Ex-Vivo Heart Perfusion and DCD Heart Donation

Abbas Ardehali, M.D., F.A.C.S.
Professor of Surgery and Medicine, Division of Cardiac Surgery
William E. Connor Chair in Cardiothoracic Transplantation
Director, UCLA Heart, Lung, & Heart-Lung Transplant Programs
Ronald Reagan UCLA Medical Center
David Geffen School of Medicine at UCLA

CEOT

CUTTING EDGE OF TRANSPLANTATION

AST | AMERICAN SOCIETY OF TRANSPLANTATION

RESOLVING THE ORGAN SHORTAGE

PRACTICE | POLICY | POLITICS

FEBRUARY 25-27, 2016 • PHOENIX, ARIZONA

Conflict of Interest Disclosure

- Organ Care System and Vivoline are not approved by FDA
- I served as the Chair of the Steering Committee for PROCEED II Trial
- There is no Financial Conflict of Interest

The Cape Argus Newspaper after the First Human Heart Transplant

The Cape Argus

CITY LATE

Patient's condition 'first class', Groote Schuur doctors say

CRISIS AFTER 7 DAYS

MAN WITH A NEW HEART

Three years' work on 'op'

Louw tells of key factor in heart transplant

THE critical part in the heart transplantation would be in about a week's time, Prof. L. H. Louw, head of the Department of Surgery at the University of Cape Town Medical School, said today.

They will miss Denise...

Woman had no chance of survival

Her kidney helps a boy (10)

HEAD OF TEAM

And a surgeon took the pictures, too!

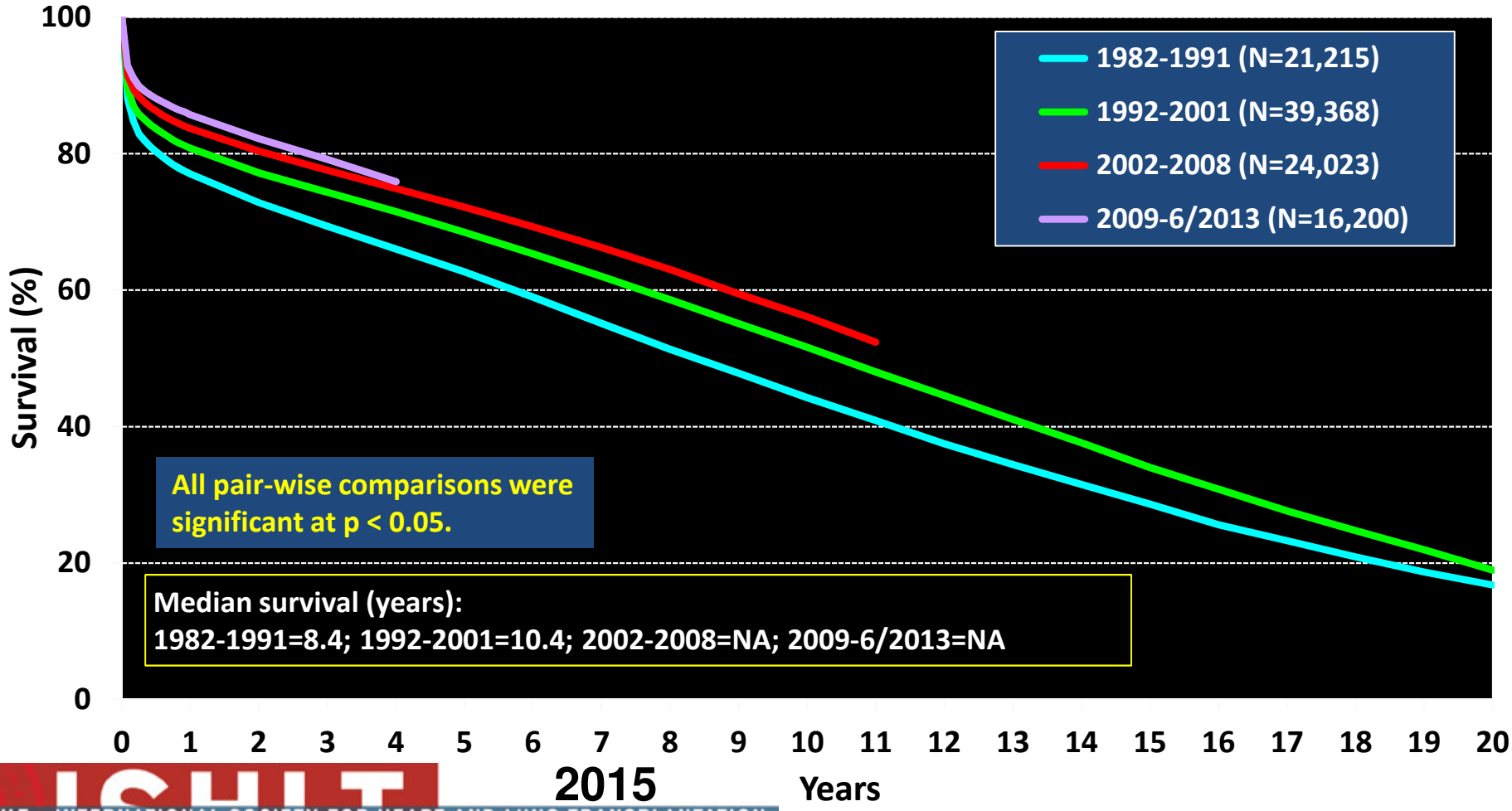
CHURCHMEN APPROVE

This month 5 people have died on W.P. roads

LOOK MA! NO PINS...

Snap Nappy

Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2013)

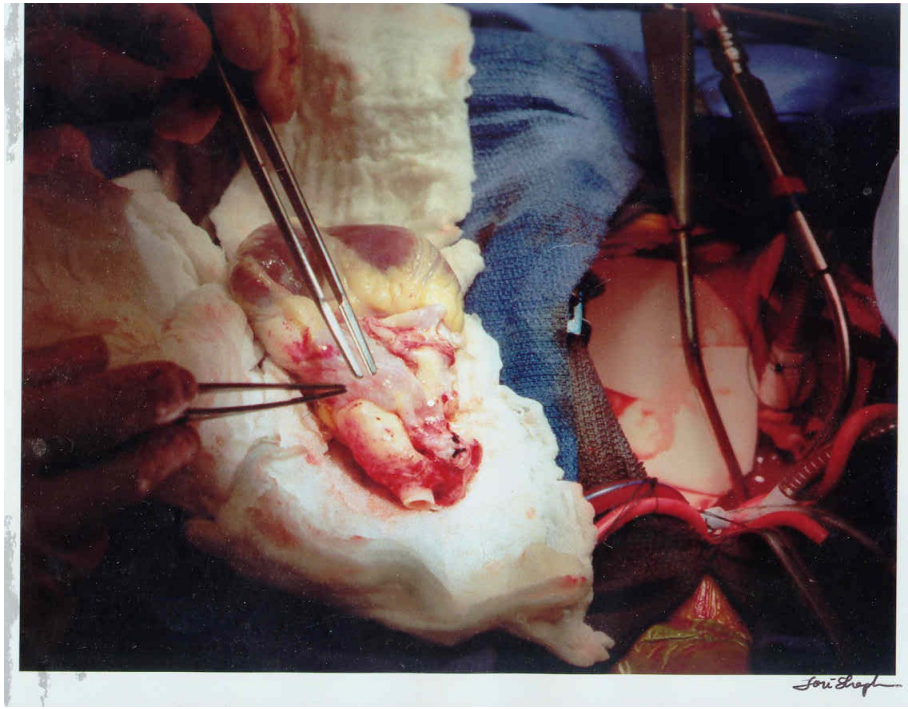


2015

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

JHLT. 2015 Oct; 34(10): 1244-1254

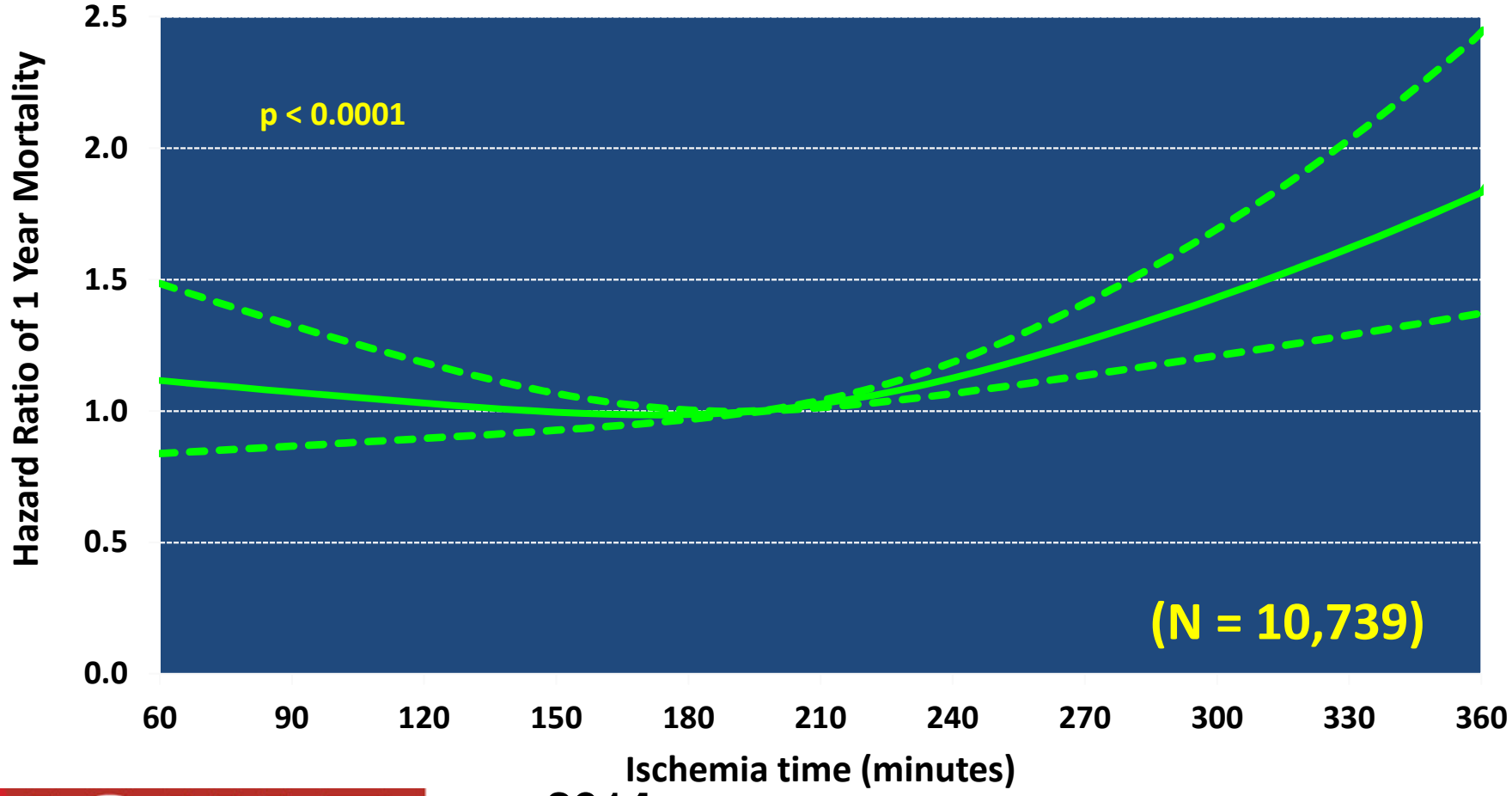
Cold Static Preservation



ADULT HEART TRANSPLANTS (2007-6/2012)

Risk Factors For 1 Year Mortality with 95% Confidence Limits

Ischemia Time

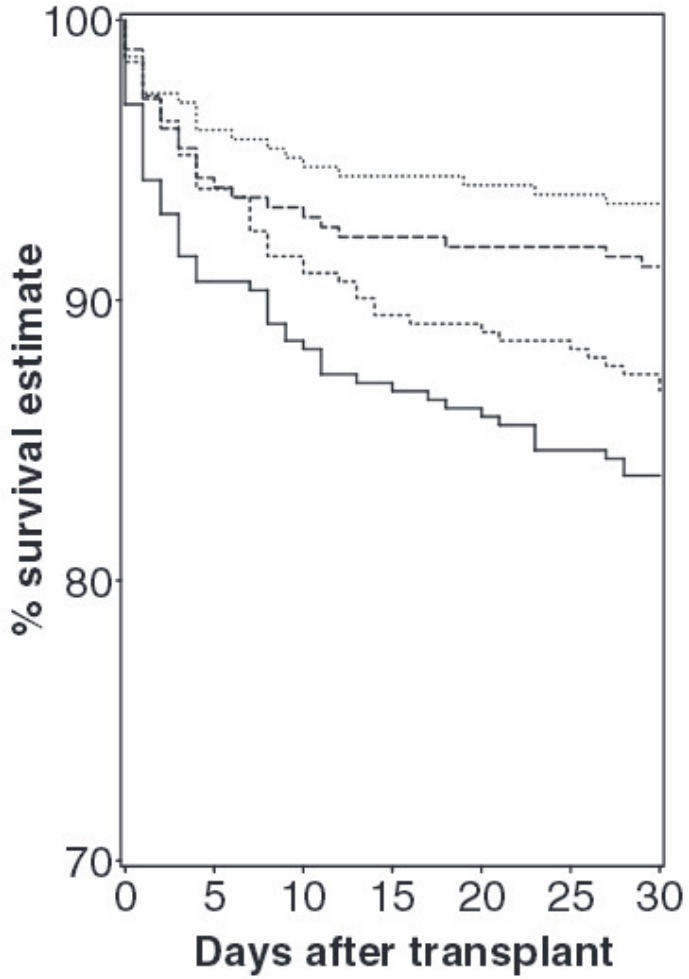


ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

2014

JHLT. 2014 Oct; 33(10): 996-1008

Cold Ischemia Time and 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

Banner NR, et al. *Transplantation* 2008; 86: 542-7.

Alternative to Cold Ischemic Preservation

- Ex Vivo Organ Perfusion
  - Platform to perfuse the donor organs

Ex-vivo Organ Perfusion

- Machine perfusion of Kidneys
  - Reduction of DGF
  - Improved 1 year graft outcome

- Ex-vivo perfusion of Liver
  - 2016, pilot trial
  - Pilot clinical use of several

    Portable platforms

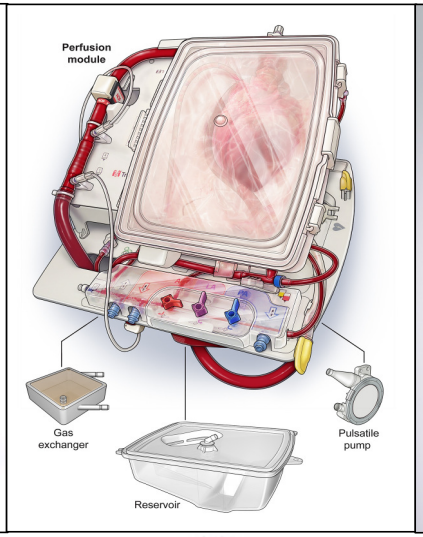
Ex-vivo Lung Perfusion

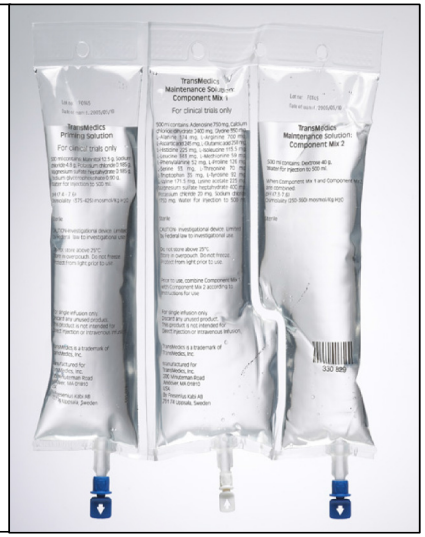
XPS (Xvivo)

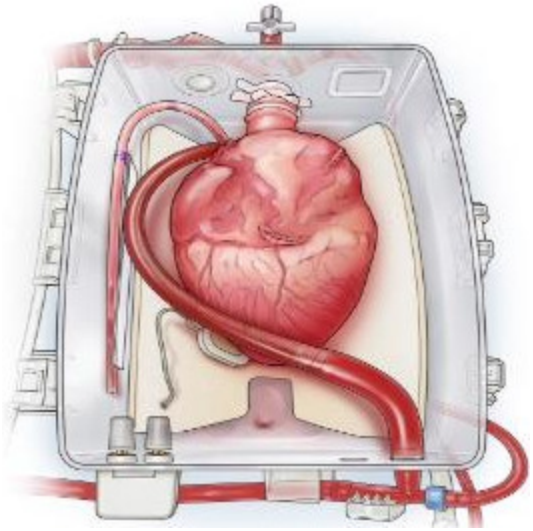
Vivoline LS1 (Vivoline)

OCS (TransMedics)

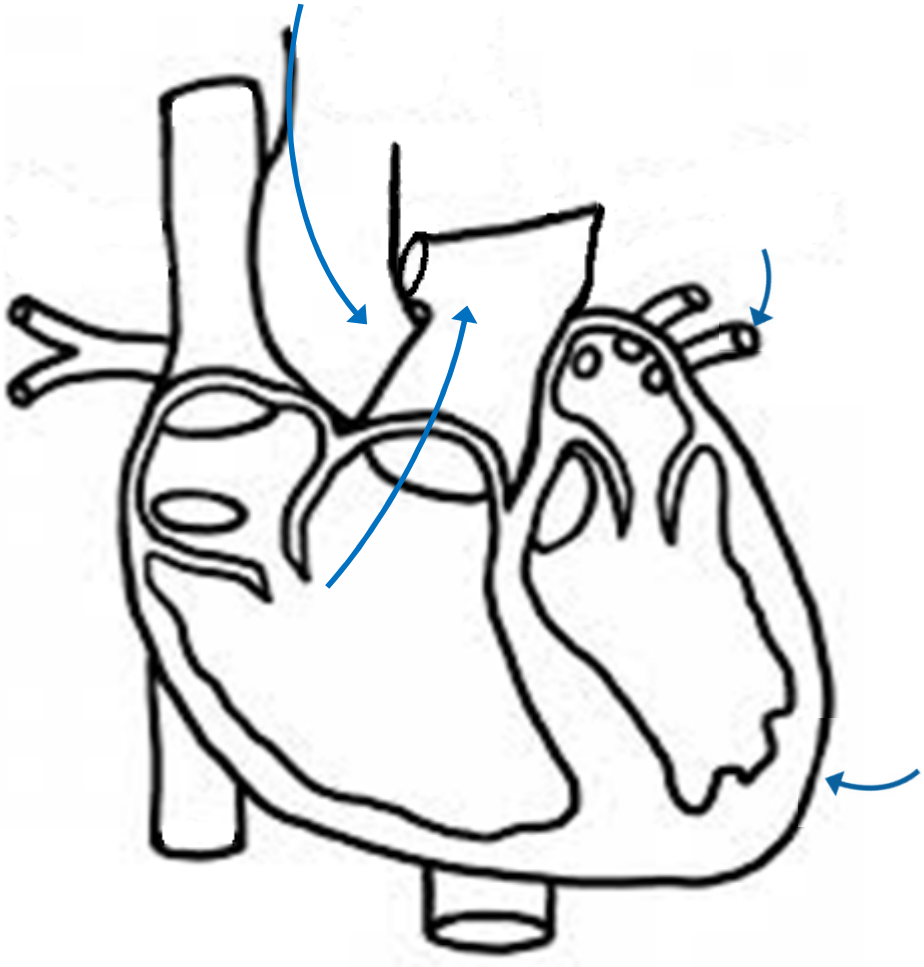
Ex-vivo Heart Perfusion-Organ Care System

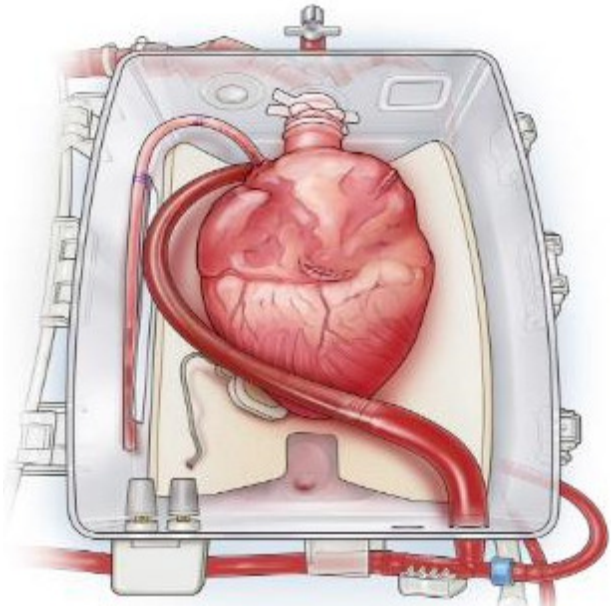






How does it work?





How to assess the donor heart on OCS?

- Hemodynamic parameters:
  - Aortic pressure (goal: 65-90 mm Hg)
  - Coronary blood flow (goal: 650-900 mL/min)
- Perfusate Lactate level
  - Arterio-venous difference
  - Absolute lactate level (goal: <5 mmol/L)
- Visual Inspection

The Organ Care System (OCS) Heart

- Physiologic preservation
  - Improve quality of donor organs
  - Reduce Cold Ischemia Time
  - Expand Time & Distance
- Resuscitative capabilities
  - Expand the donor pool
- Metabolically active platform
  - Modification of the donor heart

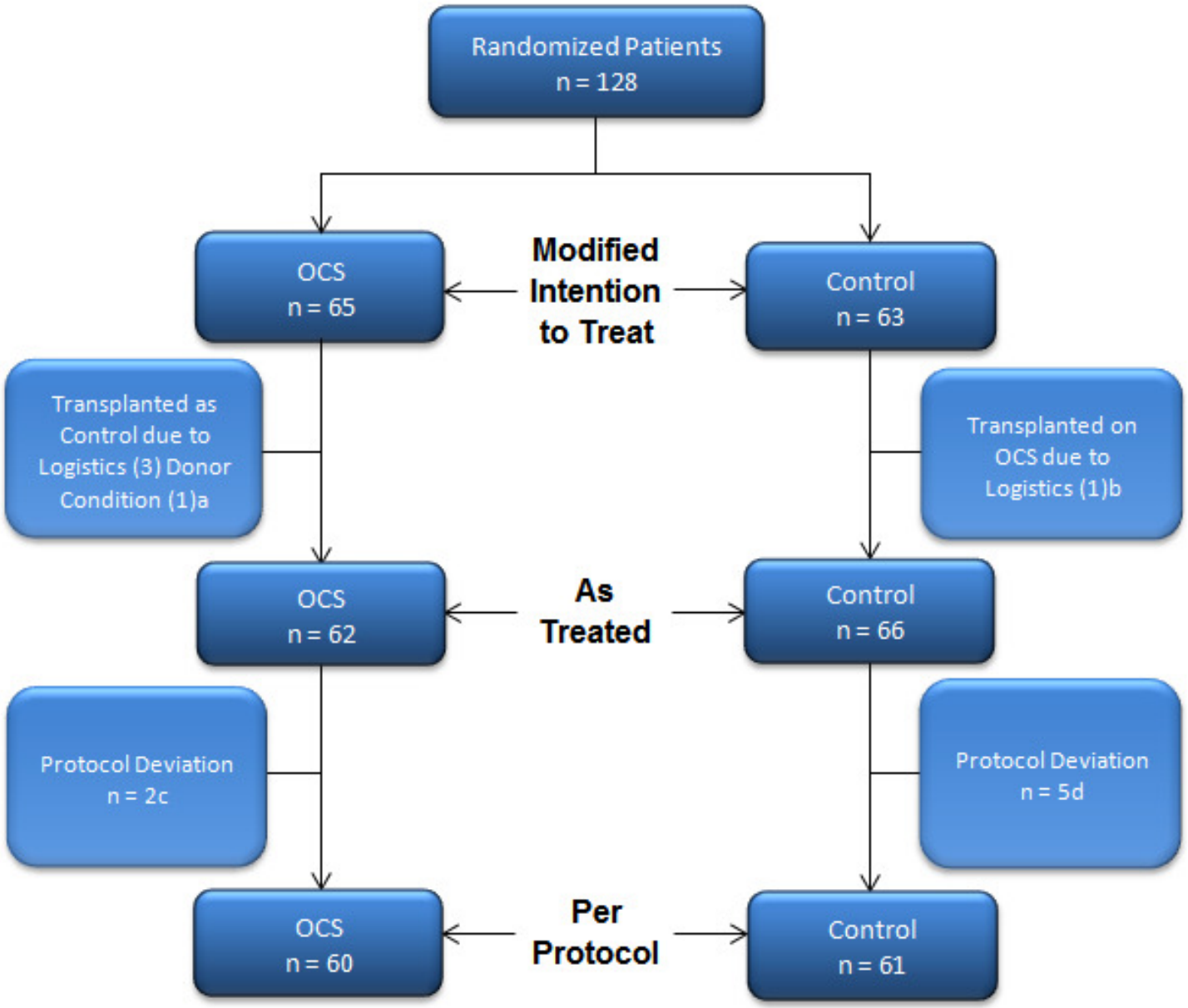
PROCEED II Trial Overview

Design: Prospective, Randomized (1:1), Multi-center, Non-Inferiority Trial Comparing the Safety & Efficacy of OCS to Cold Storage of Donor Hearts

Primary Endpoint: 30-Day Patient & Graft Survival

Secondary Endpoints:

- Incidence of Cardiac-related SAEs
- Incidence of Bx. Proven ISHLT Grade 2R or 3R Rejection
- ICU Time


Randomized Patients
n = 128
OCS
n = 65
Modified
Intention
to Treat
Control
n = 63
Transplanted as Control due to Logistics (3) Donor Condition (1)a
Transplanted on OCS due to Logistics (1)b
OCS
n = 62
As
Treated
Control
n = 66
Protocol Deviation
n = 2c
Protocol Deviation
n = 5d
OCS
n = 60
Per
Protocol
Control
n = 61

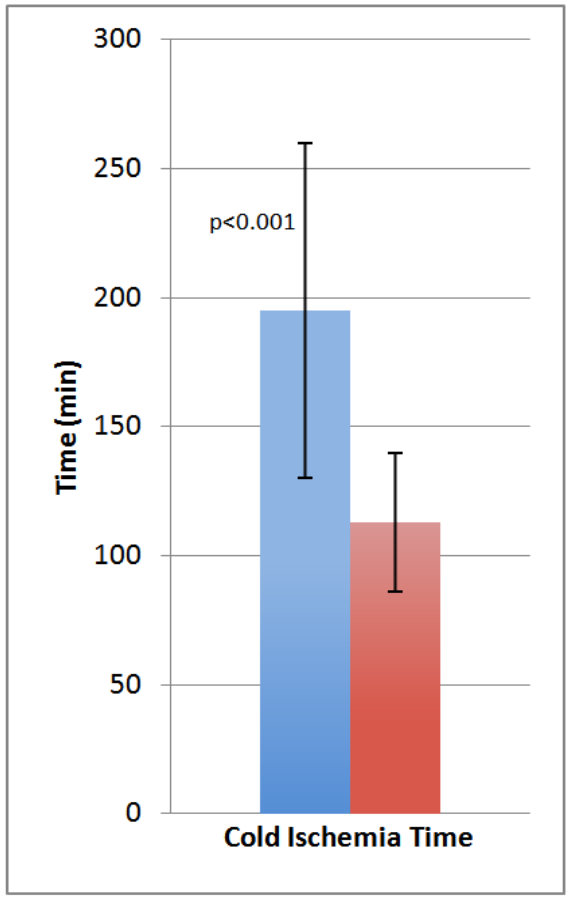
	Organ Care System group	Standard cold storage group	Between-group difference (one-sided 95% UCB or 95% CI)	p value
Primary endpoint (30 day patient and graft survival)				
Intention-to-treat	63/67 (94%)	61/63 (97%)	2·8 (8·8)	0·45
As-treated	58/62 (94%)	64/66 (97%)	3·5 (9·6)	0·36
Per-protocol	56/60 (93%)	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

Ardehali A, et al., Lancet. 2015

COLD Ischemia Time



PROCEED II Findings

- 30 day patient and graft survival are similar when the donor heart preserved on OCS vs on ice
- No different in secondary endpoints of cardiac –related SAE, Rejection, ICU stay
- Cold ischemia time significantly shorter, despite longer total preservation time

THE LANCET
Available online 14 April 2015
In Press, Corrected Proof — Note to users

Articles

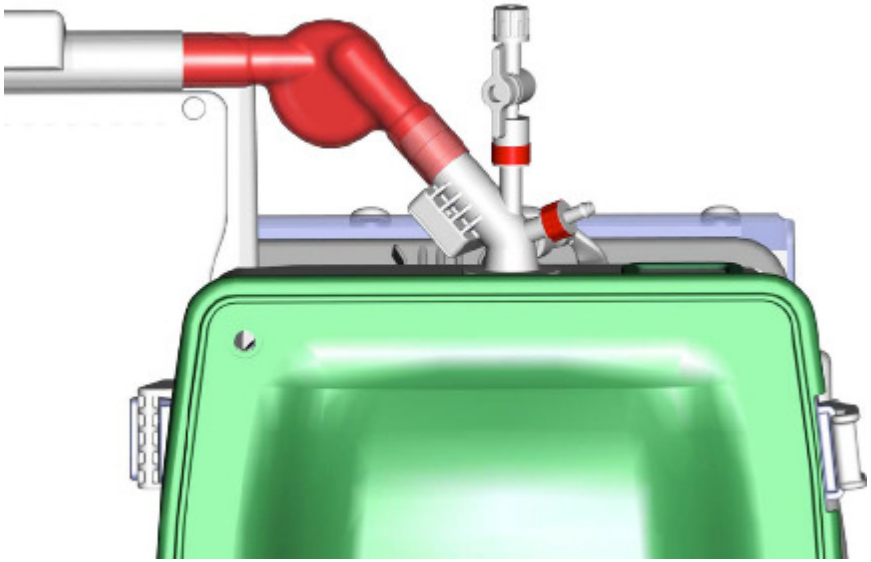
Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial

Prof Abbas Ardehali, MD[a], Prof Fardad Esmailian, MD[b], Prof Mario Deng, MD[a], Prof Edward Soltesz, MD[c], Prof Eileen Hsich, MD[c], Prof Yoshifumi Naka[d], Prof Donna Mancini, MD[d], Prof Margarita Camacho, MD[e], Prof Mark Zucker, MD[e], Prof Pascal Leprince, MD[f], Prof Robert Padera, MD[g], Prof Jon Kobashigawa, MD[b], for the PROCEED II trial investigators[†]

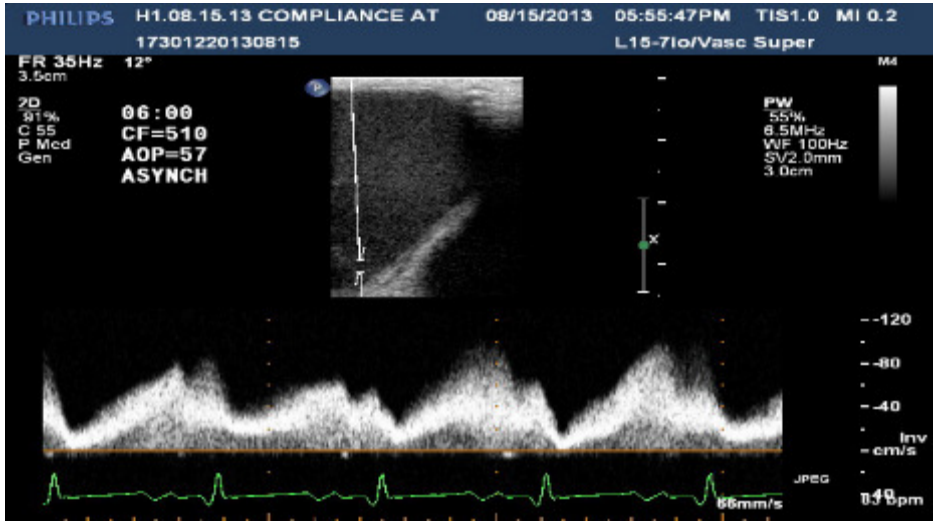
New Technology Improvements
OCS Heart Device

Optimization of Perfusion

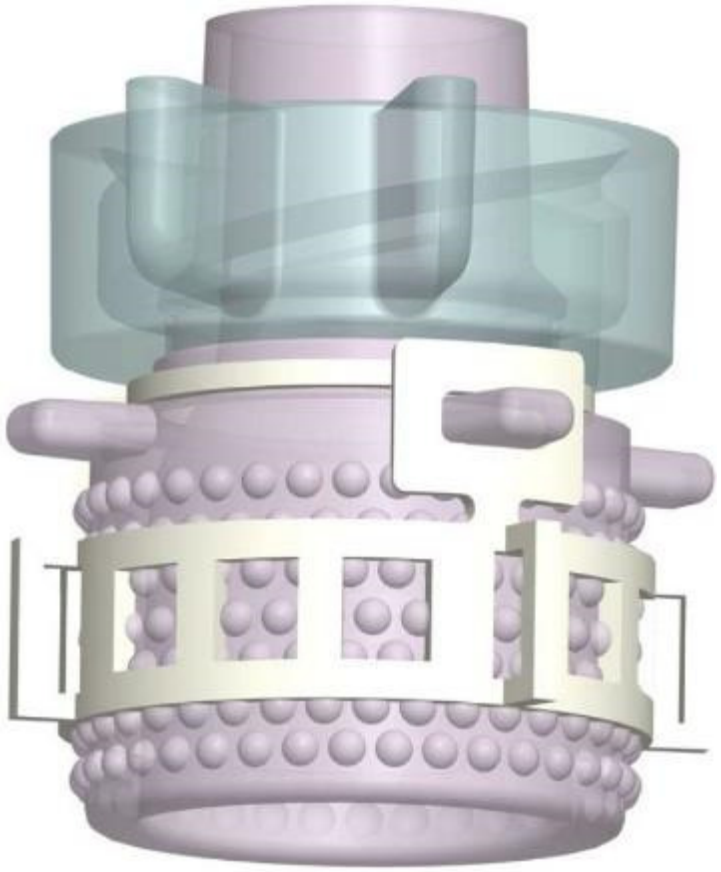
Addition of Compliance at AO Root



Optimizing Coronary Filling Time

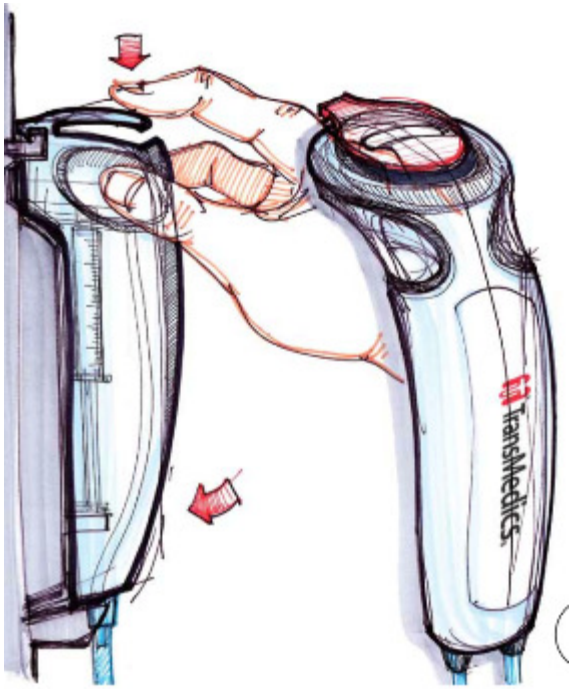


New Aorta Cannula Design



Simplified & User Friendly Cannula Design

Automated Hemodynamic Management



Integrated and Automated IV infusion Pump to Regulates AOP Based On Set Target by User

Ex-vivo Donor Heart Perfusion (OCS)

- Expand the donor pool
  - Resuscitate donor hearts
  - Assess suitability for transplantation: DCD hearts

Organ Donation after Circulatory Death

- Widely accepted in kidney, liver, and lung transplantation
- Pediatric heart transplantation with donor hearts after circulatory death
- No adult heart transplantation with DCD hearts in modern era
- Concerns:
  - Warm ischemia, how long?
  - Inability to assess the donor heart prior to implantation

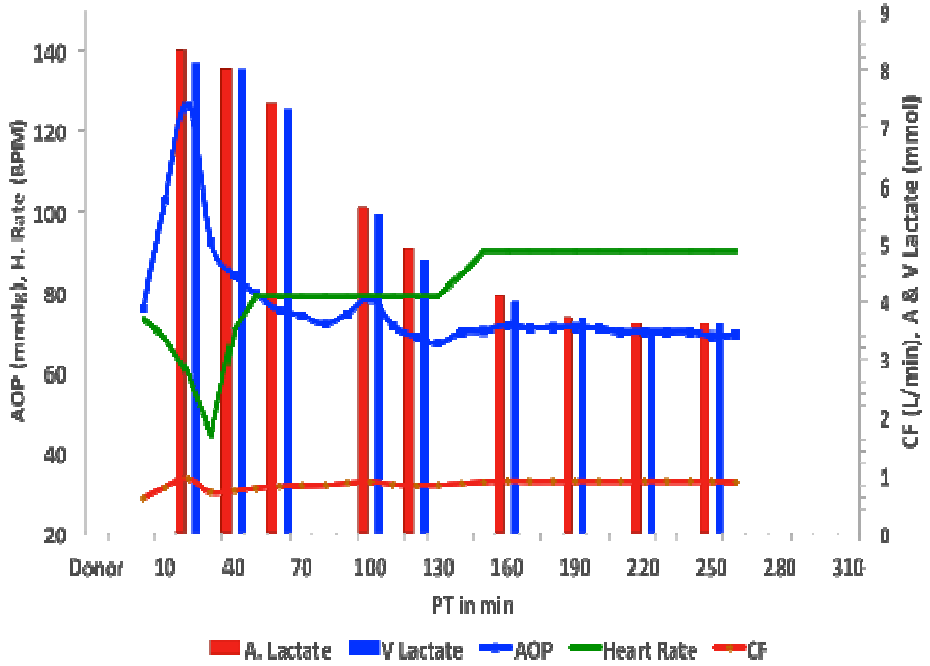
Australian DCD Heart Transplantation

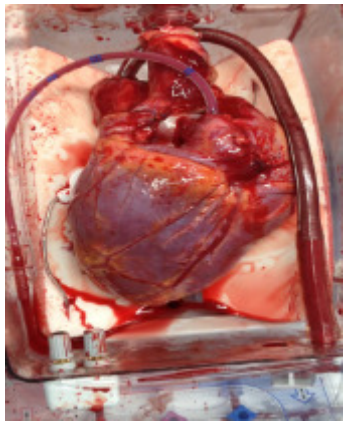
DCD Heart Donation

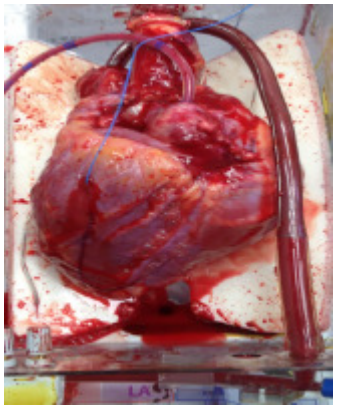
- Young donors (<40 yrs of age), Warm ischemia time of <30 min
- Transfer to OR
- Very rapid blood retrieval. Transect RAA and insert dual-stage cannula. This will allow better drainage and decompress abdominal organs- heparin in the bag only
- During blood collection, clamp descending aorta
- Antegrade Perfusion: St. Thomas cardioplegia- 1L
- OCS instrumentation

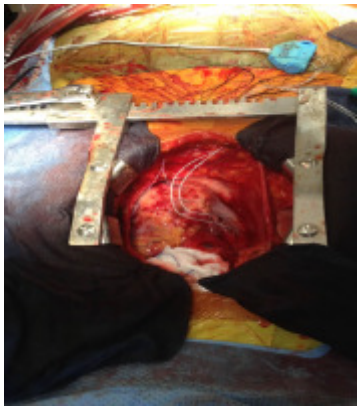
Dhittal K, et al. Lamcet. 2015:385:2585-91.

DCD HTX - CASE #1









WITHDRAWAL TO CIRCULATORY ARREST	WARM ISCHAEMIC TIME	START A-V LACTATE	END A-V LACTATE	TOTAL OCS PERFUSION	TOTAL ISCHAEMIC TIME
16	28	8.2	3.8	257	90

Worldwide DCD Adult Donor Heart Experience (1/15/16)

- Sydney, Australia
  - 8 runs, 6 implants
- Harefield, UK
  - 4 implants
- Papworth, UK
  - 12 implants

EXPAND-Heart Trial

Trial Design: prospective, pivotal, single arm trial

Non-standard Donor Hearts: Age>55, LVH>1.3 cm, Ischemia time>6 hours

Primary Endpoint

A composite endpoint of patient survival at Day-30 post transplant and absence of severe primary heart graft dysfunction (PGD) (left or right ventricle) in the first 24 hours post-transplantation.

Secondary Endpoints

Patient survival at day-30 post transplantation
Incidence of severe primary heart graft dysfunction (PGD)
Rate of donor hearts utilization that were successfully transplanted after preservation and assessment on the OCS heart device

Final Thoughts

- Ex-vivo heart perfusion technology is evolving
- Improvements in the platform will enhance donor heart perfusion, ease of use
- Ex-vivo heart perfusion may be considered in prolonged cold ischemia times, assessment or improvement of non-standard donor hearts, or resuscitation of DCD hearts

References

1. https://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry
2. Moers C, Smits JM, Maathuis MH, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med. 2009;360(1):7-19.
3. Ravikumar R, Jassem W, Mergental H, et al. Liver transplantation after ex vivo normothermic machine preservation: a Phase 1 (first-in-man) clinical trial. Am J Transplant. 2016; ePub ahead of print.
4. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Eng J Med. 2011;364(15):1431-40.
5. Ardehali A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomized non-inferiority trial. Lancet. 2015;385(9987):2577-84.
6. Boucek M, Mashburn C, Dunn, S, Frizell, R, Edwards L, Pietra B, Campbell D. Pediatric Heart Transplantation after Declaration of Cardiocirculatory Death. N Eng J Med 2008;359(7):709-14.
7. Dhital KK, Iyer A, Connellan M, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet. 2015;385(9987):2585-91.