Systematic Review

Donation after circulatory death transplantation: a systematic review and meta-analysis of outcomes and methods of donation

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Background: Heart failure remains a significant cause of morbidity and mortality internationally. With significant disparities in supply and demand for donor organs and recipients, there has been a growing need to expand the donor pool. Donation after circulatory death (DCD) heart transplantation offers such a method, with ex-situ machine perfusion (ESMP) and thoracoabdominal normothermic reperfusion (NRP) offering two potential methods of procuring DCD organs. This systematic review and meta-analysis aims to evaluate the current literature and compare DCD with donation after brain death (DBD) as well as DCD methods of transplantation.

Methods: A systematic literature review was performed according to PRISMA guidelines. Primary outcomes were 30-day, 6- and 12-month survival, as well as primary graft dysfunction (PGD) and acute rejection. Secondary outcomes were length of stay (LOS), intensive care unit (ICU) LOS and temporary dialysis. Weighted averages were utilised to summarise data with funnel plots utilised for comparisons. Reconstructed Kaplan-Meier curves were utilised to evaluate mid-term survival.

Results: A total of 10 studies were included evaluating 923 DCD recipients and 7,236 DBD recipients. Survival for DCD and DBD patients at 6 months was 93% and 91% respectively [odds ratio (OR), 1.5; 95% confidence interval (CI): 1.0–2.2; P<0.05] and at 12 months 93% and 91% for DCD and DBD respectively (OR 0.77, 95% CI: 0.1–5.3, P=0.8). Acute rejection was 15% and 19% in DCD and DBD patients respectively (OR, 1.0; 95% CI: 0.6–1.8; P=0.9). Thirty-day survival was similar between NRP (96.9%) and direct procurement and perfusion (DPP) (97%) (OR, 0.8; 95% CI: 0.2–3.9; P=0.8). PGD was higher in DCD (17%) compared with DBD (8%) patients (OR, 1.9; 95% CI: 0.98–3.7; P=0.06) whilst PGD for DPP and NRP was 21% and 14% respectively.

Conclusions: DCD may offer comparable outcomes to DBD in short and mid-term outcomes, although PGD remains a concern. Further comparative research is required to delineate the role of both techniques in the current transplant landscape.

Keywords: Cardiac transplant; donation after circulatory death (DCD); *ex-situ* perfusion; thoracoabdominal normothermic reperfusion (thoracoabdominal NRP)

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Introduction

Heart failure remains a common comorbidity throughout the world, with an increasing incidence and prevalence (1). For those with end-stage heart failure and limited comorbidities, transplantation offers successful longevity with 60–80% of patients alive at five years (2-4). However, the number of patients requiring organs is greatly outweighed by the number of available organs (5). Traditionally, donation after brain death (DBD), has been the preferred method of donation. However, with the current imbalance in demand and supply, the use of hearts donation after circulatory death (DCD) has the potential to greatly expand the donor pool (6). DCD hearts have been predominantly procured using direct procurement and perfusion (DPP) techniques, which utilise ex-situ machine perfusion (ESMP) and the organ care system (OCS) (7). Recently, the use of extracorporeal membrane oxygenation (ECMO) has been utilised in DCD donors to supply normothermic perfusion to organs and facilitates assessment of the organs *in situ* with subsequent transportation on ice or with ESMP (8,9).

Unlike DBD, both techniques require a period of warm ischaemia, from the defined time of arrest to the time of procurement or administration of cardioplegia. This period of warm ischaemia has been hypothesised as a potential mechanism which may limit the viability of what may already be marginalised donors. Notably, normothermic reperfusion (NRP) has been theorised as a method to reduce warm ischaemic times and in turn reduce its impact, although direct comparative evidence with DPP is lacking. Despite this, warm ischaemia time, in conjunction with the ethical debate surrounding post-mortem instrumentation and re-animation of the arrested heart, has led to variable international uptake of the technique.

Whilst an increasing amount of promising literature continues to be published, comparative data of both DCD techniques and between DCD and DBD is lacking with cohorts largely observational and consisting of small sample sizes. Subsequently, this systematic review and meta-analysis was performed to summarise the current literature and outcomes for both techniques.

Methods

Literature review

A systematic literature search was undertaken according to PRISMA guidelines. The search strategy can be seen in Tables S1-S5. EMBASE, Medline and Cochrane databases were searched as were Trove, Proquest, CINAHL and Clinical Trials databases. Articles were searched from inception to January 2024. References of selected studies were also searched. Literature search was undertaken by two reviewers (J.J.) and (L.Z.) with disagreements settled by a third reviewer (John Brookes). Risk of bias was assessed with either the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool, for non-randomised studies or the Risk of Bias 2 (ROB-2) tool, used for randomised studies (10,11). Risk of bias was assessed by two reviewers (J.J.) and (John Brookes) and disputes settled by a third reviewer (M.W.).

Data extraction, storage and statistical analysis

After conducting the literature search all articles were downloaded onto Endnote. Once all articles were selected, data was extracted onto a Microsoft excel spreadsheet. Primary outcomes were last recorded mortality, acute rejection and primary graft dysfunction (PGD). Secondary outcomes included mechanical circulatory support as defined by the use of intra-aortic balloon pump (IABP), ECMO or implantation of a ventricular assist device (VAD). Additional secondary outcomes included, intensive care unit (ICU) length of stay (LOS), hospital LOS, need for temporary or permanent dialysis and post-operative and greater than 6-month left ventricular ejection fraction (LVEF%). Data extraction was undertaken by two reviewers (J.J.) and (John Brookes) with discrepancies settled by a third reviewer (M.W.).

Weighted averages were calculated, for all characteristics with dichotomous data displayed as a number and percentage and continuous data displayed as a mean and standard error (SE). Methods of calculation were adopted from the Cochrane Handbook Version 6.5, Chapter 10 (12), with weighted pooled means and SE calculated utilising Comprehensive Meta Analysis (Version 4, Englewood, NJ, USA) and dichotomous data calculated utilising MedCalc (Medcalc Software Ltd., Version 23.09, Ostend, Belgium). Comparisons were made between DCD methods (DPP *vs.* NRP) as well as between DCD and DBD. For dichotomous data, odds ratios (ORs) were utilised whilst for continuous data, weighted differences were utilised, with a P value of <0.05 considered to be statistically significant. Dichotomous data was displayed as a number and percentage, whilst continuous data was displayed as a mean and 95% confidence interval (CI). Comparative data was represented

utilising forest plots. Meta-analysis of data utilised a random effects model to account for the likely differences in effect estimates between studies due to the pre-empted heterogeneity between these studies and their techniques.

Time to event mortality data at were reconstructed from Kaplan-Meier curves published in the included studies, where available, as outlined by Guyot *et al.* (13). Heterogeneity was assessed utilising I^2, Chi^2 statistics and Tau^2 statistics with a P value of <0.05 used to assess the likelihood of heterogeneity. An I^2 statistic of 0–40% suggests heterogeneity is unlikely important, 41–50% may represent moderate heterogeneity, 51–74% representing severe heterogeneity and 75–100% representing considerable heterogeneity. A random effects model was utilised given the likely heterogeneity between techniques and institutions. Publication bias was assessed utilising a funnel plot and Egger's test in the instance of more than ten papers being analysed (14). Data was calculated utilising R (Version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria), MedCalc (Medcalc Software Ltd., Version 23.09, Ostend, Belgium), Comprehensive Meta Analysis (Version 4, Englewood, NJ, USA) with DigitizeIT (Version 2.5.9, Digital River GmbH, Cologne, Germany) used to extract Kaplan-Meier data.

Eligibility criteria

Studies were included if they evaluated adult patients who underwent heart transplantation utilising DCD donors, either with NRP or DPP. Observational studies and randomised control trials were included. Grey literature including conference abstracts were included. Case reports, systematic reviews, narrative reviews, and expert opinions were excluded. If studies had overlapping data, those with the most recent, the largest sample size or with the most relevant data with respect to the primary and secondary outcomes were chosen and the others excluded. Studies which did not include heart transplantation or those where data regarding heart transplantation could not be extracted or were not supplied by authors were excluded. Studies which included only those undergoing DBD transplantation were excluded. Studies which did not include primary outcome data were also excluded.

Results

Systematic review of the literature revealed 784 articles of which 242 were duplicates, as seen in *Figure 1*. After removal of duplicates and screening of titles and abstracts, 90 papers were left for full review. Fifty-three papers were excluded due to overlapping cohorts or being derived from the same datasets (15-66), 24 papers were excluded due to inappropriate outcomes or lack of primary outcome data (6,9,67-88), one was excluded due to analysing DBD only (89), another paper excluded as it did not include cardiac transplant (90) and one due to mixed paediatric and adult patients without delineating cohorts (91). Subsequently, ten articles were included in the final review as seen in *Table 1* (92-101). Seven studies directly compared DBD with DCD (92-94,96,98,100,101). One study was a randomised control trial (100), seven were observational studies (92,93,95-98,101) and two were conference abstracts (94,99). All studies evaluated DPP, whilst only four studies published the use of NRP (*Table 1*) (92,94,96,98), with one study not differentiating outcomes between NRP and DPP (101). Detailed summary of risk of bias assessments can be found in Tables S6,S7. Five studies were considered to be high risk of bias (93,96-98,101), with one moderate risk of bias (95) and the other of low risk of bias (92). Schroder *et al.*'s. RCT was of high risk of bias which was largely driven by unbalanced baseline demographics suggestive of inconsistencies with the randomisation process potentially owing to the fact that there was no blinding (100). Publication bias was unable to be assessed due to too few studies included in meta-analysis.

Baseline demographics

A total of 923 and 7,236 patients underwent DCD and DBD transplantation respectively, with demographics outlined in Tables S8-S11 with DPP and NRP recipient demographics outlined in Tables S12-S15. The average age of DCD recipients was 53.5±1.53 years compared with 54.14±0.8 years for DBD recipients. Female patients comprised 25.85% of DCD and 33.7% of DBD recipients. Pre-operative mechanical support was utilised in 33% of DCD cases, with only two studies including data for DBD cases, in which 32–68% of patients were supported mechanically (92,101). Aetiology for recipient heart failure was inconsistently reported, with ischaemic cardiomyopathy the only result able to be pooled with 24.32% DCD and 23.22% DBD recipients suffering from the condition. Between 44.5% and 53.0% of DCD and 39.1% of DBD recipients had prior sternotomy. Prior transplant numbers were unable to be pooled for DCD patients and ranged between 1.9–6.5% (92,93,101), whilst a weighted average of

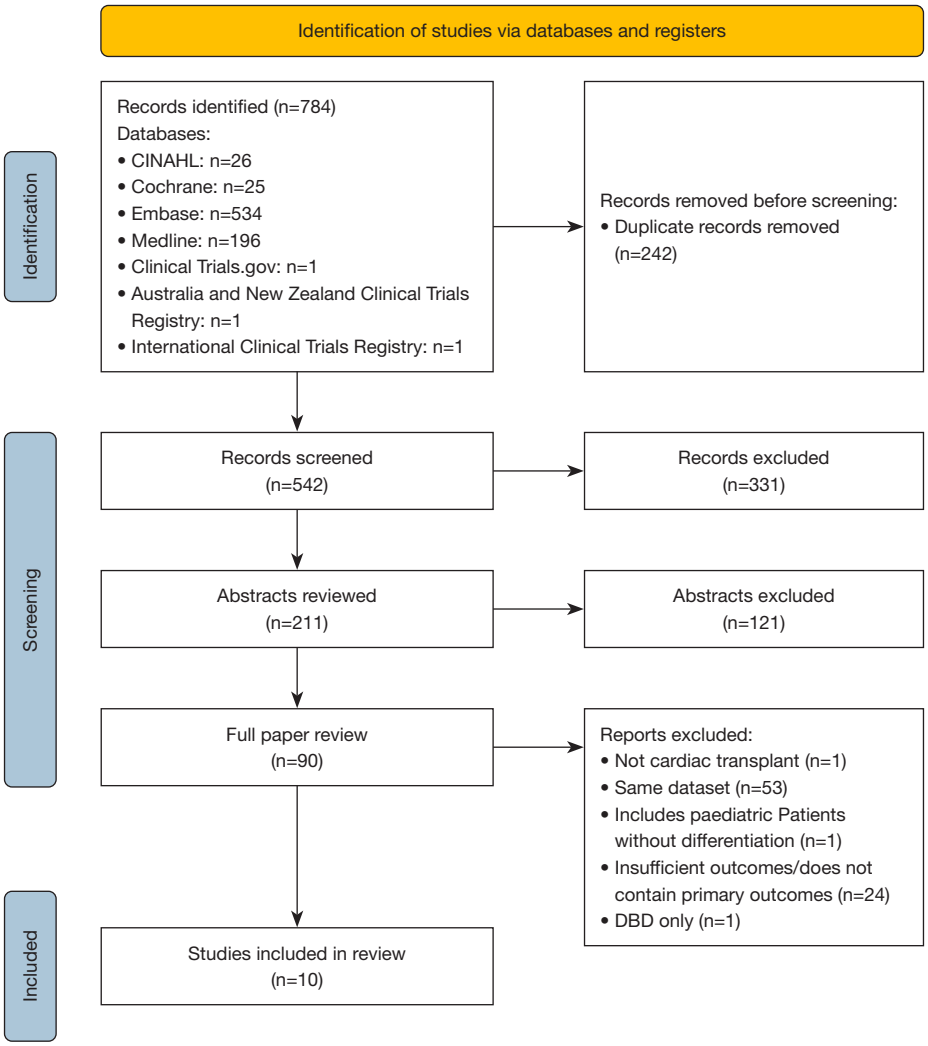


Figure 1 PRISMA flow chart. DBD, donation after brain death.

10% of DBD patients had prior transplants.

Regarding donor demographics, DCD patients had a pooled weighted average age of 30±0.8 years with 16.0% of patients being female. Comparatively, DBD donors had a pooled age of 32.8±0.8 years with 33% of donors being female. Head trauma and anoxia were the most common causes of death with 33.3% and 32.3% of DCD donors and 34.3% and 26% of DBD donors suffering from both, respectively.

DPP weighted age was 51.9±1.7 years whilst NRP age was 58.5±1.7 years. Females comprised 22.8% of DPP patients and 22.3% of NRP patients. Remaining demographic data was unavailable to pool for NRP patients. Pre-operative mechanical support for DPP patients was used in 28.8% of patients with 22.8% having prior left ventricular assist device (LVAD) implantation.

Primary outcomes

Predicted DBD and DCD survival is outlined in *Figure 2*. For DCD patients, 12-, 24-, 36-, 48- and 60-month survival was 94.5%, 92.2%, 91.7%, 90.1% and 89.5%, respectively. For DBD, survival was 90.1%, 86.7%, 83.8%, 81.6% and 80.6%, respectively. Regarding DCD, eight studies (92,94-99,101) reported 30-day mortality whilst five studies reported 6-month (92,93,97,100,101) and 12-month (95,96,98,100,101) mortality. For DBD, 30-day (92,96,98,101), 6-month (92,93,100,101) and 12-month

Table 1 Summary of included studies

Author	Patient number	Study type	Trials/registries/ institutions	Definitions of functional warm ischaemia time	Study dates	Risk of bias
Louca *et al.* [2023]	DCD =157; DBD =673	Multi-centre retrospective cohort study DCD (NRP) versus DBD	15 transplant centres (see supplementary materials)	SPB <50 mmHg → cold cardioplegia	2015–2022	High
Schroder *et al.* [2023]	DCD =90; DBD =90	Randomised control trial DPP versus DBD	Duke Medical Centre (United States)	SPB <50 mmHg, OR O_2 sats <70% → cold cardioplegia	2019–2020	Some concerns
Messer *et al.* [2020]	DCD =79: DPP =57, NRP =19; DBD =79	Single-centre retrospective cohort study DPP and NRP	Royal Papworth Hospital	SBP <50 mmHg to blood reperfusion	2015–2020	High
Coniglio *et al.* [2023]	DCD =31; DBD =54	Single centre retrospective cohort study DPP versus DBD	Duke Medical Centre (United States)	NR	2020–2021	High
Siddiqi *et al.* [2023]	DCD =122: unknown distribution of DPP and NRP; DBD =263	Sigle centre retrospective cohort study DPP and NRP versus DBD	Vanderbilt University Medical Centre	NR	2020–2023	High
Mehta *et al.* [2019]	DCD =7	Singel centre retrospective cohort study of DPP	Manchester University NHS Foundation Trust	SBP <50 mmHg to blood reperfusion	2017–2018	High
Chen *et al.* [2023]	DCD =266: DPP =175, NRP =65; DBD =5,998	Retrospective cohort study DPP, NRP versus DBD	UNOS database	NR	2019–2021	Low
Joshi *et al.* [2022]	DCD =74	Retrospective cohort study of DPP	St Vincent's Hospital Sydney Australia	Pre-2018: WLS-circulatory arrest; post-2018 SBP <90 mmHg until administration of cold cardioplegia	2014–2022	Moderate
Duran *et al.* [2023]	DCD =72: DPP =56, NRP =16; DBD =79	Abstract retrospective cohort DPP and NRP versus DBD	University of California, San-Diego	NR	2020–2022	NR
Mohite *et al.* [2022]	DCD =25	Abstract retrospective cohort study of DPP patients	Royal Brompton Hospital	NR	2015–2021	NR

DCD, donation after circulatory death; DBD, donation after brain death; DPP, direct procurement and perfusion; NRP, normothermic reperfusion; NHS, National Health Service; UNOS, United Network for Organ Sharing; SPB, systolic blood pressure; OR, operating room; O_2 sats, oxygen saturation; NR, not reported; WLS, withdrawal of life support.

(95,96,98,101) survival was reported in four studies respectively as seen in Tables S16,S17. *Table 2* outlines 30-day, 6- and 12-month mortality. Weighted survival for DCD recipients at 30 days, 6 and 12 months was 97.2%, 92.9% and 92.8%, respectively. For DBD, 30-day, 6- and 12-month weighted average survival was 95.6%, 90.7% and 90.5%, respectively. Comparative data for 30-day (92,96,98,101), 6-month (92,93,100,101) and 12-month mortality (95,96,98,101) was available in four studies respectively. No significant difference in survival was seen at 12 months between either modality, outlined in *Figure 3* with an OR of 0.77 (95% CI: 0.1–5.3, P=0.8). Heterogeneity was considered to be high with an I^2 of 95% (P≤0.0001).

Regarding DPP and NRP, only 30-day mortality data was sufficiently available for analysis, with six studies

reporting for DPP (92,94,95,97-99) whilst four were available for NRP (92,94,96,98) (Tables S18,S19). Weighted 30-day survival in those undergoing NRP was 96.9% whilst for DPP it was 97% (*Table 3*). There was insufficient data available for 6- and 12-month survival to be pooled for either intervention. However, 12-month survival for DPP patients was between 86% and 94% (95,98,100), whilst for NRP it was 93–100% (96,98). Three studies had comparative 30-day mortality data (92,94,98), with no significant difference seen between NRP and DPP with an OR of 0.8 (95% CI: 0.2–3.9; P=0.8) (*Figure 4*). Heterogeneity for 30-day mortality was low with an I^2 of 0% (P=0.9).

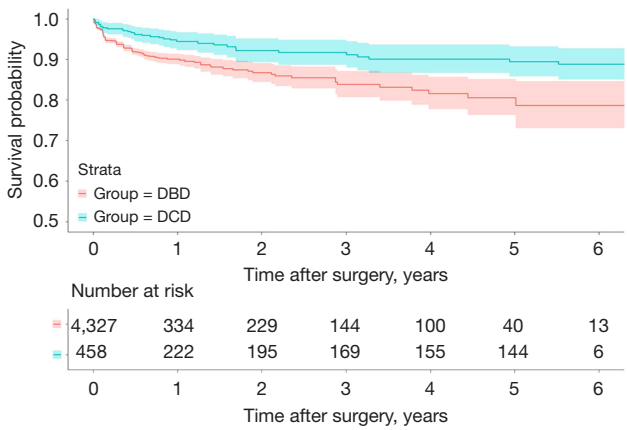


Figure 2 Kaplan-Meier curve comparing 5 survival of DCD and DBD patients. DBD, donation after brain death; DCD, donation after circulatory death.

In DCD patients, seven (93-96,98,100,101) studies reported on PGD whilst five (92,93,96,98,101) studies recorded acute rejection data, with weighted means of 17% and 15.4% respectively. For DBD patients, PGD data was recorded in five (93,96,98,100,101) studies with a weighted mean of 8%, whilst acute rejection, recorded in five studies, had a weighted mean of 19.4%. For DPP patients, PGD data was recorded in five studies (93-95,98,100) with a weighted mean of 20.5%. Whilst for NRP, recorded in three studies (94,96,98), PGD weighted mean was 14.4%. Only two studies had comparative data for PGD and thus comparative analysis was not performed. Acute rejection in DPP patients was unable to be pooled but was reported between 16% and 30% (92,93,98), whilst for NRP pooled rejection was only 9.4%. DCD carried a 1.9 times higher likelihood of PGD compared with DBD (*Figure 5*), although this did not reach significance (95% CI: 0.98–3.7; P=0.06). Heterogeneity was severe for DCD and DBD PGD comparisons with an I^2 of 61% (P=0.03). Neither intervention was associated with an increased likelihood of acute rejection (*Figure 6*).

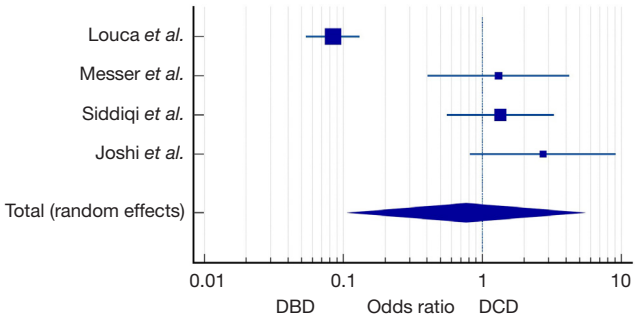
Secondary outcomes

The average LOS in DCD recipients was 19.0 days compared with 17.1 in DBD recipients, which did not reach significance (P=0.09). Heterogeneity was unlikely important with an I^2 of 0 (P=0.8) ICU LOS for DCD recipients was 8.5±1.9 days with this only recorded in one study for DBD

Table 2 DCD and DBD post-operative outcomes and weighted average

Outcome	DCD		DBD		P value	I^2 (%)
	Value	I^2 (%)	Value	I^2 (%)		
LOS, days	19.03±1.3	87.2	17.11±0.6	44.6	0.1	0
ICU LOS, days	8.5±1.9	85.5	NR	N/A	NR	NR
30-day survival (%)	97.2 (96.0–98.3)	0	95.6 (93.6–97.3)	79.3	0.07	0
6-month survival (%)	92.9 (90.5–94.9)	0	90.7 (88–93.1)	46	0.05	0
12-month survival (%)	92.8 (90–95.1)	0	90.5 (88.4–92.5)	0	0.8	95
Acute rejection (%)	15.4 (10.9–20.5)	61.7	19.4 (10.8–29.7)	92	0.9	68.2
Primary graft dysfunction (%)	17 (13.7–20.54)	24	8 (4.4–12)	68.2	0.06	61.7
Temporary dialysis (%)	33.3 (18.2–50.4)	92.8	13 (3.5–27.4)	91	NR	NR

Data are presented as mean ± SE or value (95% CI). DCD, donation after circulatory death; DBD, donation after brain death; LOS, length of stay; ICU, intensive care unit; SE, standard error; CI, confidence interval; NR, not reported; N/A, not available.



Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Louca *et al.*	67/157	381/424	0.0840	0.0538 to 0.131			65.21	26.30
Messer *et al.*	53/58	65/73	1.305	0.403 to 4.224			9.42	24.28
Siddiqi *et al.*	115/122	243/263	1.352	0.556 to 3.289			16.46	25.25
Joshi *et al.*	70/74	64/74	2.734	0.817 to 9.152			8.91	24.16
Total (fixed effects)	305/411	753/834	0.279	0.204 to 0.383	-7.891	<0.001	100.00	100.00
Total (random effects)	305/411	753/834	0.765	0.111 to 5.290	-0.271	0.786	100.00	100.00

Test for heterogeneity

Q	60.2045
DF	3
Significance level	P < 0.0001
I^2 (inconsistency)	95.02%
95% CI for I^2	90.23% to 97.46%

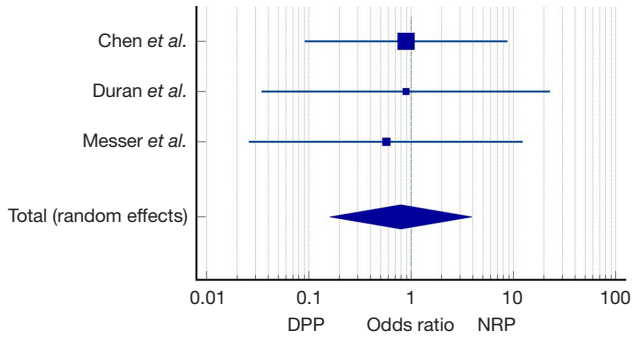
Figure 3 Forest plot of 12-month survival DCD compared with DBD. DBD, donation after brain death; DCD, donation after circulatory death; CI, confidence interval; Q, Q-score; DF, degrees of freedom.

Table 3 DPP and NRP post-operative outcomes and weighted average

Outcome	DPP		NRP		P value	I^2 (%)
	Value	I^2 (%)	Value	I^2 (%)		
LOS, days	22.3±3.5	92.7	18.19±1.01	51.2	NR	NR
ICU LOS, days	8.8±2.4	87.45	8.6±2.61	99.16	NR	NR
30-day survival (%)	97 (94.7–98.7)	0	96.9 (94.6–98.5)	0	0.8	0
Primary graft dysfunction (%)	20.5 (15.9–25.6)	0	14.4 (9.6–19.9)	12.9	NR	NR
Temporary dialysis (%)	33.3 (13.7–56.4)	54.53	19.8 (13.7–26.7)	0	0.2	0

Data are presented as mean ± SE or value (95% CI). DPP, direct procurement and perfusion; NRP, normothermic reperfusion; ICU, intensive care unit; LOS, length of stay; SE, standard error; CI, confidence interval; NR, not reported.

(*Table 2*). Post-operative mechanical support, ECMO and IABP were inconsistently reported across the included studies. ECMO support post DCD varied between 5.7–42.9% across four studies (95-98), whilst 8.3–32% (96-98) of patients required IABP post-operatively. ECMO requirements post-NRP were between 5% and 8.3% whilst for IABP it was between 5% and 26% (96,98). ECMO requirements for DPP patients were between 16% and 43% (95,97,98) and IABP requirements were only recorded in two studies which reported rates of 28.6% and 33% (97,98). In DCD patients, the weighted average temporary dialysis requirement was 33.3%, whilst for DBD it was 13%. For DPP patients, the weighted average for temporary dialysis was 33.3% whilst for NRP it was 19.8% with an OR of 0.7 (95% CI: 0.4–1.2; P=0.2) with heterogeneity unlikely to be important with an I^2 of 0 (P=0.6) (*Figure 7*).

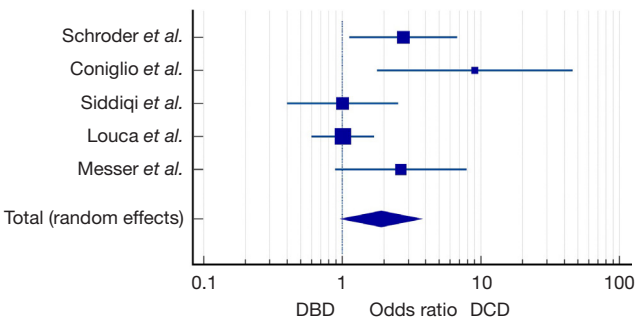


Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Chen *et al.*	172/175	64/65	0.896	0.0915 to 8.770			48.97	48.97
Duran *et al.*	16/16	55/56	0.892	0.0347 to 22.945			24.17	24.17
Messer *et al.*	55/57	19/19	0.569	0.0262 to 12.385			26.87	26.87
Total (fixed effects)	243/248	138/140	0.782	0.161 to 3.799	-0.305	0.760	100.00	100.00
Total (random effects)	243/248	138/140	0.792	0.161 to 3.910	-0.286	0.775	100.00	100.00

Test for heterogeneity

Q	0.06079
DF	2
Significance level	P = 0.9701
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00% to 0.00%

Figure 4 Forest plot of 30-day survival DPP compared with NRP. DPP, direct procurement and perfusion; NRP, normothermic reperfusion; CI, confidence interval; Q, Q-score; DF, degrees of freedom.

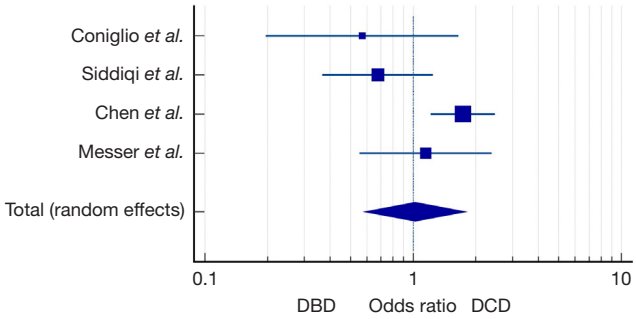


Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Schroder *et al.*	18/80	8/84	2.758	1.124 to 6.769			16.99	21.30
Coniglio *et al.*	8/31	2/54	9.043	1.780 to 45.945			5.18	11.39
Siddiqi *et al.*	7/122	15/263	1.006	0.399 to 2.535			16.04	20.83
Louca *et al.*	20/156	85/670	1.012	0.601 to 1.705			50.34	28.52
Messer *et al.*	12/79	5/79	2.651	0.887 to 7.919			11.44	17.97
Total (fixed effects)	65/468	115/1150	1.553	1.097 to 2.200	2.481	0.013	100.00	100.00
Total (random effects)	65/468	115/1150	1.909	0.977 to 3.733	1.891	0.059	100.00	100.00

Test for heterogeneity

Q	10.4379
DF	4
Significance level	P = 0.0337
I^2 (inconsistency)	61.68%
95% CI for I^2	0.00% to 85.58%

Figure 5 Forest plot of PGD DCD compared with DBD. DBD, donation after brain death; DCD, donation after circulatory death; CI, confidence interval; Q, Q-score; DF, degrees of freedom; PGD, primary graft dysfunction.

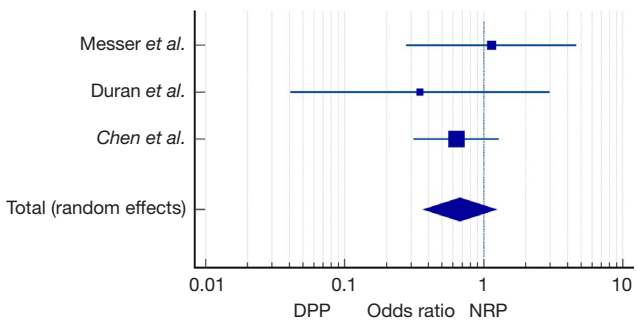


Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Coniglio *et al.*	6/31	16/54	0.570	0.196 to 1.654			6.59	16.30
Siddiqi *et al.*	16/122	48/263	0.676	0.367 to 1.247			19.99	26.63
Chen *et al.*	38/266	525/5998	1.737	1.218 to 2.478			59.40	33.57
Messer *et al.*	20/79	18/79	1.149	0.553 to 2.385			14.02	23.51
Total (fixed effects)	80/498	607/6394	1.201	0.910 to 1.585	1.292	0.196	100.00	100.00
Total (random effects)	80/498	607/6394	1.022	0.581 to 1.800	0.0770	0.939	100.00	100.00

Test for heterogeneity

Q	9.4420
DF	3
Significance level	P = 0.0240
I^2 (inconsistency)	68.23%
95% CI for I^2	7.80% to 89.05%

Figure 6 Forest plot of acute rejection DCD compared with DBD. DBD, donation after brain death; DCD, donation after circulatory death; CI, confidence interval; Q, Q-score; DF, degrees of freedom.



Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Messer *et al.*	10/57	3/19	1.135	0.277 to 4.645			18.40	18.40
Duran *et al.*	1/16	9/56	0.348	0.0407 to 2.978			7.94	7.94
Chen *et al.*	28/175	15/65	0.635	0.314 to 1.284			73.66	73.66
Total (fixed effects)	39/248	27/140	0.665	0.367 to 1.204	-1.347	0.178	100.00	100.00
Total (random effects)	39/248	27/140	0.674	0.368 to 1.233	-1.281	0.200	100.00	100.00

Test for heterogeneity

Q	0.9181
DF	2
Significance level	P = 0.6319
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00% to 92.69%

Figure 7 Forest plot of temporary dialysis in DPP compared with NRP. DPP, direct procurement and perfusion; NRP, normothermic reperfusion; CI, confidence interval; Q, Q-score; DF, degrees of freedom.

Discussion

The significant and ever-growing demand for donor hearts and the disproportionate lack of DBD donors has driven an innovative wave of DCD donation. This analysis demonstrates that DCD donation, in particular the DPP method, offers similar short-term mortality compared with DBD donation as well as acute rejection rates. Moreover, predicted five-year freedom within this analysis was superior in the DCD group mortality at 89.5% compared with 80% for DBD (P<0.001), Notably, at 5 years there was considerable loss to follow up in the DBD group, which may have resulted in an overestimation of the recorded 80% predicted survival, resulting in type 1 error. However, similar findings for five-year survival have been recorded in the literature for DBD patients ranging from 60–80% (102,103), while 6- and 12-month survivals were similar between DCD and DBD cohorts. Conclusions surrounding NRP and DPP are unfortunately limited by the few studies reporting comparisons on these different procurement methods. Based on this analysis, no significant differences in 30-day mortality were seen. Similar survival for both DPP and NRP were recorded between studies with 12-month survival for NRP between 93–100% (96,98), whilst for DCD survival ranged between 86% and 93% (98,100), once again similar to those reported in DBD cohorts.

Whilst survival was similar, patients receiving DCD donor organs were observed at having double the incidence of PGD, seen in 17% of DCD patients and 8% of DBD patients, although meta-analysis did not reach the confidence threshold (OR 1.9, 95% CI: 0.98–3.7; P=0.06). This result may reflect the impact of Siddiqi *et al.* and Louca *et al.* whose cohorts experienced no significant differences in PGD between DCD and DBD (96,101). Notably, they had the largest cohorts, contributed the most weight and unlike the other studies within the PGD analysis, either exclusively utilised NRP (96), or predominantly utilised NRP (101). Additionally, for DPP recipients, PGD occurred in 21% of cases whilst for NRP it was 14%. Moreover, Duran *et al.*'s evaluation of NRP recipients demonstrated 20% of their patients experienced significant PGD post-operatively, which is still less than the DPP group where 37.5% experienced PGD (94). Therefore, the non-significant findings may be the result of NRP's inclusion in the DCD cohorts when comparing against DBD. However, without direct comparative data from similar cohorts and institutions, it is difficult to conclude that NRP procurement method results in reduced rates of PGD, however preliminary findings from this analysis of pooled data suggests this may be the case. The relationship of PGD with mortality was not investigated in these studies and insufficient data was available for meta-regression. However, with similar mortality and rejection rates it appears the relationship with PGD does not impact these factors in the short to medium term. Coniglio *et al.*'s cardiac magnetic resonance imaging (MRI) evaluation in the immediate post-operative period also demonstrated no significant differences in scarring or fibrosis between DCD and DBD recipients adding further reassurance to the transient nature of PGD (93). The mechanisms behind the increased rates of PGD are currently debated. Hypothesised to contribute significantly is the warm ischaemic time that is imposed in DCD patients (104-107). The resultant anaerobic respiration, intra-cellular acidosis, intra-cellular accumulation of calcium and generation of free radicals results in cardiomyocyte dysfunction and potentiates reperfusion hyper-contracture increasing wall stiffness and end-diastolic pressures (5,108,109). Unfortunately, functional warm ischaemic time (FWIT) was unreliably reported, with six studies including their ischaemic data (94-99). NRP recipients in Messer *et al.*'s study were afforded significantly less FWIT compared with DPP recipients, which did result in a non-statistically significant difference in PGD (5% versus 18%) (98). Similarly, Duran *et al.* demonstrated similar FWIT between both groups, with higher PGD in those undergoing DPP compared with NRP (Table S20) (94). Disparities in the relationship between PGD and FWIT may be, in part, influenced by how FWIT is defined, with heterogenous definitions across institutions (*Table 1*). Notably, four studies utilised a systolic blood pressure (SBP) of <50 mmHg (96-98,100) with one study utilising an SBP of <90 mmHg (95), whilst end points were either the time of administration of cold cardioplegia or at the time of reperfusion. Additionally, in Joshi *et al.*'s study, their initial population was received from donors whose FWIT was from withdrawal of life-sustaining treatment. Ultimately these ranging definitions result in differing 'FWIT' and in part may explain the differences seen in PGD. Unfortunately, studies in this analysis that utilised the same criteria didn't completely capture their PGD data and thus the contribution these heterogenous definitions play cannot be concluded. Furthermore, some studies within this analysis included their PGD data without reporting FWIT times, likely due to the heterogenous definitions used by the centres included in the registry and the inaccuracy

pooling this data would cause (101). One concept worth consideration is that of asystolic warm ischaemic time (aWIT), which was analysed by Joshi *et al.* (95). They defined this as time from circulatory arrest to delivery of cardioplegia. It was found that prolonged aWIT was significantly associated with ECMO requirement in PGD patients, with FWIT not significantly different between ECMO and non-ECMO patients. Similar findings have been reproduced in abdominal organ transplant studies with respect to poor PGD (110,111). Only Joshi *et al.* and Messer at al. captured aWIT, with Joshi *et al.* being the only one to evaluate its impact on PGD. The findings from this analysis do suggest that DCD results in higher rates of PGD with minimal impact on mortality or acute rejection. It is likely that warm ischaemic times play a role in this, however the degree to which this occurs and measures to minimise it will need to be investigated further to understand its impact.

When considering method of DCD transplantation, NRP offers theoretical advantages. Firstly, it allows for more rapid reperfusion, minimising FWIT and aWIT, which may reduce PGD. As demonstrated in this analysis, FWITs were shorter in NRP recipients and may offer reductions in PGD, although the degree to which could not be directly compared. Only one study evaluated aWIT in this cohort, but when compared with OCS, this was significantly less, seen at fourteen minutes compared with twenty-two minutes. However, these numbers were similar to the OCS group in Joshi *et al.*'s paper with a time of thirteen minutes. Conversely, FWIT was identical between groups in Duran *et al.*, with higher PGD in the OCS group, which was less than that seen by Joshi *et al.* These conflicting findings reflect several factors. Firstly, comparison numbers between groups were uneven with Duran *et al.* only evaluating sixteen DPP patients compared with 56 NRP patients, whilst Messer *et al.* evaluated nineteen NRP patients compared with 57 DPP patients, of which neither matched their groups. Comparisons are therefore difficult as it is likely numbers were insufficient to generate enough power to establish the true effect. Additionally, DPP's small aWIT in Joshi *et al.* in conjunction with them having produced the lowest rates of PGD out of all the included studies may reflect local expertise and experience in a procedure and its post-operative management which may not be readily performed in other centres or jurisdictions, such as those in Duran *et al.* The other theorised advantage of NRP is the ability for *in-situ* functional assessment and concomitant NRP of abdominal organs at the same time of organ procurement. It is suggested that this may yield acceptance of older more marginal donors and result in fewer hearts being discarded (112-116). However, pooled analysis yielded similar donor ages and thus currently this theory has not been eventualised within the literature.

Ultimately, both techniques are shaping to be viable options for DCD procurement and it is likely with adequate support, planning and surgeon/facility expertise both options will continue to yield acceptable mortality and morbidity. Plaguing their further use will be the cost involved of supporting the donor organ in an *ex-situ* environment, ethical considerations surrounding the post-mortem instrumentation and re-animation of the NRP donor and their equitable distribution and access to those within marginalised communities or those not within major metropolitan centres. In particular for NRP, this will be a unique challenge in a country such as Australia, due to the significant geographical distance between fringe hospitals and regional community donation sites. This is perpetuated by the requirements for either the donor hospital to have equipment available to institute NRP or for the receiving transplant centre to facilitate the equipment's transport, a current advantage of the DPP.

A recent meta-analysis evaluating DCD outcomes demonstrated similar findings within this review (117). In particular, findings pertaining to increased PGD, similar rates of acute rejection and mortality to those seen within this analysis were observed, although risk of death at five years was lower in their DBD cohort. Whilst promising, several methodological differences exist between analysis. Firstly, whilst noted in their exclusion criteria, papers with overlapping cohorts were still included within their analysis which may have falsely increased the precision and magnitude of their effect estimates. Additionally, this analysis included grey literature minimising publication bias and mitigating positive effect bias. Moreover, the literature search for this review yielded a greater breadth of NRP recipients, allowing for an early comparison of DCD techniques, which is a first in current literature.

Limitations

Several limitations need to be considered when interpreting the findings of this analysis. Firstly, all but one study was observational in nature, two of which were abstracts and five of which were of high risk of bias. These studies were of significant risk of publication and reporting bias with several studies failing to report on key outcomes such as post-operative mechanical support and PGD, and failing

to include in the main text or supplementary material data on certain subgroups but not others. Schroder *et al.*'s RCT was also subject to some bias introduced through failed allocation concealment and differences between groups which reflected issues within the randomisation process. Significant heterogeneity in key outcome measures were encountered, in particular 12-month mortality, PGD and acute rejection in DCD versus DBD. With respect to PGD, the differing methods of transplantation, i.e., use of NRP or DPP or both, may have been significant contributors for heterogeneity, especially given pooled data may indicate reductions in PGD. With respect to mortality, several contributors likely factor which include differences in post-operative management, expertise and familiarity with particular procedures, inconsistent definitions of warm ischaemic time and PGD, and methods of transportation post NRP with some studies electing to transport their heart on ice whilst others would use *ex-situ* perfusion. Given the limited number of studies, publication bias was unable to be assessed.

Conclusions

Early and mid-term data suggests DCD transplantation methods may offer a viable option for cardiac transplantation. Such technology provides the world with the opportunity to expand its donor pool and relieve some of the disparaging burden between supply and demand. Within the limitations of this analysis, DCD may offer similar mid-term survival akin to that of DBD, however larger numbers at mid-term follow up will be required to confirm these findings. Additionally, PGD remains a concern albeit one that does not appear to impact mortality or rejection rates. Encouragingly, NRP and DPP both present themselves as potential alternatives, although superiority of one over the other cannot be concluded from this study, with too few papers in the literature encompassing or reporting NRP outcomes. It is possible that NRP offers a method of donation that minimises warm ischaemic time which may be associated with a reduction in rates of PGD, however more research in experienced centres with direct comparison to DPP methods of transplantation will be required to truly evaluate its role in the current landscape.

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