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REFLECTIONS

Implications of the updated Canadian Death Determination Guidelines for organ donation interventions that restore circulation after determination of death by circulatory criteria

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Since its implementation in 2006, organ donation after circulatory determination of death (DCD) has substantially increased the number of organs recovered for transplant in Canada.[1] Nevertheless, organs from DCD donors sustain ischemic injury that impacts graft quality and often precludes transplantation. While DCD has expanded the donor pool, it remains insufficient to meet transplantation demand.[2]

Several measures have been proposed to increase the quality and quantity of organs recovered from DCD donors. These include postmortem normothermic regional perfusion (NRP),[3] postmortem tidal ventilation,[4] and uncontrolled DCD protocols (uDCD).[5] Nevertheless, the ethical and legal permissibility of these practices is debated.[6–8] According to previous DCD guidelines reliant on the permanent cessation of circulation for determining death,[5] restoring circulation would invalidate death determination; if organ recovery proceeded, it would also violate the dead donor rule, the ethical injunction that organ recovery cannot cause a donor's death.[9]

Nevertheless, the updated Canadian Death Determination Guidelines in this Special Issue of the *Journal* clarify that postmortem resumption of regional circulation and subsequent organ recovery does not equate to a violation of the dead donor rule.[10] By articulating a unified concept of death based on the permanent loss of brain function, the Guidelines illuminate how cessation of circulation is a valid biological indicator of death only because it is a reliable proxy for the permanent cessation of intracranial circulation and brain function. Consequently, the updated Guidelines imply that—provided brain function has ceased permanently at the time of death determination (something that is inferred from cardiac arrest literature in humans and animals but awaits confirmation in a study involving patients who undergo withdrawal of treatment), and on the condition that intracranial circulation is precluded—postmortem interventions restoring regional extracranial circulation may be permissible.[4,11]

Because of their contentious nature, reflection on the implications of NRP, tidal ventilation, uDCD, and future innovations that can restore circulation postmortem in DCD is warranted. Below we outline ethical, scientific, and practical challenges facing these interventions, and we offer suggestions for how to move forward while balancing the need for innovation in DCD with donor safety and stakeholder trust. Exploring each intervention, we derive a set of principles to guide initial assessment of current and future innovations of this kind.

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Normothermic regional perfusion

Normothermic regional perfusion is an *in situ* perfusion technique that restores regional circulation in DCD donors following death determination.[3] By restoring circulation of oxygenated blood to target organs, NRP reverses ischemic damage, improves graft function, permits organ viability assessment, and enables DCD heart donation.[11] Abdominal NRP perfuses organs in the abdomen, while thoracoabdominal NRP perfuses organs in the abdomen and chest—the latter resulting in the return of spontaneous cardiac function. In both forms of NRP, surgical safeguards are designed to prevent intracranial circulation by ligating, occluding, or transecting the major blood vessels to the brain.[3]

Despite its promise, NRP is controversial because of perceived ethical challenges.[7] Critics argue that NRP violates the dead donor rule because circulation—the permanent loss of which forms the basis for death determination—is restored.[7,8] Further, some stakeholders perceive interventions precluding resumption of intracranial circulation as the induction of brain death since, in the absence of such interventions, resumption of circulation during NRP could restore brain function and invalidate the determination that death had occurred.[12]

The updated Canadian guidelines address this controversy by clarifying that cessation of circulation is a proxy for cessation of intracranial circulation and, consequently, of brain function.[10] Provided brain function has ceased before initiation of NRP, ligation, occlusion, or transection do not *induce* permanent cessation of brain function—they *maintain* it.[13] Nonetheless, such controversies reflect concerns from some quarters regarding the permissibility of NRP and its implications for the dead donor rule.[7] The return of spontaneous cardiac function in thoracoabdominal NRP may exacerbate these concerns because of the perceived significance of restoring spontaneous cardiac function for some stakeholders.[14]

In addition to ethical challenges, scientific and practical obstacles suggest a cautious approach to NRP's implementation. Chief among these are unanswered empirical questions.[15] First, the temporal relationship between the cessation of circulation and brain function is unknown. If brain function stops before, at, or within five minutes of the cessation of circulation, interventions precluding intracranial circulation during NRP merely maintain the permanent cessation of brain function. Nevertheless, if brain function persists at the time of NRP's initiation, interventions precluding intracranial circulation may indeed be perceived as contributing to death. While the latter scenario is unlikely given data suggesting rapid loss of brain function after cardiac arrest,[16] direct confirmatory data from patients who undergo controlled withdrawal of life-sustaining measures with gradual hypoxia and ischemia rather than sudden cardiac arrest are lacking. Second, although NRP involves blocking the major vessels to the brain, these safeguards are not yet proven to preclude intracranial circulation via collateral vessels or in cases of anatomic variants.[3,15] In both cases, the presence of brain function would expose donors to a risk of harm should they retain or regain sentience, and potentially lead to violations of the dead donor rule.

Substantial research is therefore required before NRP's implementation.[15] First, ethical and legal analysis by bioethicists, social scientists, and legal scholars should be brought to bear on the controversies surrounding NRP to derive policy options for consideration by organ donation organizations. Second, qualitative studies should continue to determine the acceptability of NRP among stakeholders and explore what form consent to NRP should take.[17] Third, prospective studies with imminently dying patients should document the temporal relationship between cessation of circulation and brain function. Finally, studies assessing surgical safeguards to prevent intracranial blood flow should be undertaken with rigorous neuromonitoring protocols in place.[15] Together, these initiatives will help to reassure stakeholders, maintain trust in deceased donation, and ensure that NRP poses no risk of harm to DCD donors.

Tidal ventilation in lung donation

Postmortem resumption of positive pressure ventilation cycling between inspiration and expiration in DCD lung donors during organ recovery can reduce warm ischemic time, attenuate lung injury, and increase the number of lungs recovered for transplant.[18] Nevertheless, tidal ventilation can stimulate resumption of myocardial contractility and spontaneous circulation.[4] Unlike in NRP, postmortem tidal ventilation does not involve surgical safeguards to prevent intracranial circulation and is therefore currently not practiced in jurisdictions such as Ontario.

Like NRP, tidal ventilation poses challenges relating to acceptability among stakeholders and the potential for violations of the dead donor rule. Because there are no validated surgical safeguards to prevent intracranial circulation in the event of resumption of cardiac function or anterograde flow, the latter concern is especially challenging. While the updated death determination guidelines clarify why NRP may be permissible provided surgical safeguards are employed, tidal ventilation cannot be justified on these grounds in the absence of methods to preclude intracranial circulation.

Assurances that intracranial circulation cannot be restored through tidal ventilation are therefore critically important; safeguards should be explored. For example, the UK's protocol for lung-DCD attempts to preclude resumption of cardiac function (and consequently intracranial circulation) by mandating several measures.[4] Different methods are possible, but these have yet to be standardized or rigorously studied.

To ensure donor safety and stakeholder trust, the use of postmortem tidal ventilation in DCD should be restricted to research protocols until methods to prevent resumption of cardiac activity have been validated. Should circulation resume, tidal ventilation must be halted, and death determination re-established by clinicians who are not part of the transplant team before proceeding with organ recovery.

Uncontrolled DCD

Unlike controlled DCD, uDCD is unplanned and typically follows unexpected refractory cardiac arrest outside the hospital setting.[2,6,19] Following unsuccessful attempts to revive the patient, first responders initiate cardiac compressions and ventilation for organ preservation during patient transfer to hospital. In some protocols, death is determined in the field, while in others death is determined upon arrival.[19] Extracorporeal perfusion or *in situ* cooling is then initiated, and the donor proceeds to organ recovery.[19]

The updated Canadian Death Determination Guidelines clarify that some aspects of uDCD protocols are either not permissible or likely to be logistically infeasible in Canada currently.[10] If declared dead in the field, the patient is deceased by circulatory criteria. By initiating nontherapeutic chest compressions and ventilation to preserve donation opportunities, intracranial circulation (and possibly brain function) could be restored, invalidating the determination that death had occurred because of violation of the permanence principle. Similarly, if death is declared in hospital, interventions such as extracorporeal perfusion may restore intracranial circulation, with consequent potential for brain reanimation. While some uDCD protocols involve the insertion of an intra-aortic balloon to isolate circulation to abdominal organs,[19] this intervention could conceivably fail and would likely require surrogate consent in Canada—something difficult to obtain within the time constraints of uDCD.

Although uDCD protocols are not practiced in Canada, patients with refractory cardiac arrest may still be considered for DCD after rescue efforts have failed. A crucial difference between such a scenario and uDCD is that whereas in the latter interventions are done to preserve donation opportunities, in the former they are done for rescue. For example, combined extracorporeal perfusion and cardiopulmonary resuscitation programs performed to save a life could lead to direct procurement and preservation *ex situ* of organs after termination of rescue efforts.[20]

Conclusion

The updated Canadian Death Determination Guidelines may enable novel interventions that can restore circulation postmortem in DCD donors. Proposed interventions—and others that may arise in future—can help to improve the quality and quantity of organs available for transplant, allow more donors to fulfill their donation wishes, and save or improve the lives of more Canadians. Nevertheless, given the ethical, legal, practical, and scientific challenges such novel interventions present, a prudent approach to their implementation is advisable. Because stakeholder trust is the cornerstone of deceased donation, the issues described above should be resolved in advance. Since many of these challenges are at the intersection of donation science, law, ethics, and sociology, an interdisciplinary approach to the study of any intervention that may restore circulation postmortem in DCD donors is critical to ensure these innovations are safe and acceptable to stakeholders.

Below, we propose a set of principles to adhere to when considering any intervention that can restore circulation postmortem in DCD donors.

1. Any postmortem intervention intended for organ donation procedures that may re-establish extracranial circulation must maintain the permanent cessation of intracranial circulation.
2. Until measures to preclude intracranial blood flow are validated, interventions should be undertaken in a research context only. When interventions intentionally restore circulation, an approved neuromonitoring protocol should be in place.
3. A human research ethics committee must approve all components of the research.
4. The research should have the support of the local organ donation organization.
5. A donation scientist and an expert on death determination should form part of the research team. If interventions intentionally restore circulation, a neurocritical care expert should be involved in the development of a neuromonitoring protocol.
6. Should the research team observe any intracranial blood flow, the intervention should be stopped, the clinicians who determined death notified, and death determination re-established by circulatory criteria before organ recovery.

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