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Paving the Road for the Adoption of Normothermic Regional Perfusion in Canada

ABSTRACT: Donation after circulatory determination of death has increased the number of organs available but can result in worse recipient outcomes than organs recovered from donors after neurologic death. Normothermic regional perfusion is a novel tool that can circumvent the shortcomings of donation after circulatory determination of death. However, its implementation may pose a threat to existing laws surrounding death declaration. Here, we propose a research agenda that will allow this technology to be introduced within current Canadian organ donation frameworks.

KEY WORDS: cardiac death; determination of death; extracorporeal membrane oxygenation; organ donation; transplantation

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THE POTENTIAL IMPACT OF NORMOTHERMIC REGIONAL PERFUSION

Donation after circulatory determination of death (DCDD) has increased the number of available organs and shortened the transplant waiting list (1). However, organs transplanted from DCDD donors can result in worse recipient outcomes than organs from neurologically deceased donors due to warm ischemia (ischemia that occurs during the dying process in DCDD) (2). For organs that are sensitive to ischemic injury, including the liver and heart, there is an urgent need to adopt innovative practices that improve outcomes in DCDD organ recipients.

In some jurisdictions (e.g., United Kingdom and Spain), but not all (e.g., Australia), *in situ* perfusion technologies like normothermic regional perfusion (NRP) have been used to reverse ischemic injury sustained during the dying process in DCDD donors. By selectively reperfusing abdominal or thoracic organs with oxygenated blood after circulatory determination of death (3), NRP has increased organ utilization (including grafts from marginal donors), improved graft outcomes, and enabled heart transplantation after DCDD (4, 5). However, in the absence of data from randomized trials, it remains unclear whether NRP is superior to usual DCDD care or *ex situ* perfusion systems. Furthermore, the widespread adoption of NRP is also challenged by ethical and legal concerns, as resumption of “any” circulation may violate existing laws.

Anticipated adoption of NRP in Canada provides a unique opportunity to evaluate its efficacy and associated ethical, legal, and social concerns within the confines of well-designed research studies. In this commentary, we review the differences between NRP techniques, the challenges of implementing NRP within Canada’s organ donation framework, and the knowledge gaps that we need to address prior to adopting this technology.

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AN OVERVIEW OF NORMOTHERMIC REGIONAL PERFUSION

There are two types of NRP: abdominal NRP (A-NRP) and thoracoabdominal NRP (TA-NRP). A-NRP supports the liver, kidney, and pancreas, whereas TA-NRP supports the heart, lungs, and abdominal organs. In A-NRP, cannulas are inserted either into the iliac artery and vein or into the abdominal aorta and inferior vena cava, whereas the thoracic aorta is occluded at the level of the diaphragm. In TA-NRP, the cannulas are placed in the right atrium and the iliac artery or abdominal aorta (6). A critical anatomic difference exists between these two NRP modalities: A-NRP excludes blood flow into the thoracic aorta but TA-NRP does not. This distinction raises two issues: 1) reperfusion of coronary circulation in TA-NRP results in resumption of spontaneous cardiac function and 2) perfusion to thoracic cavity may result in collateral circulation to the brain. As a result, A-NRP and TA-NRP differ in the ethical and legal challenges they pose.

IMPLICATIONS OF TA-NRP AND A-NRP FOR DEATH DETERMINATION

Restoring blood flow to the thoracic aorta results in reperfusion of the heart and coronary circulation, which enables resumption of spontaneous cardiac activity. TA-NRP, therefore, restores blood flow independent of the extracorporeal circuit. In jurisdictions where the determination of death is based on cardiac arrest, this phenomenon would vitiate death determination. Even jurisdictions where determination of death is based on circulatory arrest and not cardiac arrest are not spared; resumption of circulation in both TA-NRP and A-NRP would contradict the requirement for permanent cessation of circulation (7). However, the resumption of spontaneous cardiac activity and pulsatile blood pressure with TA-NRP may be perceived by stakeholders as a more egregious violation of death determination. Although parsing the nuances in how we define circulatory death will be paramount to the adoption of NRP, development of unified criteria for the determination of death that are based on permanent brain arrest may circumvent these challenges altogether (8).

IMPLICATIONS OF TA-NRP AND A-NRP ON BRAIN REPERFUSION

Surgical techniques such as ligation of the aortic arch vessels in TA-NRP or occlusion of the distal thoracic

aorta in A-NRP are performed to prevent brain reperfusion and potential resumption of brain function (6). Despite these surgical techniques, there is still potential for restoring brain circulation through collaterals via internal thoracic, intercostal, inferior epigastric, and anterior spinal arteries (9). Resumption of circulation to the brain by TA- and A-NRP would violate the dead-donor rule in the event that brain function is restored (10).

Unlike TA-NRP, A-NRP excludes the thoracic aorta from the extracorporeal circuit, preventing collateral flow via the internal thoracic, intercostal, and thoracic spinal arteries. Surgical techniques, such as selective cannulation of the aorta and inferior vena cava as well as manual transection of the lumbar collaterals, eliminate the possibility of collateral flow via the inferior epigastric and lumbar arteries, respectively. Although neither technique “definitively” rules out the possibility of brain reperfusion, A-NRP is the safer modality in this respect.

IMPLEMENTATION OF NRP: FUTURE DIRECTIONS

We contend that, compared with TA-NRP, A-NRP is better suited for research implementation both in terms of upholding ethical and legal DCDD standards, and potentially improving the quantity and quality of recovered organs. With appropriate safeguards, A-NRP also minimizes the risk of brain reperfusion. Although A-NRP does not obviate the need for TA-NRP (especially for heart and lung donation), we can leverage A-NRP as a platform to conduct research that can pave the road for the adoption of both A-NRP and TA-NRP. We propose the following research agenda to advance NRP implementation:

- 1) Neuromonitoring to exclude brain reanimation: Given the risk of brain reperfusion, we require a neuromonitoring strategy to ensure no resumption of brain blood flow, perfusion, and function during NRP. Specifically, we must determine the appropriate monitoring modalities (with respect to diagnostic accuracy, reliability, and scalability) for monitoring cerebral blood flow, perfusion, and function when a donor is placed on NRP. Then, we must integrate these modalities into neuromonitoring protocols that can be implemented at institutions participating in A-NRP. Finally, the neuromonitoring protocols must be piloted for feasibility and be used to generate “negative control” data in neurologically deceased donors and A-NRP donors. Here, A-NRP fosters an ideal environment to vet the optimal neuromonitoring strategy given its lower risk of brain

reperfusion; this can inform neuromonitoring protocols for future TA-NRP implementation.

- 2) Stakeholder perspectives regarding NRP: NRP is a novel technology, and its integration will depend on its acceptability to all stakeholders. Initial consultations with the public and healthcare providers suggest that there is broad support for the implementation of TA-NRP (11, 12), with ongoing work that will explore the associated challenges with more granularity (13). Implementation of A-NRP research protocols will provide an opportunity to acquaint stakeholders with NRP and “directly” explore how this technology impacts them. Furthermore, the implementation of A-NRP research programs would foster interdisciplinary collaboration and facilitate conceptual, mixed-methods, and qualitative study of important ethical, legal, and practical issues that affect donation and transplantation practice. This work will lay the foundation for similar research with TA-NRP.
- 3) Unified brain-based death definition and determination: Resumption of spontaneous cardiac activity and circulation in TA-NRP challenges the permanent cessation of circulation criterion underpinning the determination of death. An important step in addressing this challenge is the ongoing development of unified criteria for the determination of death based on defining death as permanent brain arrest secondary to cessation of brain perfusion (8). Data on perimortem neurophysiology from A-NRP research protocols will be critical to informing ongoing and future ethical, legal, and practical debates in this field.

NRP has enormous potential to enhance current organ donation practices. First, by reversing the effects of warm ischemia on organs, NRP can increase the number and quality of organs available for donation. Second, it serves to uphold the autonomy of the organ donor in ensuring that her or his wish to donate is fulfilled and leads to best outcome for the recipient. As we move toward NRP adoption, we must ensure that this promising technology does not undermine the public and professional trust that forms the bedrock of our system of voluntary organ donation. For this reason, we propose that A-NRP adoption should precede TA-NRP under the auspices of a research agenda set forth by provincial and federal jurisdictions. A-NRP will provide a framework to systematically study and address what are otherwise daunting ethical and legal challenges, thereby paving the road for safe adoption of NRP practices in Canada.

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All opinions expressed in this editorial are their own.

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REFERENCES

1. Canadian Organ Replacement Register. e-Statistics on Organ Transplants, Waiting Lists and Donors. 2020. Available at: <https://www.cihi.ca/en/e-statistics-on-organ-transplants-waiting-lists-and-donors>. Accessed March 1, 2020
2. Hernandez-Alejandro R, Wall W, Jevnikar A, et al: Organ donation after cardiac death: Donor and recipient outcomes after the first three years of the Ontario experience. *Can J Anaesth* 2011; 58:599–605
3. Hessheimer AJ, García-Valdecasas JC, Fondevila C: Abdominal regional in-situ perfusion in donation after circulatory determination of death donors. *Curr Opin Organ Transplant* 2016; 21:322–328
4. Shapey IM, Muijsan P: Regional perfusion by extracorporeal membrane oxygenation of abdominal organs from donors after circulatory death: A systematic review. *Liver Transpl* 2013; 19:1292–1303
5. Tchan-Sato V, Ledoux D, Detry O, et al: Successful clinical transplantation of hearts donated after circulatory death using normothermic regional perfusion. *J Heart Lung Transplant* 2019; 38:593–598
6. Manara A, Shemie SD, Large S, et al: Maintaining the permanence principle for death during in situ normothermic regional perfusion for donation after circulatory death organ recovery:

- A United Kingdom and Canadian proposal. *Am J Transplant* 2020; 20:2017–2025
7. Shemie SD, Baker AJ, Knoll G, et al: National recommendations for donation after cardiocirculatory death in Canada: Donation after cardiocirculatory death in Canada. *CMAJ* 2006; 175:S1
 8. Shemie SD, Gardiner D: Circulatory arrest, brain arrest and death determination. *Front Cardiovasc Med* 2018; 5:15
 9. Prince EA, Ahn SH: Basic vascular neuroanatomy of the brain and spine: What the general interventional radiologist needs to know. *Semin Intervent Radiol* 2013; 30:234–239
 10. Robertson JA: The dead donor rule. *Hastings Cent Rep* 1999; 29:6–14
 11. Honarmand K, Parsons Leigh J, Martin CM, et al: Acceptability of cardiac donation after circulatory determination of death: A survey of the Canadian public. *Can J Anaesth* 2020; 67:292–300
 12. Honarmand K, Parsons Leigh J, Basmaji J, et al: Attitudes of healthcare providers towards cardiac donation after circulatory determination of death: A Canadian nation-wide survey. *Can J Anaesth* 2020; 67:301–312
 13. Honarmand K, Ball I, Weiss M, et al: Cardiac donation after circulatory determination of death: Protocol for a mixed-methods study of healthcare provider and public perceptions in Canada. *BMJ Open* 2020; 10:e033932