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PERSPECTIVE ARTICLE

International evaluations of thoraco-abdominal normothermic regional perfusion protocols according to neurophysiological and cardiovascular implications

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Abstract

Normothermic regional perfusion (NRP) is recognized as a surgical innovation that may improve the viability of organs following circulatory death for individuals who require transplantation. Abdominal normothermic perfusion (A-NRP) and thoraco-abdominal NRP (TA-NRP) are procedures that ensure adequate oxygenated blood flow to organs *in situ* before removal. A-NRP differs from TA-NRP as the perfusion is limited to the liver, pancreas, and kidneys, whereas TA-NRP also includes perfusion of the heart and lungs. TA-NRP remains controversial, with ethical and legal challenges, particularly concerning the re-establishment of cerebral blood flow and potential violations of the dead donor rule (DDR). Debates regarding the ethical differences between A-NRP and TA-NRP have been evaluated in other publications but are not within the scope of this paper. This paper examines the implications of the methodological differences of TA-NRP between the United States and other European nations, as the US recently adopted its use in 2020. These implications are evaluated according to research and surgical ethics frameworks given the limited empirical study of TA-NRP within human models. Future directions and recommendations are proposed to ensure adequate protection of human organ donors in the US context, similar to those implemented in European TA-NRP protocols.

Keywords: Thoraco-abdominal normothermic regional perfusion; Normothermic regional perfusion; Cerebral blood flow; Organ transplant; Organ donation; Donation after circulatory death

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1. Introduction

The United States (US) legislation requires death declarations in compliance with the Uniform Declaration of Death Act (UDDA). The UDDA defines the legal criteria for determining death, either by circulatory/respiratory criteria or brain death by neurologic criteria (BD/DNC). The UDDA differs from the dead donor rule (DDR), as the DDR, while not codified into federal law, is an ethical and legal framework developed for surgical procedures pertaining to organ transplantation. The DDR holds two premises: (i) donors must be dead before organ donation and (ii) organ procurement must not be the cause of death.[1]

Thoraco-abdominal normothermic regional perfusion (TA-NRP) is an organ procurement procedure that is utilized in individuals who have been declared dead by circulatory criteria (donation after circulatory death, DCD). The process establishes *in situ* reperfusion through a machine that provides oxygenation to the organs before their removal, reducing ischemic injury. While TA-NRP may improve the pool of available organs for transplantation, there have been few multifactorial analyses that examine the cardiopulmonary and neurophysiological substrates associated with this procedure.

TA-NRP protocols are implemented after the pronouncement of death by circulatory/respiratory criteria. Following the declaration of death is a no-touch period, which typically varies from 2 to 5 minutes to ensure the absence of autoresuscitation.[2,3] The right atrium and the aorta are cannulated before ligation of the supra-aortic vessels, which cuts off cerebral circulation. TA-NRP technology is introduced following vascular occlusion with the initiation of an autologous blood transfusion through an extracorporeal membrane oxygenation circuit to re-perfuse the organs.

Physiological implications related to the re-establishment of circulation by TA-NRP to the thoracic and abdominal organs are associated with ethical and legal challenges. This process, by reinitiating cardiac output, may result in a limited re-establishment of cerebral blood flow. Despite this low risk, the possibility of residual sensory integration or pain perception remains insufficiently studied in humans. While the complexity of TA-NRP and NRP, in general, is associated with potential violations of the DDR, this innovative technology may potentially increase the pool of viable organs for transplantation as the majority of deaths are declared using circulatory/respiratory criteria. The utility of TA-NRP technology thereby aims to reduce the disparities experienced by individuals waiting for an organ transplant as most viable organs used in transplantation are procured from BD/DNC populations.

It has been estimated that there are 103,000 individuals on the transplant waitlists in the US, whereas 13 individuals die each day due to inaccessibility.[4] Global transplantation rates compared to waitlist candidates reflect that less than 10% of all individuals requiring these interventions are able to obtain organ transplantation.[5,6] Because of the physiological risks associated with TA-NRP, it is imperative that public trust is maintained through transparent communication of the transplantation process. Current practices within the US allow individuals to opt in as a form of first-person authorization to donate their organs. However, individuals who have not been registered as organ donors may receive a second-person authorization. Second-person authorization occurs when a deceased person's legally authorized representative or healthcare proxy consents to the donation because their family member did not provide prior authorization or was not of the legal age to do so.[7]

Given that biologics, investigational drugs, and medical devices often require clinical trials to be conducted before the commercialization process, the safety and efficacy of TA-NRP require further empirical research. Comparisons of TA-NRP protocols across US institutions reflect significant variation according to the methodologies and pharmacological agents used within the transplantation process. While there are robust ethical debates about potential violations of the DDR, it is imperative to maintain public trust to ensure that the integrity of the transplantation process is protected. These implications require transparent communication about the risks and benefits associated with TA-NRP, future use clauses, and differentiation between controlled TA-NRP and uncontrolled TA-NRP scenarios.

Because of the potential for miscommunication within the authorization process, this paper recommends that the US develops standardized protocols for uncontrolled TA-NRP DCD donation scenarios. Furthermore, to reduce the risk of decreased organ donation attributable to public distrust, the US should establish standardized authorization forms for individuals involved in the second-person authorization process.

2. Uniform death declaration act and implications for TA-NRP

Normothermic regional perfusion (NRP) and TA-NRP are touted as significant surgical advancements, as these procedures improve viability due to reductions in ischemic injury. Physiological improvements associated with organs procured through TA-NRP methodologies include reduced attrition rates for donated organs, graft failure rates, and risk for ischemic cholangiopathy, in the case of donated livers. While the physiological mechanisms that allow for comparison of TA-NRP to other organ procurement procedures are being empirically investigated, it is hypothesized that perfusing the organs *in situ* simulates a natural, metabolically active state.[8] These implications are associated with reduced costs of transplantation, as this methodology allows multiple organs to be procured simultaneously and enables the functionality of the organ to be assessed before transplantation.[9]

Significant impediments that affect organ transplantation within the US include, but are not limited to, the shortage of viable organs, donor-recipient compatibility, waiting time, and organ donation legislation.

While European countries such as France, Italy, Norway, and Spain have adopted TA-NRP for organ recovery, this procedure is a contentious topic within clinical medicine and surgical ethics within the United States.[9-11]

Despite the increased utilization of TA-NRP, the US has not adopted a robust national policy on its usage due to potentially unresolved ethical issues related to the DDR. The DDR states that organ procurement procedures cannot be the cause of an individual's death and that the donor must be declared dead before organ donation.

Declarations of death for individuals within the US must follow the UDDA. The UDDA states that death declarations may be determined by cardiopulmonary or neurologic criteria.[1] In general, DCD occurs after an individual has been declared dead due to the permanent cessation of cardiovascular responsiveness and respiration.[12,13] The BD/DNC differs from DCD as this determination is typically utilized for individuals who have undergone a significant neurological injury. Individuals who are BD/DNC are clinically evaluated by a neurologist that has determined that there is an irreversible cessation of functioning within the entire brain including the brain stem.

3. Ethical and legal debates for TA-NRP

Controversies of TA-NRP are attributable to the likelihood that individuals may retain some neurological functioning despite being declared dead by cardiopulmonary criteria[14]. While proponents may argue that TA-NRP only reperfuses organs within the thoracic and abdominal cavity with minimal risk of restoration of neurological function, critics have argued that the adoption of NRP and TA-NRP may be premature as there is limited data regarding its safety and efficacy.

Additional concerns related to the adoption of TA-NRP must be evaluated according to the prevalence of organ donors that have been declared using the BD/DNC rather than the DCD criteria. US estimations reflect that only 2% of deaths are eligible for organ donation, where 70% of these donors passed away due to BD/DNC.[9,15,16] Additional assessments of organ donors according to the type of death criteria reflect that DCD donors may account for only 10% of all organ donors.[17] US estimations of viable organs procured from BD/DNC donors reflect an average of 3.3 compared to 1.9 for DCD donors.[9] These implications indicate that while TA-NRP aims to increase the availability of viable organs, the lack of neurological monitoring consistent with DCD declarations, use of anesthetic pharmacological agents, and cerebrovascular substrates implicated in this procedure require further ethical evaluation.

4. Global TA-NRP surgical protocols and implications

Examinations of international TA-NRP surgical protocols reflect significant variability.[18] Medical institutions within the US that have implemented TA-NRP protocols ligate the brachiocephalic, left common carotid, and left subclavian arteries. However, due to ethical concerns associated with this methodology, Spain and other countries within the European Union require clamping of the supra-aortic vessels, which are then opened to atmospheric pressure to allow blood drainage from the cephalad ends. These precautions aim to reduce the risk of antegrade blood flow from the vertebrobasilar system after *in situ* reperfusion. The UK has taken further precautions by discontinuing TA-NRP since 2020 due to concerns associated with its potential to re-establish cerebral blood flow.[18]

The time between death declarations and implementation of TA-NRP protocols also reflects significant variation across US and international medical institutions. While there is limited data that reflects aggregated averages, Cain *et al.*[19] reported that the time between the death pronouncement after removal of the endotracheal tube or other life support measures within the US varies from 10 to 90 minutes, which is followed by a hands-off period. The utilization of a hands-off or no-touch period aims to ensure that spontaneous circulation does not occur.[20] Comparison of global and domestic implementation of the hands-off period reflects that the no-touch period is typically 2–5 min but may range from 2 to 30 min[2].

Further differences in international TA-NRP protocols compared to the US include the utilization of anesthesia. Data collected within animal models suggest that these pharmacological agents may cause disorganized neural activity.[21] While the specific pharmacological agents utilized for anesthetic purposes vary across patients and institutions, limited data are available to evaluate the use of anesthesia within organ donor populations.[17,22] Utilization of anesthesia has been justified for use within end-of-life patients to reduce the symptomatology associated with the dying process.[11] However, the ethical permissibility of anesthesia specific to TA-NRP protocols remains a contentious issue. Specifically, because anesthesia is implemented before the hands-off period, monitoring of autoresuscitation is not possible. Furthermore, the pharmacologic properties of anesthesia suggest that the risk of ischemic damage and organ graft dysfunction is lower compared to opioids and other prescription drugs used in patients who will be declared dead by cardio-circulatory criteria. These implications suggest that because anesthesia may be utilized during the time interval between the withdrawal of life support and cardiac arrest,

the necessity to standardize ethical and legal guidelines for anesthesiologists who are involved in TA-NRP is imperative.[17,22]

5. Animal models and human subject research

Despite assertions that TA-NRP does not restore consciousness due to blood flow to the brain after ligation of the supra-aortic vessels, limited controlled studies within animal and human subjects have been conducted. Preliminary data within animal models suggest that a return of some neurological functioning is possible after the no-touch period required for human organ donors.[23,24] Dalsgaard *et al.*[21] conducted a randomized trial that examined hemodynamic processes after TA-NRP using porcine models (n = 16) that were assigned to the vessel ligation or no-clamp group. While no cerebral blood flow was observed within the animals that had their vessels occluded, the no-clamp group exhibited some restoration of cerebral perfusion, as measured with cerebral blood flow and PaO_2 (partial pressure of oxygen in arterial blood). Cortical activity was also observed within the no clamp group which was measured by somatosensory evoked potentials and the electroencephalogram.

Research by Frontera *et al.*[25] utilized transcranial Doppler ultrasound (TCD) to examine intracranial blood flow after TA-NRP within human subjects according to pulsatile flow. While the TCD analyses reflected that there was no cerebral blood flow after DCD, the study utilized an underpowered sample of n = 2. Despite the potential utility that TCD and neurological assessments would provide for examining whether TA-NRP is associated with antegrade cerebral blood flow and restoration of consciousness, these methodologies are not standard practice in DCD donors.

6. Animal models and human subject research

Legal and medical scholars have suggested that the ethical permissibility of TA-NRP rests on the premise that this procedure does not induce restoration of cerebral blood flow.[10] However, physiological evaluations of the restoration of blood flow to the brain due to improper clamping of the aortic arch vessels before the implementation of TA-NRP have not been adequately researched.[25]

The commercialization process for pharmacological drugs, medical devices, and innovative surgeries often requires substantial investigation to ensure safety, efficacy, and utility. Because TA-NRP is a novel invasive procedure that is associated with significant risk for physiological harm, the US should require robust clinical trials to be conducted before further implementation in hospitals and other medical settings.

Given that US TA-NRP protocols vary across institutions, neurophysiological monitoring technologies should be implemented to ensure the absence of cerebral reperfusion. Despite assertions that TA-NRP does not pose violations of the DDR, these conclusions are primarily based on controlled DCD scenarios. Controlled DCD TA-NRP includes donors who have undergone withdrawal of life support and will experience a planned cardiac arrest.[26]

Uncontrolled donation differs from controlled DCD as these individuals have received resuscitation that is unsuccessful or were pronounced dead before arriving at a medical facility.[26,27] Because uncontrolled scenarios involve individuals in which circulatory death occurs unexpectedly, legal and ethical debates reflect that the compressed time restrictions required for TA-NRP do not allow for proper deliberation for individuals involved in the second-person authorization process. Furthermore, because the uncontrolled scenarios present significant time constraints, additional criticisms of TA-NRP may reflect that it is unethical within these populations, as there is insufficient time to transition between providing interventions that may be in the donor's best interest and the time required for organ procurement.[11]

7. Conclusion

TA-NRP is an innovative surgical advancement that may lead to significant improvements for organ transplant recipients. While the utility of this procedure is often discussed in surgical and organ transplant literature, it is imperative that US medical centers conduct additional research. The utilization of larger samples should be reflective of standard multicenter clinical trials involving investigational biologics and devices. Because other countries such as Spain have utilized TA-NRP since 2012 and have implemented specific safeguards to reduce the risk of antegrade cerebral perfusion, it is recommended that these safeguards are also implemented in TA-NRP protocols conducted in the US.[11] Additional considerations for differences in international TA-NRP protocols compared to the US include uncontrolled DCD scenarios. Given that the UK has stopped using TA-NRP due to unresolved ethical conflicts related to cerebral reperfusion, international medical centers should aim to develop standardized protocols and guidelines specific to uncontrolled DCD TA-NRP populations.[18]

The feasibility of organ transplantation relies on public trust. Because organ donation relies on societal

perceptions and public trust of the transplantation process, it is imperative that clinicians, ethicists, and legal scholars engage in multidisciplinary discussions to develop educational resources related to TA-NRP. Because this procedure utilizes advanced surgical approaches, prospective donors and their healthcare proxies must be given sufficient information to make informed choices in the authorization process.[7,27] These implications are tantamount as any reported technical error for TA-NRP may taint public trust and impede the advances made in organ donation rates. Thus, while TA-NRP may remain controversial within legal and medical settings, the use of large multi-center clinical trials with adequately powered sample sizes may lead to robust acceptability of this methodological approach. However, it is imperative that the safety of this procedure for prospective donors is equally balanced with any significant potential that TA-NRP may have for organ transplant recipients.

8. Future directions

Given the significant time restraints required for organ procurement, physiological investigations to examine whether vascular abnormalities affect cerebral perfusion after ligation of the supra-aortic vessels are necessary. Because the identification of the aortic branches and cerebrovascular anatomical variations requires computed tomography scans and/or other imaging technology, the time constraints required for organ procurement may not allow for proper assessment. These implications suggest that further empirical investigations are warranted to ensure that these physiological abnormalities are not clinical contradictions for TA-NRP. Comprehensively, these implications suggest that incorporating continuous neurological monitoring and diagnostic tests to identify potential atypical configurations of cardiopulmonary vessels may be necessary for the standardization of international TA-NRP protocols.

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