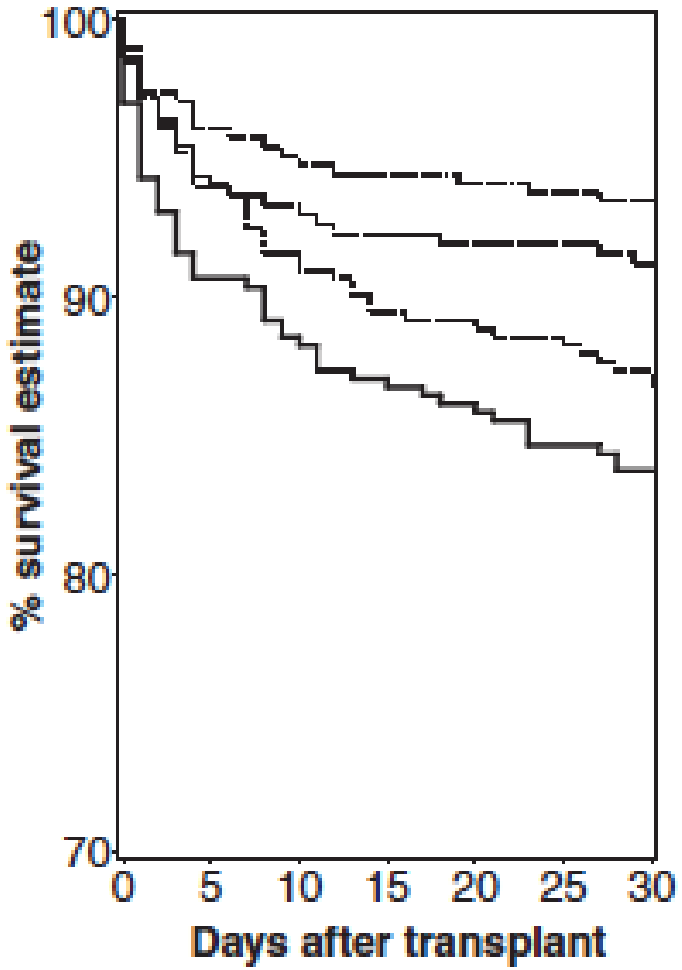
Retrieval from the **DBD** Donor

Single Dose Cardioplegic Flush Followed by Static Cold Storage

Effect of Ischaemic Time on risk of early death in Hearts currently used for transplant



IT (mins)	Number at risk at day 0	% survival estimate
<155	305	93
155-189	284	91
190-229	332	87
≥230	332	84

Quartiles of Ischaemic Time for 1253 UK Cardiac Transplants

30 Day Survival of 93% v 84% in the first and fourth quartiles

Ex-Situ Heart Perfusion

Why we might need it

- Reduce Ischaemic Burden
  - Better early function
  - Enlarged donor pool
  - Simplifies complex logistics

- Potentially better long term outcome

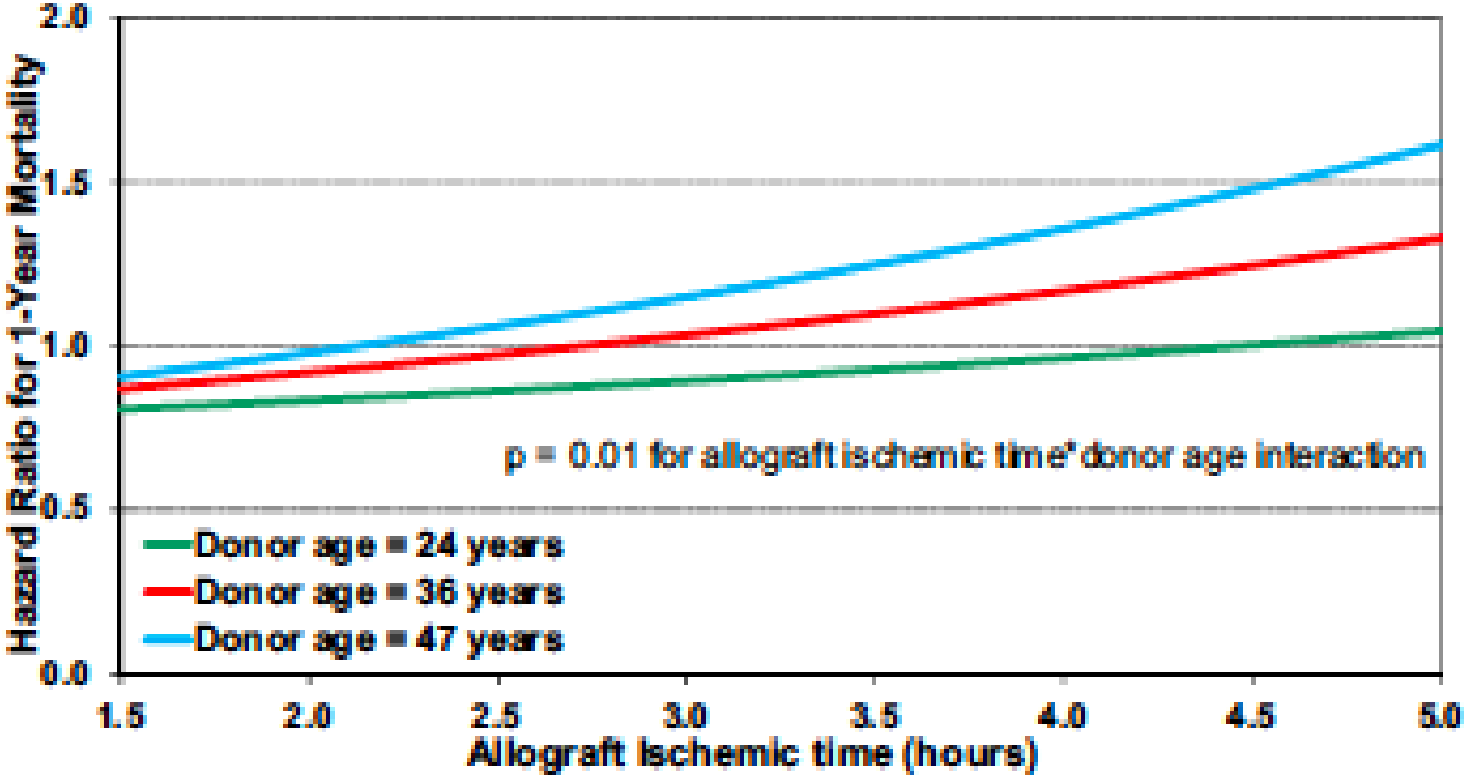


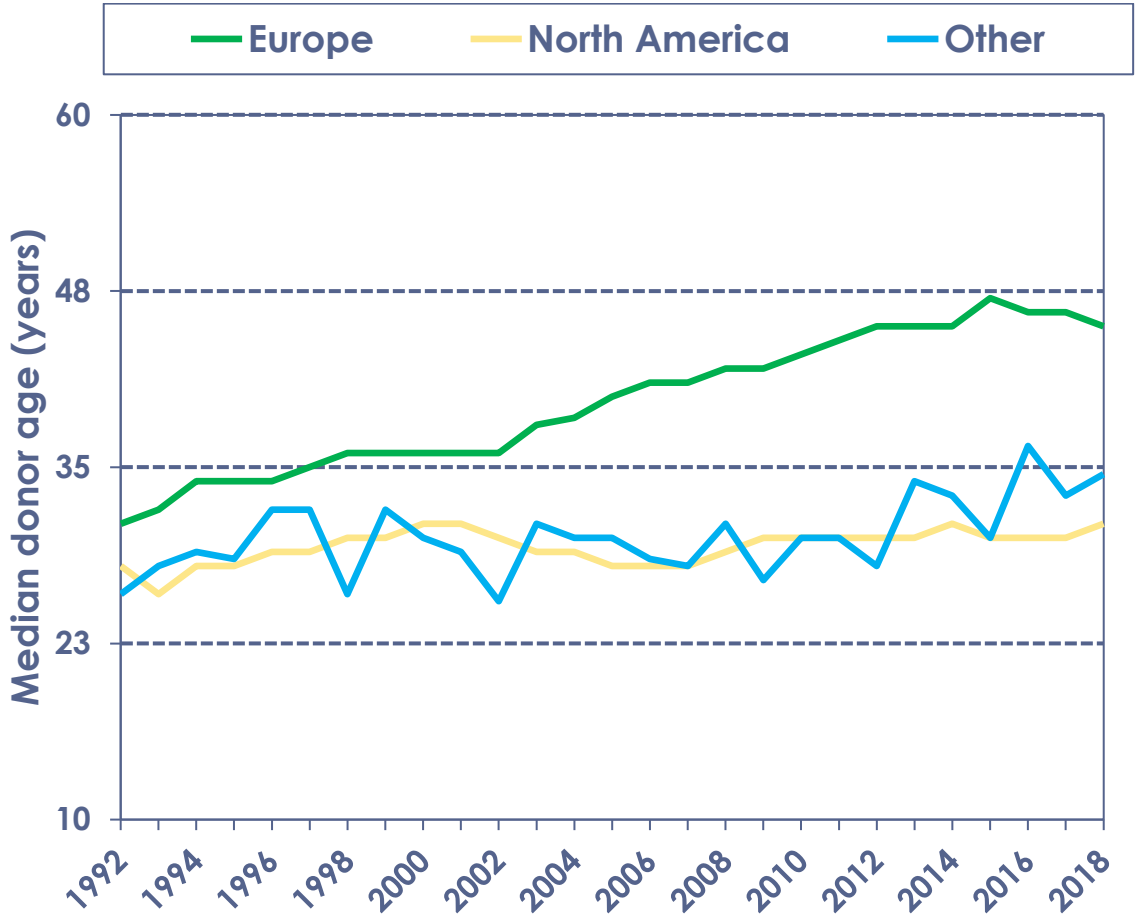
Figure 17 Independent hazard ratio for 1-year mortality according to allograft ischemic time as a continuous variable and in different donor age categories (n = 21,614 adult heart transplants: January 2010–June 2015).

JHLT 2017;36:1038-1047 34th Adult Heart Transplantation Report

Adult Heart Transplants

Median Donor Age by Location

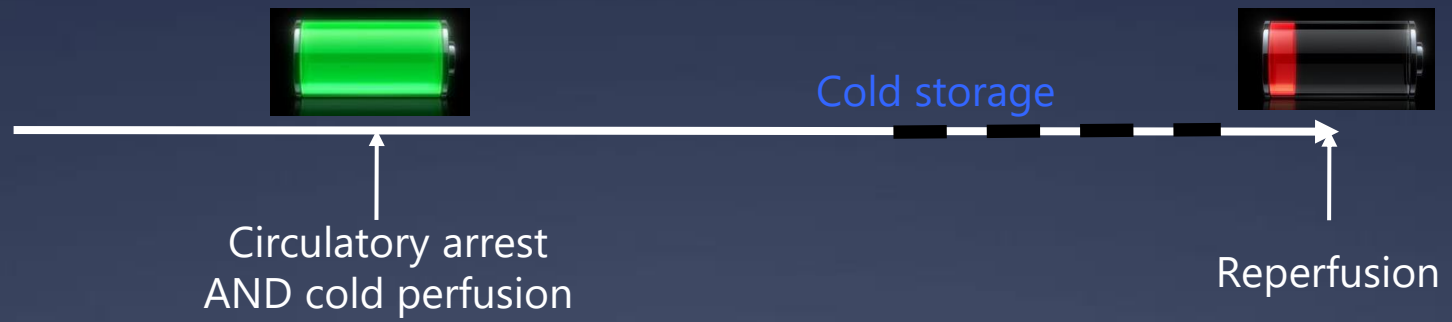
(Transplants: Jan 1992 – Jun 2018)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2020
JHLT. 2020 Oct; 39(10): 1003-1049

DCD vs DBD donors: The effect of warm ischaemia

DBD Donor



DCD Donor

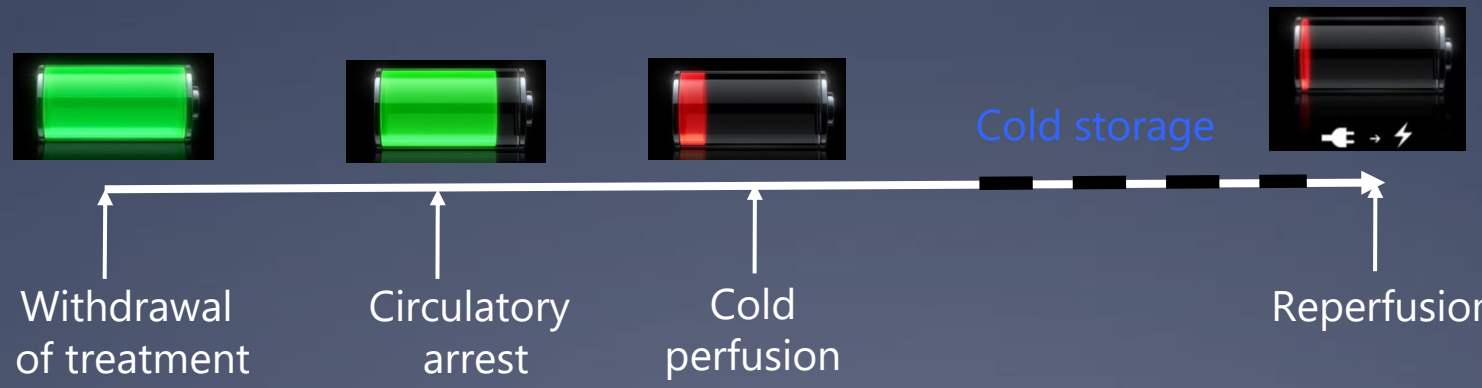
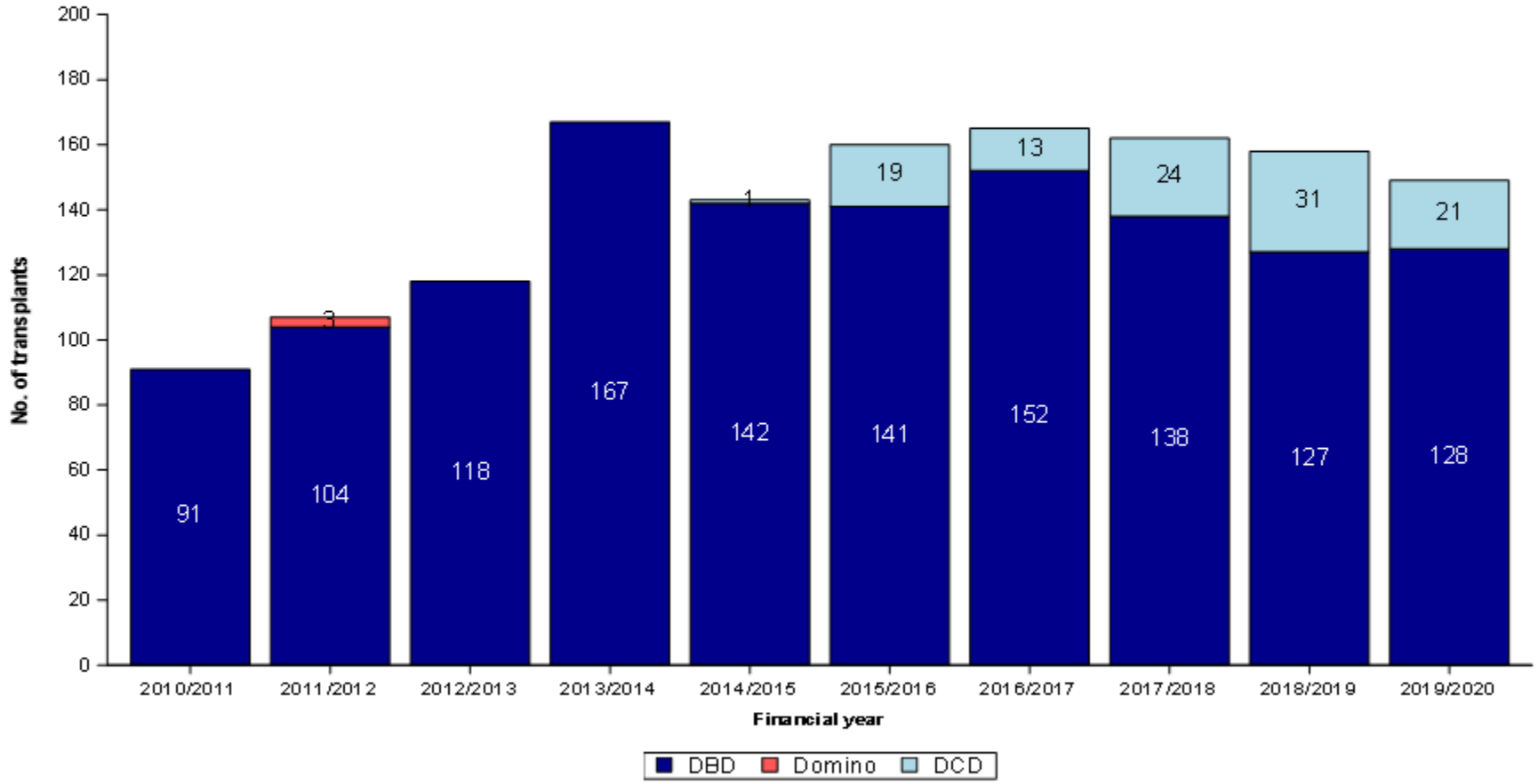


Figure 5.1 Number of adult heart transplants in the UK, by financial year and donor type, 1 April 2010 to 31 March 2020



Source: Annual Report on Cardiothoracic Organ Transplantation 2019/2020, NHS Blood and Transplant

Ex-Situ Heart Perfusion

Choice of Approach

- Hypothermic
- Normothermic

Ex-Situ Heart Perfusion

Choice of Approach

- Hypothermic
  - Simpler technology
  - Lower flow
  - Option not to have blood in perfusate
  - No Functional Assessment

Ex-Situ Heart Perfusion

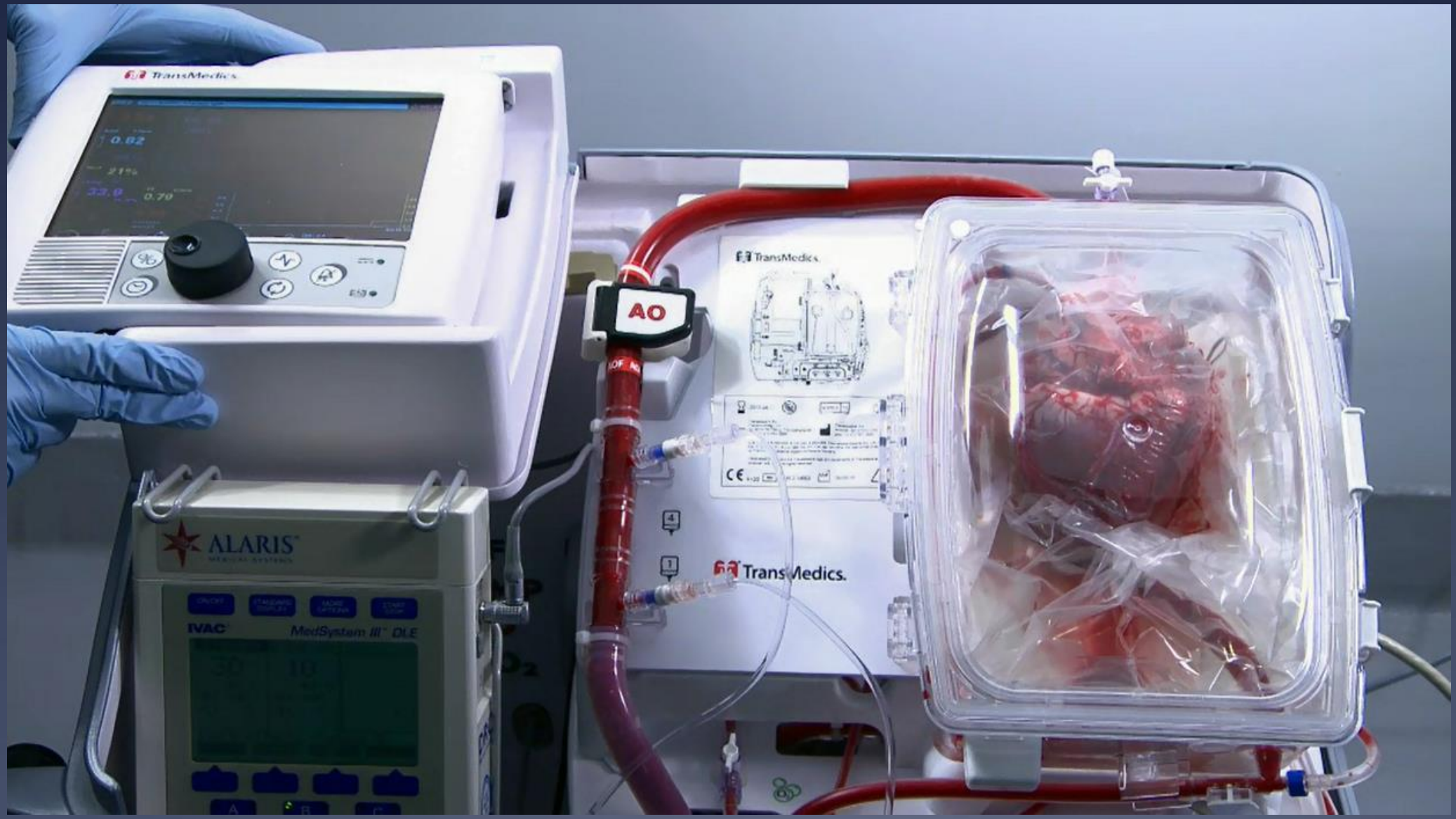
Choice of Approach

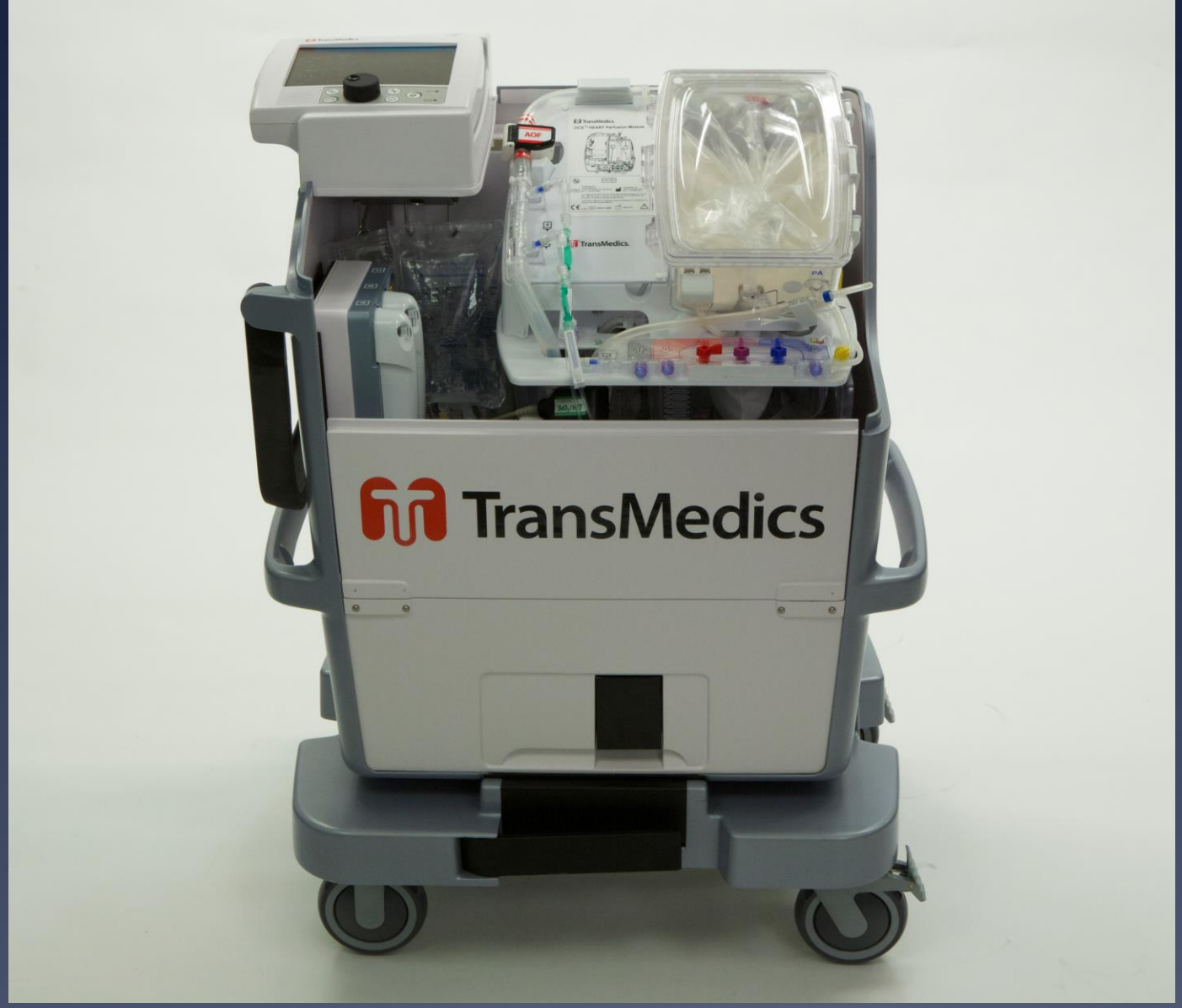
- Hypothermic
- Normothermic
  - More “Physiolgical”
  - Technically more complex?
  - Requires blood in perfusate
  - Functional Assessment possible

Organ Care System (OCS™)

- Pulsatile perfusion of the donor heart with warm, oxygenated, nutrient enriched donor blood

Confidential © 2011 TransMedics, Inc.


TransMedics
AO
ALARIS
IVAC
MedSystem III OLE
TransMedics


TransMedics

£££ !!!

THE LORD OF THE RIG

Prof. Stig Steen, Lund

Image 1. The HOP machine primed with blood-based perfusate (left) and attached to a heart (right). (Photos taken during the first HOP preservation run.)

Scandinavian Cardiovascular Journal

2016; 50:193-200

ISSN: 1401-7431 (Print) 1651-2006 (Online) Journal homepage: http://www.tandfonline.com/loi/icdv20

Safe orthotopic transplantation of hearts harvested 24 hours after brain death and preserved for 24 hours

Stig Steen, Audrius Paskevicius, Qiuming Liao & Trygve Sjöberg

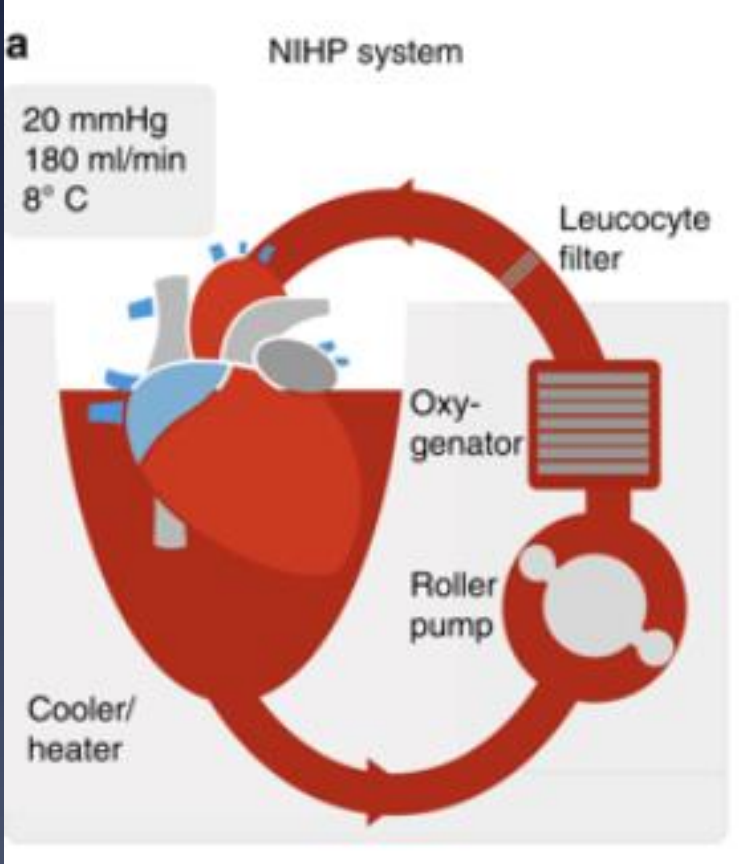
Article | Open Access | Published: 12 June 2020

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

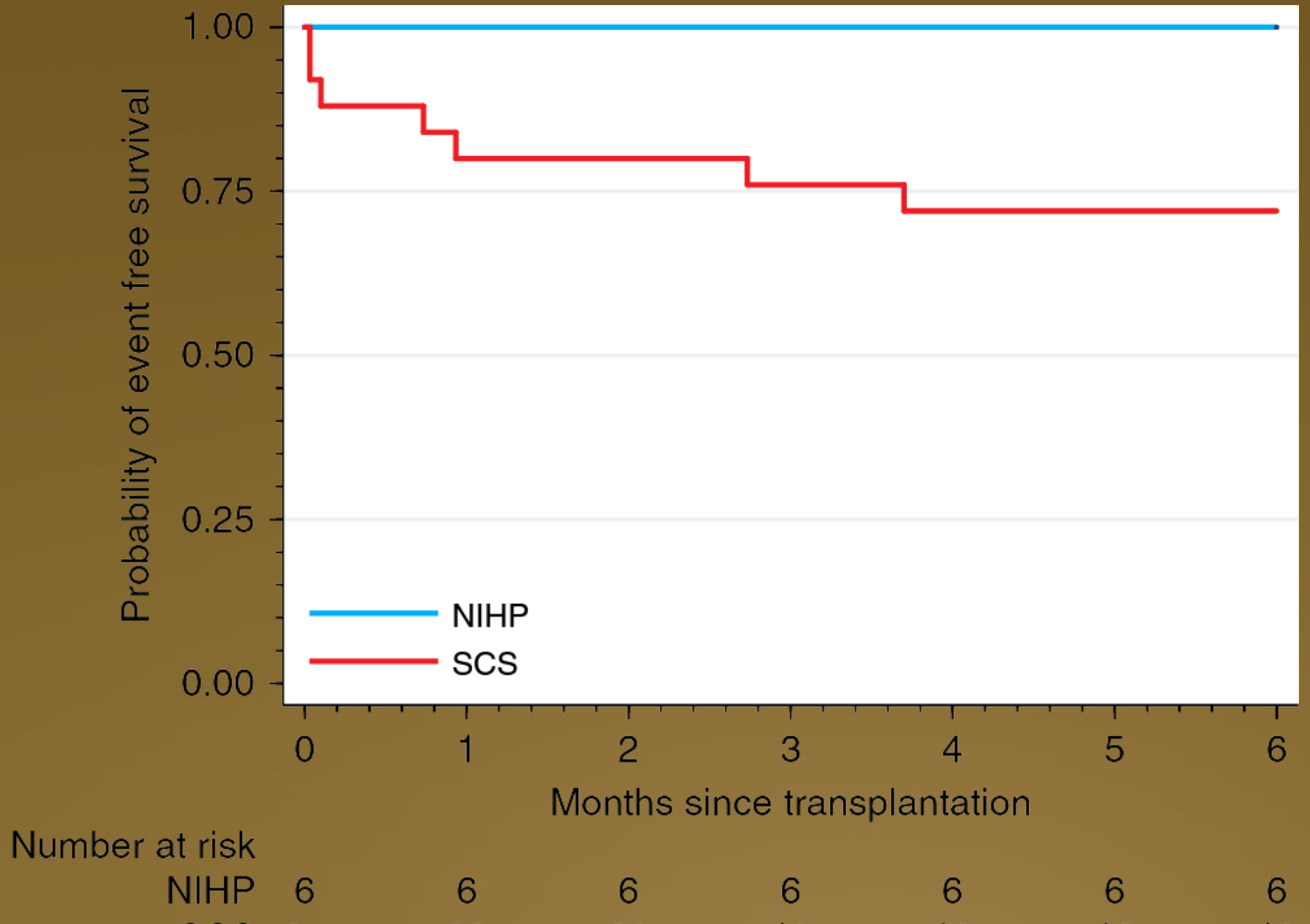
Johan Nilsson ✉, Victoria Jernryd, Guangqi Qin, Audrius Paskevicius, Carsten Metzsch, Trygve Sjöberg & Stig Steen

Nature Communications **11**, Article number: 2976 (2020) | Cite this article

Hearts already accepted for transplant, SCS controls



Perfusion with albumin/dextran/blood based solution, HCT c15%, 8C
Aortic Perfusion Pressure 20mmHg, flow rate150 – 250 ml/min
Normal lactate, no other markers measured at point of care


1.00
0.75
0.50
0.25
0.00
Probability of event free survival
NIHP
SCS
0
1
2
3
4
5
6
Months since transplantation
Number at risk
NIHP 6 6 6 6 6 6 6

Hypothermic Oxygenated Perfusion

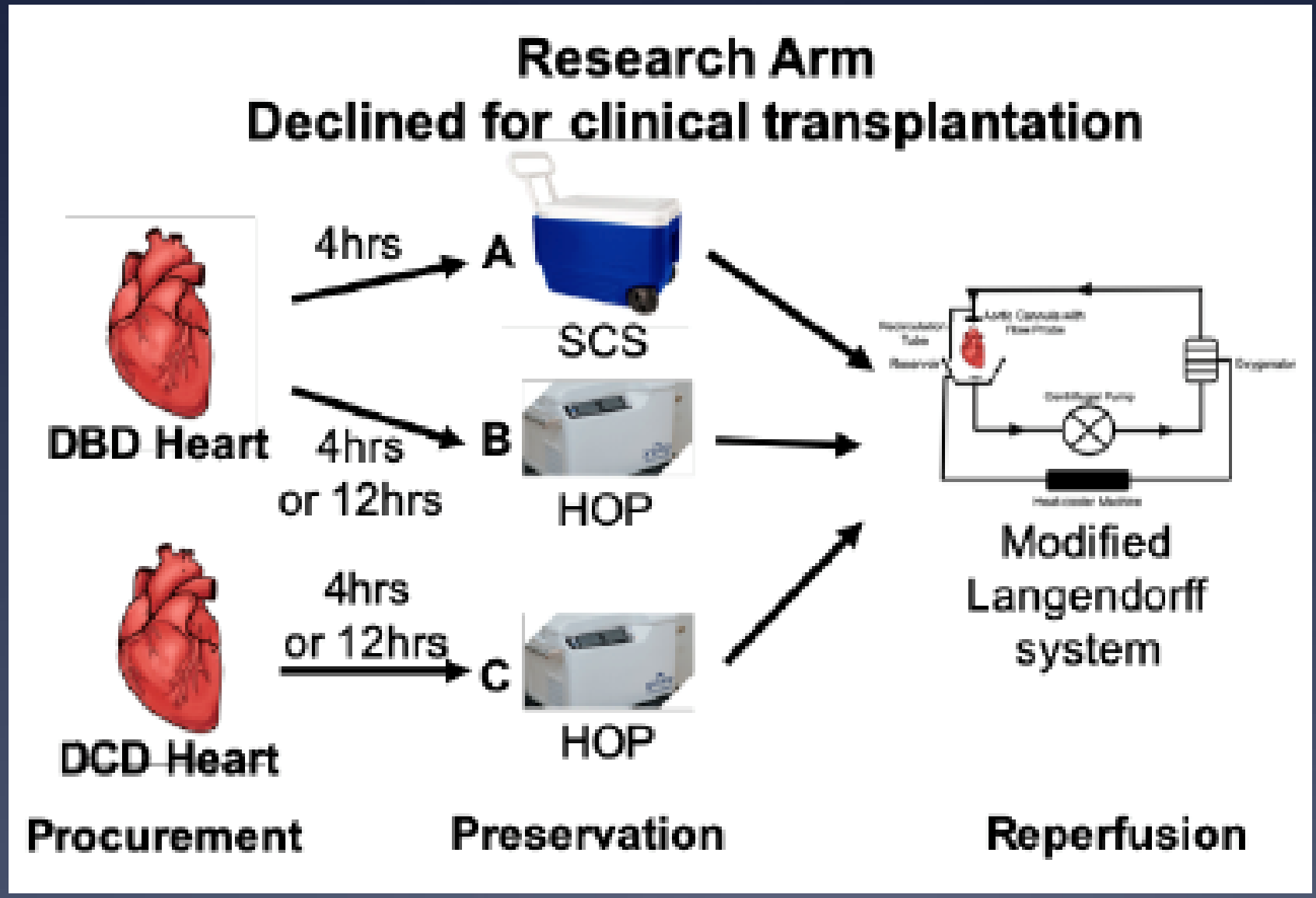
The next steps

1. Test system with Extended Donor Hearts
2. Test system with DCD hearts
3. Develop biomarkers to identify hearts with good function

Research Summary: 1

What do we already know?

- In the Pig, the Steen Box will keep a heart for 24 hours, with good function
- The box allows “resuscitation” of the heart after it has had an initial insult
- Hypothermic Perfusion may be of particular benefit for the DCD Heart


Research Arm
Declined for clinical transplantation
DBD Heart
4hrs
A
SCS
4hrs
or 12hrs
B
HOP
DCD Heart
4hrs
or 12hrs
C
HOP
Modified
Langendorff
system
Procurement
Preservation
Reperfusion

Hypothermic Oxygenated Perfusion

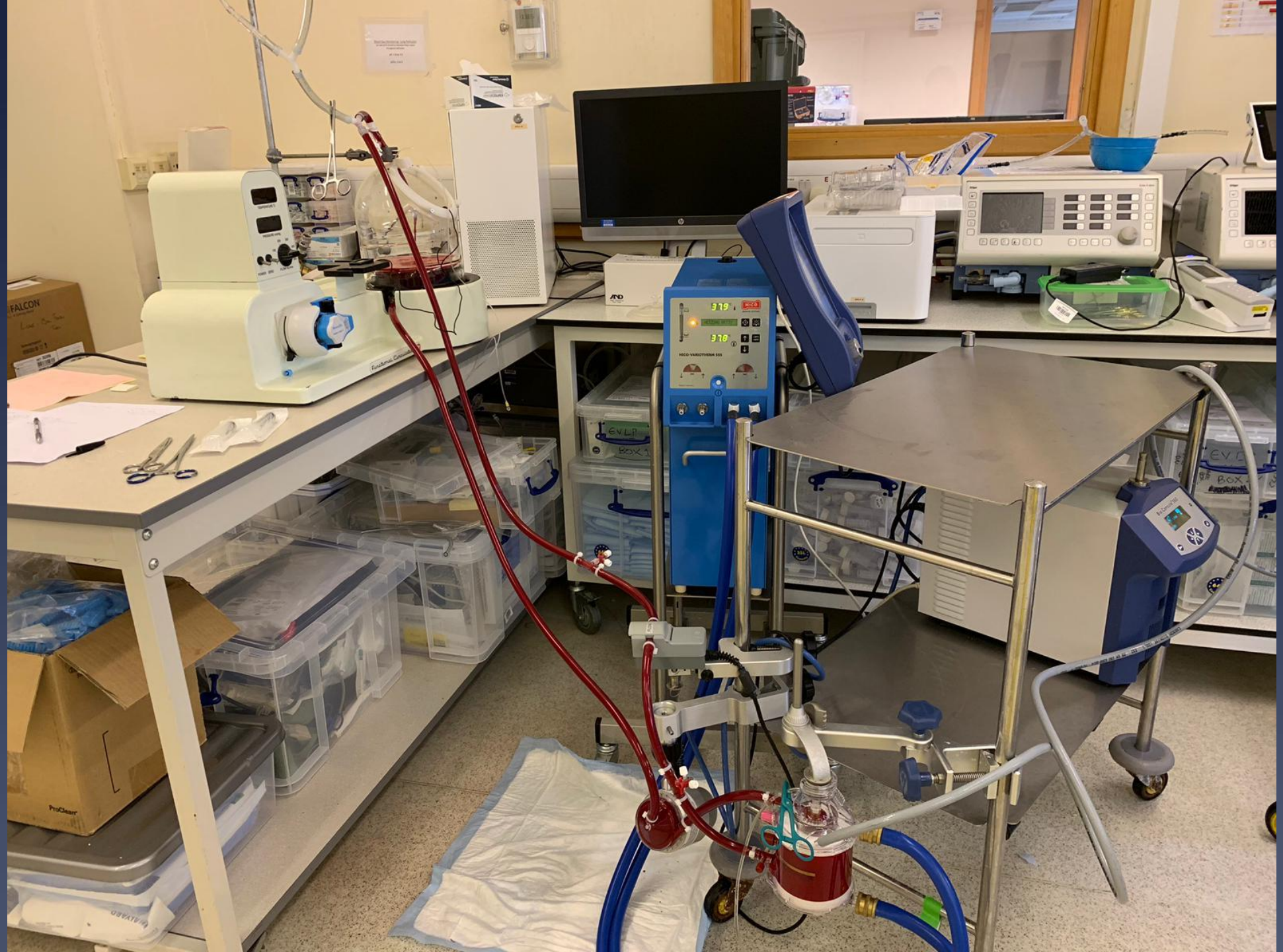
Travel to donor hospital

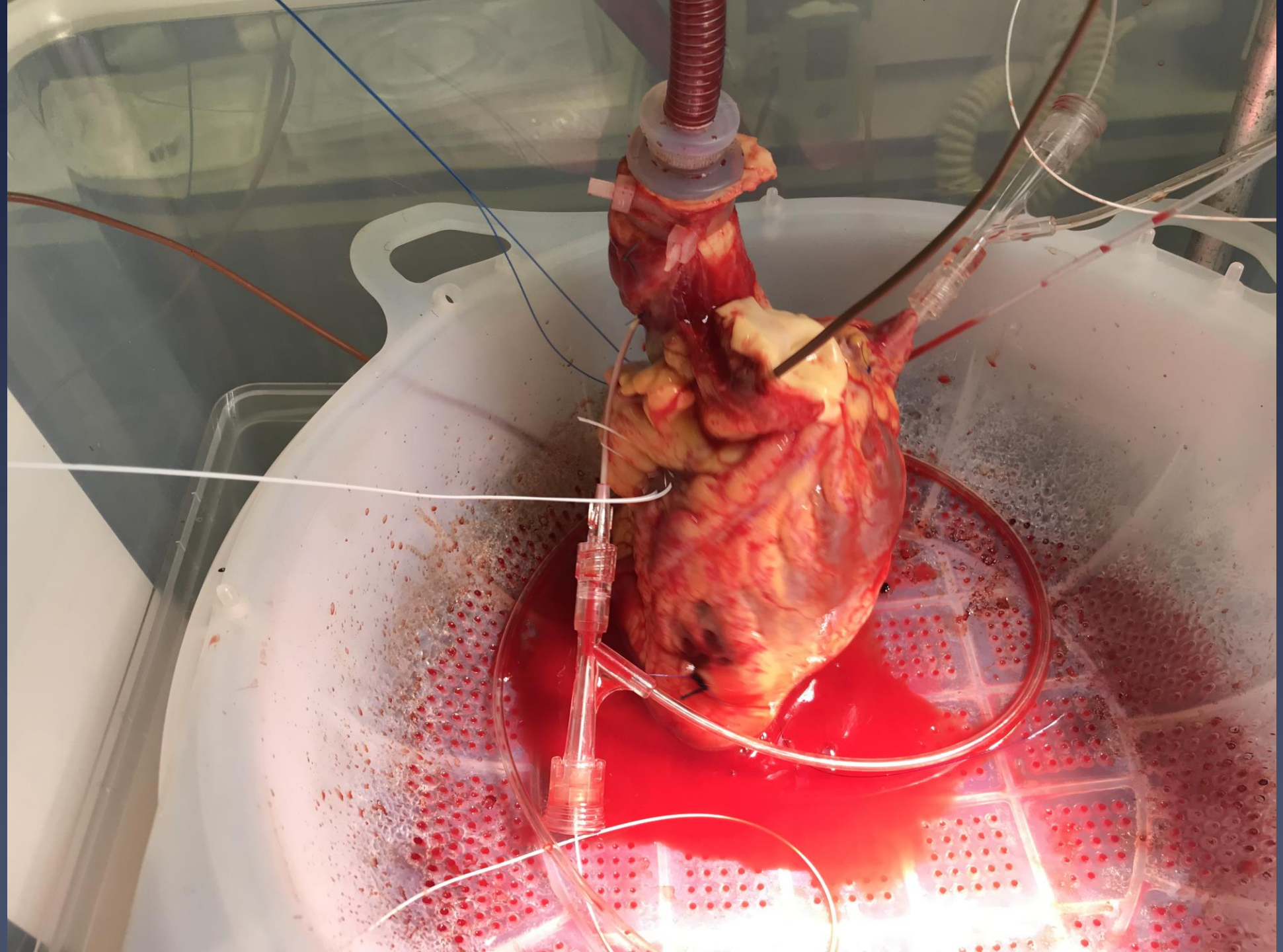
Prime Perfusion device

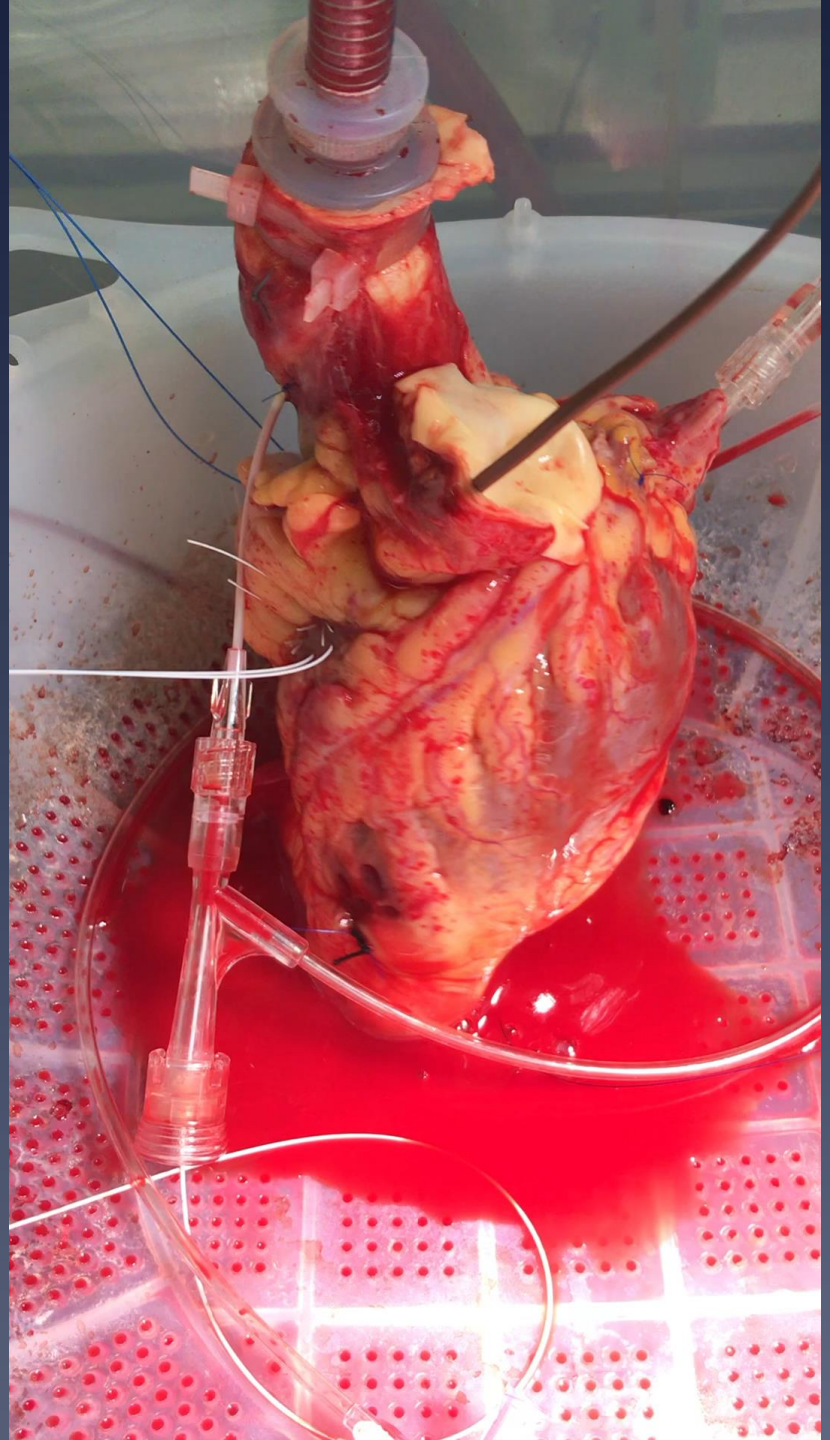
Attach heart to device

Return to Newcastle for testing


25
mmHg
8.2
°C
233
ml/min
$O_2 + CO_2$
ON
Perfusion - Locked
Perfusion running: 04:06:35
Press UNLOCK for 3 s to unlock buttons.
Total preservation time: 04:10:14
UNLOCK
XVIVO
PERFUSION
XVIVO
PERFUSION


FALCON
ProClear





HOP Study

Core Assessment is Ventricular Function

Balloon in Left ventricle

Sequential measurements every hour, with stepwise inflation

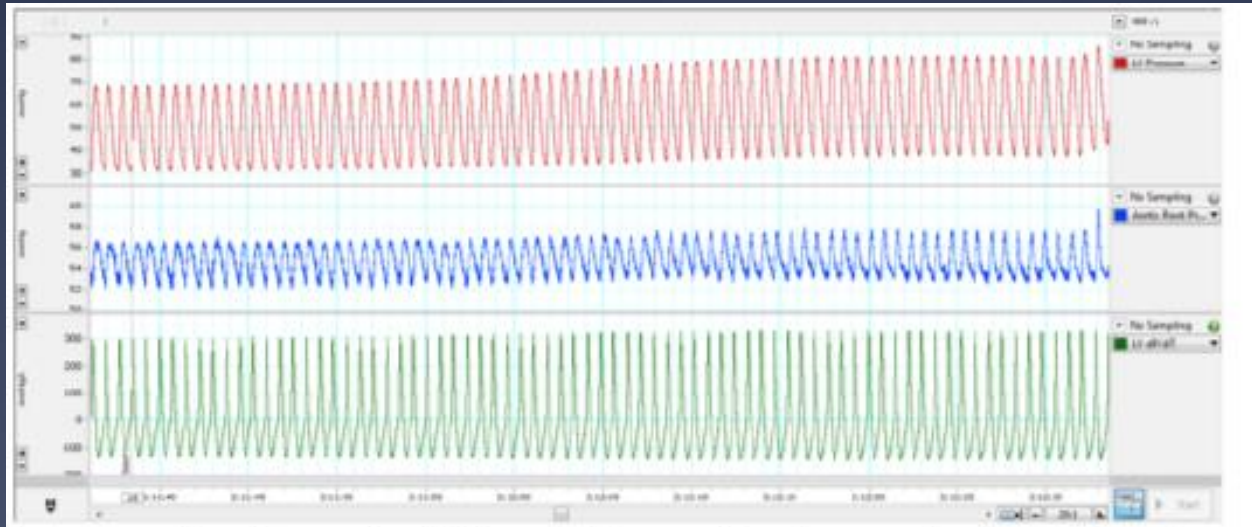


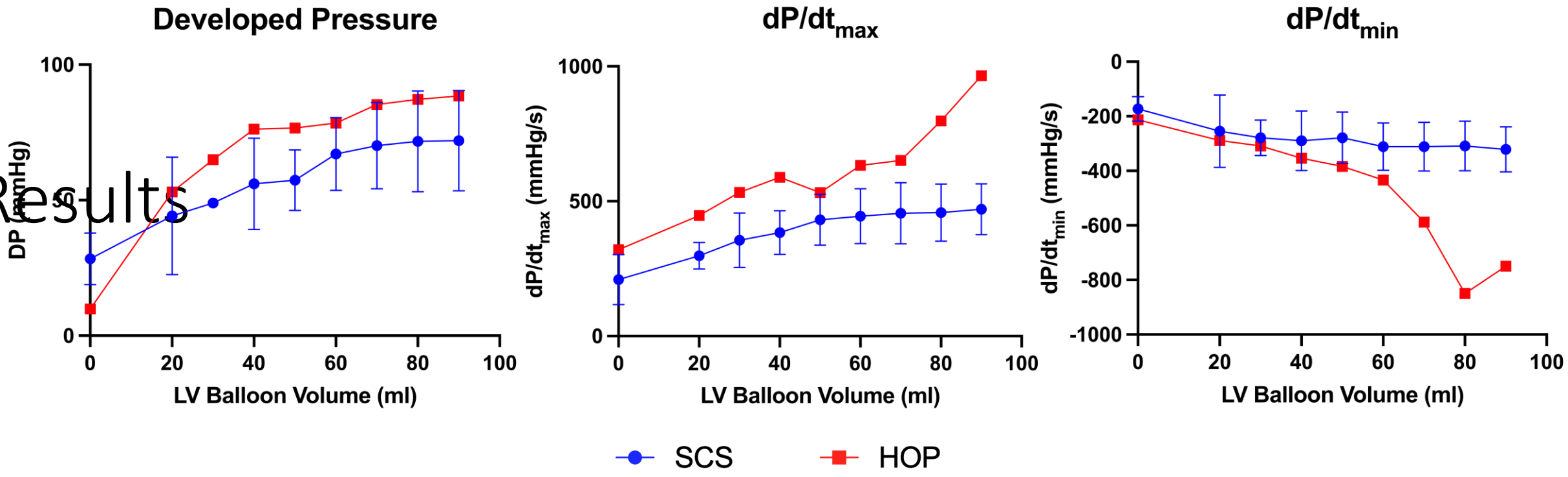
Image 3. The LabChart Pro display window. During normothermic reperfusion of heart on the modified Langendorff system, LV pressure and aortic root pressure are constantly measured. The derived LV dP/dt is displayed as well.

HOP Progress so Far

- Ü RINTAG Approval Jan 2019
- Ü NHSBT roll-out, 4 local hospitals, Specific Consent May 2019
- Ü 2 Successful DBD Machine Perfusions
- Ü 3 SCS control retrievals
  - Ü 3 DBD
  - Ü 1DCD

Left ventricular functional assessment at 1 hour of reperfusion

Results



NIHR | Blood and Transplant Research Unit in Organ Donation and Transplantation at Cambridge and Newcastle Universities

MRC Medical Research Council

Newcastle University

The Impact of Pre-Formed Donor Specific Antibodies (DSAs) on Cardiothoracic Transplantation

Grace Ting Tsin Yan

Prof. John Dark , Dr. Gareth Parry,

Institute of Transplantation, Freeman Hospital, Newcastle Upon Tyne

Dr Arash Akbarzad-Yousefi, Head of H&I, Newcastle

Newcastle University

The Newcastle upon Tyne Hospitals NHS

NHS Foundation Trust

Introduction

- DSAs – antibodies targeted against donor antigens
- Pre-formed DSAs
  - Present before transplantation
  - Patients can develop DSAs after pregnancy, previous blood transfusion or previous transplantation
- Historically, transplantation “across” pre-formed DSA’s was to be avoided

  => long waiting time for sensitised patients - **BUT CDC Assay**
- Currently, transplant across low or medium-strength pre-formed DSAs -
- **MFI with Luminex Assay**
- Literature
  - Presence of low or medium strength pre-formed DSAs does not affect survival post-transplantation
  - Persistent pre-formed DSAs post-transplantation are associated with worse survival

Aim

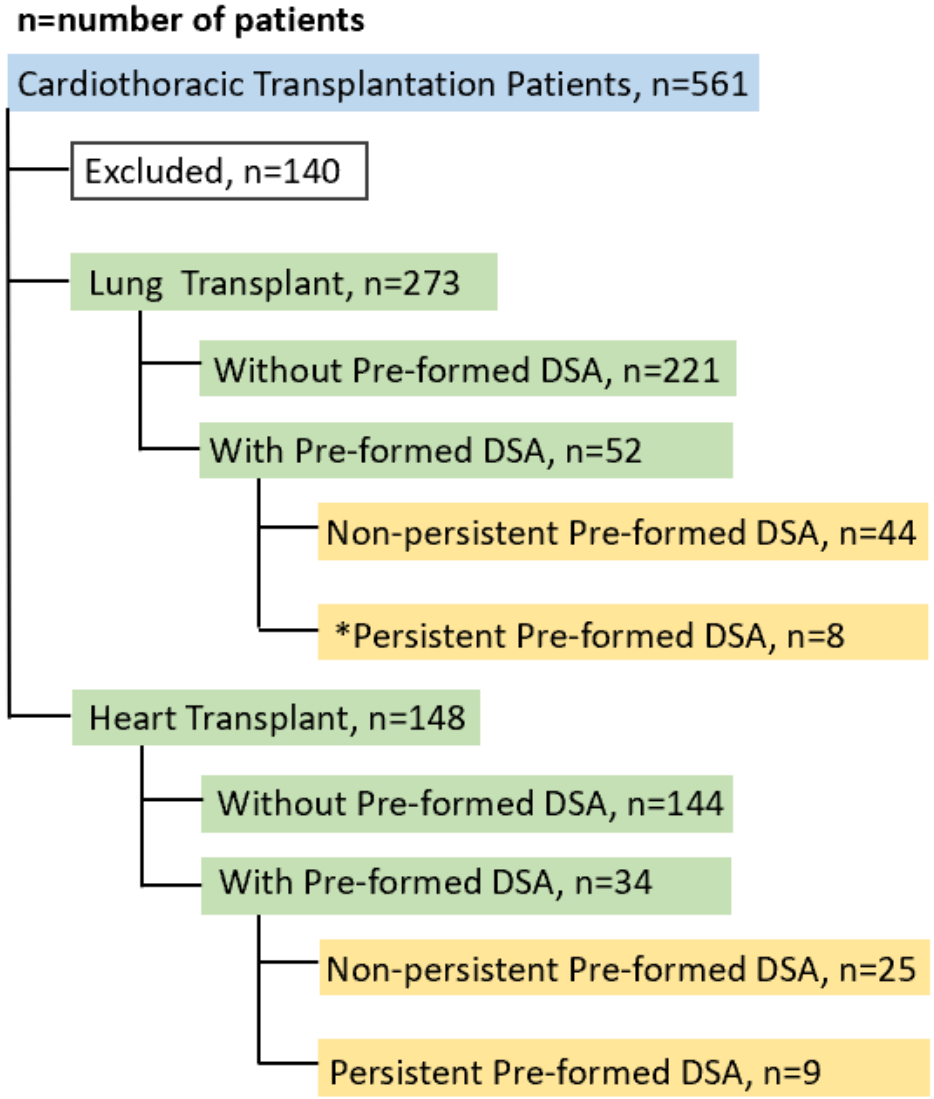
- To investigate the impact of pre-formed DSAs on survival post-cardiothoracic transplantation in Newcastle

Method

1. The data of all adult cardiothoracic transplant patients between 1st Jan 2012 to 31st May 2020 at Freeman Hospital were collected
2. In patients with pre-formed DSAs, only those with two low or one medium strength pre-formed DSAs proceeded with transplant
3. Patients who survived less than 1 year were excluded from this study
4. The data collected include:
   - Results of DSA tests done before and post-transplantation.
   - Duration of survival till death or follow-up date (31st May 2021)
5. Kaplan-Meier graphs were plotted to show the survival curves between the groups
6. Log-rank test was done to compare the survival difference between the groups

*Persistent pre-formed DSAs – the same preformed DSAs that remained detected at 1-year post-transplantation

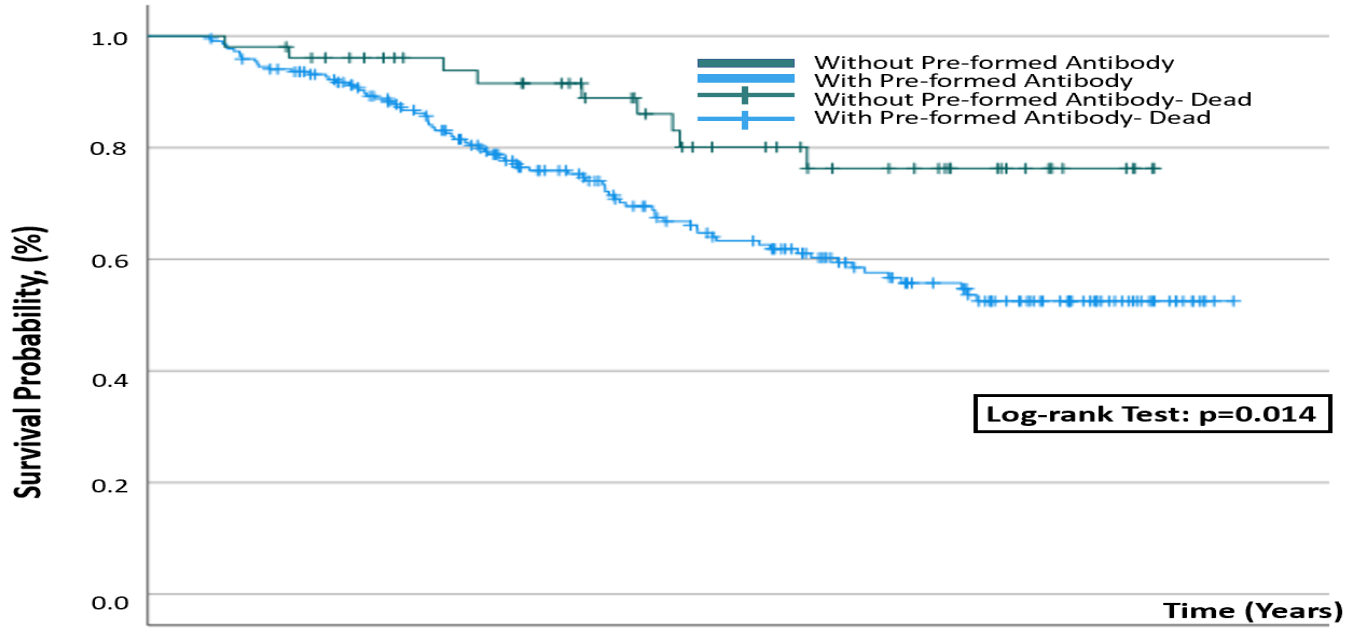
Method


n=number of patients
Cardiothoracic Transplantation Patients, n=561
Excluded, n=140
Lung Transplant, n=273
Without Pre-formed DSA, n=221
With Pre-formed DSA, n=52
Non-persistent Pre-formed DSA, n=44
*Persistent Pre-formed DSA, n=8
Heart Transplant, n=148
Without Pre-formed DSA, n=144
With Pre-formed DSA, n=34
Non-persistent Pre-formed DSA, n=25
Persistent Pre-formed DSA, n=9

Results

Kaplan Meier survival plot for lung transplant patients with or without pre-formed DSA

- Survival post-lung transplantation in patients with pre-formed DSAs was **significantly better** than patients without pre-formed DSAs

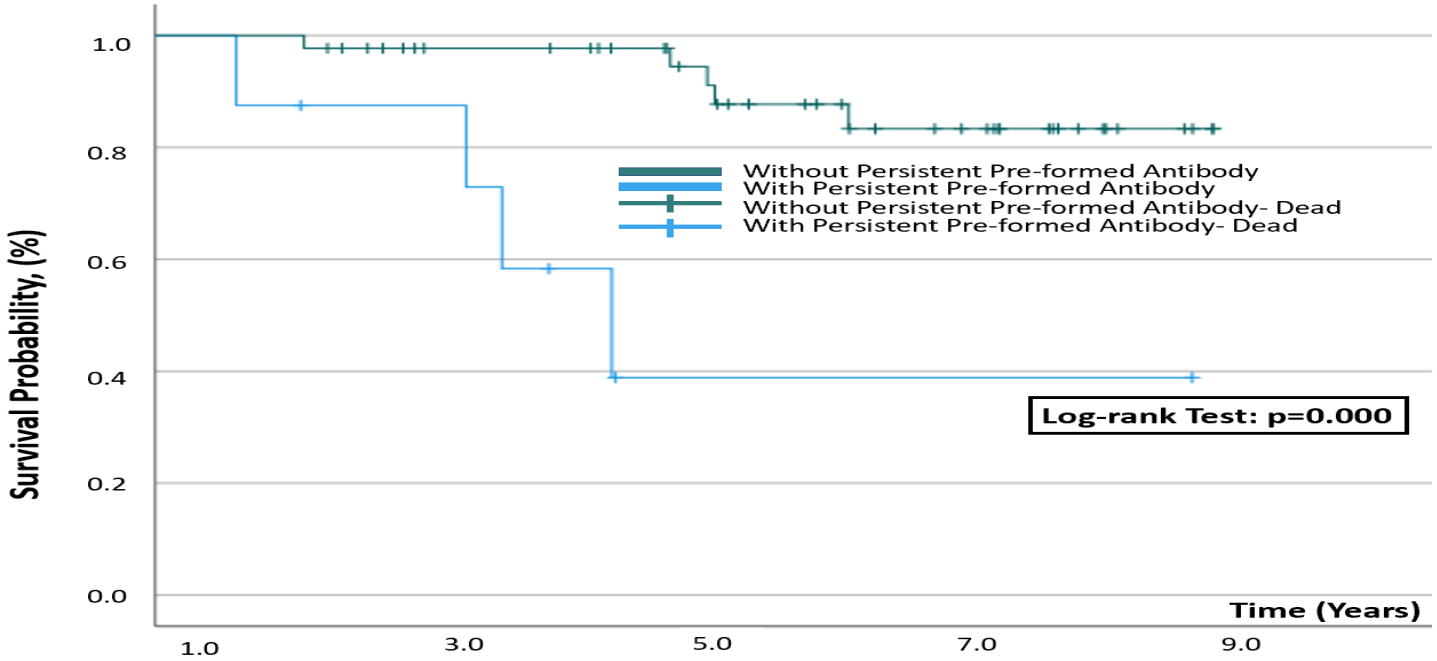


Number of Patients, n		
Total	Dead (%)	Alive(%)
221	79 (36%)	142(64%)
52	9 (17%)	43 (83%)

Results

Kaplan Meier survival plot for lung transplant patients with or without persistent pre-formed DSA

- Survival post-lung transplantation in patients with persistent pre-formed DSAs was **significantly lower** than patients without persistent pre-formed DSAs

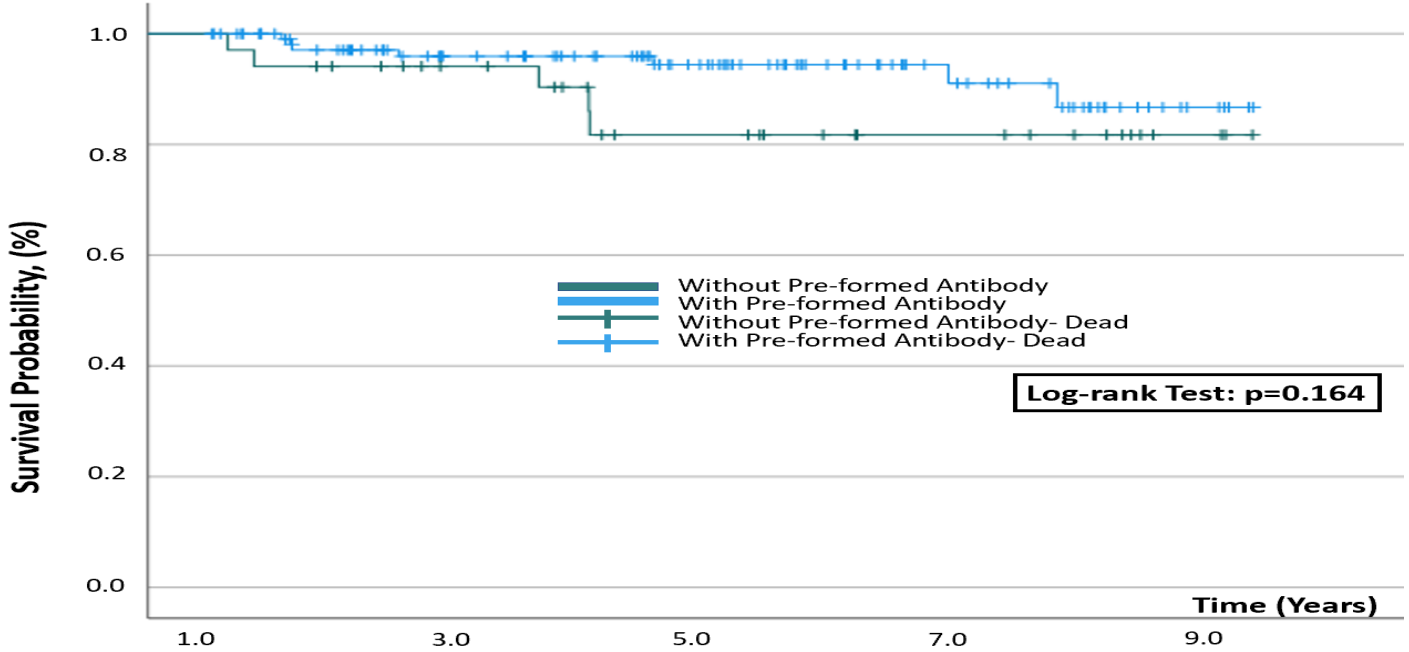


Number of Patients, n		
Total	Dead (%)	Alive(%)
44	5 (11%)	39 (88%)
8	4 (50%)	4 (78%)

Results

Kaplan Meier survival plot for heart transplant patients with or without pre-formed DSA

- There was **no significant difference** in survival post-heart transplantation in patients with or without pre-formed DSAs

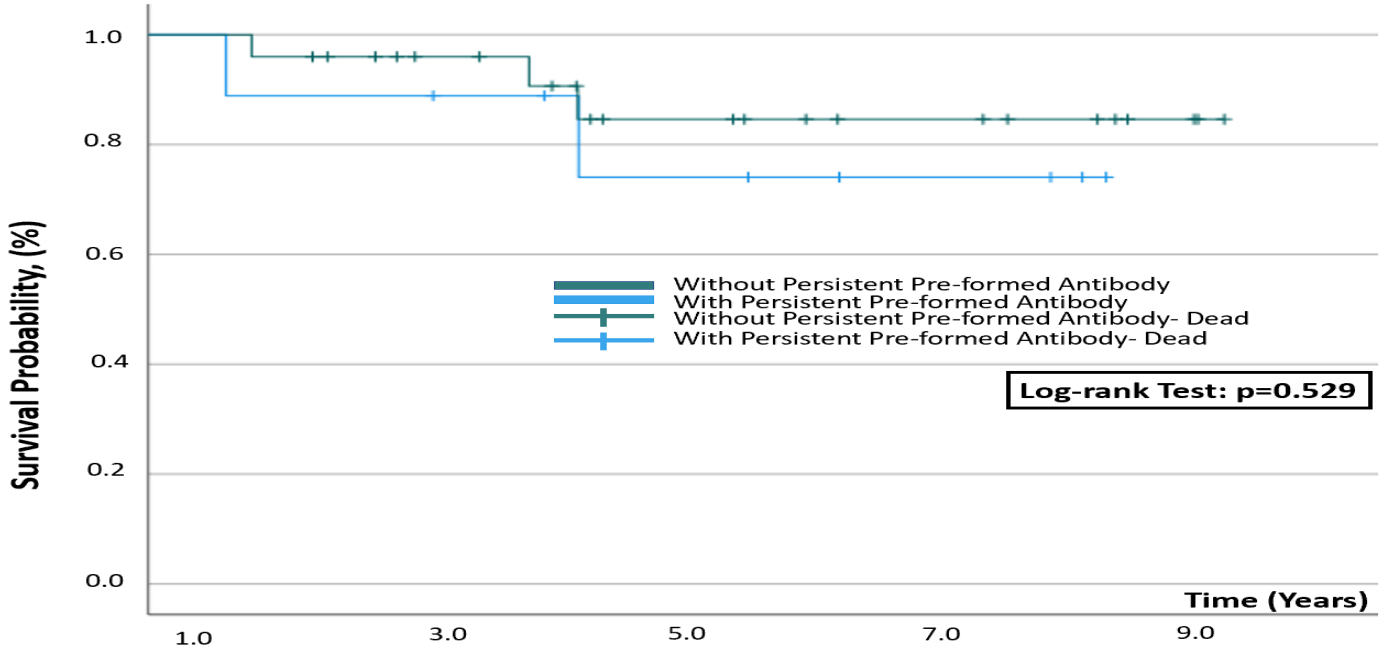


Number of Patients, n		
Total	Dead (%)	Alive(%)
114	7 (%)	107 (94%)
34	5(15%)	29 (85%)

Results

Kaplan Meier survival plot for heart transplant patients with or without persistent pre-formed DSA

- There was **no significant difference** in survival post-heart transplantation in patients with or without persistent pre-formed DSA



Number of Patients, n		
Total	Dead (%)	Alive(%)
25	3 (12%)	22 (88%)
9	2 (22%)	7 (78%)

Conclusion

- **Lung Transplantation**:
  - The presence of pre-formed DSAs is associated with better survival post-transplantation
  - Persistent pre-formed DSA negatively impacts survival post-transplantation

- **Heart Transplantation**:
  - The presence or persistence of pre-formed DSA does not negatively impact survival post- transplantation

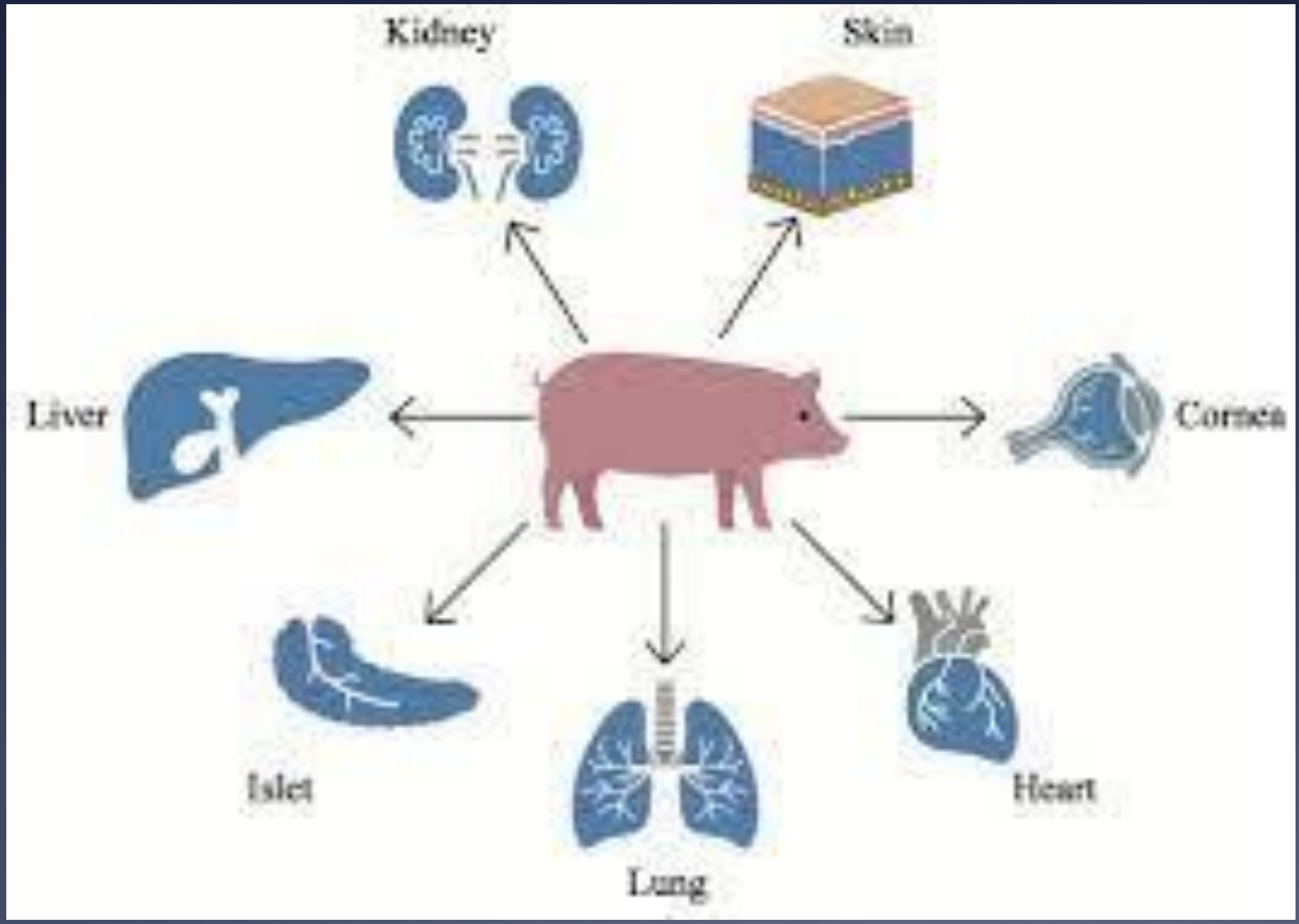
Significance and Future Work

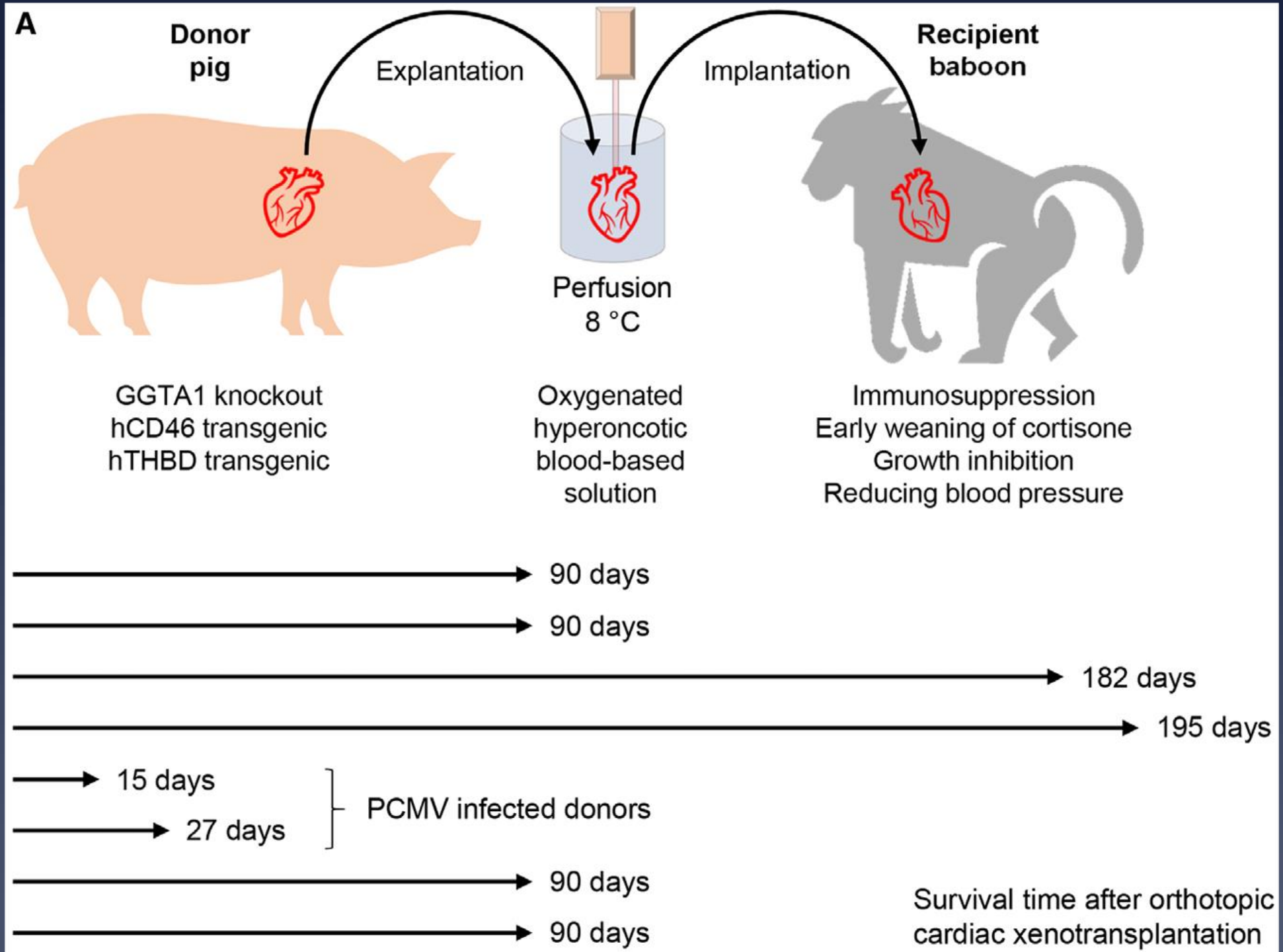
- Safe for cardiothoracic transplant across pre-formed DSAs at low or medium-strength
- Other factors such as age, gender, pre-transplant disease and other possible confounding factors should be taken into consideration
- The negative impact of persistent pre-formed DSAs in lung transplantation need to be investigated further so antibody-removing treatment can be considered in patients with persistent pre-formed DSAs

What is the Future?

What is the Future?

Is there a role for Organs from Animals?

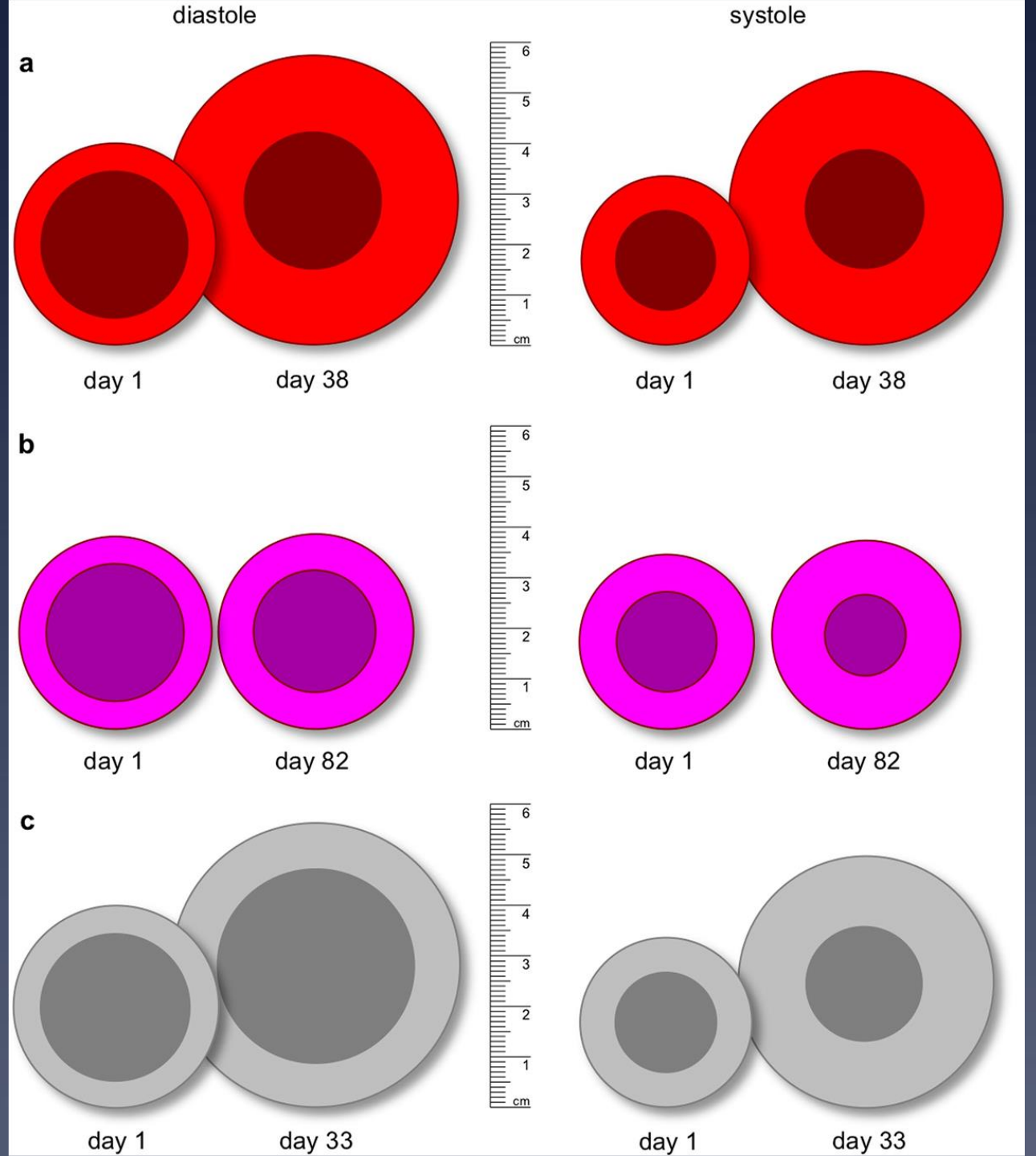

Kidney
Skin
Liver
Cornea
Islet
Lung
Heart


A
Donor pig
Explantation
Implantation
Recipient baboon
Perfusion 8 °C
GGTA1 knockout
hCD46 transgenic
hTHBD transgenic
Oxygenated hyperoncotic blood-based solution
Immunosuppression
Early weaning of cortisone
Growth inhibition
Reducing blood pressure
90 days
90 days
182 days
195 days
15 days
27 days
PCMV infected donors
90 days
90 days
Survival time after orthotopic cardiac xenotransplantation

Letter
https://doi.org/10.1038/s41586-018-0765-z

Consistent success in life-supporting porcine cardiac xenotransplantation

Here we show that α1,3-galactosyltransferase-knockout pig hearts that express human CD46 and thrombomodulin require non-ischaemic preservation with continuous perfusion and control of post-transplantation growth to ensure long-term orthotopic function of the xenograft in baboons, the most stringent preclinical xenotransplantation model. Consistent life-supporting function of xenografted hearts for up to 195 days is a milestone on the way to clinical cardiac xenotransplantation[7].


diastole
systole
a
6
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cm
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day 38
day 1
day 38
b
6
5
4
3
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1
cm
day 1
day 82
day 1
day 82
c
6
5
4
3
2
1
cm
day 1
day 33
day 1
day 33

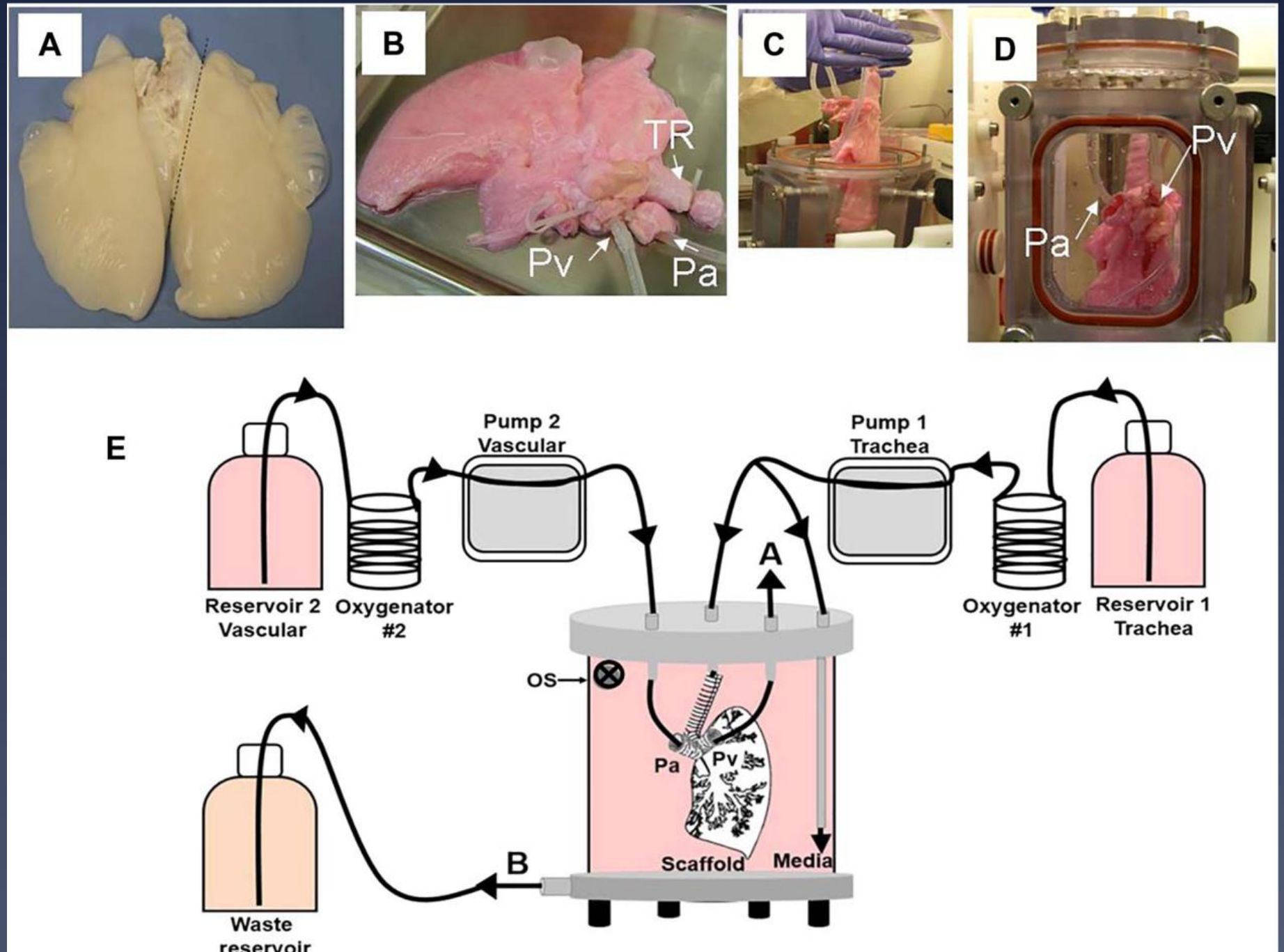
Science Translational Medicine

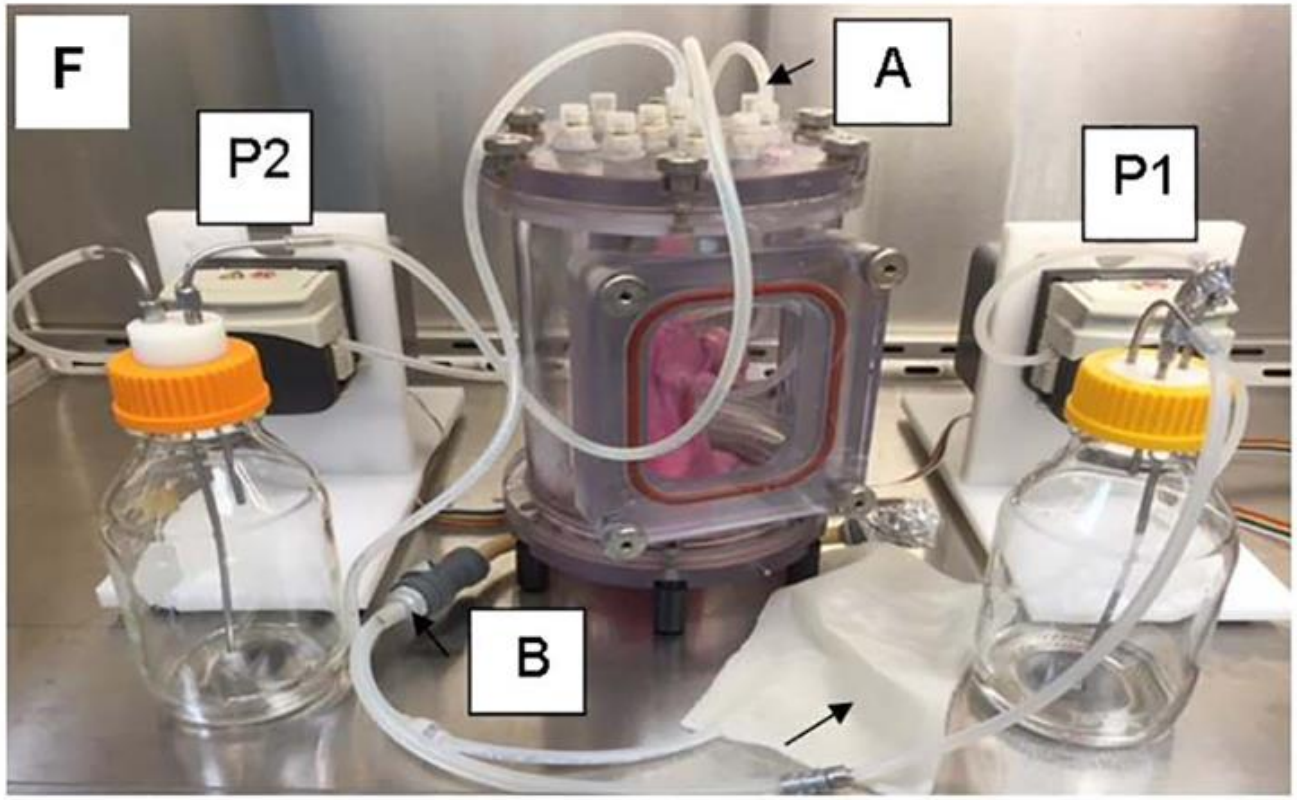
Production and transplantation of bioengineered lung into a large-animal model

Joan E. Nichols, Saverio La Francesca, Jean A. Niles, Stephanie P. Vega, Lissenya B. Argueta, Luba Frank, David C. Christiani, Richard B. Pyles, Blanca E.

Sci Transl Med **10**, eaao3926.

DOI: 10.1126/scitranslmed.aao3926


A
B
TR
Pv
Pa
C
D
Pv
Pa
E
Pump 2
Vascular
Pump 1
Trachea
A
Reservoir 2
Vascular
Oxygenator
#2
Oxygenator
#1
Reservoir 1
Trachea
OS
Pa
Pv
B
Scaffold
Media
Waste
reservoir



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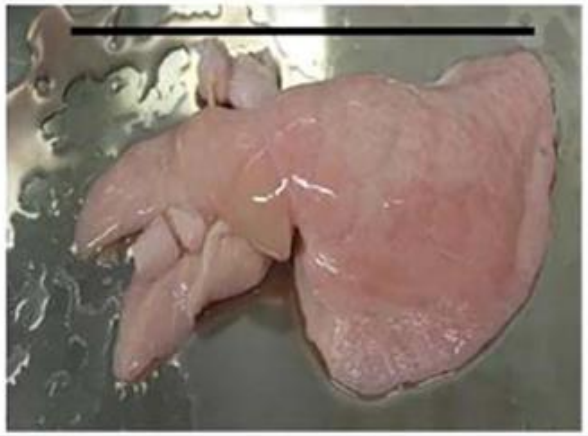

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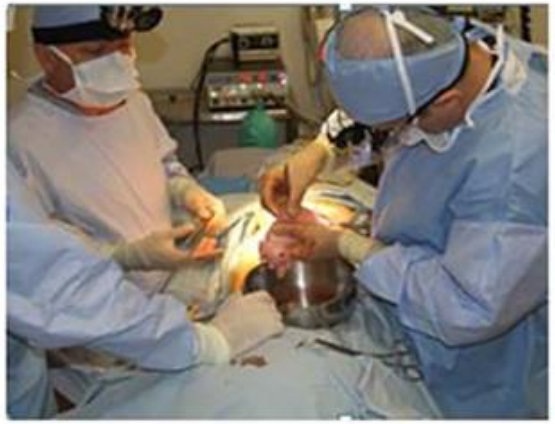

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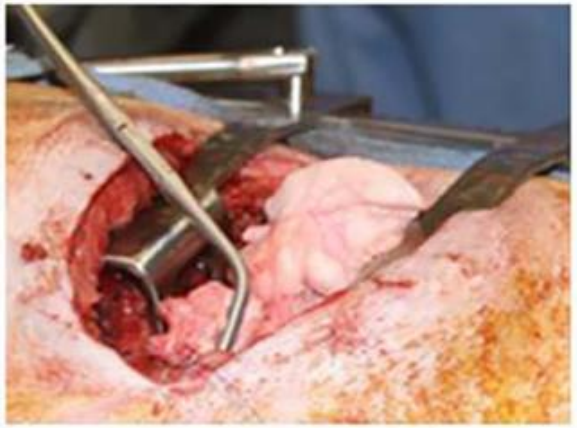

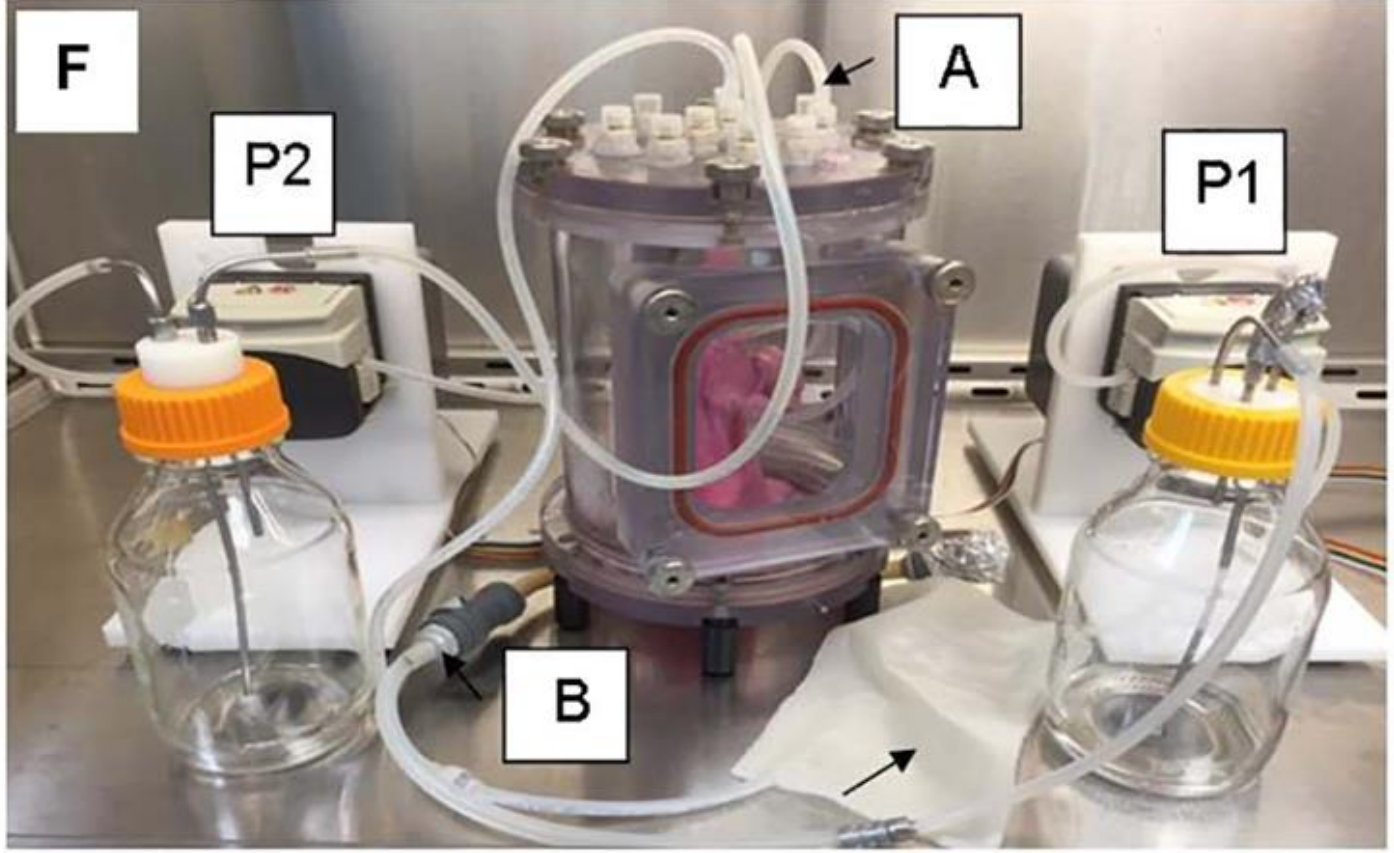

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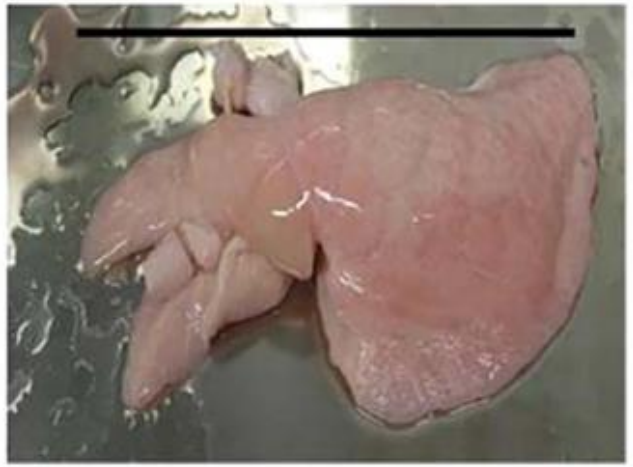

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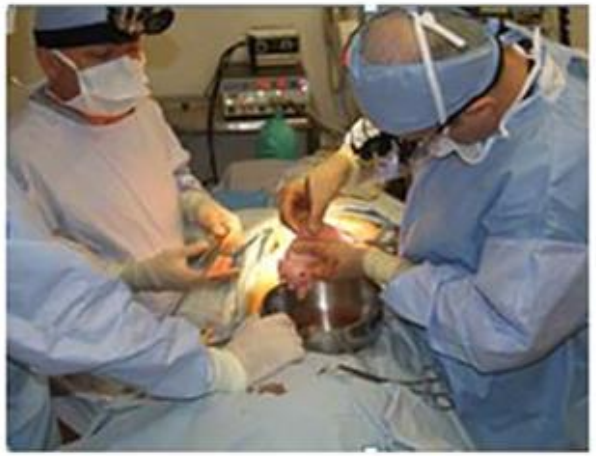

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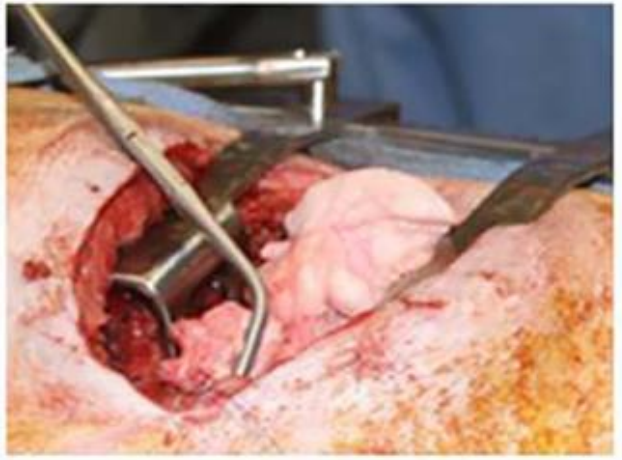

New life for lungs

Autologous cell–seeded bioengineered lungs showed vascular perfusion via collateral circulation within 2 weeks after transplantation.

The transplanted bioengineered lungs became aerated and developed native lung-like microbiomes. One pig had no respiratory symptoms when euthanized a full 2 months after transplant. This work represents a considerable advance in the lung tissue engineering field and brings tissue-engineered lungs closer to the realm of clinical possibility.

Organ Perfusion is a key to these future technologies

- Perfusion technologies now available are poised to transform Cardiac Transplantation
- The same technologies are credited with a major contribution to successful pig to baboon xenotransplantation
- Whether we use direct organs from pigs, or bio-engineered organs, central processing is inevitable, and machine perfusion likely to be key to distributing organs to patients