Ex-vivo Heart Preservation

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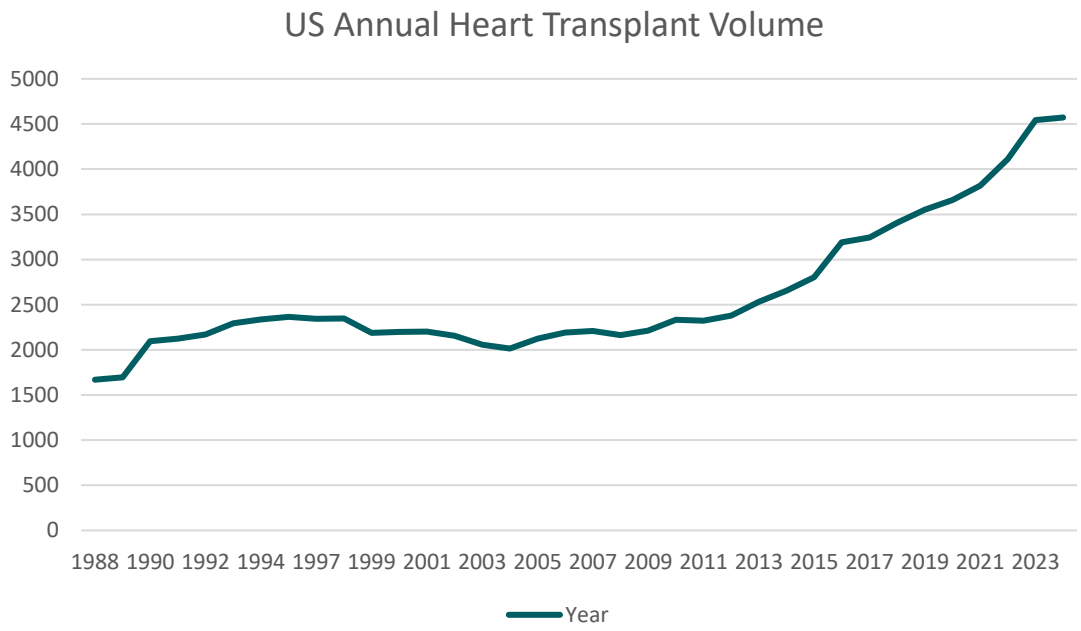
Relevant Financial Relationship Disclosure Statement

I have no relationships to disclose.

Epidemiology

Heart transplantation as a treatment modality for advanced heart failure

- 6.7 million US adults living with heart failure
- Just under 700,000 deaths (~20%) annually from heart disease
  - Heart failure attributed to 456,000 deaths (13.9%)



SRTR/OPTN 2025

Donor Pool Expansion

Extended donor criteria (EXPAND criteria)*

1. Anticipated ischemic time > 4 hours or anticipated time > 2 hours and:
   - -Age > 55y or age 45-55y with no cath
   - -LVH (13-16mm);
   - -LVEF 40-50%
   - -Downtime > 20 min
   - -DM, CO toxicity, coronary artery disease
2. Limitation to acceptance: Concerns of elevated risks to recipient

Donation after circulatory death (DCD) traditionally not deemed suitable for use in heart transplantation

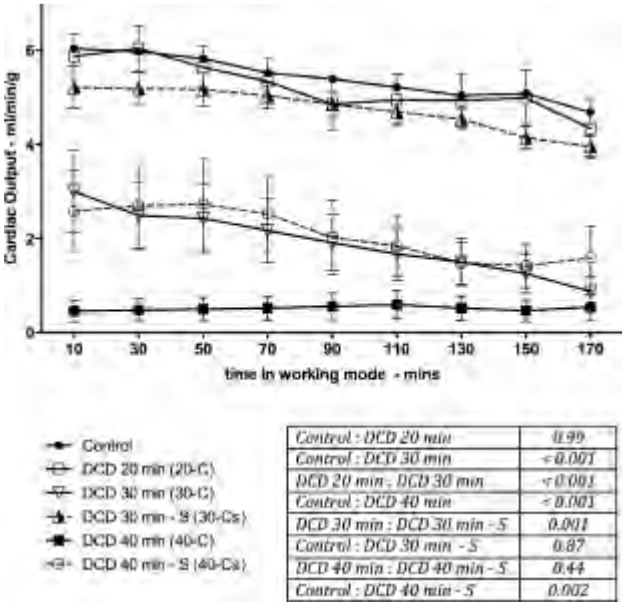
1. Concern for prolonged warm ischemic time
   leading to hypoperfusion, LV distention, end-organ ischemia
2. Combined with inability to assess allograft function prior to implantation (with standard DBD techniques)

*Schroder JN, et al. JHLT. 2022;41(4S):S73

Overcoming concerns for DCD heart transplantation

Prolonged ischemic time

- Limit functional warm ischemic time to 30 minutes
  - Large animal experiments suggest ~ 40 min ischemia before necrosis*
  - Pig hearts at 20 min warm ischemic or 30 min with supplemented cardioplegia have complete recovery**
- Case report: Human in situ heart successful resuscitation with cardiopulmonary bypass
  - Functional warm ischemic time 23 minutes***



Control : DCD 20 min	0.99
Control : DCD 30 min	< 0.001
DCD 20 min : DCD 30 min	< 0.001
Control : DCD 40 min	< 0.001
DCD 30 min : DCD 30 min - S	0.001
Control : DCD 30 min - S	0.87
DCD 40 min : DCD 40 min - S	0.44
Control : DCD 40 min - S	0.002

*Gundry SR, et al. Ann Thorac Surg. 1992 May;53(5):772-4
Danforth WH, et al. Circ Research. 1960 Sept;8(5):965
**Iyer A, et al. American Journal of Transplantation 2014; 14: 1744–1752
**Ali A, et al. JHLT. 2009 28:290

Overcoming concerns for DCD heart transplantation

Allograft assessment - 2 techniques for DCD procurement

1. Thoracoabdominal normothermic regional perfusion (TA-NRP) in situ resuscitation and assessment
    - Functional assessment under conditions mimicking typical physiologic conditions, e.g. RHC, TEE
    - Biomarker assessment, e.g. lactic acid, troponin

2. Direct heart procurement (typically) and perfusion (DPP) – machine perfusion (MP)

    A. Techniques

        Normothermic machine perfusion (NMP)

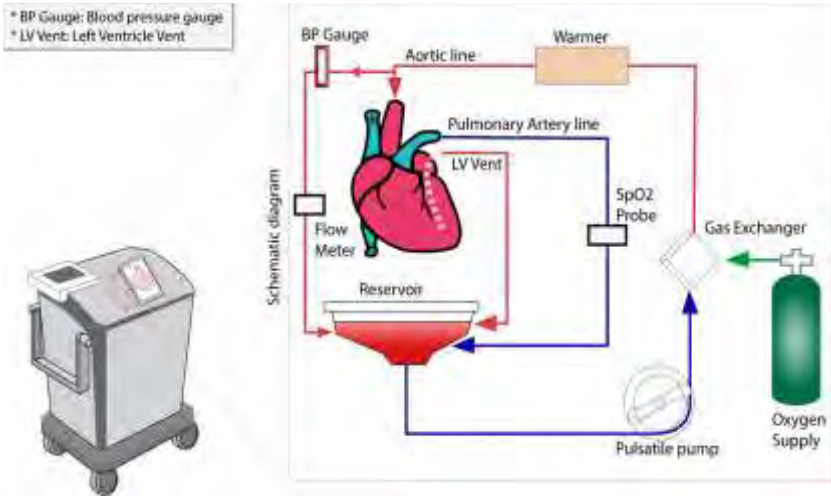
        Hypothermic machine perfusion (HMP)

    B. Addressing concerns related to:
    - Ex situ perfusion time
    - Warm and cold ischemic times
    - Ex situ assessment

Normothermic Machine Perfusion Procedure

Organ Care System (OCS) by Transmedics, Inc.

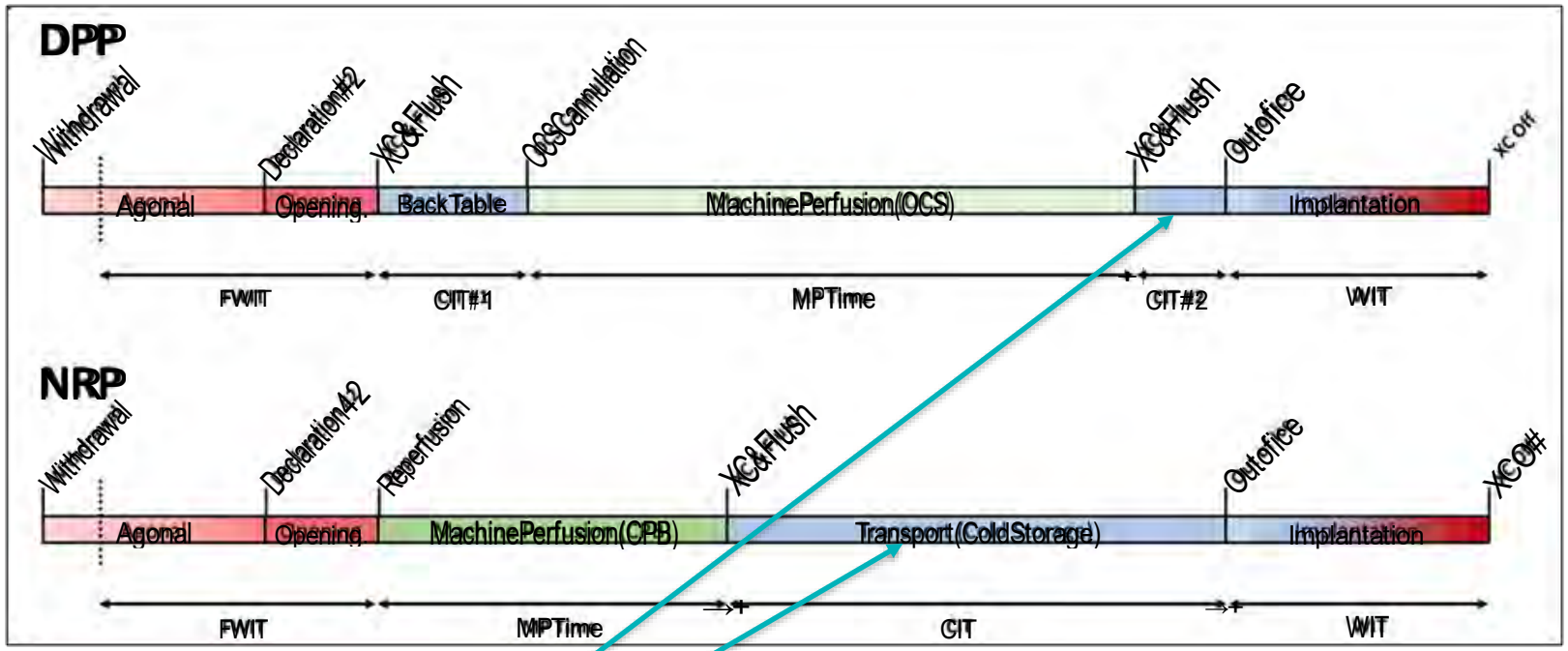
- The only commercially available and clinically approved device



Procedural highlights

- Prior to aortic cross clamp, ~1500 cc of blood removed to prime OCS
- Cross clamp applied and cardioplegia administered
- Cardiectomy performed
    - SVC/IVC closed
    - Aorta and PA cannulated
    - LV vented via LA across MV
    - Connected to circuit and perfused with blood mixed with proprietary solution (steroid, antibiotic, dextrose, heparin, insulin, electrolytes)

Cold Ischemic Time



With DCD donation, the care is withdrawn, and the donor is allowed to expire. The donor reaches a period of low perfusion (agonal phase), typically defined as systolic blood pressure <50 mmHg and oxygen saturation <70%. The time from when the agonal phase begins to cold organ flushing (in DPP) or machine perfusion (NRP) is the functional warm ischemic time (f-WIT). *Courtesy of Lee C, Tsai C, Adler E, Pretorius V.*

DPP = direct procurement and machine perfusion, NRP = normothermic regional perfusion, f-WIT = functional warm ischemic time, XC = aortic cross clamp, MP = machine perfusion, CIT = cold ischemic time, WIT = warm ischemic time

Reducing cold ischemic time

Lee C, et al. ACC Latest in Cardiol. 2022

Cold Ischemic Time

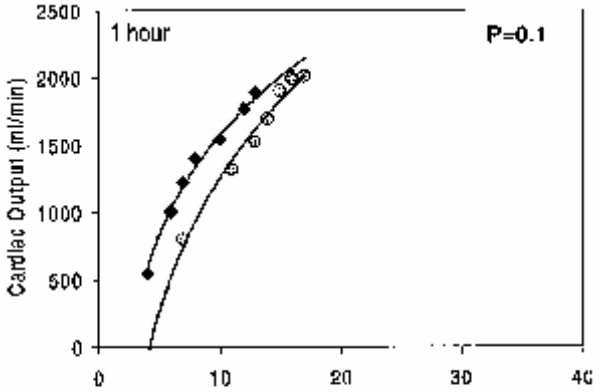
Basic Science/Large Animal Studies

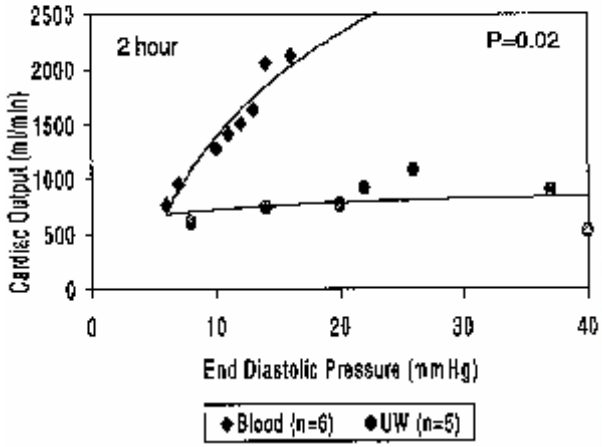
Multiple studies have demonstrated deleterious effects of cold static storage (CSS) on endothelial and myocardial function*

CSS associated with accumulation of:

- free radicals accumulation, lactic acidosis,cellular edema
- Leading to increase intracellular Na+
- And then cytosolic Ca++ increases
- Implicated in ischemia-reperfusion injury

Typically limited to 4-6 hours





*Parolari A, et al. Ann Thorac Surg 2002;73:682–90

**Hassanein WH, et al. J Thorac Cardiovasc Surg 1998;116:821-30)

Cold Ischemic Time

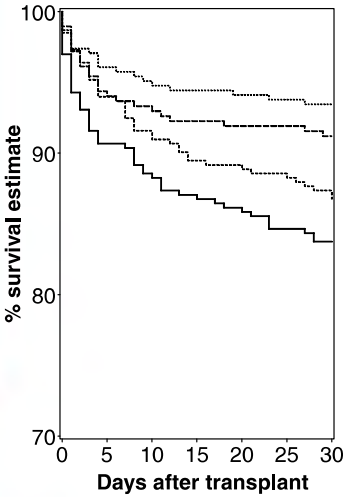
Clinical Correlation

UKT Registry 1986-2005*

- For each additional hour of ischemic time, 25% increased risk of mortality in first year, followed by a 5% increased mortality risk

Clinical correlate: UK Cardiothoracic Transplant Audit database analysis April 1995-March 2004**

- Ischemic time directly correlates with 30d mortality



IT (mins)	Number at risk at day 0	% survival estimate	95% CI
<155	305	93	90 – 96
155-189	284	91	87 – 94
190-229	332	87	83 – 90
≥230	332	84	79 – 87

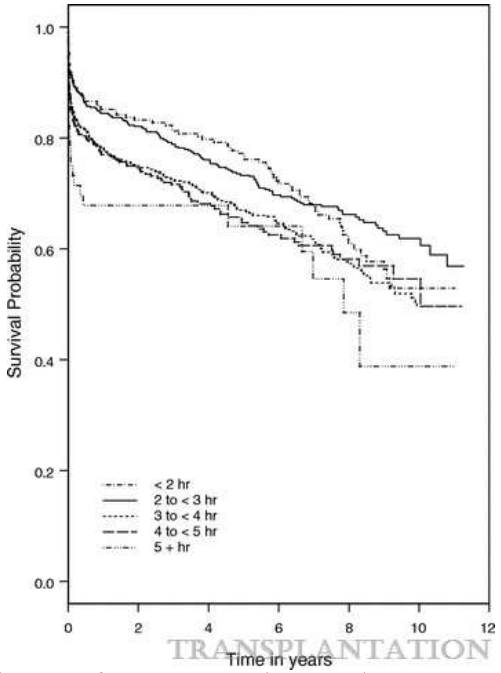


TABLE 2. Influence of transport and implant times on 30-day mortality in the logistic regression model

Parameter	Odds ratio	95% Confidence interval for odds ratio	*P*
Transport time (per 15-min increment)	1.06	1.01–1.12	0.0283
Surgical implant time (per 15-min increment)	1.11	1.04–1.18	0.0012

Model also included adjustment for recipient peripheral vascular disease, recipient ventilation, diabetic recipient, recipient creatinine clearance less than or equal to 50 mL/min at transplant, more than one previous open heart operation, donor age, and recipient adult congenital heart disease.

*Goldsmith KA, et al. Transplantation.2009; 87(2):243.

**Banner NR, et al. *Transplantation* 2008;86: 542–547

Cold Ischemic Time

Counter-point

Of note, single center studies have not noted a correlation with cold ischemic time and mortality*

Paragonix SherpaPak GUARDIAN Registry

- Reliable temperature regulation may extend limits of cold ischemic time for SCS?**

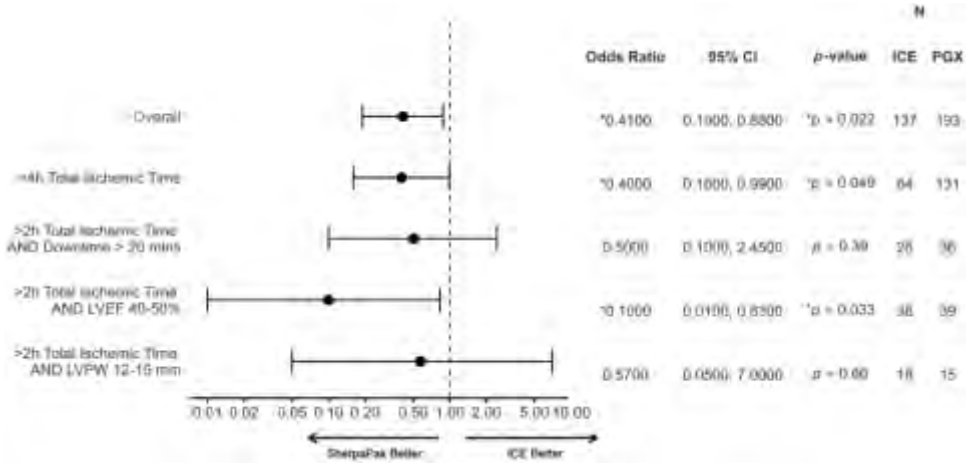
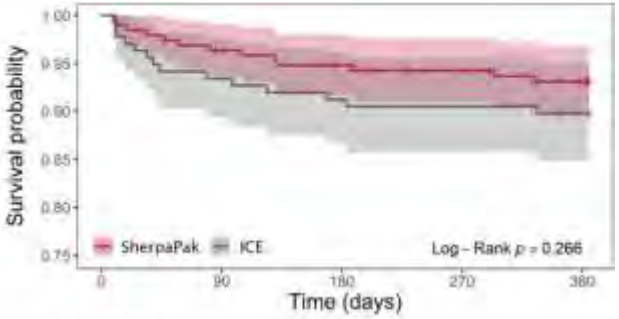


Table 3 Posttransplant Outcomes After Extended Donor Heart Transplants in the Two Study Cohorts

Variables	Ice (n = 137)	SherpaPak (n = 193)	p-value
Time to first wean	77.4 ± 79.7	75.8 ± 88.0	0.87
Number of attempts to wean	1.1 ± 0.44	1.2 ± 0.70	0.30
All post-Tx MCS	48/137 (35.0%)	43/193 (22.3%)	0.012
New post-Tx IABP	20/137 (14.6%)	19/193 (9.8%)	0.23
New post-Tx ECMO/VAD	21/137 (15.3%)	15/193 (7.8%)	0.033
PGD	35/137 (25.5%)	28/193 (14.5%)	0.015
PGD severe[a]	19/137 (13.9%)	12/193 (6.2%)	0.022
LVEF at 24 hours (%)	53.0 ± 14.0	57.1 ± 12.5	0.012
In-hospital survival	130/137 (94.9%)	189/193 (97.9%)	0.21
30-day survival	132/137 (96.4%)	190/193 (98.4%)	0.28
1-year survival	121/135 (89.6%)	156/168 (92.9%)	0.41

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; PGD, primary graft dysfunction; Tx, transplant; VAD, ventricular assist device.

[a]Note: Severe PGD is defined by the need for new ECMO/VAD use initiated within the first 24 hours posttransplant.



*Morgan JA, et al. 2003 Nov;126(5):1624

*Mitropoulos FA, et al. 2005;28(1):143

**Moayedifer R, et al. JHLT. 2024.

Ex situ Assessment

Allograft assessment

OCS Module Measurements	Laboratory Studies	Surgical Interrogation
Aortic pressure	Lactate absolute value	Ex-vivo coronary angiography
Coronary flow	Lactate differential between arterial and venous blood	Clinical evaluation
Blood temperature	Calcium levels	
Heart rate	Potassium levels	
Mixed venous oxygen saturation		
Pulmonary artery pressures		

Heart maintained in the unloaded state

Mean aortic pressure 60-90 mm Hg
Coronary flow 650 – 850 cc/min
Temperature at 34°C (normothermic)

*Ardehali A, et al. Lancet 2015;385:2577

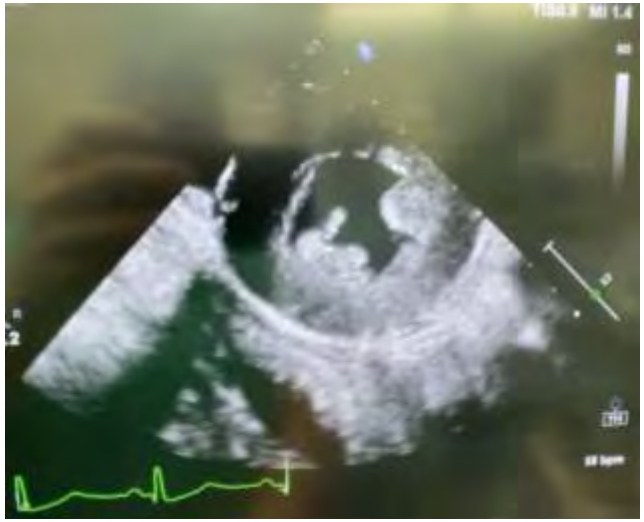
Ex situ Assessment

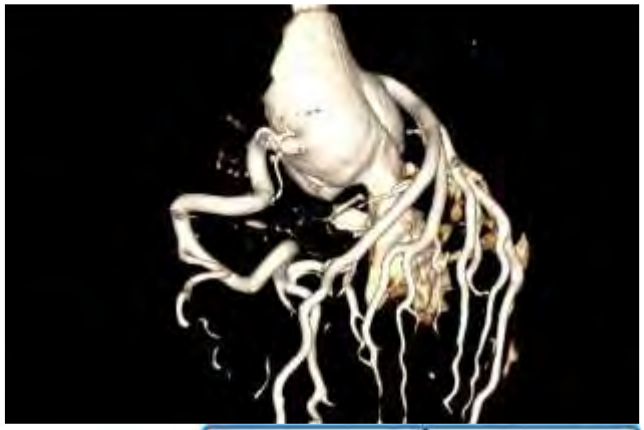
Ex situ assessment

Biomarker
Lactic acid
- Early global OCS experience (N=49)
    - Lactic acid 4.96mmol associated with 30d graft failure (sensitivity 0.625, specificity 0.975)*

Physical inspection
Unloaded heart

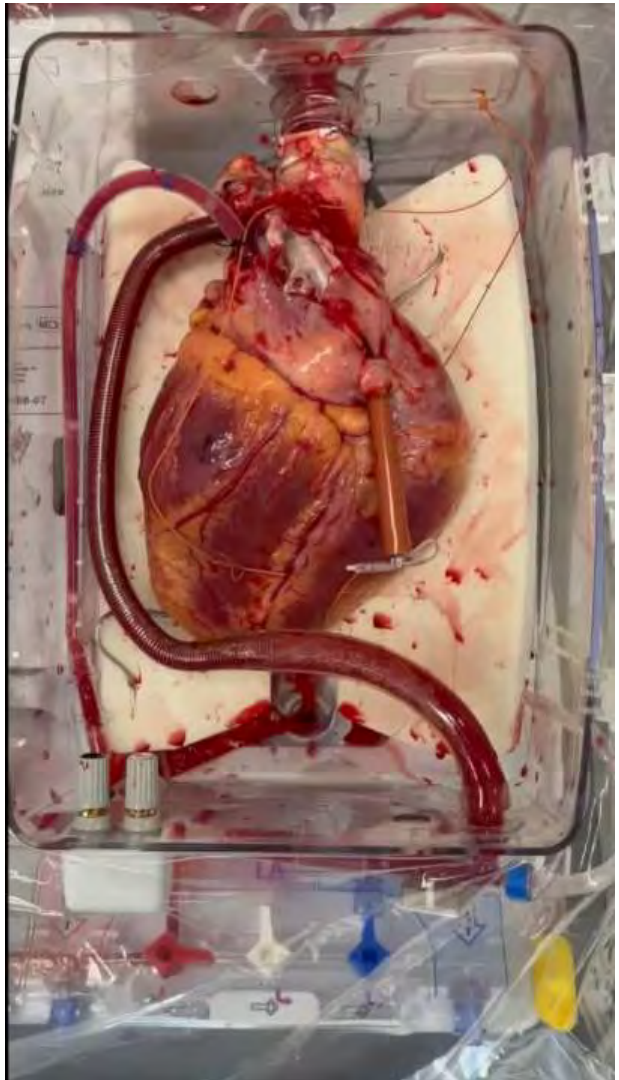
Radiographic
- Coronary CTA on OCS**
- Coronary angiography on OCS***





*Hamed A, et al. JHLT. 2009;28(2S):S71
**Tweed D, et al. JHLT 2020;39(4S):244
***Meredith T, et al. Cath Cardiovasc Interven. 2022;100:1252.

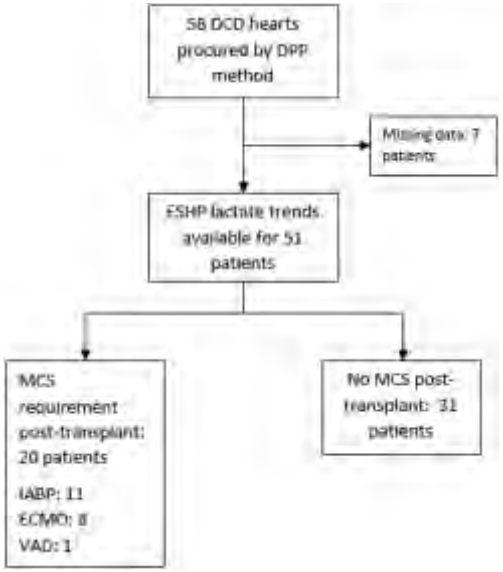
OCS Ex-vivo Assessment



Ex situ Assessment

Biomarker

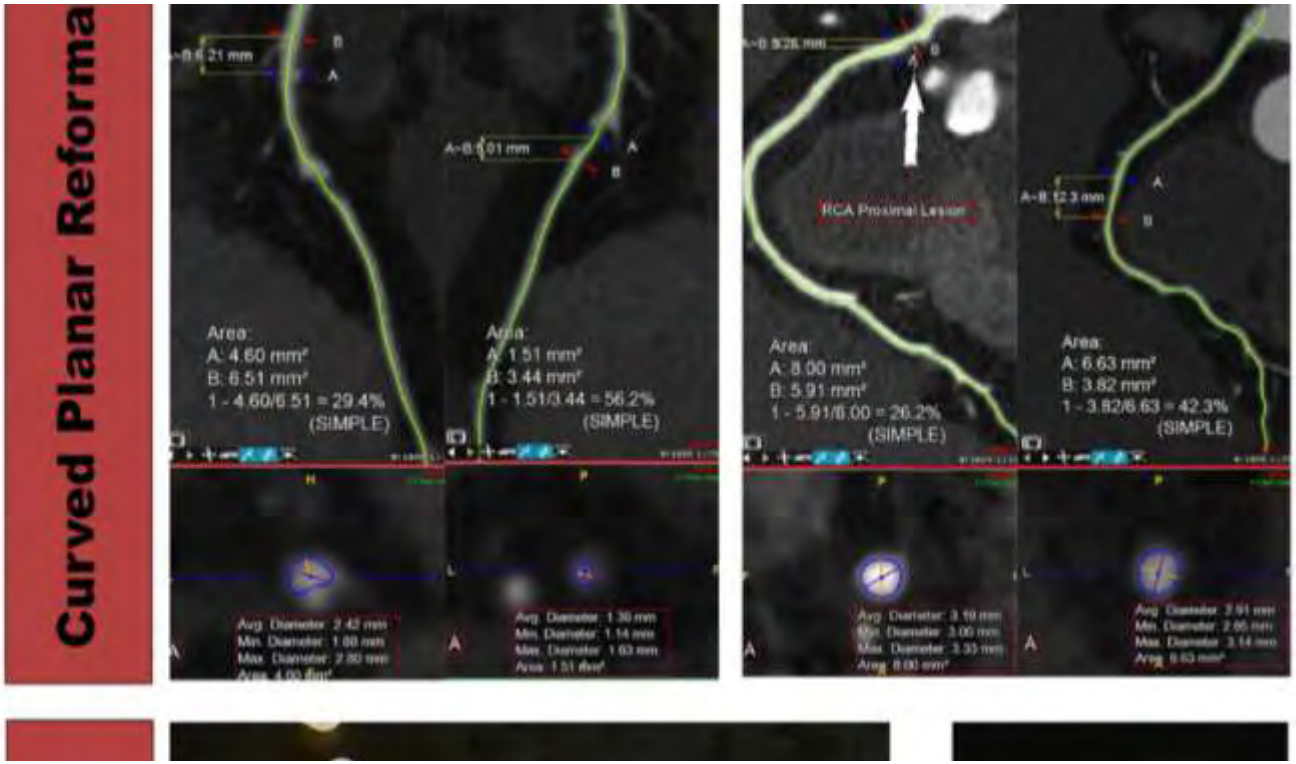
Lactic acid not correlated with outcomes
Retrospective single center review



	Requirement for post-transplant mechanical support		
	MCS[*n* = 20]	No MCS[*n* = 31]	*p* value
Rising Lactate Trend, *n* [%]	3 [15]	4 [13]	1.00
Lactate gradient, mmol/L/h [IQR][b]	0.6 [0.3-0.9]	0.6 [0.3-1.2]	0.67
Last measured arterial lactate, mmol/L/h [IQR]	6.1 (4.6-7.1)	5.4 [3.1-6.9]	0.22

Cernic S, et al. JHLT. 2022;41:1294.

Ex-vivo Coronary Assessment



Urban M, et al. JHLT Open 2024;6:100142

Clinical Trials - OCS

Establishing safety of OCS device

PROTECT I

- 20 patients reached primary endpoint – 30 day survival w 5 SAE

Combined with PROCEED I trial

- 14 hearts procured with 13 utilized
- 11/13 reached primary endpoint w 5 SAE
- 1 death and 1 re-transplant

FDA allowed proceeding with:

PROCEED II trial*

- 130 patients randomized (67/63) to OCS vs CSS
- Comparable short term (30 day graft and patient survival) outcomes

	Organ Care System group	Standard cold storage group	Between-group difference (one-sided 95% UCB or 95% CI)	p value
Primary endpoint (30 day patient and graft survival)				
Intention-to-treat	63/67 (94%)	61/63 (97%)	2·8 (8·8)	0·45
As-treated	58/62 (94%)	64/66 (97%)	3·5 (9·6)	0·36
Per-protocol	56/60 (93%)	59/61 (97%)	3·4 (9·9)	0·39
Secondary endpoints (as-treated population)				
Patients with cardiac-related serious adverse events	8 (13%)	9 (14%)	1 (–12 to 11)	0·90
Incidence of severe rejection	11 (18%)	9 (14%)	4 (–8 to 17)	0·52
Median ICU length of stay (h)	147 (107–212)	137 (97–197)	10 (–10 to 42)	0·24

Data are n/N (%) or n (%), or median (IQR), unless otherwise indicated. UCB=upper confidence bound. ICU=intensive-care unit.

	Organ Care System group (n=62)	Standard cold storage group (n=66)	p value
Left ventricular dysfunction	5 (8%)	4 (6%)	0·657
Right ventricular dysfunction	2 (3%)	6 (9%)	0·170
Graft failure	1 (2%)	0	0·330

Data are n (%). We defined left ventricular dysfunction as a left atrial pressure greater than 18 mm Hg with a cardiac index less than 2·0 L/min per m², requiring implantation of a left ventricular assist device or inotropic treatment for more than 7 days. We defined right ventricular dysfunction as central venous pressure greater than 18 mm Hg with a cardiac index less than 2·0 L/min per m², in absence of left atrial pressure greater than 18 mm Hg, requiring implantation of a right ventricular assist device or inotropic treatment for more than 7 days. We defined graft failure as heart dysfunction requiring sustained (>30 days) assist devices or relisting for transplantation. Numbers in this table differ from those in table 2, because this table depicts the number of events.

*Ardehali A, et al. Lancet 2015;385:2577

**Dhital KK, et al. Lancet. 2015;385:2585.

Clinical Use in Extended Donor Criteria

EXPAND trial: 30 days and 6 months (short term)*

- 75/93 hearts utilized (81%)
- Severe PGD 10.7% at 24 hours
- Survival 94.7% (30d); 88% (6m)

EXPAND trial at 2 years (long term)**

- 116/138 hearts utilized (84%)
- patient survival 85.3% vs 87.8% (control)
- graft survival 94.2% vs 95% (control)

Donor Characteristics	EXPAND Trial (N=116)	Concurrent Controls* (N=1813)	p-value
Age (years) – mean ± SD	37.1 ± 11.8	33.5 ± 11.4	0.0010
Age ≥ 55 years	12 (10.3%)	84 (4.6%)	0.0128
LV Ejection Fraction	58.2 ± 8.4	61.5 ± 6.5	<0.0001
LVH >12 ≤ 16 mm	22 (19.0%)	Not collected	
Cross-clamp time ≥ 4 hours (Expected)	53 (45.7%)	268 (14.8%)	< 0.0001
Cross-clamp time ≥ 4 hours (Actual)	113 (97.4%)	268 (14.8%)	< 0.0001
LVEF between 40% - 50%	27 (23.3%)	93 (5.1%)	< 0.0001
Downtime ≥ 20 minutes	33 (28.4%)	69 (3.8%)	< 0.0001

*data from 2015-2022 SRTR heart transplant registry

*Schroder JN, et al. JHLT. 2019;38(4S):S42
**Schroder JN, et al. JHLT. 2022;41(4S):S73

Clinical Use in DCD

First series of DCD heart transplants performed with DPP-OCS and donor-recipient not co-located*

- All three recipients survived to discharge
- ECMO 1; IABP 1

Australian experience with DCD (DPP-OCS)**

- Of note – WIT begins at SBP<90, failure to progress 25% (69 attended); 62% used (49 recovered); 32 transplanted

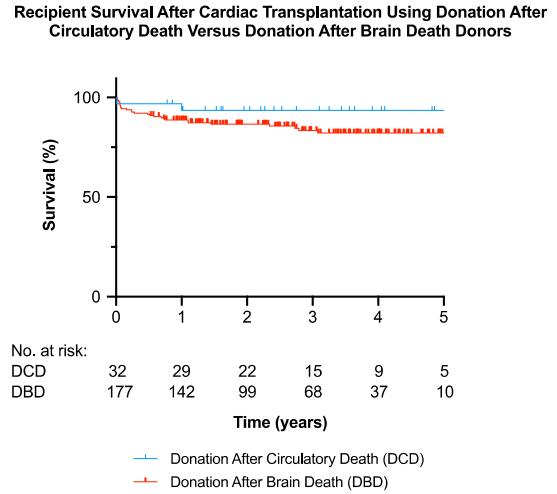


Table 3 Key intra- and peri-operative details for all 32 DCD heart recipients

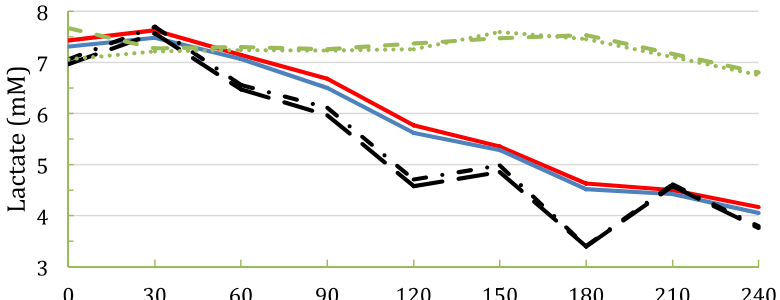
	(mean ± std. dev.)
Cross-clamp time (min)	89 ± 32
Bypass time (min)	188 ± 66
Mechanical support (MCS)	12*/32 (34%)
ECMO	10/32 (31%)
IABP	3/32 (9%)

*One patient was supported with both intra-aortic balloon pump (IABP) and ECMO

Table 4 Comparison of withdrawal and retrieval timings between DCD transplant recipients who required initial ECMO support and those that did not (mean ± std. dev.)

Time interval (min)	No-ECMO ($n = 22$)	ECMO ($n = 10$)	p value
Time to asystole	12 ± 5	9 ± 3	0.036
Warm ischaemic time	24 ± 6	23 ± 3	0.458
Asystole to cardioplegia	12 ± 2	15 ± 3	0.002
Cold ischaemic time	29 ± 5	27 ± 6	0.197
OCS run time	281 ± 68	306 ± 60	0.155

DCD: 96%,94%,94%
DBD: 89%, 83%, 82%



*Dhital KK, et al. Lancet 2015; 385: 2585–91
**Dhital K, et al. Indian Journal of Thoracic and Cardiovascular Surgery (August 2020) 36 (Suppl 2):S224–S232

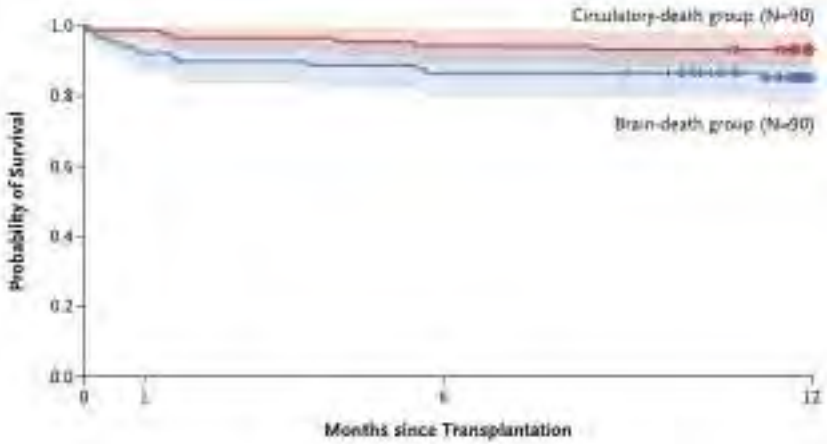
Clinical Use in DCD

Randomized control trial for DCD-OCS vs. DBD-SCS

Non-inferiority at 6 months
- Trend toward improved survival
  - 94% vs. 89% (unadjusted overall)

Moderate or severe ISHLT graft dysfunction
- 22% (18/80) vs 10% (8/84)

Severe graft dysfunction: 15% vs 5%
- Of note: 2 re-transplants in the DBD arm only



Schroder JN, et al. NEJM. 2023;388(23):2121.

Characteristic	Donation after Circulatory Death (N=90)	Donation after Brain Death (N=90)
Donor		
Age		
Mean — yr	29.3±7.5	33.2±11.4
Range — yr	15.7–47.0	12.3–65.3
≥55 yr — no. (%)†	0	3 (3)
Sex — no. (%)		
Female	6 (7)	21 (23)
Male	84 (93)	69 (77)
Race — no. (%)‡		
Black	11 (12)	25 (28)
White	70 (78)	55 (61)
Other	2 (2)	6 (7)
Not available	7 (8)	4 (4)
Ethnic group — no. (%)‡		
Hispanic or Latino	7 (8)	7 (8)
Not available	62 (69)	47 (52)
Body-mass index§		
Mean	27.3±6.21	28.5±6.5
Range	7.9–49.7	16.9–47.6
Cold ischemic time ≥4 hr — no. (%)	0	25 (28)
Sex mismatch, female donor to male recipient — no. (%)	1 (1)	6 (7)
Recipient		
Age		
Mean — yr	51.3±12.6	55±11.4
Range — yr	20.0–73.1	22.3–73.9
≥65 yr — no. (%)	13 (14)	17 (19)
Sex — no. (%)		
Male	66 (73)	66 (73)
Female	24 (27)	24 (27)
Race — no. (%)‡		
Black	28 (31)	20 (22)
White	62 (69)	66 (73)
Other	0	1 (1)
Not available	0	3 (3)
Ethnic group — no. (%)‡		
Hispanic or Latino	3 (3)	3 (3)
Not available	5 (6)	3 (3)
Heart allocation status — no. (%)¶		
1	1 (1)	5 (6)
2	18 (20)	47 (52)
3	16 (18)	15 (17)
4	43 (48)	14 (16)
6	12 (13)	9 (10)
Mechanical circulatory support before transplantation — no. (%)		
Left ventricular assist device	44 (49)	27 (30)
Intraaortic balloon pump	14 (16)	38 (42)
Mechanical ventilation at transplantation — no. (%)	0	0

OCS Use and PGD

UK Transplant Database Oct. 2012-Oct 2015 risk factors for PGD

- OHT N=450, any PGD 36.2% incidence

30-d Mortality:

- No PGD: 4.5% vs. any PGD 19%
- Severe PGD: 30% vs. Mod PGD: 5%

Subset analysis of OCS (n=66)

But incidence of PGD similar

- 30.3% vs 37.2%, P = 0.279

OCS use had significantly longer extracorporeal times

- 309.4 ± 88.4 min vs 100.3 ± 45.8 min; P < 0.001.

Within OCS, extracorporeal time was significantly longer in the PGD group

- 344.9 ± 95 min vs 294.8 ± 81 min, P = 0.048

No subgroup analysis, i.e. mortality difference with PGD in OCS group or rate of severe PGD (did PGD fare better with OCS?)

?Limits to MP time?

Cardiac function declines in time-dependent manner on ESHP

May be mitigated by working mode **

Extended MP times reported – case series

- MP 955 min; ex situ 1023 min ***
- 503 min; 611 min ****

Singh SSA, et al. Transplantation. 2019;103:336.

***Kaliyev R, et al. Art Org. 2019;43(3):319

****Stamp NL, et al. Heart Lung Circ. 2015;24(6):P611

**Hatami S, et al. Ann Thorac Surg. 2019;108:499.

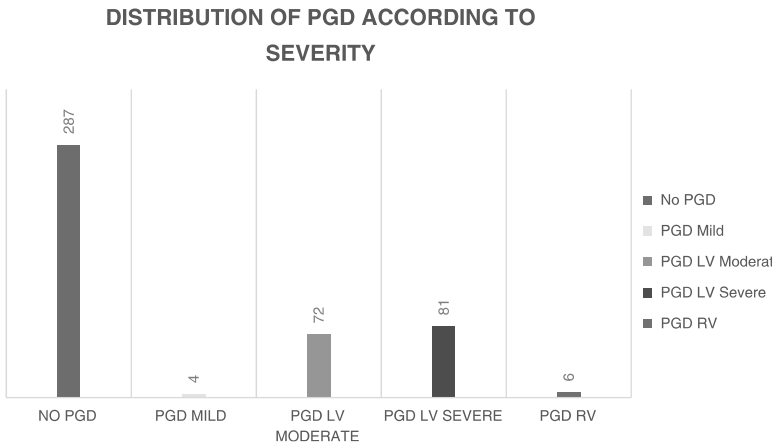


Table 1. Left Ventricular Function During Ex Vivo Heart Perfusion in Working Mode and Nonworking Mode Experimental Groups

Variable	Group	T1	T5	T11	*p* Value
CI, mL · min^{-1} · g^{-1}	WM	17.40 ± 1.75	11.48 ± 1.77	5.39 ± 1.01	0.008
	NWM	16.36 ± 1.65	6.12 ± 0.91	1.66 ± 0.80	0.005
SW, mm Hg × mL	WM	4,444.53 ± 448.16	2,394.47 ± 531.19	1,012.46 ± 245.72	<0.001
	NWM	4,655.05 ± 784.93	1,111.28 ± 365.11	303.41 ± 121.647	0.017
dP/dT max, mm Hg/s	WM	2,750.52 ± 341.91	1,871.49 ± 124.53	1,616.40 ± 131.77	0.015
	NWM	3,722.80 ± 526	2,068.81 ± 476.08	893.27 ± 353.81	0.012
Sys pressure, mm Hg	WM	180.50 ± 9.83	132.66 ± 8.32	117.66 ± 7.80	0.007
	NWM	179.83 ± 16.28	137.30 ± 12.87	89.85 ± 10.23	0.020
ME, %	WM	14.90 ± 1.60	13.2 ± 1.90	15 ± 3.60	0.155
	NWM	15.20 ± 1.90	6.3 ± 0	3.90 ± 1.90	0.056
PRSW	WM	702.09 ± 81.68	357.04 ± 58.31	197.81 ± 52.10	<0.001
	NWM	729.72 ± 107.52	255.13 ± 36.88	89.29 ± 28.99	0.011
dP/dT min, mm Hg/s	WM	−2,675.56 ± 81.59	−1,940.53 ± 153.94	−1,190.28 ± 126.51	<0.001
	NWM	−2,923.68 ± 364.81	−1,423.50 ± 133.81	−693.16 ± 164.62	0.020

Values are presented as mean ± SEM.

CI = cardiac index; dP/dT max = maximum rate of pressure change; dP/dT min = minimum rate of pressure change; LV = left ventricle; ME = mechanical efficiency; NWM = nonworking mode perfusion; PRSW = preload recruitable stroke work; SW = stroke work; Sys = systolic; T1 = 1 hour of ex vivo perfusion; T5 = 5 hours of ex vivo perfusion; T11 = 11 hours of ex vivo perfusion; WM = working mode perfusion.

ISHLT PGD Severity Criteria

Table 6 Definition of Severity Scale for Primary Graft Dysfunction (PGD)

1. **PGD-Left ventricle (PGD-LV):**	*Mild PGD–LV*: *One* of the following criteria must be met:	LVEF $\leq$ 40% by echocardiography, *or* Hemodynamics with RAP $>$ 15 mm Hg, PCWP $>$ 20 mm Hg, CI $<$ 2.0 L/min/m^2 (lasting more than 1 hour) requiring low-dose inotropes
	Moderate PGD-LV: Must meet one criterion from I *and* another criterion from II:	I. *One* criteria from the following: Left ventricular ejection fraction $\leq$ 40%, *or* Hemodynamic compromise with RAP $>$ 15 mm Hg, PCWP $>$ 20 mm Hg, CI $<$ 2.0 L/min/m^2, hypotension with MAP $<$ 70 mm Hg (lasting more than 1 hour) II. *One* criteria from the following: i. High-dose inotropes—Inotrope score $>$ 10[a] *or* ii. Newly placed IABP (regardless of inotropes)
	Severe PGD–LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.
2. **PGD-right ventricle (PGD-RV):**	Diagnosis requires either both i and ii, or iii alone:	i. Hemodynamics with RAP $>$ 15 mm Hg, PCWP $<$ 15 mm Hg, CI $<$ 2.0 L/min/m^2 ii. TPG $<$15 mm Hg and/or pulmonary artery systolic pressure $<$ 50 mm Hg, *or* iii. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.

[a]Inotrope score = dopamine ($\times$1) + dobutamine ($\times$1) + amrinone ($\times$1) + milrinone ($\times$15) + epinephrine ($\times$100) + norepinephrine ($\times$100)[67] with each drug dosed in µg/kg/min.

Kobashigawa, J, et al. JHLT 2014;33:327

Significance of PGD in DCD-OCS

Retrospective analysis, single center

- March 2016-Dec 2021
- N=459 isolated OHT
- DCD 65 (*all OCS)
- DBD 394

Table 2. Incidence and Subclassification of PGD Following DCD or DBD Heart Transplantation

PGD Classification	DCD (n = 65)	DBD (n = 394)	Total (n = 459)	*P* value
BiV-PGD, Severe	12 (18.5%)	29 (7.4%)	41 (8.9%)	0.004
BiV-PGD, Moderate	3 (4.6%)	35 (8.9%)	38 (8.3%)	0.25
LV-PGD, Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
LV-PGD, Moderate	1 (1.5%)	3 (0.8%)	4 (0.9%)	0.46
RV-PGD, Severe	2 (3.1%)	6 (1.5%)	8 (1.7%)	0.32
RV-PGD, Moderate	4 (6.2%)	19 (4.8%)	23 (5.0%)	0.55
Total Moderate/Severe PGD	22 (33.8%)	92 (23.4%)	114 (24.8%)	0.07

BiV-PGD, biventricular primary graft dysfunction; DBD, donation after brain death; DCD, donation after circulatory death; LV-PGD, left ventricular primary graft dysfunction; PGD, primary graft dysfunction; RV-PGD, right ventricular primary graft dysfunction.

PGD rates higher with DCD but shorter MCS duration
Severe PGD: 18.5% (DCD)vs 7.4% (p=0.004)
Trend toward improved 1-yr survival with PGD-DCD vs. PGD-DBD: 91.7% (DCD)vs. 68.6%

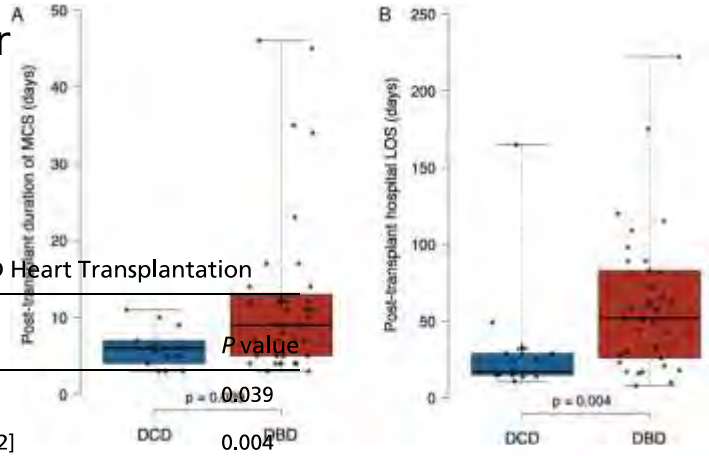


Table 3. Clinical Outcomes of Patients with Severe PGD following DCD Compared with DBD Heart Transplantation

Outcomes*	DCD (n = 14)	DBD (n = 35)	Total (n = 49)	*P* value
Post-transplant duration of MCS,† days	6 [4, 7]	9 [5, 14]	7 [5, 11]	0.039
Post-transplant hospital length of stay, days	17 [15, 29]	52 [26, 83]	38 [17, 72]	0.004
Discharge disposition				0.11
Home/self-care	11 (84.6%)	17 (48.6%)	28 (58.3%)	
Rehabilitation facility	1 (7.7%)	9 (25.7%)	10 (20.8%)	
Expired	1 (7.7%)	9 (25.7%)	10 (20.8%)	
60-day KM survival	100% (95% CI: 76.8–100%)	80.0% (95% CI: 63.1–91.6%)	85.7% (95% CI: 72.8–94.1%)	0.17
1-year KM survival	91.7% (95% CI: 53.9–98.8%)	68.6% (95% CI: 50.5–81.2%)	75.1% (95% CI: 60.3–85.1%)	0.16

Ayer A, et al. J Card Fail. 2023;29(1):67.

Nebraska Medicine Experience

Donor	Time to Asystole	Aystole to XC	FWIT	CIT	MP	WIT	Lactate (A/V)-start	Lactate (A/V)-end	Op. – Re-do	
1 (31M)	1’	8’	9’	50’	289’	55’	7.08/8.39	4.9/4.4	OHT - y	V-A ECMO
2 (20F)	4’	6’	10’	48’	244’	44’	7.12/7.05	9.17/8.80	rOHT/CRT - y	
3 (16F)	10’	8’	8’	45’	287’	79’	7.38/7.29	7.84/7.89	OHT - y	
4 (31M)	0’	8’	8’	41’	231’	57’	8.4/8.02	8.22/8.19	OHT - n	
5 (36M)	13’	9’	22’	52’	158’	56’	8.89/9.06	9.60/9.33	OHT - y	
6 (29M)	5’	8’	13’	37’	389’	75’	7.28/7.01	5.65/5.57	OHT - n	
7 (37F)	7’	11’	18’	48’	255’	63’	8.37/9.83	4.59/4.51	OHT - y	
8 (40M)	3’	10’	13’	63’	180’	55’	5.54/5.43	4.53/4.21	OHT - n	
9 (33M)	4’	9’	13’	24’	204’	47’			OHT - y	
10 (36M)	5’	11’	16’	46’	174’	46’	8.87/8.81	8.02/8.10	OHT - n	
11 (38M)	10’	5’	16’	46’	185’	52’	6.72/6.78	6.52/6.54	OHT - y	
33	5.6±4.0	8.5±1.9	14.1±4	45.5±9.7	236±68	57±11				

Hypothermic Machine Perfusion

Porcine hearts transplanted after 24 hours of brain death and then:

- 24 hrs in St. Thomas solution at 4°C (0/3) vs.
- 24 hrs of hypothermic (8°C) machine perfusion (10/10)

Canine DCD model, 4 hours of:

- cold perfusion vs CSS

Composition of the Perfusion Solution

Composition	Function	Concentration
Potassium chloride	Cardioplegic	15 mmol/L
Calcium chloride	Cardioplegic	0.5 mmol/L
Magnesium chloride	Cardioplegic	7.5 mmol/L
Trizma HCl	Buffer	20 mmol/L
Sodium bicarbonate	Buffer	20 mmol/L
Adenosine	Vasodilatation	5 mmol/L
Glutathione (reduced)	Antioxidant	3 mmol/L
Sodium lactobionate	Oncotic agent	70 mmol/L
Sodium L-aspartate	Energy preservation	20 mmol/L
Fructose-1,6 bisphosphate	Energy preservation	5 (mmol/L)
D-Glucose	Energy preservation	14 mmol/L
Insulin	Energy preservation	6 unit
Oxygen	Aerobic metabolism	600 mm Hg
Sodium hydroxide	Adjust pH	pH 7.3
Osmolarity	Prevent edema	380 mOsm

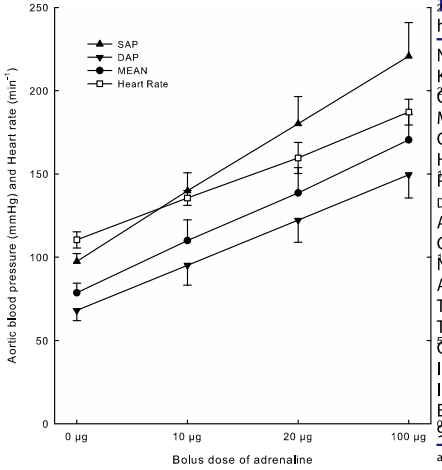
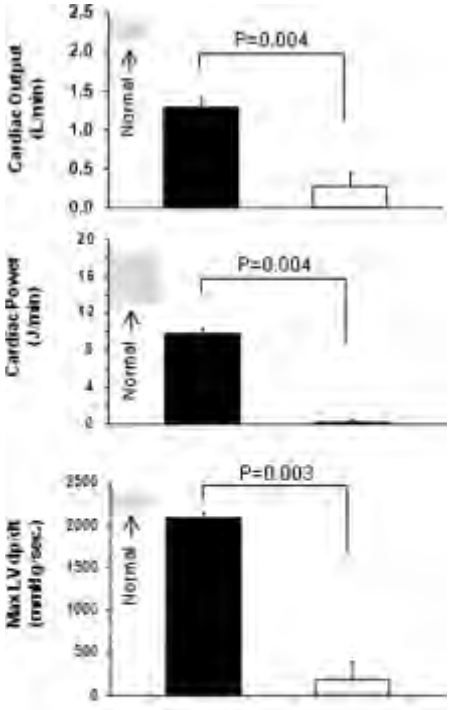


Table 3. The perfusion medium used for 24-hour heart preservation.

Na^+	136 mmol/L
K^+	23 mmol/L
Ca^{2+}	1.3 mmol/L
Mg^{2+}	8.0 mmol/L
Cl^-	142 mmol/L
HCO_3^-	25 mmol/L
PO_4^{2-}	1.3 mmol/L
D-Glucose	6.3 mmol/L
Albumin	75 g/L
Cocaine	6 pmol/L
Noradrenaline	6 pmol/L
Adrenaline	6 pmol/L
T3	3 pmol/L
T4	2 pmol/L
Cortisol	420 pmol/L
Insulin	8 U/L
Imipenen	20 mg/L
Erythrocytes (Hct)[a]	15%
96% O_2 + 5% CO_2[b]	0.2 L/min

[a]When all drugs and erythrocytes have been added and mixed and the PCO_2 has stabilized, pH is adjusted to 7.40 by means of sodium bicarbonate.
[b]Administered through the oxygenator.



Steen S, et al. Scand Cardiovasc J. 2016;50(3):193
Choong JW, et al. Transplantation. 2016;100(3):546

Hypothermic Machine Perfusion

4 patients, including on previous heart transplant recipient underwent heterotopic heart transplantation from brain-dead donors

The perfusate was both oxygenated and circulated throughout this period of perfusion by the air-lift pump principle [5]. A mixture of 97% O_2 and 3% CO_2 was bubbled through a sterile gas filter into the perfusate in the lower reservoir through an air-ejector port inserted into the delivery tube. By this system the fluid was transported to the upper chamber (reservoir) through a Cobe 20 μ filter at a gas flow rate of approximately 500 cc/min.

This gaseous solution maintained perfusate pH at 7 to 7.8 and perfusate flow into the upper chamber at approximately 60 to 120 ml/min. When determined at 30°C, perfusate oxygen tension has been measured at a partial pressure of between 1,000 and 2,000 mm Hg.

From the upper chamber, perfusate flowed by gravity into the ascending a[illegible]

ng Storage of the
othermic Perfusion System

[illegible]., Ph.D.,
M.S., Ph.D., D.Sc.(Hon Causa)

[illegible]8, M	Cardio-myopathy	38, F	10/1/81	Required considerable dobutamine support; mean arterial pressure fell to 25 mm Hg	7 hr 12 min	8 hr 7 min	Sinus rhythm; recipient heart provided major support of circulation for 20 hr; considerable inotropic support required	Four major acute jection episode *toxoplasma* infec of both hearts, treated success fully; donor he functioned well until death of p tient at 10 mo to tuberculous meningitis
[illegible]7, M	Cardiomyopathy; [illegible]	19, M	10/4/81	Stable, minimal inotropic support	15 hr	16 hr 50 min	Sinus rhythm; recipient heart provided major sup-	Cessation of dono heart function days due to ac-

Wicomb WN, et al. Ann Thorac Surg. 1984;37(3):243.

Hypothermic Oxygenated Perfusion

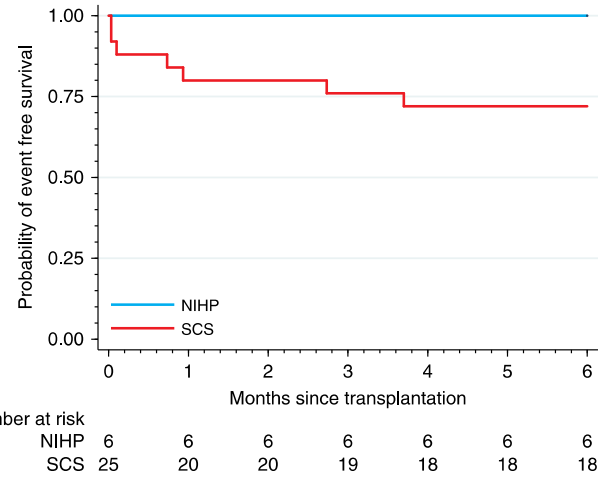
Ex-vivo non-ischemic heart preservation (NIHP)

- Nonrandomized trial of CSS (25) vs. NIHP (6)
- Primary endpoint: Survival free of severe PGD,
- ECMO in 7d, ACR≤2R at 180d: 100% vs 72%
- Overall mortality: 0 vs. 4

XVIVO perfusion system

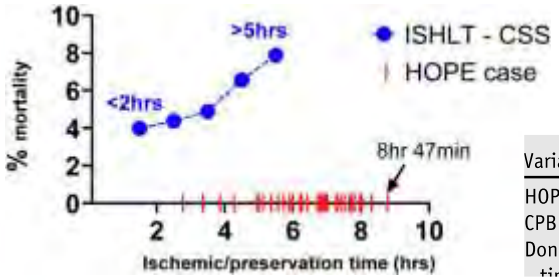
- Continuous cold, oxygenated, perfusion with cardioplegic solution with nutrients, hormones, red blood cells (Hct 15%)
    - heart maintained in cold, non-beating static state
    - root pressure maintained at 20 mm Hg, coronary flow at 150-200 cc/min

Nonrandomized 36 patients to anticipated preservation time 6-8hrs (n=29) w/ 7 donors of shorter time



b Heart preservation solution

Sodium (Na^+)	136 mmol/L
Potassium (K^+)	23 mmol/L
Calcium (Ca^{2+})	1.3 mmol/L
Magnesium (Mg^{2+})	8.0 mmol/L
Chloride (Cl^-)	142 mmol/L
Bicarbonate (HCO_3^-)	25 mmol/L
Phosphate (PO_4^{2-})	1.3 mmol/L
D-Glucose	6.3 mmol/L
Albumin	75 g/L
Dextran-40	1 g/L
Cocaine	6 nmol/L
Noradrenaline	6 nmol/L
Adrenaline	6 nmol/L
Triiodothyronine (T3)	3 nmol/L
Cortisol	420 nmol/L
Insulin	8 U/L
Imipenem	20 mg/L
Erythrocytes (Hct)	15%
95% O_2 + 5% CO_2	0.2 L/min



Variable	All ($n = 36$)	Long preservation time ($n = 29$)	Short preservation time ($n = 7$)
HOPE perfusion time, min	290 (101)	328 (71)	136 (46)
CPB time, min	165 (135, 235)	165 (134, 231)	227 (146, 257)
Donor heart preservation time, min	382 (84)	414 (53)	252 (55)

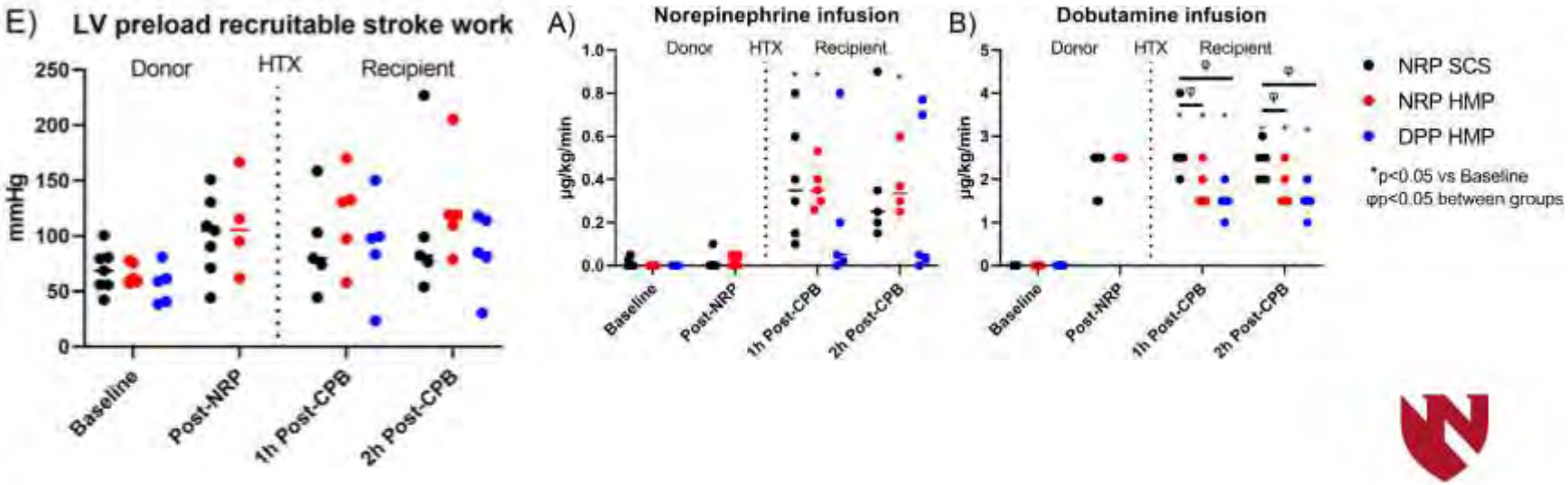
Nilsson J, et al. Nat Comm. 2020;11:2976.
McGiffin DC, et al. JHLT. 2024;43(3):485

Hypothermic Oxygenated Perfusion

Porcine DCD heart transplant model

- Comparison of 1. NRP to CSS, 2. NRP to HOPE (XVIVO), 3. DPP to HOPE
- Overall good cardiac function but with HOPE: better contractility (LV end-systolic elastance), lower dobutamine requirement, lower troponin

Next: ?HOPE with DPP



Moeslund N, et al. JHLT. 2023;42:730.

EVHP for Reconditioning Therapy

Ischemic post-conditioning attenuates myocardial reperfusion injury

Mitigation of ischemic-reperfusion injury (IRI)
Inhibition of MPT pore
- erythropoietin, cyclosporin

Activation of reperfusion injury salvage kinase (RISK)
- erythropoietin, adenosine, insulin

Activation of survivor activator factor enhancement (SAFE)
- erythropoietin

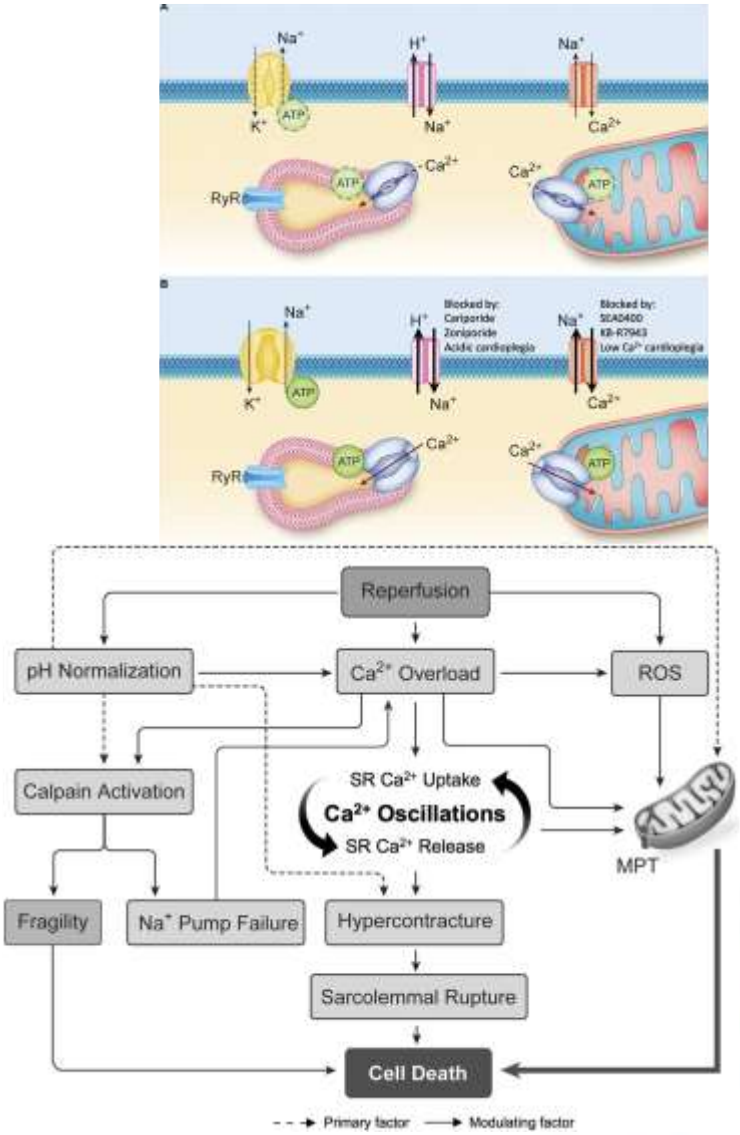
Inhibit apoptosis
- upregulation of Bcl-2
  - adenosine, glyceryl-trinitrate, insulin
- si-RNA

Attenuate ROS generation
- adenosine, insulin, MCI-186**

Na/H exchange inhibition
- carbiporide, zoniporide
- maintaining acidosis

Protein kinase inhibition with necroptosis inhibition
- necrostatin-1***

Modifying cardioplegic solution
- delay pH normalization (maintain early acidosis)
- hypocalcemic (minimize ca gradient driving reverse Na-Ca exchange)
  - hyperkalemia may increase intracellular Na and then Cl
  - lidocaine inhibits Na pump
  - adenosine to maintain cell membrane polarization



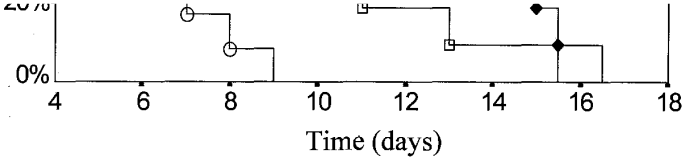
White C, et al. Ann Thorac Surg. 2017;103:122.
Garcia Dorado D, et al. Cardiovasc Res. 2012;94(2):168.
***Smith CC, et al. Cardiovasc Drugs Ther. 2007;21:227.
**Kotani Y et al. JTCVS. 2007;133:1626.
Wei L, et al. Mol Ther Nucleic Acids 2017;9:428-39

EVHP for Therapeutic Intervention

Adenovirus vector with anti-inflammatory cytokines IL-10 and TGF-ß-1 delivered to rabbit hearts on ESHP demonstrated attenuated acute rejection and improved graft survival after heterotopic heart transplantation

Ad vector to deliver CTLA4Ig in rat heterotopic heart transplant model demonstrated indefinite allograft survival

However, subsequent skin graft provoked rejection and allograft failiure suggesting faiure to develop tolerance



plan-Meier survival curves for control (Ad5dl434), AdSvIL10, and AdCMVTGF
Significant prolongation of survival was observed with both cytokines but was mo
β_1.

:e the viral early expression regions
rtly E4.[29] Although the use of viral
raises safety concerns, the wide-
denovirus has not been associated
malignancies and has been used for
on in human beings with no appar-
) The viral particle enters the cell by

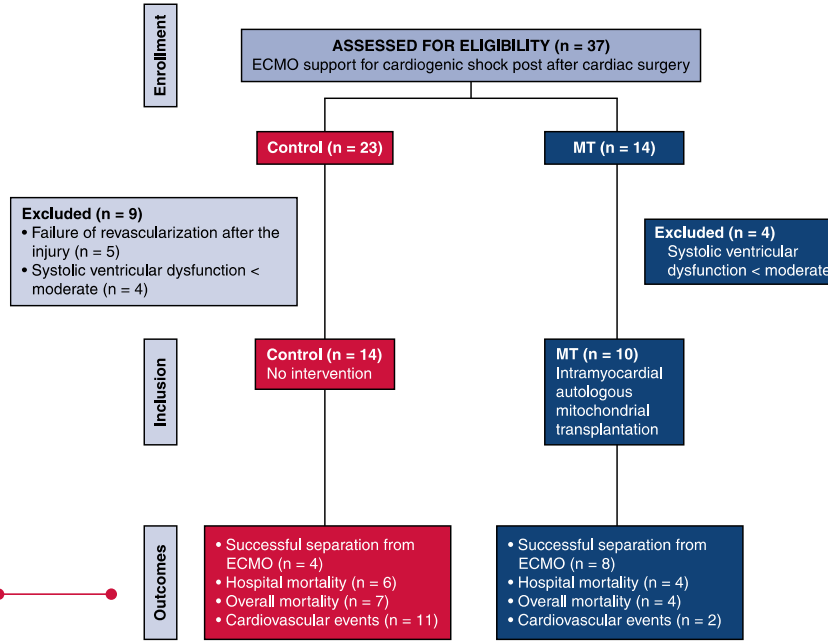
matic staining, thus having the a
localization of gene expression. T
transfer obtained in the present s
pressure intracoronary infusion
hypothermic conditions is comp
previously reported with normoth
ter intracoronary infusion in viv

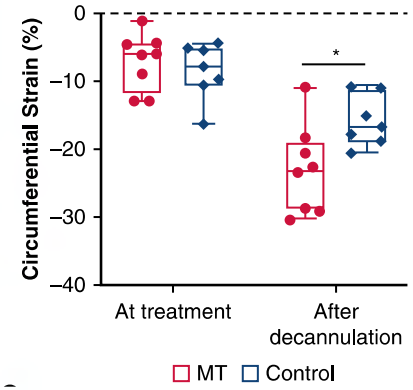
Brauner R, et al. JTCVS. 1997;114(6):923.
Yang Z, et al. Transplantation. 1999;67(12):1517.

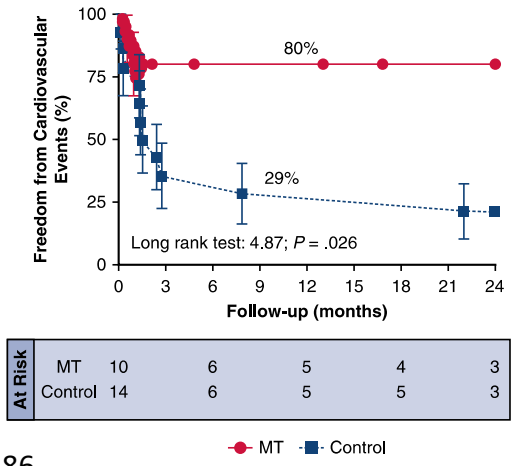
Mitochondrial Transplantation

Case series of autologous mitochondrial transplant in pediatric patients

- 5 patients on ECMO post-cardiotomy
  - 4 patients separated from ECMO. 2 deaths
  - Followup 24 patient series: 10 MT; 14 Control
  - overall mortality approximately same
  - but with decreased successful MCS time, CV event rate, and improved strain





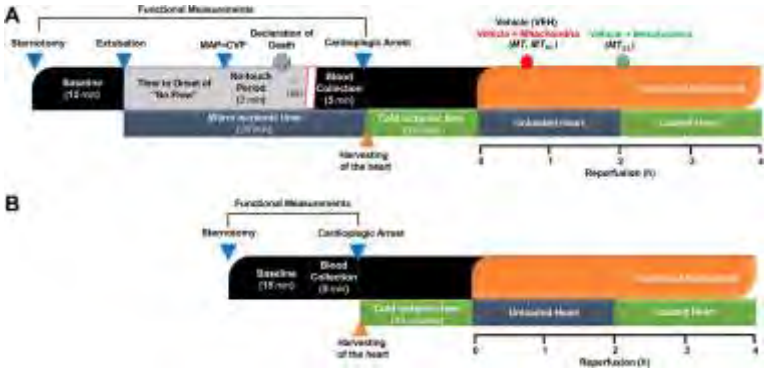


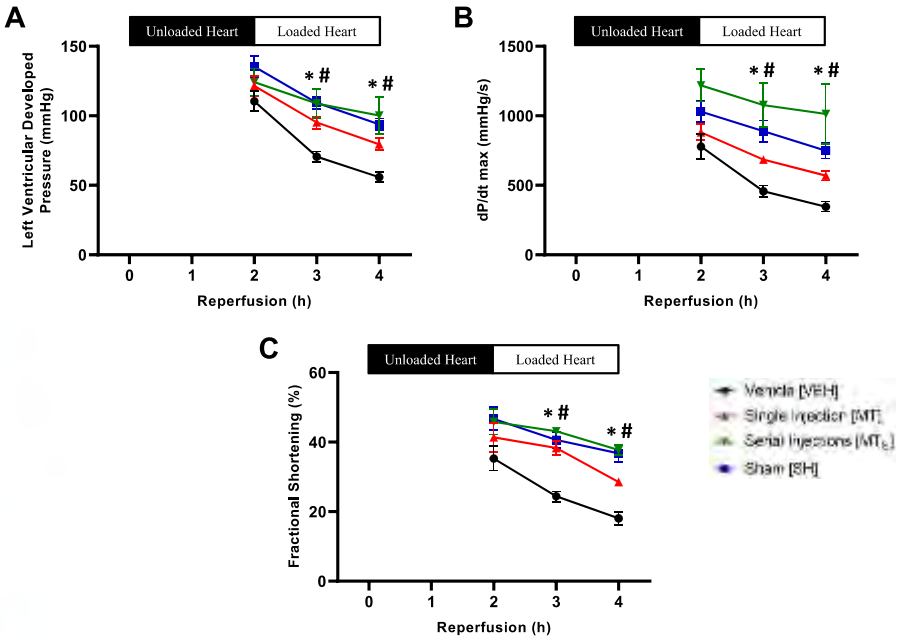
Emani SM, et al. JTCVS. 2017;154(1):286.
Guariento A, et al. JTCVS 2021;162(3):992

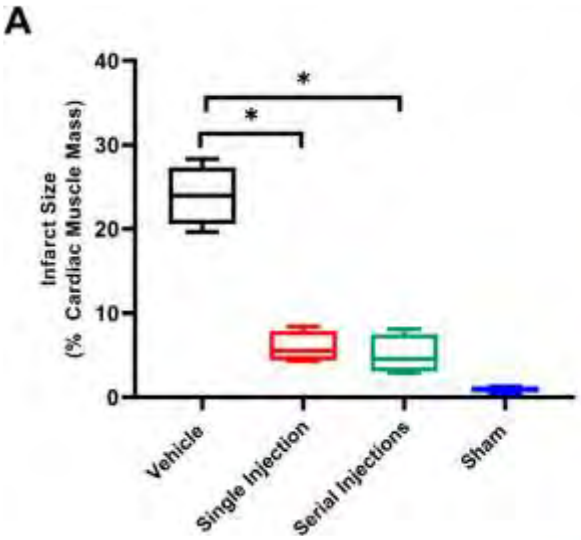
Mitochondrial Transplantation

Porcine DCD model with DPP and MP followed by mitochondrial transplant vs. vehicle-only and a separate sham group (no ischemia)

- Improvements in LVDP, FS, myocardial oxygen consumption







Guariento A, et al. JHLT. 2020;39(11):1279

Nebraska Medicine

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