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Ensuring the Permanent Cessation of Brain Function during Normothermic Regional Perfusion

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Ensuring the Permanent Cessation of Brain Function During Normothermic Regional Perfusion

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Normothermic regional perfusion (NRP) is an in situ perfusion technique that may improve the quality and quantity of organs in donation after circulatory determination of death (DCDD).[1] By restoring perfusion with oxygenated blood to abdominal or thoracoabdominal (TA-NRP) organs after circulatory determination of death, NRP reverses warm ischemia injury sustained by organs during the dying process and enables in situ assessment of marginal or previously excluded grafts (eg, DCDD hearts, older age donors). Data from observational studies suggest that NRP lowers risk of early liver graft dysfunction and biliary complications and results in rates of delayed kidney graft function that are comparable with those from brain-dead donors.[1]

Although public and healthcare stakeholders appear to be supportive of NRP,[2,3] in situ resumption of circulation in DCDD donors presents several challenges.[4] First, resumption of in situ circulation contradicts the permanent cessation of circulation criterium used for death determination in DCDD and may be perceived as a violation of the dead donor rule.[5] Establishing unified death determination criteria that are based on permanent cessation of circulation to the brain will address this challenge.[6,7] Second, reperfusion of the heart via coronaries in TA-NRP causes resumption of spontaneous cardiac activity, which may be perceived by some stakeholders as a more egregious violation of death determination. Furthermore, in jurisdictions where death determination is based on cardiac arrest, resumption of spontaneous cardiac activity may violate the dead donor rule.[4] Third, restoring circulation during NRP risks reperfusion of the brain, resumption of brain activity, and potential for sentience and donor suffering.

To prevent restoring circulation to the brain, several surgical techniques have been described, including ligation or transection of aortic arch vessels in TA-NRP and balloon occlusion of the distal thoracic aorta in abdominal normothermic regional perfusion.[8] Additional assurance methods have been proposed, including interventions to drain the aorta to atmosphere to divert any risk of collateral brain blood flow.[8] Although theoretically sound, these surgical assurance techniques do not address *all* possible sources of brain blood flow and remain speculative in the absence of direct data confirming their effectiveness in preventing resumption of brain circulation and activity during NRP.

In the current issue, Dalsgaard et al[9] demonstrate that clamping of aortic arch vessels in a pig model of NRP is sufficient to prevent resumption of cortical blood flow, cortical electrical activity, and brain stem function during NRP. The authors prospectively randomized 16 female pigs to clamping of aortic arch vessels versus sham surgery during NRP. They monitored cortical blood flow and oxygen tension using laser and fiberoptic probes, cortical electrical activity using intracranial electroencephalography (EEG), and brain stem function using intracranial electrodes with median nerve somatosensory evoked potentials (SSEPs). In both groups, cortical blood flow, oxygen tension, and EEG activity were comparable at baseline and absent at asystole. In the sham group, initiation of NRP restored cortical blood flow back to baseline levels, increased cerebral oxygen tension, restored EEG activity in all 8 pigs, and led to resumption of SSEPs and agonal breathing in 6 of 8 pigs. In the intervention group, clamping of aortic arch vessels following asystole and before initiation of NRP prevented resumption of cortical blood flow, EEG, SSEPs, and breathing during NRP and following NRP weaning.

Predictably, the authors confirm that in an animal model without preexisting brain injury, reperfusion of the brain during NRP led to a return of brain activity with the presence of EEG, SSEP response, and agonal breathing. Conversely and reassuringly, clamping of the arch vessels halted cerebral and brain stem circulation and function

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indicated by the sustained absence of cerebral perfusion parameters, EEG, and SSEPs. The study findings are reassuring, particularly as the vast majority of controlled DCDD occurs in potential donors with preexisting brain injury.

The study had several limitations including limited spatial resolution of brain blood flow and cortical electrical activity measurements, which prevents generalizability of findings to the whole brain, and lack of flow and activity data during NRP, which prevents establishing how long it takes for brain blood flow and activity to resume after initiation of NRP. Neurologically, this study provides data regarding cortical and brain stem electrical activity but does not provide evidence regarding the potential for consciousness or brain stem blood flow. Furthermore, anatomical differences between pig and human vasculature and brain structure cannot be overlooked and will require further confirmation in humans. Nonetheless, Dalsgaard et al provide good quality animal data to support that proposed surgical safeguards with reliable clamping of aortic arch vessels may be sufficient to prevent restoring brain blood flow and activity during NRP and that perhaps additional interventions to drain the aorta to atmosphere to divert any risk of collateral brain flow are not necessary.[8]

The international uptake of NRP is first and foremost predicated on medicolegal acceptance that death in DCDD is not based on arrest of cardiac or circulatory function but arrest of circulation to the brain. Although this study provides some reassurance for jurisdictions conducting or considering NRP, confirmation that surgical safeguards are indeed effective will ultimately require human research. Although randomization to sham occlusion of aortic arch vessels would not be ethically permitted in humans, observational studies with multimodal neuromonitors to demonstrate lack of resumption of brain blood flow and activity with ligation/transection of aortic arch vessels during NRP will be needed. Neuromonitoring in observational studies will likely consist of scalp recordings of EEG and evoked SSEPs rather than intracranial EEG. This may lead to a decrease in sensitivity for detecting cortical and brain stem electrical activity, in which case supporting animal data such as those described by Dalsgaard et al will provide important and complementary evidence. If such studies are implemented, they should include 3 considerations. First, brain blood flow and activity data should be monitored in real time to identify potential instances of resumption. Second, if such resumption is detected, there should be clear protocols regarding discontinuation of NRP and change to usual direct procurement methods of organ recovery. Finally, ethical analysis of stakeholder perspective would be an important step to build trust and to support these research protocols and clinical implementation of NRP.

REFERENCES

1. De Beule J, Vandendriessche K, Pengel LHM, et al. A systematic review and meta-analyses of regional perfusion in donation after circulatory death solid organ transplantation. *Transpl Int.* 2021;34:2046–2060.
2. 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.
3. 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.
4. Basmaji J, Weijer C, Skaro A, et al. Paving the road for the adoption of normothermic regional perfusion in Canada. *Crit Care Explor.* 2021;3:e0553.
5. Robertson JA. The dead donor rule. *Hastings Cent Rep.* 1999;29:6–14.
6. Shemie SD, Hornby L, Baker A, et al; The International Guidelines for Determination of Death phase 1 participants, in collaboration with the World Health Organization. International guideline development for the determination of death. *Intensive Care Med.* 2014;40:788–797.
7. Shemie SD, Gardiner D. Circulatory arrest, brain arrest and death determination. *Front Cardiovasc Med.* 2018;5:15.
8. 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.
9. Dalsgaard FF, Moeslund N, Zhang ZI, et al. Clamping of the aortic arch vessels during normothermic regional perfusion after circulatory death prevents the return of brain activity in a porcine model. *Transplantation*. 2022;106:1763–1769.