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Review

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 donors[6]

Category I		Description
Uncontrolled	IA. Out-of-hospital IB. In-hospital	Found dead due to a sudden unexpected CA without any attempt of resuscitation in the out-of-hospital or in-hospital setting
Category II		
Uncontrolled	IIA. Out-of-hospital IB. In-hospital	Witnessed CA with unsuccessful resuscitation, including the addition of the location
Category III		
Controlled		Ventilated patients awaiting CA where the WLST is planned
Category IV		
Uncontrolled Controlled		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)
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 guideline[20] 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 OUR[21] 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 al[22] 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

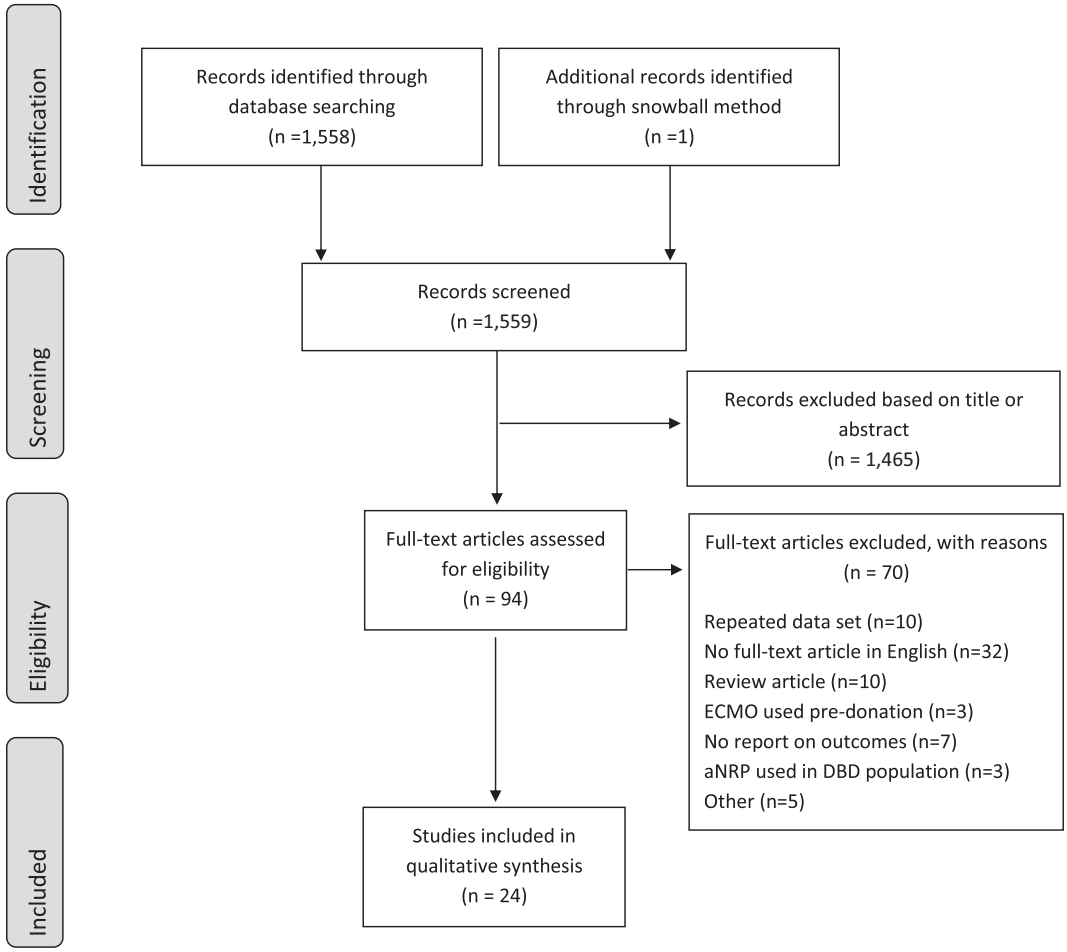

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. aNRP, abdominal normothermic regional perfusion; DBD, donation after brain death; ECMO, extracorporeal membrane oxygenation.

TABLE 2.
Study characteristics

Study (country)	Organ(s)	Study design	Study period	Actual donors (n) Control group (n)	Donor type[6]	Donor selection criteria	Donor age, y	Recipient age, y
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 Río 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 Carlis et al[25] 2018 (Italy)	Liver	Single-center Observational	2015 to 2017	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

TABLE 2. (Continued)

Study (country)	Organ(s)	Study design	Study period	Actual donors (n) Control group (n)	Donor type[6]	Donor selection criteria	Donor age, y	Recipient age, y
Olivieri et al[46] 2019 (Italy)	Liver	Single-center Observational	August 2017 to January 2019	1 uDCD 9 cDCD No control group	uDCD cDCD	–	55.8 (35–67)	55.8 (46–60)
Ruiz et al[39] 2018 (Spain)	Liver	Single-center Observational	January 2015 to June 2017	57 No control group	cDCD III	Age <65 (first 10 patients, thereafter no age limit but avoid comorbidities, <30 min WIT, ALT/AST <3× ULN (start aNRP), ALT/AST <4× ULN (end aNRP)	58 (27–76)	56 (19–69)
Watson et al[21] 2019 (United Kingdom)	Liver	Multicenter Observational	January 2011 to June 2017	43 187 cDCD-ISP[b]	cDCD III	<45 min fWIT for liver/pancreas, <60 min fWIT for kidneys, a stable ALT of <500 IU	41 [33–57] (16–69)	60 [51–64] (34–73)
Hessheimer et al[32] 2019 (Spain)[f]	Liver	Multicenter Observational	June 2012 to December 2016	95 117 cDCD-ISP	cDCD III	<30 min fWIT, ALT/AST <3x ULN (start aNRP), ALT/AST <4x ULN (end aNRP)	53.8 ± 15.2 57 [45–65]	54.8 ± 11.9 56 [52–61]
Hagness et al[31] 2019 (Norway)	Liver	Single-center Observational	November 2015 to November 2017	8[b] No control group	cDCD III	Age 16–60 (first 2 patients, thereafter age altered to 70), expected CA <60 min after WLST, <30 min fWIT	49.5 (23–63)	59 (35–68)
Miñambres et al[44] 2019 (Spain)[g]	Liver	Multicenter Retrospective	September 2014 to December 2018	19 34 DBD[b]	cDCD III	–	54 [47–59]	60 [52–64]
Ding et al[42] 2019 (China)	Liver	Single-center Observational	December 2014 to June 2017	7 12 cDCD (IV)-ISP	cDCD IV	Age <65	44 ± 11.8	51.7 ± 8.3
Foss et al[30] 2018 (Norway)	Kidney Liver	Single-center Observational	2014 to 2015	8 114 DBD[b]	cDCD III	Age 16–60, expected CA <60 min after WLST, <30 min fWIT for livers, <60 min fWIT for kidneys	50.3 (34–60)	Kidney: 58 (34–71) Liver: –
Rojas-Peña et al[38] 2014 (US)	Kidney Liver Pancreas	Single-center Observational	October 2000 to July 2013	37 No control group	cDCD III	Age <65, <60 min WIT (before 2006, thereafter <90 min)	38.7 (9–65)	–
Oniscu et al[35] 2014 (United Kingdom)	Kidney Liver Pancreas	Multicenter Observational	to	21 No control group	cDCD III	<30 min fWIT for liver/pancreas, <60 min fWIT for kidneys, ALT <3× ULN (start aNRP), ALT <4× ULN (end aNRP)	46 (16–74)	Kidney: – Liver: 63 (43–74) Pancreas: –
Miñambres et al[33] 2017 (Spain)	Kidney Liver[f] Pancreas	Single-center Observational	September 2014 to September 2016	27 51 DBD[b]	cDCD III	Age ≤70, <30 min fWIT for liver/pancreas, <60 min fWIT for kidneys, ALT/AST <4× ULN (30 and 60 min of aNRP)	58 [50–67]	Kidney: 57 [47–63] Liver: 55.2 ± 13 Pancreas: –

Numerical figures are reported as mean ± SD or median with [IQR] or (range) in brackets unless otherwise specified.
[a]Three cases converted to ISP.
[b]Selection on recipients.
[c]This value is calculated by the authors based on the information provided in the article.
[d]Please note that Antoine et al[24] included the French hospitals from Delsuc et al[27] and Demiselle et al.[28]
[e]Please note that Del Rio et al[26] included the Spanish hospitals from Miñambres et al[33] and Molina et al.[34]
[f]Please note that Hessheimer et al[32] included all the livers from Miñambres et al.[33]
[g]Please note that there is an overlap of n = 6 subjects in this study and Miñambres et al.[33]
ALT, alanine transaminase; aNRP, abdominal normothermic regional perfusion; AST, aspartate transaminase; CA, circulatory Arrest; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; CPR, cardiopulmonary resuscitation; CRS, cardiorespiratory support; DBD, donation after brain death; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygenation; fWIT, functional warm ischemia time; HRP, hypothermic regional perfusion; IQR, interquartile range; ISP, in situ perfusion; IU/L, International units per litre; TBC, total body cooling; TBI, traumatic brain injury; uDCD, uncontrolled donation after circulatory death; ULN, upper limit of normal; WIT, warm ischemia time; WLST, withdrawal of life-sustaining therapy.

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 al[26] 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 mm Hg 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 al[42] using cDCD (IV), there is no WIT as aNRP immediately started when the systolic blood pressure fell below 60 mm Hg 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 al[40] did not use a heat-exchanger, resulting in temperatures of 32–33°C (Table 4). Reznik et al[37] 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 al[26] 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 al[41] 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 al[37] 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 study[42] 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 Low flow	6.4 ± 6.8 135.9 ± 11.5	60	36	2–3.7	11.2 ± 3.57	HMP	–	–	–
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 Low flow	10 ± 10 123 ± 20	203 ± 46	37	2	13.6 ± 3.5	HMP	No	No	5
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 [116–141][d]	170 [140–218][d]	35.5–37.5	>1.7	15 [11–18][d]	SCS (67%) HMP (33%)	No[b]	–	–
cDCD										
Ravaioli 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 O_2 <70%/80% and the start of perfusion.
5. Total WIT: Time between WLST and the start of perfusion.

[a]Valero et al[41] used TBC (15–20°C) after 60 min of aNRP.

[b]After diagnosis of death CPR and mechanical ventilation is restart for the purpose of preserving organ viability.

[c]This value includes all uDCDs, including ISP (n = 303).

[d]This value includes all uDCDs, including HRP and ISP (n = 303).

[e]Please note that there was a discrepancy in this value if this was self-calculated by the authors using the provided information.

[f]Central 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										
Fondevila 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 uDCD: Standard WIT	125 [72–143][d]	352 [308–434]	–	–	8 [6–9]	HMP[f]	uDCD: No cDCD: –	uDCD: – cDCD: –	20
Olivieri et al[46]	fWIT	38.1 ± 7.3[c,e]	252.6 (150–624)	–	>2	7.4 ± 1[c]	HMP[f]	uDCD: – cDCD: –	uDCD: – cDCD: –	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 (87% yes)	Depending on center	5
	fWIT	18 [13–23] 13.3 ± 5.3 12 [9–16]				5.3 [4.4–6.1]				
Hagness et al[31]	fWIT	28 (13–24)	94 (73–221)	37	–	7.14 (3.43–9.55)	–	No[g]	Yes	5
Miñambres 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) 5.8 (4.5–7.5)	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 O_2 <70%/80% and the start of perfusion.
5. Total WIT: Time between WLST and the start of perfusion.
[a]This does not include the 5-min no touch.
[b]After diagnosis of death CPR and mechanical ventilation is restart for the purpose of preserving organ viability.
[c]This value is calculated by the authors based on the information provided in the article.
[d]These values include both donor types.
[e]This value includes only cDCD.
[f]Unknown if oxygen was added during ex situ machine perfusion of the graft.
[g]Central lines were placed in the common femoral artery and vein before the declaration of death.
[h]aNRP was immediately started when SBP <60 mm Hg to maintain blood flow to the organs while awaiting cardiac arrest.
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; IQR, interquartile range; NA, not applicable; SBP, systolic blood pressure; SCS, static cold storage; uDCD, 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) $P<0.05$	–	Up to 5 y
	uDCD-ISP, n = 37[b]	44		44/80 (55)			9 (22.5)	22 (55)		
	uDCD-TBC, n = 11[b]	8		8/16 (50)			0 (–)	6 (75)		
Reznik et al[37]	aNRP, n = 22 (24/22)	44	4	44/44 (100)	44 (100)	42 (95.5)	0 (0)	23 (52.3)	0.116 ± 0.004	Up to 1 y
	DBD, n = 74	92		NA[c]	87 (94.6) $P=0.221$	87 (94.6) $P=0.312$	– (–)	34 (36.9)	0.115 ± 0.004 $P>0.05$ 1-y creatinine levels (mmol/L)	
Demiselle et al[28]	aNRP, n = 19 (–/19)	19	NA[c]	NA[c]	18 (100)	18 (94.4)	1 (–)	10 (53)	50.7	26.8 ± 16.9 mo[r]
	uDCD-ISP, n = 31	31		NA[c]	27 (96.6)	27 (93.5)	2 (–)	25 (81) $P=0.036$	43.2 1-y MDRD-eGFR (mL/min/1.73 m^2)	
Molina et al[34]	aNRP, n = 186 (568/213)	241	131 (35.2)[d]	241/372 (64.8)[e]	–[f]	–[f]	16 (6.8)	174 (73.4)	50.5 ± 18.4[d]	65 mo (46–90 mo)
	DBD, n = 237	237		NA[c]			10 (4.2) $P=0.226$	110 (46.4) $P<0.001$	54.8 ± 18.8 $P=0.007$ 3 mo eGFR (mL/min/1.73 m^2)	72 [28–108]
Delsuc et al[27]	aNRP, n = 24 (–/24)	32	NA[c]	NA[c]	–[g]	–[g]	1 (3)	23 (72)	53.8 ± 12.8 (n = 24)	2 y[r]
	uDCD-ISP, n = 22	32		NA[c]			1 (3)	27 (84) $P=0.23$	43.0 ± 12.8 $P=0.007$[h] 1-y mGFR (mL/min/1.73 m^2)	
Antoine et al[24]	aNRP, n = 142 (–/–)	251	NA[c]	NA[c]	–	–	15 (6.0)	– (75.7)[j]	–	–
	uDCD-ISP, n = 161	248		NA[c]			22 (8.9) $P=0.16$[i]	– (–)		
Del Río et al[26]	aNRP, n = 151 (–/–)	277	NA[c]	NA[c]	–	– (91)[c]	21 (8)	177 (71)[j]	–	Up to 1 y
	uDCD-HRP, n = 99	179		NA[c]		– (87.5)	14 (8) $P=0.372$	129 (82)		
	uDCD-ISP, n = 35	58		NA[c]		– (62)	18 (31) $P<0.001$	34 (87)		
cDCD										
Ravaioli et al[36]	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)
Mori et al[45]	aNRP, n = 6 (–/6) No control group	9[q]	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 (–/–)	14	2	14/16 (87.5)	–	13 (93)	–	1 (7.1)	75 (65–76)	Up to 1 y
	DBD, n = 114	163	NA[c]	NA[c]		– (95) $P=0.53$		8 (4.9) $P=0.53$	61 (37–112) $P=0.23$ 1-y mGFR (mL/min/1.73 m^2)	

Continued next page

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)	48	25	48/74 (64.9)[l]	–	– (100)	1 (3.5)	– (31)	–	Up to 3 y
	No control group					– (100) ISP[c]				
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][c]	11 mo (3–39 mo)
	No control group								1-y sCr (mg/dL)	
Miñambres et al[33]	aNRP, n = 27 (–/27)	37	11	37/54 (68.5)[o]	–	– (91.8)[p]	2 (5)	10 (27)	1.3 [1.0–1.8]	17 mo (7–22 mo)[r]
	DBD, n = 51	36		NA[c]		– (97.2)			1-y sCr (mg/dL)	
						$P = 0.315$				

[a]These values are reported as mean ± SD or median with [IQR] or (range) in brackets unless otherwise specified.
[b]Three cases of TBC were converted to ISP.
[c]Selection on recipients.
[d]This value is calculated by the authors based on the information provided in the article.
[e]After consent was obtained, 186 effective uDCD donors received aNRP.
[f]Data are available for 5- and 10-y patient and graft survival.
[g]Data are available for 2-y patient and graft survival.
[h]After multivariate analysis the difference remained significant (adjusting for recipient age, sex, CIT, duration of perfusion; $P = 0.03$).
[i]After sensitivity analysis 1 center was excluded resulting in $P = 0.015$.
[j]PNF cases were excluded.
[k]Data are available for 6-mo patient and graft survival.
[l]Seventy-three grafts were procured from the 37 uDCD donors.
[m]Four double transplants were performed.
[n]One donor had a previous nephrectomy.
[o]Forty-eight grafts were recovered from the 27 uDCD donors.
[p]These data are death censored.
[q]Three double kidney transplants were performed.
[r]This 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 (%)		EAD, n (%)	Retransplantation, n (%)	Follow-up
								Overall	IC			
uDCD												
Fondevila et al[29]	aNRP, n = 34 (400/290)	34	111	34/290 (11.72)	– (82)	– (70)	–	4 (12)	3 (8)	–	3 (8.8)	24 mo (0–111 mo)
	DBD, n = 538	538		NA[a] (76% in text)	– (90)	– (87)					– (–)	44 mo
					$P = 0.141$	$P = 0.011$						
Savier et al[40]	aNRP, n = 13 (299/183)	13	–	13/183 (7.10)	– (85)	– (69)	3 (23)	2 (22)	1 (11)	4 (–)	3 (23)	32 mo [10.2–39.5 mo]
	DBD, n = 41	41	–	NA[a]	– (93)	– (93)			1 (2)		0 (0)	23.6 [8.9–36.7]
					$P = 0.39$	$P = 0.03$						
Jiménez-Romero et al[43]	aNRP, n = 100 (–/256)	75	181 (70.7)	75/256 (29.3)	– (82.7)[i,m]	– (73.3)[i,m]	6 (8)	23 (30.6)	12 (16)	–	9 (12)	63.5 ± 2.5 mo[n]
	DBD, n = 265	265	–	NA[a]	– (89)	– (87.1)	4 (1.5)	32 (12.1)	8 (3)		12 (4.5)	
					$P = 0.180$	$P = 0.013$	$P = 0.031$	$P = 0.001$	$P = 0.018$		$P = 0.028$ (12)	
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]	3 (15)	14 mo [8–26 mo]
	DBD n = 52	52	NA[a]	NA[a]	– (94) (82%–98%)	– (91) (80%–97%)	2 (4)	7 (13)	2 (4)	13 (27)	3 (6)	17 mo [11–23 mo]
		17		NA[a]	95% CI	95% CI						
					$P = 0.94$	$P = 0.20$	$P = 0.58$	$P = 0.65$	$P = 0.52$	$P > 0.99$	$P = 0.35$	
	ECMO-DBD n = 17				– (87) (58%–97%)	– (87) (58%–97%)	1 (6)	1 (6)	0	7 (44)	0 (0)	20 mo [7–29 mo]
					95% CI	95% CI						
					$P = 0.47$	$P = 0.76$	$P > 0.99$	$P = 0.35$	$P = 0.49$	$P = 0.28$	$P = 0.23$	
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)	–	–	0 (0)	–
cDCD												
Ruiz et al[39]	aNRP, n = 46 (57/57)	46	11	46/57 (80.70)	46 (100)[f]	46 (100)[f]	0 (0)	1 (2)	0 (0)	11 (23)	–	19 mo (9–40 mo)
	No control group	169										
Watson et al[21]	aNRP, n = 43 (–/70)	43	27	43/70 (61.43)	– (97.7)[g,h]	– (97.7)[g,h]	0 (0)	6 (14)	0 (0)	5 (12)	–	Up to 5 yr
	cDCD-ISP, n = 187	187	NA[a]	NA[a] (27%–36% in text)	– (94.2)	– (86.5)	13 (7)	64 (37)	47 (27)	55 (32)		
							$P = 0.1347$		$P < 0.0001$	$P = 0.0076$		
Hessheimer et al[32]	aNRP, n = 95 (342*/152)	95	52 (34)	95/152 (62.5)	– (93)[i]	– (88)[i]	2 (2)	8 (8)	2 (2)	21 (22)	5 (5)	20 mo[n]
	cDCD-ISP, n = 190	117	73 (38)	117/190 (61.58)	– (88)	– (83)	3 (3)	36 (31)	15 (13)	32 (27)	11 (9)	
	* All potential cDCDs						$P = 0.827$	$P < 0.001$	$P = 0.012$	$P = 0.381$	$P = 0.263$	
							$P = 0.135$[j]	$P < 0.001$[j]	$P = 0.008$[j]	$P = 0.931$[j]		

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)	8	–	8/8 (100)	–	7 (100)	0 (0)	2 (25)	0 (0)	–	–	1 y[o]
	No control group											
Miñambres et al[44]	aNRP, n = 19 (–/19)[l]	16	3	16/19 (84.2)	– (87.5)	–	2 (12.5)	0 (0)	0 (0)	3 (18.8)	1 (6.3)	6 mo [3–18 mo]
	DBD, n = 34	29	5	29/34 (85.3)	– (96)		0 (0)	–	–	5 (17.2)	1 (3.4)	16 mo [12–20 mo]
					$P = 0.496$		$P = 0.121$			$P = 0.6$	$P = 0.590$	
Ding et al[42]	aNRP, n = 7 (–/7)	7	–	7/7 (100)	6 (85.7)[g]	7 (100)[g]	0 (0)	0 (0)	0 (0)	–		12 mo (12–30 mo)[n]
	cDCD (IV)-ISP, n = 12	12	–	12/12 (100)				2 (16.7)	1 (8.3)			
Foss et al[30]	aNRP, n = 8 (–/8)	2	3	2/8 (25)	2 (100)[k]	2 (100)[k]	0 (0)	0 (0)	0 (0)	–	0 (0)	Up to 2 y
	No control group											
Rojas-Peña et al[38]	aNRP, n = 13 (50/37)	13	8	13/37 (35.14)	–	– (85.7)[k]	1 (7.7)	1 (7.7)	–	–	–	Up to 2 y
	No control group											
Oniscu et al[35]	aNRP, n = 11 (36/21)	11	8	11/21 (52.38)	–	–	1 (9.1)	2 (–)	0 (0)	4 (–)	–	10 mo (3–36 mo)
	No control group											

[a]Selection on recipients.
[b]After 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.
[c]Cumulative survival.
[d]The data are death censored.
[e]These percentages were calculated after excluding the recipients that received a retransplantation.
[f]Medium follow-up was 19 mo.
[g]This value is calculated by the authors based on the information provided in the article.
[h]Data are available for 3-mo patient and graft survival.
[i]Data are available for 3-y patient and graft survival.
[j]After inverse probability of treatment weighting analysis.
[k]Data are available for 2-y survival.
[l]Please note that this study only includes the combined procedure of aNRP for abdominal grafts and ISP for the lungs.
[m]Data are available for 5-y patient and graft survival.
[n]This includes the follow-up of all recipients.
[o]One 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.

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 al[21] described an OUR of 61.4% compared with 27%–36% when using cold ISP. However, Hessheimer et al[32] demonstrated a comparable OUR for both perfusion methods (62.5% cDCD-aNRP versus 61.6% controls). Furthermore, Ding et al[42] 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 al[44] 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 al[44] 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 al[33] reported appropriate graft function in 1 SPK transplantation after 6 months, and Oniscu et al[35] 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 premortem 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]
[a]1-y and 5-y PS only reported in the text for the whole group.
[b]These 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.
[c]1-y PS only reported in the text for the whole group.
[d]The risk of bias for this domain is not applicable due to the lack of a control group.
[e]Please 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]	●	●	●	●	●	●	●	●	●	●	●	●
Savier 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]
[a]These 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.
[b]The risk of bias for this domain is not applicable due to the lack of a control group.
[c]1-y and 5 y PS only reported in the text for the whole group.
[d]1-y PS only reported in the text for the whole group.
[e]Please 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).

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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