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Invited review

ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION IN DONATION AFTER CIRCULATORY DEATH: ORGAN VIABILITY OR ORGAN PRESERVATION?

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Summary

Transplants from donation after circulatory death (DCD) provide a viable means to deal with the ever-growing shortage of donors but are burdened by a higher rate of complications and graft loss. Dismal results have prompted the application of stricter donor and graft selection criteria and the use of machine perfusion technologies, such as normothermic regional perfusion (NRP). In this review, we first describe the diffusion of NRP worldwide. Next, the role of NRP in liver transplantation is discussed, with a particular focus on graft selection during perfusion and posttransplant outcomes. Finally, we review the clinical studies reporting on NRP in kidney transplantation. The emerging use of NRP with complementary *ex-situ* machine perfusion is also described. NRP improves organ quality and maintenance before cold preservation, turns the DCD procedure into a more unhurried one, and allows the assessment of organ function following the warm ischemic injury. Moreover, it is beneficial for both the liver and the kidneys from the same donor.

Key words: extracorporeal membrane oxygenation, kidney transplant, liver transplant, organ preservation, organ procurement

Abbreviations

ALT: alanine transaminase
cDCD: controlled donation after circulatory death
DBD: donation after brain death
DCD: donation after circulatory death
DGF: delayed graft function
FMN: flavin mononucleotide
HOPE: hypothermic oxygenated perfusion
ITBL: Ischemic-type biliary lesions
KT: kidney transplant
LT: liver transplant
NMP: normothermic machine perfusion
NRP: normothermic regional perfusion
RCT: randomized controlled trial
SCS: static cold storage
SRR: super-rapid recovery
uDCD: uncontrolled donation after circulatory death
UK: United Kingdom

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INTRODUCTION

Donation after circulatory death (DCD) provides a viable means to deal with the ever-growing shortage of donors. Nevertheless, transplants from DCD are traditionally burdened by a higher rate of complications and graft loss. Dismal results have prompted the application of stricter donor and graft selection criteria in some settings and the use of machine perfusion technologies in others [1].

DCD inevitably involves compromised hemodynamics in the agonal phase, followed by an obligatory additional circulatory standstill for the declaration of death. In super-rapid recovery (SRR), this is hurriedly followed by incision, aortic cannulation, and organ perfusion with hypothermic preservation solution. Normothermic regional perfusion (NRP) temporarily re-establishes blood flow following declaration of death, through arterial and venous cannulae placed in the femoral vessels or directly in the aorta and vena cava after rapid laparotomy (Fig. 1). Supraceliac aortic balloon occlusion prevents cerebral reperfusion during NRP and restricts perfusion to the abdomen [2]. This way, NRP restores previously depleted energy substrates, clears by-products of anaerobic metabolism, and induces endogenous antioxidants, thus helping to improve organ quality and maintenance before cold preservation [3]. Moreover, in contrast to SRR, NRP also allows the assessment of organ function following the warm ischemic injury [4].

Although some ethical concerns have been raised, especially with premortem cannulation, heparin administration, and potential brain reperfusion, NRP is currently spreading in many European countries[5]. To maintain the permanence principle for death, Manara et al. have recently suggested inserting a cannula in the ascending aorta to identify inadequate occlusion and divert any collateral flow away from the brain [6]. Moreover, antemortem interventions in the potential donor should follow national legislation and are ethically acceptable if they do not add risk, harm, or discomfort to the patient [3].

In this review, we first describe the diffusion of NRP worldwide. Next, the role of NRP in liver transplantation (LT) is discussed, with a particular focus on graft selection during perfusion and posttransplant outcomes. Finally,

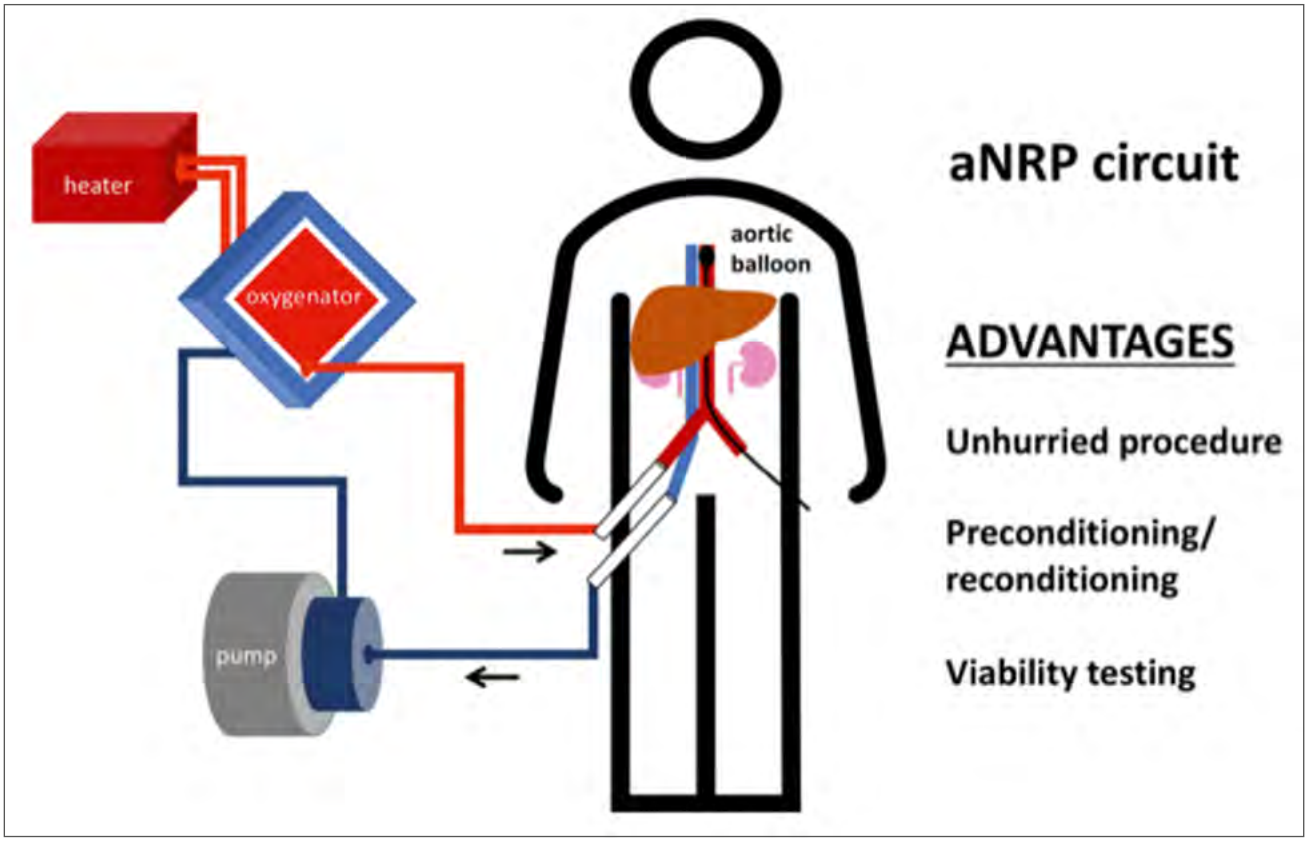

Figure 1. NRP circuit and advantages. The abdominal NRP circuit relies on extracorporeal membrane oxygenation technology and includes a pump, an oxygenator, and a heater. The blood is pumped through arterial and venous cannulae in the femoral vessels. Supraceliac aortic balloon occlusion prevents cerebral reperfusion. aNRP: abdominal normothermic regional perfusion.

we review the clinical studies reporting on NRP in kidney transplantation (KT). The emerging use of NRP with complementary *ex-situ* machine perfusion is also described.

DIFFUSION OF NRP

Currently, NRP is mandatorily applied in DCD organ recovery in 3 European countries (Italy, France, and Norway) and is permitted in 5 (Spain, United Kingdom, Belgium, the Netherlands, and Switzerland) [1,3,7,8]. Moreover, a progressive increase in NRP use has been registered over time even in those countries where NRP is not mandatory. In Spain, NRP is currently far more frequent than SRR for liver recovery [9]. Nevertheless, this practice is still less embraced in the United States, although good results have been reported recently in a series of 13 DCD donors maintained on NRP [2]. A few cases have also been reported from Russia and Korea [7,10].

NRP IN LIVER TRANSPLANTS

Clinical studies on LTs with NRP are reported in Table I.

Results of LT with NRP

NRP has originally allowed recovery and utilization of uncontrolled DCD liver grafts (uDCD; Maastricht category II and IV) in Spain, France, and Italy. Then its use has been shifted to controlled DCD grafts (cDCD; Maastricht category III). NRP turns the cDCD procedure into a more unhurried one compared to SRR, thus enabling graft evaluation and even warm dissection. Ischemic-type biliary lesions (ITBL) are the leading cause of patient morbidity and early graft loss in LTs from DCD. Many retrospective studies have shown that NRP treatment is effective in preventing the occurrence of ITBL compared to SRR, but randomized trials comparing these two techniques have not been reported yet [9,11]. Nevertheless, given the ever-increasing use of NRP instead of SRR, such clinical trials are unlikely to be carried out in the future.

Selection of livers during NRP

Different criteria are used for graft selection during NRP, and progressive evolution of both parameters and thresholds has been noticed over time (Tab. II). A combination of macroscopic and microscopic assessment, alanine transaminase (ALT) levels, and lactate in perfusate are used to assess the suitability of the liver for transplantation in most protocols. All of these parameters inform about both liver viability and quality of the perfusion and have contributed to the selection of LT series with excellent results. Nevertheless, no strong correlation has been found between each parameter and the transplantation outcome [12,13]. According to a recent review, the most used acceptation criterion

Table I. Main series of LT from controlled and uncontrolled DCD donors maintained on NRP.

Author, year	Country	DCD type, n	Utilization rate (from NRP to LT)	EAD	PNF	AKI	ITBL	Graft survival (follow-up)	Patient survival (follow-up)
uDCD									
Fondevila, 2012 [34]	Spain	uDCD: 34	34/290 (12%)	N/A	N/A	N/A	8%	70% (1y)	82% (1y)
Savier, 2015 [35]	France	uDCD: 13	13/183 (7%)	31%	23%	N/A	8%	69% (1y)	85% (1y)
Justo, 2020 [36]	Spain	uDCD: 75	N/A	N/A	8%	20%	4%	78.3% (1y) excluding PNF	82% (1y) excluding PNF
cDCD (multicentre/national)									
Watson, 2019 [11]	UK	cDCD: 43	61%	12%	0%	N/A	0%	97.7% (90d)	100% (90d)
Savier, 2020 [37]	France	cDCD: 50	20%	18%	N/A	26%	2%	88% (2y)	90% (2y)
De Carlis, 2021 [12]	Italy	cDCD: 44	85%	N/A	5%	36%	2%	91% (2y)	98% (2y)
Hessheimer, 2021[9]	Spain	cDCD: 545	70%	15%	3%	N/A	1%	90% (1y)	92% (1y)
Sellers, 2022 [2]	US	cDCD: 13	N/A	23%	0%	N/A	0%	92% (439d)	92% (439d)
Mixed series (uDCD and cDCD)									
De Carlis, 2018 [38]	Italy	cDCD: 6 uDCD: 14	20/25 (80%)	24%	10%	30%	10%	85% (1y)	95% (1y)
Ghinolfi, 2020 [24]	Italy	cDCD: 7 uDCD: 11	18/31 (58%)	28%	0%	28%	6%	94% (15mo.)	94% (15mo.)

AKI: acute kidney injury; cDCD: controlled donation after circulatory death; EAD: early allograft dysfunction; ITBL: ischemic-type biliary lesions; LT: liver transplant; NRP: normothermic regional perfusion; PNF: primary nonfunction; SRR: super-rapid recovery; uDCD: uncontrolled donation after circulatory death; UK: United Kingdom; US: United States

Table II. Main selection criteria of the liver during NRP.

Author, year	Type	Pump flow	Lactate	Transaminase	Macroscopical aspect	Liver biopsy
Fondevila, 2007[39]	uDCD	>1.7 L/min (>4h)	-	Initial < 3 ULN Final > 4 ULN	Before/after cold flush	-
Oniscu, 2014[13]	cDCD	1.7-4 L/min/m^2 (60-120 min)	-	Initial ALT < 3 ULN Final ALT < 4 ULN	-	-
Savier, 2015[35]	uDCD	efficient flow for > 240 min	-	ALT at 2h < 200 IU/L	-	MaS < 20%
De Carlis, 2017[40]	uDCD cDCD	-	Stable or downward	ALT < 1000 IU/L	Color, surface, margins, consistency	MaS < 30% Ishak 0-1
Watson, 2019[11]	cDCD	2.5-3 L/min	Fall is encouraging	ALT < 200 IU/L ALT < 500 IU/L	Steatosis	-
Savier, 2020[37]	cDCD	> 60 min	-	AST-ALT < 200 IU/L	-	MaS < 20%
Hesseimer, 2021[9]	cDCD	2.2-2.4 L/min/m^2 (60-120 min)	Ideally downward	Ideally stable and < 200 IU/L	Liver, gallbladder, bile duct and bowel	-
De Carlis, 2021[12]	cDCD	1.7-3 L/min/m^2 (ideally 120 min, no upper limit if stable)	Ideally stable or downward	Ideally final ALT < 1000 IU/L	Perfusion, congestion	Ideally MaS < 30% Ishak 0-2

ALT: alanine aminotransferase; cDCD: controlled donation after circulatory death; MaS: macrosteatosis; uDCD: uncontrolled donation after circulatory death; ULN: upper limits of normal

in cDCD is the macroscopic aspect, while in uDCD ALT level is considered the most reliable [4]. This attitude has been partially reflected in a recent Italian survey, where macroscopic assessment was highly considered in the opinion of the participants, along with the stability of NRP perfusion conditions [14]. Although transaminase release is a widely accepted marker of liver injury, its cut-off has, however, been modified from initially 3-4 times the normal values to upper thresholds reported in the most recent series [11,12]. Lactate clearance has been proposed as a parameter to assess liver function, as in normothermic machine perfusion, with a downward lactate trend indicating a well-functioning liver [4]. However, Watson et al. noted that lactate leaking back from non-perfused areas in the donor decreases the reliability of this parameter as an indicator of liver function [15]. Wang et al. have recently analysed flavin mononucleotide (FMN) in the perfusate during NRP and found that FMN levels were significantly higher in those livers that were declined for transplantation [16]. Unfortunately, no correlation was made with the LT outcomes in the livers that were accepted. Further insight on this topic will probably be given by a nonrandomized trial on viability assessment during NRP, which is currently ongoing in France (NCT05361044).

NRP *vs* machine perfusion

Various dynamic *ex-situ* preservation strategies have been explored to ameliorate the outcomes of DCD livers, including hypothermic oxygenated perfusion (HOPE) and normothermic machine perfusion (NMP). Preference for *in-situ* NRP or *ex-situ* techniques varies among centres and countries. NRP is most frequently undertaken in tertiary hospitals with extracorporeal membrane oxygenation devices and cardiothoracic intensive care units, although good results have also been reported with mobile NRP teams [17,18]. A few studies have compared NRP with HOPE or NMP, but no randomized trials have been published. In a large-scale international multicentric study, the utilization rate was significantly lower in the NRP group, despite shorter warm ischemic times and lower donor age compared to the HOPE group. However, after propensity-score adjustment of donor-recipient combinations, both strategies achieved similar posttransplant outcomes [19]. In a single-centre retrospective analysis from the United Kingdom (UK), the NRP group had a lower incidence of cholangiopathy than static cold storage, but the same benefit was not achieved with NMP (NMP *vs* NRP: hazard ratio 3.5, p = 0.02) [17]. Conversely, a multicentric study comparing NRP cases from France with NMP cases from the UK, Germany, Spain, and Belgium, failed to show any significant difference in the incidence of non-anastomotic biliary strictures (1.5 *vs* 2.9%; p > 0.99) and 30-day graft loss (4.4 *vs* 8.8%; p = 0.40) between the two groups [20].

NRP and subsequent HOPE or NMP

Prolonged cold ischemia and indication for retransplantation were found to be independent risk factors for graft loss among 545 DCD livers treated with NRP in Spain [9].

These data support a potential role for complimentary *ex-situ* perfusion preservation for those cases with prolonged cold ischemia and/or technically complex recipients. The combined use of NRP with subsequent HOPE was first proposed in 2016 by our group to face the detrimental effects of the 20-min stand-off period in Italy, thus providing safe prolonged preservation and further reconditioning to the DCD livers [21]. Although a direct comparison between NRP with subsequent HOPE and NRP only is still lacking in the Italian population, some indirect evidence exists to support this approach [14]. In a recent multicentric analysis, the combined protocol has yielded good results compared to a static-preserved comparator group from the UK, despite the higher risk profile in Italy [12]. Moreover, the same Italian cohort had shown similar results to the benchmark outcomes in LT from DCD[22]. The combined use of NRP and NMP was first reported by Pavel et al. [23]. More recently, Ghinolfi et al. have proposed a flow-chart, where machine perfusion is used following the initial DCD liver evaluation during NRP. While HOPE is suggested for cases partially fulfilling the criteria, the authors recommend NMP when the criteria are not fulfilled [24]. This proposal sounds promising but is still mainly based on a small number of uDCD cases, and only a few centres currently use both HOPE and NMP in Italy [14]. The results of a currently ongoing randomized trial in Italy between sequential HOPE and NMP after NRP (NCT04744389) will hopefully provide further insight into this matter.

NRP IN KIDNEY TRANSPLANTS

A few clinical series on KT after NRP have been published, mainly from cDCD donors (Tab. III).

Results of KTs with NRP

Foss et al. compared the outcome of 14 DCD kidneys recovered with NRP with 163 transplants from donation after brain death (DBD) and observed no differences in delayed graft function (DGF) and 1-year graft survival between the groups [25]. Similarly, Miñambres et al. reported nonsignificant differences in DGF and short-term graft survival comparing DCD kidneys treated with NRP with DBD controls [26]. However, these studies did not compare the use of NRP with the widespread SRR. Ramirez et al. found that DCD kidneys treated with NRP had a lower rate of DGF than those with SRR [27]. In a recent Spanish nationwide propensity score analysis, Padilla et al. have found that NRP was associated with improved rates of DGF and 1-year graft loss compared to SRR [28].

Selection of kidneys during NRP

For the acceptance of the kidneys during NRP, published reports mention macroscopic aspect, microscopic findings, and urine production. However, the absence of urine output is frequent during NRP and should not per se lead to organ discard [3]. Rodríguez-Villar et al. investigated the evolution of biochemical parameters during NRP between

Table III. Clinical series of KTs from cDCD with NRP.

Author, year	Study type	n	Donor fWIT (min)	MP	PNF	DGF	Graft survival (follow-up)	Patient survival (follow-up)
Foss, 2018 [25]	Single-centre, retrospective, observational	NRP: 14 DBD: 163	NRP: 26.5 (20-49)	No	NRP: 0% DBD: 0%	NRP:7.1% DBD: 4.9%	NRP: 93% DBD: 95% (1y)	N/A
Miñambres, 2017 [26]	Single-centre, retrospective, observational	NRP: 37 DBD: 36	NRP: 12 (10-19)	No	NRP: 5% DBD: 0%	NRP: 27% DBD: 33.3%	NRP: 91.8% DBD: 97.2% (18mo.)	N/A
Ravaioli, 2018 [30]	Single-centre, retrospective, observational	NRP: 5	NRP: 151.2 (40-325)	HOPE	NRP: 0%	NRP: 30%	NRP: 100% (6mo.)	NRP: 100% (6mo)
Padilla, 2020 [28]	Nation-wide, retrospective, observational	NRP: 865 SRR: 1437	NRP: 13 (10-17) SRR: 18 (13-3)	NRP: 15.9% SRR: 7.3%	NRP: 4.8% SRR: 4.4%	NRP: 30.3% SRR: 48.4%	NRP: 93.1% SRR: 91.5% (1y)	NRP: 97.6% SRR: 95.6% (1y)
Ramirez, 2021 [27]	Single-centre, retrospective, observational	NRP: 22 SRR: 62 DBD: 98	NRP: 10 (10-35) SRR: 15 (11-28)	No	NRP: 4,55% SRR: 6,45% DBD: 10,20%	NRP: 36.36% SRR: 46.77% DBD: 20.41%	NRP: 91% SRR: 87% DBD: 84,4% (15mo.)	NRP: 77.27% SRR: 88.71% DBD: 85.71% (1y)

DBD: donation after brain death; DGF: delayed graft function; MP: machine perfusion; NRP: normothermic regional perfusion; PNF: primary nonfunction; SRR: super-rapid recovery

accepted and discarded kidneys in 38 uDCD donors. Neither creatinine nor lactate sequential values was a useful tool to predict kidney allocation. Nevertheless, the authors did not correlate any posttransplant outcome with these variables [29]. Ravaioli et al. reported the preliminary experience with sequential NRP and HOPE in 10 KTs from cDCD in Italy. They reported a 30% incidence of DGF and did not find any correlation with creatinine or lactate values during NRP. However, they found that lactate levels in the HOPE perfusate were significantly higher in those cases developing DGF [30]. Marginal kidneys are usually assessed histologically with the Karpinski score, which however does not take into account the ischemic insult [30]. In this context, Zagni et al. have recently reported that ischemic alterations of the proximal tubule are correlated with functional recovery in DCD kidneys [31]. Centres using ex-situ hypothermic perfusion report using renal resistance for further selection, though studies outside the NRP field have shown kidneys should not be discarded based upon renal resistance only [32,33].

CONCLUSIONS

NRP is beneficial for both the liver and the kidneys from the same donor. Therefore, NRP improves organ quality and maintenance before cold preservation, turns the DCD procedure into a more unhurried one, and allows the assessment of organ function following the warm ischemic injury. Different parameters inform about both graft viability and quality of the perfusion, but no strong correlation has been found between each parameter and the transplantation outcome. Nevertheless, a combination of macro-microscopic assessment, biochemical, and perfusion parameters has contributed to the selection of liver and kidney transplant series with excellent results.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

RDC performed data collection, interpreted data, and wrote the paper; LC, MM, LP, RC, and IV performed data collection and reviewed the paper; AL and LDC critically reviewed the paper.

Ethical consideration

The present study did not imply any direct investigation on humans or animals. Formal consent was not required.

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