP as a means for increasing the supply of transplantable organs also requires diligent consideration of unanswered ethical questions summarized here, promoting respect for donors and their bodies to foster community trust in the transplant system.

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