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REVIEW

Regional Perfusion by Extracorporeal Membrane Oxygenation of Abdominal Organs From Donors After Circulatory Death: A Systematic Review

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Organs from donors after circulatory death (DCDs) are particularly susceptible to the effects of warm ischemia injury. Regional perfusion (RP) by extracorporeal membrane oxygenation (ECMO) is increasingly being advocated as a useful remedy to the effects of ischemia/reperfusion injury, and it has been reported to enable the transplantation of organs from donors previously deemed unsuitable. The MEDLINE, Embase, and Cochrane databases were searched, and articles published between 1997 and 2013 were obtained. A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Two hundred ten articles were identified, and 11 were eligible for inclusion. Four hundred eighty-two kidneys and 79 livers were transplanted from regional perfusion–supported donor after circulatory death (RP-DCD) sources. One-year graft survival was lower with uncontrolled RP-DCD liver transplantation, whereas 1-year patient survival was similar. Primary nonfunction and ischemic cholangiopathy were significantly more frequent with RP-DCDs versus donors after brain death (DBDs), but there was no difference in postoperative mortality between the 2 groups. The 1-year patient and graft survival rates for RP-DCD kidney transplantation were better than the rates with standard DCDs and were comparable to, if not better than, the rates with DBDs. At experienced centers, delayed graft function (DGF) for kidney transplantation from RP-DCDs was much less frequent in comparison with all other donor types. In conclusion, RP aids the recovery of DCD organs from ischemic injury and enables transplantation with acceptable survival. RP may help to increase the donor pool, but its benefits must still be balanced with the recognition of significantly higher rates of complications in liver transplantation. In kidney transplantation, significant reductions in DGF can be obtained

Abbreviations: ABI, anoxic brain injury; ALS, advanced life support; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; CA, cardiac arrest; CI, confidence interval; CVA, cerebrovascular accident; DBD, donor after brain death; DCD, donor after circulatory death; DGF, delayed graft function; DM, diabetes mellitus; DWIT, donor warm ischemia time; ECMO, extracorporeal membrane oxygenation; HAT, hepatic artery thrombosis; HIV, human immunodeficiency virus; HR, hazard ratio; HTK, histidine-tryptophan-ketoglutarate; HTN, hypertension; IC, ischemic cholangiopathy; IVDU, intravenous drug use; MOF, multiorgan failure; MP, machine perfusion; N/A, not applicable; NRP, normothermic regional perfusion; NRP-DCD, normothermic regional perfusion–supported donor after circulatory death; PNF, primary nonfunction; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RP, regional perfusion; RP-DCD, regional perfusion–supported donor after circulatory death; TBI, traumatic brain injury; ULN, upper limit of normal; UPC, until procurement completed; UW, University of Wisconsin.

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with RP, and there are potentially important implications for long-term outcomes. Significant ethicolegal issues exist, and they are preventing a worldwide consensus on optimum RP protocols and an accurate appreciation of outcomes. ***Liver Transpl 19:1292-1303, 2013***. © **2013 AASLD.**

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Organ transplantation is the most cost-effective treatment for end-stage organ failure, but almost 8000 patients in the United Kingdom are awaiting an organ.[1] New donor pools are being sought, and the criteria for existing pools are being expanded, but over the past decade, the number of donors after brain death (DBDs) has slightly decreased. In recent years, improved road safety, changes in neurosurgical practice, and a reduction in subarachnoid hemorrhage due to antihypertensive treatment have led to a reduction in deaths and a decline in available DBDs.[2-4] Contemporaneously, a 3-fold increase in living donors and an 8-fold surge in donors after circulatory death (DCDs) have occurred.[1] In the United Kingdom, DCDs now contribute more than a third of the total deceased donor pool, and they have demonstrated comparable outcomes for kidneys and acceptable outcomes for livers with carefully selected donors and recipients.[1,5-9] DCDs are first classified into 1 of 4 categories: (I) dead upon arrival at the emergency department, (II) unsuccessful resuscitation attempt, (III) cardiac arrest (CA) following the withdrawal of treatment in a patient with brain damage insufficient for declaring brain death, and (IV) unanticipated CA following the declaration of brain death. Because of the circumstances under which death and subsequent donation occur, categories I, II, and IV are often called uncontrolled, whereas category III is termed controlled.[10] Other revisions and classifications have also since been reported.[11,12]

DCD organs (especially livers) are more susceptible than DBDs to damage from warm ischemia and ischemia/reperfusion injury. Cold-stored organs from DCDs are injured during 4 consecutive stages: warm ischemia (before retrieval), cold ischemia (during storage), a second episode of warm ischemia (during rewarming), and, finally, reperfusion (at transplantation).[13] Multiple pathways have been implicated in ischemia/reperfusion injury, including the inflammatory response, oxygen free radicals, and the activation of T cell lymphocytes.[14] Ischemic injury that accumulates during the cold storage phase is exacerbated in DCDs by the preceding phase of warm ischemia.[15]

Regional perfusion (RP) by extracorporeal membrane oxygenation (ECMO) is an emerging method for perfusing organs from DCDs. RP was first used in 1989 by Spanish transplant surgeons using a percutaneously placed RP cardiopulmonary bypass circuit.[11] Although primarily confined to DCDs, cardiopulmonary bypass has also been used to support heart-lung grafts in brain-dead donors.[16] The RP circuit closely resembles cardiopulmonary bypass, although there are subtle differences, including the anatomical location of cannulae (peripheral versus central) and the flow rates (lower with RP). RP is used in situ before organ retrieval, whereas ex situ machine perfusion (MP) is used to support single organs, including the heart, lungs, liver, and kidneys, from DCDs.[17-20] RP works in 3 ways. First, it acts as a perfusion bridge between asystole and procurement and thus permits dissection without the risk of ischemic injury. Second, by replenishing mitochondrial stores of adenosine triphosphate (ATP) and thus reversing anaerobic metabolism mimicking a period of ischemic preconditioning, it enables rehabilitation on a cellular level.[21-23] Third, it permits the assessment of donor organs under nonischemic conditions over a period of time and the tracing of the physiological response to reperfusion.

To date, there has been no systematic review of regional perfusion–supported donor after circulatory death (RP-DCD) organ transplantation, although several articles make isolated references to RP as an emerging organ perfusion technique.[24-27] The aim of this study was to systematically review the role of RP-DCDs in current practice and determine their efficacy in comparison with other donor types

PATIENTS AND METHODS

A search of the MEDLINE, Embase, and Cochrane electronic databases was performed with the following Medical Subject Headings terms: *extracorporeal membrane oxygenation*, *donors after cardiac death*, *non–heart-beating donors*, *donors after circulatory death*, *normothermic recirculation*, *normothermic perfusion*, *regional perfusion*, *liver transplantation*, *kidney transplantation*, and *pancreas transplantation*. Terms were combined with Boolean operators, and the references of all identified articles were searched to ensure a comprehensive review. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[28] Ethical approval was not required; however, the study protocol underwent a rigorous review process.

Inclusion and Exclusion Criteria

A wide range of study designs, including randomized control trials, cohort studies, case-control studies, and case series, were considered eligible. Studies performed between January 1997 and June 2013 were included. Case reports, review articles, animal studies, and studies of nonabdominal organs were excluded. Studies in which donors were perfused via an ex situ (ie, postretrieval) RP circuit and articles not written in English were also excluded.

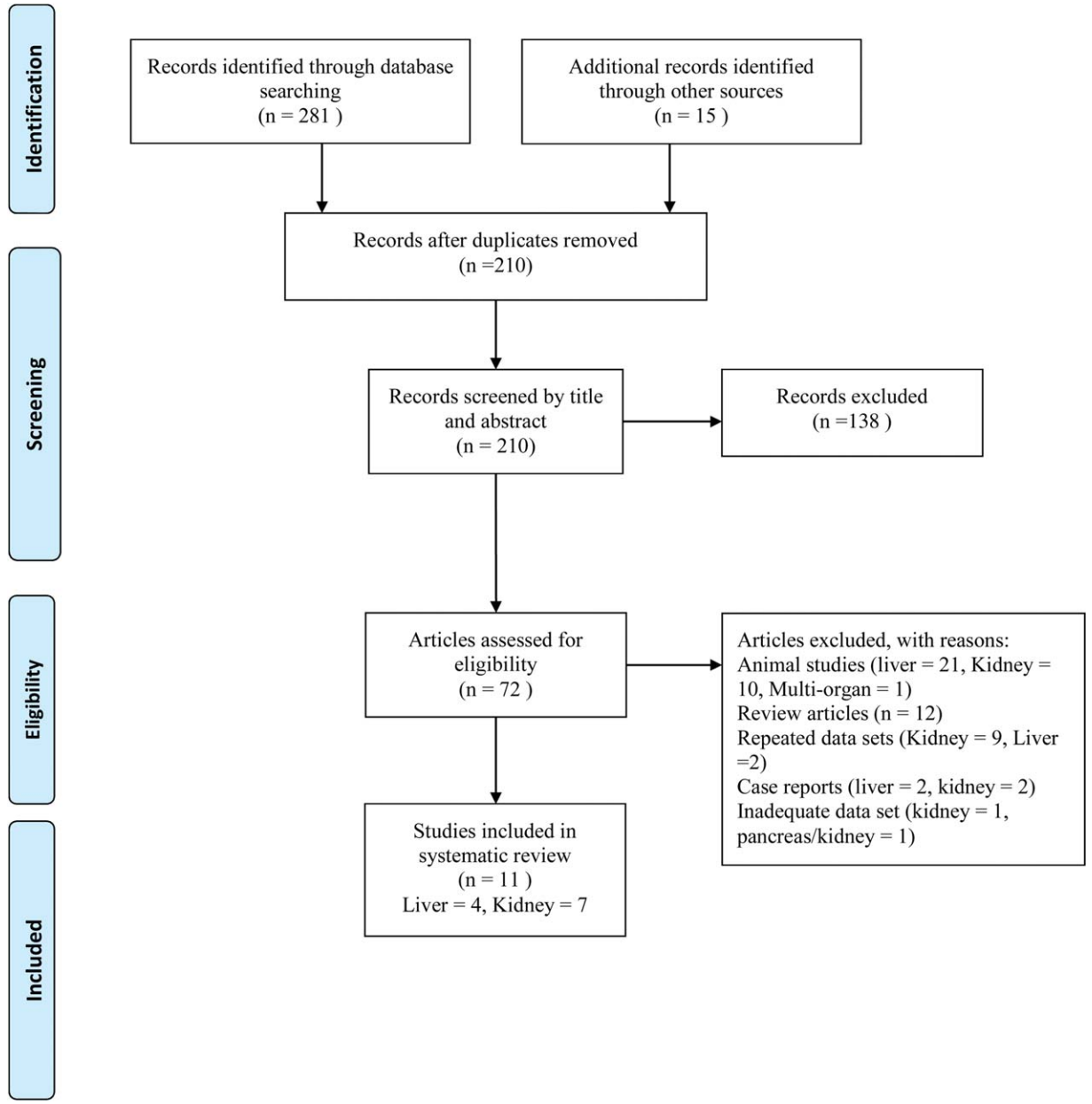

Figure 1. PRISMA flow diagram for study selection.

Data Extraction

Data extraction was performed with a pro forma standard. Donor data, including ages, causes of death, inclusion/exclusion criteria, Maastricht categories, types of organs donated, and proportions of potential donors to actual donors, were recorded. RP protocols were interrogated, and the circuit temperature, the donor warm ischemia time (DWIT), the cold ischemia time, the RP duration, the flow rates, the method of organ storage, and the type of perfusion solution were documented. DWIT was defined in all cases (uncontrolled and controlled DCDs) as the time from CA to the commencement of RP. Studies were further categorized according to the perfusion temperature with the hypothermia classification described by Marx et al.[29]: normothermia (35-37°C), mild hypothermia (32-35°C), moderate hypothermia (28-32°C), severe hypothermia (20-28°C), and profound hypothermia (<20°C). An additional grade was also used to describe perfusion at cold/nearly freezing temperatures (<5°C). Methods of vascular access were identified and defined as premortem or postmortem interventions. Survival data and complication rates were recorded, and when it was necessary, survival data were extracted from original Kaplan-Meier curves.

Outcome Measures

The primary endpoints were 1-year graft and patient survival for livers and kidneys. The secondary

TABLE 1. Donor Inclusion Criteria and Characteristics

Study	Organ	Potential Donors (n)/ Actual Donors [n (%)]	Maastricht Category	Inclusion Criteria	Cause of Death	Mean Age (Years)*
Fondevila et al.[30] (2012), Barcelona, Spain	Liver	400/34 (8.5)	II	Age < 65 years No contraindicated pathologies (as for DBDs) No major thoracoabdominal trauma AST/ALT < 3 × ULN (initial) AST/ALT < 4 × ULN (final)	Cardiac arrhythmia (10), myocardial infarct (416), trauma (5), CVA (1), other (2)	47 (27-56)
Jiménez-Galanes et al.[31] (2009), Madrid, Spain (Octubre)	Liver	43/20 (46.5)	II	Age < 50 years No contraindicated pathologies (as for DBDs) No major thoracoabdominal trauma AST/ALT < 4 × ULN	Cardiac arrhythmia/myocardial infarct (13), head trauma (3), intracranial bleeding (3), hanging (1)	30.6 (18-46)
Otero et al.[32] (2003), Madrid, Spain (San Carlos)	Liver	—/14	II	Age < 50 years Known cause of death No contraindicated pathologies (as for DBDs) No major thoracoabdominal trauma No liver necrosis Steatosis < 30%	—	23 (17-50)
Pelletier et al.[33] (2009), Michigan†	Liver	19/12 (63.0%)	III	Age of 6 months to 65 years No HTN or DM if 55-65 years old Weight > 2 kg Coma with documented severe and irreversible neurological injury requiring mechanical ventilation	Sublethal neurological injury (11)	—
Sánchez-Fructuoso et al.[34] (2006) Madrid, Spain	Kidney	—	I (85.3%) II (14.7%)	No effective heartbeat after 30 minutes of ALS Known cause of death No major thoracoabdominal trauma No external signs of IVDU suggesting HIV, hepatitis B, or hepatitis C Age < 60 years	—	36.4 ± 11.5
Valero et al.[35] (2000) Barcelona, Spain	Kidney	17/8 (47.0%)	II	Same as for DBDs Age < 65 years	Not polytrauma (7), polytrauma (1)	39.5 ± 15.6
Reznik et al.[36] (2011) St Petersburg, Russia	Kidney	—/10	II	—	TBI (5), CVA (5)	44 (22-55)
Magliocca et al.[37] (2005) Michigan, USA	Kidney, liver‡	20/15 (75.0%)	III	Age of 6 month to 65 years No HTN or DM if 55-65 years Weight > 2 kg Coma with documented severe and irreversible neurological injury requiring mechanical ventilation	TBI (13), ABI (5), CVA (2)	—

TABLE 1. *Continued*

Study	Organ	Potential Donors (n)/ Actual Donors [n (%)]	Maastricht Category	Inclusion Criteria	Cause of Death	Mean Age (Years)*
Farney et al.[38] (2008) North Carolina, USA	Kidney, liver[§]	—/10	III	Age < 60 years No more than 1 comorbidity, including death from CVA, HTN, serum creatinine > 1.5 mg/dL, recent malignancy, and HIV	—	—
Lee et al.[39] (2005) Taiwan	Kidney	16/16 (100.0%)	III	Same as for DBDs	TBI (9), CVA (3), ICH (2), Dissecting Aortic Aneurysm (1) Arteriovenous malformation rupture (1)	38.6 ± 11.3
Koyama et al.[40] (2002) Tokyo, Japan	Kidney	23/23 (100.0%)	IV	—	CVA (12), TBI (9), ischemic brain damage (2)	44.7 ± 17.3

*Ranges are shown in parentheses.
†Pelletier et al.'s study[33] has been reported in abstract form only. Follow up data was only available for 11 transplants.
‡Liver results from Magliocca et al.[37] were included in Pelletier et al.'s study.[33]
§Liver results were excluded because of the lack of follow-up data.

endpoints for livers included primary nonfunction (PNF), ischemic cholangiopathy (IC), hepatic artery thrombosis (HAT), death, and retransplantation. The secondary endpoints for kidneys included delayed graft function (DGF), PNF, and acute rejection. DGF was defined as the need for hemodialysis within 1 week of kidney transplantation.

Data Analysis

Data were arranged in a tabular form and qualitatively reviewed. A meta-analysis was performed, but the results were deemed inappropriate for inclusion because of heterogeneity among the studies due to marked differences among RP protocols for the kidney transplant studies and due to the small numbers of studies and patients for liver transplants.

RESULTS

The search revealed 210 unduplicated articles, and 72 of these articles underwent a detailed assessment for eligibility. Figure 1 shows the PRISMA flow diagram for study selection. The search revealed 4 cohort studies related to liver transplantation and 7 observational studies related to kidney transplantation.[30-40] Four hundred eighty-two kidneys and 79 livers were transplanted from RP-DCD sources. Data from 1 successfully transplanted liver graft were excluded because it was not transplanted by the retrieving center and was lost to follow-up.[33,34] Other series of RP-DCD transplants were also excluded from this review because of a lack of data; these included 31 kidney transplants from Paris and 4 simultaneous pancreas-kidney transplants from Miami.[38,41] Isolated case reports also exist. They include a 15-year-old male who was treated with ECMO for severe adult respiratory distress syndrome and for whom temporary malfunction of the ECMO circuit led to brain death and a 22-year-old woman suffering irreversible brain injury who entered CA twice and was supported on ECMO while she awaited brain-stem testing.[42,43] Table 1 outlines the donor characteristics. Most studies did not comment on the donor sex.

Regional Perfusion Protocols

In each study, vascular access was obtained via the femoral vessels with inflation of a supraceliac balloon in the aorta, and the correct placement was confirmed radiologically. Cannulae were connected to an extracorporeal circuit incorporating a membrane oxygenator, a centrifugal pump or roller, a heat exchanger, and a perfusate reservoir. Autologous blood perfusate from the donor's cadaver was used and anticoagulated with heparin. Cannulae were placed post mortem after a 5-minute standoff period for category I, II, and IV DCDs. For category III donors, cannulae were placed under local anesthesia before the withdrawal of treatment and the disconnection of the mechanical ventilator, and after 5 minutes, standoff RP was

TABLE 2. RP Protocol Parameters

Study	Perfusion Temperature	Mean DWIT (Minutes)	Maximum DWIT (Minutes)	Mean NRP (Minutes)	Maximum NRP (Minutes)	Cold Ischemia Time	Flow Rate (L/Minute)	Cold Storage Method	Perfusion Solution
Fondevila et al.[30] (2012)	Normothermia	— (7 for CA, 112 for ALS)	165 (15 for CA, 150 for ALS)	198	240	380 (325-430) minutes*	1.7	Static	UW (2002-2010) Celsior (2010)
Jiménez-Galanes et al.[31] (2009)	Normothermia	133 (7 for CA, 126 for ALS)	165 (15 for CA, 150 for ALS)	174	240 (later 270)	432 (240-565) minutes*	3.1	Static	UW (most cases)
Otero et al.[32] (2003)	Normothermia (n = 7) Profound hypothermia (n = 7)	104 (10 for CA, 93 for ALS)	170 (20 for CA, 150 for ALS)	140	240	647 (460-720) minutes*	—	Static	UW
Pelletier et al.[33] (2009)	Normothermia	5 (CA)	—	—	UPC	—	4	Static	—
Sánchez-Fructuoso et al.[34] (2006)	Profound hypothermia	Not reported	120 (15 for CA, 105 for ALS)	—	240	17.7 ± 3.5 hours	—	—	—
Valero et al.[35] (2000)†	Normothermia Profound hypothermia	82 ± 11 81 ± 15	180 (30 for CA, 150 for ALS)	—	60 (at 37°C) + time to reach 15-20°C and UPC Time to reach 15-20°C and UPC	17.8 ± 6.7 hours 15.3 ± 4.6 hours	1-2	Static	UW
Reznik et al.[36] (2011)	Moderate hypothermia	75.9 (45-92)*	No maximum	159 (120-210)*	210	—	2.5	—	HTK
Magliocca et al.[37] (2005)	Normothermia	5 (CA)	—	94	UPC	—	4	—	—
Farney et al.[38] (2008)	Severe hypothermia	5 (CA)	—	—	UPC	<40 hours	4-6	MP	—
Lee et al.[39] (2005)	Cold/near freezing	10 (CA)	—	57.6 ± 11.6	UPC	—	2	—	—
Koyama et al.[40] (2002)	Profound hypothermia	1-147‡	—	30.8	UPC	12 hours 55 minutes	2-3.5	—	Euro-Collins

*The range is shown within parentheses.

†Valero et al.'s study[35] included 2 NRP groups with different protocols pertaining to the perfusion temperature and the time on the NRP circuit.

‡Only the range is provided.

TABLE 3. Liver Survival and Complications

Study	1-Year Graft Survival [n (%)]	1-Year Patient Survival [n (%)]	PNF [n (%)]	HAT [n (%)]	IC [n (%)]	Mortality [n (%)]
Fondevila et al.[30] (2012)						
RP-DCDs (n = 34)	19 (70.0)*	24 (82.0)*	†	†	3 (8.8.0)	†
DBDs (n = 538)	444 (87.0)*	463 (90.0)*			0 (0.0)	
Comparison of NRP-DCDs and DBDs from the same data period (2002-2010)	$P < 0.05$	$P = 0.141$				
Jiménez-Galanes et al.[31] (2009)						
RP-DCDs (n = 20)	16 (80.0)	17 (85.0)	2 (10.0)‡	0 (0.0)	1 (5.0)	3 (15.0)‖
DBDs (n = 40)	35 (87.5)	35 (87.5)	1 (2.5)	0 (0.0)	0 (0)	5 (12.5)¶
Concurrent matched controls (1:2 ratio)	$P = 0.774$	$P = 0.768$	$P = 0.154$		$P = 0.209$	
Otero et al.[32] (2003)						
RP-DCDs (n = 14)	6 (42.9)	10 (71.0)	5 (35.7)**	0 (0.0)	4 (28.6)	4 (28.6)††
DBDs (n = 40)	29 (72.5)	29 (72.5)	1 (2.5)	0 (0.0)	3 (7.5)	11 (27.5)#
Concurrent matched controls (1:2 ratio)	$P > 0.05$	$P > 0.05$	$P > 0.05$		$P > 0.05$	
Pelletier et al.[33] (2009)						
RP-DCDs (n = 11)	10 (91.0)	10 (91.0)	0 (0)	—	1 (9.0)	—
Standard DCDs (n = 876)	(78.0)	(82.0)	—	—	—	—
DBDs (n = 27,251)	(83.0)	(86.0)	—	—	—	—

*Censored survival percentages are provided.
†Data were available for the first 10 patients only (2002-2006), and they were obtained from earlier published results (2007). One of the 10 patients (10%) had PNF and underwent retransplantation; 1 of the 10 patients had HAT (10%); and 3 of the 10 patients (30%) died because of hepatitis C virus recurrence (1), sepsis (1), or MOF (1).
‡All patients underwent retransplantation.
§PNF (1), sepsis (1), and MOF after retransplantation (1).
‖Septic shock (2), MOF (2), and PNF (1).
¶There were no retransplants.
#PNF (1), MOF (1), and sepsis (2).
**Sepsis (4), MOF (2), hepatitis C virus recurrence (2), PNF (1), hemoptysis (1), and portal vein thrombosis (1).
††Survival percentages for standard DCDs and DBDs were extracted from Kaplan-Meier graphs provided by the authors. Historical controls were taken from the United Network for Organ Sharing database.

commenced. Parameters for the different RP protocols are displayed in Table 2.

Endpoints: Liver

Raw data for RP-DCD liver transplantation are shown in Table 3. In all 3 uncontrolled RP-DCD studies, the rates of 1-year graft survival were lower than the rates with DBDs. However, no statistical significant difference was demonstrated for 1-year patient survival.[30-32] PNF and IC rates were higher with RP-DCD grafts, but the rates of operative mortality and HAT were similar for the RP-DCD and DBD groups in all these studies.

Pelletier et al.,[33] in the only study of controlled normothermic regional perfusion–supported donors after circulatory death (NRP-DCDs), reported the successful procurement and transplantation of 12 livers, and follow-up data were available for 11 of these livers. The data were compared to those for 27,251 historical DBD controls and 876 standard controlled DCD controls from the United Network for Organ Sharing database. They reported a rate of 91% for 1-year patient and graft survival (10/11), and this resulted in a risk of graft loss comparable to that with DBDs [hazard ratio (HR) = 1.14, confidence interval (CI) = 0.59-2.20, $P = 0.69$] and better than that with standard DCDs (HR = 1.85, CI = 0.96-3.58, $P = 0.69$). Patient survival was similar to that for DBD recipients (HR = 1.23, CI = 0.64-2.36, $P = 0.54$) but was significantly better than that for DCD recipients (HR = 2.16, CI = 1.12-4.17, $P = 0.02$). IC and PNF occurred in 9% and 0% of their cases, respectively.

Endpoints: Kidneys

Raw data for RP-DCD kidney transplantation are shown in Table 4. Significant heterogeneity between the studies meant that a meta-analysis was not appropriate. The 1-year patient and graft survival rates were better with RP-DCDs versus standard DCDs, and they were comparable to, if not better than, the rates with DBDs of all ages. Most studies reported PNF rates of 0%, with the remainder reporting rates comparable to those for DBDs older than 60 years. The rates of acute rejection in all RP-DCD groups were lower than the rates with other donor

TABLE 4. Kidney Results

Study	1-Year Graft Survival [n (%)]	1-Year Patient Survival [n (%)]	DGF [n (%)]	PNF [n (%)]	Acute Rejection [n (%)]
Sánchez-Fructuoso et al.[34] (2006)					
RP-DCDs (n = 320)	(87.4)	(95)	(60.9)	14 (4.4)	14 (4.4)
DBDs: age < 60 years (n = 458)	(90.7)	(97)	(20.4)	5 (1.1)	24 (5.2)
DBDs: age > 60 years (n = 126)	(79.8)	(93)	(27.4)	5 (4)	13 (10.3)
Valero et al.[35] (2000)					
RP-DCDs (n = 16)	14 (87.5)	(90)*	1/8 (12.5) and 6/8 (75)†	0 (0)	—
Standard DCDs (n = 40)	27 (72)‡		22 (55)	9 (22.5)	—
Reznik et al.[36] (2011)					
RP-DCDs (n = 20)	20 (100) at 3 months	20 (100) at 3 months	14 (70)	0 (0)	(10)
Magliocca et al.[37] (2005)					
RP-DCDs (n = 24)	—	—	2 (8.3)	0 (0)	0 (0)
DBDs (n = 100)§	—	—	24 (24)	1 (1)	5 (5)
Farney et al.[38] (2008)‖					
RP-DCDs (n = 25)	25 (100)	25 (100)	2 (8)	0 (0)	0 (0)
Standard DCDs (n = 53)	(87)	(94)	30 (57)	1 (2)	10 (19)
Standard Criteria DBDs (n = 178)	(90)	(99)	34 (19)	3 (2)	15 (8)
Extended Criteria DBDs (138)	(83)	(95)	26 (19)	4 (3)	17 (12)
Lee et al.[39] (2005)					
RP-DCDs (n = 31)	31 (100)	31 (100)	13 (41.9)	0 (0)	11 (35.5)
DBDs: age < 60 years (n = 120)	(90)	(93)	31/120 (26)	—	48 (40.3)
Koyama et al.[40] (2002)					
RP-DCDs (n = 46)	(88.3)	—	40 (87)	3 (6.5)	—

*The data were combined for RP-DCDs and standard DCDs.
†Valero et al.[35] reported different DGFs according to the perfusion temperature: normothermic and hypothermic.
‡The data are censored.
§DBDs in Magliocca et al.'s study[37] were <65 years old.
‖Data from Farney et al.'s study[38] included kidney grafts from simultaneous pancreas-kidney transplantation as well as organs retrieved by Farney et al.'s group but implanted at other centers. Standard Criteria DBDs were donors younger than 50 years or 50-59 years without additional risk factors. xtended Criteria DBDs were donors who did not meet the standard criteria.

types. Wide variations in DGF existed between the study groups. In the American studies, the rates of DGF with controlled RP-DCDs were far superior to the rates with all other donor types.[37,38]

DISCUSSION

A systematic review of the literature has demonstrated the increasing use of organs from RP-DCD sources for transplantation, and this may represent a viable method of increasing the number of available organs. This is best illustrated by centers where DCD transplantation did not previously take place or where religious and cultural practices precluded the use of DBD or controlled DCD sources. The learning curve may explain the superior results of established centers from the United States and Western Europe in comparison with the newcomer centers of Russia and Asia. In Barcelona, Spain, outcomes from uncontrolled RP-DCDs have significantly improved over the duration of the program, with an improvement in 6-month graft survival from 53% in the first half of the program to 88% in the second half ($P < 0.05$).[30]

Given the virtually identical perfusion protocols and DWITs of the 3 uncontrolled RP-DCD liver transplant studies, we find it surprising that such a wide range of 1-year graft survival rates was seen (42.9%-80%).[30-32] Differences in the cold ischemia time alone are unlikely to account for such a wide range of graft survival rates. One possible explanation for this variation may be found in the proportions of potential donors to actual donors, which ranged from 8.5% (Fondevila) to 46.5% (Jimenez-Galanes). Conversion rates were not provided by Otero et al.,[32] but if the implied 100% conversion rate is assumed, the lower survival rates may be explained by their less stringent donor criteria and greater acceptance of suboptimal grafts. Donor rejection in the other studies was primarily due to an unsatisfactory macroscopic appearance related to hepatic steatosis, cirrhosis, or fibrosis (30%) and unsuccessful organ perfusion (40%).[30,31] Hepatic steatosis less than 30% was deemed acceptable by Otero et al., but no such figure was provided by the other studies.[32] The British Transplantation Society has deemed liver grafts to be suboptimal when there is greater than 10% hepatic steatosis and the donor age is >50 years.[44] A more stringent view

on donor age and hepatic steatosis (implied only) in Jiménez-Galanes et al.'s study[31] may account for their superior outcomes. Biliary complications remain a significant cause of morbidity in DCD liver transplantation.[8,45] Rates of IC and PNF with uncontrolled RP-DCDs were nonetheless lower than rates with standard DCDs reported elsewhere in the published literature.[46] Morbidity and its associated costs should remain a clear reminder of the compromises accepted for increased numbers of liver grafts and the importance of careful donor selection.[47] Fondevila et al.[30] clearly demonstrated how stricter criteria and the careful selection of recipients corresponded to an improvement in outcomes: the liver donation rate in 2002-2006 was 25% with a 6-month graft survival rate of 53%, whereas the donation rate for 2006-2010 was 11% with a 6-month survival rate of 88%.

Marked reductions in DGF were seen in the NRP-DCD cohorts in both Valero et al.'s and Farney et al.'s studies,[35,38] and they suggest that this is one of the main advantages of NRP-DCD kidney transplantation.[35,38] Reducing DGF remains an important goal because of the greater risk of graft failure and rejection and the associated costs of additional hemodialysis and hospital stays.[27,34] The recirculation of blood at the homeostatic temperature (37°C) has been shown to reduce DGF and replenish antioxidant and ATP levels.[48-50] Hosgood et al.[51] demonstrated increased graft survival for porcine kidneys that were subjected to 30 minutes of warm ischemia, preserved for 20 hours with hypothermic MP, and then subjected to 2 hours of ex situ normothermic MP with autologous blood before transplantation. Increased creatinine clearance, replenishment of ATP stores, and reduced markers of oxidative stress and inflammation have also been demonstrated in porcine kidneys resuscitated with normothermic MP, although the extent to which the recovery of metabolic function occurs is warm ischemia time–dependent.[15,48,52] Greater perfusion pressures and leukocyte and platelet depletion are also associated with improved renal function and blood flow.[53-56]

Experimental research on animal livers has also demonstrated the superiority of normothermic perfusion over cold static storage; synthetic and metabolic unction can be maintained for up to 72 hours with normothermic perfusion.[57-62] Similar findings have been reported up to 24 hours when it is preceded by a 60-minute period of warm ischemia.[14,63,64] Full recovery occurs after 20 minutes of warm ischemia when they are rehabilitated with normothermic regional perfusion (NRP), but the capacity for recovery diminishes markedly when DWIT exceeds 30 minutes.[23,65] The addition of nutritional supplements such as cholate and amino acids may also aid in the prevention of ischemia-related complications such as cholestasis and cholangiopathy through the mediation of ischemic preconditioning.[22,66-68] The use of MP provides an alternative means for assessing liver function after procurement and an opportunity for liver repair.[19,20,69,70]

Cost-Effectiveness

The cost-effectiveness of RP-DCD transplantation remains to be calculated, and this needs to be done before we can form conclusions about the economic value of RP-DCDs. Although a portable RP machine costs in the region of £40,000 ($60,000), an accurate cost-effectiveness analysis must reflect the true operating costs of RP-DCDs, including consumables, equipment maintenance, and, most costly of all, the availability of appropriately trained retrieval surgeons and intensive care or emergency physicians. Higher costs with standard DCDs due to greater rates of morbidity and complications are well known.[47] However, RP-DCD programs in both Spain and the United States have demonstrated significantly lower rates of DGF, and this has significant associated cost savings. It is also important to consider the cost-effectiveness of RP-DCDs not on the basis of individual organs in isolation but rather on the basis of the potentially multiorgan donor. This is imperative in the case of type II RP-DCD liver transplantation: in some cases, as few as 10% of potential donors actually donated for liver transplantation, but approximately 70% of the same potential donors donated other organs.[30] This ratio is quite favorable in comparison with the proportion of potential standard DCDs in the United Kingdom who actually donate organs (390/793 or 49%).[71]

Ethical Considerations

Various ethical barriers to the widespread application of RP-DCDs exist, and they include the use of premortem cannulation and systemic heparinization, variable definitions of the standoff time, donor transport, and the theoretical potential restoration of cerebral perfusion and cardiac reanimation during RP. Overcoming such obstacles requires an appreciation of the ethicolegal frameworks that are specific to each country; as such, no common worldwide consensus is possible. In many cases, the ethicolegal barriers are inextricably linked to the technical difficulties that ensue.

Spanish law (Real Decreto 2070/1999) permits the use of RP (and the necessary interventions to perform it) until appropriate consent or judiciary approval can be obtained for organ procurement. This means that RP can commence as soon as possible so that the warm ischemia time can be kept to a minimum. In the United States, RP has been used only for controlled DCDs, and the same law applies for conventional DCDs and RP-supported donors.[34,37,38] In these cases, specific consent from the next of kin was obtained for the premortem insertion of cannulae and heparinization, and this represented a significant step in minimizing DWIT. Meanwhile, new programs in Taiwan, Japan, and Russia have not reported requiring any additional ethicolegal provisions for using RP-DCDs other than those required for DCDs.[36,39,40] In these countries, cultural and religious beliefs play an important part in the understanding of death, so the declaration of death must be performed by the local

judiciary before any organ-preserving measures and donation.

In the United Kingdom, the legal provisions and guidelines for the use of RP by ECMO and premortem interventions are somewhat complicated. The Human Tissue Act 2004 and joint guidelines from the British Transplantation Society and the Intensive Care Society state that RP is permissible so long as any possible flow of blood to the coronary arteries and cerebral circulation is prevented.[44,72] However, balloon occlusion of the thoracic aorta, as described in the protocols in this review, is considered inadequate for preventing postmortem cardiac and cerebral reperfusion. Satisfactory exclusion of the coronary and cerebral circulations from the RP circuit can be obtained only by cross-clamping of the supraceliac or thoracic aorta. In uncontrolled donors, a delaying cessation of cardiac massage is permitted to allow the organ donor register to be checked and preparations for postmortem cannulation to be made.[44] After consent has been obtained, the same guidelines apply for the cross-clamping of the aorta before RP. This may be logistically difficult and can contribute to increased DWIT if the deceased patient's family requests time with the body after the confirmation of death but before organ procurement. Premortem interventions are not lawful in the United Kingdom, and at present, there is no evidence to show that such interventions would decrease the likelihood of thrombotic events in DCDs.

Logistical Considerations

The transport of donors to an appropriate receiving center with an RP-DCD program poses further logistical difficulties. Roberts et al.[73] estimated that an uncontrolled DCD program supported by highly skilled prehospital care practitioners on board air ambulances might contribute more than 300 additional potential donors annually in the United Kingdom. Such a program would be similar to one currently in existence in Spain, where potential donors are taken by emergency ambulance directly to the nearest procurement center.[74] The importance of coordinated organ procurement efforts is highlighted by the increasing use of DCDs and the advent of new techniques such as RP. In the United Kingdom, the creation of the National Organ Retrieval Service and the placement of specialist nurses in organ donation in intensive care units throughout the country have facilitated a 50% increase in organ donation rates over the past few years.[1]

Limitations

The small number of studies included in this review reflects the emerging nature of this intervention but prohibits the formation of firm conclusions and thus represents a significant limitation. Moreover, the absence of long-term follow-up makes an accurate assessment of outcomes difficult. Variations in perfusion temperatures and prior transplant experience between centers also appear to be confounding factors. A comparison of RP-DCDs (both controlled and uncontrolled), standard DCDs, and DBDs has not yet been undertaken. Such research is required, but it may prove to be difficult because of the wide variations in the donor programs of different countries and in their religious and ethicolegal practices. The inclusion of the study by Pelletier et al.[33] (published in abstract form only) was justified by the scarcity of meaningful data from other cases of controlled NRP-DCD liver transplantation and was balanced by its valuable contribution to this review. In this instance, additional raw data (survival rates) were requested from and provided by the authors, whereas the NRP protocol was previously published in full by Magliocca et al.[37]

CONCLUSIONS

RP by ECMO is an emerging technique for improving the quality of grafts from DCDs and expanding the donor pool. RP is best delivered at normothermic temperatures, helps with the recovery of organs damaged by ischemia, and enables transplantation with acceptable survival. Subsequently, the donor pool may be increased, but these benefits must still be balanced against the recognition of significantly higher rates of PNF and IC after liver transplantation. The preliminary results for RP for category III DCDs appear promising as more liver grafts from marginal controlled DCDs are being offered for transplantation. Meanwhile, RP offers a major opportunity for reducing DGF rates after kidney transplantation. Significant ethicolegal issues exist and prevent a worldwide consensus on optimum RP protocols and an accurate appreciation of outcomes.

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