Chapter

Normothermic Regional Perfusion in Solid Organ Transplantation

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Abstract

Normothermic regional perfusion (NRP) is used to restore the flow of oxygenated blood following cardiac arrest and reverse warm ischemic injury in donation after circulatory death (DCD) organ transplantation. The use of NRP in this setting has typically been limited to the abdominal cavity, though its use has recently been expanded to chest to help recover DCD hearts, as well. This chapter evaluates the principles behind the use of NRP in DCD organ transplantation as well as not only technical but also ethical and legal aspects associated with its application and the clinical results that have been achieved to date when it has been used to recover various solid organs through the DCD process.

Keywords: controlled donation after circulatory death, kidney transplantation, liver transplantation, uncontrolled donation after circulatory death, warm ischemia

1. Introduction

Donation after circulatory death (DCD) donors, which are declared dead following cardiorespiratory arrest, are an increasingly more common source of organs for transplantation. They may be classified among four categories depending on events and conditions surrounding arrest: category I, dead on arrival (no attempt at resuscitation); category II, sudden cardiac arrest followed by unsuccessful resuscitation; category III, arrest following intentional withdrawal of life support in ventilated patient not meeting brain death criteria; and category IV, cardiac arrest while brain dead. Categories 1, 2 and 4 are classified as uncontrolled DCD (uDCD) and category 3 as controlled DCD (cDCD) [1]. In practice, category III cDCD and, to a lesser extent, category II uDCD donors comprise essentially all DCD donors that are used for transplantation globally. The period of warm ischemia surrounding arrest, however, provokes organ injury, and DCD in general yields fewer organs per donor and ones of inferior quality when compared with donation after brain death (DBD) [2]. For this reason, there has been increasing interest in forgoing rapid cold preservation and recovery following the declaration of death (still the "gold standard" for DCD organ recovery in most transplant centers) and instead using normothermic regional perfusion (NRP) to temporarily restore oxygenated blood flow the abdominal and more recently thoracic organs prior to recovery.

2. Principles behind the use of normothermic regional perfusion in donation after circulatory death

During warm ischemia, ATP degradation leads to the progressive accumulation of xanthine and hypoxanthine, important sources of superoxide radical at organ reperfusion [3]. A period of post-ischemic NRP in DCD donors is useful to restore cellular energy substrates [4], reduce levels of nucleotide degradation products [5], improve the concentrations of endogenous antioxidants [6], and even stimulate processes of cellular repair prior to graft recovery [7] (**Figure 1**). An experimental study demonstrates that by blocking the A2 receptors of adenosine, the beneficial effects of NRP are abolished, indicating that NRP mediates its effect, at least in part, through adenosine as a form of ischemic preconditioning [8]. Post-ischemic NRP may also be useful to reduce the vasoconstrictive effects of cold graft washout with the static cold storage solution [9] and offers an opportunity to assess organ viability prior to recovery [10, 11].

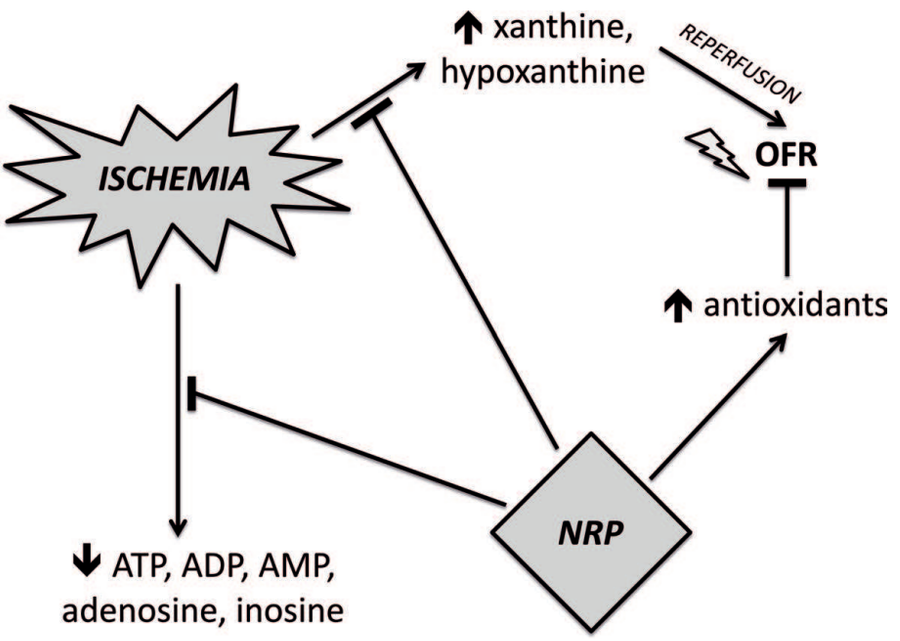

Figure 1.
During ischemia, the concentrations of adenine nucleotides (ATP, ADP, AMP) and nucleosides (adenosine, inosine) progressively decline. Also, the concentrations of nucleotide breakdown products (xanthine, hypoxanthine) increase, thereby leading to the production of oxygen free radicals upon reperfusion. Normothermic regional perfusion is capable of reversing these processes and increases the concentrations of endogenous antioxidants, effectively recharging and reconditioning organs in the abdomen and chest prior to recovery for transplantation.

3. Techniques for establishing normothermic regional perfusion in donation after circulatory death

While NRP relies on extracorporeal membrane oxygenation (ECMO) technology, its clinical application is, in general, less complex than that of therapeutic ECMO. A venous cannula is placed to derive blood from the donor inferior vena cava or right atrium, which is then pumped through a membrane oxygenator and a heat exchanger before returning to the donor arterial bed (aorta or iliac or femoral artery). An in-line reservoir may be included in the circuit, as well, to allow for replacement of volume prior to circuit failure in the event of volume loss or inadequate venous return due to severe vasoplegia (particularly relevant in the setting

of uDCD). The precise positioning of occlusion balloon catheters or clamps used to exclude other vascular beds is what determines whether NRP is either thoracoabdominal or abdominal only.

3.1 Abdominal normothermic regional perfusion

In uDCD, cannulation for the establishment of abdominal NRP is performed post-mortem after death is declared, typically in the emergency department. In cDCD, in contrast, cannulation for abdominal NRP may be performed either prior to the withdrawal of life support (pre-mortem) or following the declaration of death. Pre-mortem cannulation may be performed either percutaneously or via femoral cut-down in a variety of settings (intensive care unit, radiology suite, operating room). Post-mortem cannulation, on the other hand, is most often done in open abdomen in the operating room, though some centers have used femoral artery and vein catheters or guidewires placed prior to withdrawal of care to access and thereby cannulate the femoral vasculature following the declaration of death [12].

For uDCD donors and cDCD donors with pre-mortem cannulation, a bolus of heparin is administered, and cannulation of unilateral femoral vessels is performed either via open femoral cutdown and isolation of the femoral artery and vein or percutaneously using Seldinger technique [11]. Cannulae are left clamped and connected to the tubing of the primed NRP circuit. The contralateral femoral artery is also cannulated with an aortic occlusion balloon catheter, which is left deflated in the case of cDCD and advanced into the supraceliac aorta under radiographic control. Following the withdrawal of life support and the declaration of death in cDCD, the aortic occlusion balloon is inflated, and the abdominal NRP circuit is initiated (**Figure 2**). Proper positioning of the balloon excluding the aortic arch vessels is confirmed by chest radiograph and absence of flow measured in a left radial arterial catheter.

For cDCD donors undergoing open post-mortem cannulation, once death has been declared, the surgical team performs midline laparotomy to cannulate the abdominal aorta immediately proximal to and the infrarenal inferior vena cava immediately distal to their respective bifurcations. Cannulae are connected to the tubing of the primed NRP circuit, the supraceliac aorta is clamped, and NRP is initiated.

Blood is sampled at baseline and every 30 minutes during abdominal NRP to determine biochemical, hematological, and acid-base parameters. In general, pump flow is maintained >1.7 L/min/m^2, temperature 35–37°C, PaO_2 100–150 mmHg, and hemoglobin >7 g/dL. Hepatic transaminases should remain stable throughout NRP; levels >3× the upper limit of normal at baseline and/or >4× the upper limit of normal at the end of NRP may be considered relative contraindications for recovery of the liver and pancreas [10, 11]. In general, NRP is run for a minimum of 1 hour and a maximum of 4 hours to allow adequate reconditioning of the abdominal organs and recovery of energy substrates without provoking additional end-organ injury [4, 5, 7, 8, 13, 14].

3.2 Thoracoabdominal normothermic regional perfusion

While the circuit for abdominal NRP may be established pre-mortem, cannulation to establish a complete thoracoabdominal NRP circuit is done post-mortem in the operating room. After the declaration of death, the chest is entered through a midline sternotomy, and the pericardium is opened. A bolus of heparin is injected into the heart directly, an arterial cannula is inserted into the distal ascending aorta/aortic arch, and a venous cannula is inserted into the right atrium. Cannulae are connected to the tubing of the primed NRP circuit, the aortic arch vessels are clamped, and NRP is initiated.

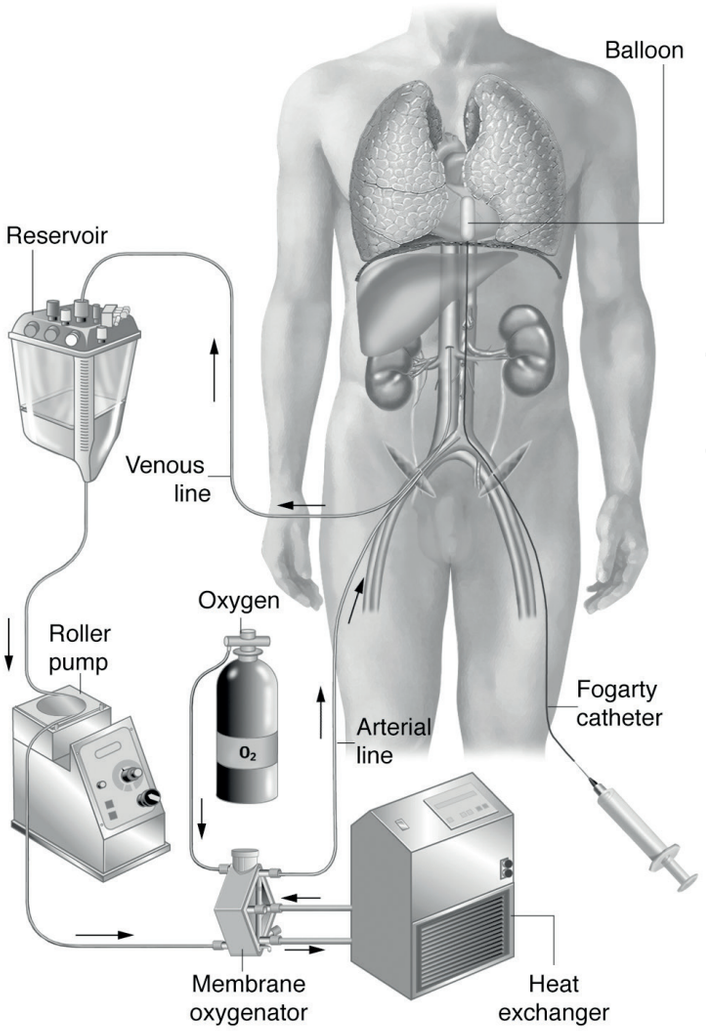

Figure 2.
Abdominal normothermic regional perfusion. Cannulae are placed in the femoral artery and vein in the groin region. A Fogarty balloon catheter is introduced through the contralateral femoral artery and positioned in the supraceliac abdominal or thoracic aorta.

During thoracoabdominal NRP, pump flow is maintained ≥2.5 L/min/m^2, temperature 35°C, and hemoglobin >10 g/dL. Prompt laparotomy is performed to assess hepatic and intestinal perfusion and to exclude the lower extremities from the perfusion circuit. Once cardiac contractility has been restored, weaning from NRP is attempted. If the heart is able to take over circulation, functional assessment is performed using transesophageal echocardiography and pulmonary artery flotation catheter (Swan-Ganz) monitoring. In general, acceptance criteria for a cDCD heart recovered with NRP include central venous pressure ≤12 mmHg, pulmonary capillary wedge pressure ≤12 mmHg, cardiac index ≥2.5 L/min/m^2, and left ventricular ejection fraction ≥50% [15–17].

4. Clinical outcomes using normothermic regional perfusion in donation after circulatory death

To date, the great majority of human transplants performed using organs recovered with NRP have been donor using DCD kidneys and livers. In more recent years, the use of DCD pancreata and even hearts recovered with NRP has also been reported.

4.1 Kidney transplantation

When compared with other solid organs for transplantation, the kidney is relatively resilient and withstands the ischemic insult inherent to the DCD process relatively well. Nonetheless, kidneys from DCD donors recovered with NRP as opposed to rapid *in situ* cold preservation or hypothermic perfusion/"total body cooling" (TBC) have demonstrated significantly better immediate as well as ongoing graft function [18–20]. Reports from different groups in Europe, the United States, and Asia have described the use of NRP in both uDCD and cDCD kidney transplantation, with rates of delayed graft function (DGF) around 50–70% and 30–40%, respectively; negligible (if any) primary non-function (PNF); and excellent 1-, 5-, and even 10-year graft survival rates [19–27]. While reported rates of DGF may still seem to be high even among DCD kidneys recovered with NRP (especially those arising through uDCD), the pathogenesis and, consequentially, implications of DGF seem to be less severe than those associated with DGF arising in the context of DBD kidney transplantation. Ischemic injury appears to be implicated to a greater extent in the development of DGF among DCD kidneys, whereas, in DBD, alloimmune phenomena prevail [28]. A recent large single-center study reported 73% DGF among 237 uDCD kidneys recovered with NRP versus 46% among a contemporary cohort of matched DBD kidneys, but 10-year graft survival rates did not vary at all between the two groups and were excellent in both (82 and 80%, respectively). The authors also noted that while donor age >50 years was significantly associated with graft loss among uDCD kidneys, the development of DGF in the immediate post-transplant period was not [27].

4.2 Liver transplantation

The cells of the liver, in particular those lining the biliary tree, are particularly sensitive to warm ischemia, and initial experiences with DCD liver transplantation described high rates of graft dysfunction and non-function and non-anastomotic biliary strictures/ischemic type biliary lesions (ITBL) in up to 50% of cases [29]. While complication rates have improved with experience, the rate of post-transplant ITBL remains higher among recipients of DCD versus DBD grafts: 16 versus 3%, according to two meta-analyses [30, 31]. The clinical relevance of ITBL lies in the fact that up to 70% of patients with ITBL require re-transplantation or die [32].

After an initial period where different donor maintenance techniques were used, including rapid *in situ* cold preservation, simultaneous chest and abdominal compressions, and TBC, NRP has come to be the "gold standard" and primary means by which uDCD livers are recovered for transplantation. Using NRP, even livers with extensive pre-recovery warm ischemic periods of up to 2.5 hours have been successfully transplanted, with biliary complication and graft survival rates comparable to those seen using cDCD livers that have suffer considerably less warm ischemia [10, 11, 33–35].

In spite of its relative success in the setting of uDCD, the application of NRP in cDCD liver transplantation remains more limited. The great majority of cDCD livers that are transplanted in the world today are still recovered with rapid *in situ* cold preservation, and reports on the use of NRP in cDCD liver transplantation have been, until recently, anecdotal [12, 24–26, 36, 37]. In the past year, however, two larger multicenter studies have come out describing the benefits that may be achieved with post-mortem NRP in cDCD liver transplantation. First, a Spanish national study compared the results of 95 cDCD liver transplants performed with post-mortem NRP with those of 117 cDCD liver transplants performed with super rapid recovery (SRR). Median donor age in the study was relatively high (57 years [25-75% interquartile range, IQR 45–65] NRP, 56 years [25-75% IQR, 47–64] SRR). With a median

follow-up of 20 months, the use of post-mortem NRP appeared to significantly reduce rates of postoperative biliary complications (overall 8% NRP vs. 31% SRR, $p < 0.001$; ischemic type biliary lesions 2% NRP vs. 13% SRR, $p = 0.008$) and graft loss (12% NRP vs. 24% SRR, $p = 0.008$) [38]. Similarly, a combined experience from centers in Cambridge and Edinburgh in the United Kingdom compared the results of 43 cDCD liver transplants performed with post-mortem NRP with those of a contemporary cohort of 187 cDCD liver transplants performed with SRR. Median donor age was less for cDCD livers with NRP versus those with SRR: 41 years (25-75% IQR 33–57) vs. 54 years (25-75% IQR 38–63), respectively. Reported rates of anastomotic biliary strictures were 7% NRP vs. 27% SRR ($p = 0.004$), ITBL 0 NRP vs. 27% SRR ($p < 0.001$), and 90-day graft loss 2% NRP vs. 10% SRR ($p = 0.102$) [39].

4.3 Pancreas transplantation

The Michigan Group described one cDCD pancreas transplant in which the donor was maintained with NRP, though the outcome of the graft was not mentioned [24]. In another multicenter report from the United Kingdom, two SPK were described (again, outcomes not mentioned), and two more pancreata were sent for isolation of islets, one with good yield [25]. In Spain, where NRP is now routinely used to recover abdominal organs when cDCD liver and/or pancreas transplantation is contemplated, a total of five cDCD pancreas transplants were performed between 2015 and 2017, and all these grafts remain functional at the time of this writing [40].

4.4 Heart transplantation

The application of thoracoabdominal NRP has been described in clinical series on cDCD heart transplantation; however, no report has been published to date describing the transplantation of the lungs from these same cDCD donors. (Transplantation of DCD lungs recovered with "dual temperature" *in situ* cold flushing in the chest with abdominal NRP running simultaneously, on the other hand, has been described and is performed routinely in some settings.) The fact remains that DCD donor lungs tolerate warm ischemia and the process of DCD donation and recovery relatively well, and post-DCD lung transplantation outcomes without NRP appear to be comparable to those of DBD lung transplantation [41].

The cDCD heart, on the other hand, is more susceptible to warm ischemic injury, and cDCD hearts recovered and transplanted after *in situ* cold preservation followed by static *ex situ* cold storage can offer suboptimal outcomes. A recent report on pediatric cDCD heart transplantation describes 61% 1-year graft survival as opposed to 91% for DBD hearts of similar baseline characteristics [42]. Performing thoracic NRP, on the other hand, allows for restoration of contractile function and performance of a standard functional assessment in ischemically injured cDCD cardiac allografts prior to recovery. Clinical application of thoracoabdominal NRP in cDCD heart transplantation has been described by the Papworth Hospital Group from the United Kingdom. In combination with subsequent *ex situ* normothermic machine perfusion (NMP), the use of thoracoabdominal NRP has allowed 100% utilization of organs subsequently undergoing NMP and lower early allograft dysfunction versus cDCD hearts undergoing NMP only (8% vs. 17%, respectively) [16, 17]. Thoracoabdominal NRP followed by static cold storage has even been used to successfully transplant a cDCD heart procured at the same center [17]. If broader application of this last strategy is shown to be just as efficacious, it has the potential to significantly reduce the costs associated with cDCD heart transplantation by obviating the need for *ex situ* NMP, which is a very expensive modality costing approximately $45,000 for each heart perfusion unit.

5. Ethical and legal concerns surrounding the use of normothermic regional perfusion in donation after circulatory death

There are some ethical concerns surrounding the use of NRP in donation after circulatory death, and laws vary from one country to another regarding whether or not NRP may be applied in DCD and, if so, how and when.

5.1 Uncontrolled donation after circulatory death

In uDCD, cardiac arrest is sudden and unexpected, and death is declared based on the irreversible loss of cardio-respiratory function (demonstrated after prolonged efforts to reverse it have failed). Death is usually declared in the emergency room by a team entirely independent of that responsible for organ recovery and preservation. More often than not, potential uDCD donors are declared dead prior to the arrival of next-of-kin. Based on a consequentialist ethical standpoint and the principles of utility and donor autonomy, certain countries, including Spain and France, allow cannulation maneuvers to commence in this setting, even in cases where first-person consent may not have yet been obtained [43, 44]. The will of the patient regarding donation is always subsequently investigated in the context a family interview, where information regarding the circumstances of the arrest, the outcome of resuscitation maneuvers, and the measures taken related to the donation process is relayed. Next-of-kin then decide, taking into consideration the potential donor's wishes, whether to proceed with donation or abort the process.

It should be clear that NRP is organ maintenance and not therapy. While the technology employed is similar, terms such as "extracorporeal membrane oxygenation/ECMO" and "extracorporeal life support/ECLS" should not be used in relation to organ donation. Such terminology is confusing, especially considering the fact that it is used to describe therapeutic maneuvers that may be used to recover patients suffering sudden cardiac arrest more commonly occurring inside the hospital itself.

5.2 Controlled donation after circulatory death

In cDCD, the usual stand-down period of 2–5 min of asystole that is used to declare death does not necessarily reflect an irreversible loss of cardiac function, evidenced by the fact that cDCD hearts have been recovered and successfully transplanted [17, 45]. The "irreversibility" of death in cDCD is therefore predicated on the concept of permanence—the fact that loss of cardiac function will eventually become irreversible because it will not be reversed (and eventually lead to the loss of all brain and brain stem functions, as well). As it re-establishes circulation to some parts of the body, however, the use of NRP in this context remains controversial. At the least, clear and effective measures need to be put in place to ensure that cerebral reperfusion does not occur when NRP is established. Through the use of NRP, circulation is only restored to a limited region of the body, and a critical aspect of NRP in cDCD is ensuring lack of flow to the aortic arch vessels, thereby maintaining the permanence of circulatory arrest in the brain and brainstem. With pre-mortem cannulation, positioning of the aortic occlusion balloon in the supradiaphragmatic aorta distal to the left subclavian artery is confirmed radiographically prior to withdrawal of care. As additional measure, the aortic occlusion balloon may be briefly inflated for a few seconds prior to ventilatory withdrawal, in order to ensure disappearance of femoral arterial pressure and simultaneous maintenance of a normal pressure waveform in the left radial arterial line. In doing so, the minimum filling volume needed to entirely blocks the supradiaphragmatic aorta may be recorded [46]. Once NRP is initiated, adequate occlusion is confirmed through the use of a left radial artery catheter demonstrating absence of flow.

The timing of when cannulation for abdominal NRP may be performed in potential cDCD donors varies by country. In certain countries, such as Spain and the United States, pre-withdrawal heparinization and cannulation are permitted [24, 43]. In the United Kingdom, on the other hand, a potential cDCD donor may only be cannulated once death has been declared [25]. Pre-mortem cannulation is advantageous in that it is performed in a less stressful and more orderly fashion, and regional perfusion may be commenced immediately after the death declaration, thereby limiting the length of warm ischemia suffered. Ideally, pre-mortem cannulation should be performed in the least invasive manner possible (e.g., percutaneously).

6. Summary and future directions

Table 1 summarizes the current state of NRP in the various fields of clinical DCD organ transplantation. The application of post-mortem NRP appears particularly relevant and advantageous in DCD kidney, liver, and heart transplantation, and the future will tell if it can have impact the fields of DCD pancreas and lung transplantation, as well. Some ethical concerns remain surrounding its use, primarily in the context of cDCD, and clear and effective steps need to always be taken to ensure lack of reperfusion of the brain and brainstem once NRP has been initiated. Through these measures and continued dialog with both intensive care as well as extra- and intrahospitalary emergency medical professionals, the hope is that the use of NRP and, thereby, DCD organ transplantation in general may be expanded to offer more organs and ones of better quality to a greater number of patients with end-stage organ disease.

Kidney	Lower rates of immediate post-transplantation delayed graft function and primary non-function and improved ongoing graft function among both uDCD and cDCD allograft recipients.
Liver	Lower rates of post-transplantation biliary complications, including ischemic type biliary lesions, and less graft loss among cDCD livers; considered essential for the evaluation and recovery of uDCD livers
Pancreas	Feasible, though more experience is required to determine its true impact
Lung	No reports to date
Heart	Less early allograft dysfunction; allows for *in situ* functional assessment that can not only help avoid subsequent costly and potentially unsuccessful *ex situ* normothermic machine perfusion functional assessment but perhaps even the use of NMP altogether

Table 1.
Clinical results observed to date with application of normothermic regional perfusion in donation after circulatory death organ transplantation.

Conflict of interest

None to declare.

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