



Minireview

Increasing the acceptance of thoracoabdominal normothermic regional perfusion in donation after circulatory determination of death heart donation: A case for collaborative donor research

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Abbreviations: aNRP, abdominal normothermic regional perfusion; DBD, donation after brain death; DCD, donation after circulatory determination of death; DPP, direct procurement and preservation; HT, heart transplant; ODDCAT, Outcomes after DCD Cardiac Transplantation; PGD, primary graft dysfunction; taNRP, thoracoabdominal normothermic regional perfusion.

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ABSTRACT

Donation after circulatory determination of death transplantation offers an effective and safe method of increasing the number of heart transplants performed. Donation after circulatory determination of death heart is ischemic at the time of recovery, and therefore, requires reperfusion. This may take place in the donor, known as thoracoabdominal normothermic regional perfusion (taNRP) or outside of the donor, known as direct procurement and preservation. There is a growing body of evidence that taNRP is associated with better utilization of thoracic and abdominal organs from the donor and with superior recipient outcomes. taNRP offers a cheaper alternative to organ recovery than direct procurement and preservation. In addition, taNRP can also be used in pediatric transplantation. However, there are still concerns regarding the ethical acceptability of taNRP. These concerns center around the possible restoration of brain blood flow during taNRP through collaterals to the vertebrobasilar system. Early studies have demonstrated no brain blood flow or perfusion, but these are limited by small numbers. Further work, with significantly more cases, will need transatlantic collaboration to definitively establish the absence of brain blood flow or perfusion. We have a moral responsibility to both donors and recipients to expedite this work.

1. Introduction

Heart transplantation (HT) improves the survival and quality of life for patients with advanced heart failure that is refractory to conventional treatment.¹ However, HT is limited by a shortage of suitable donor hearts, resulting in 30% of patients on the waiting list not receiving a transplant.^{2,3} Various initiatives have attempted to increase the number of heart donors, and the most successful of these has been the introduction of donation after circulatory determination of death (DCD) heart transplantation programs. In 2023, there were 823 HT from DCD donors across 9 countries, out of a total of 10 121 transplants.⁴ A recent international study demonstrated that DCD HT resulted in a 23% increase in activity.^{2,5} The contribution of DCD to the total number of heart transplants undertaken is likely to increase as this is adopted by more countries.

HT from DCD donors is feasible and safe,^{5,6} with equivalent posttransplant survival to HT from donation after brain death (DBD) donors.^{5,7} However, unlike the DBD heart, the DCD heart is exposed to a period of warm ischemia after the withdrawal of mechanically assisted treatment. The DCD heart requires reperfusion to stop and possibly reverse this deleterious ischemic damage and preserve graft function.⁸ This process of perfusion can either take place inside the donor—an in situ process known as thoracoabdominal normothermic regional perfusion (taNRP) or outside the donor using ex situ machine perfusion, known as direct procurement and perfusion (DPP).^{9,10} Although these 2 techniques are not mutually exclusive in theory, it is rare to use both together in practice.^{5,9}

Literature comparing the 2 DCD procurement techniques of taNRP and DPP remains limited. Before taNRP can become more widely accepted and considered the reperfusion technique of choice, 2 elements must be addressed. Firstly, concerns of the possibility of collateral blood vessels restoring flow through the vertebrobasilar system during taNRP, with theoretical restoration of some brain perfusion and resumption of brain function, retroactively negating the previous diagnosis of death. Secondly, taNRP must offer a distinct advantage to DPP, whether it be superior recipient outcomes, lower costs, or improved organ utilization from the donor.

2. The case for taNRP

A recent international observational study has shown that DCD HT with taNRP increases the number of hearts transplanted with similar survival, requirement for posttransplant mechanical circulatory support, and organ utilization to that after DBD transplantation.¹¹ However, few studies have compared outcomes after taNRP and DPP. The recent international Outcomes after DCD Cardiac Transplantation (ODDCAT) study of 504 DCD heart transplants from 22 centers in 4 countries compared the outcomes after taNRP with those after DPP.¹² In this study, taNRP was associated with a 60% reduction in the incidence of severe primary graft dysfunction (PGD) and a 40% reduction in the incidence of acute cellular rejection requiring treatment compared to DPP. These differences were observed despite similar donor and recipient demographics in both taNRP

and DPP groups.¹² However, an analysis of the United Network for Organ Sharing (UNOS) database demonstrated similar rates of PGD between NRP and DPP—with a severe PGD rate of 9.4% and 9.7%, respectively.¹³ In addition to this, data from a contemporaneous group of DPP transplants from St Vincent's in Australia have demonstrated a severe PGD rate of 8%, which is very similar to that seen in the taNRP group in the ODDCAT study. In this paper, the authors note that their initial PGD rate was 35%. It therefore seems that there is a learning curve for DPP that seems to improve with time.¹⁴ This improvement may be due in part to more experience with the recovery process, as well as better donor heart selection. It is, therefore, difficult to confirm whether the differences in severe PGD in the ODDCAT study are due to selection bias or in fact real. Moreover, it points to the need for a randomized controlled trial with well-defined, objective outcomes to definitively establish the differences in recipient outcomes between taNRP and DPP. In the meantime, until such a trial is performed, continued international multicenter observational studies will be of use in informing clinicians of the possible advantages and disadvantages of each technique.

However, there are several plausible mechanisms by which taNRP may exert a protective effect on the donor heart. Firstly, longer ischemic time in DPP is likely to result in greater degrees of myocardial stunning and possible ischemic damage to the heart. In addition to this, the longer functional total ischemic time in DPP may result in more endothelial damage upon reperfusion, subsequently exposing more donor antigens to the host's immune system and increasing the subsequent risk of rejection. Secondly, it has been demonstrated that ex situ heart perfusion is deleterious for heart function, and hearts perfused for longer durations exhibit greater impairment in function.^{15,16} The exact reasons behind this are unclear, but are believed to be linked in part to the inflammatory conditions during ex situ machine perfusion.¹⁵

There are additional advantages of using taNRP. In the United States, taNRP is reported to be associated with a lower turn-down rate of DCD hearts offered after median sternotomy than DPP.¹⁷ Increased confidence in utilizing taNRP hearts may relate to the retrieving surgeon's ability to objectively assess donor cardiac structure and function. There are currently no validated biomarkers for heart function ex situ, and although lactate is widely used as a surrogate for heart viability ex situ, it has no correlation with PGD or survival posttransplant.¹⁸ In contrast, taNRP enables assessment of the heart after, on average, 15 minutes of functional warm ischemia, well within the 30 minutes of normothermic ischemia required to cause myocardial infarction.¹⁹ Detailed assessment of donor heart function using transesophageal echocardiography, right heart catheterization, and visual inspection of the heart after stopping mechanical circulatory support⁹ can be performed with taNRP. Additionally, taNRP more easily facilitates postmortem coronary evaluation than DPP. This is important in countries like the UK, which do not allow these investigations prior to confirmation of death in the DCD donor.

Unlike DPP, taNRP may be used in pediatric cases, with several documented cases of successful taNRP organ recovery

performed in infants and children.^{20,21} DPP, however, is limited by a minimum donor weight. For normothermic machines, this is a minimum weight of 40 kg. This effectively precludes DPP for the majority of pediatric DCD cases.²² This is significant given the fact that a recent analysis of the American pediatric heart transplant waiting list has demonstrated that at 1-year postlisting, 15% of patients are removed due to deterioration or death.²³

Recovering organs for transplantation using taNRP is also cost-effective. Because taNRP rapidly perfuses all organs, it results in a higher organ yield at significant cost savings compared to DPP. Institutional experience demonstrates a greater number of organs recovered using TA-NRP for every one organ recovered using ex situ machine perfusion.²⁴ This significantly lower cost is mainly because ex situ perfusion machines are not required when taNRP is used.^{4,11} In taNRP, one relatively cheap extracorporeal membrane oxygenation machine and circuit reperfuses all abdominal and thoracic organs to be transplanted prior to cold storage for transportation. In DPP, the cost of the ex situ perfusion machine adds significantly to the expense, and this cost is associated with each organ procured individually, unlike taNRP, where the circuit reperfuses all abdominal and thoracic viscera. The significantly lower costs of taNRP organ recovery may remove financial barriers and increase access to high-quality DCD HT in less affluent jurisdictions.

In addition to offering cost-saving with each organ recovered for transplantation, taNRP also enables a greater number of abdominal and thoracic organs to be recovered and transplanted per donor.^{24–26} Despite concerns that taNRP may exert a detrimental effect on the donor lungs,³ a recent international study found no difference in lung utilization between taNRP and DPP.¹² Moreover, outcomes from lungs recovered using taNRP are similar to those recovered using DPP,^{27,28} with a Spanish study additionally reporting significantly lower rates of PGD in lungs recovered using taNRP compared to those recovered during abdominal normothermic regional perfusion (aNRP).²⁹

Early data demonstrate that taNRP is associated with increased abdominal organ utilization, which may also be associated with improved organ outcomes compared with the standard recovery technique.²⁴ aNRP is associated with greater numbers of kidneys and livers recovered per donor. In addition, livers obtained with aNRP have lower rates of ischemic cholangiopathy, biliary complications, and early allograft dysfunction^{30–32}; lower rates of early graft dysfunction are reported in kidneys obtained with aNRP.³³ It is worth noting that in these studies, the use of liver normothermic machine perfusion was done at the recipient and not the donor hospital. Therefore, utilizing normothermic machine perfusion at the donor hospital may improve liver outcomes related to ischemic injury. Nonetheless, it is likely that taNRP offers the same advantages to abdominal viscera as aNRP, and in fact, some centers exclusively use taNRP for abdominal organ recovery.

Although a randomized controlled trial comparing taNRP to DPP may never be performed, the currently available observational data would suggest that taNRP is superior to DPP.^{12,24,34} However, current observational data are limited by small

numbers in most cases, or by a lack of granularity when using larger national data sets.^{13,14,35–37} There has only been 1 international retrospective study, with sufficient granularity to suggest superior outcomes with taNRP with regard to severe PGD and acute cellular rejection requiring treatment in DCD HT.¹² However, there is a growing body of evidence that suggests no difference in PGD rates between NRP and DPP.^{13,14} Given the other advantages, such as significantly reduced cost associated with taNRP, use in pediatric transplantation, and advantages for abdominal organs, there may be no need for a randomized controlled trial. Future studies should try to incorporate the various benefits that NRP may offer and should take a holistic approach, rather than simply looking at outcomes of heart transplant recipients.

3. Ethical concerns with taNRP

NRP is a technology that promises an increase in the quality and quantity of organs available for transplantation. However, it raises some ethical issues that concern the donation and transplantation communities. Until these issues are resolved, it is unlikely that the promise of NRP will be fully realized.³⁸ One of the major issues is whether NRP invalidates the previous diagnosis of death or whether the procedures applied to isolate the brain are ethically acceptable. A unified concept of death that defines death by the permanent loss of brain function, irrespective of whether it is determined by circulatory or neurologic criteria, may help in settling the debate.³⁹ If this concept is more widely accepted, it may help in settling the debate because it addresses both issues. There is universal acceptance that the presence of brain function is inconsistent with the determination of death and that resumption of brain function is resuscitation and restoration of life.⁴⁰ The absence of brain blood flow or perfusion is a surrogate for absent brain function. There can be no brain perfusion without brain blood flow, and there can be no brain function without brain perfusion. After death is confirmed using circulatory criteria, it is only the continuation of permanent cessation of brain blood flow that matters, as it ensures the permanent loss of brain function.⁹ The resumption of circulation to other organs after the circulatory confirmation of death, therefore, becomes irrelevant. Surgical procedures to prevent restoration of brain blood flow are not undertaken to induce brain death. Death has already been confirmed using accepted circulatory criteria, and preventing the restoration of blood flow to the brain maintains the continued permanence of loss of brain circulation and function. This allows the process of death to continue uninterrupted, as it would after any other cardiac arrest or after clamping of vessels and explant of the heart, as practiced during standard DCD heart recovery. Studies confirming the absence of brain blood flow or perfusion during aNRP and taNRP, when appropriate measures are applied, are essential if NRP is to be more widely adopted.

The concern is greater with taNRP, because there is more potential for collateral blood flow to the brain than during aNRP.⁴¹ Porcine models have confirmed the absence of brainstem reflexes, brain blood flow, EEG activity, and

somatosensory evoked potentials during taNRP with clamping of the arch vessels.^{42,43} Small human studies from Spain and the US, using intracerebral artery pressure monitoring and transcranial Doppler ultrasound, respectively, are reassuring in demonstrating the absence of intracerebral blood flow during either aNRP or taNRP.^{44,45} However, these 2 studies are limited by the small number of cases between them (4 taNRP cases in total). A further study, using scintigraphy, has demonstrated the absence of cerebral perfusion in 5 taNRP cases.⁴⁶ There is, therefore, growing evidence for a lack of cerebral blood flow and perfusion during taNRP. Further cases will be needed to confidently exclude any presence of cerebral blood flow or perfusion.

4. Next steps for increasing taNRP implementation

There is a similarity with the debate that surrounded the introduction of controlled DCD programs. Addressing the legal, ethical, professional, and logistical challenges associated with DCD led to a progressive expansion in the number of countries incorporating this type of donation—26 countries in 2023, when DCD accounted for 25% of the 45 861 deceased donors globally.^{4,47,48} It is essential that the legal, ethical, and professional issues surrounding taNRP are similarly discussed and addressed. However, in the case of taNRP, the conceptual discussions need to be underpinned by scientific studies demonstrating the lack of brain blood flow, perfusion, and function during the procedure. For taNRP practice to expand, the collection of donor data should be considered as important as data on recipient outcomes.³⁴

At present, few human donor studies are being undertaken during taNRP. Spain routinely monitors all DCD donors undergoing taNRP using transcranial Doppler and bispectral index, whereas an ongoing study in the UK is using CT angiography initially during aNRP, then in taNRP to confirm or exclude the possibility of brain blood flow during the procedure.⁴⁹

However, this work is slow, especially given that neither the UK nor Spain performs the same volume of transplants as the US, as a large country. Transatlantic collaboration with high-volume centers in Europe and the US could greatly expedite the completion of these studies and provide a definitive answer to whether brain blood flow is restored during taNRP when appropriate safety measures are applied. Moreover, studies attempting to demonstrate the absence of cerebral circulation are logistically complicated, given that recoveries take place in a wide range of hospitals, many of which may not have the necessary facilities to carry out these studies. Thus, multicenter collaborations across the Atlantic will be pivotal to ensuring these studies progress and are sufficiently powered.

There is also a need for a standardized, rigorous method of performing taNRP. In Spain and in the UK (prior to the current moratorium), aortic arch vessels are clamped, divided, and the cephalad ends vented to atmospheric or negative pressure, as described previously.⁴¹ In the US, there is considerable heterogeneity in the methods used, with some centers only clamping and others clamping, dividing, and applying suction on the cephalad ends. This variability makes collaborative research

more challenging and raises additional questions.^{49,50} However, the US has recently made a positive move with a consensus statement on the technical standards for taNRP.¹⁰ It is essential that taNRP meets the highest ethical and professional standards to maintain not only public confidence in donation and transplant systems but also that of intensive care and operating theater staff.

5. Conclusion

Some have argued that NRP may destroy public confidence in transplant systems.⁴⁴ However, current observational evidence suggests that DCD organ recovery utilizing taNRP offers better recipient outcomes with a more cost-effective method of DCD heart recovery than DPP. Arguably, delaying the wider implementation of taNRP and continuing to utilize a possibly inferior technique that is associated with worse recipient outcomes, while we do little to confirm or refute the safety of taNRP, may also damage public confidence in our transplant and wider health care systems. There is an ethical imperative to expedite this research, and this should be a high priority for the donation and heart transplant communities.

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Declaration of competing interest

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