Normothermic regional perfusion in donor heart recovery: Establishing a new normal

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▶ Video clip is available online.

Almost every article, research document, or administrative manifesto in heart transplantation begins with the following statements/keywords: donors are scarce, donors are limited, the donor pool has not improved, donor shortage, donor shortage limits total number of transplants. Moreover, the number of patients with heart failure who are potentially transplant candidates continues to increase. This notion that somehow dramatic increases in donors will meet the actual demand has quietly been stifled, and instead, alternative therapies are now the real focus of heart failure innovation. Nonetheless, heart transplantation remains an effective and lifesaving therapy. It stands out as one of the great scientific achievements of the 20th century. Certainly, any improvements or novel ways to generate even a few more donors merit serious consideration. The first 21st century strategy to increase the pool of potential organs has been the use of hepatitis C–infected hearts. Taking such hearts with a potentially lethal virus, knowingly transplanting the organ in a naïve recipient, and then treating them after infecting them has to date has been exceptional successful.¹ But even with the rise in drug overdose deaths, the actual increase in acceptable heart donors has been modest. Xenotransplantation is, well, xenotransplantation. The next more immediate frontier is in using hearts from donors who are not formally brain dead. These terminally injured patients fall into a terrible and unique form of purgatory where they do not meet criteria for brain death, have acceptable cardiac, hepatic, and renal function, and likely would persist unless ventilatory support is withdrawn. If a family wants to end this suffering but donate their organs for transplantation, a unique and complex process is required.

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CENTRAL MESSAGE

NRP adds another powerful tool for organ recovery. However, it will further complicate an already imperfect process.

This Invited Expert Opinion offers a perspective based on the following article: https://www.acponline.org/system/files/documents/clinical_information/resources/end_of_life_care/ethics_determination_of_death_and_organ_transplantation_in_nrp_2021.pdf.

Donation after cardiac death (DCD) has been a begrudgingly acceptable process around the world.² For years now, DCD has provided viable livers, lungs, and kidneys. The clinical results have been reasonable and better than the alternative of discarding organs and death on the transplant waitlist. The notion that a heart may be usable after a period of standstill and warm ischemia was thought unlikely until recently. The first modern report among pediatric DCD was certainly favorable.³ Machine perfusion and the Transmedics Organ Care System (OCS) ushered in the new era, when DCD hearts could be recovered, reanimated, and then assessed *ex vivo*.^{4,5} That system, however, significantly increases organ recovery costs and access is currently limited to a few centers. One alternative solution is to reanimate such hearts using cardiopulmonary bypass (CPB) or modified extracorporeal membrane oxygenation (ECMO) circuits. This *in situ* reperfusion, reanimation, and recovery have distinct advantages to all the organs and one complex disadvantage: normothermic regional perfusion (NRP).

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TECHNIQUE AND THE VANDERBILT APPROACH

Unlike conventional brain-dead donors, DCD requires the donor to die first, and this involves essentially anticoagulation and terminal extubation. The ensuing hypercarbia and hypoxia lead to a cessation of cardiac activity. Once the systolic blood pressure is less than 50 mm Hg, the donor enters an agonal phase and all the organs are subjected to warm ischemia. Once the heart stops, the patient is declared dead. Of note, agonal phases have also been defined by oxygen desaturation, but it is increasingly clear that oxygen saturation and blood pressure do not reflect similar degrees of warm ischemia. At Vanderbilt, we are less concerned about oxygen saturation and focused on blood pressure. Nonetheless, when the patient is declared dead and, depending on local regulations, a standoff period is observed, which can be from 5 to 10 minutes. At that point, the patient is considered irreversibly dead and organ recovery can begin. The acceptable limits of warm ischemia are currently unknown in humans. Current opinion based on preclinical work supports 30 minutes as a threshold after which irreversible injury may occur. Clinically, we have recovered hearts for as long as 60 minutes in this agonal phase with acceptable post-transplant function.⁶ Future work will need to focus on true limits as they relate to individual donors considering age, diabetes, hypertrophy, and so forth. Moreover, there is a fantastic opportunity to study potential therapeutics to either precondition hearts or rescue these hearts.

The thoracic team then begins to rapidly perform a sternotomy, pericardiotomy, clamping of the arch vessels, cannulation of the aorta and right atrium, and initiation of circulatory support. The bloodless field allows this to occur faster than one might imagine. In our experience, this can be done in less than 5 minutes with 2 experienced and well-organized surgeons. The goal is to minimize the warm ischemic time to all the organs and safely initiate circulatory support.

Once the cannulas are secured, the donor may be reintubated if lungs are recovered. We place a venting cannula in the main pulmonary artery (PA) to protect the right ventricle and the period of resuscitation begins. The PA cannula obviates the need to reintubate and provides both decompression of the left ventricle and minimizes afterload to the right ventricle. This resuscitative period has no agreed upon strategy, although most centers use well-studied and benign free radical scavengers in their perfusate: steroids, mannitol, erythropoietin, and n-acetyl cysteine.⁶

The reassessment of the heart may be done in a number of ways. The Papworth team, a leader in this field, have reported using PA catheters and serial cardiac output measurements to assess the organ.^{7,8} In an effort to be mobile and adaptable to any environment, our approach at Vanderbilt has been more pragmatic. In our experience, and in a young donor cohort, visual inspection and a brief period of volume loading off circulatory support have been

sufficient. We look for obvious right ventricle dysfunction, bradycardia, malignant arrhythmias, and blood pressure development. We also limit the circulatory time to 50 to 60 minutes to minimize the potential inflammation related to CPB and bleeding. This is an early experience, and we continue to work to better refine this process. Whether biomarkers or these hemodynamic assessments are predictive of early allograft dysfunction is unknown. Our own experience suggests that among young donors, the experienced eyeball test works quite well (Video 1).

Organ recovery then is done in the usual fashion with aortic crossclamping, infusion of cold crystalloid preservation, and standard cardiectomy. We have used Del Nido solution exclusively with satisfactory results, but again, future studies will need to determine the optimal preservation medium.

Control of the cerebral vessels is the cornerstone of the technique to respect the basic premise of death in this setting. There are multiple methods, and although some have argued for some form of cerebral monitoring to ensure a cessation of blood flow, clamping the arch vessels makes any clinically meaningful blood flow impossible.

We have encountered several pitfalls in our early experience. The first is difficulty with aortic cannulation in a depressurized aorta. We had 3 aortic dissections likely due to the placement of the cannula that rendered the heart recovery inadvisable. The abdominal organs were successfully recovered in all 3 cases. We have since added an endotracheal tube stylet in our aortic cannula and place the tip well into the arch. We also take a moment to de-air the cannula because coronary air can delay the cardiac recovery.

Most important, it is critical to have multiple conversations with the procuring teams and local organ procurement organizations. Having the patients die in an operating room, prepping ahead of time, and having the CPB lines up on the field before withdrawal all minimize ischemic time. Unfortunately, there are no agreed upon standards, and teams need to communicate and adhere to the hospital and family wishes. Abdominal teams may not fully understand the implications of CPB and the great advantages to them, so again it is critical to effectively communicate the process.

ADVANTAGES

DCD donors represent a new source of heart donors. Beyond the obvious increase in total donors, the absence of brain death may have both short-term (less early allograft dysfunction) and long-term (less vasculopathy) benefits. Time will tell, but our own short-term experience had less inotrope needs and postoperative ECMO. The circuit is mobile, and NRP does not require transporting donors to another hospital. We bring all of our NRP equipment, including disposables, portable blood gas analyzers, and the entire ECMO circuit with us to all the donor hospitals.⁶ Finally, compared with ex vivo machine perfusion, the costs

are significantly less. Because the period of warm ischemia is aborted by circulatory support, there are likely advantages to the abdominal organs. As a result of NRP, the abdominal team can proceed with their dissection without time pressure. Moreover, the restoration of hyperoxygenated blood may minimize ischemic injury to the biliary system. Although there is an experience with using ECMO for abdominal only recoveries, it relies on retrograde perfusion via the femoral arteries and aortic interruption via a left thoracotomy. Central cannulation may provide better perfusion of the abdominal organs and venous decompression. Finally, the overall costs are centered around the pump, oxygenator, and disposables. However, the necessary personnel are also more than a conventional recovery team. At Vanderbilt, we have 2 perfusionists, 2 surgeons, and 1 preservationist on every case.

CLINICAL RESULTS TO DATE

NRP was pioneered in the United Kingdom and Europe with a landmark series from the Papworth group.⁷ There are 2 relevant techniques as described by the series. The first is to use NRP and then recover the hearts using ex vivo perfusion, in this case the Transmedics OCS. The other is to recover the heart conventionally using cold storage after a period of in situ resuscitation. Overall, rates of primary graft dysfunction and ECMO use have been low. No studies have examined long-term outcomes or incidence of graft coronary vasculopathy. In a small study of brain-dead donors on the OCS, there were no significant differences in intimal thickening at 1 year.⁹

ABDOMINAL ORGAN OUTCOMES

Along with hearts and lungs, attention to outcomes for abdominal organs is also relevant. Traditionally, DCD liver and kidneys have been associated with acceptable although somewhat inferior outcomes compared with donation after brain death. Likely related to the period of warm ischemia, biliary complications remain higher among DCD organ recipients.¹⁰

NRP appears to improve outcomes compared with DCD. A series from Spain details the improvement. A total of 95 patients underwent NRP compared with 117 with standard DCD recovery. Biliary complications were reduced from 31% in the standard group to 8% in the NRP group.¹⁰

MACHINE PERFUSION VERSUS NORMOTHERMIC REGIONAL PERFUSION

A truly novel 21st century debate is emerging between ex vivo machine perfusion versus in situ NRP. Machine perfusion allows for a less complex recovery, organ assessment, and portability. However, the costs are significant. Moreover, the absence of loading, limited assessment tools, and secondary effects of ex vivo perfusion remain problematic. NRP adds significant complexities, both technically

and emotionally, limits myocardial injury, potentially improves outcomes for extra thoracic organs, and is currently cheaper. When we develop potential therapeutic measures on both platforms, this debate will become even more complex, agonizing, but certainly interesting.

LIMITS OF WARM ISCHEMIA

How long can a human heart withstand warm ischemia if resuscitated and reanimated using extracorporeal circulation and unloading. Current thinking is focused on 30 minutes. However, when warm ischemia actually begins is unclear. The agonal phase is defined by both oxygen saturations and blood pressure. However, in our experience they may not be synchronous and young donors may have incredibly low saturations for more than 30 minutes without any significant declines of blood pressure. Moreover, we really do not have any sense for actual ischemia at the tissue level. This matters because abdominal teams will abandon organs after 30 minutes and hospitals will abandon the entire process if the donor does not die after 90 minutes. Because the mortality in these cases is 100% and potentially beneficial organs will be discarded and incinerated, having a firm understanding of viability is critical.

PREDICTING DEATH

Because we do put limits on these types of recoveries, predicting which donors will pass and those who will not is also an increasingly relevant question. Given the resources in both time, travel, and moral fortitude, developing reliable ways to predict this unique form of death is meaningful and important. In the existing literature, there are some data that support age, mechanism of injury, and residual reflexes.^{11,12}

THE DISADVANTAGE AND RETHINKING OUR NOTION OF DEATH

"Mostly dead is also slightly alive" is a memorable line in the movie *The Princess Bride* but does frame the perspectives on death and organ donation. The notion of benefiting from another person's expedited death was difficult enough. In the United States, this was detailed in the landmark case of *Tucker v Lower*.¹³ Although beyond the scope of this review, the details of this case are worth reading. *Tucker v Lower* essentially separated the notion of death and brain death, without which modern transplantation in the United States would be impossible. However, the details of the case illuminate the different perspectives on organ donation. Although the transplant community see all the good, those outside of the field see real conflicts of interest. Transplant teams benefit from the transplant process: more transplants, more money, more research, more television shows, more social media. On the other hand, organ donation is also predicated on the wishes of the donor to help others with their death. NRP adds another challenge. The dead donor

VIDEO 1. DCD donor cannulated and resuscitated using NRP. Video available at: [https://www.jtcvs.org/article/S0022-5223\(21\)01735-9/fulltext](https://www.jtcvs.org/article/S0022-5223(21)01735-9/fulltext).

rule is designed to protect people from being killed for their organs. So, people have to be dead to donate: They have irreversible brain injury, brain death, or irreversible cessation of cardiac function. No circulation means death. NRP restores circulation and restarts the heart itself. The very notion of death for all recorded time is that your heart has stopped. NRP challenges this premise and then has recovery teams stopping the heart *again* to recover it for another person. Transplant professionals recognize that the alternative is that all of these organs would be discarded, so why not?

In a beautifully written editorial, Parent and colleagues¹⁴ and the team from NYU nicely articulate why NRP remains within the guardrails of a civilized society. First, death, they argue is about permanence. NRP does temporarily restore the circulation, but the outcome remains unquestioned. The restoration is not intended to resuscitate the patient.

Moreover, NRP is intended to respect the donors wishes to provide viable hearts, lungs, livers, and kidneys to others so they may benefit. Medical ethics is usually filled with multiple and dynamic voices that are advocating for their agendas. Parent and colleagues¹⁴ rightfully remind us that we all need to consider the donor who cannot advocate for himself at his journey's end.

CONCLUSIONS

Today, NRP offers a way to use hearts that would otherwise be thrown away, respect a donor's last wish, and save lives. What we learn about reanimating and resituating hearts in this platform may also provide important insights into how we protect and rescue all hearts from injury. Today, NRP will help increase organs for transplant, and ultimately by illuminating key biochemical or genetic recovery pathways may actually help decrease the need for transplant. While challenging our 20th century notions, NRP opens a new 21st century frontier to boldly explore whole organ physiology, our own ideas of death, and an individual's last full measure of devotion.

Conflict of Interest Statement

The author reported no conflicts of interest.

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