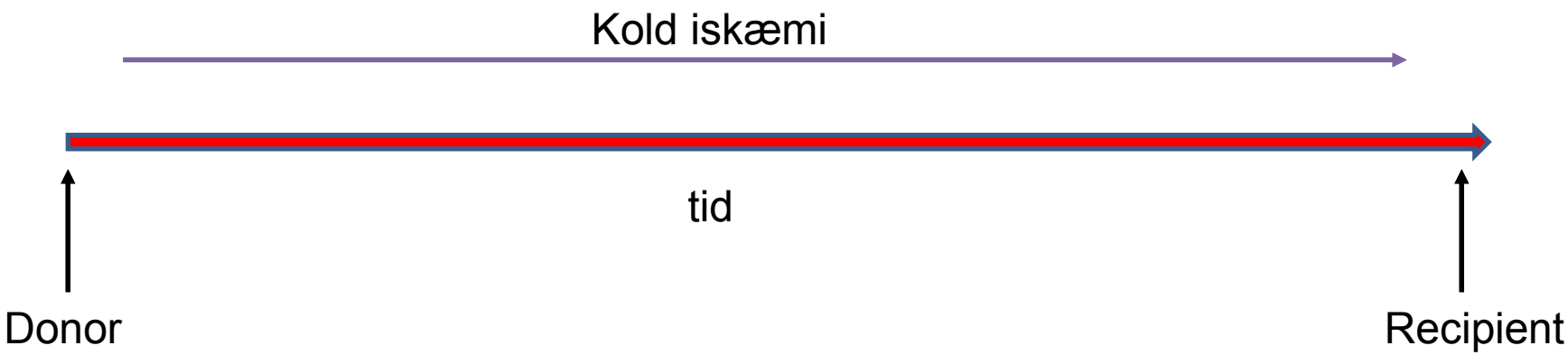
Optimering af hjertet efter udtagning til transplantation

Hjertecentret
Rigshospitalet

Handling of donor heart



Monitorering

Behandle

THE OPERATION

A HUMAN CARDIAC TRANSPLANT: AN INTERIM REPORT OF A SUCCESSFUL OPERATION PERFORMED AT GROOTE SCHUUR HOSPITAL, CAPE TOWN

C. N. BARNARD, M.D., M.MED., M.S., PH.D., D.SC. (HON. CAUSA), F.A.C.S., F.A.C.C., *Department of Surgery, University of Cape Town and Groote Schuur Hospital, Cape Town*

The venous catheter in the donor heart was removed from the right atrium. The arterial cannula and left ventricular vent were disconnected from the heart-lung machine but were left in place as positioned in the heart. The heart was placed in a bowl containing Ringer's lactate solution at 10°C and was transferred to the adjacent theatre where, in the meantime, the recipient had been connected to the heart-lung machine.

Heart, Lung and Vessels. 2015; 7(3): 246-255

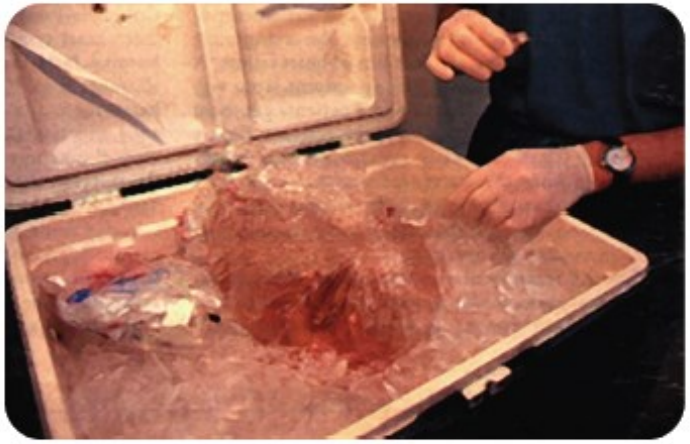
Procedure i dag:

- Cold storage arrest (CSA)
- Kan ikke gentages
- Iskæmitid < 6 timer
- Ca. 10-15% har betydelig graftfailure
- Ca 50-60% har behov for inotropi støtte det første døgn
- Kuldeskader
- Stort set ingen monitorering af hjertet (iskæmitid)
    - Biokemisk
    - Funktionelt (tryk-flow)
    - EKG
    - Tp.

Background on Organ Transplant Problems

Deprived of O_2, blood & nutrients

Time dependent injury & death



Metabolically & functionally inactive

Unable to resuscitate or assess

Unpredictable Outcomes

- 10-20% primary graft failure
- 50-70% suffer severe complications
- Short- and long-term survival is a function of time with cold storage

Under utilization of Donor Organs

- 60-80% of current thoracic donors are wasted annually due to technology limitations:
  - logistics (long ischemia time)
  - lack of assessment
  - lack of resuscitative capability


PROL GUERRERO
FLORES MAGON
INSURGENTES SUR
1 ANTONIO ALZATE
2 MANUEL GONZALEZ
CTO BICENTENARIO
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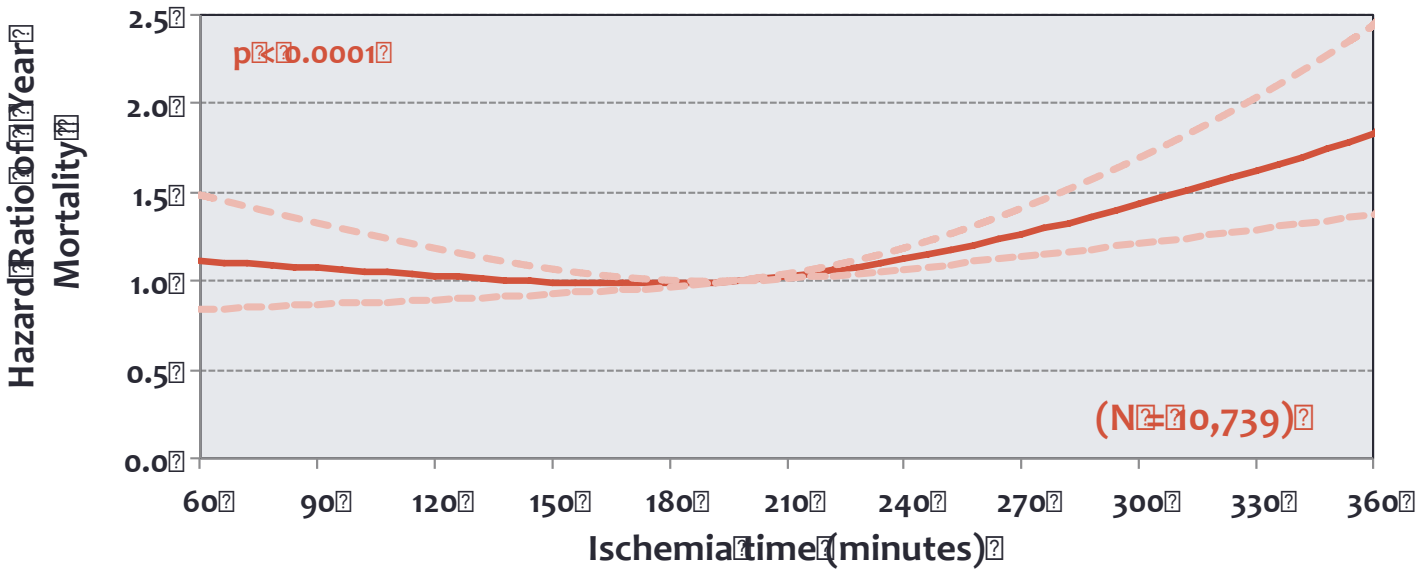
PARAGONIX
SherpaPak


CUTAWAY
VIEW

Impact of Heart Ischemia Time

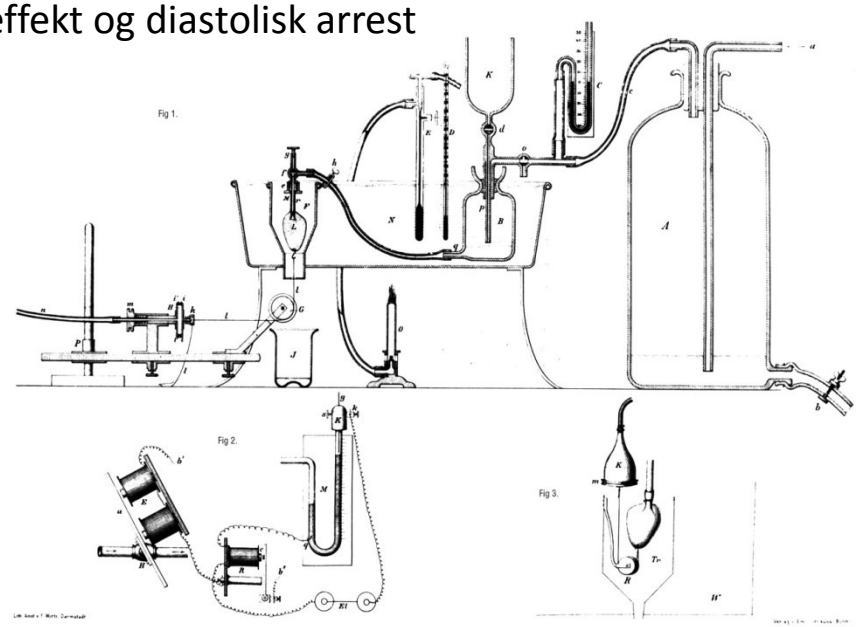


The risk of mortality at one year increases steadily with every minute of ischemic time in excess of 3 hours:

Stehlik et al, J Heart Lung Transplant, 29:3, 291-298, 2010

Det isolerede perfunderede hjerte

- Ludwig/Langendorf 1840-1870 mus/kanin/hund
- Perfunderet med defibrineret blod
- Konklusion:
- Det udtagne ”døde” hjerte kunne bringes til at slå igen når koronarperfusionen blev genoptaget
- Fyldning af ventriklerne var uden betydning for exitabiliteten
- Vagusstimulation og kaliumklorid medførte bradychardi/asystoli
- Muscarin inducerede neg. chronotop og inotrop effekt og diastolisk arrest
- Atropin virkede som en antagonist
- Høj tp. førte til tachycardi
- Lav tp til bradychardi
- ……



Langendorff's isolated perfused mammalian heart.

Heinz-Gerd Zimmer Physiology 1998;13:203-210

Cold Storage vs. Warm Perfusion

- Time dependent organ injury or organ loss
- No capability for optimizing organ condition or assessing organ function
- Limits utilization of potentially viable organs

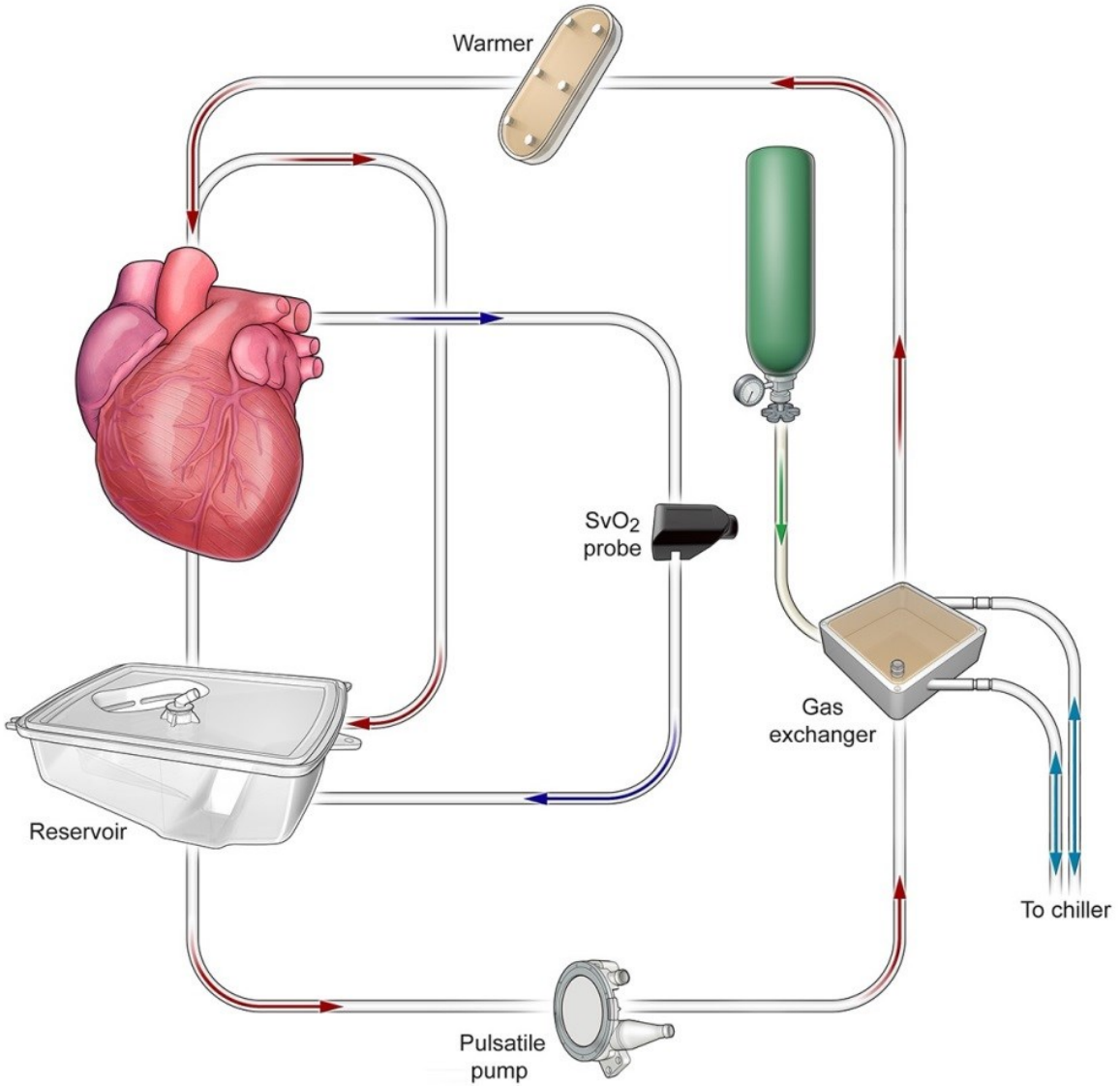
- **Limits organ utilization**
- **Compromised clinical outcomes**

- Organ preserved in warm, functioning state
- Minimized time pressure (Long distance retrieval, VAD explants)
- Optimize organ's clinical parameters ex-vivo
- Enables organ viability/function assessment

- **Potential to expand organ utilization and improve clinical outcomes**

TransMedics OCS Heart

OCS Heart Perfusion Circuit



Organ Care System (OCS™)

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

The Organ Care System (OCS™)

Wireless Monitor

Controls and displays heart parameters in real time

Heart Perfusion Module (HPM)

Provides the sterile blood circuit and protected environment for the donor heart

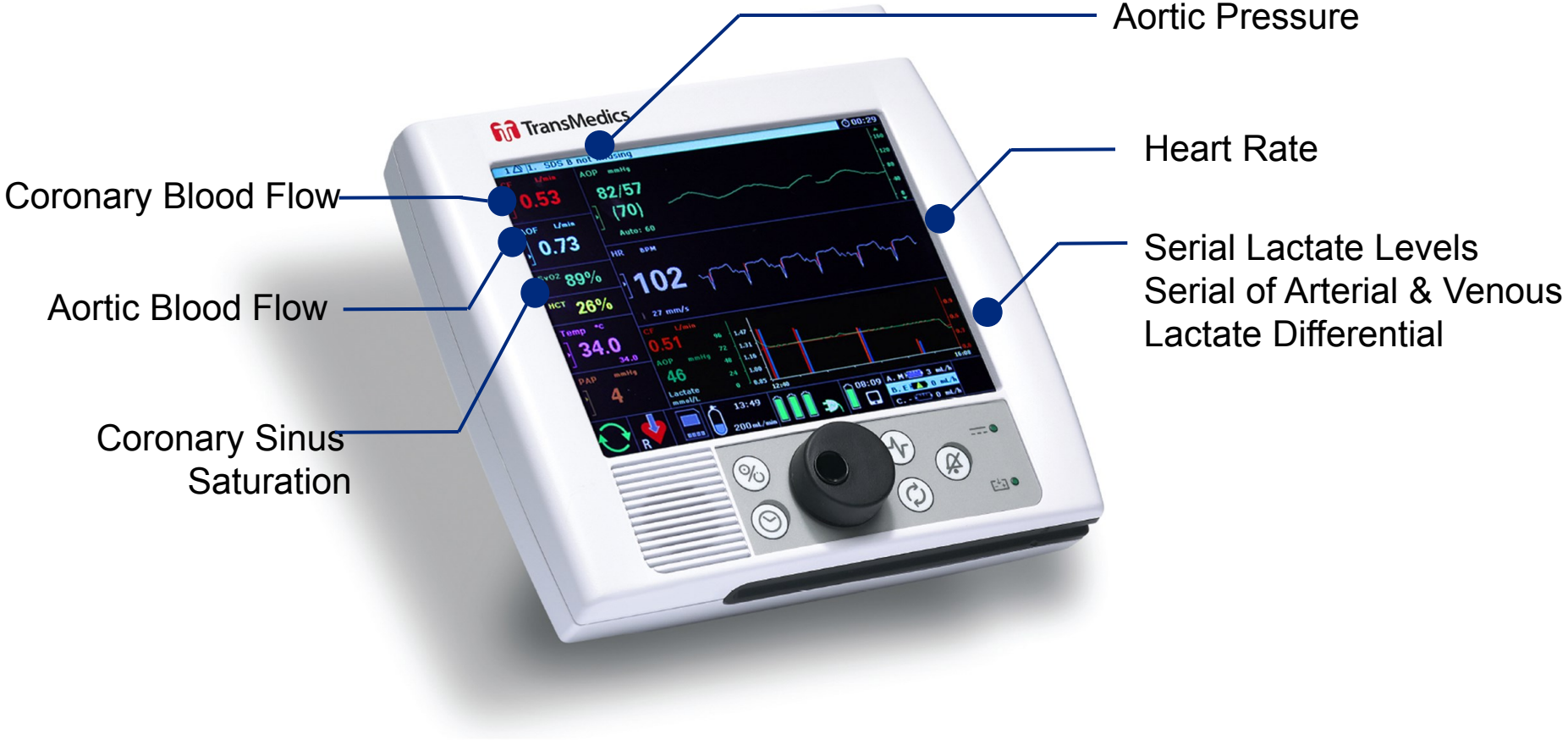
Organ Care System Console

Portable, easy to use and fits within all modes of transportation

Heart Solution Set (HSS)

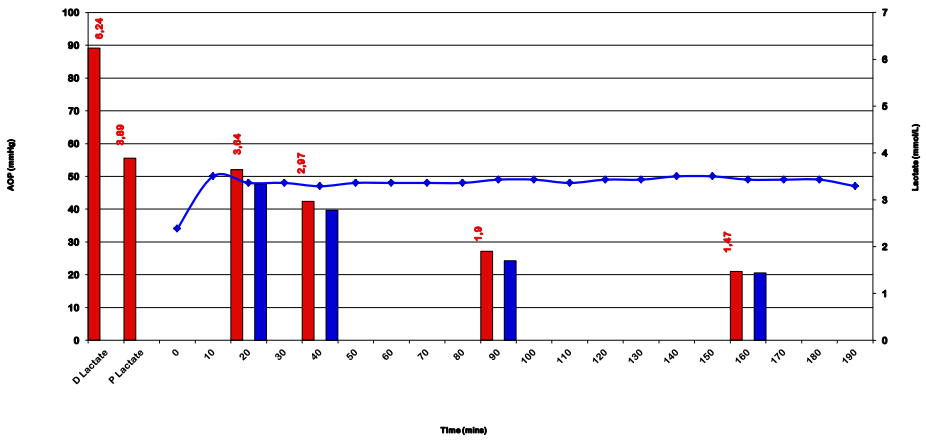
Infused using Alaris infusion pump to enrich blood with nutrients, electrolytes and hormones

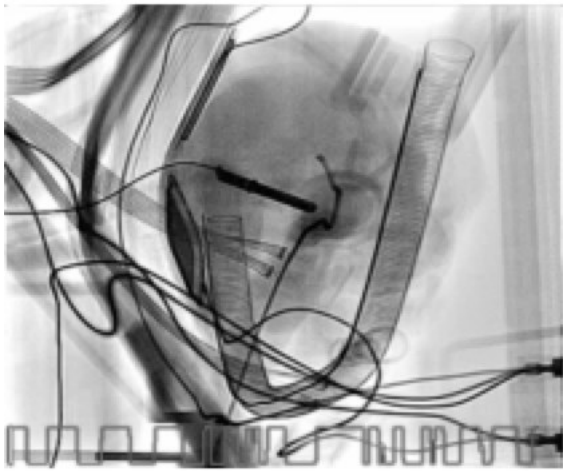
OCS™ Heart Monitored Parameters



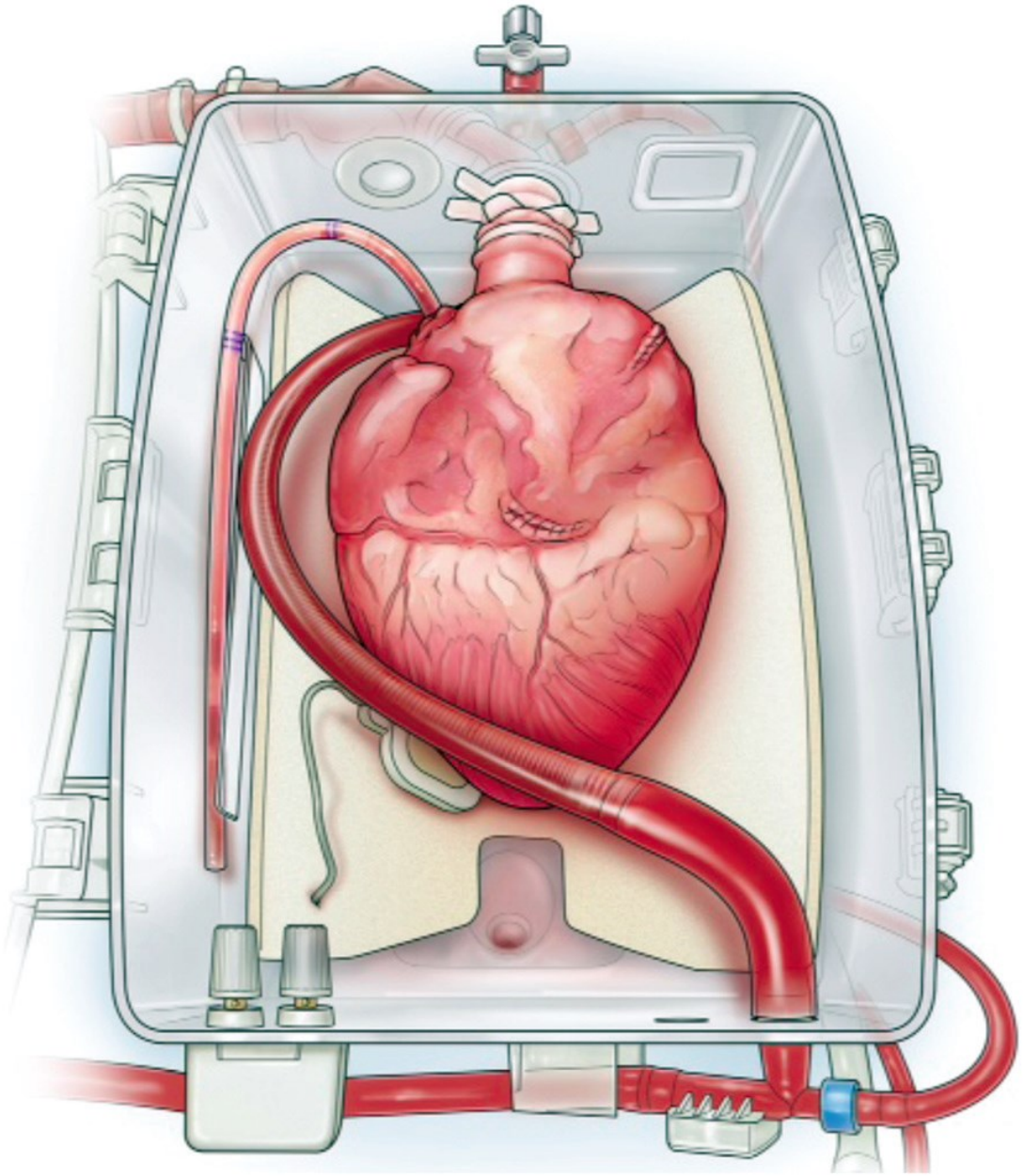
OCS™ Heart Assessment & Diagnostic Capabilities

- Perfusion parameters
- Lactate Production
- ECG Activities
- Coronary Angiogram
- Echocardiogram

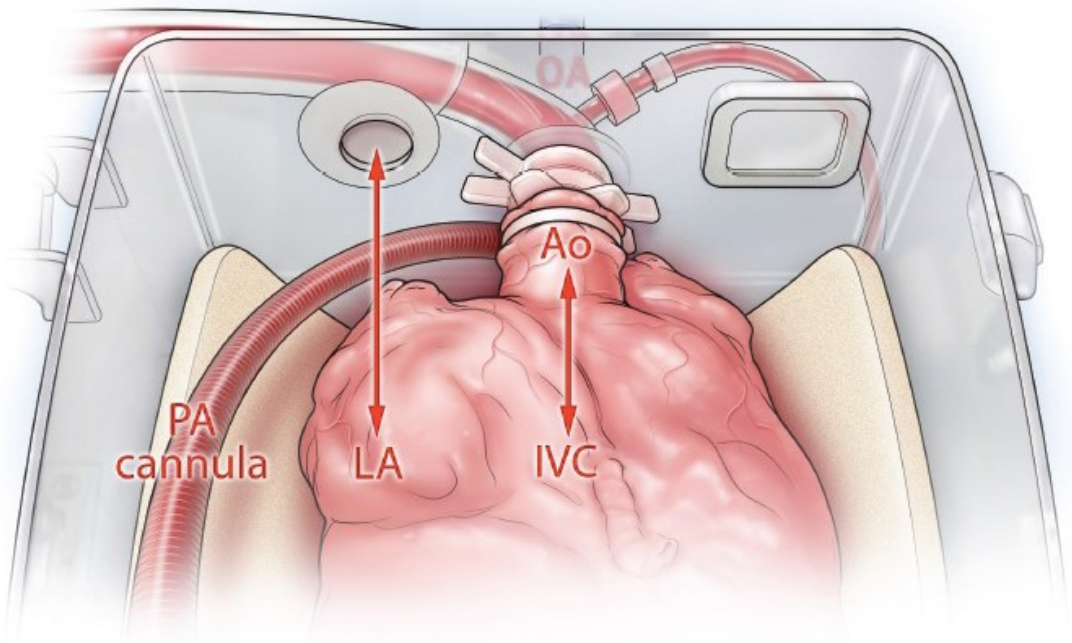


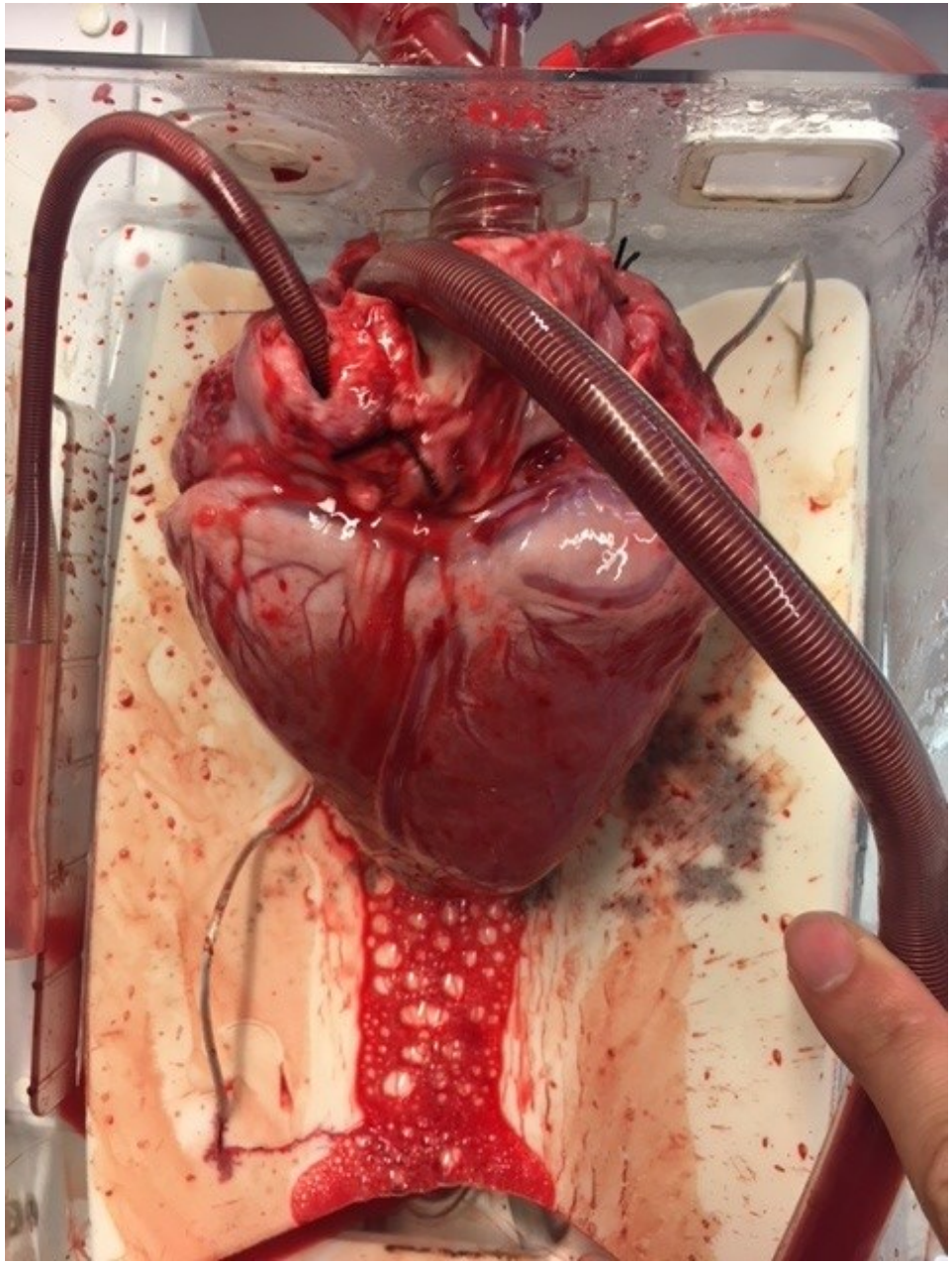


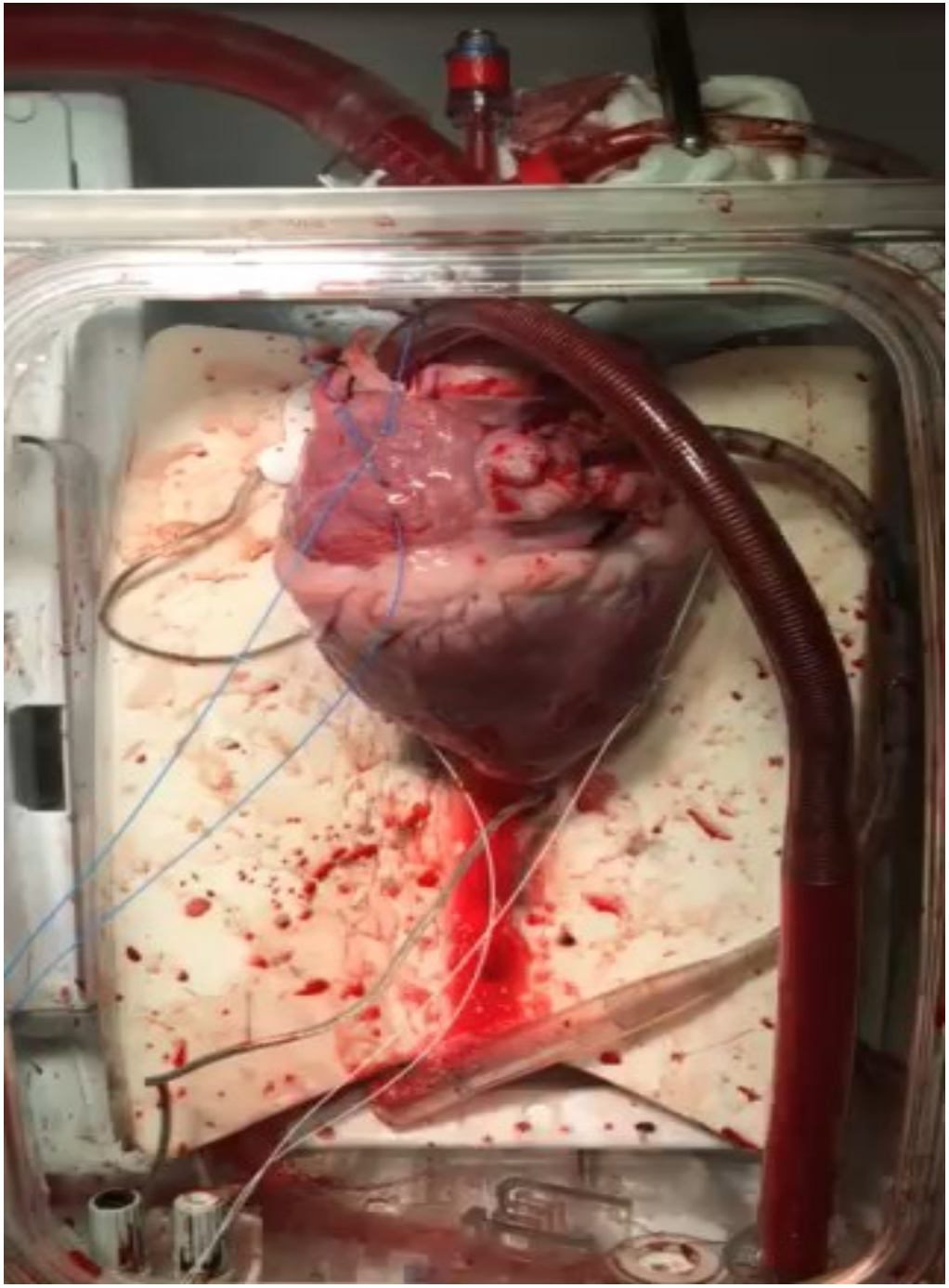
OCS Angio –Courtesy of DHZB Berlin



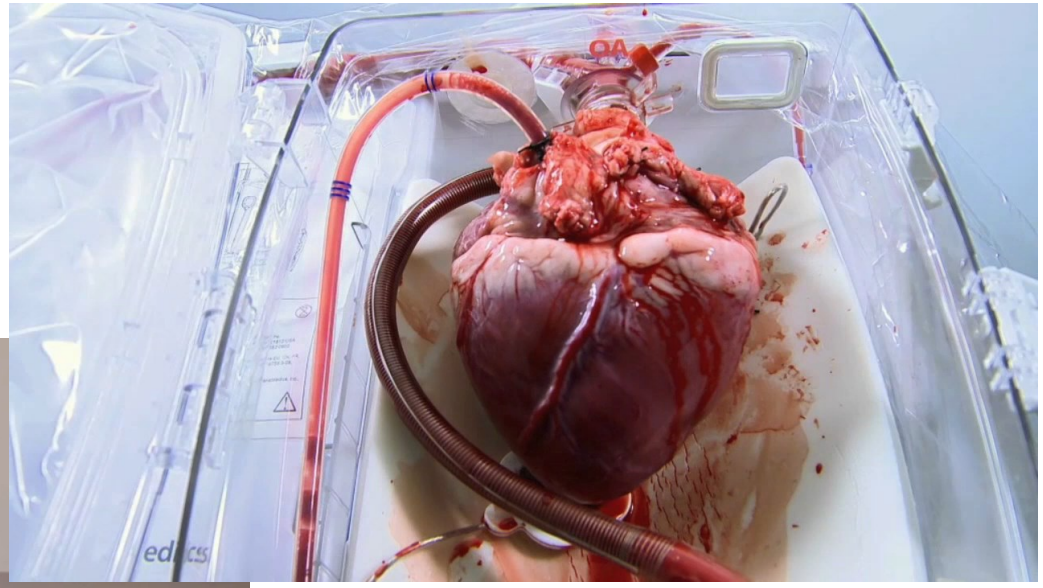
Heart Alignment

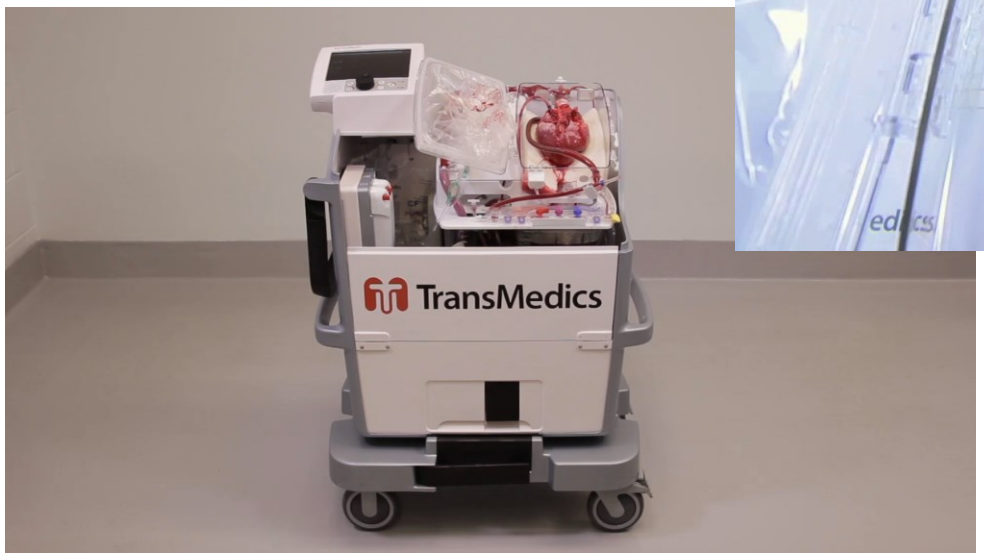


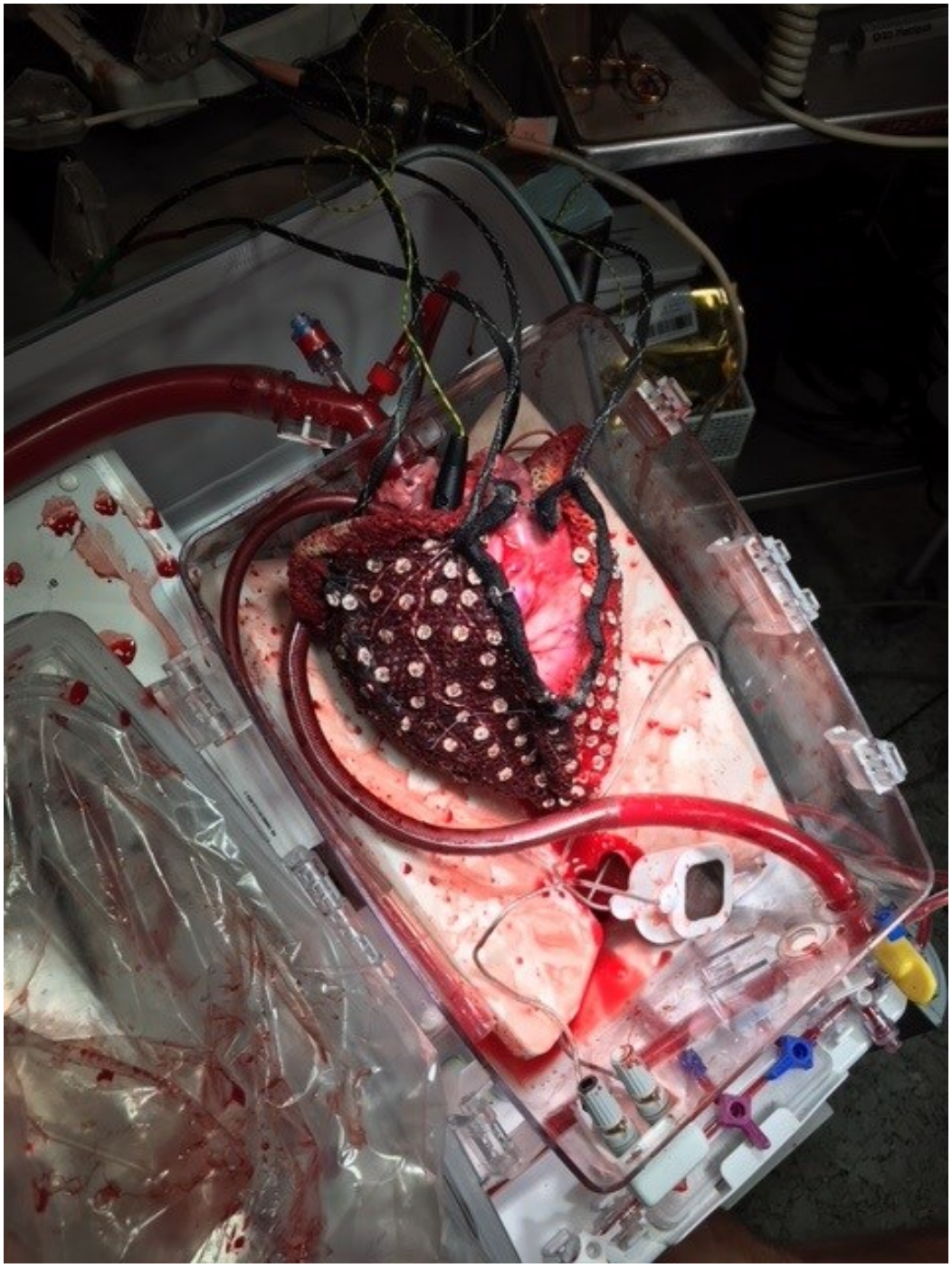




The OCS™ Heart

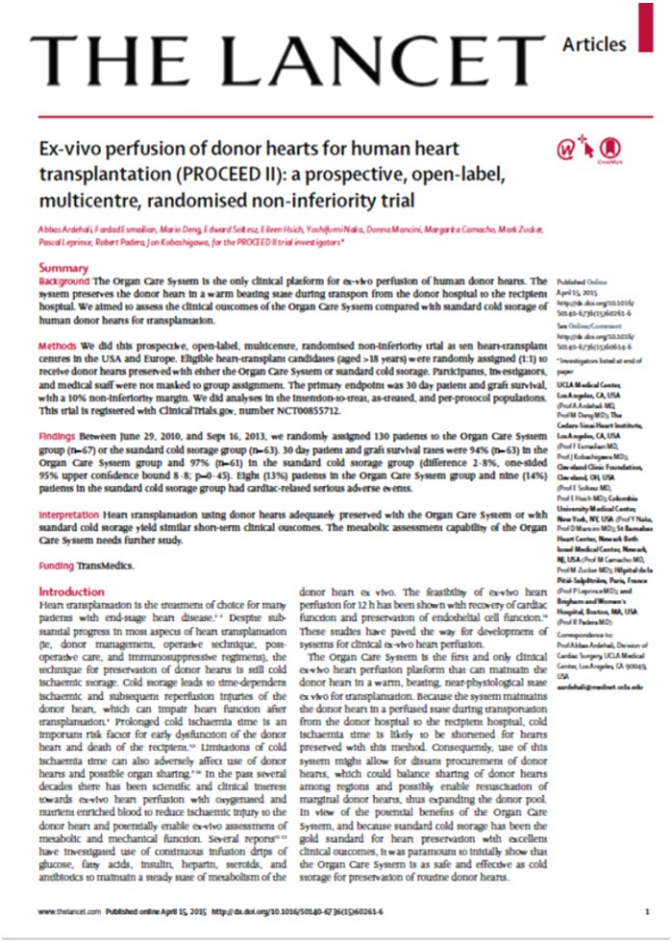






PROCEED II Study

- Prospective, Multi-center, Randomized Non-Inferiority Trial Comparing the Safety & Efficacy of the OCS™ Heart to Cold Storage
- 10 centers, 62 OCS™ & 66 cold storage heart transplantations
- Primary Endpoint Met: 30-Day Patient & Graft Survival
- Mean total cold ischemia time significantly shorter with OCS™ Heart versus cold storage, despite longer out-of-body time in the OCS™ group (p<0.0001)



THE LANCET Articles

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

Abbas Ardehali, Farshad Esmailian, Mario Deng, Edward Soltesz, Eileen Hsich, Yoshifumi Naka, Donna Mancini, Margarita Camacho, Mark Zucker, Pascal Leprince, Robert Padera, Jon Kobashigawa, for the PROCEED II trial investigators*

Summary

Background The Organ Care System is the only clinical platform for ex-vivo perfusion of human donor hearts. The system preserves the donor heart in a warm beating state during transport from the donor hospital to the recipient hospital. We aimed to assess the clinical outcomes of the Organ Care System compared with standard cold storage of human donor hearts for transplantation.

Methods We did this prospective, open-label, multicentre, randomised non-inferiority trial at ten heart-transplant centres in the USA and Europe. Eligible heart-transplant candidates (aged >18 years) were randomly assigned (1:1) to receive donor hearts preserved with either the Organ Care System or standard cold storage. Participants, investigators, and medical staff were not masked to group assignment. The primary endpoint was 30 day patient and graft survival, with a 10% non-inferiority margin. We did analyses in the intention-to-treat, as-treated, and per-protocol populations. This trial is registered with ClinicalTrials.gov, number NCT00855712.

Findings Between June 29, 2010, and Sept 16, 2013, we randomly assigned 130 patients to the Organ Care System group (n=67) or the standard cold storage group (n=63). 30 day patient and graft survival rates were 94% (n=63) in the Organ Care System group and 97% (n=61) in the standard cold storage group (difference 2·8%, one-sided 95% upper confidence bound 8·8; p=0·45). Eight (13%) patients in the Organ Care System group and nine (14%) patients in the standard cold storage group had cardiac-related serious adverse events.

Interpretation Heart transplantation using donor hearts adequately preserved with the Organ Care System or with standard cold storage yield similar short-term clinical outcomes. The metabolic assessments capability of the Organ Care System needs further study.

Funding TransMedics.

Introduction

Heart transplantation is the treatment of choice for many patients with end-stage heart disease.[1,2] Despite substantial progress in most aspects of heart transplantation (ie, donor management, operative technique, postoperative care, and immunosuppressive regimens), the technique for preservation of donor hearts is still cold ischaemic storage. Cold storage leads to time-dependent ischaemic and subsequent reperfusion injuries of the donor heart, which can impair heart function after transplantation.[3] Prolonged cold ischaemia time is an important risk factor for early dysfunction of the donor heart and death of the recipient.[4,5] Limitations of cold ischaemia time can also adversely affect use of donor hearts and possible organ sharing.[6,7] In the past several decades there has been scientific and clinical interest towards ex-vivo heart perfusion with oxygenated and nutrient enriched blood to reduce ischaemic injury to the donor heart and potentially enable ex-vivo assessment of metabolic and mechanical function. Several reports[8-11] have investigated use of continuous infusion drips of glucose, fatty acids, insulin, heparin, steroids, and antibiotics to maintain a steady state of metabolism of the donor heart ex vivo. The feasibility of ex-vivo heart perfusion for 12 h has been shown with recovery of cardiac function and preservation of endothelial cell function.[12] These studies have paved the way for developments of systems for clinical ex-vivo heart perfusion.

The Organ Care System is the first and only clinical ex-vivo heart perfusion platform that can maintain the donor heart in a warm, beating, near-physiological state ex vivo for transplantation. Because the system maintains the donor heart in a perfused state during transportation from the donor hospital to the recipient hospital, cold ischaemia time is likely to be shortened for hearts preserved with this method. Consequently, use of this system might allow for distant procurement of donor hearts, which could balance sharing of donor hearts among regions and possibly enable resuscitation of marginal donor hearts, thus expanding the donor pool. In view of the potential benefits of the Organ Care System, and because standard cold storage has been the gold standard for heart preservation with excellent clinical outcomes, it was paramount to initially show that the Organ Care System is as safe and effective as cold storage for preservation of routine donor hearts.

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See Online/Comment http://dx.doi.org/10.1016/S0140-6736(15)60614-6

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Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial, Ardehali, Abbas et al. The Lancet , Volume 385 , Issue 9987 , 2577 - 2584

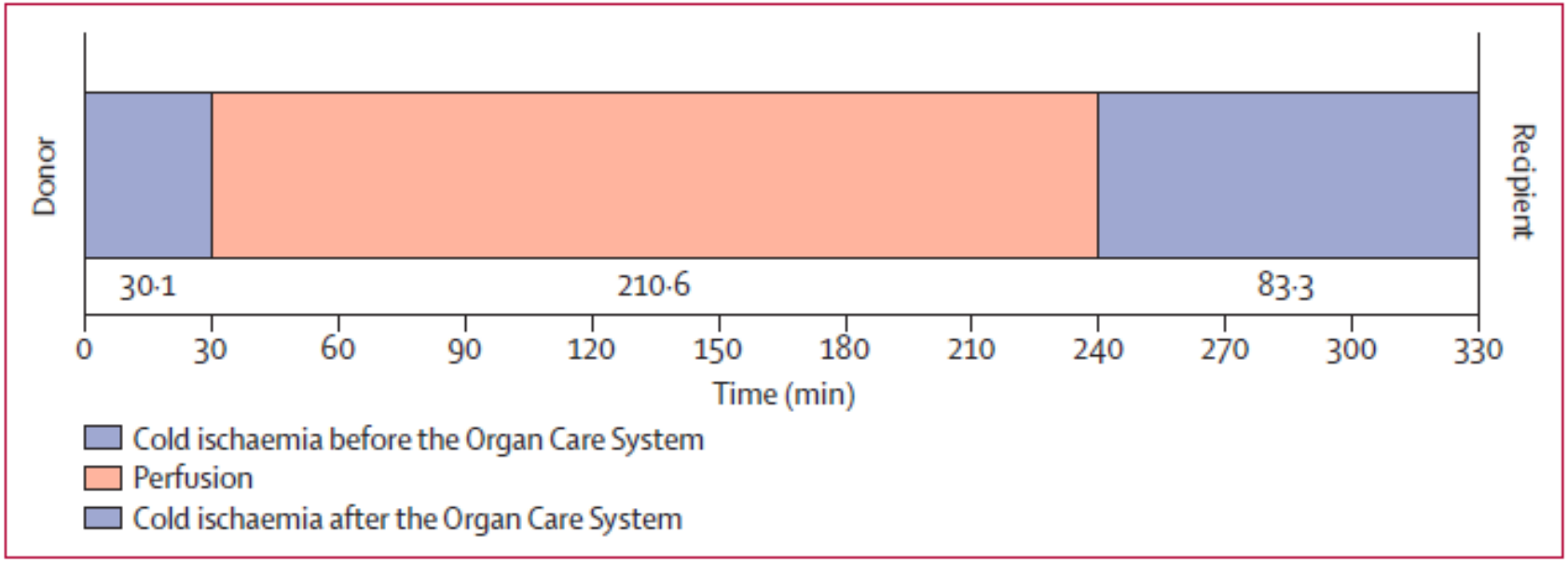
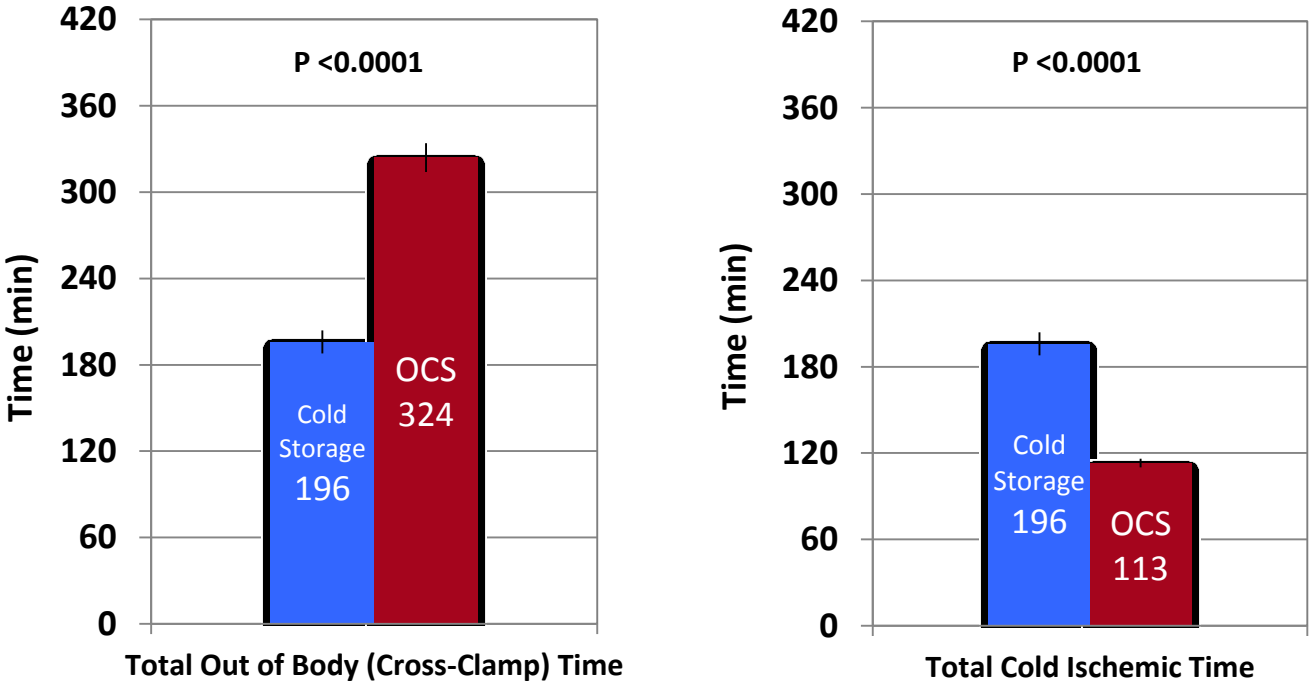


Figure 4: **Cold ischaemia time and perfusion time for donor hearts preserved with the Organ Care System**
Cold ischaemia time consists of the initial retrieval phase (time needed to harvest and implement the heart into the Organ Care System) and the final re-implantation phase (to place the donor heart into the recipient).

PROCEED II Results: Total Cross Clamp & Ischemia Times



Mean Total Cold Ischemic Time significantly shorter with OCS™ Heart versus Cold Storage, despite longer Out-Of-Body Time in the OCS™ group (p<0.0001)

Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial, Ardehali, Abbas et al. The Lancet , Volume 385 , Issue 9987 , 2577 - 2584

	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.

Table 2: Outcomes of primary and secondary endpoints

OCS Heart – Overview Summary

- The only platform which allows hearts to be transported with normothermic perfusion.
- Minimises the potential for ischaemic damage to the organ.
- Technology has been tried and tested clinically since 2006.
- Allows continuous organ assessment.
- Fully transportable.

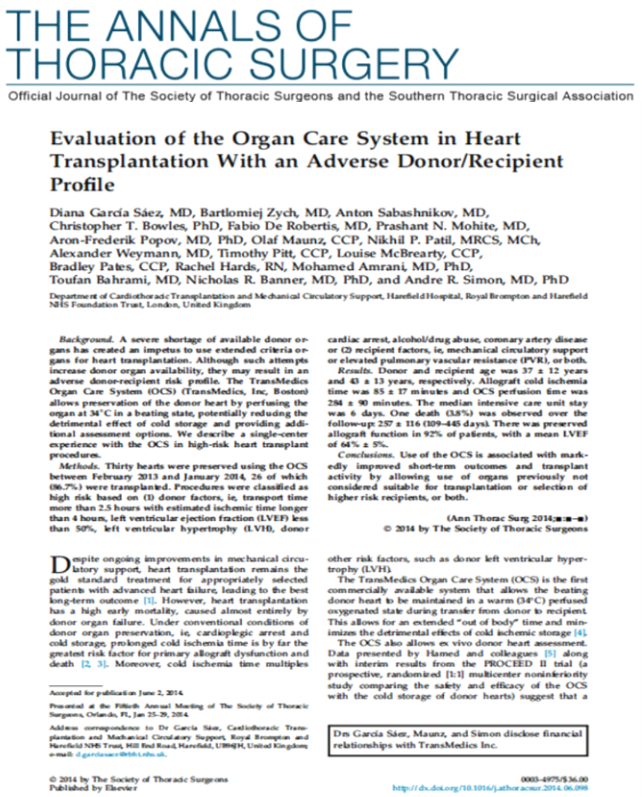
Den marginale hjertedonor

1. Forventet lang kold iskæmitid (> 4 timer) f.eks. pga lang transportvej eller lang operationstid på recipient
2. Generelt anvendes donorer med alder over 65 år ikke men hvis alder > 65 år er eneste risikofaktor kan man anvende EVHP til at nedbringe varigheden af den kolde iskæmitid og til vurdering af hjertet
3. Varighed af hjertestop > 20 min men med stabil hæmodynamik min. 24 timer
4. Nedsat EF dvs mellem 35 og 45 kan udtages og vurderes på EVHP
5. Hypertrofi af septum over 16 mm men under 20 mm
6. Inotropibehandling. Donorer kan være på inotropibehandling af multiple årsager der ikke nødvendigvis er af kardial oprindelse. Denne type hjertet kan udtages og vurderes på EVHP .
7. Donorer med sepsis hvor vi normalt ville afvise hjertet kan udtages og vurderes på EVHP.

OCS™ Heart Clinical Highlight

Extended Criteria

- Single-center experience in the assessment of the utilization of extended criteria hearts using the OCS™
- 26 high risk transplants conducted using OCS™ Heart with either donor- or recipient-based risk factors LVEF ≤50%, LV hypertrophy (LVH); interventricular septum in diastole >14 mm, donor cardiac arrest, coronary artery disease
- Allograft function was preserved in 92% of recipients at follow-up (257±116 days) with a mean left ventricular ejection fraction of 64±5 %.
- Conclusion: Use of the OCS™ is associated with markedly improved short term outcomes by allowing use of organs not previously considered for transplantation



THE ANNALS OF THORACIC SURGERY

Official Journal of The Society of Thoracic Surgeons and the Southern Thoracic Surgical Association

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

Diana García Sáez, MD, Bartlomiej Zych, MD, Anton Sabashnikov, MD, Christopher T. Bowles, PhD, Fabio De Robertis, MD, Prashant N. Mohite, MD, Aron-Frederik Popov, MD, PhD, Olaf Maunz, CCP, Nikhil P. Patil, MRCS, MCh, Alexander Weymann, MD, Timothy Pitt, CCP, Louise McBrearty, CCP, Bradley Pates, CCP, Rachel Hards, RN, Mohamed Amrani, MD, PhD, Toufan Bahrami, MD, Nicholas R. Banner, MD, PhD, and Andre R. Simon, MD, PhD

Department of Cardiothoracic Transplantation and Mechanical Circulatory Support, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom

Background. A severe shortage of available donor organs has created an impetus to use extended criteria organs for heart transplantation. Although such attempts increase donor organ availability, they may result in an adverse donor-recipient risk profile. The TransMedics Organ Care System (OCS) (TransMedics, Inc, Boston) allows preservation of the donor heart by perfusing the organ at 34°C in a beating state, potentially reducing the detrimental effect of cold storage and providing additional assessment options. We describe a single-center experience with the OCS in high-risk heart transplant procedures.

Methods. Thirty hearts were preserved using the OCS between February 2013 and January 2014, 26 of which (86.7%) were transplanted. Procedures were classified as high risk based on (1) donor factors, ie, transport time more than 2.5 hours with estimated ischemic time longer than 4 hours, left ventricular ejection fraction (LVEF) less than 50%, left ventricular hypertrophy (LVH), donor cardiac arrest, alcohol/drug abuse, coronary artery disease or (2) recipient factors, ie, mechanical circulatory support or elevated pulmonary vascular resistance (PVR), or both.

Results. Donor and recipient age was 37 ± 12 years and 43 ± 13 years, respectively. Allograft cold ischemia time was 85 ± 17 minutes and OCS perfusion time was 284 ± 90 minutes. The median intensive care unit stay was 6 days. One death (3.8%) was observed over the follow-up 257 ± 116 (109–445 days). There was preserved allograft function in 92% of patients, with a mean LVEF of 64% ± 5%.

Conclusions. Use of the OCS is associated with markedly improved short-term outcomes and transplant activity by allowing use of organs previously not considered suitable for transplantation or selection of higher risk recipients, or both.

(Ann Thorac Surg 2014;■:■–■)

Despite ongoing improvements in mechanical circulatory support, heart transplantation remains the gold standard treatment for appropriately selected patients with advanced heart failure, leading to the best long-term outcome [1]. However, heart transplantation has a high early mortality, caused almost entirely by donor organ failure. Under conventional conditions of donor organ preservation, ie, cardioplegic arrest and cold storage, prolonged cold ischemia time is by far the greatest risk factor for primary allograft dysfunction and death [2, 3]. Moreover, cold ischemia time multiplies other risk factors, such as donor left ventricular hypertrophy (LVH).

The TransMedics Organ Care System (OCS) is the first commercially available system that allows the beating donor heart to be maintained in a warm (34°C) perfused oxygenated state during transfer from donor to recipient. This allows for an extended "out of body" time and minimizes the detrimental effects of cold ischemic storage [4].

The OCS also allows ex vivo donor heart assessment. Data presented by Hamed and colleagues [5] along with interim results from the PROCEED II trial (a prospective, randomized [1:1] multicenter noninferiority study comparing the safety and efficacy of the OCS with the cold storage of donor hearts) suggest that a

Accepted for publication June 2, 2014.

Presented at the Fiftieth Annual Meeting of The Society of Thoracic Surgeons, Orlando, FL, Jan 25–29, 2014.

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Drs García Sáez, Maunz, and Simon disclose financial relationships with TransMedics Inc.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2014.06.098

García Sáez D, Zych B, Sabashnikov A, et al. Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. Ann Thorac Surg. 2014;98(6):2099-105.

OCS Heart – Potential Benefits for Transplant Programme

- Less constraints when considering organ offers from hospitals at a greater distance.
- Can consider cheaper forms of transportation when accepting organs from donor sites < 4 hours away.
- Reduced time pressure on recipient procedure – particularly important for VAD explant procedures.
- Marginal organs can be assessed at recipient site before explant procedure is started.
- Potential for DCD Heart transplantation.

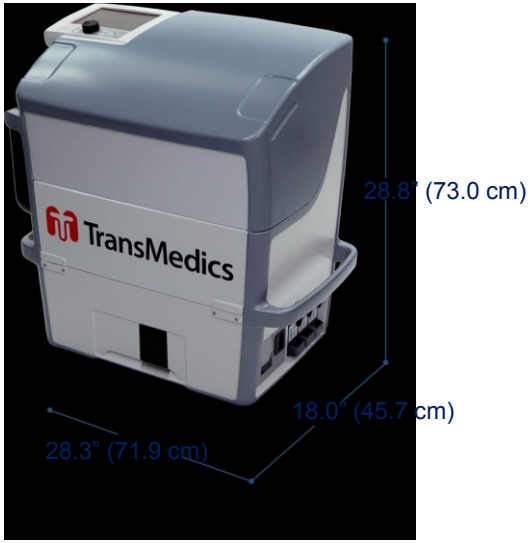
Designed for Maximum Portability

Wheels On

For easy rolling between destinations:

- Aircraft to SUV
- SUV to hospital
- Within hospital

Wheels Off



For placement inside transport:

- Aircraft
- Helicopter
- Ambulance
- SUV

Designed for Maximum Portability

- Detachable wheels allow it to fit in all standard modes of transportation for organ retrieval
- Lightweight carbon-fiber construction, weighs ~38kg and can be easily lifted by two adults
- Three on-board batteries
- Easy rolling between destinations