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REVIEW

Hypothermic or normothermic abdominal regional perfusion in high-risk donors with extended warm ischemia times: impact on outcomes?

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Summary

Donation after circulatory determination of death (DCD) has the potential to increase the applicability of transplantation as a treatment for end-stage organ disease; its use is limited, however, by the warm ischemic damage suffered by potential grafts. Abdominal regional perfusion (ARP) has been employed in this setting to not only curtail the deleterious effects of cardiac arrest by re-establishing oxygenated flow but also test and even improve the viability of the kidneys and liver prior to transplantation. In the present review article, we discuss experimental and clinical studies that have been published to date on the use of ARP in DCD, differentiating between its application under hypothermic and normothermic conditions. In addition to describing results that have been achieved thus far, we describe the major obstacles limiting the broader implementation of ARP in this context as well as potential means for improving the effectiveness of this modality in the future.

The remarkable success of transplantation as a treatment for end-stage kidney and liver disease over the past several decades has led to a substantial gap between the number of transplant indications and actual transplants performed. Given the current situation of organ donation in which the donor pool continues to fail to meet demands, alternative sources of organs are continuously sought. One such source that in theory offers considerable promise but in practice has yet to come close to meeting its supposed potential is that of donation after circulatory determination of death (DCD).

The main limitation to widespread successful application of DCD is the fact that organs recovered through DCD are by and large suboptimal due to the prerecovery period of warm ischemia that they suffer [1]. In order to achieve transplantable grafts in this setting, the donor preservation process needs to be modified so as to limit and even partially reverse the ischemic insult prior to transplantation. In this sense, abdominal regional perfusion (ARP) may be used to restore the flow of oxygenated blood to the kidneys, liver, and pancreas after death has been declared based on cardiorespiratory criteria [2,3]. It offers the opportunity to not only improve but also assess graft viability prior to reperfusion in the recipient.

Principles behind abdominal regional perfusion

Abdomen regional perfusion involves isolation of the subdiaphragmatic from the systemic circulation and perfusing

the abdominal region with continuous flow. It relies on cardiopulmonary bypass (CPB)/extracorporeal membrane oxygenation (ECMO) technology and uses an in-line pump to recover donor venous blood, mix it with substrates and solutions, deliver it to a membrane oxygenator, and then return the oxygenated blood to the donor subdiaphragmatic aorta. Large-bore cannulae are typically placed peripherally in the femoral vasculature, and the supraceliac aorta may be excluded from the circuit via a Fogarty balloon catheter introduced in the contralateral femoral artery. Alternatively, the abdominal aorta and inferior vena cava may be cannulated in the open abdomen and the thoracic aorta excluded through the use of a clamp placed proximal to the celiac trunk, or the thoracic aorta and inferior vena cava may be cannulated after median sternotomy and the supradiaphragmatic circulation excluded using clamps placed separately across the ascending aorta and arch vessels. Good illustrations depicting ARP circuits have been published previously [4,5].

Hypothermic regional perfusion

In hypothermic regional perfusion (HRP), the temperature of the diluted blood solution is actively cooled to anywhere from 4 to around 20 °C. Theoretical benefits for its use include more efficient cooling, reduced warm ischemia, and continuous gas exchange during the organ recovery process when compared with *in situ* cold flush (CF) techniques (Table 1).

In the experimental setting, continuous hypothermic perfusion ("core-cooling technique") has been studied by the group from Saitama, Japan, and has been shown to improve energy charge and post-transplantation outcomes over the use of *in situ* CF in both normal and ischemically damaged liver grafts [6,7]. Interestingly, this group was unable to demonstrate significant improvements in post-transplantation renal function versus *in situ* CF using the same experimental model [8]; they also experienced relatively high rates of delayed graft function (DGF) and primary nonfunction (PNF) among DCD kidneys maintained in this manner and transplanted clinically [9]. In spite of the theoretical benefit of improved gas exchange throughout the organ recovery process, it was demonstrated that oxygen consumption after only 15–20 min of hypothermic perfusion was minimal [10], highlighting the fact that normal metabolic processes are significantly reduced at subnormothermic temperatures.

More recently, in a porcine model, Mendes and colleagues demonstrated improved post-transplantation survival among the recipients of DCD kidneys maintained with HRP at 4 °C versus normothermic regional perfusion (NRP) at 37 °C, in spite of the fact that renal artery flow and the concentrations of several vasoactive agents (TXB2, NO, ET-1, PGI2) and energy substrates (ATP, ADP, AMP) did not vary between groups [11]. These results are in contrast to those of a clinical study that demonstrates significantly better post-transplantation outcomes among DCD kidneys maintained with NRP versus either total body cooling (TBC) or *in situ* CF [12].

Table 1. Potential benefits of abdominal regional perfusion in donation after circulatory determination of death.

Hypothermic
More efficient organ cooling
Reduced warm ischemia
Continuous gas exchange during organ recovery and repletion of cellular energy stores
Normothermic
Restoration of normal metabolism and cell processes prior to cold ischemia
Repletion of cellular energy stores
Reduction in nucleotide degradation products
Induction of endogenous antioxidants
Reduced vasoconstrictive effects of hypothermic flush
Comprehensive assessment of organ viability prior to recovery

Normothermic regional perfusion

Normothermic regional perfusion is performed without any active cooling of the perfusate. Unlike hypothermic perfusion, in which metabolic processes are suppressed and metabolic requirements significantly reduced, normothermic perfusion relies on an adequate supply of oxygen and other substrates to fuel processes of cellular homeostasis as well as repair. Given that cellular metabolism is fully restored, normothermic perfusion allows for a more comprehensive assessment of organ viability prior to recovery and transplantation [13,14]. In DCD organs, in particular, a period of normothermic perfusion after cardiac arrest and prior to cold preservation may help reduce the vasoconstrictive effects and thereby improve the effectiveness of the subsequent hypothermic flush [15] (Table 1).

During warm ischemia, ATP degradation leads to the progressive accumulation of xanthine and hypoxanthine, important sources of superoxide radical at organ reperfusion [16]. A period of NRP after warm ischemia helps to restore cellular energy substrates [17], reduce levels of nucleotide degradation products [13], and improve the concentrations of endogenous antioxidants [18] (Fig. 1). An experimental study demonstrated that by blocking the A2 receptors of adenosine, the beneficial effect of NRP was abolished in the liver, indicating that NRP mediates its effect through adenosine and essentially converts the prerecovery period of cardiac arrest into one of ischemic preconditioning [19].

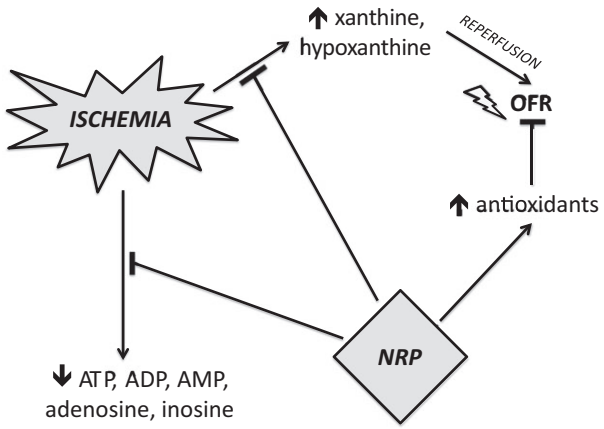

Figure 1 During ischemia, the concentrations of adenine nucleotides (ATP, ADP, AMP) and nucleosides (adenosine, inosine) progressively decline. Also, the concentrations of nucleotide breakdown products (xanthine, hypoxanthine) increase, thereby leading to the production of oxygen free radicals upon reperfusion.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

Clinical outcomes with hypothermic regional perfusion

Kidney

The group in Clínico San Carlos in Madrid, Spain, published one of the first clinical series of renal transplantation performed using grafts arising from Maastricht categories 1 and 2 DCD donors (sudden and unexpected extrahospitalary cardiac arrest followed by failed attempts at resuscitation and extrahospitalary – Maastricht 1 – or intrahospitalary – Maastricht 2 – declaration of death) maintained with hypothermic perfusion [20]. Total body cooling performed using extracorporeal CPB was initiated immediately after the diagnosis of death and run for up to 240 min. In the 2006 update on their series, the group reported on 320 kidneys transplanted over a 16-year period. Initial graft function was observed in 111 grafts (35%), DGF in 195 (61%), and PNF in 14 (4%) [21].

Another early series of reports from the group in Saitama, Japan, describes kidney transplants performed using grafts recovered from category 3 DCD donors (cardiac arrest precipitated by the intentional removal of life support) maintained with HRP at 15 °C [9,10,22]. Donors were heparinized prior to the withdrawal of life support, but the femoral vessels were not cannulated until after the declaration of death. In their 1997 update, the group describes 34 kidney transplants performed from 17 donors. Initial graft function was observed in three recipients (9%), DGF in 29 (85%), and PNF in 2 (6%) [9].

More recently, the National Taiwan University has published several updates on their series of kidney transplants performed with grafts recovered from category 3 DCD donors maintained with HRP at 4 °C. Femoral vessels were prepared prior to withdrawal, but actual cannulation was not performed after cardiac arrest and the declaration of death [23–26]. In their most recent report, the group compares 31 DCD transplants with 120 donation after brain of death (DBD), and 68 live donation transplants performed during the same 5-year time period. While 5-year graft and patient survival rates were not statistically different between the three groups, DGF occurred at a significantly higher rate among DCD recipients: 42% vs. 27% and 11%, respectively ($P = 0.003$). The authors also observed a correlation between longer HRP duration and the subsequent development of DGF among DCD recipients.

Finally, the group from Wake Forest University in the United States recently reported the results of their series of 134 category 3 DCD kidney transplants performed during a 7-year time period. Nineteen grafts were recovered from donors managed with hypothermic perfusion at 22 °C, with vascular cannulation and systemic heparinization performed prior to the withdrawal of life support; the rest were recovered after rapid *in situ* CF. Among recipients transplanted from donors managed with hypothermic perfusion, only 4 (21%) developed DGF, compared with 69 (60%) transplanted from donors undergoing rapid CF ($P = 0.002$). Perfused grafts also demonstrated lower renal vascular resistive indices during *ex situ* hypothermic machine perfusion and better eGFR at 1 month [27].

Liver

Clinical data on the use of livers arising from DCD donors maintained with HRP is scarce. One report from Taiwan describes the successful use of a liver from a Maastricht category 4 DCD donor (irreversible neurological injury followed by cardiac arrest) maintained with hypothermic ECMO/TBC in the period following the arrest and during organ recovery [28]. The group from Wake Forest University has also described six liver transplants performed using grafts arising from category 3 DCD donors maintained with hypothermic perfusion at 22 °C, all of which apparently experienced good initial graft function [29].

The group from La Coruña, Spain, has described their series of category 2 DCD liver transplants, in which potential donors were maintained with HRP ($n = 7$), NRP ($n = 10$), or simultaneous chest and abdominal compressions ($n = 10$). Five-year graft survival in the series was relatively low (49%), while the rate of biliary complications was high, with 25% of DCD recipients developing ischemic-type biliary strictures. As the number of patients in each subset was small, however, the authors were unable to

detect any differences in outcome based on the method of DCD donor maintenance that they used [30].

Table 2 summarizes clinical outcomes with HRP in DCD organ transplantation.

Clinical outcomes with normothermic regional perfusion

Kidney

The Hospital Clínic in Barcelona, Spain, reported one of the first series using NRP in clinical renal transplantation performed in the context of category 2 DCD. Kidneys transplanted from donors maintained with NRP were compared with ones arising from donors maintained with either *in situ* CF or TBC (n = 8, 40, and 8, respectively). Rates of PNF and DGF were significantly lower in the NRP group (PNF 0, DGF 13%) when compared with both *in situ* CF (23% and 55%, respectively) and TBC (0 and 75%, respectively). The postoperative decrease in serum creatinine was also faster in recipients of kidneys maintained with NRP [12].

The group at the University of Michigan recently reported an update on the results of their series of category 3 DCD donors maintained with NRP in which vascular cannulation was performed prior to ventilator withdrawal. From 37 donors treated during a 13-year period, a total of 48 kidneys were transplanted. Among the 29 that were transplanted at the authors' institution, initial graft function was observed in 19 recipients (66%), DGF in 9 (31%), and PNF in 1 (3%) [31].

Normothermic regional perfusion has also been used in clinical DCD kidney transplantation in France [32,33], Korea [34], and Russia [35] with similarly good results. In particular, the group from La Pitié-Salpêtrière in Paris, France, has recently compared kidneys from category 2 DCD donors procured after either *in situ* CF or NRP. In recipients of kidneys maintained with NRP, there was a significantly earlier return to urine output, and serum creatinine levels at 1 month were significantly lower in comparison with recipients of kidneys that were flushed *in situ* [36].

Liver

In 2002, the Hospital Clinic in Barcelona initiated a protocol to transplant livers arising from human category 2 DCD donors treated with NRP [5,37]. Since then, 42 such transplants have been performed. With a median follow-up of 45 months, 1-year graft and patient survival rates are 73% and 81%, respectively. Seven recipients have developed postoperative biliary complications (17%), including three patients who have been retransplanted for ischemic-type biliary strictures (7%). While these rates of morbidity and mortality are respectable and at least comparable to those achieved with livers from so-called controlled category 3 DCD donors, the applicability of this procedure, nonetheless, remains relatively low, based on the number of potential category 2 DCD donors that are seen [38].

A couple of other groups have used NRP to maintain DCD donors in the clinical setting. The University of Michigan has been using NRP since 2000 to preserve category 3 DCD donors and has thus far performed 13 liver transplants using this technique [4,31,39]. The Hospital 12 de Octubre in Madrid, Spain, has successfully transplanted livers procured under the same Barcelona cate-

Table 2. Clinical outcomes with hypothermic regional perfusion in DCD organ transplantation.

Group, period	DCD category	Temperature (°C)	*N*	DGF (%)	PNF (%)	One-year graft survival (%)
Kidney						
Hospital Clínic, Barcelona, 1986–1999 [12]	2	15–20	8	75	0	88
Saitama, Japan, 1989–1997 [9]	3	15	34	85	6	88
Clínico San Carlos, Madrid, 1989–2004 [21]	1 & 2	15	320	61	4	87
National Taiwan University, 1998–2003 [26]	3	4	31	42	0	97
Wake Forest University, 2003–2010 [27]	3	22	19	21	0	88
Liver						
La Coruña, Spain, 1994–2005 [30]	2	15–20	7	–	NR*	NR
Wake Forest University, 2003–2007 [29]	2	22	6	–	0	NR
Kaohsiung, Taiwan, 2005 [28]	4	5	1	–	0	100

NR, not reported; DCD, donation after circulatory determination of death; DGF, delayed graft function; HRP, hypothermic regional perfusion; NRP, normothermic regional perfusion; PNF, primary nonfunction.

Clinical outcomes of DCD kidney and liver transplantation in which the donor was maintained with hypothermic regional perfusion. As this table demonstrates, very little clinical experience has been reported regarding the transplantation of livers arising from DCD donors maintained with HRP.

*Primary nonfunction occurred in five grafts arising from 27 donors that were maintained according to diverse methods: HRP (n = 7), NRP (n = 10), or simultaneous chest and abdominal compressions (n = 10).

gory 2 DCD protocol [40], while hospitals in France have also recently started using NRP in categories 1 and 2 DCD donors [33].

Table 3 summarizes clinical outcomes with NRP in DCD organ transplantation.

Controversies surrounding abdominal regional perfusion

The use of ARP, in particular NRP, is not always well perceived in the context of organ donation. In the absence of circulation, organs arising from uncontrolled DCD (categories 1, 2, and 4) quickly become unviable for transplantation. Initiating preservation maneuvers prior to obtaining first-person consent has the potential to upset family members of the deceased and lead to public backlash. However, several recent studies have shown that attitudes toward uncontrolled DCD programs are, by and large, positive, even when the start of preservation precedes any conversation with next of kin [41]. In some settings, public perception of uncontrolled DCD is even more favorable than it is regarding controlled (category 3) DCD or DBD [42–44].

Based on the argument that re-establishing circulation negates the "permanence" of the cessation of cardiorespiratory function and, thereby, the diagnosis of death based on cardiorespiratory criteria, there have been very strong critiques of DCD protocols that employ the use of NRP [45,46]. While in uncontrolled DCD, cardiac arrest has been shown to be irreversible after prolonged efforts to reverse it have failed, some still feel that the use of NRP in this setting may blur the boundaries between a patient who might become a donor but could still benefit from resuscitation and someone who is very definitely dead and can only become a donor. Very precise criteria for cardiorespiratory death have to be defined and used to prevent such misconceptions. While the use of extracorporeal life support (ECLS) has been associated with favorable outcomes in cases of intrahospitalary cardiac arrest, the results are much worse for its use in arrest occurring outside the hospital, mainly due to the delay in its implementation [47–49]. Based on this fact, guidelines have been established in France to help determine whether a patient suffering out-of-hospital cardiac arrest could benefit from ECLS or should be considered a potential DCD donor. According to these recommendations, ECLS should not be implemented in patients with a no-flow period lasting longer than 5 min, a low-flow period lasting longer than 100 min, or an end-tidal CO_2 level lower than 10 mmHg [50].

In the case of controlled DCD, ARP may be considered an invasive technique employed without any possible benefit for the patient. Furthermore, given that hearts have been recovered and successfully transplanted in this setting [51], the claim of the irreversibility of cardiorespiratory arrest can hardly be made, thereby necessitating a definition of death based on permanence [45]. 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 must be put in place to ensure that cerebral reperfusion does not occur when NRP is run.

Finally, the cost-effectiveness of DCD programs that rely on NRP for kidney and liver recovery is also an issue, particularly in the setting of uncontrolled DCD, where the yield of viable organs for transplantation may be low [38]. In the case of kidneys, the issue is less pronounced, given

Table 3. Clinical outcomes with normothermic regional perfusion in DCD organ transplantation.

Group, period	DCD category	*N*	DGF (%)	PNF (%)	One-year graft survival (%)
Kidney					
University of Michigan, 2000–2013 [31]	3	48	31*	3*	NR
Hospital Clínic, Barcelona, 2002–2014	2	158	65	9	88
St. Petersburg, Russia, 2009–2011 [35]	2	44	52	0	96
La Pitié Salpêtrière, Paris, 2007–2013	2	43	56	0	91
Suwon, Korea, 2012 [34]	2	2	0	0	NR
Liver					
La Coruña, Spain, 1994–2005 [30]	2	10	–	NR†	NR
University of Michigan, 2000–2013 [31]	3	13	–	0	86
Hospital Clínic, Barcelona, 2002–2014	2	42	–	10	73
12 de Octubre, Madrid, 2006–2007 [40]	2	20	–	10	86

NR, not reported; DCD, donation after circulatory determination of death; DGF, delayed graft function; HRP, hypothermic regional perfusion; NRP, normothermic regional perfusion; PNF, primary nonfunction.

Clinical outcomes of DCD kidney and liver transplantation in which the donor was maintained with normothermic regional perfusion.

*Rates of DGF and PNF are for 29 kidneys transplanted at the University of Michigan.

†Primary nonfunction occurred in five grafts arising from 27 donors that were maintained according to diverse methods: HRP ($n = 7$), NRP ($n = 10$), or simultaneous chest and abdominal compressions ($n = 10$).

that the alternative to transplantation – dialysis – is also responsible for high healthcare expenditures and worse long-term outcomes. Costs associated with DBD are not trivial, either, as they include not only the organ recovery itself but also days spent in intensive care between the identification of a potential donor and the actual act of organ donation (costs that are, furthermore, absent in uncontrolled DCD).

Future perspectives

While it does appear that ARP is capable of improving the quality of grafts that, through the DCD process, have suffered extended periods of warm ischemia, the applicability of DCD, in particular uncontrolled DCD, remains low [38]. In the future, improvements need to be made to ARP to make it more efficient and effective and capable of producing many more suitable quality grafts for transplantation.

Reconditioning during ARP may be enhanced by the addition of metabolic precursors and other cytoprotective substrates [52,53]. The use of a fibrinolytic drug such as tissue plasminogen activator during ARP is another potential strategy to improve its efficiency and, thereby, its reconditioning effects. During cardiac arrest, red-cell stasis in end-organ microvasculature may lead to the formation of microthrombi and ongoing ischemia even when gross inflow to the organ is restored. Administering an anticoagulant, such as heparin, prior to withdrawal of life support in category 3 DCD should help prevent clot formation. However, in instances where heparin may not be administered prior to cardiac arrest (such as in category 2 DCD or in countries where pre-arrest heparinization is not legally permitted in category 3 DCD), the addition of a fibrinolytic agent during ARP should help lyse any preformed clots and, consequently, improve microvascular flow and overall graft viability [54]. The results of studies on the use of fibrinolytic drugs during ARP are pending.

One important reason that more grafts from DCD donors are not used is the fact that cold storage (CS) is a suboptimal means of maintaining their viability. In this regard, increasing importance has been given in recent years to the use of machine perfusion (MP) for the *ex situ* phase of DCD organ preservation. A wealth of experimental data backs the use of both hypothermic and normothermic MP as superior means of preservation when compared to CS [55–61]. In the clinical setting, hypothermic MP is widely used to preserve kidneys with risk factors for an adverse outcome, including those arising from DCD, although results from recent RCT regarding the impact of its application are mixed [62–64]. Proof-of-concept clinical trials have also been performed on the application of normothermic MP in kidney transplantation [65] and hypothermic MP in liver transplantation [66], including one recent trial using hypothermic oxygenated MP to preserved controlled DCD livers [67], while clinical trials on normothermic liver MP are currently underway.

Final comments

Donation after circulatory determination of death is a well-established means to counter an increasing shortage of organs for transplantation. Even though its application may be technically and/or logistically challenging, NRP, in particular, has considerable potential to restore the quality of these ischemically compromised grafts. In some countries, the use of NRP in DCD is mandatory for the recovery of livers and highly recommended in the case of kidneys. In the future, the association of NRP with subsequent MP should offer the greatest opportunity to improve the viability and transplantability of ischemically damaged organs arising from DCD.

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