The challenge of quality assessment and regional perfusion to increase donor organ utilisation

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Part II

Optimisation of organ preservation strategies

Chapter 6

Abdominal Normothermic Regional Perfusion in Donation after Circulatory Death: A systematic review and critical appraisal

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Transplantation. 2020; doi: 10.1097/TP.0000000000003345

Abstract

Background

Abdominal Normothermic Regional Perfusion (aNRP) for donation after circulatory death (DCD) is an emerging organ preservation technique that might lead to increased organ utilisation per donor by facilitating viability testing, improving transplant outcome by early reversal of ischaemia, 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.

Material & Methods

The PRISMA guideline for systematic reviews was used and relevant literature databases were searched. Primary outcomes were organ utilisation rate and patient- and graft survival after one year. Secondary outcomes included delayed graft function, primary non-function, 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 characterised by considerable heterogeneity and bias.

Conclusions

Uniform reported outcome measures are needed to draw more definitive conclusions on transplant outcomes and organ utilisation. A randomised controlled trial comparing aNRP with standard procurement technique in DCD donors would be needed to show the added value of the procedure and determine its place amongst modern preservation techniques.

Introduction

Donation after Circulatory Death (DCD) remains associated with significantly lower organ recovery rates per donor compared to 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 to 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 underutilisation of these organs is justified and unnecessarily reduces the size of the potential donor organ pool.

To date, in some countries (e.g., UK, the Netherlands, USA), 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, more than 57% of deceased donors were controlled DCD (cDCD)[7], whilst in the UK, cDCD is now a main pathway to donation.[8]

To reduce uncertainty and increase utilisation, better assessment of organ viability and optimisation of preservation strategies are required, reducing ischaemia reperfusion injury and enhancing quality and function of the potential grafts.

Abdominal Normothermic Regional Perfusion (aNRP), also called normothermic recirculation or normothermic extra-corporeal 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 ischaemia, adenosine triphosphate (ATP) declines progressively. During aNRP, the cellular energy status was found to increase due to partial restoration of ATP content, which suggests that the ischaemic injury obtained during the warm ischaemia time can be partially reversed prior to transplantation.[11,13,17] Therefore, an 'ischaemic preconditioning' effect can be observed, when using aNRP. Not only 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, UK,

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 utilisation as these cDCD donors exceeded the existing 'regular' criteria (e.g., cDCD donors >60 years).

The concept of aNRP in DCD donors is based on three principles: (i) after Circulatory Arrest (CA) and a mandatory no-touch period normothermic oxygenated circulation is re-established. As such, it not only reduces the extent of ischaemic injury but is also allows all abdominal organs to recover by recharging their energy content; (ii) 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; (iii) damage to donor organs may be minimised by converting a 'hasty' DCD procedure into a less rushed DBD-type operation, resulting in less organ damage and increased organ utilisation.[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 Utilisation 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.

Table 1. Modified Maastricht Classification for DCD donors.[6]

Category I		
Uncontrolled	IA. Out-of-hospital IB. In-hospital	Found dead due to a sudden unexpected circulatory arrest 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 circulatory arrest with unsuccessful resuscitation, including the addition of the location
Category III		
Controlled	III	Ventilated patients awaiting circulatory arrest where the withdrawal of life sustaining therapy is planned
Category IV		
Uncontrolled Controlled	IV	Sudden (or unexpected) circulatory arrest after declaration of brain death (uDCD IV). In China the law does not permit declaration of brain death resulting in DBD followed by controlled circulatory arrest (cDCD IV).
Category V		
Controlled	V	Euthanasia or medically assisted cardiocirculatory death

Material & Methods

Search strategy

A systematic literature review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 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 29 January 2020. For the complete search strategy, see *Appendix S1*.

Inclusion and exclusion criteria

We aimed to include randomised 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 one organ were included, however, 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. Articles focusing on ex-vivo machine perfusion, animal studies or non-abdominal organs were excluded.

Outcomes

Primary outcomes included Organ Utilisation Rate (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 Non-Function (PNF), serum Creatinine (sCr), estimated or measured Glomerular Filtration Rate (eGFR/mGFR) for kidneys, PNF, biliary complications including Ischaemic 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 two independent reviewers (FvdL and VH) 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**. When additional information was needed, the corresponding authors of the studies were contacted.

Risk of bias

Two reviewers determined independent the risk of bias according to the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool (**Table S2**) for cohort and case-control studies.[23]

Statistical analysis

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

Results

The literature search identified 1,558 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 randomised controlled trials were found. The transplanted 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 through 2019.

Fifteen studies were single-centre studies[25,27,29-31,33,34,36-39,41-43,46] and seven multi-centre studies [21,28,32,35,40,44,45] were included in this review. Two articles[24,26] used the national registry system to analyse 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 to 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 (HRP) as controls (**Table 2**). The remaining seven 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.

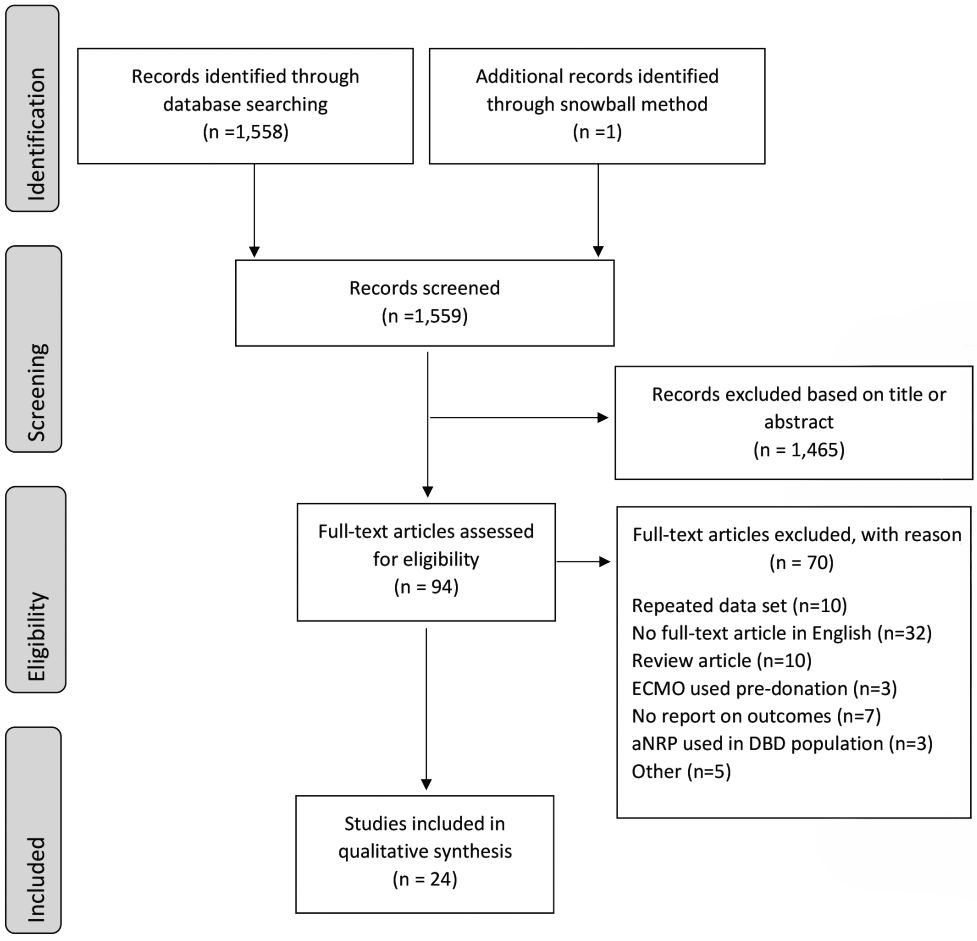

Figure 1. PRISMA flow diagram.

Table 2. Study characteristics

Study *(Country)*	Organ(s)	Study Design	Study period	Actual donors (n) *Control group (n)*	Donortype[6]	Donor selection criteria	Donor age in years	Recipient age in years
Valero et al. [41] 2000 *(Spain)*	Kidney	Single-centre Observational	Oct 1986 – Mar 1999	6 *37 uDCD-ISP* *11 uDCD-TBC* [a]	uDCD II	Age <65, <150min WIT (incl. <30min WIT without cardiopulmonary resuscitation (CPR))	-	46.7 ± 8.1
Reznik et al. [37] 2013 *(Russia)*	Kidney	Single-centre Observational	2009 – 2011	22 *74 DBD* [b]	uDCD IIb	-	41.8 ± 2.1	49.3 ± 1.4
Demiselle et al. [28] 2016 *(France)*	Kidney	Multi-centre Observational	May 2008 – Jul 2013	19 [b] *31 uDCD-ISP* [b]	uDCD II	Age 18-55, >30min without CPR after initial <30min no-flow, <150min WIT, <18hr CIT	45.7 ± 5.7	41.4 ± 10.1
Molina et al. [34] 2018 (*Spain)*	Kidney	Single-centre Observational	Jun 2005 – Dec 2013	186 *237 DBD* [b]	uDCD IIa	Age 18-60, known time of CA, <15min between CA-CPR, >30min CPR, <150min WIT (CA-perfusion)	43.5 ± 9.9	47.9 ± 10.9
Delsuc et al. [27] 2018 *(France)*	Kidney	Single-centre Observational	Sep 2006 – Sep 2013	24 [b] *22 uDCD-ISP* [b]	uDCD IIa	Age ≥18-≤55, known time of CA, <30min no-flow, <150min 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 – 2014	142 [b] *161 uDCD-ISP* [b]	uDCD II	Age <55yr, known time of CA, <30min no-flow, <150min fWIT	42 ± 9.3	-
Del Río et al. [26] 2019 *(Spain)*[e]	Kidney	Spanisch CORE information system Retrospective	Jan 2012 – Dec 2015	151 [b] *99 uDCD-HRP* [b] *35 uDCD-ISP* [b]	uDCD IIa & b	Age <55-60, <15min CA, <150min WIT	47 ± 11	51 ± 11
Ravaioli et al. [36] 2018 *(Italy)*	Kidney	Single-centre Observational	Jan 2016 – Feb 2017	5 [b] *No control group*	cDCD III	Irreversible brain or cardiac injury sustained by life therapies and cardiorespiratory support (CRS).	44.8 ± 17.3 [c]	59.7 ± 7.7 [c]
Mori et al. [45] 2019 *(Italy)*	Kidney	Multi-centre Observational	Nov 2017 – Jun 2018	6 [b] *No control group*	cDCD III	-	57.3 ± 7.53	57.5 ± 4.97

Study *(Country)*	Organ(s)	Study Design	Study period	Actual donors (n) *Control group (n)*	Donortype[6]	Donor selection criteria	Donor age in years	Recipient age in years
Fondevila et al. [29] 2012 *(Spain)*	Liver	Single-centre Observational	Apr 2002 – Dec 2010	145 *538 DBD*[b]	uDCD II	Age ≤65, <15min between CA-CPR, <150min of CRS, <4hr of aNRP, ALT/AST <3x ULN (start aNRP), ALT/AST <4x ULN (during aNRP)	47 [27-56]	55 [49-60]
Savier et al. [40] 2015 *(France)*	Liver	Multi-centre Observational	Jan 2010 – Dec 2013	30 *41 DBD*[b]	uDCD II	Age <55, known time of CA, <15 min no-flow, <150min CPR, <240min aNRP, ALT/AST <200 IU/L (after 2hr aNRP), <15-20% steatosis, <8hr CIT	37 ± 3 (mean ± S.E. mean)	54.4 ± 4.4[c]
Jiménez-Romero et al. [43] 2019 *(Spain)*	Liver	Single-centre Observational	Jan 2006 – Feb 2018	75 *265 DBD*[b]	uDCD II	Age 14-55, <15min of CA, <150min between CPR-perfusion, <5hr of aNRP, <30% macrosteatosis, ALT/AST <4x ULN	41.7 ± 9.7 (18-55)	58.8 ± 7.7 (36-70)
De Carlis et al. [25] 2018 *(Italy)*	Liver	Single-centre Observational	2015 – 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]
Olivieri et al. [46] 2019 *(Italy)*	Liver	Single-centre Observational	Aug 2017 – Jan 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-centre Observational	Jan 2015 – Jun 2017	57 *No control group*	cDCD III	Age <65 (first 10 patients, thereafter no age limit but avoid comorbidities, <30min WIT, ALT/AST <3x ULN (start aNRP), ALT/AST <4x ULN (end aNRP)	58 (27-76)	56 (19-69)
Watson et al. [21] 2019 *(UK)*	Liver	Multi-centre Observational	Jan 2011 – Jun 2017	43 *187 cDCD-ISP*[b]	cDCD III	<45 min fWIT for liver/pancreas, <60min 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	Multi-centre Observational	Jun 2012 – Dec 2016	95 *117 cDCD-ISP*	cDCD III	<30min 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]

Study *(Country)*	Organ(s)	Study Design	Study period	Actual donors (n) *Control group (n)*	Donortype[6]	Donor selection criteria	Donor age in years	Recipient age in years
Hagness et al. [31] 2019 *(Norway)*	Liver	Single-centre Observational	Nov 2015 – Nov 2017	8 [b] *No control group*	cDCD III	Age 16-60 (first 2 patients, thereafter age altered to 70), expected CA <60min after WLST, <30min fWIT	49.5 (23-63)	59 (35-68)
Miñambres et al. [44] 2019 *(Spain)*[g]	Liver	Multi-centre Retrospective	Sep 2014 – Dec 2018	19 *34 DBD* [b]	cDCD III	-	54 [47-59]	60 [52-64]
Ding et al. [42] 2019 *(China)*	Liver	Single-centre Observational	Dec 2014 – Jun 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-centre Observational	2014 – 2015	8 *114 DB*D [b]	cDCD III	Age 16-60, expected CA <60min after WLST, <30min fWIT for livers, <60min fWIT for kidneys	50.3 (34-60)	Kidney: 58 (34-71) Liver: -
Rojas-Peña et al. [38] 2014 *(USA)*	Kidney Liver Pancreas	Single-centre Observational	Oct 2000 – Jul 2013	37 *No control group*	cDCD III	Age <65, <60min WIT (before 2006, thereafter <90min)	38.7 (9-65)	-
Oniscu et al. [35] 2014 *(UK)*	Kidney Liver Pancreas	Multi-centre Observational	-	21 *No control group*	cDCD III	<30min fWIT for liver/pancreas, <60min fWIT for kidneys, ALT <3x ULN (start aNRP), ALT <4x ULN (end aNRP)	46 (16-74)	Kidney: - Liver: 63 (43-74) Pancreas: -
Miñambres et al. [33] 2017 *(Spain)*	Kidney Liver [f] Pancreas	Single-centre Observational	Sep 2014 – Sep 2016	27 *51 DBD* [b]	cDCD III	Age ≤70, <30min fWIT for liver/ pancreas, <60min fWIT for kidneys, ALT/AST <4x ULN (30 min and 60min of aNRP)	58 [50-67]	Kidney: 57 [47-63] Liver: 55.2 ± 13 Pancreas: -

Numerical figures are reported as mean ± standard deviation 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]

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, where repeated attempts of resuscitation failed, the donor is declared dead in the hospital. In some countries, cardiopulmonary resuscitation (CPR) 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 (e.g., 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 anaesthesia before withdrawal of life sustaining therapy (WLST) differ 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 haemodynamic instability in a brain-dead donor (uDCD IV). In some countries (i.e., 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 Warm Ischaemia Time (WIT) varies widely amongst the articles (**Table 3a-3b**). 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 mmHg while cardiac arrest was awaited. Overall, the flow for aNRP was targeted at >1.7L/min. 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 3b**). Reznik et al.[37] perfused with subnormothermic perfusion varying between 27 - 32°C (**Table 3a**).

After aNRP and procurement, preservation of grafts during Cold Ischaemia Time (CIT) 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 analysed in their Spanish National registry cohort, were subjected to HMP. HMP for kidneys was also used in three other studies.[36,38,45] Regarding the liver-graft, HMP was used in two studies.[25,46] The remaining studies used static cold storage for organ preservation.

Table 3a. aNRP protocols for kidneys

Study	WIT definition	WIT (minutes)	aNRP time (minutes)	Temperature (°C)	Flow (liter/ minute)	CIT (hours)	Ex-situ graft preservation	Interventions before declaration of death		No touch period (minutes)
								Cannulation	Heparinisation	
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 [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	29 (13-50) [e]	207.2 ± 70.4 [e]	37	2 (1.7-4)	10 ± 3	$HMPO_2$	Yes	No	20
	fWIT	151 ± 132								
Mori et al. [45]	Standard WIT	20	207 ± 40 (171-284)	-	-	11.7 ± 2.6 11.5 (7.35-15.42)	$HMPO_2$	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

Study	WIT definition	WIT (minutes)	aNRP time (minutes)	Temperature (°C)	Flow (liter/ minute)	CIT (hours)	Ex-situ graft preservation	Interventions before declaration of death		No touch period (minutes)
								Cannulation	Heparinisation	
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 ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specified

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

- No flow period: time between circulatory arrest and start cardiopulmonary resuscitation (CPR)/cardiorespiratory support (CRS)
- Low flow period: time between CPR/CRS and the start of perfusion
- Standard WIT: time between circulatory arrest and the start of perfusion
- Functional WIT (fWIT): time between SBP <50/60 mmHg and/or O_2 <70/80% and the start of perfusion
- Total WIT: time between withdrawal of life sustaining therapy and the start of perfusion

[a] Valero used total body cooling (15-20°C) after 60 minutes 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 hypothermic regional perfusion and in situ persuion (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

Table 3b. aNRP protocols for livers

Study	WIT definition	WIT (minutes)	aNRP time (minutes)	Temperature (°C)	Flow (liter/minute)	CIT (hours)	Ex-situ graft preservation	Interventions before declaration of death		No touch period (minutes)
								Cannulation	Heparinisation	
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 ± S.E. Mean)	SCS	No [b]	No [b]	5
	Low flow	129.3 ± 13.3 [c]								
Jimenez-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 & 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 18 [13-23]	120 [79-136]	37	>1.7 L/min/m2	5.6 ± 1.8	-	Depending on centre (87% yes)	Depending on centre	5
	fWIT	13.3 ± 5.3 12 [9-16]				5.3 [4.4-6.1]				

Study	WIT definition	WIT (minutes)	aNRP time (minutes)	Temperature (°C)	Flow (liter/minute)	CIT (hours)	Ex-situ graft preservation	Interventions before declaration of death		No touch period (minutes)
								Cannulation	Heparinisation	
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]	N/A [h]	N/A [h]	- (180-300)	-	-	4.7 ± 1.3	-	Yes [h]	-	N/A [h]
Foss et al. [30]	fWIT	23 & 26	97 (54-106)	37	3 (1.7-4.0)	3.8 & 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 ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specified

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

- No flow period: time between circulatory arrest and start cardiopulmonary resuscitation (CPR)/cardiorespiratory support (CRS)
- Low flow period: time between CPR/CRS and the start of perfusion
- Standard WIT: time between circulatory arrest and the start of perfusion
- Functional WIT (fWIT): time between SBP <50/60 mmHg and/or O_2 <70/80% and the start of perfusion
- Total WIT: time between withdrawal of life sustaining therapy and the start of perfusion

[a] This does not include the 5min 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 includes 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 mmHg to maintain blood flow to the organs while awaiting cardiac arrest

Clinical outcomes

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

Kidney (Table 4a)

Thirteen articles [24,26-28,30,33-38,41,45] described the effect of aNRP on clinical outcomes in kidney transplantation. Seven articles included uDCD-aNRP of which five [24,26-28,41] and two [34,37] used uDCD and DBD as controls, respectively. cDCD-aNRP was described in six studies of which two [30,33] used DBD as controls. The remaining four studies [35,36,38,45] did not compare their results to controls.

Organ Utilisation Rate

OUR varied from 64.8 - 100% and 64.9 - 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 (TBC)(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 two studies[28,37] reported 1-year patient survival. This was 100% compared to 94.6% in DBD and 96.6% in uDCD. The 1-year patient survival was not reported in the six cDCD-aNRP studies.[30,33,35,36,38,45]

Regarding 1-year graft survival, two studies[26,28] demonstrated a graft survival of 91 - 94.4% in uDCD-aNRP compared to 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, two studies[30,33] reported a lower 1-year graft survival when compared to DBD. The remaining seven studies[24,27,34-36,41,45] did not mention 1-year graft survival outcomes.

Secondary outcomes

PNF rate was described in eleven 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 - 5%, however, no control group was used to compare these outcomes.[33,36,38,45]

DGF, generally defined as the need for at least one 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 sCr at 1-year, others preferred to assess the kidney function after transplantation via the estimated or measured GFR.

Liver (Table 4b)

Fourteen studies[21,25,29-33,35,38-40,42-44,46] reported on the outcome of liver transplantation. Three[29,40,43] of those included uDCD-aNRP compared with DBDs. Ten studies included cDCD-aNRP with two studies [33,44] using DBD as control and two others [21,32] using cDCD as control, respectively. One study[42] performed in China, were organ donation after brain death is followed by circulatory death, included cDCD type IV and compared aNRP in this type of donor with ISP. The remaining five studies [30,31,35,38,39] did not have a control group. For two studies [25,46], we will not discuss the outcomes as these studies analysed both uDCD and cDCD donors and did not distinguish between those two donor types in their analysis.

Organ Utilisation Rate

The OUR in uDCD-aNRP[29,40,43] varied from 7.1 - 29.3%. This was lower when compared to DBD (76%).[29] In cDCD-aNRP, Watson et al.[21] described an OUR of 61.4% compared to 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 three studies[29,40,43] using uDCD-aNRP, the rates of 1-year patient and graft survival was lower than in DBD. In cDCD-aNRP,[21,32] 1-year patient survival varied between 93 - 97.7% when compared to 88 - 94.2% in controls of the same donor type. Minambres 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 to cDCD[21,32] (88-97.7% versus 83-86.5%).

Secondary outcomes

Only two 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 to 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 to DBD(2 - 3%). However, the incidence was statistically significantly lower (0 - 2%) in cDCD-aNRP when compared to cDCD[21,32] (13 - 27%).

The EAD rate was reported in six studies.[21,32,35,39,40,44] When compared to controls, it ranged from 12-22% in cDCD-aNRP versus 17.2 - 32% in cDCD[21,32,44] and was found to be statistically different in one study.[21] When compared to DBD, Miñambres et al.[44] found similar EAD rates (18.8% cDCD-aNRP versus 17.2% DBD).

Pancreas

Only three 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], three simultaneous pancreas-kidney (SPK) transplants and one islet transplantation were performed. Miñambres et al.[33] reported appropriate graft function in one SPK transplantation after 6 months, and Oniscu et al.[35] described primary kidney and pancreas function in two SPKs. The islet isolation was performed from two pancreases of which one 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 whilst seven 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, eleven studies[24,25,30,32-34,40-44] were considered to have serious overall risk of bias and five[21,26-28,37] to have moderate overall risk of bias (**Table 5a - 5b**). 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.

Table 4a. Clinical outcomes for the kidneys

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilisation Rate [n (%)]	1-year patient survival [n (%)]	1-year 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*		*N/A* [c]	*87 (94.6)* *p = 0.221*	*87 (94.6)* *p = 0.312*	*- (-)*	*34 (36.9)*	*0.115 ± 0.004* *p > 0.05* 1-year Creatinine levels (mmol/L)	
Demiselle et al. [28]	aNRP n = 19 (-/19)	19	N/A [c]	N/A [c]	18 (100)	18 (94.4)	1 (-)	10 (53)	50.7	26.8 M ± 16.9 [r]
	uDCD-ISP n = 31	*31*		*N/A* [c]	*27 (96.6)*	*27 (93.5)*	*2 (-)*	*25 (81)* *p = 0.036*	*43.2* 1-year MDRD-eGFR (mL/min/1.73m^2)	
Molina et al. [34]	aNRP n = 186 (568/213)	241 *237*	131 (35.2) [d]	241/372 (64.8) [e]	- [f]	- [f]	16 (6.8)	174 (73.4)	50.5 ± 18.4 [d]	65 M [46-90]
	DBD n = 237			*N/A* [c]			*10 (4.2)* *p = 0.226*	*110 (46.4)* *p < 0.001*	*54.8 ± 18.8* *p = 0.007* 3 months e-GFR (mL/min/1.73m^2)	*72 [28-108]*
Delsuc et al. [27]	aNRP n = 24 (-/24)	32	N/A [c]	N/A [c]	- [g]	- [g]	1 (3)	23 (72)	53.8 ± 12.8 (n = 24)	2 Y [r]
	uDCD-ISP n = 22	*32*		*N/A* [c]			*1 (3)*	*27 (84)* *p = 0.23*	*43.0 ± 12.8* *p = 0.007* [h] 1-year mGFR (mL/min/1.73m^2)	
Antoine et al. [24]	aNRP n = 142 (-/-)	251	N/A [c]	N/A [c]	-	-	15 (6.0)	- (75.7) [j]	-	-
	uDCD-ISP n = 161	*248*		*N/A* [c]			*22 (8.9)* *p = 0.16* [i]	*- (-)*		

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilisation Rate [n (%)]	1-year patient survival [n (%)]	1-year graft survival [n (%)]	PNF [n (%)]	DGF [n (%)]	Posttransplant kidney function [a]	Follow-up
Del Río et al. [26]	aNRP n = 151 (-/-)	277	N/A [c]	N/A [c]	-	- (91) [c]	21 (8)	177 (71) [j]	-	Up to 1 Y
	uDCD-HRP n = 99	*17*		*N/A [c]*		*- (87.5)*	*14 (8)* *p = 0.372*	*129 (82)*		
	uDCD-ISP n = 35	*58*		*N/A [c]*		*- (62)*	*18 (31)* *p < 0.001*	*34 (87)*		
cDCD										
Ravaioli et al. [36]	aNRP n = 5 (5/5) *No control group*	10	N/A [c]	N/A [c]	- [k]	- [k]	0 (0)	3 (30)	1.20 ± 0.17 [c] 6-months sCr (mg/dL)	449.5 D (201-627)
Mori et al. [45]	aNRP n = 6 (-/6) *No control group*	9 [q]	N/A [c]	N/A [c]	-	-	0 (0)	1 (16.7)	51.17 ± 13.86 6-months 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*	*N/A [c]*	*N/A [c]*		*- (95)* *p = 0.5*		*8 (4.9)* *p = 0.53*	*61 (37-112)* *p = 0.23* 1-year mGFR (mL/min/1.73m^2)	
Rojas-Peña et al. [38]	aNRP n = 37 (50/37) *No control group*	48	25	48/74 (64.9) [l]	-	- (100) *- (100) ISP [c]*	1 (3.5)	- (31)	-	Up to 3 Y
Oniscu et al. [35]	aNRP n = 21 (36/21) *No control group*	38 [m]	3	38/41 (92.7) [n]	-	-	-	13 (40)	1.36 [1.03-1.58] [c] 1-year sCr (mg/dL)	11 M (3-39)
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] 1-year sCr (mg/dL)	17 M (7-22) [r]
	DBD n = 51	*36*		*N/A [c]*		*- (97.2)* *p = 0.315*				

[a] These values are reported as mean ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specified
[b] Three cases of total body cooling (TBC) were converted to in situ perfusion (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 year and 10 year patient and graft survival
[g] Data are available for 2 year patient and graft survival
[h] After multivariate analysis the difference remained significant (adjusting for recipient age, gender, cold ischaemia time (CIT), duration of perfusion p = 0.03)
[i] After sensitivity analysis one centre was excluded resulting in p = 0.015
[j] PNF cases were excluded
[k] Data are available for 6 months patient and graft survival
[l] 73 grafts were procured from the 37 uDCD donors
[m] Four double transplants were performed
[n] One donor had a previous nephrectomy
[o] 48 grafts were recovered from the 27 uDCD donors
[p] This data is death censored
[q] Three double kidney transplants were performed
[r] This includes the follow-up of all recipients

Table 4b. Clinical Outcomes for the livers

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilisation Rate [n (%)]	1-year patient survival [n (%)]	1-year graft survival [n (%)]	PNF [n (%)]	Biliary complications [n (%)]		EAD [n (%)]	Re-transplant-ation [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 M (0-111)
	DBD n = 538	*538*		N/A [a] (76% in text)	*- (90) p = 0.141*	*- (87) p = 0.011*					*- (-)*	*44 M*
Savier et al. [40]	aNRP n = 13 (299/183)	13	-	13/183 (7.10)	- (85)	- (69)	3 (23)	2 (22)	1 (11) *1 (2)*	4 (-)	3 (23)	32 M [10.2-39.5]
	DBD n = 41	*41*	-	N/A [a]	*- (93) p = 0.39*	*- (93) p = 0.03*					*0 (0)*	*23.6 [8.9-36.7]*

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilisation Rate [n (%)]	1-year patient survival [n (%)]	1-year graft survival [n (%)]	PNF [n (%)]	Biliary complications [n (%)]		EAD [n (%)]	Re-transplant-ation [n (%)]	Follow-up
								Overall	IC			
Jimenez-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 M [n]
	DBD n = 265	*265*	-	N/A [a]	*- (89) p = 0.180*	*- (87.1) p = 0.013*	*4 (1.5) p = 0.031*	*32 (12.1) p = 0.001*	*8 (3) p = 0.018*		*12 (4.5) p = 0.028 (12)*	
uDCD & 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 M [8-26]
	DBD n = 52	*52*	*N/A [a]*	N/A [a]	*- (94) (82-98%) 95%CI p = 0.94*	*- (91) (80-97%) 95%CI p = 0.20*	*2 (4) p = 0.58*	*7 (13) p = 0.65*	*2 (4) p = 0.52*	*13 (27) p > 0.99*	*3 (6) p = 0.35*	*17 M [11-23]*
	ECMO-DBD n = 17	*17*		N/A [a]	*- (87) (58-97%) 95%CI p = 0.47*	*- (87) (58-97%) 95%CI p = 0.76*	*1 (6) p > 0.99*	*1 (6) p = 0.35*	*0 p = 0.49*	*7 (44) p = 0.28*	*0 (0) p = 0.23*	*20 M [7-29]*
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) *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 M (9-40)
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 Y
	cDCD-ISP n = 187	*187*	*N/A [a]*	N/A [a] (27-36% in text)	*- (94.2)*	*- (86.5)*	*13 (7) p = 0.1347*	*64 (37)*	*47 (27) p < 0.0001*	*55 (32) 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 M [n]
	*cDCD-ISP n = 190 * All potential cDCDs*	*117*	*73 (38)*	117/190 (61.58)	*- (88)*	*- (83)*	*3 (3) p = 0.827 p = 0.135 [j]*	*36 (31) p < 0.001 p < 0.001 [j]*	*15 (13) p = 0.012 p = 0.008 [j]*	*32 (27) p = 0.381 p = 0.931 [j]*	*11 (9) p = 0.263*	

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilisation Rate [n (%)]	1-year patient survival [n (%)]	1-year graft survival [n (%)]	PNF [n (%)]	Biliary complications [n (%)]		EAD [n (%)]	Re-transplant-ation [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) [l]	16	3	16/19 (84.2)	- (87.5)	-	2 (12.5)	0 (0)	0 (0)	3 (18.8)	1 (6.3)	6 M [3-18]
	DBD n = 34	*29*	*5*	*29/34 (85.3)*	*- (96) p = 0.496*		*0 (0) p = 0.121*	-	-	*5 (17.2) p = 0.6*	*1 (3.4) p = 0.590*	*16 M [12-20]*
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 M (12-30) [n]
	cDCD(IV)-ISP n = 12	*12*	-	*12/12 (100)*				*2 (16.7)*	*1 (8.3)*			
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)	0 (0)	-	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 M (3-36)

[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 re-transplantation
[f] Medium follow up was 19 months
[g] This value is calculated by the authors based on the information provided in the article
[h] Data are available for 3 months patient and graft survival
[i] Data are available for 3 years patient and graft survival
[j] After inverse probability of treatment weighting analysis
[k] Data are available for 2 years survival
[l] Please note that this study only includes the combined procedure of aNRP for abdominal grafts and in situ perfusion (ISP) for the lungs.
[m] Data are available for 5 years patient and graft survival
[n] This includes the follow-up of all recipients
[o] One patient reached 6 months follow-up

Table 5a. 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]	●	●	●	●	●	●[c]	●	●	●	●	●
Reznik et al.[37]	●[a]	●	●	●	●	●	●	●	●	●	●
Demiselle et al.[28]	●	●	●	●		●	●	●	●	●	●
Molina et al.[34]	●	●	●	●	●	●	●	●	●	●	●
Delsuc et al.[27]	●	●	●	●	●	●	●	●	●	●	●
Antoine et al.[24]	●	●	●	●	●	●	●	●	●	●	●
Del Río et al.[26]	●	●	●	●	●	●[d]	●	●	●	●	●
Ravaioli et al.[36]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●
Mori et al. [45]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●
Foss et al.[30,e]	●[a]	●	●	●	●	●	●	●	●	●	●
Rojas-Peña et al.[38,e]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●
Oniscu et al.[35,e]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●
Miñambres et al.[33,e]	●[a]	●	●	●	●	●	●	●	●	●	●

[a] These studies used different donor type as control group. In order to reduce the risk of confounding bias the two 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-year & 5 year patient survival (PS) only reported in the text for the whole group.

[d] 1-year PS only reported in the text for the whole group.

[e] Please note that these studies report the outcomes on kidney and liver.

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

● Moderate risk of bias (the study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised 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 judgement about risk of bias for this domain).

Table 5b. 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]	●	●	●	●	●	●	●	●	●	●	●
Jimenez-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.[30,e]	●[a]	●	●	●	●	●	●	●	●	●	●	●
Rojas-Peña et al.[38,e]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●	●
Oniscu et al.[35,e]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●	●

[a] These studies used different donor type as control group. In order to reduce the risk of confounding bias the two 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-year & 5 year PS only reported in the text for the whole group.

[d] 1-year PS only reported in the text for the whole group.

[e] Please note that these studies report the outcomes on kidney and liver.

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

● Moderate risk of bias (the study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised 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 judgement about risk of bias for this domain).

Discussion

Despite the fact that aNRP was introduced in the 1990s, only in recent years its use has 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 UK 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 (e.g., cannulation and heparinisation) 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 (e.g., the definition of WIT, approach for lung donation and the use of continuous vs. end-ischaemic 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 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 ischaemic biliary complications in order 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, while 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

Summarising, 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 ischaemic cholangiopathy in liver transplantation, and 1-year eGFR in kidney transplantation.[47-49] Also, we suggest to define 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 randomised 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 randomised controlled trials are considered. Procurement in abdominal cDCD donors can be randomised to either aNRP or regular cold ISP in the donor. In this regard, the possible effect of end-ischaemic 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 utilisation and graft survival but also cost-effectiveness of the labour-intensive procedure will have to be analysed.

In uDCD donation, a randomised 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 to cold ISP in uDCD donors.

Another future development involves standardisation of dual temperature perfusion, integrating aNRP and thoracic cold ISP for lung procurement. Whilst this has been undertaken successfully, the experience is limited.[44,50] Even combined thoraco-abdominal-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. Standardisation of protocols and outcome measures will help to further elucidate its potential positive effect on donor organ utilisation and outcomes after transplantation.

Acknowledgments

The authors thank J.W. Schoones, clinical librarian, for assistance with the literature search and R.A. Bulder and R.E.A. van de Leemkolk for their support in making the visual abstract.

Supplementary Information

Appendix S1. Complete literature search strategy.

The first query consisted of the combination of two subjects: Normothermic Regional Perfusion and Transplantation with multiple synonyms. The search strategy was optimised for all consulted databases. For PubMed, a second, less specific query was compiled consisting of the combination of two subjects: **Transplantation and Perfusion, both as major topics. Due to the unspecific character of this search, we excluded case reports, editorials and limited to articles published from 2013 onwards.** Animal-only studies and reviews without original data were also excluded from this search. The final search was performed on the 29th of January 2020.

Database	Search Strategy First Query	Number of references	Number of unique references
PubMed (incl. MEDLINE)	("normothermic regional perfusion"[tw] OR "normothermic regional circulation"[tw] OR "normothermic recirculation"[tw] OR ((("normothermic"[tw] OR normotherm*[tw] OR "normo-thermic"[tw] OR normo-therm*[tw]) AND ("NRP"[tw] OR "regional perfusion"[tw] OR "extracorporeal perfusion"[tw] OR "extra-corporeal perfusion"[tw] OR "extracorporeal membrane oxygenation"[tw] OR "extra-corporeal membrane oxygenation"[tw] OR "extracorporeal membranous oxygenation"[tw] OR "extra-corporeal membranous oxygenation"[tw] OR (("Perfusion"[mesh] OR "perfusion"[tw] OR perfus*[tw]) AND ("regional"[tw] OR regional*[tw])) OR "recirculation"[tw] OR recirculat*[tw] OR "regional circulation"[tw]) OR "novel perfusion system"[tw] OR "novel perfusion technique"[tw] OR "new perfusion method"[tw] OR "new perfusion system"[tw] OR "new perfusion technique"[tw] OR ("shift"[tw] AND "organ perfusion"[tw])) AND ("Transplants"[Mesh] OR transplant*[all fields] OR "transplants"[all fields] OR "transplantation"[all fields] OR graft*[tw] OR organ transplant*[tw] OR organ graft*[tw] OR "Transplantation"[Mesh] OR "deceased donors"[tw] OR "deceased donor"[tw] OR "DCD donors"[tw] OR "DCD donor"[tw] OR "dcd organ donors"[tw] OR "deceased kidney donor"[tw] OR "deceased kidney donors"[tw] OR "deceased liver donor"[tw] OR "deceased liver donors"[tw] OR "deceased heart beating donor"[tw] OR "deceased heart beating donors"[tw] OR "dcd"[tw] OR "donation after circulatory death"[tw] OR "donation after cardiac death"[tw] OR "donation after cardiocirculatory death"[tw] OR "donation after cardio circulatory death"[tw] OR "non heart beating donor"[tw] OR "non heart beating donors"[tw] OR "nonheart beating donor"[tw] OR "nonheart beating donors"[tw] OR "Circulatory Death"[tw] AND (uncontrolled donat*[tw] OR uncontrolled organ don*[tw] OR uncontrolled donor*[tw])))	253 regular references	229 regular references
Embase (OVID-version)	("normothermic regional perfusion".mp OR "normothermic regional circulation".mp OR "normothermic recirculation".mp OR ((("normothermic".mp OR normotherm*.mp OR "normo-thermic".mp OR normo-therm*.mp) AND ("NRP".mp OR "regional perfusion".mp OR "extracorporeal perfusion".mp OR "extra-corporeal perfusion".mp OR "extracorporeal membrane oxygenation".mp OR "extra-corporeal membrane oxygenation".mp OR "extracorporeal membranous	270 regular references	55 regular references

	oxygenation".mp OR "extra-corporeal membranous oxygenation". mp OR ((exp "Perfusion"/ OR "Regional Perfusion"/ OR "perfusion". mp OR perfus*.mp) AND ("regional".mp OR regional*.mp)) OR "recirculation".mp OR recirculat*.mp OR "regional circulation".mp) OR "novel perfusion system".mp OR "novel perfusion technique".mp OR "new perfusion method".mp OR "new perfusion system".mp OR "new perfusion technique".mp OR ("shift".mp AND "organ perfusion". mp)) AND (exp "Transplantation"/ OR transplant*.af OR "transplants". af OR "transplantation".af OR graft*.mp OR organ transplant*.mp OR organ graft*.mp OR "deceased donors".mp OR "deceased donor".mp OR "DCD donors".mp OR "DCD donor".mp OR "dcd organ donors".mp OR "deceased kidney donor".mp OR "deceased kidney donors".mp OR "deceased liver donor".mp OR "deceased liver donors".mp OR "deceased heart beating donor".mp OR "deceased heart beating donors".mp OR "dcd".mp OR "donation after circulatory death".mp OR "donation after cardiac death".mp OR "donation after cardiocirculatory death". mp OR "donation after cardio circulatory death".mp OR "Circulatory Death" AND ("uncontrolled donat*" OR "uncontrolled organ don*" OR "uncontrolled donor*").mp)))		
Web of Science	TS=("normothermic regional perfusion" OR "normothermic regional circulation" OR "normothermic recirculation" OR ((("normothermic" OR normotherm* OR "normo-thermic" OR normo-therm*) AND ("NRP" OR "regional perfusion" OR "extracorporeal perfusion" OR "extra-corporeal perfusion" OR "extracorporeal membrane oxygenation" OR "extra-corporeal membrane oxygenation" OR "extracorporeal membranous oxygenation" OR "extra-corporeal membranous oxygenation" OR (("Perfusion" OR perfus*) AND ("regional" OR regional*)) OR "recirculation" OR recirculat* OR "regional circulation") OR "novel perfusion system" OR "novel perfusion technique" OR "new perfusion method" OR "new perfusion system" OR "new perfusion technique" OR ("shift" AND "organ perfusion")) AND ("Transplantation" OR transplant* OR graft* OR "deceased donors" OR "deceased donor" OR "DCD donors" OR "DCD donor" OR "dcd organ donors" OR "deceased kidney donor" OR "deceased kidney donors" OR "deceased liver donor" OR "deceased liver donors" OR "deceased heart beating donor" OR "deceased heart beating donors" OR "dcd" OR "donation after circulatory death" OR "donation after cardiac death" OR "donation after cardiocirculatory death" OR "donation after cardio circulatory death" OR "Circulatory Death" AND ("uncontrolled donat*" OR "uncontrolled organ don*" OR "uncontrolled donor*"))))	273 regular references	96 regular reference

Cochrane Library	(“normothermic regional perfusion” OR “normothermic regional circulation” OR “normothermic recirculation” OR (((“normothermic” OR normotherm* OR “normo-thermic” OR normo-therm*) AND (“NRP” OR “regional perfusion” OR “extracorporeal perfusion” OR “extra-corporeal perfusion” OR “extracorporeal membrane oxygenation” OR “extra-corporeal membrane oxygenation” OR “extracorporeal membranous oxygenation” OR “extra-corporeal membranous oxygenation” OR ((“Perfusion” OR perfus*) AND (“regional” OR regional*)) OR “recirculation” OR recirculat* OR “regional circulation”) OR “novel perfusion system” OR “novel perfusion technique” OR “new perfusion method” OR “new perfusion system” OR “new perfusion technique” OR (“shift” AND “organ perfusion”)) AND (“Transplantation” OR transplant* OR graft* OR “deceased donors” OR “deceased donor” OR “DCD donors” OR “DCD donor” OR “dcd organ donors” OR “deceased kidney donor” OR “deceased kidney donors” OR “deceased liver donor” OR “deceased liver donors” OR “deceased heart beating donor” OR “deceased heart beating donors” OR “dcd” OR “donation after circulatory death” OR “donation after cardiac death” OR “donation after cardiocirculatory death” OR “donation after cardio circulatory death” OR “Circulatory Death” AND (“uncontrolled donat*” OR “uncontrolled organ don*” OR “uncontrolled donor*”))):ti,ab,kw	8 regular references	0 regular references
Emcare	(“normothermic regional perfusion”.mp OR “normothermic regional circulation”.mp OR “normothermic recirculation”.mp OR (((“normothermic”.mp OR normotherm*.mp OR “normo-thermic”. mp OR normo-therm*.mp) AND (“NRP”.mp OR “regional perfusion”. mp OR “extracorporeal perfusion”.mp OR “extra-corporeal perfusion”. mp OR “extracorporeal membrane oxygenation”.mp OR “extra-corporeal membrane oxygenation”.mp OR “extracorporeal membranous oxygenation”.mp OR “extra-corporeal membranous oxygenation”. mp OR ((exp “Perfusion”/ OR “Regional Perfusion”/ OR “perfusion”. mp OR perfus*.mp) AND (“regional”.mp OR regional*.mp)) OR “recirculation”.mp OR recirculat*.mp OR “regional circulation”.mp) OR “novel perfusion system”.mp OR “novel perfusion technique”.mp OR “new perfusion method”.mp OR “new perfusion system”.mp OR “new perfusion technique”.mp OR (“shift”.mp AND “organ perfusion”. mp)) AND (exp “Transplantation”/ OR transplant*.af OR “transplants”. af OR “transplantation”.af OR graft*.mp OR organ transplant*.mp OR organ graft*.mp OR “deceased donors”.mp OR “deceased donor”.mp OR “DCD donors”.mp OR “DCD donor”.mp OR “dcd organ donors”.mp OR “deceased kidney donor”.mp OR “deceased kidney donors”.mp OR “deceased liver donor”.mp OR “deceased liver donors”.mp OR “deceased heart beating donor”.mp OR “deceased heart beating donors”.mp OR “dcd”.mp OR “donation after circulatory death”.mp OR “donation after cardiac death”.mp OR “donation after cardiocirculatory death”. mp OR “donation after cardio circulatory death”.mp OR “Circulatory Death” AND (“uncontrolled donat*” OR “uncontrolled organ don*” OR “uncontrolled donor*”).mp)))	84 regular references	2 regular references
Academic Search Premier	TI(“normothermic regional perfusion” OR “normothermic regional circulation” OR “normothermic recirculation” OR (((“normothermic” OR normotherm* OR “normo-thermic” OR normo-therm*) AND (“NRP” OR “regional perfusion” OR “extracorporeal perfusion” OR “extra-corporeal perfusion” OR “extracorporeal membrane oxygenation” OR	118 regular references	25 regular references

"extra-corporeal membrane oxygenation" OR "extracorporeal membranous oxygenation" OR "extra-corporeal membranous oxygenation" OR (("Perfusion" OR perfus*) AND ("regional" OR regional*)) OR "recirculation" OR recirculat* OR "regional circulation") OR "novel perfusion system" OR "novel perfusion technique" OR "new perfusion method" OR "new perfusion system" OR "new perfusion technique" OR ("shift" AND "organ perfusion")) AND ("Transplantation" OR transplant* OR graft* OR "deceased donors" OR "deceased donor" OR "DCD donors" OR "DCD donor" OR "dcd organ donors" OR "deceased kidney donor" OR "deceased kidney donors" OR "deceased liver donor" OR "deceased liver donors" OR "deceased heart beating donor" OR "deceased heart beating donors" OR "dcd" OR "donation after circulatory death" OR "donation after cardiac death" OR "donation after cardiocirculatory death" OR "donation after cardio circulatory death" OR "non heart beating donor" OR "non heart beating donors" OR "nonheart beating donor" OR "nonheart beating donors"))) OR SU("normothermic regional perfusion" OR "normothermic regional circulation" OR "normothermic recirculation" OR ((("normothermic" OR normotherm* OR "normo-thermic" OR normo-therm*) AND ("NRP" OR "regional perfusion" OR "extracorporeal perfusion" OR "extra-corporeal perfusion" OR "extracorporeal membrane oxygenation" OR "extra-corporeal membrane oxygenation" OR "extracorporeal membranous oxygenation" OR "extra-corporeal membranous oxygenation" OR (("Perfusion" OR perfus*) AND ("regional" OR regional*)) OR "recirculation" OR recirculat* OR "regional circulation") OR "novel perfusion system" OR "novel perfusion technique" OR "new perfusion method" OR "new perfusion system" OR "new perfusion technique" OR ("shift" AND "organ perfusion")) AND ("Transplantation" OR transplant* OR graft* OR "deceased donors" OR "deceased donor" OR "DCD donors" OR "DCD donor" OR "dcd organ donors" OR "deceased kidney donor" OR "deceased kidney donors" OR "deceased liver donor" OR "deceased liver donors" OR "deceased heart beating donor" OR "deceased heart beating donors" OR "dcd" OR "donation after circulatory death" OR "donation after cardiac death" OR "donation after cardiocirculatory death" OR "donation after cardio circulatory death" OR "non heart beating donor" OR "non heart beating donors" OR "nonheart beating donor" OR "nonheart beating donors"))) OR KW("normothermic regional perfusion" OR "normothermic regional circulation" OR "normothermic recirculation" OR ((("normothermic" OR normotherm* OR "normo-thermic" OR normo-therm*) AND ("NRP" OR "regional perfusion" OR "extracorporeal perfusion" OR "extra-corporeal perfusion" OR "extracorporeal membrane oxygenation" OR "extra-corporeal membrane oxygenation" OR "extracorporeal membranous oxygenation" OR "extra-corporeal membranous oxygenation" OR (("Perfusion" OR perfus*) AND ("regional" OR regional*)) OR "recirculation" OR recirculat* OR "regional circulation") OR "novel perfusion system" OR "novel perfusion technique" OR "new perfusion method" OR "new perfusion system" OR "new perfusion technique" OR ("shift" AND "organ perfusion")) AND ("Transplantation" OR transplant* OR graft* OR "deceased donors" OR "deceased donor" OR "DCD donors" OR "DCD donor" OR "dcd organ donors" OR "deceased kidney donor" OR "deceased kidney donors" OR "deceased liver donor" OR "deceased liver donors" OR "deceased heart beating donor" OR "deceased

	heart beating donors" OR "dcd" OR "donation after circulatory death" OR "donation after cardiac death" OR "donation after cardiocirculatory death" OR "donation after cardio circulatory death" OR "non heart beating donor" OR "non heart beating donors" OR "nonheart beating donor" OR "nonheart beating donors"))) OR AB("normothermic regional perfusion" OR "normothermic regional circulation" OR "normothermic recirculation" OR ((("normothermic" OR normotherm* OR "normo-thermic" OR normo-therm*) AND ("NRP" OR "regional perfusion" OR "extracorporeal perfusion" OR "extra-corporeal perfusion" OR "extracorporeal membrane oxygenation" OR "extra-corporeal membrane oxygenation" OR "extracorporeal membranous oxygenation" OR "extra-corporeal membranous oxygenation" OR (("Perfusion" OR perfus*) AND ("regional" OR regional*)) OR "recirculation" OR recirculat* OR "regional circulation") OR "novel perfusion system" OR "novel perfusion technique" OR "new perfusion method" OR "new perfusion system" OR "new perfusion technique" OR ("shift" AND "organ perfusion")) AND ("Transplantation" OR transplant* OR graft* OR "deceased donors" OR "deceased donor" OR "DCD donors" OR "DCD donor" OR "dcd organ donors" OR "deceased kidney donor" OR "deceased kidney donors" OR "deceased liver donor" OR "deceased liver donors" OR "deceased heart beating donor" OR "deceased heart beating donors" OR "dcd" OR "donation after circulatory death" OR "donation after cardiac death" OR "donation after cardiocirculatory death" OR "donation after cardio circulatory death" OR "non heart beating donor" OR "non heart beating donors" OR "nonheart beating donor" OR "nonheart beating donors" OR ("Circulatory Death" AND ("uncontrolled donat*" OR "uncontrolled organ don*" OR "uncontrolled donor*")) OR SU("Circulatory Death" AND ("uncontrolled donat*" OR "uncontrolled organ don*" OR "uncontrolled donor*")) OR KW("Circulatory Death" AND ("uncontrolled donat*" OR "uncontrolled organ don*" OR "uncontrolled donor*")) OR AB("Circulatory Death" AND ("uncontrolled donat*" OR "uncontrolled organ don*" OR "uncontrolled donor*")))))		
Science Direct	TITLE-ABSTR-KEY("normothermic regional perfusion" OR "normothermic regional circulation" OR "normothermic recirculation")	19 regular references	9 regular references
Google Scholar	title:"normothermic regional perfusion"|"normothermic regional circulation"|"normothermic recirculation"	105 regular references	69 regular references

Database	**Search Strategy Second Query**	**Number of references**	**Number of unique references**
PubMed (incl. MEDLINE)	(("Transplants"[majr] OR transplant*[ti] OR graft*[ti] OR organ transplant*[ti] OR organ graft*[ti] OR "Transplantation"[majr] OR "deceased donors"[tw] OR "deceased donor"[tw] OR "DCD donors"[tw] OR "DCD donor"[tw] OR "dcd organ donors"[tw] OR "deceased kidney donor"[tw] OR "deceased kidney donors"[tw] OR "deceased liver donor"[tw] OR "deceased liver donors"[tw] OR "deceased heart beating donor"[tw] OR "deceased heart beating donors"[tw] OR "dcd"[tw] OR "donation after circulatory death"[tw] OR "donation after cardiac death"[tw] OR "donation after cardiocirculatory death"[tw] OR	1,120 regular references	1,073 regular references

	"donation after cardio circulatory death"[tw]) AND ("Perfusion"[majr] OR "Perfusion"[ti] OR "normothermic regional perfusion"[tw] OR "normothermic recirculation"[tw] OR "abdominal regional perfusion"[tw] OR "Extracorporeal Membrane Oxygenation"[Mesh] OR "extracorporeal membrane oxygenation"[tw] OR "ECMO"[tw] OR "Reperfusion"[ti]) NOT ("case reports"[ptyp] OR "case report"[ti] OR "comment"[ptyp] OR "comment"[ti] OR "letter"[ptyp] OR "letter"[ti] OR "editorial"[ptyp] OR "editorial"[ti]) AND ("2013/01/01"[PDAT] : "3000/12/31"[PDAT]) NOT ("Coronary Artery Bypass"[majr] OR "Coronary bypass"[ti] OR "coronary bypasses"[ti] OR "Coronary Artery Bypass"[ti] OR "coronary artery bypasses"[ti] OR "Ischemia"[majr] OR "Ischemia"[ti] OR "Ischaemia"[ti] OR ischemi*[ti] OR ischaemi*[ti] OR "Reperfusion"[majr] OR "reperfusion"[ti] OR reperfus*[ti] OR "bridge to lung transplantation"[ti] OR "bridge to lung transplant"[ti] OR "bridge"[ti] OR bridg*[ti]))		
Total		**2,250** regular references	**1,558** unique regular references

Table S1. Data extraction variables.

Study characteristics	Name of the first author, publication year, study design, location, study period and follow-up
Study population characteristics	Samples size, donor type according to the Modified Maastricht Classification for DCD, donor selection criteria, donor age, recipient age, organs donated
Transplantation data	Donor warm ischaemia time, aNRP time, temperature, flow rates, cold ischaemia time, interventions performed before declaration of death, no touch period
Primary outcomes	Organ utilisation, patient and graft survival at one year
Secondary outcomes	Kidney: Primary non-function, delayed graft function, serum creatinine, estimated or measured glomerular filtration rate Liver: Primary non-function, biliary complications, ischaemic cholangiopathy, early allograft dysfunction Pancreas: yield after islet isolation

Table S2. Risk of Bias judgements for the seven domains in the ROBINS-I tool[23] specified for the subject of this review.

Overall judgement for each of the seven domains.	
Low risk of bias	*The study is comparable to a well-performed randomised trial with regard to this domain.*
Moderate risk of bias	*The study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised 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 judgement about risk of bias for this domain.*

Domain. Bias due to confounding	
Low risk of bias	No confounding expected
Moderate risk of bias	Confounding expected. Important confounding domains (e.g., donor age, donor type) appropriately measured and controlled for (propensity score matching, stratification, regression, standardisation).
Serious risk of bias	At least one known important domain (e.g., donor age, donor type) not controlled for.
Critical risk of bias	Confounding inherently not controllable (no baseline characteristics reported the study).
Domain. Bias in selection of participants into the study	
Low risk of bias	All participants who would have been eligible were included in the study.
Moderate risk of bias	Selection (e.g., gender or age in donor and recipient, duration fWIT or duration aNRP) may have been related to intervention and outcome but appropriate methods to adjust were used (e.g., nearest neighbour matching algorithm).
Serious risk of bias	Selection (e.g., gender or age in donor and recipient, duration fWIT or duration aNRP) have been related to intervention and outcome and this could not be adjusted for in analyses.
Critical risk of bias	Selection into study was very strongly related to intervention and outcome and this could not be adjusted for in analyses.
Domain. Bias in classification of intervention	
Low risk of bias	Status of aNRP or standard perfusion technique is well defined and data was prospectively collected.
Moderate risk of bias	Status of aNRP or standard perfusion technique is well defined but the assignments of intervention status was determined retrospectively.
Serious risk of bias	Status of aNRP or standard perfusion technique is not well defined.
Critical risk of bias	An extremely high amount of misclassification of intervention status.
Domain. Bias due to deviations from intended interventions	
Low risk of bias	Deviations from intended intervention reflected usual practice and were unlikely to impact on the outcome.
Moderate risk of bias	Deviations from intended intervention reflected usual practice but their impact on the outcome is expected to be slight (e.g., CIT, immunosuppression, end-ischaemic ex-situ machine perfusion).
Serious risk of bias	Deviations were unbalanced between the intervention groups and likely to have affected the outcome (e.g., end-ischaemic ex-situ machine perfusion).
Critical risk of bias	Substantial deviations that were unbalanced between intervention groups and likely to have affected the outcome.
Domain. Bias due to missing data	
Low risk of bias	Data were reasonably complete (± 10%) or proportions of and reasons for missing participants were similar across intervention groups.
Moderate risk of bias	Proportion of and reasons for missing participants differ slightly across intervention groups.
Serious risk of bias	Proportion of and reasons for missing participants differ substantially across intervention groups.
Critical risk of bias	Critical differences between interventions in participants with missing data were observed and were not or could not be addressed through appropriate analysis.

Domain. Bias in measurement of outcomes	
Low risk of bias	Comparable methods of outcome assessment across intervention groups, and outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants and any error in measuring the outcome is unrelated to intervention status. E.g., patient survival, graft survival, PNF, DGF.
Moderate risk of bias	Comparable methods of outcome assessment across intervention groups, outcome measure is only minimally influenced by knowledge of the intervention and any error is minimally related to intervention status (e.g., image proven or clinical ischaemic cholangiopathy).
Serious risk of bias	Not comparable methods of outcome assessment across intervention groups.
Critical risk of bias	Different methods of outcome assessment that cannot reasonably be compared across intervention groups.
Domain. Bias in selection of the reported results	
Low risk of bias	Clear evidence (via a preregistered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and subcohorts.
Moderate risk of bias	Outcome measurements and analyses are consistent with an a priori plan and no indication of selection of the reported analysis from among multiple analyses and no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Serious risk of bias	High risk of selective reporting from among multiple analyses (e.g., exclusion of PNF or exclusion of one participating centre).
Critical risk of bias	Evidence or strong suspicion of selective reporting of results and unreported results are likely to be substantially different from the reported results.

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