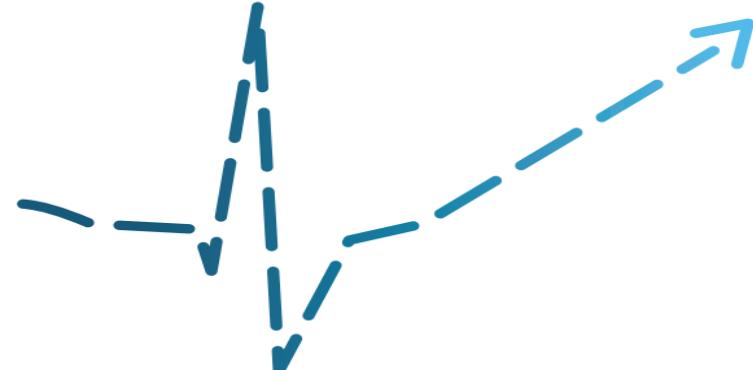
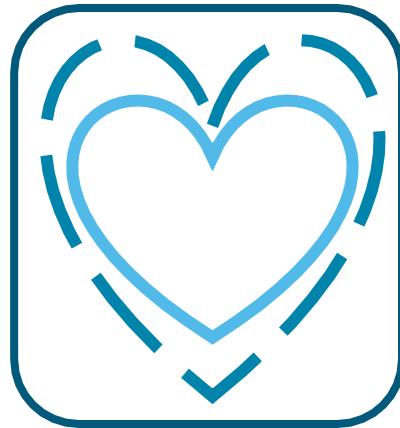


Ex-vivo heart preservation system in heart transplantation



Julia Dumfarth

Department of Cardiac Surgery,
Medical University of Innsbruck



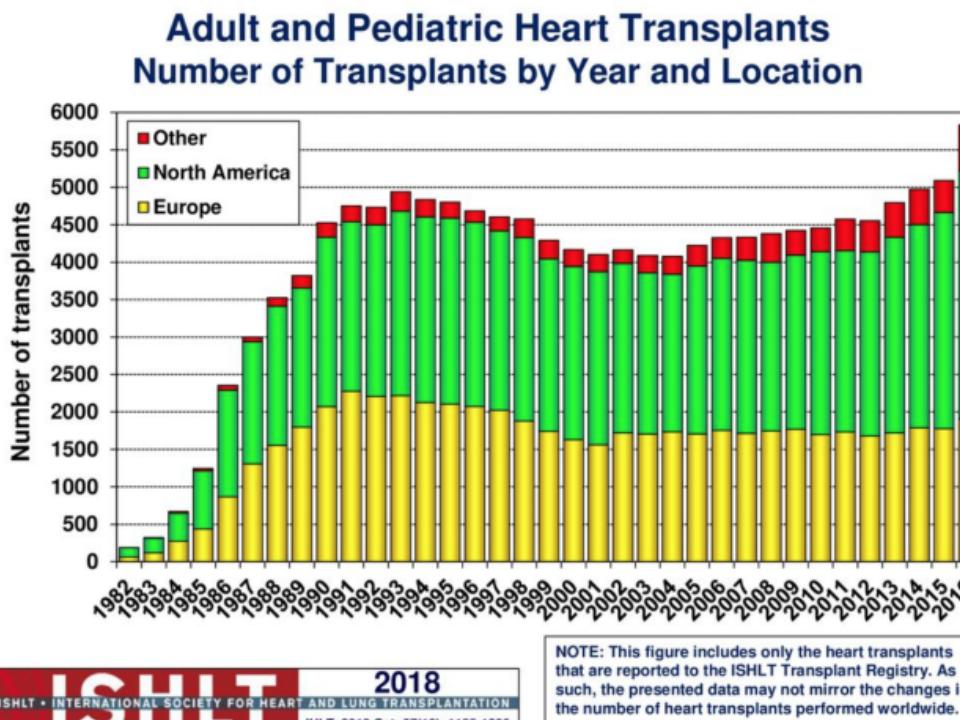
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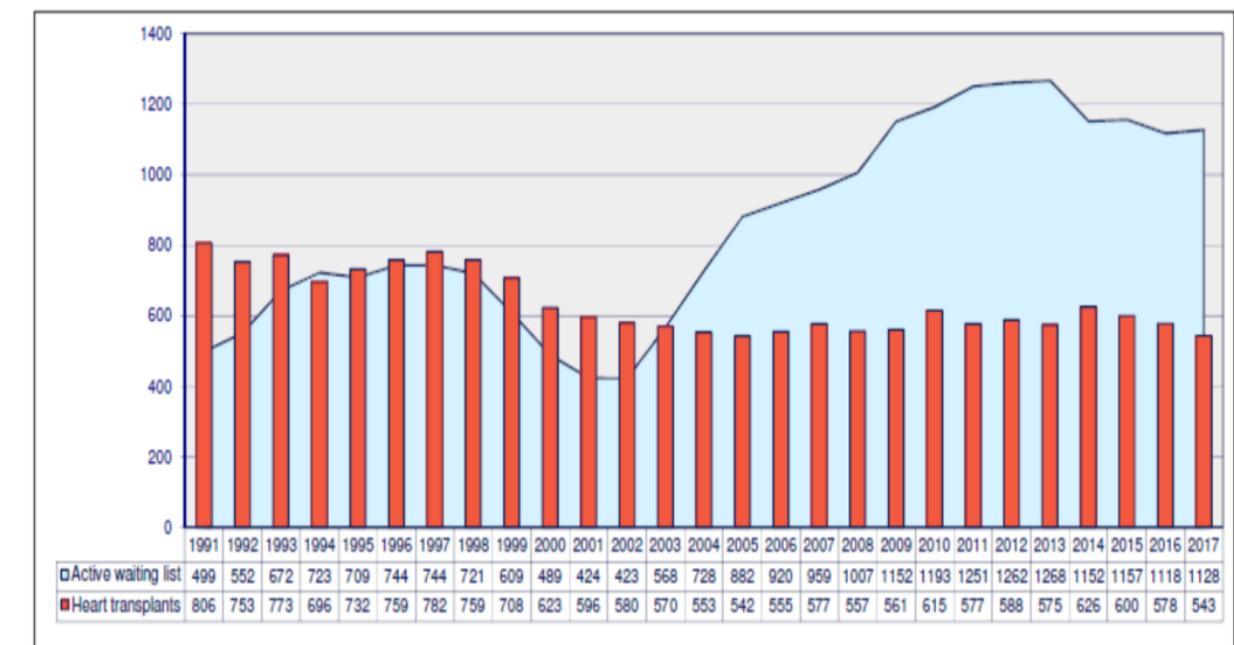


Background

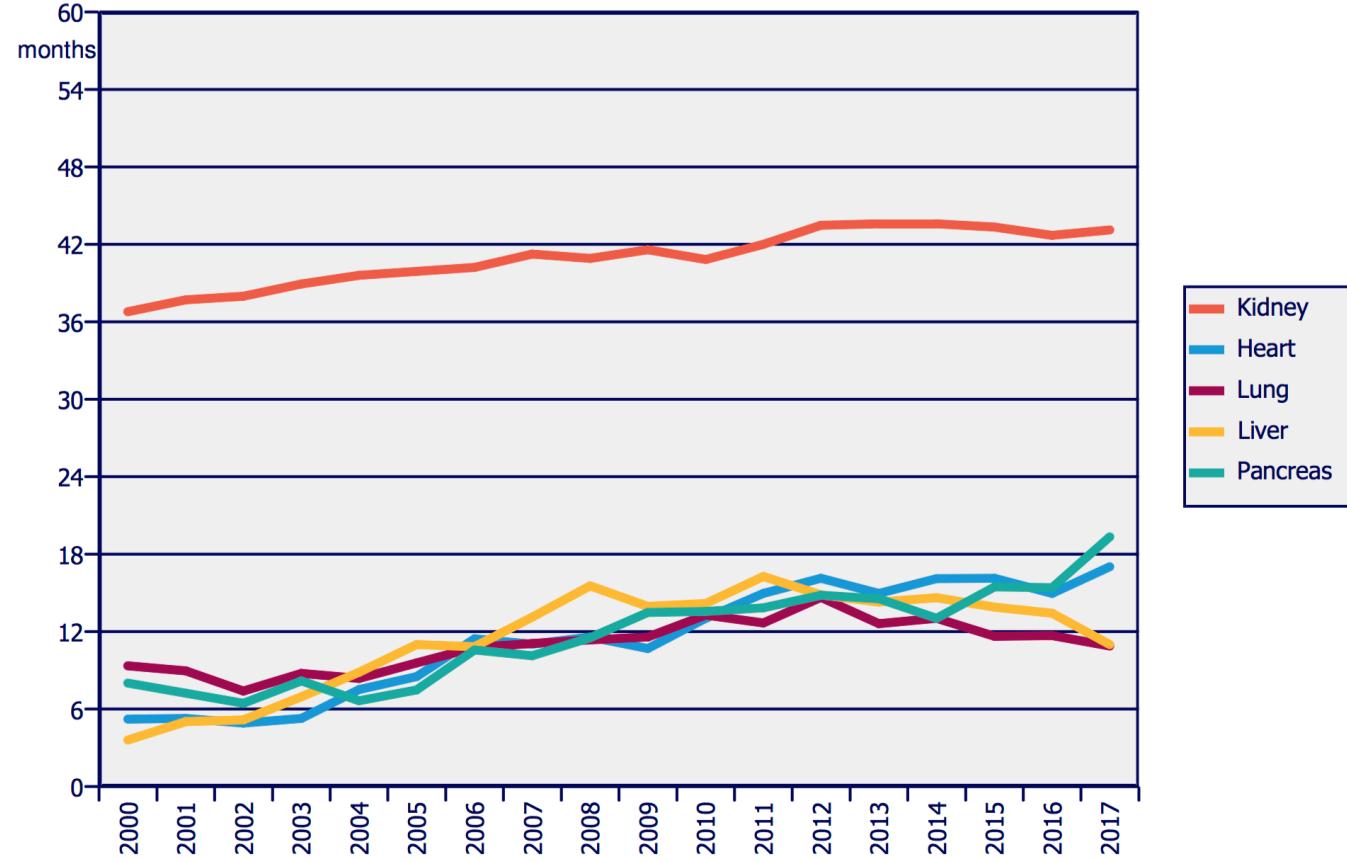
ISHLT Registry



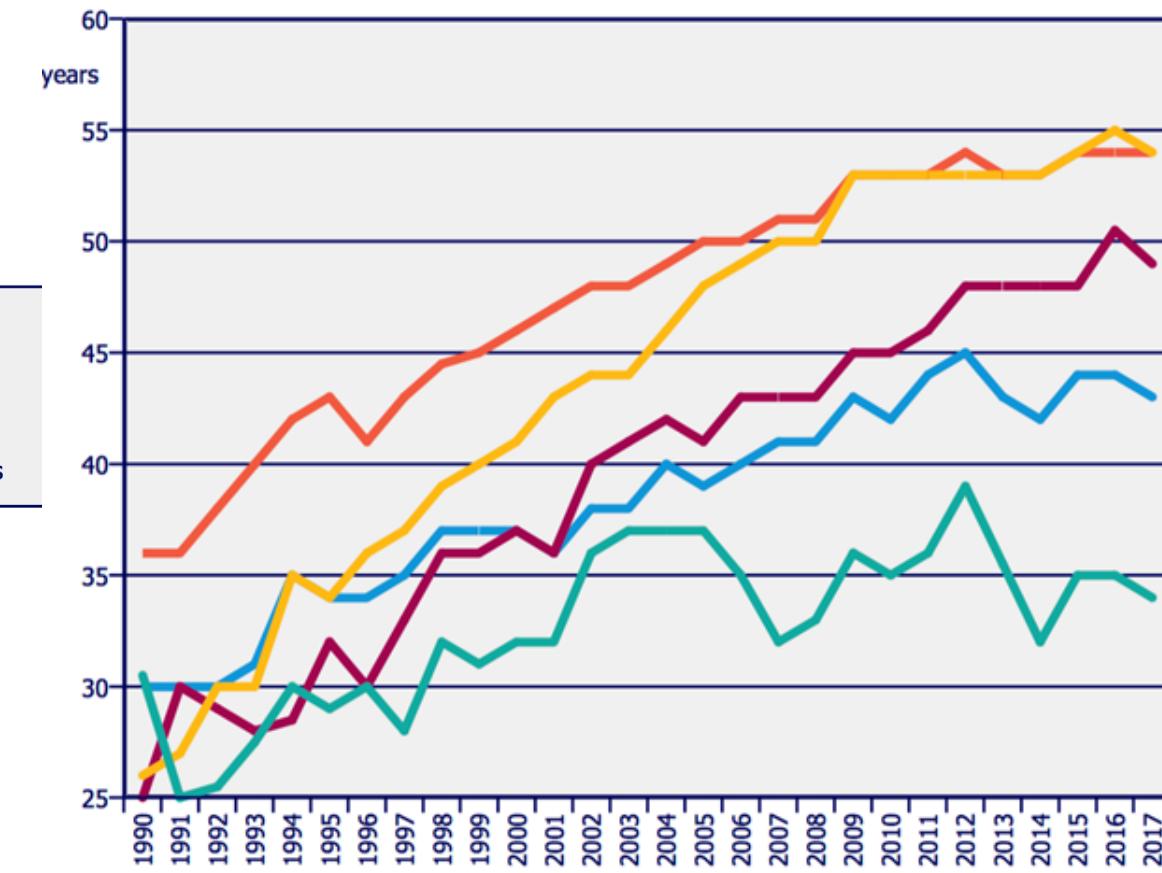
Eurotransplant Registry



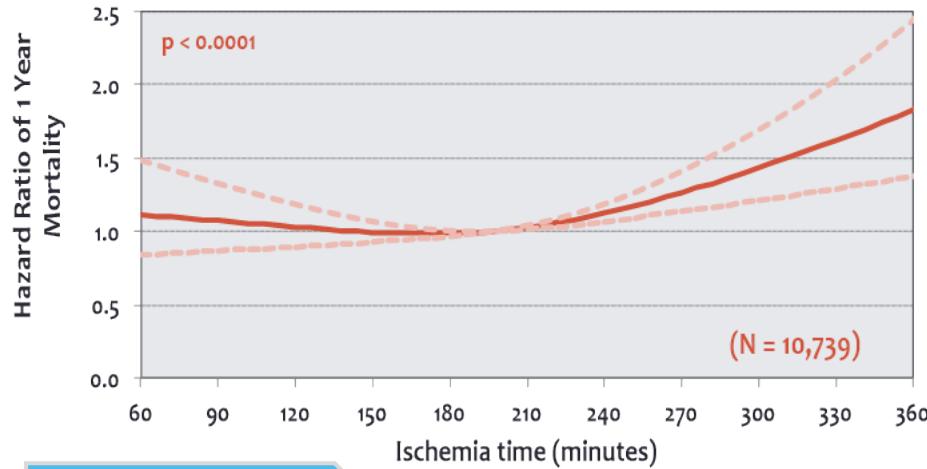
Waiting Time



Donor Age



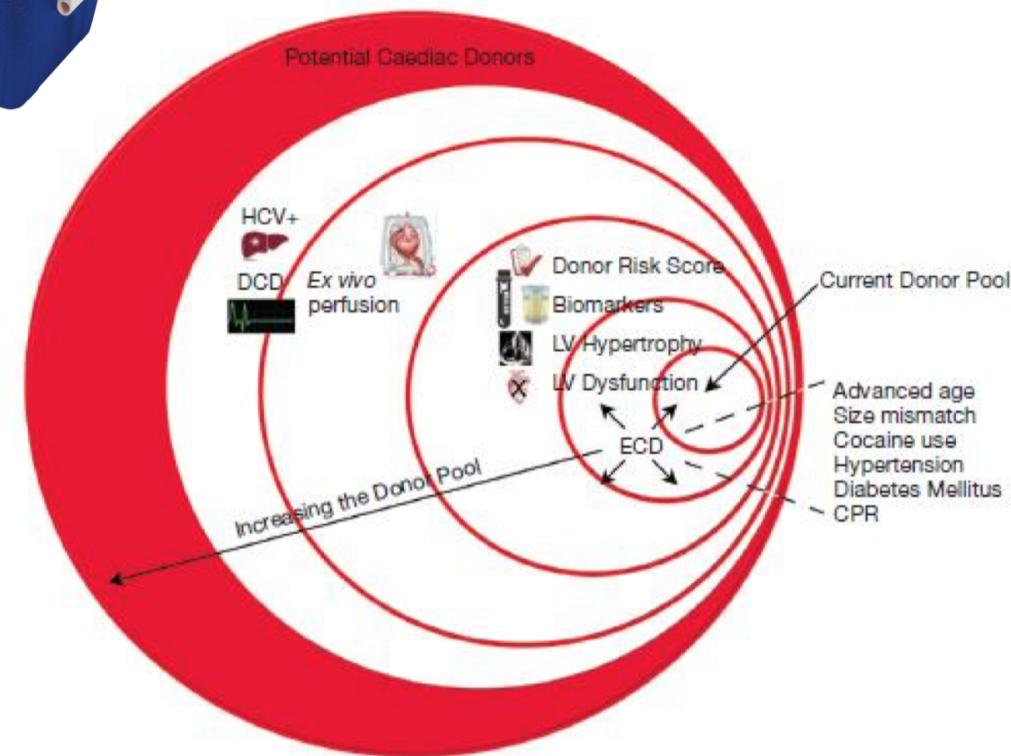
Cold storage



Time limit

No possibility of evaluation

No possibility of organ optimization



Khush. Ann Cardiothorac Surg. 2017

Safety and feasibility

THE LANCET

Ex-vivo perfusion of donor hearts for human transplantation (PROCEED II): a prospective multicentre, randomised non-inferiority trial

Summary
Background The Organ Care System is the only clinical platform for ex-vivo perfusion of donor hearts. In a warm beating state during transplant the system preserves the donor heart. In a stop-beating state during transport the system preserves the donor heart. However, suitable cardiac donors are scarce. We aimed to assess the clinical outcomes of the Organ Care System compared to standard donor hearts for transplantation.

Methods We did this prospective, open-label, multicentre, randomised non-inferiority trial in the USA and Taiwan. Eligible heart-transplant candidates aged 18 years or older were randomised to the Organ Care System or standard of care. Donors were matched by gender and medical staff were masked to group assignment. The primary endpoint was a 10% non-inferiority margin. We did analysis in the intention-to-treat, as-received donor heart for transplantation.

Findings Between June 22, 2008, and Sept 30, 2011, we randomly assigned 130 patients to the standard cold storage group (n=65), 30 to the patients and grafts Organ Care System group, and 97% of those in the standard cold storage group were operated on within 4 h post-45 min. Eighty-four patients in the Organ Care System group had cardiac-related grafts. The primary endpoints were met in all groups. We did analysis in the intention-to-treat, as-received donor heart for transplantation.

Interpretation Heart transplantation using donor hearts adequately preserved with standard cold storage yields similar short-term clinical outcomes. The nephrotoxic standard cold storage yields similar short-term clinical outcomes. The nephrotoxic

Funding TransMedics.

Introduction
Heart transplantation is the treatment of choice for many patients with end-stage heart disease.^{1–3} Despite substantial progress in many aspects of heart transplantation, donor management, operating technique, post-operative care, and transplantation outcome remain challenging.^{4–10} The technique for preservation of donor hearts is well described.^{11–13} In contrast, cold storage leads to time-dependent ischemic and reperfusion lesions, especially of the donor heart, which may limit function after transplantation.^{14–16} Prolonged cold storage times after transplantation, prolonged warm ischemia times, and an increased risk factor for early dehiscence of the anastomosis are associated with a higher rate of late graft failure.^{17–20} Shorter cold storage times are an important goal to reduce the risk of graft failure. In addition, the use of donor hearts from brain-dead donors can also adversely affect use of donor hearts and post-operative outcome.^{21–23} In the past several decades there has been some interest in clinical thermal and passive reperfusion blood to reduce ischemic injury with donor heart and potentially enable twelve assessments of myocardial viability and function.^{24–26} Several reports have investigated use of continuous infusion drops of glucose, few acids, insulin, heparin, steroids, and antibiotics to maintain a steady state of circulation of the donor heart for preservation.

THE ANNALS OF THORACIC SURGERY

Adult heart transplantation with distant procure ex-vivo preservation of donor hearts after circulatory death

Summary
Background Human heart transplantation is the standard long-term treatment for stage heart failure. However, suitable cardiac donors are scarce. Although donation after circulatory death (DCD) is used for heart transplantation, we report transplantation from donor after circulatory death.

Methods The techniques were performed at the Veterans' Hospital, Sydney, Australia. They took III controlled donor deceased after circulatory death from persons younger than 65 years and a time of 30 min. We reviewed four hours through initial resuscitative process and transported via the Organ Care System (TransMedics, Inc.) to the recipient hospital.

Findings Three recipients (one male, one female; median age 52 years) with low cardiopulmonary group (n=7) or the standard cold storage group (n=13) 30 to 40 patients and grafts. Organ Care System group and 97% of those in the standard cold storage group were operated on within 4 h post-45 min. Eighty-four patients in the Organ Care System group had cardiac-related grafts. The primary endpoints were met in all groups. We did analysis in the intention-to-treat, as-received donor heart for transplantation.

Interpretation Heart transplantation using donor hearts adequately preserved with standard cold storage yields similar short-term clinical outcomes. The nephrotoxic

THE ANNALS OF THORACIC SURGERY

Evaluation of the Organ Care System in Heart Transplantation With an Adverse Donor/Recipient Profile

Summary
Background Orthotopic heart transplantation is the standard treatment for stage heart failure. However, suitable cardiac donors are scarce. Although donation after circulatory death (DCD) is used for heart transplantation, we report transplantation from donor after circulatory death.

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Heart Lung and Circulation

Successful Heart Transplant after Hours Out-of-body Time using the TransMedics Organ Care System

Summary
Background The Organ Care System (OCS) is the standard long-term treatment for stage heart failure. However, suitable cardiac donors are scarce. Although donation after circulatory death (DCD) is used for heart transplantation, we report transplantation from donor after circulatory death.

Methods The techniques were performed at the Veterans' Hospital, Sydney, Australia. They took III controlled donor deceased after circulatory death from persons younger than 65 years and a time of 30 min. We reviewed four hours through initial resuscitative process and transported via the Organ Care System (TransMedics, Inc.) to the recipient hospital.

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Interpretation Heart transplantation using donor hearts adequately preserved with standard cold storage yields similar short-term clinical outcomes. The nephrotoxic

Organ preservation with the organ care system

Applied Cardiopulmonary Pathophysiology

Organ preservation with the organ care system

Ruth Yeter, Michael Hübner, Miralem Pasic, Roland Hetzer, Christoph Kressler

Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin

Abstract
Clinical heart transplantation is limited by the shortage of donor organs. The recent development of new donor organ maintenance systems may help to increase the utilization of available organs. This article reviews current experience with the Organ Care system for heart transplantation.

Key words: organ preservation, warm preservation, heart donor, heart transplantation

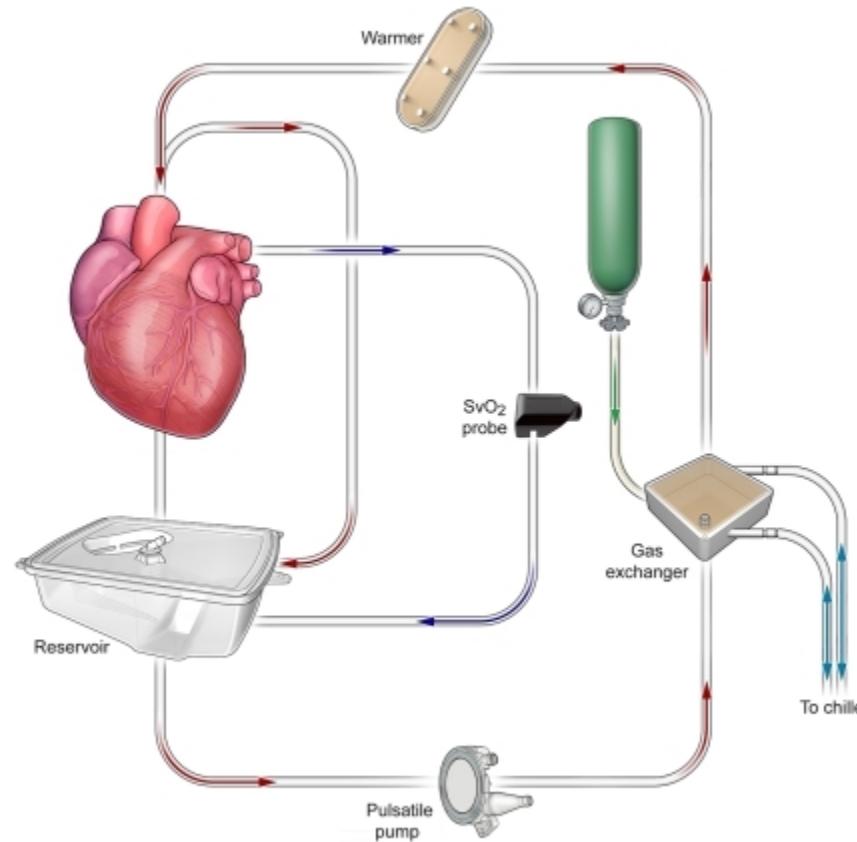
Introduction
Heart transplantation presents the most effective therapy for end stage heart disease. Until today orthotopic heart transplantation has been performed in 89,000 patients worldwide (1). With the success of heart transplantation the criteria for acceptance of donor hearts have been continuously expanded. Nevertheless, transplantation is limited by the shortage of suitable donor organs.

The standard method of organ preservation in this context is cold hypothermic static preservation. The heart is perfused with a cold preservative solution, then explanted and stored at 4°C in a solution for transportation to the recipient hospital. There are two main groups of preservation solutions: intracellular solutions such as Breischneider solution, University of Wisconsin (UW), Euro-Collins and Stanford solution and the extracellular solutions Celsior, St. Thomas Hospital, Lyon Preservation and modified University of Wisconsin solution (2). The preference for a specific cardioplegia solution often depends on the individual experience of each transplant center. A whole arsenal of different preservation solutions are used today and this fact may suggest that there is no "superior" one available. Despite the large number of different solutions there are limitations for cold preservation. The generally accepted ischemic time for cold preservation lies within 4 hours. Data from the ISHLT registry sug-

Cold hypothermic organ preservation

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Transmedics Organ Care System (OCS)





Prolonging the
“ischemia time”

- Longer transport possible
- Increased patient security during reoperation

Evaluation possibility

- Marginal donor
- DCD organ donation

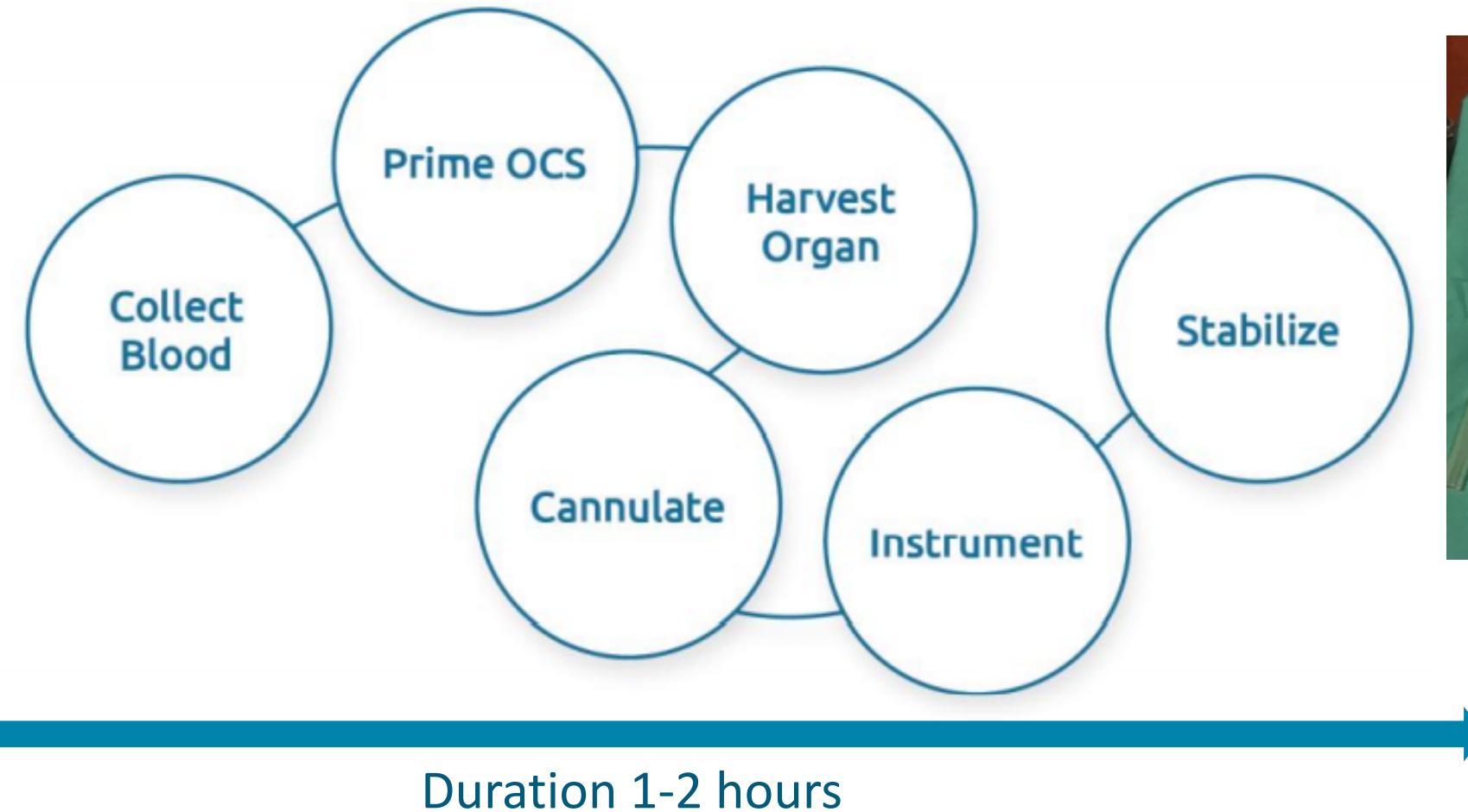
Optimization of organ
function

- DCD organ donation
- Takotsubo
- Future therapy options

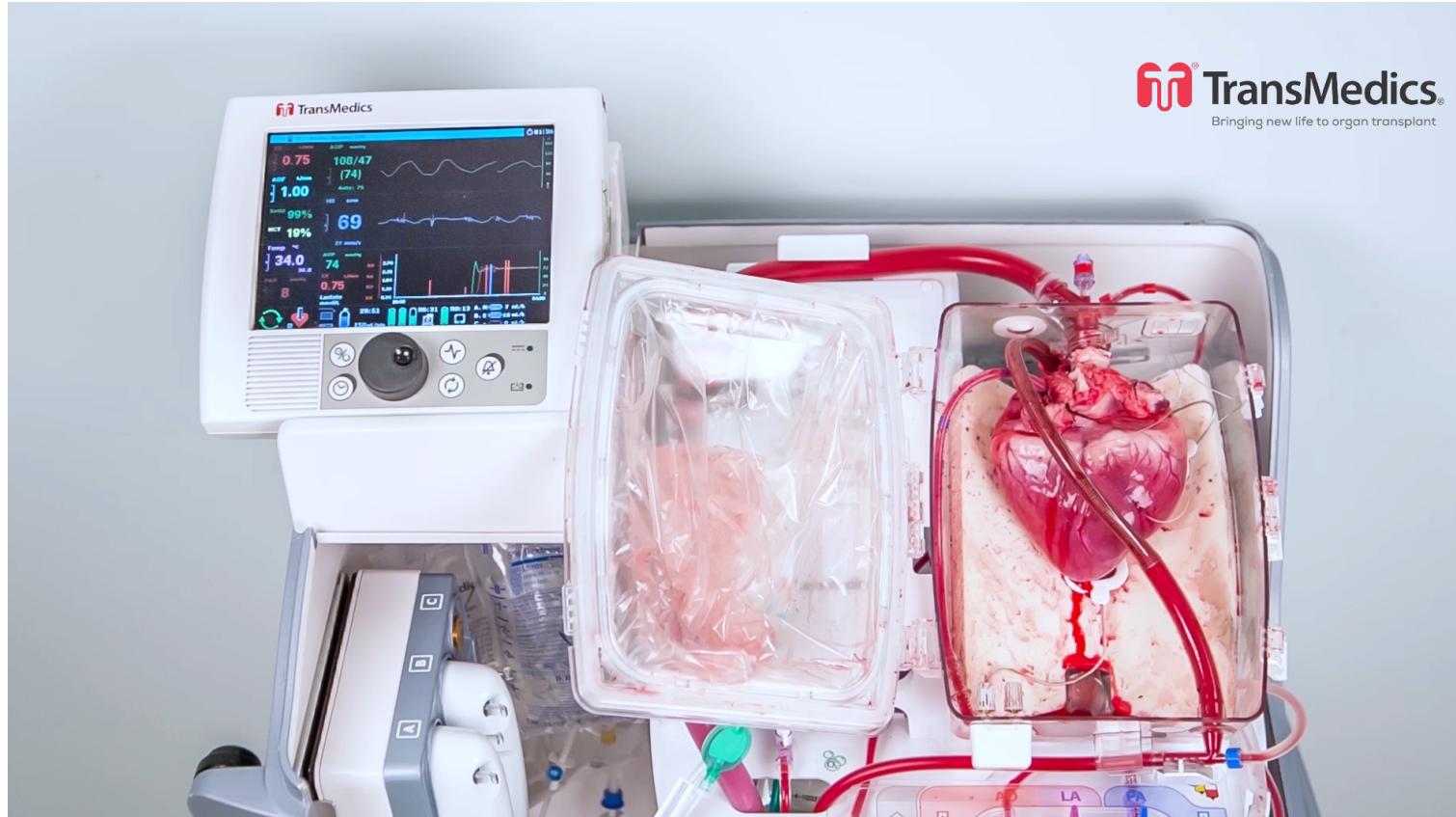
What you need?



Work flow



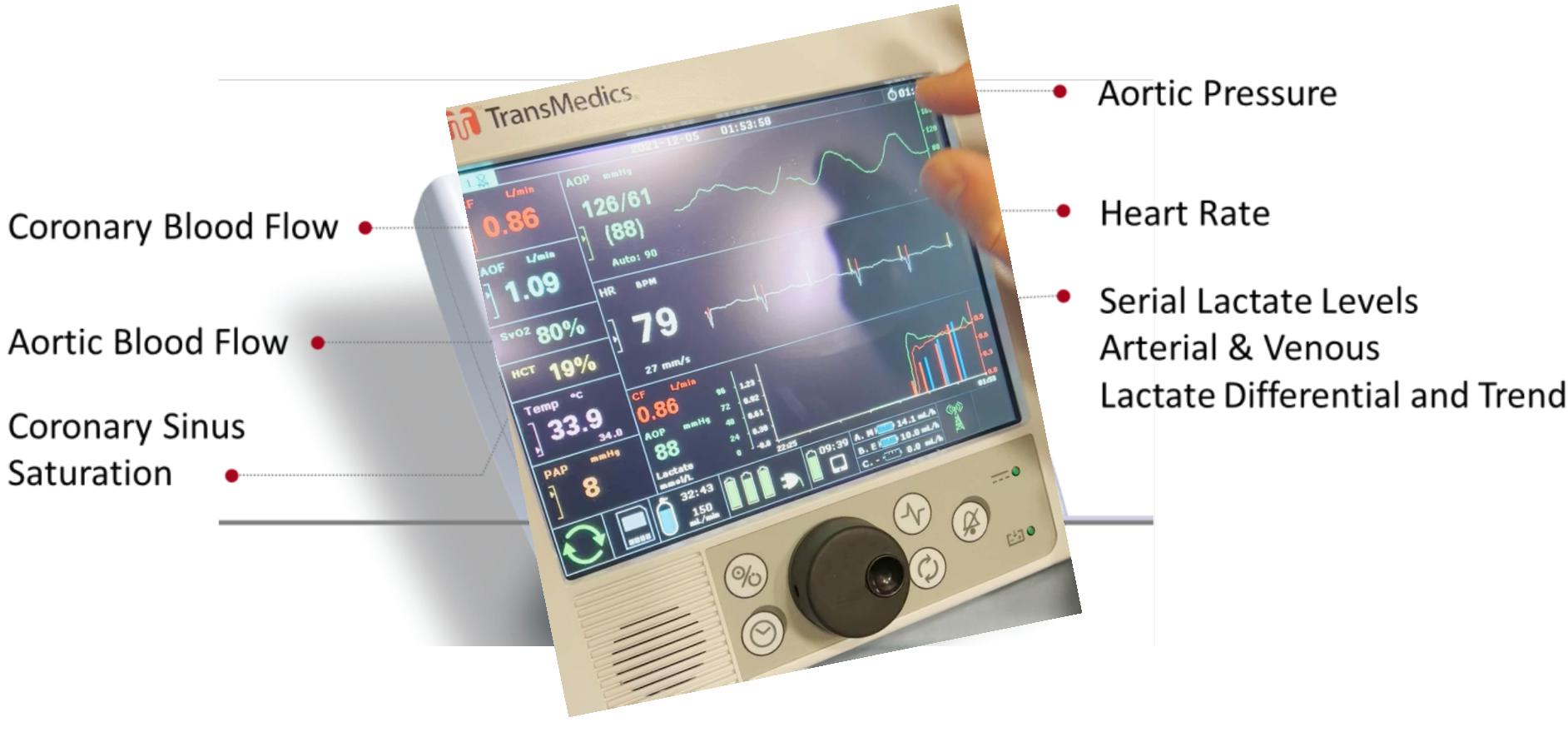
Running system



TransMedics®
Bringing new life to organ transplant

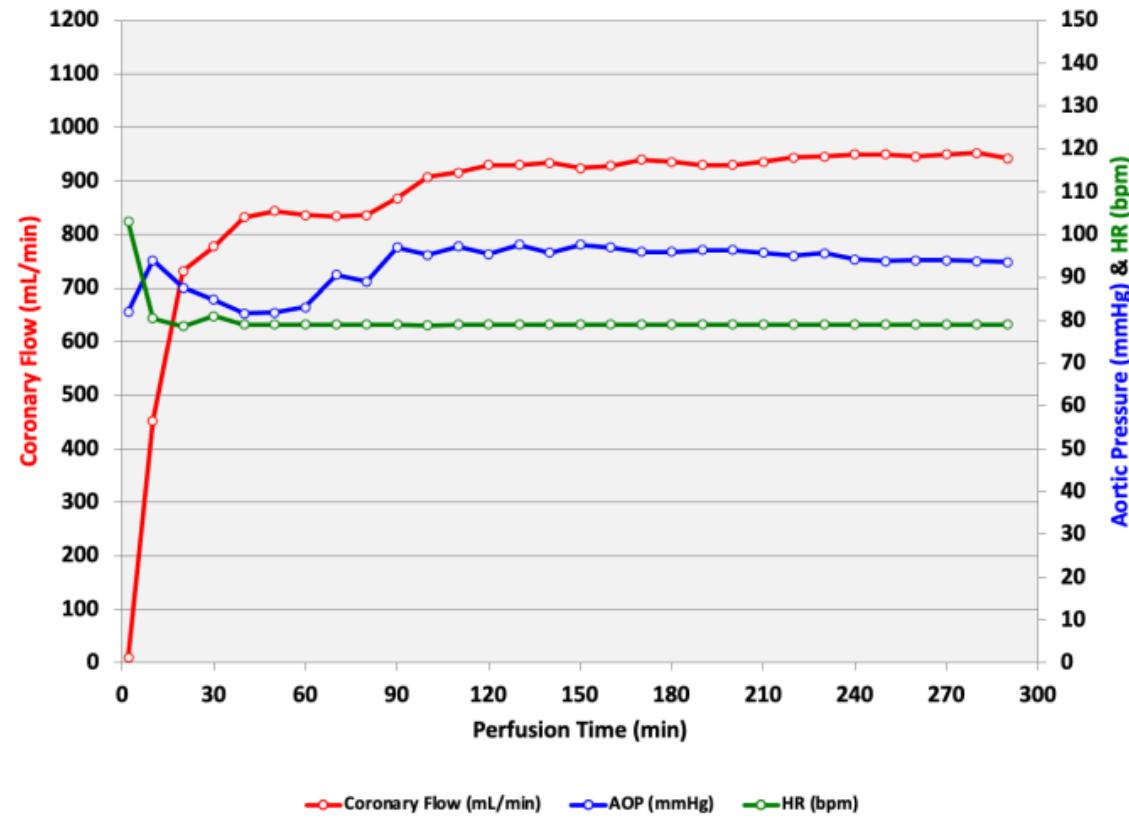


Current monitoring possibilities

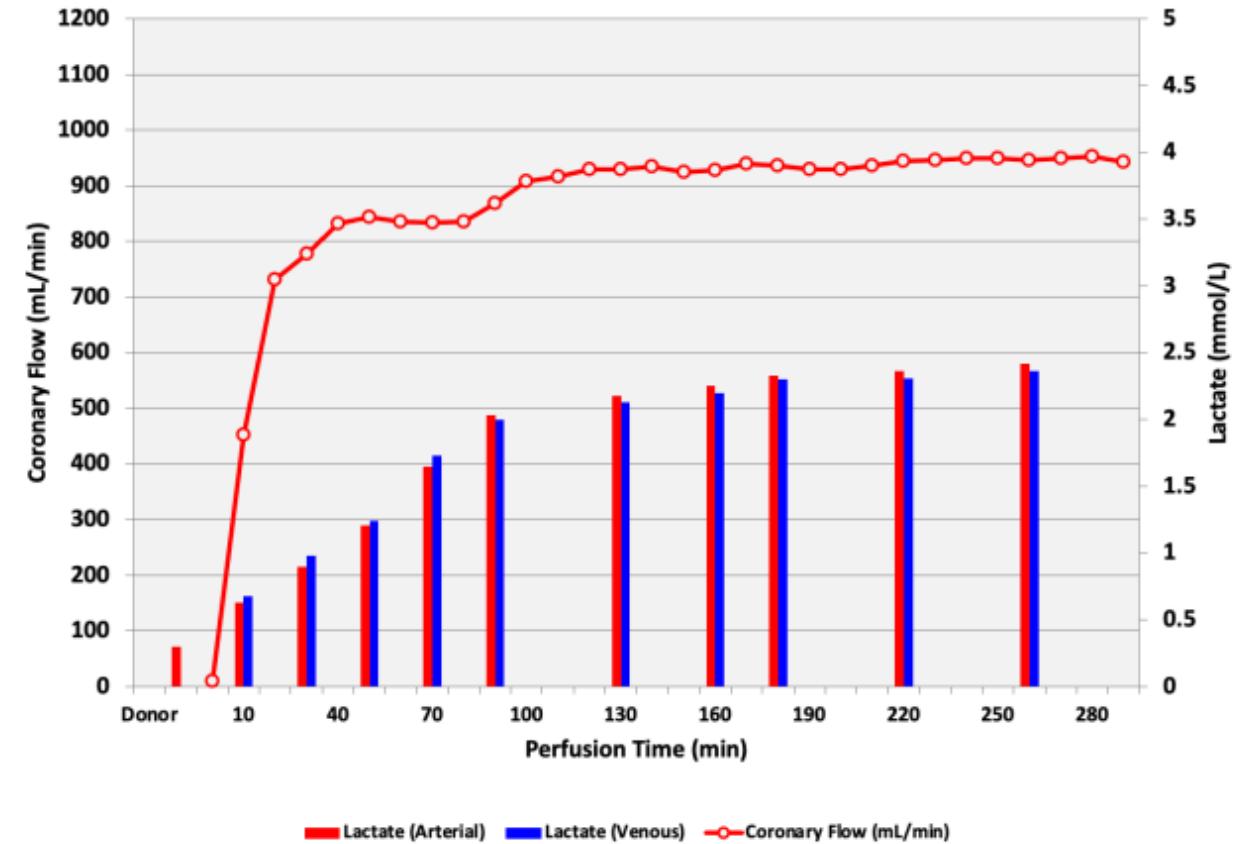


Monitoring Data

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%.

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

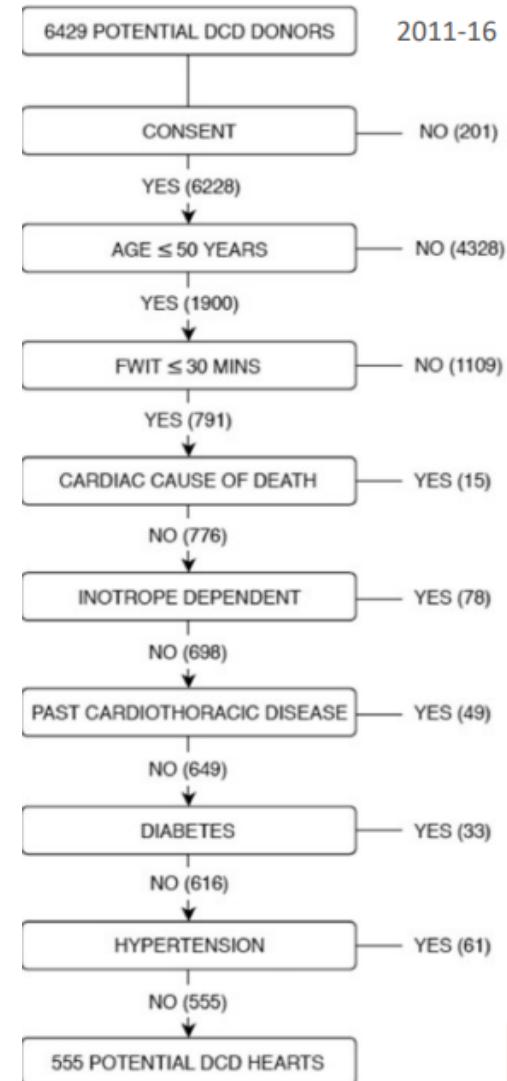
Simon Messer, MRCS PhD • Aravinda Page • Sally Rushton • ... Steven Tsui • Pedro Catarino •

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

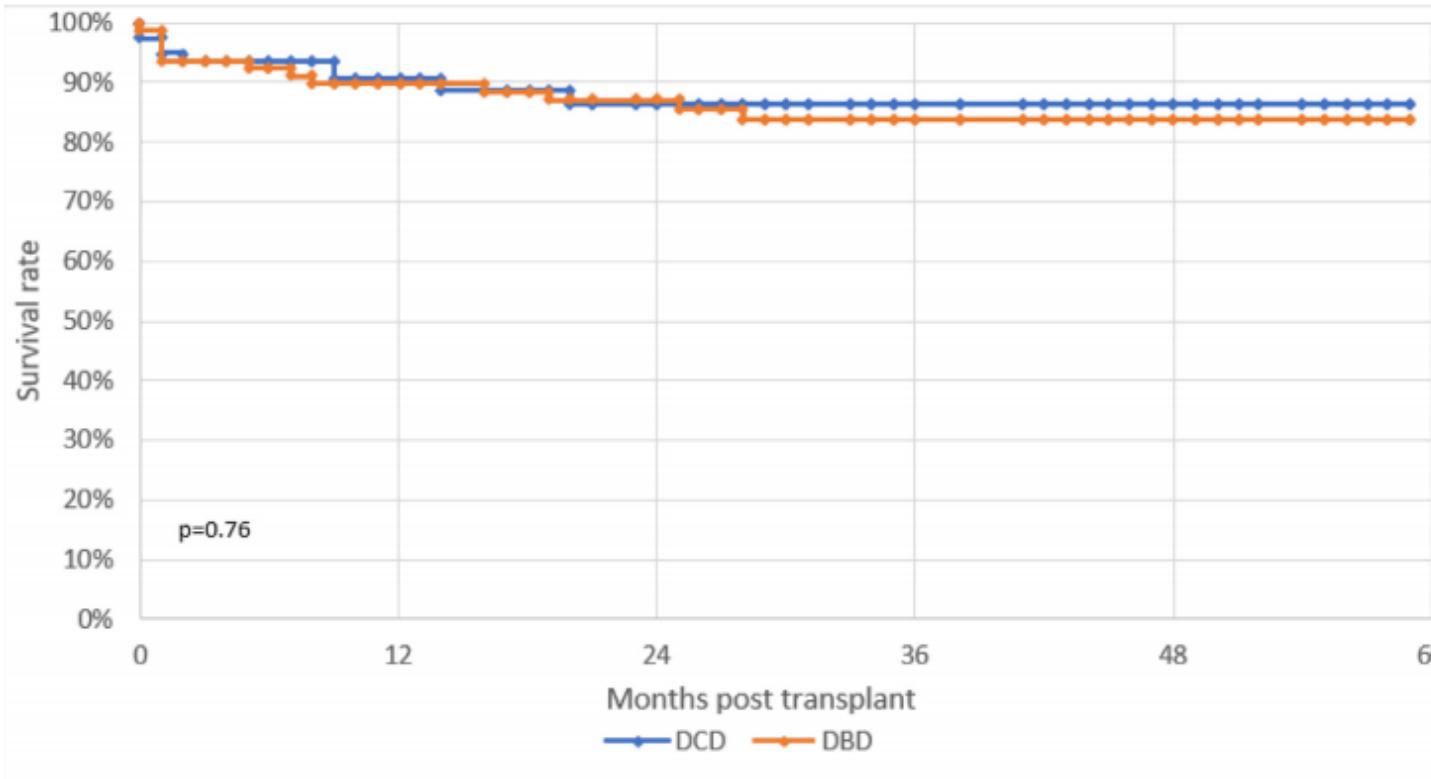
Great potential to increase number of donor hearts → 56%

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

Graft
evaluation

Extended
donor
criteria/
DCD organ
donation

Non
ischemic
heart
perfusion

Prolonged
perfusion

Intervention

Nonischemic heart perfusion

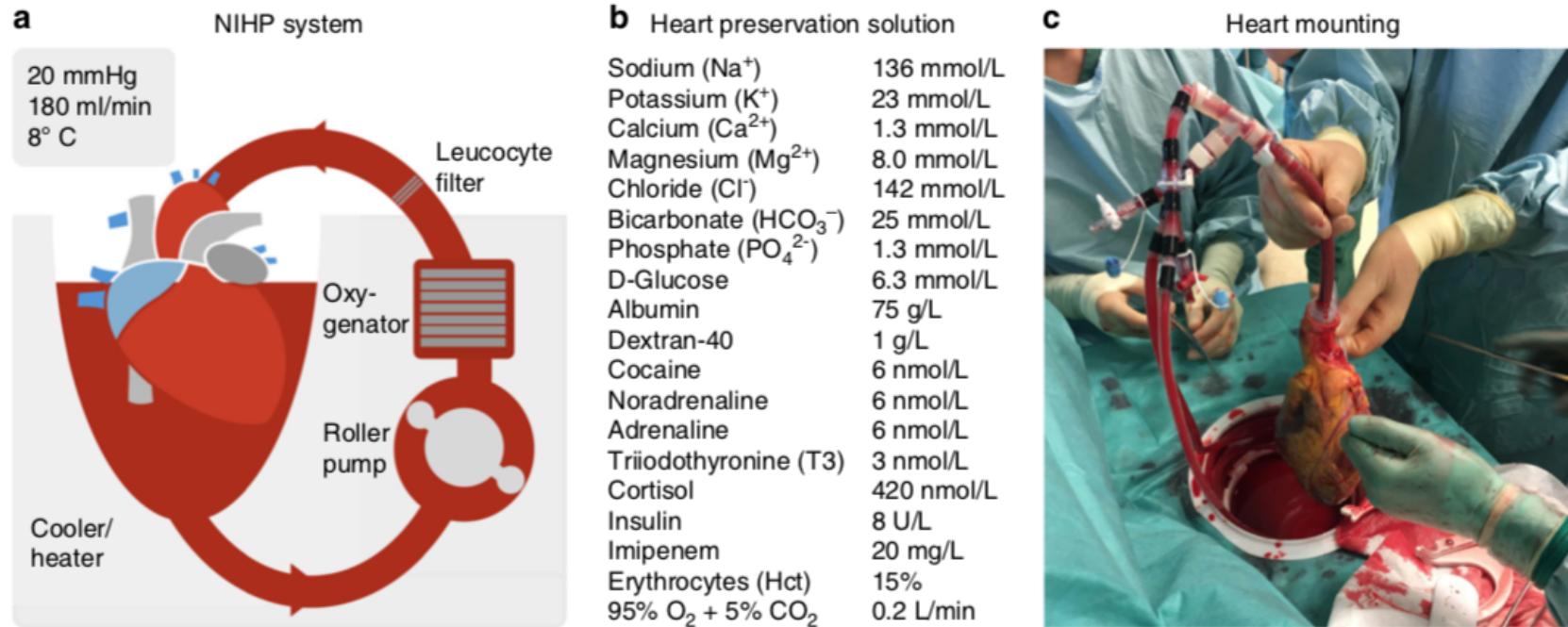


Fig. 1 The nonischemic heart-preservation method (NIHP). Shown is a drawing of the NIHP method (a). The equipment consists of a reservoir, a pressure-controlled roller pump, an oxygenator, an arterial-leukocyte filter, a heater-cooler unit, oxygen and carbon dioxide containers, a gas mixer, sensors, 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



ARTICLE

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

OPEN

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

Johan Nilsson¹, Victoria Jernryd¹, Guangqi Qin¹, Audrius Paskevicius¹, Carsten Metzsch¹, Trygve Sjöberg¹ & Stig Steen¹



CK-MB (ng/mL)



Number of patients	NIHP	6	6	6	6	6	6
	SCS	25	20	20	19	18	18

Julia Dumfarth

70th ESCVS Liège



Universitätsklinik für
Herzchirurgie

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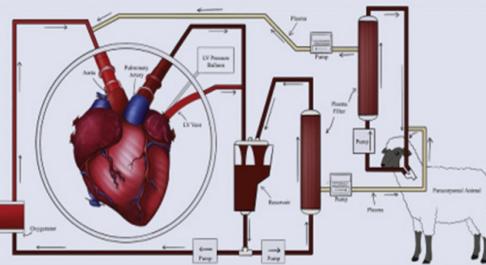
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UNIVERSITÄT
INNSBRUCK

Prolonged perfusion

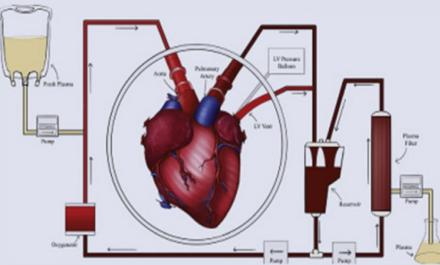
→ Necessary for future interventions

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.

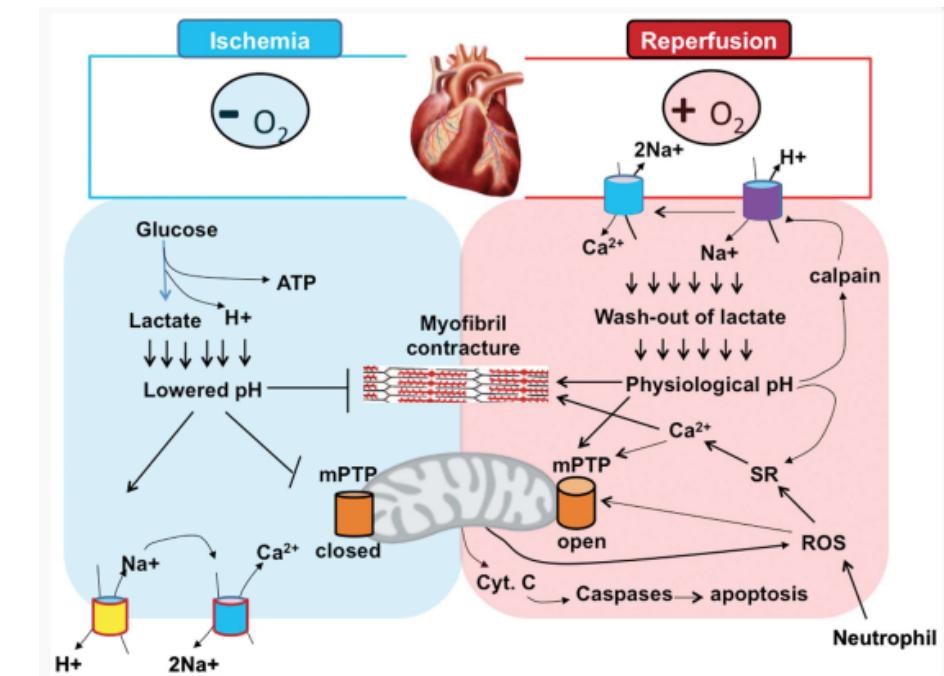
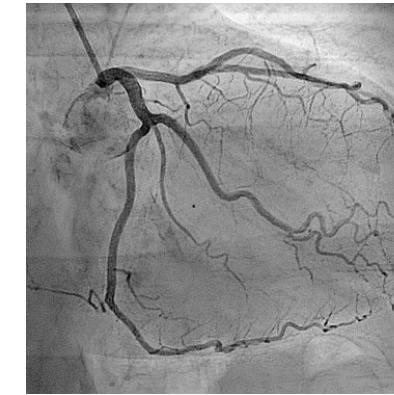
EVHP: *Ex Vivo* Heart Perfusion; LV: Left Ventricle; PX: Plasma Exchange

- Animal model
- 24 hours of *ex situ* heart perfusion
- Perfusion is 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

