Ex-vivo heart preservation system in heart transplantation

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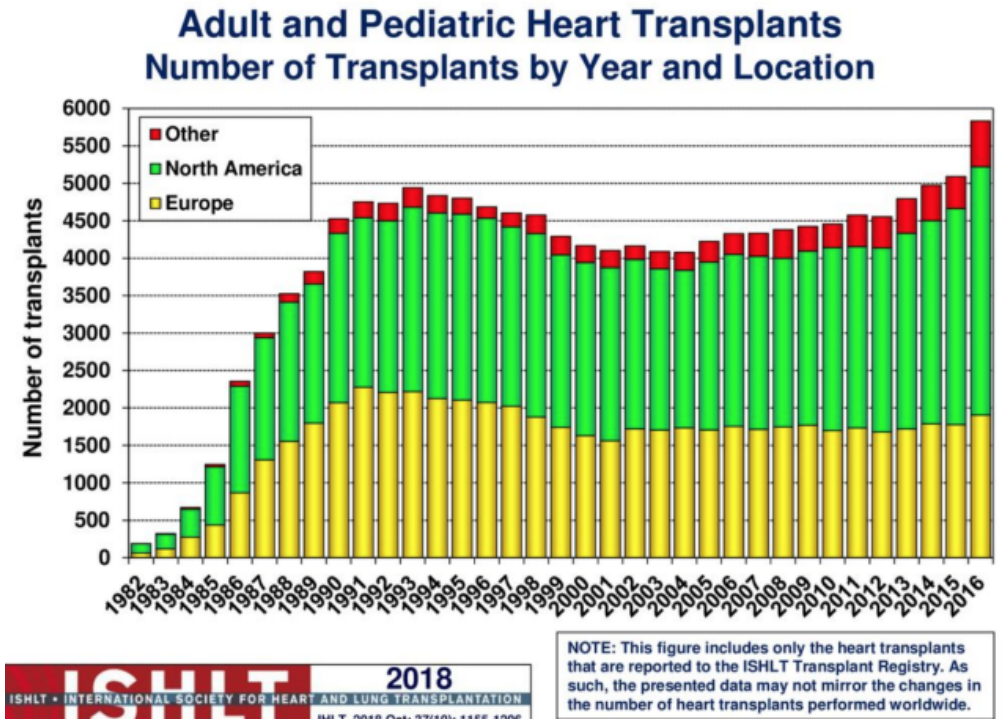
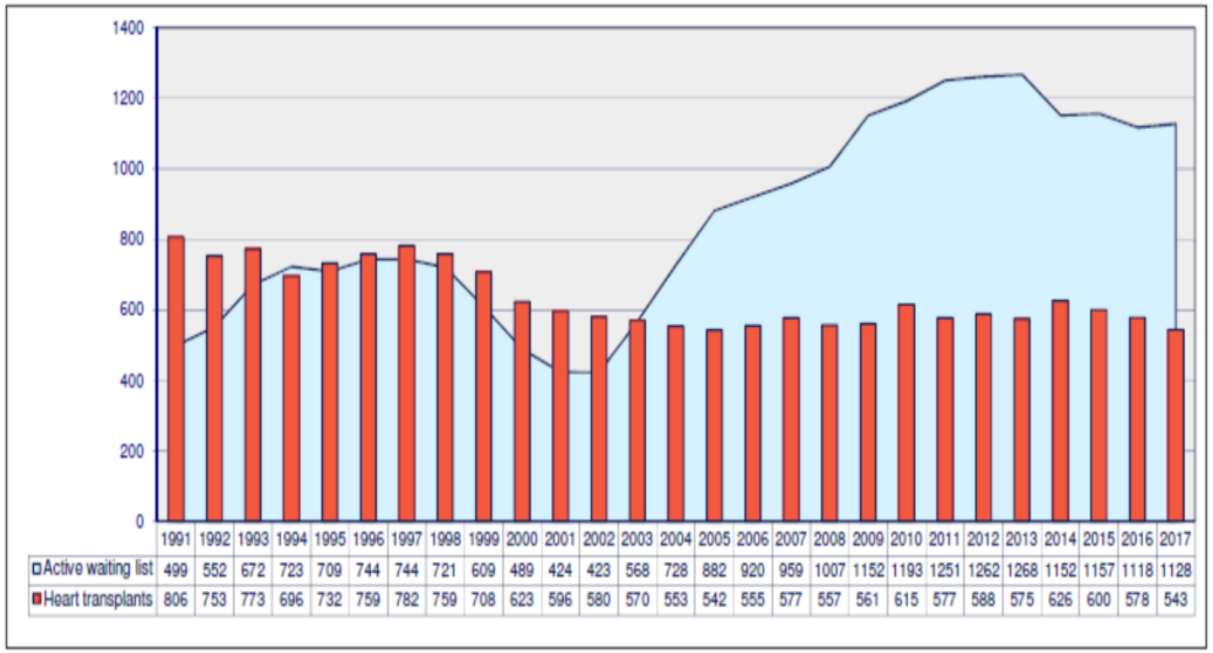
Background

ISHLT Registry

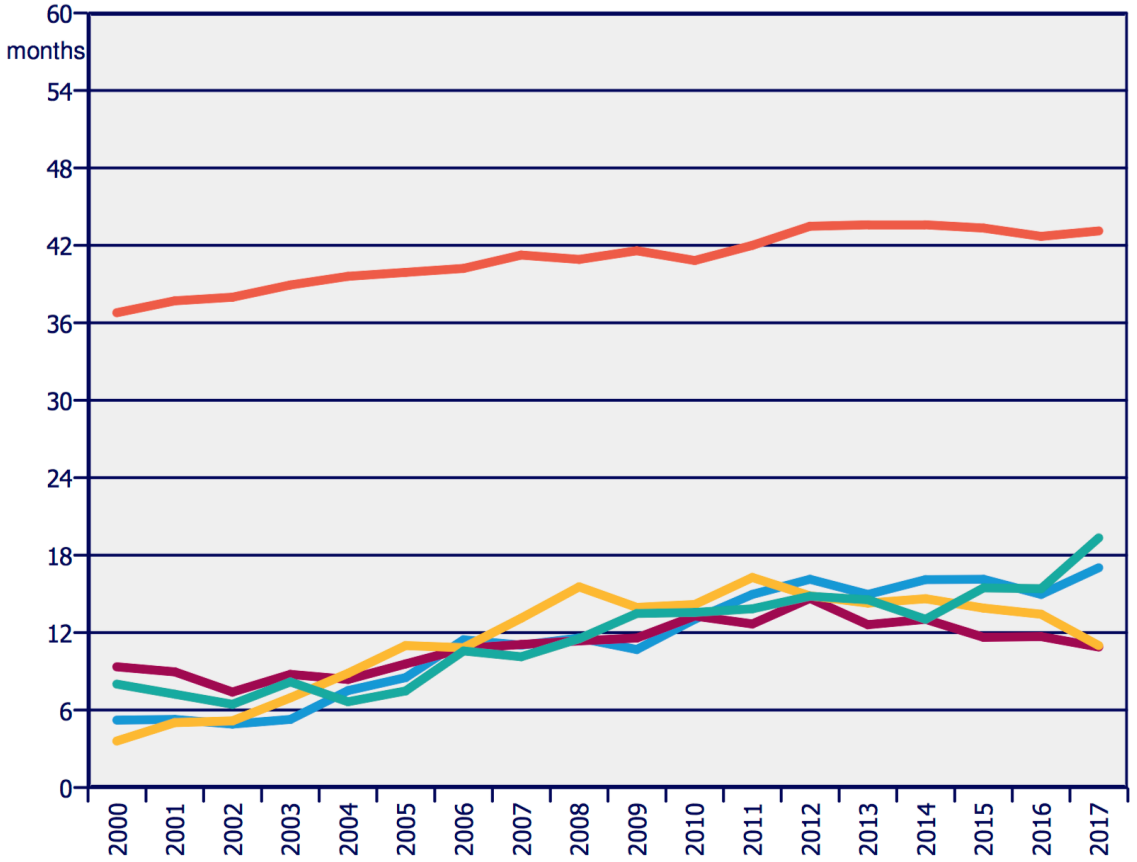


Eurotransplant Registry

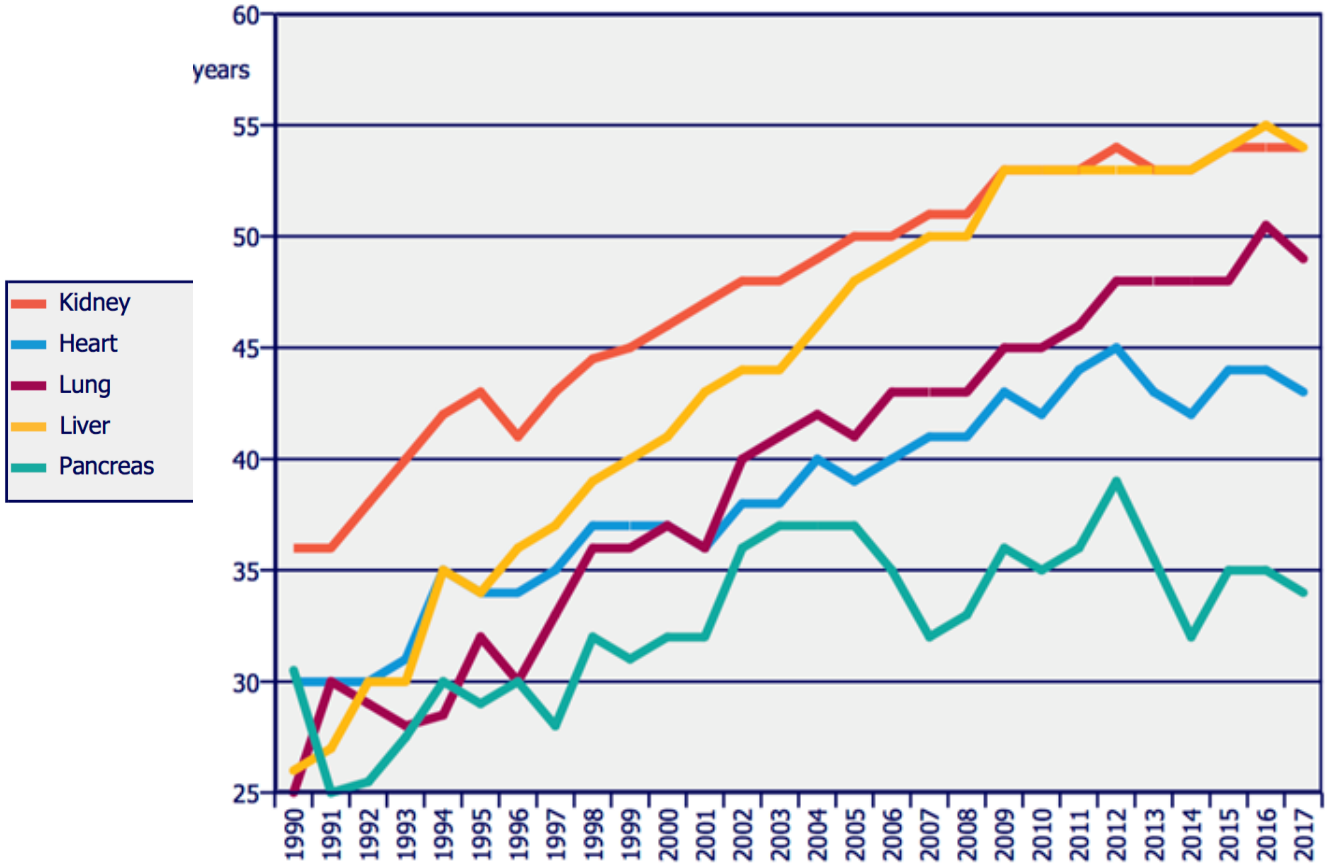


	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Active waiting list	499	552	672	723	709	744	744	721	609	489	424	423	568	728	882	920	959	1007	1152	1193	1251	1262	1268	1152	1157	1118	1128
Heart transplants	806	753	773	696	732	759	782	759	708	623	596	580	570	553	542	555	577	557	561	615	577	588	575	626	600	578	543

Waiting Time



Donor Age



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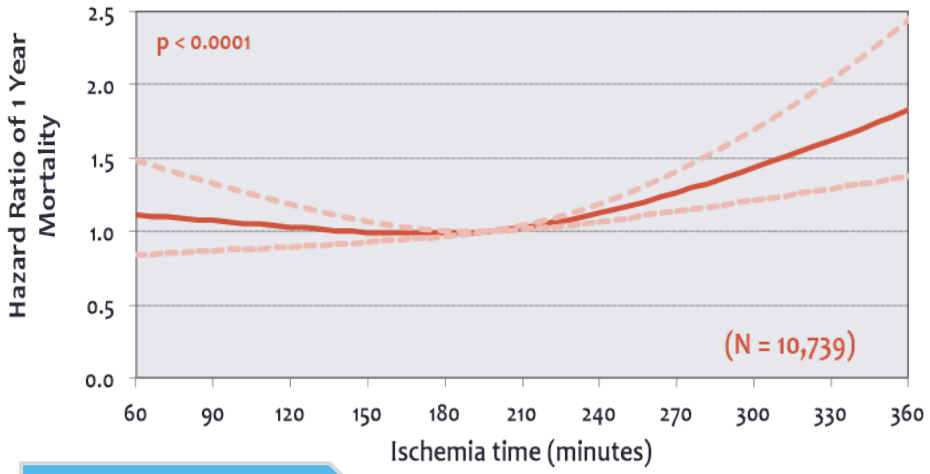
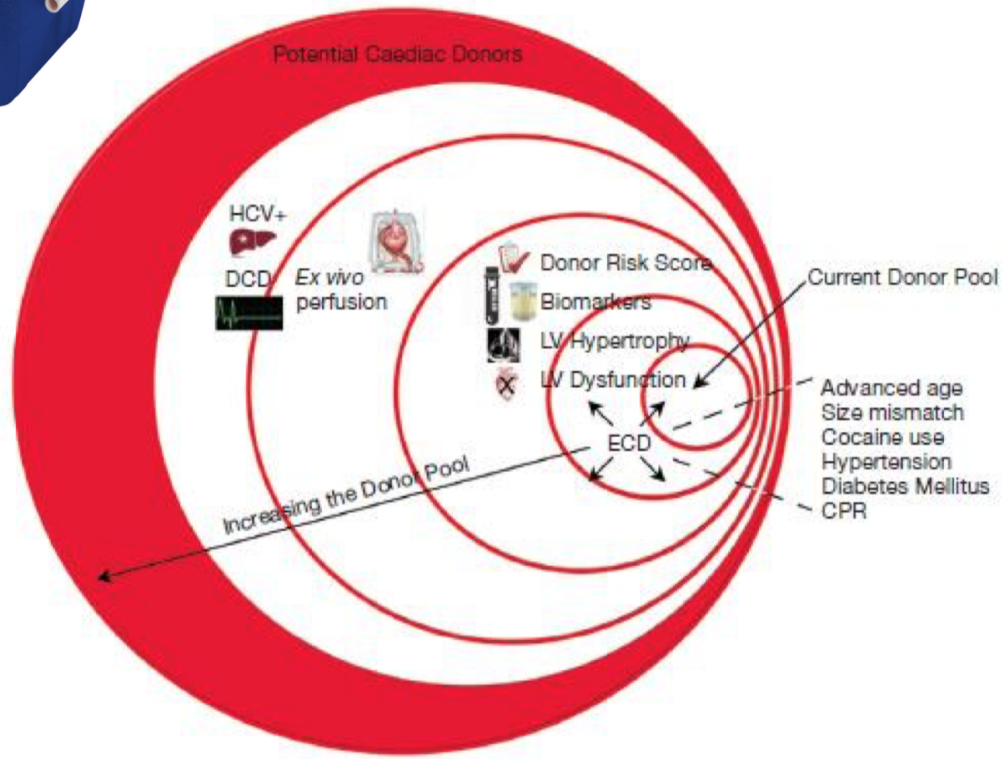
Cold storage



Time limit

No possibility of evaluation

No possibility of organ optimization



Khush. Ann Cardiothorac Surg. 2017

Safety and feasibility

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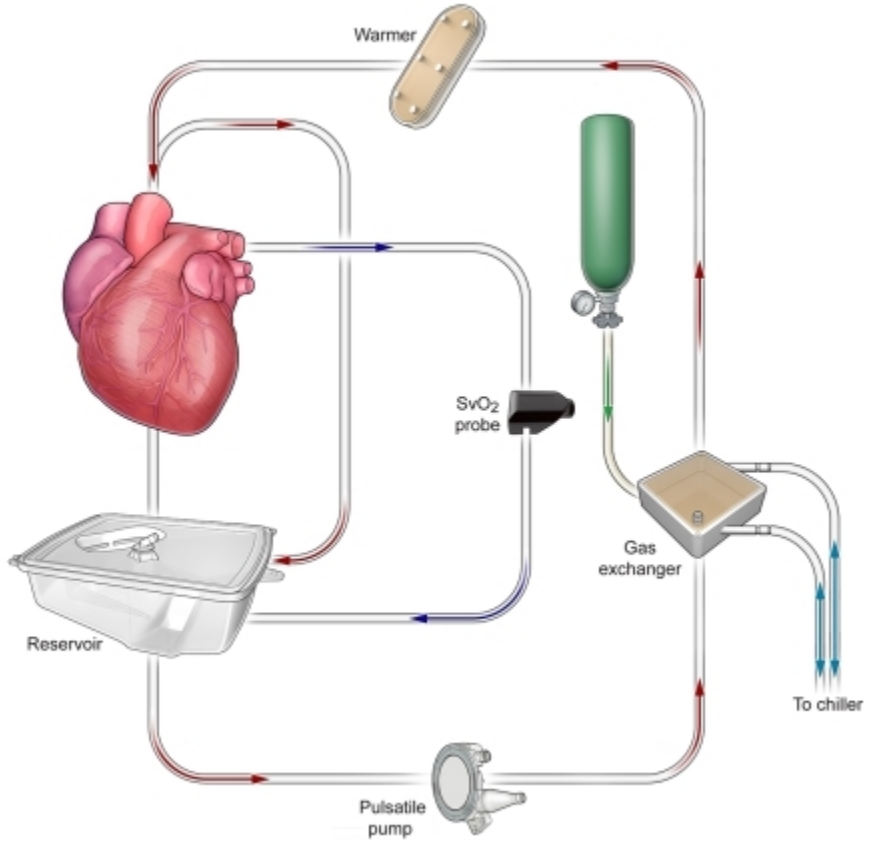
Transmedics Organ Care System (OCS)



Prolonging the "ischemia time"

- Longer transport possible
- Increased patient security during reoperation

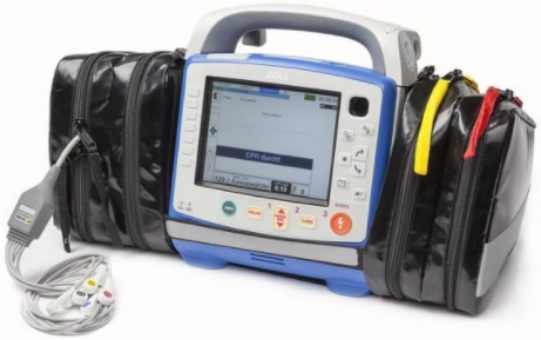
Evaluation possibilty

- Marginal donor
- DCD organ donation

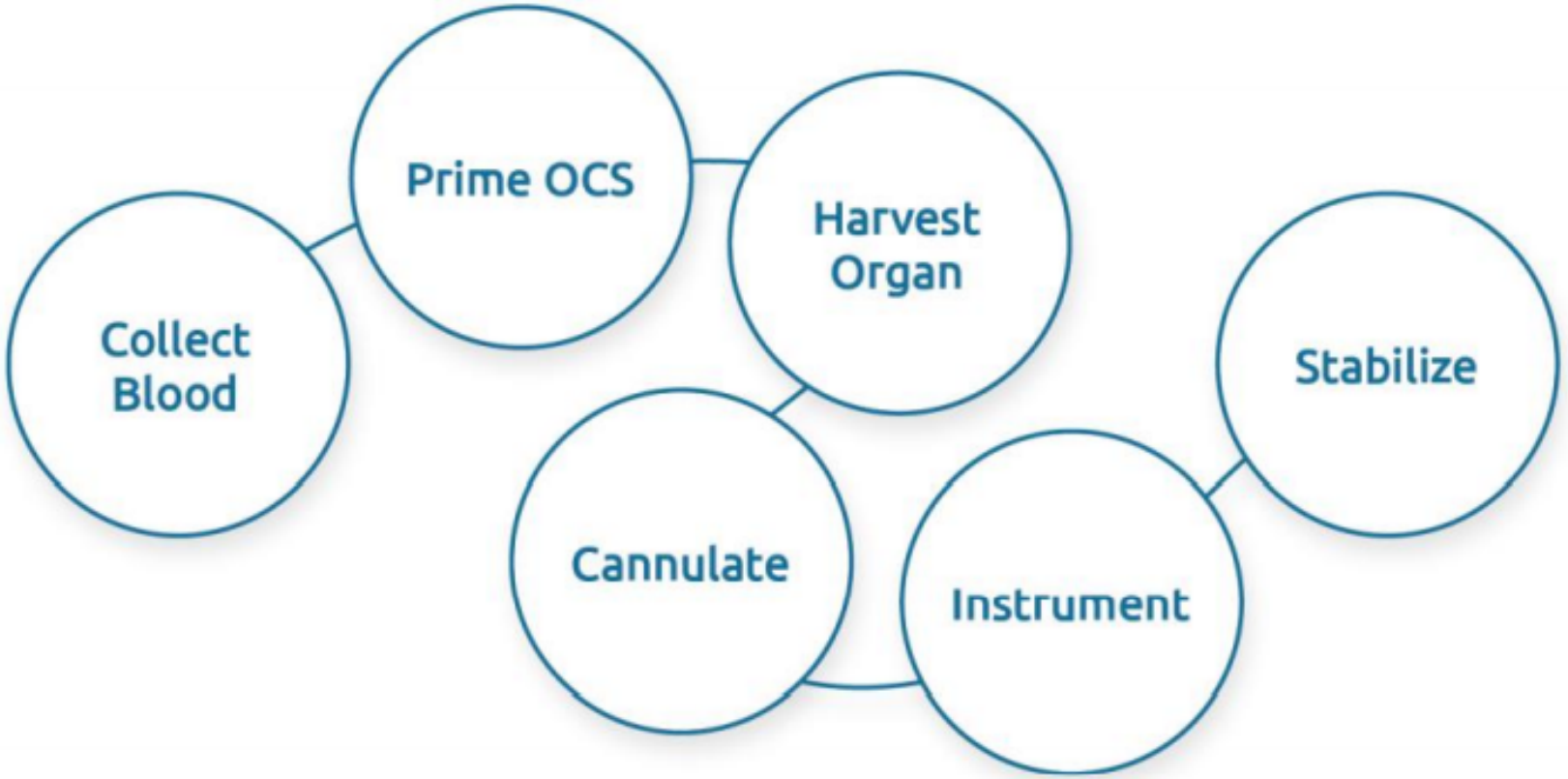
Optimization of organ function

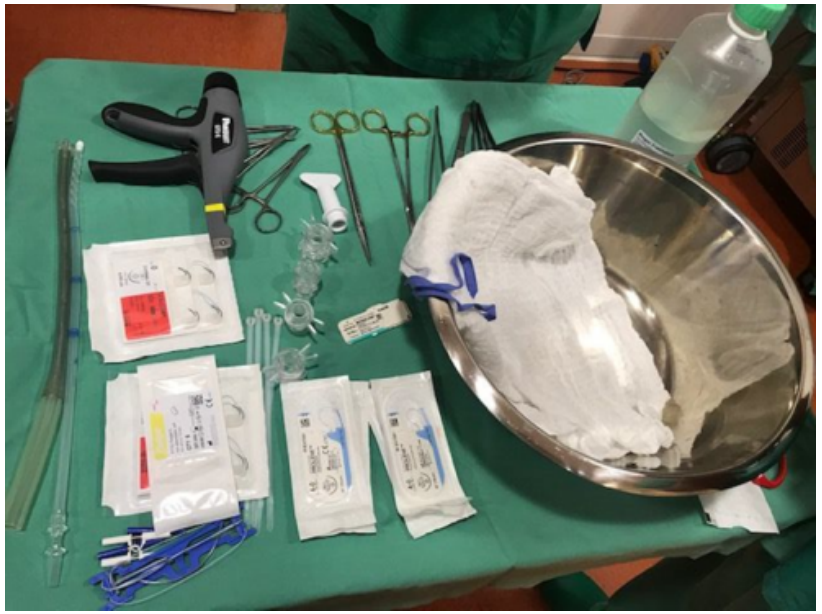
- DCD organ donation
- Takotsubo
- Future therapy options

What you need?



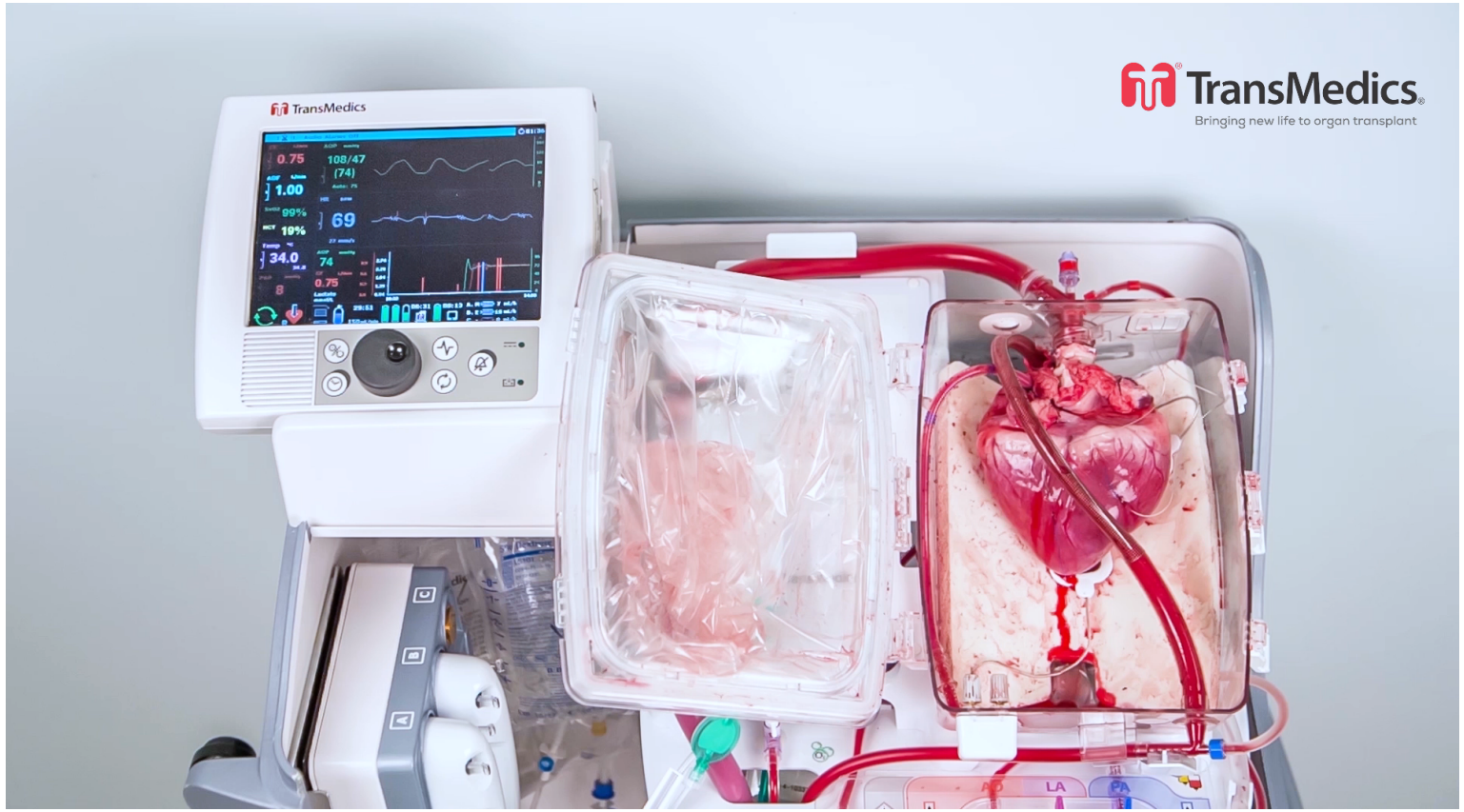
Work flow





Duration 1-2 hours

Running system



Current monitoring possibilities

Coronary Blood Flow

Aortic Blood Flow

Coronary Sinus Saturation

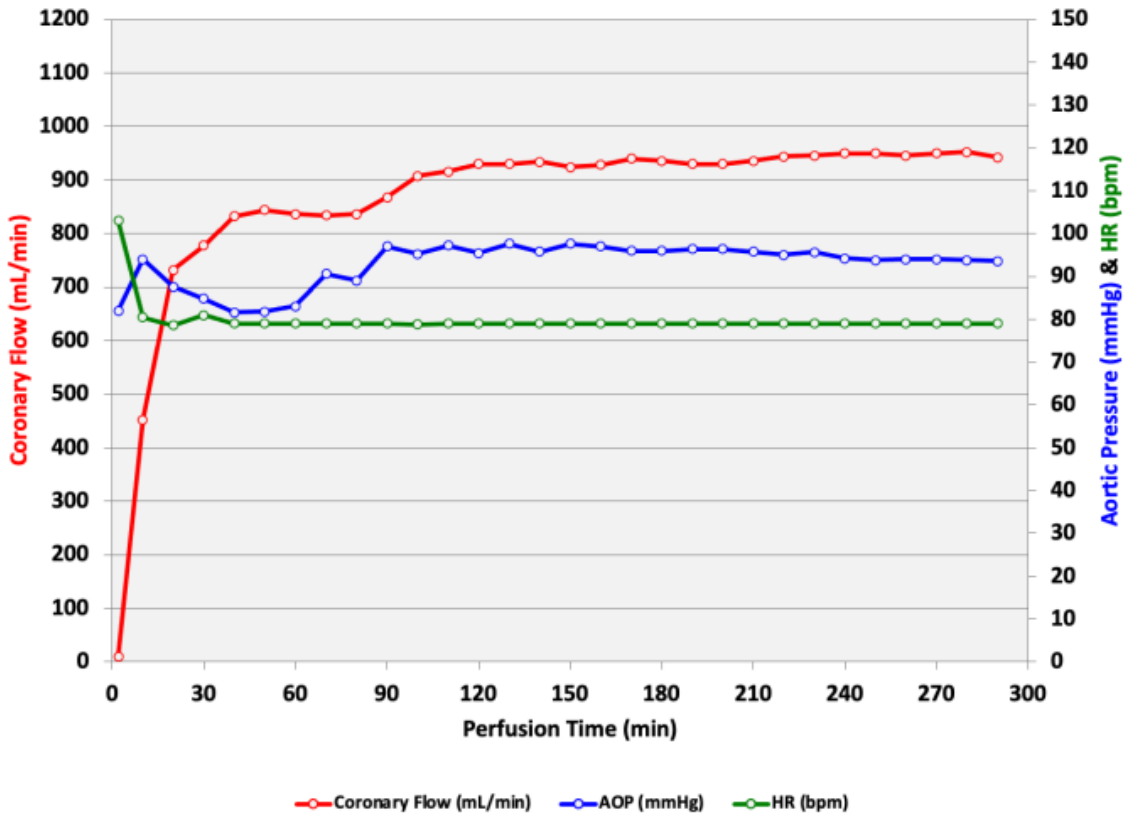
Aortic Pressure

Heart Rate

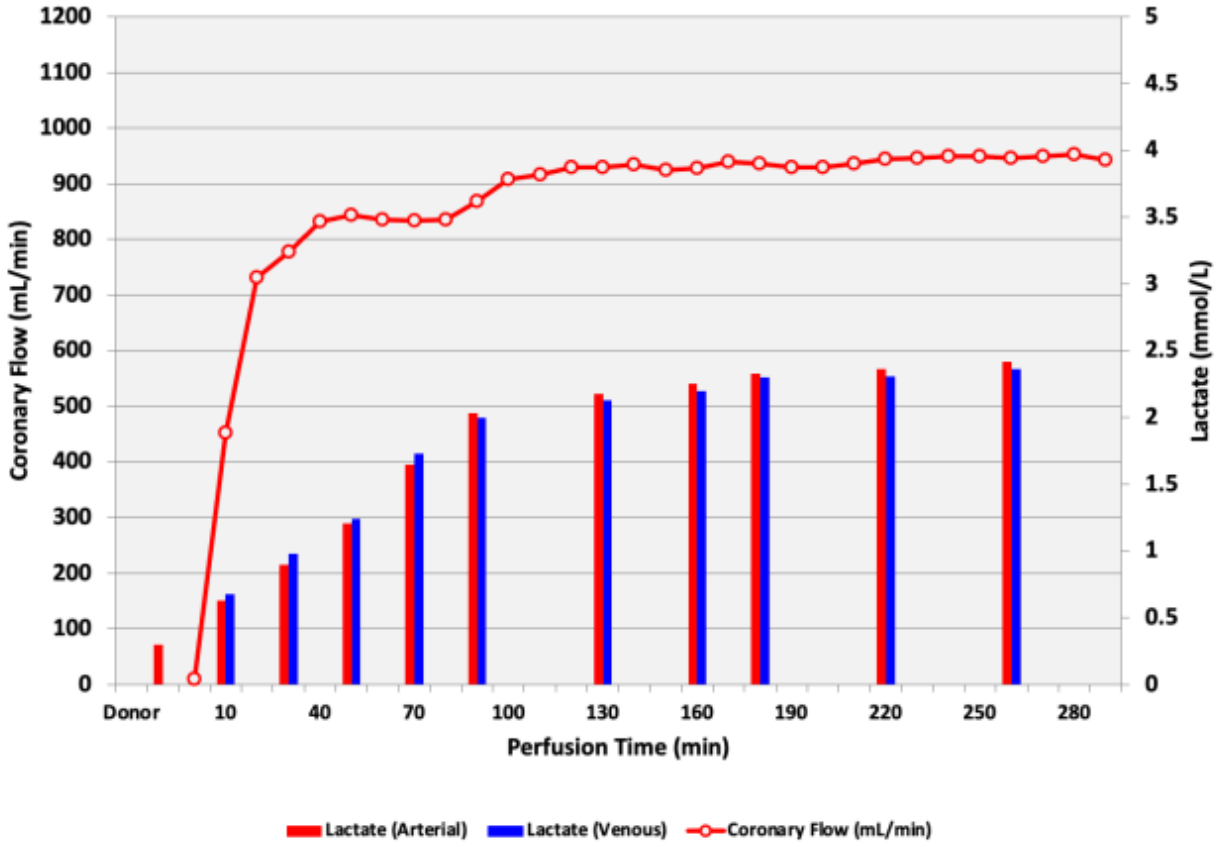
Serial Lactate Levels
Arterial & Venous
Lactate Differential and Trend

Monitoring Data

Perfusion parameter



Lactate profile



EXPAND trial

- Evaluation of ex-situ heart perfusion for extended criteria
- 2015 – 2020 138 extended criteria donor hearts perfused
- On average 60 times refused from other centers
- **116 successfully implanted**

J.N. Schroder et al. J Heart Lung Transplant. 1. April 2022;41(4):S73.

EXPAND trial – Donor characteristics

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

EXPAND trial center. The Kaplan-Meier 2-year patient and graft survival results were comparable between the two comparator arms: patient survival – EXPAND OCS 85.3% vs Control standard criteria hearts 87.8% SOC (p=0.8893), graft survival – EXPAND OCS 94.2% vs Control standard criteria hearts 95%.

J.N. Schroder et al. J Heart Lung Transplant. 1. April 2022;41(4):S73.

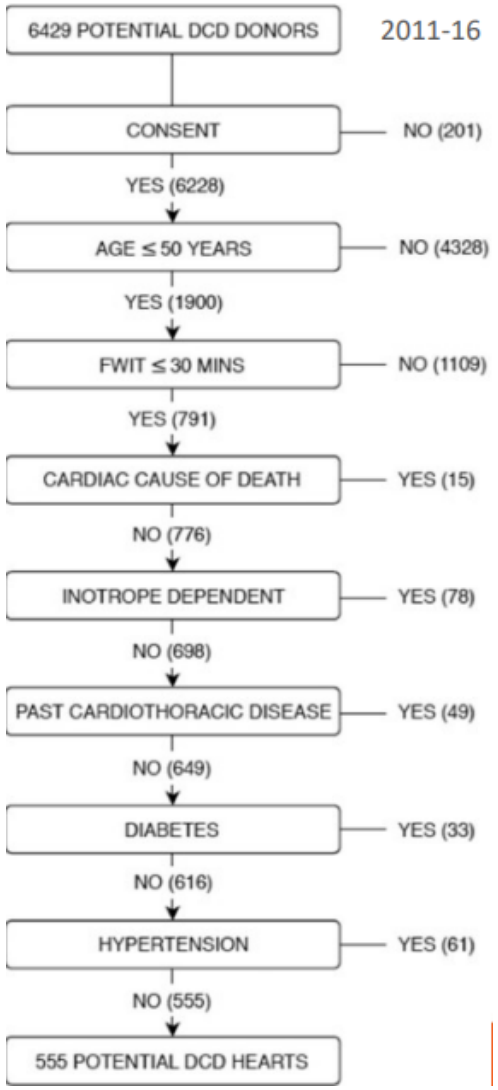
Donation after circulatory death - DCD

RESEARCH CORRESPONDENCE | VOLUME 38, ISSUE 8, P872-874, AUGUST 01, 2019

The potential of heart transplantation from donation after circulatory death donors within the United Kingdom

Simon Messer, MRCS PhD • Aravinda Page • Sally Rushton • ... Steven Tsui • Pedro Catarino • Stephen R. Large, FRCS MBA • Show all authors

Published: April 29, 2019 • DOI: https://doi.org/10.1016/j.healun.2019.04.007 • Check for updates

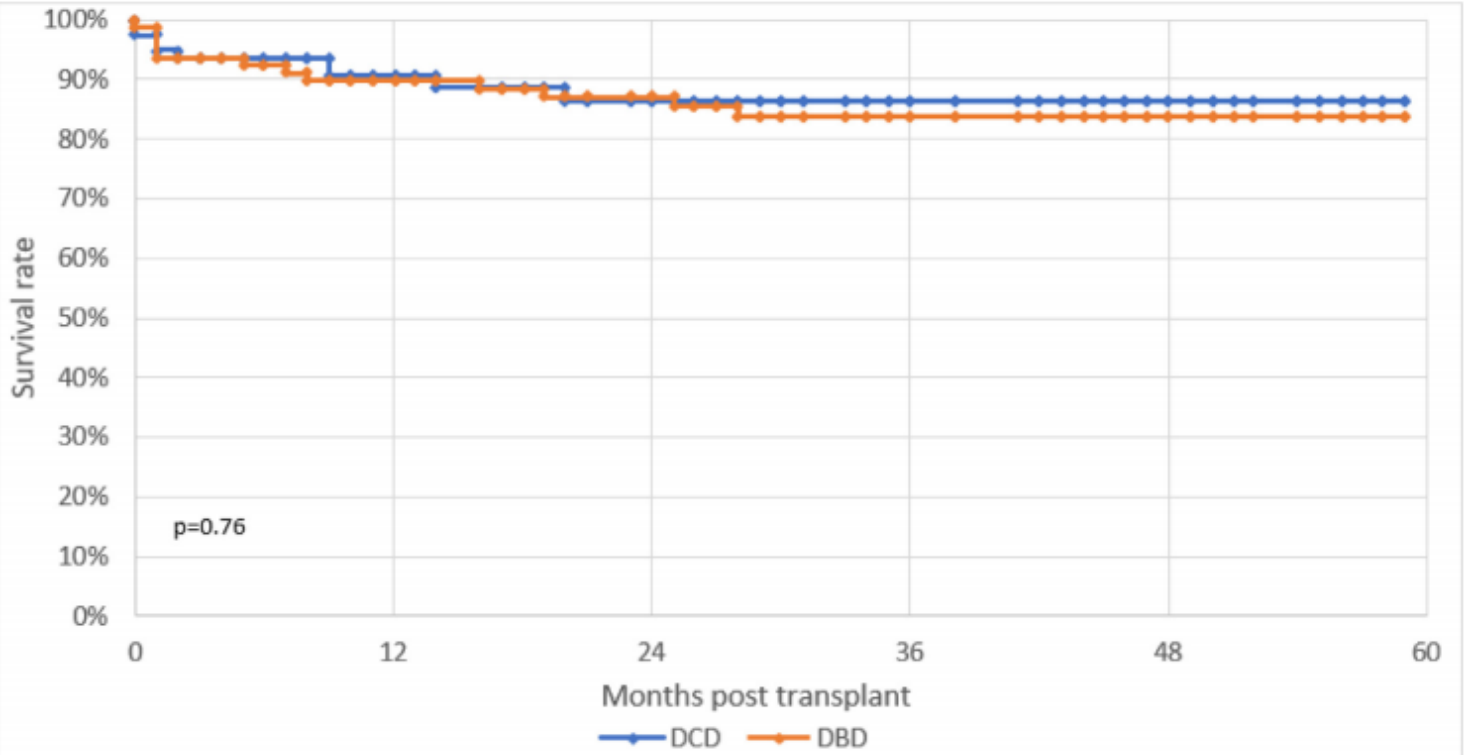


Great potential to increase number of donor hearts→ 56%

Messer S, et al. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2019;38(8):872-4.

Results DCD – Great Britain

A 5-year single-center early experience of heart transplantation from donation after circulatory-determined death donors



2015 – 2020

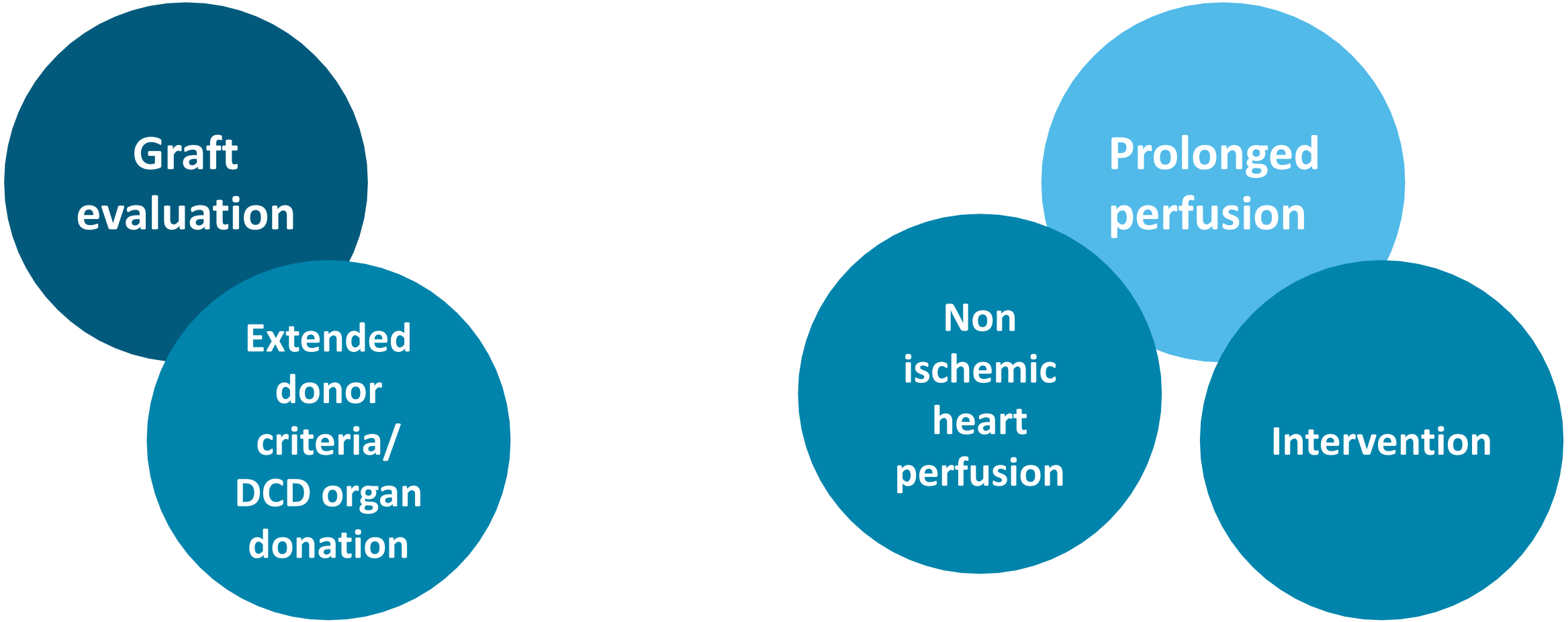
→ 79 DCD heart transplantation (164 DBD)

Messer S, Cernic S, Page A, Berman M, Kaul P, Colah S, et al. A 5-year single-center early experience of heart transplantation from donation after circulatory-determined death donors. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2020;39(12):1463-75.

Limitations of ex – situ heart perfusion

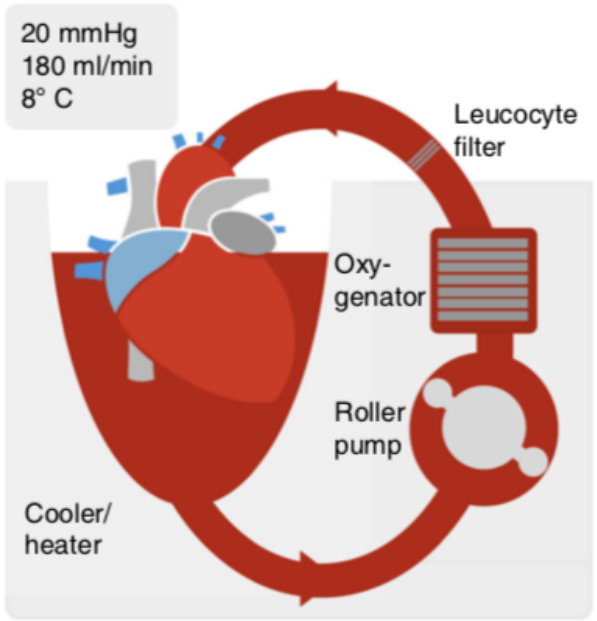
- Donor blood usage
  - Amount of blood can be limited
  - Hematocrit ↑
  - Catecholamines in organ donor
- Perfusion time limited to 6-12 hours
  - Myocardial edema
  - Myocardial function declines with longer perfusion
- Costs and personal intensive

Future perspectives



Nonischemic heart perfusion

a NIHP system



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

c Heart mounting

Fig. 1 The nonischemic heart-preservation method (NIHP). Shown is a drawing of the NIHP method (**a**). The equipment consists of a reservoir, a pressure-controlled roller pump, an oxygenator, an arterial-leukocyte filter, a heater–cooler unit, oxygen and carbon dioxide containers, a gas mixer, sensors, and a programmable control system. The reservoir is filled with 2.5 L of the perfusion solution (**b**) plus ~500 mL compatible irradiated and leukocyte-reduced blood cells from the hospital blood bank, providing a hematocrit of ~15%. Perfusion is provided through the aortic cannula to the coronary vessels. The picture (**c**) shows the first human heart transplantation using the NIHP method. The heart is mounted and submerged into the heart-preservation solution, which is actively regulated to maintain a pH of ~7.4 and a temperature of 8 °C. The device software is adjusted to maintain a mean blood pressure of 20 mmHg in the aortic root, providing a coronary flow between 150 and 250 mL/min.

Nonischemic heart perfusion

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-16782-9 OPEN

Check for updates

A nonrandomized open-label phase 2 trial of nonischemic heart preservation for human heart transplantation

Johan Nilsson[1✉], Victoria Jernryd[1], Guangqi Qin[1], Audrius Paskevicius[1], Carsten Metzsch[1], Trygve Sjöberg[1] & Stig Steen[1]

The first pig to human heart transplant was carried out in Baltimore

CK-MB (ng/mL)

Number at risk

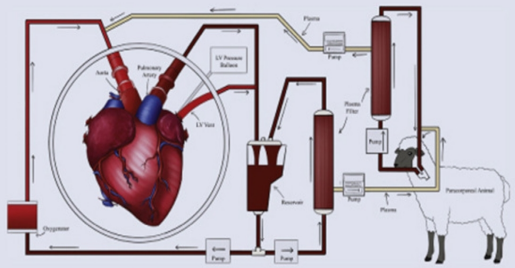
NIHP	6	6	6	6	6	6	6
SCS	25	20	20	19	18	18	18

Prolonged perfusion

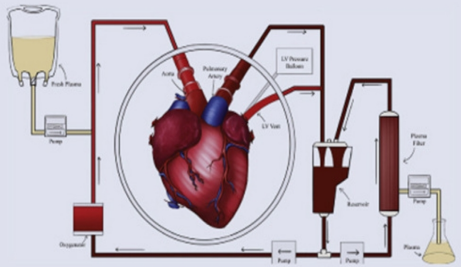
→ **Necessary for future interventions**

Twenty-Four-Hour Normothermic Perfusion of Isolated *Ex Vivo* Hearts Using Plasma Exchange

EVHP Plasma Cross-circulation with Paracorporeal Animal Ovine Model - 2019



EVHP Plasma Exchange (PX) Porcine Model - 2020



Perfusion Outcomes in PX (vs Control without PX)

- EVHP lasting 24 hours: 100% in PX vs 20% in controls
- Average LV systolic pressure: 63 mmHg vs 37 mmHg
- Average coronary resistance: 1.06 mmHg*mL/min vs 0.58 mmHg*mL/min
- Average oxygen consumption: 2.89 mL/min/100g vs 1.80 mL/min/100g
- Lactate: 2.8-4.2 mmol/L vs 3.6-7.6 mmol/L
- Response to epinephrine challenge: positive in 5 PX (vs 2 controls)
- Pathology: less myocardial degeneration and interstitial edema in PX.

Plasma exchange (PX) is an effective substitute for plasma cross-circulation from a paracorporeal animal in 24-hour normothermic *ex vivo* heart perfusion. Data comparing PX perfusion compared to control showed better hemodynamic metrics, metabolic profile, and histology.

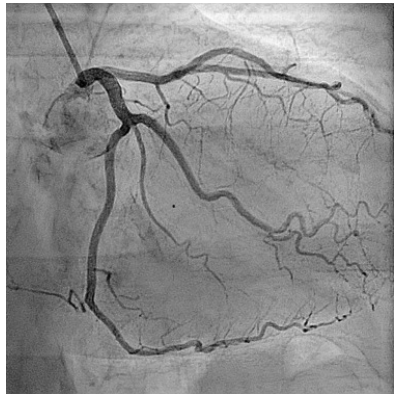
EVHP: *Ex Vivo* Heart Perfusion; LV: Left Ventricle; PX: Plasma Exchange

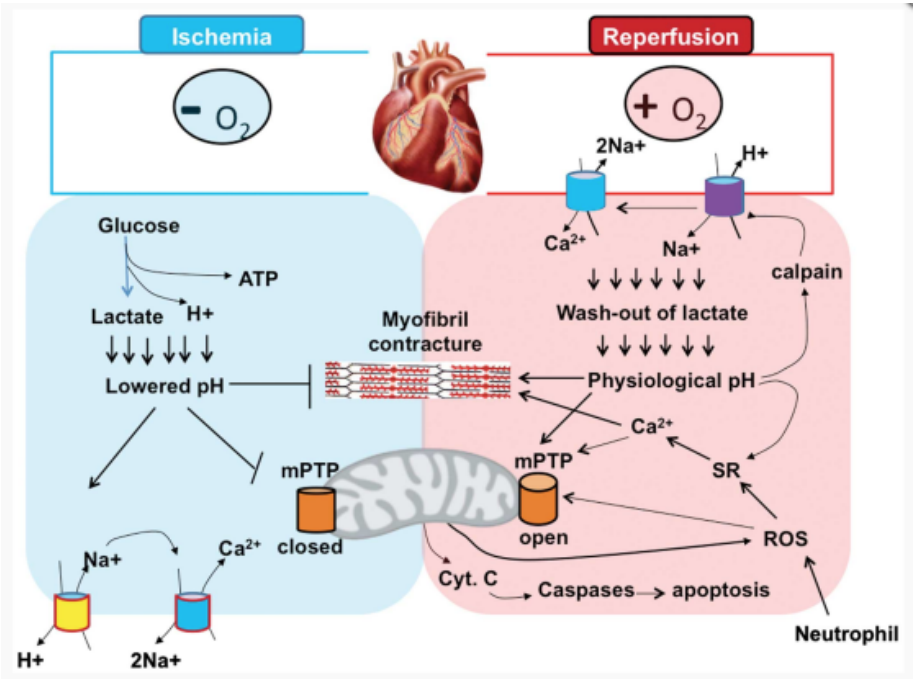
- Animal model
- 24 hours of ex situ heart perfusion
- Perfusate the major factor for graft performance

Tchouta, L. *et al.* Twenty-four-hour normothermic perfusion of isolated ex vivo hearts using plasma exchange. *J. Thorac. Cardiovasc. Surg.* **164**, 128–138 (2022).

Possible Interventions

- Diagnostic interventions → Coronary angiography
- Ischemia/Reperfusion Injury → target for novel therapies
- Mitochondrial transplantation
- Mesenchymal stem cells





Thank you for your attention