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Abdominal Normothermic Regional Perfusion in Donation After Circulatory Death: A Systematic Review and Critical Appraisal

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Background. Abdominal normothermic regional perfusion (aNRP) for donation after circulatory death is an emerging organ preservation technique that might lead to increased organ utilization per donor by facilitating viability testing, improving transplant outcome by early reversal of ischemia, and decreasing the risk of unintentional surgical damage. The aim of the current review is to evaluate the recent literature on the added value of aNRP when compared to local standard perfusion technique. **Methods.** The Preferred Reporting Items for Systematic reviews and Meta-Analyses guideline for systematic reviews was used, and relevant literature databases were searched. Primary outcomes were organ utilization rate and patient and graft survival after 1 year. Secondary outcomes included delayed graft function, primary nonfunction, serum creatinine, and biliary complications. **Results.** A total of 24 articles were included in this review. The technique is unanimously reported to be feasible and safe, but the available studies are characterized by considerable heterogeneity and bias. **Conclusions.** Uniform reported outcome measures are needed to draw more definitive conclusions on transplant outcomes and organ utilization. A randomized controlled trial comparing aNRP with standard procurement technique in donation after circulatory death donors would be needed to show the added value of the procedure and determine its place among modern preservation techniques.

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INTRODUCTION

Donation after circulatory death (DCD) remains associated with significantly lower organ recovery rates per donor compared with donation after brain death (DBD). Furthermore, the results after transplantation using DCD donors are acceptable but remain associated with poorer initial graft function when compared with organs from DBD donors.^{1–5} Due to the uncertainty about their quality and ability to provide immediate life-sustaining function, DCD organs are often declined and discarded. This raises the question whether the underutilization of these organs

is justified and unnecessarily reduces the size of the potential donor organ pool.

To date, in some countries (eg, United Kingdom, Netherlands, United States), DCD donors are an important resource to balance the persistent shortage of donor organs. The different categories of DCD donors are described in Table 1.⁶ In 2018 in The Netherlands, > 57% of deceased donors were controlled DCD (cDCD),⁷ while in the United Kingdom, cDCD is now a main pathway to donation.⁸

To reduce uncertainty and increase utilization, better assessment of organ viability and optimization of

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TABLE 1.**Modified Maastricht classification for DCD donors⁶**

Category I		Description
Uncontrolled	IA. Out-of-hospital	Found dead due to a sudden unexpected CA without any attempt of resuscitation in the out-of-hospital or in-hospital setting
	IB. In-hospital	
Category II		
Uncontrolled	IIA. Out-of-hospital	Witnessed CA with unsuccessful resuscitation, including the addition of the location
	IB. In-hospital	
Category III		
Controlled		Ventilated patients awaiting CA where the WLST is planned
Category IV		
Uncontrolled		Sudden (or unexpected) CA after declaration of brain death (uDCD IV). In China, the law does not permit declaration of brain death resulting in DBD followed by controlled CA (cDCD IV)
Controlled		
Category V		
Controlled		Euthanasia or medically assisted cardiocirculatory death

CA, circulatory arrest; cDCD, controlled donation after circulatory death; DBD, donation after brain death; DCD, donation after circulatory death; uDCD, uncontrolled donation after circulatory death; WLST, withdrawal of life-sustaining therapy.

preservation strategies are required, reducing ischemia-reperfusion injury and enhancing quality and function of the potential grafts.

Abdominal normothermic regional perfusion (aNRP), also called normothermic recirculation or normothermic extracorporeal membrane oxygenation, is an emerging in situ organ preservation technique in the donor. First pioneered in 1989 in Spain, it demonstrated to improve liver graft viability in a porcine DCD model.^{9,10} Experimental studies, mostly performed in pig models of liver or kidney transplantation, have evaluated the possible beneficial effects of aNRP.¹¹⁻¹⁶ During a period of warm ischemia, ATP declines progressively. During aNRP, the cellular energy status was found to increase due to partial restoration of ATP content, which suggests that the ischemic injury obtained during the warm ischemia time (WIT) can be partially reversed before transplantation.^{11,13,17} Therefore, an “ischemic preconditioning” effect can be observed when using aNRP. Not only do intracellular adenosine levels rise, but also a significant decrease in xanthine levels, as an important nucleotide degradation product, has been observed.^{14,15}

The initial clinical experience with aNRP was obtained with uncontrolled DCD (uDCD) type II donors. In these donors, who suffered from an unexpected circulatory arrest and where resuscitation was unsuccessful, aNRP is often started before the donor is subjected to the mandatory screening process and before consent is obtained. Currently, aNRP is used in both uDCD and cDCD donors in several countries, such as Spain, United Kingdom, Norway, France, and Italy.¹⁸ aNRP was implemented for marginal cDCD donors in part of the Netherlands in 2018, aiming at an increase of liver organ utilization as these cDCD donors exceeded the existing “regular” criteria (eg, cDCD donors >60 y).

The concept of aNRP in DCD donors is based on 3 principles: (1) after circulatory arrest and a mandatory no-touch period normothermic oxygenated circulation is reestablished. As such, it not only reduces the extent of ischemic injury but is also allows all abdominal organs to recover by recharging their energy content; (2) during aNRP, organs can be inspected, and blood samples are

obtained for biochemical analyses. This allows for better assessment of the quality of the perfused organ, assisting the clinician in deciding whether to accept or decline the organ; and 3) damage to donor organs may be minimized by converting a “hasty” DCD procedure into a less rushed DBD-type operation, resulting in less organ damage and increased organ utilization.¹⁹

Despite the rapid development of aNRP in clinical practice, the number of large cohort studies is limited, and reports are hampered by heterogeneity. To date, the evidence that aNRP increases the organ utilization rate (OUR) and improves outcomes after transplantation remains limited. Such evidence is needed to allow for wider clinical implementation and necessary approval by regulatory and healthcare authorities in countries considering implementation of aNRP.

In this systematic review, we aim to evaluate the present clinical evidence for the use of aNRP to improve donor organ assessment and better function and outcomes following transplantation of abdominal donor organs.

MATERIALS AND METHODS

Search Strategy

A systematic literature review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guideline²⁰ and was registered with PROSPERO (CRD42019125387).

A search strategy was developed, and the following databases were explored: PubMed (incl. MEDLINE), Embase (OVID-version), Web of Science, COCHRANE Library, Emcare, Academic Search Premier, ScienceDirect, and Google Scholar. The final search was performed on January 29, 2020. For the complete search strategy, see **Appendix S1, SDC**, <http://links.lww.com/TP/B954>.

Inclusion and Exclusion Criteria

We aimed to include randomized trials and cohort studies comparing clinical aNRP to local standard perfusion techniques or single-arm cohorts with data on outcomes. Furthermore, only articles written in English were considered. In case of duplicate data, the most recent article

was included. Articles with duplicate data on 1 organ were included. However, articles with duplicate data on one organ were included if one of the articles also included additional data of another organ. Case reports, editorials, letters to the editors, meeting abstracts, and reviews without original data were excluded.

Outcomes

Primary outcomes included OUR²¹ and 1-year patient and graft survival. For the purpose of this review, OUR was calculated as the number of organs actually transplanted, divided by the total number of available organs when procurement was initiated. In studies that based their selection on recipients, the OUR could not be calculated.

Secondary outcomes included delayed graft function (DGF), primary nonfunction (PNF), serum creatinine, estimated glomerular filtration rate (eGFR) or measured glomerular filtration rate for kidneys, PNF, and biliary complications, including ischemic cholangiopathy (IC), early allograft dysfunction (EAD) as defined by Olthoff et al²² for livers and yield after islet isolation for pancreas.

Data Extraction

Title and abstracts were screened by 2 independent reviewers (F.E.M.v.d.L. and V.A.L.H.) to meet predefined inclusion criteria, followed by full-text review of eligible articles. Consensus regarding inclusion was obtained

between reviewers. Data extraction was performed using a predetermined Microsoft Excel template. The extracted variables are provided in Table S1, SDC, <http://links.lww.com/TP/B954>. When additional information was needed, the corresponding authors of the studies were contacted.

Risk of Bias

Two reviewers determined independently the risk of bias according to the Risk of Bias In Nonrandomized Studies of Interventions tool (Table S2, SDC, <http://links.lww.com/TP/B954>) for cohort and case-control studies.²³

Statistical Analysis

We did not consider statistical pooling appropriate because of sparsity and heterogeneity of data.

RESULTS

The literature search identified 1558 records. One additional reference was identified through the snowball method. After initial screening of titles and abstracts, 94 full-text articles were assessed for eligibility. In total, 24 studies^{21,24-46} were included in the systematic review (Figure 1).

Study Characteristics

All studies were observational in their design; no randomized controlled trials were found. The transplanted

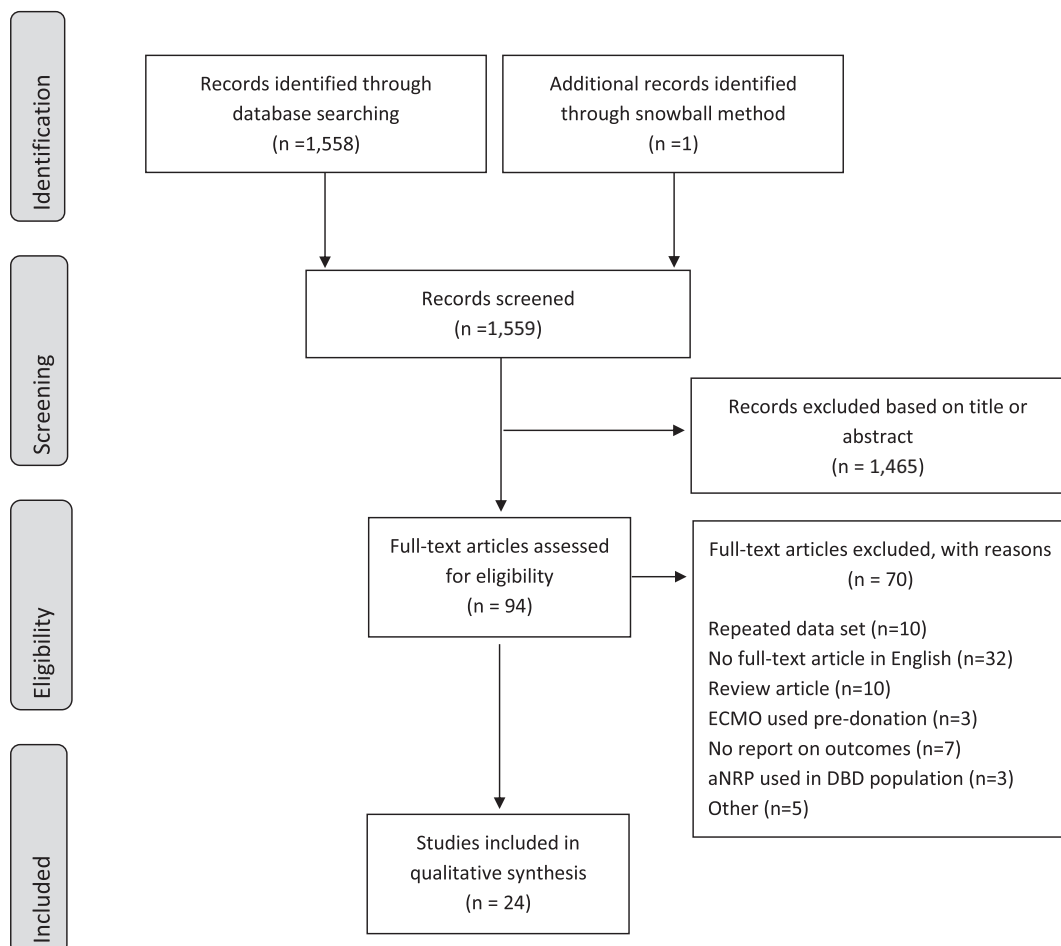


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. aNRP, abdominal normothermic regional perfusion; DBD, donation after brain death; ECMO, extracorporeal membrane oxygenation.

TABLE 2.
Study characteristics

Study (country)	Organ(s)	Study design	Study period	Actual donors (n)		Donor type ^e	Donor selection criteria	Donor age, y	Recipient age, y
				Control group (n)	Donor group (n)				
Valero et al ⁴¹ 2000 (Spain)	Kidney	Single-center Observational	October 1986 to March 1999	6	37 uDCD-ISP 11 uDCD-TBC ^a	uDCD II	Age <65, <150 min WIT (incl. <30 min WIT without CPR)	–	46.7 ± 8.1
Reznik et al ³⁷ 2013 (Russia)	Kidney	Single-center Observational	2009 to 2011	22	74 DBD ^b	uDCD IIb	–	41.8 ± 2.1	49.3 ± 1.4
Demiselle et al ²⁸ 2016 (France)	Kidney	Multicenter Observational	May 2008 to July 2013	19 ^b	31 uDCD-ISP ^b	uDCD II	Age 18–55, >30 min without CPR after initial <30 min no flow, <150 min WIT, <18 h CIT	45.7 ± 5.7	41.4 ± 10.1
Molina et al ³⁴ 2018 (Spain)	Kidney	Single-center Observational	June 2005 to December 2013	186	237 DBD ^b	uDCD IIa	Age 18–60, known time of CA, <15 min between CA-CPR, >30 min CPR, <150 min WIT (CA-perfusion)	43.5 ± 9.9	47.9 ± 10.9
Delsuc et al ²⁷ 2018 (France)	Kidney	Single-center Observational	September 2006 to September 2013	24 ^b	22 uDCD-ISP ^b	uDCD IIa	Age ≥18 to ≤55, known time of CA, <30 min no flow, <150 min interval before preservation protocol initiation	43.2 ± 8.6	47.9 ± 10.7
Antoine et al ²⁴ 2019 (France) ^d	Kidney	French transplant Registry Retrospective	2007 to 2014	142 ^b	161 uDCD-ISP ^b	uDCD II	Age <55 known time of CA, <30 min no flow, <150 min fWIT	42 ± 9.3	–
Del Rio et al ²⁶ 2019 (Spain) ^e	Kidney	Spanish transplant registry system Retrospective	January 2012 to December 2015	151 ^b	99 uDCD-HRP ^b 35 uDCD-ISP ^b	uDCD IIa and b	Age <55–60, <15 min CA, <150 min WIT	47 ± 11	51 ± 11
Ravaioli et al ³⁶ 2018 (Italy)	Kidney	Single-center Observational	January 2016 to February 2017	5 ^b	No control group	cDCD III	Irreversible brain or cardiac injury sustained by life therapies and CRS	44.8 ± 17.3 ^c	59.7 ± 7.7 ^c
Mori et al ⁴⁵ 2019 (Italy)	Kidney	Multicenter Observational	November 2017 to June 2018	6 ^b	No control group	cDCD III	–	57.3 ± 7.53	57.5 ± 4.97
Fondevila et al ²⁹ 2012 (Spain)	Liver	Single-center Observational	April 2002 to December 2010	145	538 DBD ^b	uDCD II	Age ≤65, <15 min between CA-CPR, <150 min of CRS, <4 h of aNRP, ALT/AST <3 × ULN (start aNRP), ALT/AST <4 × ULN (during aNRP)	47 [27–56]	55 [49–60]
Savier et al ⁴⁰ 2015 (France)	Liver	Multicenter Observational	January 2010 to December 2013	30	41 DBD ^b	uDCD II	Age <55, known time of CA, <15 min no flow, <150 min CPR, <240 min aNRP, ALT/AST <200 IU/L (after 2 h aNRP), <15%–20% steatosis, <8 h CIT	37 ± 3 (mean ± SEM)	54.4 ± 4.4 ^c
Jiménez-Romero et al ⁴³ 2019 (Spain)	Liver	Single-Center Observational	January 2006 to February 2018	75	265 DBD ^b	uDCD II	Age 14–55, <15 min of CA, <150 min between CPR-perfusion, <5 h of aNRP, <30% macrosteatosis, ALT/AST <4 × ULN	41.7 ± 9.7 (18–55)	58.8 ± 7.7 (36–70)
De Caritis et al ²⁵ 2018 (Italy)	Liver	Single-center Observational	2015 to 2017	19 uDCD 6 cDCD 52 DBD ^b 17 ECMO + DBD ^b	19 uDCD 6 cDCD 52 DBD ^b 17 ECMO + DBD ^b	uDCD II cDCD III	Age <65, ≤160 min WIT, ALT ≤1000 IU/L, downward trend in serum lactate, macrosteatosis ≤30%, Ishak score ≤1	51 [46–61]	56 [54–63]

Continued next page

abdominal organs included in the studies concerned: kidney (n = 9),^{24,26-28,34,36,37,41,45} liver (n = 11),^{21,25,29,31,32,39,40,42-44,46} kidney and liver (n = 1),³⁰ and kidney, liver, and pancreas/islets (n = 3).^{33,35,38} The overlap in partly duplicate reporting on the same organ is outlined in Table 2. The inclusion period of the studies ranged from 1986 to 2019.

Fifteen studies were single-center studies,^{25,27,29-31,33,34,36-39,41-43,46} and 7 multicenter studies^{21,28,32,35,40,44,45} were included in this review. Two articles^{24,26} used the national registry system to analyze data.

The articles described results in uDCD type I or II (n = 10),^{24,26-29,34,37,40,41,43} cDCD type III (n = 12),^{21,30-33,35,36,38,39,42,44,45} cDCD type IV (n = 1),⁴² or both uDCD and cDCD (n = 2).^{25,46} Regarding control groups, aNRP was compared with DBD,^{25,29,30,33,34,37,40,43,44} uDCD,^{24,27,28,41} or cDCD^{21,32,42} without aNRP. Del Río et al²⁶ used both cold in situ perfusion (ISP) and hypothermic regional perfusion as controls (Table 2). The remaining 7 studies^{31,35,36,38,39,45,46} did not use controls.

The sample sizes in the actual donor cohort ranged from 5 to 186 donors. However, the potential donor cohort (including mostly donors not yet exposed to the different inclusion or exclusion criteria) accumulated to approximately 568 donors.

aNRP Protocols

For clarification purposes, the technique used for aNRP in clinical practice is briefly described below for uDCD and cDCD donors.

In uDCD type II, in which repeated attempts of resuscitation failed, the donor is declared dead in the hospital. In some countries, cardiopulmonary resuscitation using cannulas in the femoral vessels and mechanical ventilation is then restarted to preserve organ viability. To prevent blood flow to the thoracic organs, a balloon catheter is introduced via the contralateral femoral artery and inflated, thus occluding the supraceliac aorta. To ensure proper positioning of the balloon, a chest radiograph can be used. The aNRP system, already primed with perfusate solution (eg, Ringers lactate added with heparin and/or antibiotics), is then connected to the cannulas, and the pump is started. A regular DBD-like surgical procurement will take place after the donation consent is obtained.

In cDCD type III, the opportunity to cannulate under local anesthesia before withdrawal of life-sustaining therapy differs per country. If allowed, rapidly after the declaration of death (including the obligated no-touch period), the balloon is inflated, and the cannulas are connected to the aNRP system, after which perfusion is commenced. However, if interventions, such as cannulation or the administration of heparin, before the declaration of death are prohibited, time becomes an important factor. After death has been declared and a no-touch period has been observed, the rapid laparotomy is undertaken by the surgical team. The abdominal aorta and infrarenal inferior vena cava are cannulated. aNRP is initiated when the thoracic aorta, just above the diaphragm, is cross clamped.

In DCD type IV, cardiac arrest occurs unexpectedly due to hemodynamic instability in a brain-dead donor (uDCD IV). In some countries (ie, Japan and China), there is no legislation on brain death criteria resulting in withdrawal

of treatment followed by cardiac arrest in a controlled setting (cDCD IV). In the latter case, the femoral vessels are cannulated before treatment is withdrawn, and aNRP is started when systolic blood pressure drops below 60 mmHg while cardiac arrest is awaited.

The definition of donor WIT varies widely among the articles (Tables 3 and 4). In the study of Ding et al⁴² using cDCD (IV), there is no WIT as aNRP immediately started when the systolic blood pressure fell below 60 mmHg while cardiac arrest was awaited. Overall, the flow for aNRP was targeted at >1.7 L/minute. The majority of studies used normothermic perfusion (36–37°C) during aNRP, while Savier et al⁴⁰ did not use a heat-exchanger, resulting in temperatures of 32–33°C (Table 4). Reznik et al³⁷ perfused with subnormothermic perfusion varying between 27°C and 32°C (Table 3).

After aNRP and procurement, preservation of grafts during cold ischemia time has been managed differently per country. In France, ex situ hypothermic machine perfusion (HMP) is systematically used for kidney grafts.^{24,27,28} Del Río et al²⁶ described that 33% of kidneys analyzed in their Spanish National registry cohort were subjected to HMP. HMP for kidneys was also used in 3 other studies.^{36,38,45} Regarding the liver graft, HMP was used in 2 studies.^{25,46} The remaining studies used static cold storage for organ preservation.

Clinical Outcomes

For the purpose of this review, clinical outcomes are reported per abdominal organ transplanted.

Kidney

Thirteen articles^{24,26-28,30,33-38,41,45} described the effect of aNRP on clinical outcomes in kidney transplantation (Table 5). Seven articles included uDCD-aNRP, of which 5^{24,26-28,41} and 2^{34,37} used uDCD and DBD as controls, respectively. cDCD-aNRP was described in 6 studies, of which 2^{30,33} used DBD as controls. The remaining 4 studies^{35,36,38,45} did not compare their results to controls.

Organ Utilization Rate

OUR varied from 64.8% to 100% and 64.9% to 92.7% in uDCD-aNRP^{34,37,41} and cDCD-aNRP,^{30,33,35,38} respectively. Valero et al⁴¹ demonstrated an OUR in uDCD-aNRP of 66.7% comparing with cold ISP (55%) and total body cooling (50%). In the remaining studies,^{24,26-28,36,45} the OUR was not described or was not calculated as selection was based on recipients.

1-year Patient and Graft Survival

As regards uDCD-aNRP, only 2 studies^{28,37} reported 1-year patient survival. This was 100% compared with 94.6% in DBD and 96.6% in uDCD. The 1-year patient survival was not reported in the 6 cDCD-aNRP studies.^{30,33,35,36,38,45}

Regarding 1-year graft survival, 2 studies^{26,28} demonstrated a graft survival of 91%–94.4% in uDCD-aNRP compared with 62%–93.5% in uDCD. When uDCD-aNRP was compared with DBD, Reznik et al³⁷ has shown similar 1-year graft survival in both groups. In cDCD-aNRP, however, 2 studies^{30,33} reported a lower 1-year graft survival when compared with DBD. The remaining 7

studies^{24,27,34-36,41,45} did not mention 1-year graft survival outcomes.

Secondary Outcomes

PNF rate was described in 11 studies.^{24,26-28,33,34,36-38,41,45} Five studies showed a range of 0%–8% in uDCD-aNRP compared with 3%–31% in uDCDs.^{24,26-28,41} When using DBD as controls, no differences were observed.³⁴ In cDCD-aNRP, the PNF rate varied from 0% to 5%; however, no control group was used to compare these outcomes.^{33,36,38,45}

DGF, generally defined as the need for at least 1 dialysis treatment in the first week after transplantation, varied from 12.5%–75.7% to 7.1%–40% in uDCD-aNRP and cDCD-aNRP, respectively. As regards the controls, DGF varied from 4.9%–46.4% in DBDs to 55%–87% in uDCDs.

Posttransplant kidney function was described differently. Whereas some studies used serum creatinine at

1-year, others preferred to assess the kidney function after transplantation via the eGFR or measured glomerular filtration rate.

Liver

Fourteen studies^{21,25,29-33,35,38-40,42-44,46} reported on the outcome of liver transplantation (Table 6). Three^{29,40,43} of those included uDCD-aNRP compared with DBDs. Ten studies included cDCD-aNRP with 2 studies^{33,44} using DBD as control and 2 others^{21,32} using cDCD as control, respectively. One study⁴² performed in China, in which organ DBD is followed by circulatory death, included cDCD type IV and compared aNRP in this type of donor with ISP. The remaining 5 studies^{30,31,35,38,39} did not have a control group. For 2 studies,^{25,46} we will not discuss the outcomes as these studies analyzed both uDCD and cDCD donors and did not distinguish between those 2 donor types in their analysis.

TABLE 3.
aNRP protocols for kidneys

Study	WIT definition	WIT (min)	aNRP time (min)	Temperature (°C)	Flow (L/min)	CIT (h)	Ex situ graft preservation	Interventions before declaration of death		No-touch period (min)
								Cannulation	Heparinization	
uDCD										
Valero et al ⁴¹	–	82 ± 11	60	37 ^a	1–2	17.8 ± 6.7	–	No ^b	No ^b	10
Reznik et al ³⁷	Standard WIT	61.4 ± 4.5 (20–92)	145.5 ± 6.1 (105–210)	27–32	0.5 (initial) 3.5 (final)	13.9 ± 0.64	SCS	No	No	–
Demiselle et al ²⁸	No flow	6.4 ± 6.8	60	36	2–3.7	11.2 ± 3.57	HMP	–	–	–
	Low flow	135.9 ± 11.5								
Molina et al ³⁴	Standard WIT	132.5 ± 20.6	196.3 ± 45.8	37	–	12.4 ± 4.4	SCS	No ^b	–	5
Delsuc et al ²⁷	No flow	10 ± 10	203 ± 46	37	2	13.6 ± 3.5	HMP	No	No	5
	Low flow	123 ± 20								
Antoine et al ²⁴	Standard WIT	135 ± 15 ^c	210 ± 42.2	33–36	–	14 ± 4	HMP	–	–	5
Del Río et al ²⁶	Standard WIT	130	170	35.5–37.5	>1.7	15 [11–18] ^d	SCS (67%) HMP (33%)	No ^b	–	–
		[116–141] ^d	[140–218] ^d							
cDCD										
Ravaoli et al ³⁶	Standard WIT fWIT	29 (13–50) ^e 151 ± 132	207.2 ± 70.4 ^e	37	2 (1.7–4)	10 ± 3	HMP O ₂	Yes	No	20
Mori et al ⁴⁵	Standard WIT	20	207 ± 40 (171–284)	–	–	11.7 ± 2.6 11.5 (7.35–15.42)	HMP O ₂	No	–	20
Foss et al ³⁰	fWIT	26.5 (20–49)	97 (54–106)	37	3 (1.7–4.0)	6 (2.9–10.4)	–	No ^f	Yes	5
Rojas-Peña et al ³⁸	–	–	86 ± 5	37	3.5	17.4	HMP	Yes	Yes	5
Oniscu et al ³⁵	fWIT	26 (13–48)	120 (34–156)	35.5–37.5	1.7–4	12.5 (5.4–18)	SCS	No	No	5
Miñambres et al ³³	fWIT	12 [10–19]	109 [93–138]	37	2–2.4	16 [7.9–21.5]	–	Yes	Yes	5

Numerical figures are reported as mean ± SD or median with [IQR] or (range) in brackets unless otherwise specified.

As different definitions of warm ischemia time were included in the studies, the authors used the following definitions:

1. No flow period: Time between CA and start CPR/CRS.
2. Low flow period: Time between CPR/CRS and the start of perfusion.
3. Standard WIT: Time between CA and the start of perfusion.
4. fWIT: Time between SBP <50/60 mm Hg and/or O₂ <70%/80% and the start of perfusion.
5. Total WIT: Time between WLST and the start of perfusion.

^aValero et al⁴¹ used TBC (15–20°C) after 60 min of aNRP.

^bAfter diagnosis of death CPR and mechanical ventilation is restart for the purpose of preserving organ viability.

^cThis value includes all uDCDs, including ISP (n = 303).

^dThis value includes all uDCDs, including HRP and ISP (n = 303).

^ePlease note that there was a discrepancy in this value if this was self-calculated by the authors using the provided information.

^fCentral lines were placed in the common femoral artery and vein before the declaration of death.

aNRP, abdominal normothermic regional perfusion; CA, circulatory arrest; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; CPR, cardiopulmonary resuscitation; CRS, cardiorespiratory support; fWIT, functional warm ischemia time; HMP, hypothermic machine perfusion; HRP, hypothermic regional perfusion; IQR, interquartile range; ISP, in situ perfusion; SBP, systolic blood pressure; SCS, static cold storage; TBC, total body cooling; uDCD, uncontrolled donation after circulatory death; WIT, warm ischemia time; WLST, withdrawal of life-sustaining therapy.

TABLE 4.
aNRP protocols for livers

Study	WIT definition	WIT (min)	aNRP time (min)	Temperature (°C)	Flow (L/min)	CIT (h)	Ex situ graft preservation	Interventions before declaration of death		No-touch period (min)
								Cannulation	Heparinization	
uDCD										
Fondevilla et al ²⁹	No flow	7 [5–10] ^a	198 [183–225]	35.5–37.5	>1.7	6.3 [5.4–7.2]	–	No ^b	No ^b	5
	Duration CRS	112 [103–135]								
Savier et al ⁴⁰	No flow	7.4 ± 4.4 ^c	249 ± 32 ^c	32–33	2–3	5.8 ± 0.5 (mean ± SEM)	SCS	No ^b	No ^b	5
	Low flow	129.3 ± 13.3 ^c								
Jiménez-Romero et al ⁴³	Standard WIT	130 ± 21.5 (40–165)	204.7 ± 37.3 (118–285)	36–37.5	3.79 ± 0.4 (3.0–4.8)	6.4 ± 1.4	–	No ^b	No ^b	5
uDCD and cDCD										
De Carlis et al ²⁵	cDCD: fWIT	125 [72–143] ^d	352 [308–434]	–	–	8 [6–9]	HMP ^f	uDCD: No	uDCD: –	20
	uDCD: Standard WIT							cDCD: –	cDCD: –	
Olivieri et al ⁴⁶	fWIT	38.1 ± 7.3 ^{c,e}	252.6 (150–624)	–	>2	7.4 ± 1 ^c	HMP ^f	uDCD: –	uDCD: –	20
cDCD										
Ruiz et al ³⁹	fWIT	10 (6–22)	126.5 (86–161)	37	>1.7	4.7 (2.5–6.8)	SCS	Yes	Yes	5
Watson et al ²¹	Total WIT	30 [26–36]	123 [103–130]	–	2.5–3 abdominal 4–6 thoracoabdominal	6.4 [5.1–8.4]	SCS	No	No	5
Hessheimer et al ³²	Total WIT	19.2 ± 8.2	120 (79–136)	37	>1.7 L/min/m ²	5.6 ± 1.8	–	Depending on center	Depending on center	5
	fWIT	18 [13–23]				5.3 [4.4–6.1]		(87% yes)		
	fWIT	13.3 ± 5.3								
	fWIT	12 [9–16]								
Hagness et al ³¹	fWIT	28 (13–24)	94 (73–221)	37	–	7.14 (3.43–9.55)	–	No ^g	Yes	5
Minambres et al ⁴⁴	fWIT	12 [10–13]	114 [58–121]	37	2–2.4	5.2 ± 1.5	–	Yes	Yes	5
Ding et al ⁴²	NA ^h	NA ^h	– (180–300)	–	–	4.7 ± 1.3	–	Yes ^h	–	NA ^h
Foss et al ³⁰	fWIT	23 and 26	97 (54–106)	37	3 (1.7–4.0)	3.8 and 7.1	–	No ^g	Yes	5
Rojas-Peña et al ³⁸	–	–	86 ± 5	37	3.5	–	SCS	Yes	Yes	5
Oniscu et al ³⁵	fWIT	26 (13–48)	120 (34–156)	35.5–37.5	1.7–4	6 (2.8–7.5)	SCS	No	No	5

Numerical figures are reported as mean ± SD or median with [IQR] or (range) in brackets unless otherwise specified.

As different definitions of warm ischemia time were included in the studies, the authors used the following definitions:

1. No flow period: Time between CA and start CPR/CRS.
2. Low flow period: Time between CPR/CRS and the start of perfusion.
3. Standard WIT: Time between CA and the start of perfusion.
4. fWIT: Time between SBP <50/60 mm Hg and/or O₂ <70%/80% and the start of perfusion.
5. Total WIT: Time between WLST and the start of perfusion.

^aThis does not include the 5-min no touch.

^bAfter diagnosis of death, CPR and mechanical ventilation is restarted for the purpose of preserving organ viability.

^cThis value is calculated by the authors based on the information provided in the article.

^dThese values include both donor types.

^eThis value includes only cDCD.

^fUnknown if oxygen was added during ex situ machine perfusion of the graft.

^gCentral lines were placed in the common femoral artery and vein before the declaration of death.

^haNRP was immediately started when SBP <60 mm Hg to maintain blood flow to the organs while awaiting cardiac arrest.

uANRP, abdominal normothermic regional perfusion; CA, circulatory arrest; cDCD, controlled donation after circulatory arrest; CIT, cold ischemia time; CPR, cardiopulmonary resuscitation; CRS, cardiorespiratory support; fWIT, functional warm ischemia time; HMP, hypothermic machine perfusion; IQR, interquartile range; NA, not applicable; SBP, systolic blood pressure; SCS, static cold storage; WLST, uncontrolled donation after circulatory death; WIT, warm ischemia time; WLST, withdrawal of life-sustaining therapy.

TABLE 5.

Clinical outcomes for the kidneys

Study	Number of actual donors (potential/aNRP)	Organs used for transplantation	Discarded, n (%)	Organ utilization rate, n (%)	1-y patient survival, n (%)	1-y graft survival, n (%)	PNF, n (%)	DGF, n (%)	Posttransplant kidney function ^a	Follow-up
uDCD										
Valero et al ⁴¹	aNRP, n = 6 (-/6)	8	—	8/12 (66.7)	—	—	0 (0)	1 (12.5) <i>P</i> < 0.05	—	Up to 5 y
Reznik et al ³⁷	uDCD-ISP, n = 37 ^b	44	—	44/80 (55)	—	—	9 (22.5)	22 (55)	—	Up to 1 y
	uDCD-TBC, n = 11 ^b	8	—	8/16 (50)	—	—	0 (-)	6 (75)	—	
	aNRP, n = 22 (24/22) DBD, n = 74	44	4	44/44 (100) NA ^c	44 (100) 87 (94.6) <i>P</i> = 0.221	42 (95.5) 87 (94.6) <i>P</i> = 0.312	0 (0) — (-)	23 (52.3) 34 (36.9)	0.116 ± 0.004 0.115 ± 0.004 <i>P</i> > 0.05	
Demiselle et al ²⁸	aNRP, n = 19 (-/19) uDCD-ISP, n = 31	19 31	NA ^c	NA ^c NA ^c	18 (100) 27 (96.6)	18 (94.4) 27 (93.5)	1 (-) 2 (-)	10 (53) 25 (81) <i>P</i> = 0.036	50.7 43.2 1-y MDRD-eGFR (mL/min/1.73 m ²)	26.8 ± 16.9 mo ^c
Molina et al ³⁴	aNRP, n = 186 (568/213) DBD, n = 237	241 237	131 (35.2) ^d	241/372 (64.8) ^e NA ^c	— ^f	— ^f	16 (6.8) 10 (4.2) <i>P</i> = 0.226	174 (73.4) 110 (46.4) <i>P</i> < 0.001	50.5 ± 18.4 ^d 54.8 ± 18.8 <i>P</i> = 0.007	65 mo (46–90 mo) 72 [28–108]
Delsuc et al ²⁷	aNRP, n = 24 (-/24) uDCD-ISP, n = 22	32 32	NA ^c	NA ^c NA ^c	— ^g	— ^g	1 (3) 1 (3)	23 (72) 27 (84) <i>P</i> = 0.23	53.8 ± 12.8 (n = 24) 43.0 ± 12.8 <i>P</i> = 0.007 ^h	2 y ⁱ
Antoine et al ²⁴	aNRP, n = 142 (-/—) uDCD-ISP, n = 161	251 248	NA ^c	NA ^c NA ^c	—	—	15 (6.0) 22 (8.9) <i>P</i> = 0.16 ^j	— (75.7) ^j — (-)	—	—
Del Río et al ²⁶	aNRP, n = 151 (-/—) uDCD-HRP, n = 99	277 179	NA ^c	NA ^c NA ^c	—	— (91) ^c — (87.5)	21 (8) 14 (8) <i>P</i> = 0.372	177 (71) ^j 129 (82)	—	Up to 1 y
cDCD	uDCD-ISP, n = 35	58	—	NA ^c	—	— (62)	18 (31) <i>P</i> < 0.001	34 (87)	1-y mGFR (mL/min/1.73 m ²)	—
	aNRP, n = 5 (5/5) No control group	10	NA ^c	NA ^c	— ^k	— ^k	0 (0)	3 (30)	1.20 ± 0.17 ^c 6 mo sCr (mg/dL)	449.5 d (201–627 d)
	aNRP, n = 6 (-/6) No control group	9 ^l	NA ^c	NA ^c	—	—	0 (0)	1 (16.7)	51.17 ± 13.86 6 mo CKD-eGFR (mL/min)	—
Foss et al ³⁰	aNRP, n = 8 (-/—) DBD, n = 114	14 163	2 NA ^c	14/16 (87.5) NA ^c	—	13 (93) — (95) <i>P</i> = 0.53	—	1 (7.1) 8 (4.9) <i>P</i> = 0.53	75 (65–76) 61 (37–112) <i>P</i> = 0.23	Up to 1 y

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TABLE 5. (Continued)

Study	Number of actual donors (potential/aNRP)	Organs used for transplantation	Discarded, n (%)	Organ utilization rate, n (%)	1-y patient survival, n (%)	1-y graft survival, n (%)	PNF, n (%)	DGF, n (%)	Posttransplant kidney function ^a	Follow-up
Rojas-Peña et al ³⁸	aNRP, n = 37 (50/37) No control group	48	25	48/74 (64.9) ^f	–	– (100) SP ^c	1 (3.5)	– (31)	–	Up to 3 y
Oniscu et al ³⁵	aNRP, n = 21 (36/21)	38 ^m	3	38/41 (92.7) ⁿ	–	–	–	13 (40)	1.36 [1.03–1.58] ^o 1-y sCr (mg/dL)	11 mo (3–39 mo)
Miñambres et al ³³	aNRP, n = 27 (–/27) DBD, n = 51	37 36	11	37/54 (68.5) ^o NA ^c	–	– (91.8) ^p – (97.2) P = 0.315	2 (5)	10 (27)	1.3 [1.0–1.8] 1-y sCr (mg/dL)	17 mo (7–22 mo) ^r

^aThese values are reported as mean ± SD or median with [IQR] or (range) in brackets unless otherwise specified.

^bThree cases of TBC were converted to ISP.

^cSelection on recipients.

^dThis value is calculated by the authors based on the information provided in the article.

^eAfter consent was obtained, 186 effective uDCD donors received aNRP.

^fData are available for 5- and 10-y patient and graft survival.

^gData are available for 2-y patient and graft survival.

^hAfter multivariate analysis the difference remained significant (adjusting for recipient age, sex, CIT, duration of perfusion; P = 0.03).

ⁱAfter sensitivity analysis 1 center was excluded resulting in P = 0.015.

^jPNF cases were excluded.

^kData are available for 6-mo patient and graft survival.

^lSeventy-three grafts were procured from the 37 uDCD donors.

^mFour double transplants were performed.

ⁿOne donor had a previous nephrectomy.

^oForty-eight grafts were recovered from the 27 uDCD donors.

^pThese data are death censored.

^qThree double kidney transplants were performed.

^rThis includes the follow-up of all recipients.

aNRP, abdominal normothermic regional perfusion; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; HRP, hypothermic regional perfusion; IQR, interquartile range; ISP, in situ perfusion; mGFR, measured glomerular filtration rate; MDRD, modification of diet in renal disease; NA, not applicable; PNF, primary nonfunction; sCr, serum creatinine; TBC, total body cooling; uDCD, uncontrolled donation after circulatory death.

TABLE 6.
Clinical Outcomes for the livers

Study	Number of actual donors (potential/aNRP)	Organs used for transplantation	Discarded, n (%)	Organ utilization rate, n (%)	1-y patient survival, n (%)	1-y graft survival, n (%)	PNF, n (%)	Biliary complications, n (%)		Retransplantation, n (%)	Follow-up
								Overall	IC		
uDCD											
Fondevila et al ²⁹	aNRP, n = 34 (400/290) DBD, n = 538	34 538	111 NA ^a (76% in text)	34/290 (11.72) NA ^a (76% in text)	– (82) – (90) P = 0.141	– (70) – (87) P = 0.011	– – 3 (23)	4 (12)	3 (8)	– – 3 (8.8)	24 mo (0–111 mo) 44 mo
Savier et al ⁴⁰	aNRP, n = 13 (299/183) DBD, n = 41	13 41	– – NA ^a	13/183 (7.10) NA ^a	– (85) – (93) P = 0.039	– (69) – (93) P = 0.03	3 (23) – 6 (8)	2 (22)	1 (11) 1 (2)	4 (–) – –	32 mo [10.2–39.5 mo] 23.6 [8.9–36.7]
Jiménez-Romero et al ⁴³	aNRP, n = 100 (–/256) DBD, n = 265	75 265	181 (70.7) –	75/256 (29.3) NA ^a	– (82.7) ^{im} – (89) P = 0.180	– (73.3) ^{im} – (87.1) P = 0.013	2 (10)	23 (30.6)	12 (16)	– – –	63.5 ± 2.5 mo ^o
uDCD and cDCD											
De Carlis et al ²⁵	aNRP, n = 20* (–/25) *14 uDCD, 6 cDCD	20	5	20/25 (80)	– (95) (69%–99%) 95% CI	– (85) (60%–95%) 95% CI ^d	2 (10)	4 (20)	2 (10)	4 (24) ^e	14 mo [8–26 mo]
	DBD n = 52	52 17	NA ^a	NA ^a NA ^a	– (94) (82%–98%) 95% CI	– (91) (80%–97%) 95% CI	2 (4)	7 (13)	2 (4)	13 (27)	17 mo [11–23 mo]
	ECMO-DBD n = 17	17	–	–	– (87) (58%–97%) 95% CI	– (87) (58%–97%) 95% CI	1 (6)	1 (6)	0	7 (44)	20 mo [7–29 mo]
Olivieri et al ⁴⁶	aNRP, n = 16* (–/16) *2 uDCD, 14 cDCD No control group	10	6	10/16 (62.5)	–	–	0 (0)	4 (40)	–	–	–
cDCD											
Ruiz et al ³⁹	aNRP, n = 46 (57/57) No control group	46 169	11	46/57 (80.70)	46 (100) ^f	46 (100) ^f	0 (0)	1 (2)	0 (0)	11 (23)	19 mo (9–40 mo)
Watson et al ²¹	aNRP, n = 43 (–/70) cDCD-ISP, n = 187	43 187	27 NA ^a	43/70 (61.43) NA ^a (27%–36% in text)	– (97.7) ^{gh} – (94.2)	– (97.7) ^{gh} – (86.5)	0 (0)	6 (14)	0 (0)	5 (12) 55 (32)	Up to 5 yr
Hessheimer et al ³²	aNRP, n = 95 (342/152) cDCD-ISP, n = 190 * All potential cDCDs	95 117	52 (34) 73 (38)	95/152 (62.5) 117/190 (61.58)	– (93) ⁱ – (88)	– (88) ⁱ – (83)	2 (2) 3 (3)	8 (8) 36 (31)	2 (2) 15 (13)	21 (22) 32 (27)	20 mo ^o

Continued next page

TABLE 6. (Continued)

Study	Number of actual donors (potential/aNRP)	Organs used for transplantation	Discarded, n (%)	Organ utilization rate, n (%)	1-y patient survival, n (%)	1-y graft survival, n (%)	PNF, n (%)	Biliary complications, n (%)		EAD, n (%)	Retransplantation, n (%)	Follow-up
								Overall	IC			
Hagness et al ³¹	aNRP, n = 8 (-/8) No control group	8	–	8/8 (100)	–	7 (100)	0 (0)	2 (25)	0 (0)	–	–	1 y ^o
Miñambres et al ⁴⁴	aNRP, n = 19 (-/19) ^f DBD, n = 34	16 29	3 5	16/19 (84.2) 29/34 (85.3)	– (87.5) – (96) P = 0.496	– 0 (0) P = 0.121	2 (12.5) 0 (0)	0 (0)	0 (0)	3 (18.8) 5 (17.2) P = 0.6	1 (6.3) 1 (3.4) P = 0.590	6 mo [3–18 mo] 16 mo [12–20 mo] 12 mo (12–30 mo) ^g
Ding et al ⁴²	aNRP, n = 7 (-/7) cDCD (V)-ISP, n = 12	7 12	– –	7/7 (100) 12/12 (100)	6 (85.7) ^g	7 (100) ^g	0 (0)	0 (0)	0 (0)	–	–	Up to 2 y
Foss et al ³⁰	aNRP, n = 8 (-/8) No control group	2	3	2/8 (25)	2 (100) ^k	2 (100) ^k	0 (0)	0 (0)	1 (8.3)	–	0 (0)	Up to 2 y
Rojas-Peña et al ³⁸	aNRP, n = 13 (50/37) No control group	13	8	13/37 (35.14)	–	– (85.7) ^k	1 (7.7)	1 (7.7)	–	–	–	Up to 2 y
Oniscu et al ³⁵	aNRP, n = 11 (36/21) No control group	11	8	11/21 (52.38)	–	–	1 (9.1)	2 (-)	0 (0)	4 (-)	–	10 mo (3–36 mo)

^oSelection on recipients.

^fAfter consent was obtained, 38 uDCD donors received aNRP. In 12 of these donors, it was unsuccessful to establish aNRP mostly due to major thoracic or abdominal trauma.

^gCumulative survival.

^hThe data are death censored.

ⁱThese percentages were calculated after excluding the recipients that received a retransplantation.

^jMedium follow-up was 19 mo.

^kThis value is calculated by the authors based on the information provided in the article.

^lData are available for 3-mo patient and graft survival.

^mData are available for 3-y patient and graft survival.

ⁿAfter inverse probability of treatment weighting analysis.

^oData are available for 2-y survival.

^pPlease note that this study only includes the combined procedure of aNRP for abdominal grafts and ISP for the lungs.

^qData are available for 5-y patient and graft survival.

^rThis includes the follow-up of all recipients.

^sOne patient reached 6-mo follow-up.

aNRP, abdominal normothermic regional perfusion; cDCD, controlled donation after circulatory death; CI, confidence interval; DBD, donation after brain death; EAD, early allograft dysfunction; ECMO, extracorporeal membrane oxygenation; IC, ischemic cholangiopathy; ISP, in situ perfusion; NA, not applicable; PNF, primary nonfunction; uDCD, uncontrolled donation after circulatory death.

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Organ Utilization Rate

The OUR in uDCD-aNRP^{29,40,43} varied from 7.1% to 29.3%. This was lower when compared with DBD (76%).²⁹ In cDCD-aNRP, Watson et al²¹ described an OUR of 61.4% compared with 27%–36% when using cold ISP. However, Hessheimer et al³² demonstrated a comparable OUR for both perfusion methods (62.5% cDCD-aNRP versus 61.6% controls). Furthermore, Ding et al⁴² demonstrated a 100% OUR for both perfusion methods in cDCD type IV.

1-year Patient and Graft Survival

In all 3 studies^{29,40,43} using uDCD-aNRP, the rates of 1-year patient and graft survival were lower than in DBD. In cDCD-aNRP,^{21,32} 1-year patient survival varied between 93% and 97.7% when compared with 88%–94.2% in controls of the same donor type. Miñambres et al⁴⁴ found a lower 1-year patient survival but compared the outcomes with DBDs (87.5% versus 96%). The graft survival was higher in cDCD-aNRP compared with cDCD^{21,32} (88%–97.7% versus 83%–86.5%).

Secondary Outcomes

Only 2 studies^{21,32} compared the incidence of PNF in cDCD-aNRP to cDCD, demonstrating a lower incidence of PNF (0%–2% cDCD-aNRP versus 3%–7% cDCD); however, the differences were not statistically significant for each study. When cDCD-aNRP was compared with DBD, the incidence of PNF was higher (12.5% cDCD-aNRP versus 0% DBD) but did not reach significance as well.

With regard to biliary complications after liver transplantation, the overall incidence varied widely, influenced by the donor type. In uDCD-aNRP,^{40,43} the incidence of IC was higher (11%–16%) when compared with DBD (2%–3%). However, the incidence was statistically significantly lower (0%–2%) in cDCD-aNRP when compared with cDCD^{21,32} (13%–27%).

The EAD rate was reported in 6 studies.^{21,32,35,39,40,44} When compared with controls, it ranged from 12% to 22% in cDCD-aNRP versus 17.2%–32% in cDCD^{21,32,44} and was found to be statistically different in 1 study.²¹ When compared with DBD, Miñambres et al⁴⁴ found similar EAD rates (18.8% cDCD-aNRP versus 17.2% DBD).

Pancreas

Only 3 studies^{33,35,38} reported data on pancreas or islet transplantation when using aNRP. One pancreas as whole organ transplant with no information on short- or long-term outcomes,³⁸ 3 simultaneous pancreas-kidney (SPK) transplants and 1 islet transplantation were performed. Miñambres et al³³ reported appropriate graft function in 1 SPK transplantation after 6 months, and Oniscu et al³⁵ described primary kidney and pancreas function in 2 SPKs. The islet isolation was performed from 2 pancreases, of which 1 transplant was performed after obtaining a sufficient yield.

Risk of Bias Within Studies

The domains confounding, selection of participants into the study, and selection of reported results were frequently judged as moderate or serious risk of bias. Seven

studies^{31,35–38,45,46} did not have a control group, resulting in a “non-applicable” judgment on different bias domains, whereas 7 studies^{25,30,33,37,40,43,44} used DBD as controls, resulting in a serious risk of bias in the confounding domain. In total, 11 studies^{24,25,30,32–34,40–44} were considered to have serious overall risk of bias and 5^{21,26–28,37} to have moderate overall risk of bias (Tables 7 and 8). The most important selection bias was caused by surgical assessment of abdominal organs on its macroscopic appearance, resulting in declining or accepting the organ. However, this is present in all studies and probably inevitable as it is the only way that DCD organs are currently assessed in standard clinical practice.

DISCUSSION

Despite the fact that aNRP was introduced in the 1990s, only in recent years has its use become more widespread. Especially in countries with an extensive DCD donation population, it was found to increase the OUR from DCD donors and improve transplant outcomes. For this reason, in France, Italy, and Norway, aNRP has become the standard procurement procedure for DCD donors mandated by the health authorities or preferred routine in several regions in the United Kingdom and Spain.¹⁸ This systematic review aims to assess the level of clinical evidence justifying expansion of aNRP in both donor types, uDCD and cDCD.

The results of this review show that aNRP is feasible and safe in both uDCD and cDCD. All available studies demonstrated successful implementation of the technique into clinical practice. Function and outcomes after kidney and liver transplantation using aNRP appear superior to non-aNRP DCD donors when comparing data to large cohorts described elsewhere.^{1–3} Some studies found increased survival and lower complication rates.^{21,32} Due to the low number of pancreas or islet transplantation after aNRP, it is difficult for the pancreas to draw conclusions whether this approach results in improved outcomes.

Local and national practice how DCD donors and organs are managed and procured differ across countries. The possibility of pre-mortem interventions (eg, cannulation and heparinization) in both uDCD and cDCD may affect the OUR in countries where these are allowed. As such, reports of successful aNRP in uDCD donors may have convinced national competent authorities to implement such a program, while legal and ethical, but also practical concerns may prohibit its widespread applicability in similar settings in other countries. Therefore, these results should be considered in each individual country's context.

In addition, the current definitions and protocols concerning aNRP will differ (eg, the definition of WIT, approach for lung donation, and the use of continuous versus end-ischemic ex situ machine perfusion). Protocols include different approaches for the addition of medication during aNRP, duration of perfusion, temperature, organ acceptance criteria, and uniform outcome measures. Uniform reporting of definitions and outcome measures would be preferable for aNRP and other novel perfusion technologies.⁴⁷ Consensus on the definition of OUR should be reached and patient and graft survival mentioned, as well as short- and long-term graft function. Concerning

TABLE 7.

Risk of bias in studies focusing on the kidney

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes				Bias in selection of the reported results	Overall risk of bias
						PS	GS	PNF	DGF		
Valero et al ⁴¹	●	●	●	●	●	● ^a	●	●	●	●	●
Reznik et al ³⁷	● ^b	●	●	●	●	●	●	●	●	●	●
Demiselle et al ²⁸	●	●	●	●	●	●	●	●	●	●	●
Molina et al ³⁴	●	●	●	●	●	●	●	●	●	●	●
Delsuc et al ²⁷	●	●	●	●	●	●	●	●	●	●	●
Antoine et al ²⁴	●	●	●	●	●	●	●	●	●	●	●
Del Río et al ²⁶	●	●	●	●	●	● ^c	●	●	●	●	●
Ravaioli et al ³⁶	NA ^d	●	●	NA ^d	●	●	●	●	●	●	●
Mori et al ⁴⁵	NA ^d	●	●	NA ^d	●	●	●	●	●	●	●
Foss et al ^{30e}	● ^b	●	●	●	●	●	●	●	●	●	●
Rojas-Peña et al ^{38e}	NA ^d	●	●	NA ^d	●	●	●	●	●	●	●
Oniscu et al ^{35e}	NA ^d	●	●	NA ^d	●	●	●	●	●	●	●
Miñambres et al ^{33e}	● ^b	●	●	●	●	●	●	●	●	●	●

Risk of Bias In Nonrandomized Studies of Interventions.²³

^a1-y and 5-y PS only reported in the text for the whole group.

^bThese studies used different donor types as a control group. To reduce the risk of confounding bias, the 2 donor groups should be of the same donor type.

^c1-y PS only reported in the text for the whole group.

^dThe risk of bias for this domain is not applicable due to the lack of a control group.

^ePlease note that these studies report the outcomes on kidney and liver.

DGF, delayed graft function; GS, graft survival; NA, not applicable; PNF, primary nonfunction; PS, patient survival.

● Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain).

● Moderate risk of bias (the study is sound for a nonrandomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial).

● Serious risk of bias (the study has some important problems).

● Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention).

● No information (on which to base a judgment about risk of bias for this domain).

TABLE 8.

Risk of bias in studies focusing on the liver

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes					Bias in selection of the reported results	Overall risk of bias
						PS	GS	PNF	EAD	Bili		
Fondevila et al ²⁹	●	●	●	●	●	●	●	●	●	●	●	●
Savner et al ⁴⁰	● ^a	●	●	●	●	●	●	●	●	●	●	●
Jiménez-Romero et al ⁴³	● ^a	●	●	●	●	●	●	●	●	●	●	●
De Carlis et al ²⁵	● ^a	●	●	●	●	●	●	●	●	●	●	●
Olivieri et al ⁴⁶	NA ^b	●	●	NA ^b	●	●	●	●	●	●	●	●
Ruiz et al ³⁹	NA ^b	●	●	NA ^b	●	●	●	●	●	●	●	●
Watson et al ²¹	●	●	●	●	●	●	●	●	●	●	●	●
Hessheimer et al ³²	●	●	●	●	●	●	●	●	●	●	●	●
Hagness et al ³¹	NA ^b	●	●	NA ^b	●	●	●	●	●	●	●	●
Miñambres et al ⁴⁴	● ^a	●	●	●	●	●	●	●	●	●	●	●
Ding et al ⁴²	●	●	●	●	●	●	●	●	●	●	●	●
Foss et al ^{30e}	● ^a	●	●	●	●	●	●	●	●	●	●	●
Rojas-Peña et al ^{38e}	NA ^b	●	●	NA ^b	●	●	●	●	●	●	●	●
Oniscu et al ^{35e}	NA ^b	●	●	NA ^b	●	●	●	●	●	●	●	●

Risk of Bias In Nonrandomized Studies of Interventions.²³

^aThese studies used different donor types as a control group. To reduce the risk of confounding bias, the 2 donor groups should be of the same donor type.

^bThe risk of bias for this domain is not applicable due to the lack of a control group.

^c1-y and 5-y PS only reported in the text for the whole group.

^d1-y PS only reported in the text for the whole group.

^ePlease note that these studies report the outcomes on kidney and liver.

bili, biliary complications; EAD, early allograft dysfunction; GS, graft survival; NA, not applicable; PNF, primary nonfunction; PS, patient survival.

● Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain).

● Moderate risk of bias (the study is sound for a nonrandomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial).

● Serious risk of bias (the study has some important problems).

● Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention).

● No information (on which to base a judgment about risk of bias for this domain).

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liver transplantation, biliary complications appear to be an essential outcome parameter in DCD cohorts.⁴⁸ As such, this outcome should be considered when reporting aNRP results. However, in this regard, a uniform definition needs to be agreed on by liver transplant groups on the precise classification of ischemic biliary complications to facilitate reporting. In January 2020, at the International Liver Transplantation Society Consensus Conference in Venice, an approach was made to achieve such consensus regarding DCD liver preservation and machine perfusion. In kidney transplantation, the use of DGF as outcome parameter is currently under heavy debate, as definitions differ and the correlation of DGF in DCD donors with graft survival is absent or at best limited. One-year graft function (expressed in eGFR) may therefore provide a better surrogate marker for long-term graft survival.⁴⁹

This systematic review has its limitations. Current reports are heterogeneous and contain considerable bias. For example, although DBD and DCD donors are essentially different, both are used as control groups in different studies. Such heterogeneity may not be surprising due to the rapid development and innovation in the field. Unfortunately, due to the heterogeneity of the available data, pooled meta-analysis was precluded.

Recommendations and Future Developments

Summarizing, aNRP has been shown to be a feasible and safe strategy and technique, and organs can be successfully transplanted after this procedure. In addition to its successful clinical introduction, however, consensus is needed how to quantify its success by establishing guidelines of aNRP protocols, including viability assessment, acceptance criteria, and outcomes both after uDCD and cDCD donation. With regards to outcomes, studies should report a minimum dataset including 1-year graft and patient survival, image-proven and clearly defined IC in liver transplantation, and 1-year eGFR in kidney transplantation.⁴⁷⁻⁴⁹ Also, we suggest defining the OUR as the number of organs actually transplanted divided by the total number of available organs where procurement was initiated.

In order to be able to definitively answer the question whether aNRP leads to more and hopefully better quality grafts in cDCD donation, future studies should include a prospectively randomized comparison between current standard (cold ISP) and aNRP. Current clinical reports suggest superior outcomes for aNRP; however, many of them are somewhat hindered by selection or reporting bias. Therefore, to date, in many countries, randomized controlled trials are considered. Procurement in abdominal cDCD donors can be randomized to either aNRP or regular cold ISP in the donor. In this regard, the possible effect of end-ischemic perfusion techniques should not be underestimated. Therefore, such trials should be designed taking into account the current “standard of care” strategies in the different countries. This allows for comparison of multiple perfusion technologies and might help elucidating which technique is most effective. In such studies, not only organ utilization and graft survival, but also cost-effectiveness of the labor-intensive procedure will have to be analyzed.

In uDCD donation, a randomized trial may be of less significance and more difficult to achieve, due to the nature

of the procurement and the clearer added value of aNRP compared with cold ISP in uDCD donors.

Another future development involves standardization of dual temperature perfusion, integrating aNRP, and thoracic cold ISP for lung procurement. Although this has been undertaken successfully, the experience is limited.^{44,50} Even combined thoracoabdominal NRP is possible, allowing resuscitation of both heart and lungs according to the promising results reported.^{51,52}

Awaiting future developments on this subject, aNRP is likely to be wider implemented and studied in multiple countries. Standardization of protocols and outcome measures will help to further elucidate its potential positive effect on donor organ utilization and outcomes after transplantation.

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