



Editorial

Normothermic regional perfusion in donation after circulatory determination of death—Confirming the absence of brain reperfusion

Commentary on [<https://doi.org/10.1016/j.ajt.2025.03.029>]

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Normothermic regional perfusion (NRP) has transformed organ utilization and graft outcomes following donation after the circulatory determination of death (DCDD). The restoration of an oxygenated circulation after the determination of death mitigates warm ischemic injury to abdominal or thoracoabdominal organs, allows for functional assessment, and improves transplantation outcomes. The evidence supporting NRP in DCDD continues to accumulate, and while randomized prospective controlled studies on the effectiveness of NRP have not and are unlikely to ever be performed, this technique is based on sound physiologic rationale. Weight of existing evidence has led to implementation in many countries worldwide.¹

There is active debate within medical, ethical, and legal literature on whether NRP is consistent with the dead donor rule, given that oxygenated circulation is restarted after death has been determined based on the permanent absence of circulation.² Surgical interventions are deployed to eliminate the risk of brain reperfusion and include distal thoracic aortic occlusion/crossclamp in abdominal NRP (A-NRP) and ligating, dividing and venting the arch vessels in thoracoabdominal NRP (TA-NRP).³

The following adapted logic model⁴ can serve to guide programs considering the implementation of NRP.

If:

1. Death in DCDD is defined by the permanent cessation brain function
2. The act of occluding the aorta with balloon or crossclamp or ligating, dividing, and venting the aortic arch vessels after confirmation of death and before starting NRP is medically and ethically acceptable
3. Absence of potential for brain perfusion as a surrogate of brain function can be assured (to adhere to the principle of permanence for death).

Then:

1. Restarting oxygenated circulation after death does not invalidate the definition of death in DCDD
2. Restarting the heart and other organs in the donor's body after death does not invalidate the definition of death in DCDD
3. NRP may be considered permissible.

In this issue, Roya-Villanova et al⁵ evaluated brain scintigraphy in the setting of DCDD, confirming the absence of brain perfusion during NRP. The strengths of this study include 20 consecutive adults (n = 15 A-NRP, n = 5 TA-NRP), including

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those with and without pre-existing brain injury, using distal thoracic aortic balloon occlusion for A-NRP and dividing the aortic arch vessels and venting the cephalad ends to atmosphere in TA-NRP. Following injection of the radiopharmaceutical technetium-99 hexamethylpropyleneamine oxime, the authors acquire static brain images in anterior and lateral projections on a portable γ camera in the operating room. The use of scintigraphy in this setting is original and based on the validity of this technique in ancillary testing as recommended in international brain death protocols.⁶ Royo-Villanova et al have creatively made use of these validated techniques in addressing the question of whether perfused abdominal or thoracic blood reaches the cerebral circulation, which would contravene the circulatory determination of death if cerebral blood flow was reestablished.

The surgical approach to the arch vessels in TA-NRP requires emphasis.³ To isolate the cerebral circulation before reperfusion of the thoracic region, the surgeon clamps or ligates the arch vessels and then divides the supra-aortic vessels leaving the cephalad ends vented to atmospheric or negative pressure. This latter maneuver, although not universally practiced, is intended as a failsafe method of preventing cerebral blood flow, by establishing a sink for any perfusion reaching the head via non-interrupted collaterals. It is interesting to note in this case series that neither brain nor face were reperfused. This appears to be convincing evidence of no perfusion to the head and brain and supports the previous studies in Spain by the lead author where they placed pressure lines via direct carotid puncture into the circle of Willis.⁷ It is applicable in the context of having the innominate, left subclavian and left common carotid divided with the cephalad ends draining freely, such that there can be no perfusion pressure in the circle of Willis consistent with recommendations that simply ligating the arch vessels is not sufficient.³ If the great vessels are not divided and vented during TA-NRP, there may be potential for significant flow via the supreme intercostal arteries into the subclavian and on to the vertebral arteries, for example. The main circumstance where this strategy³ may fail will be where there is abnormal anatomy, most likely with an anomalous right subclavian origin arising caudal to the left subclavian origin. In such circumstances its presence may be overlooked, and in spite of apparent division of the 3 cardinal vessels, the right subclavian artery may remain perfused, with consequent perfusion of the right vertebral artery. Vascular imaging (thoracic computed tomography angiography or ultrasound) would confirm anatomy and identify the vessels that need clamping.

This novel study adds to the existing literature to date ($n = 9$ for TA-NRP, $n = 23$ for A-NRP),^{1,7,8} which has not demonstrated brain reperfusion in NRP in circumstances where the cranial circulation is vented, albeit in a limited sample size. The questions that remain include the following:

1. How many more studies are necessary to confirm these findings and reassure the international community?
2. In A-NRP, where the most cases have been performed, if distal thoracic aorta occlusion and venting of the proximal thoracic aorta is performed, is there any ongoing concern?

3. Do all NRP cases require neuromonitoring to ensure the absence of brain blood flow or those under research protocols only? What is the most reliable form of neuromonitoring? While the authors have shown that use of powerful radionuclide techniques can non-invasively answer their clinical questions in real-time. Portable γ cameras, allowing for imaging in the operating room, are not routinely available, which may present an impediment to widespread adoption of this novel method.
4. While the number of studies of TA-NRP is smaller, the results are incrementally convincing. However, for those centers that ligate the arch vessels but do not divide and vent to atmosphere, is this a sufficiently safe technique?

We collectively look forward to further studies to respond to these issues. It is more difficult to prove the absence of a rare but potentially substantial event. At this stage of investigation, it is premature to make any evidence-based decisions in responding to these questions. From our personal perspective, for cases of A-NRP with confirmation of reliable occlusion and venting of the thoracic aorta, the risks for brain reperfusion are exceedingly low and therefore, we question the need for neuromonitoring in these cases. For TA-NRP, given the higher risks of collateral flow, we urge the international community to routinely vent the distal ends of the arch vessels, and continue routine neuromonitoring during the procedure. The choice of neuromonitoring (differing angiographic techniques) require validation. We would advocate national and international registries for neuromonitored TA-NRP to increase the sample size required to inform practice.

Declaration of Competing Interest

The authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

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