# The Organ Repair Center

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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

No disclosure

# Outline

- Shortcomings of cold storage
- Normothermic perfused organ preservation
- Graft assessment during perfusion
- Graft repair strategies

# Cold Static Preservation


- Easy to perform
- Low costs
- Effective for “good grafts”


- Ongoing organ damage
- No graft assessment
- No graft repair
- Poorly tolerated by marginal grafts

# Protective Strategies in the Lab

Ischemic Preconditioning; Pentoxifylline; histidine; glycine; Cyclosporine, FK506, FTY, epoprostenol; caspase-inhibitors; prostaglandins; CGS21680; anisomycine; soluble TNF receptors; tauroursodeoxycholate; dipyridamole; doxorubicine; ozone; NO; CO; superoxide dismutase; cobra venom factor; adenosine; alanine; picroliv; geranyl-geranyl-acetone; vitamine E; arginine; salviainolic acid A; L-carnitine; cobalt protoporphyrin; diethylmaleate; p38 mitogen-activated protein kinase inhibitor; phentolamine; ascorbic acid 2-glucoside; sodium nitroprusside; calcium; taxol; dichloroacetate; anti-ICAM-1 mAb; hydrophilic bile salts; linomide; magnolol; nicaraven . . . .

# Protective Strategies in the Lab

**none**

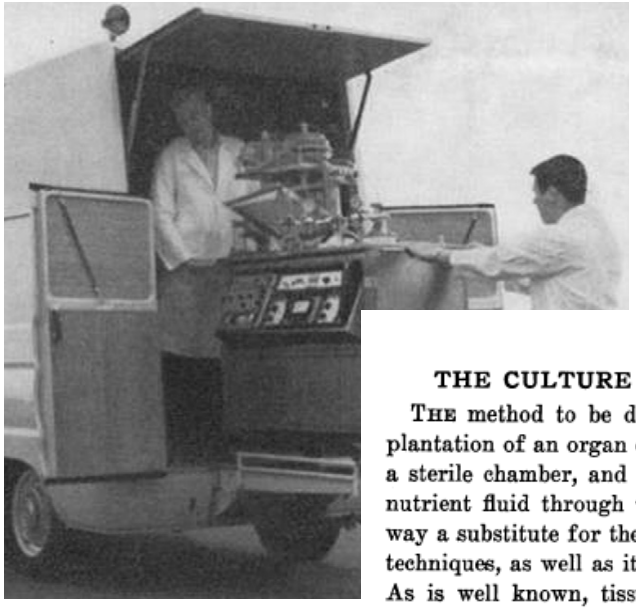
# Problems Implementing Protective Strategies for Organ Preservation

- Limited time for donor intervention
- Donor interventions affect all organs
- Organ cooling slows metabolism
- Graft injury within minutes of reperfusion

# Optimal Preservation Technique

- Allows prolonged organ storage
- No preservation injury
- Assessment of organ function during preservation
- Allow organ repair and graft improvement

# Normothermic Graft Perfusion for Organ Preservation



## SPECIAL ARTICLES

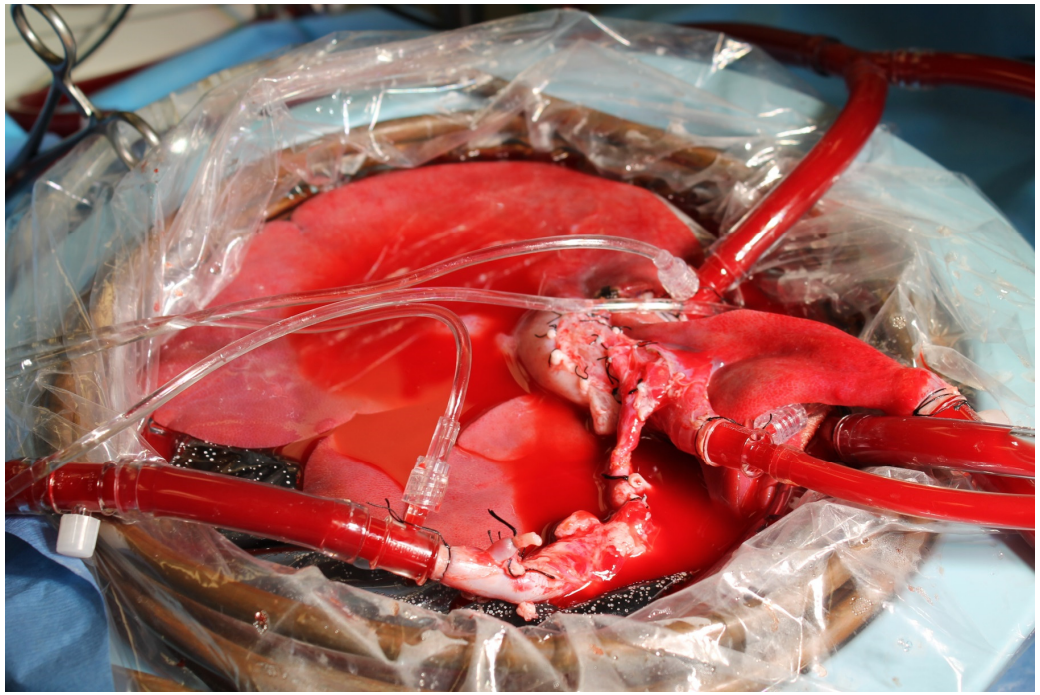
### THE CULTURE OF WHOLE ORGANS

THE method to be described consists of the transplantation of an organ or of any part of the body into a sterile chamber, and of its artificial feeding with a nutrient fluid through the arteries. It is not in any way a substitute for the method of tissue culture. Its techniques, as well as its purposes, are quite different. As is well known, tissues and blood cells grow like bacteria in flasks containing appropriate media. The techniques for the cultivation of tissues are somewhat analogous to bacteriological techniques, although far more delicate. But it is through the employment of complex mechanical and surgical procedures that organs are enabled to live isolated from the body. Tissue culture deals with cells as units of bodily structures; the new method, with cellular societies as organic wholes. Its ultimate purposes are the manufacture *in vitro* of the secretions of endocrine glands, the isolation of the substances essential to the growth, differentiation and functional activity of those glands, the discovery of the laws of the association of organs, the production *in vitro* and the treatment of organic and arterial diseases, etc.

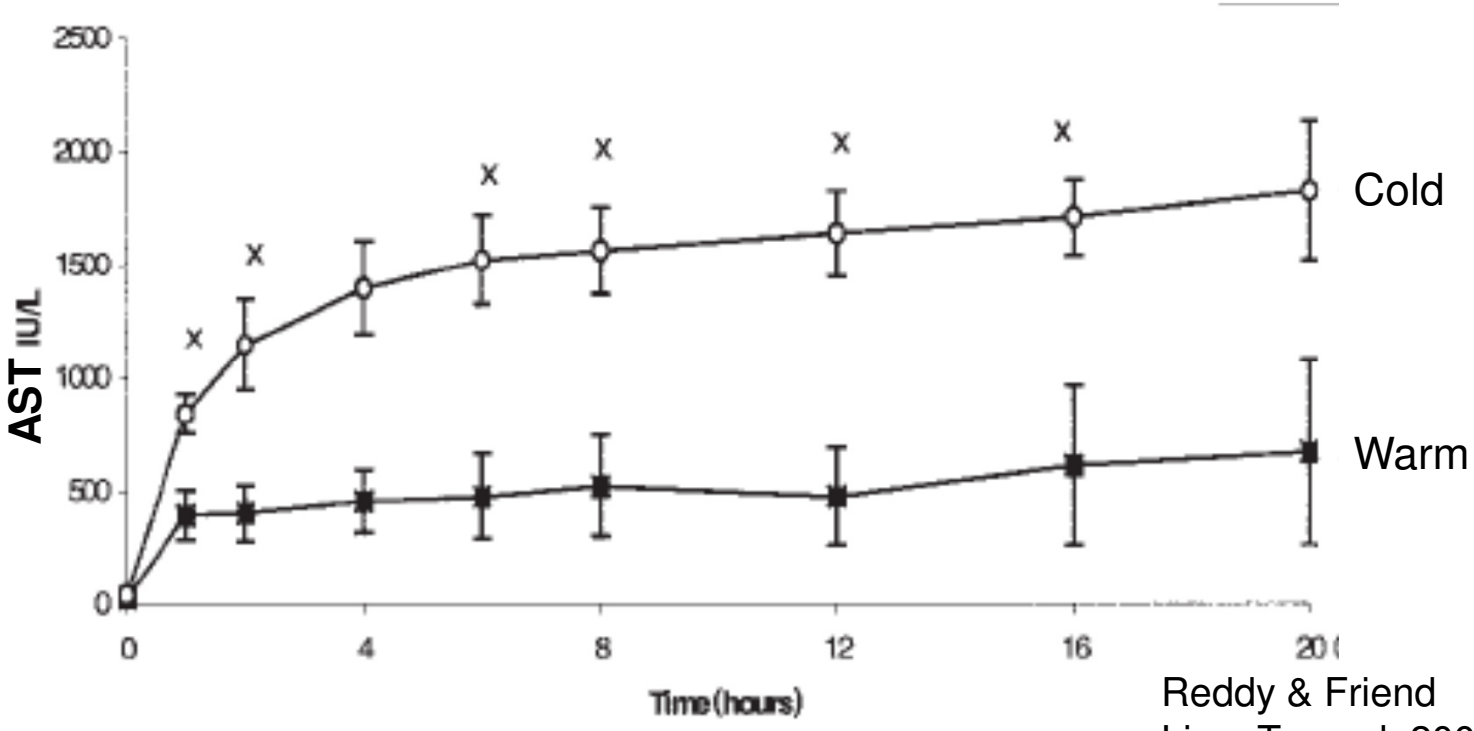
The idea of maintaining alive a portion of the body in order to study its functions is not new. In 1812, the physiologist Le Gallois[1] wrote that, "if one could sub-

Lindbergh, *Science*, 1935

# Normothermic Ex Vivo Liver Perfusion

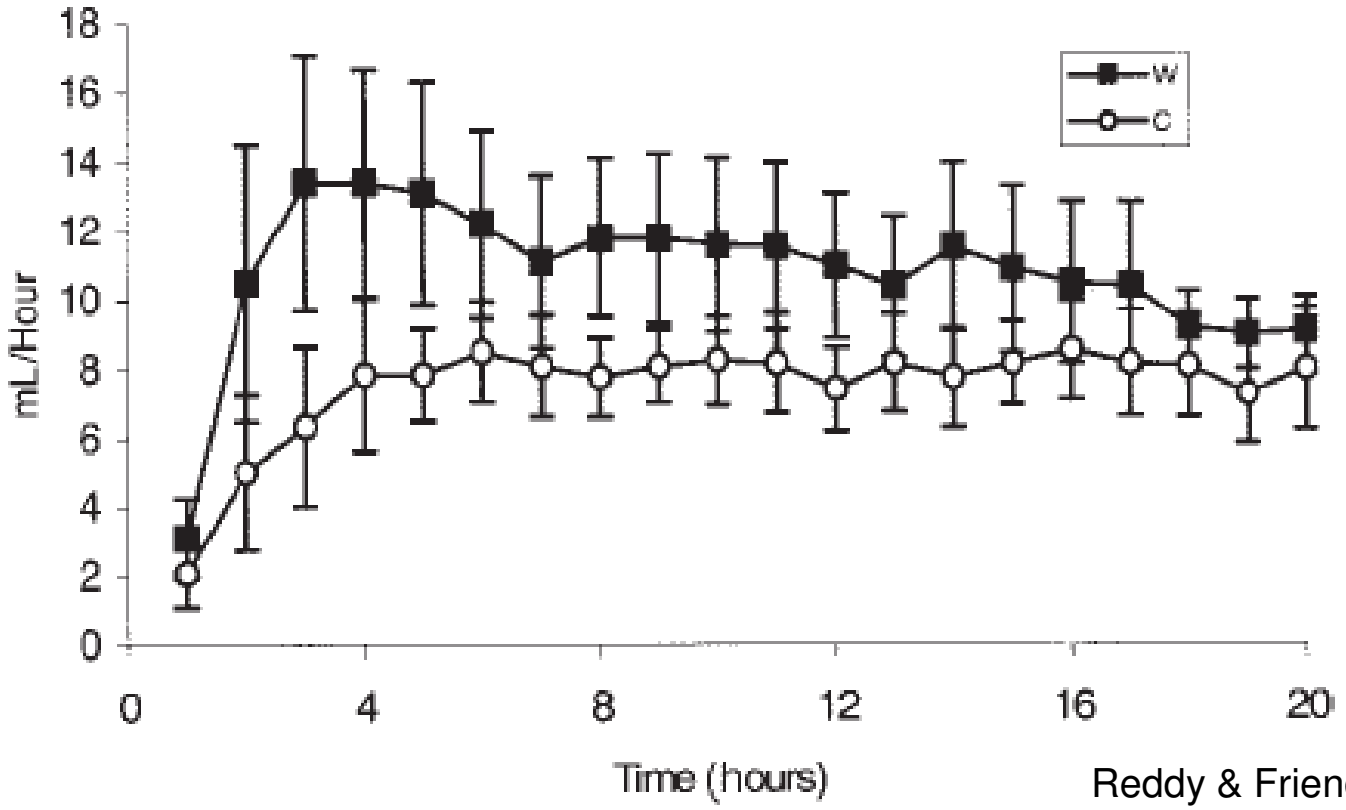


# Liver Injury During Perfusion



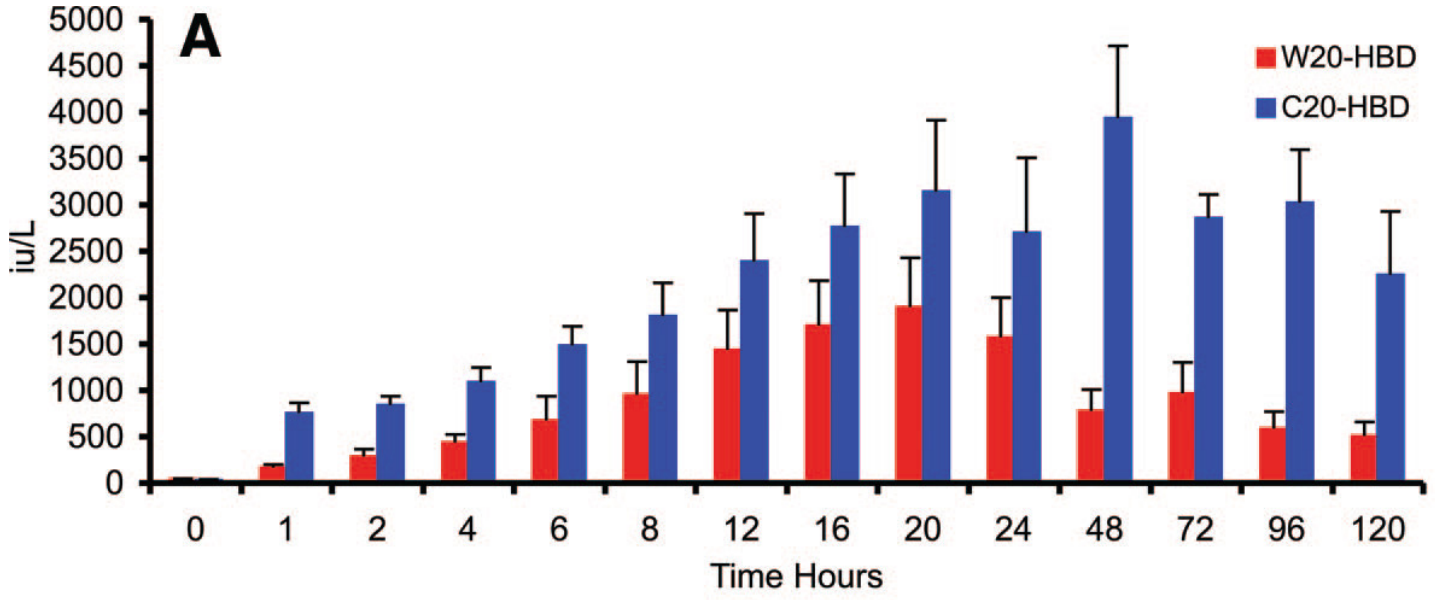

Reddy & Friend
Liver Transpl, 2005

# Bile Production During Perfusion



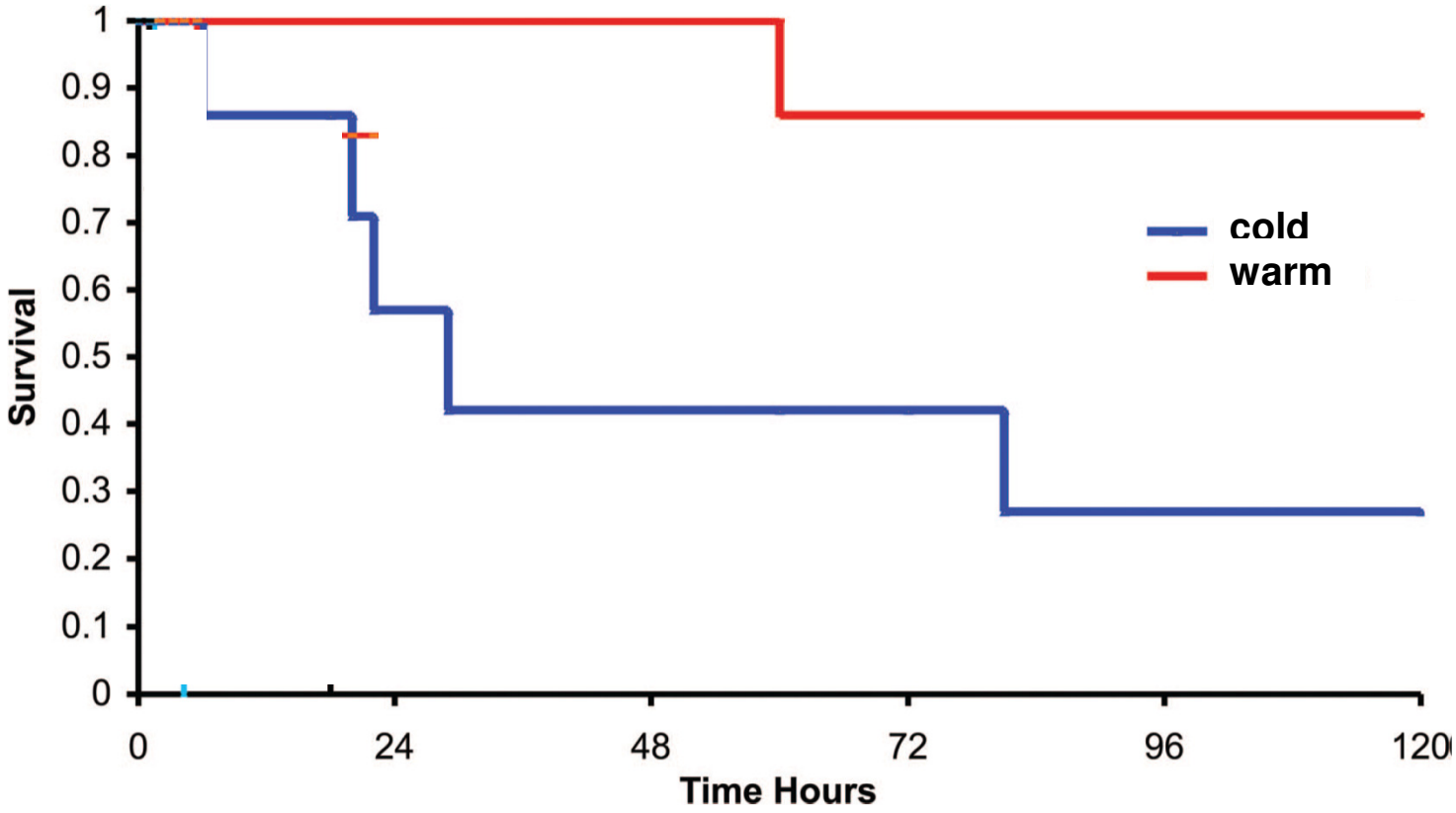

Reddy & Friend
Liver Transpl, 2005

# AST Post Transplantation



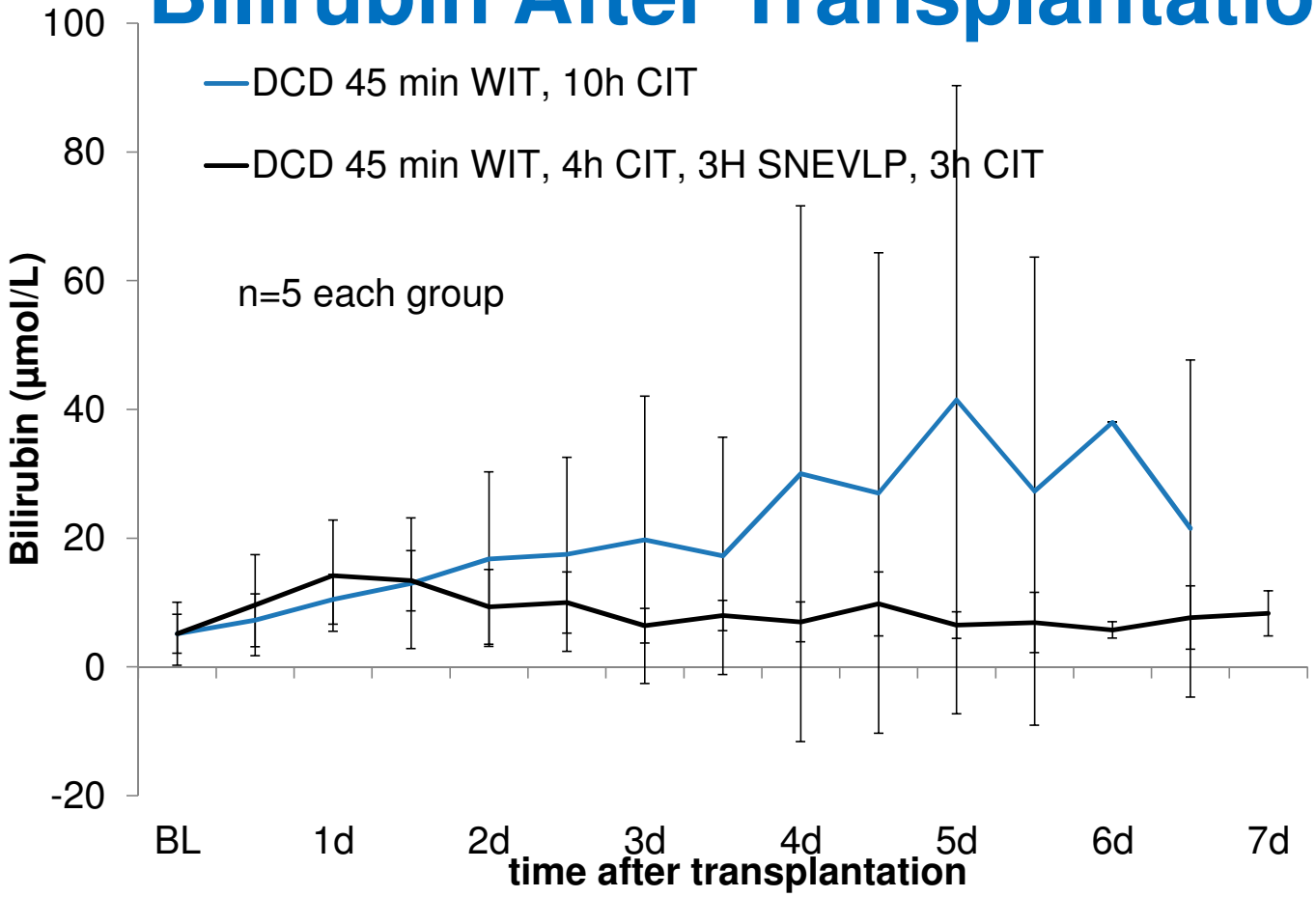

Brockmann & Friend, Ann Surg 2009

# Animal Survival

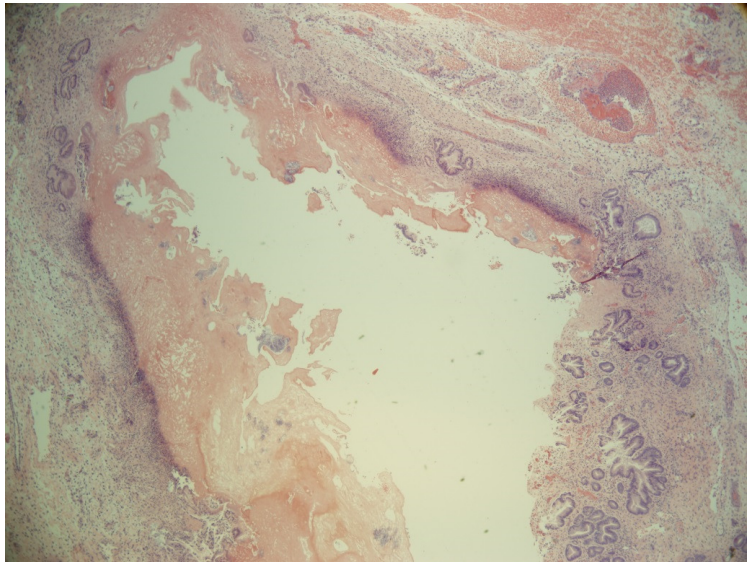



Brockmann & Friend, Ann Surg 2009

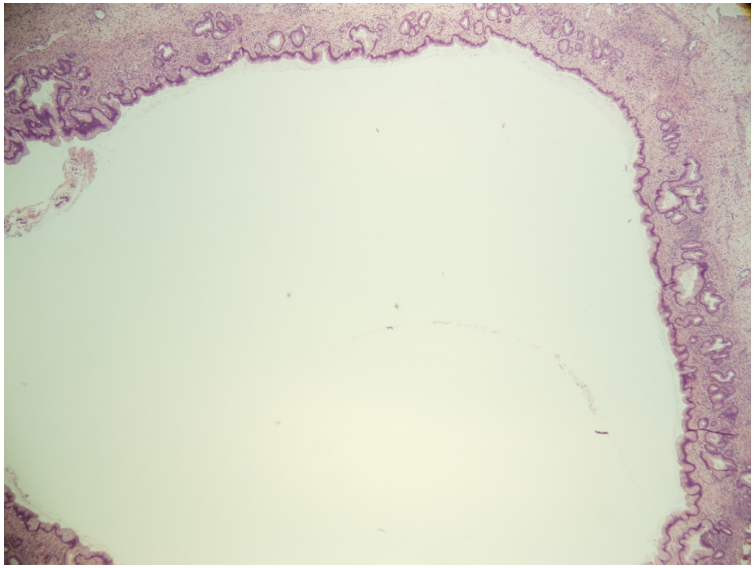
# Bilirubin After Transplantation



# Bile Duct Histology



DCD cold



DCD SNEVLP

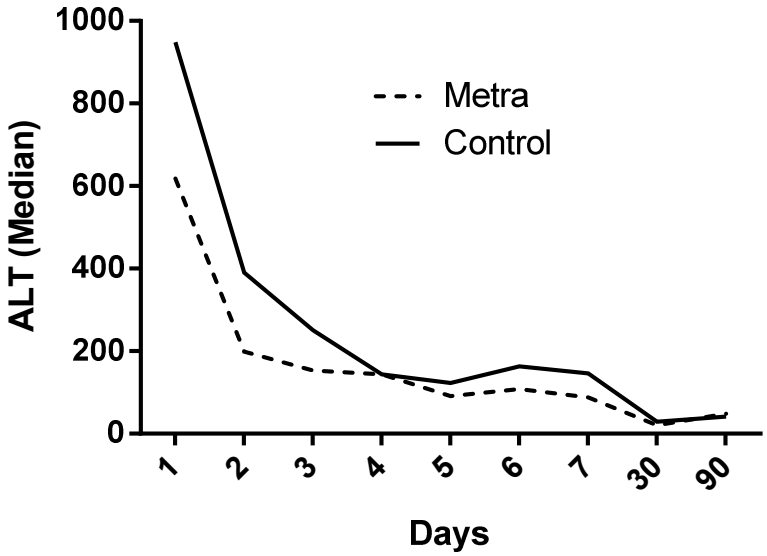
DCD cold: 3/5 animals severe bile duct injury
DCD SNEVLP: no bile duct injury

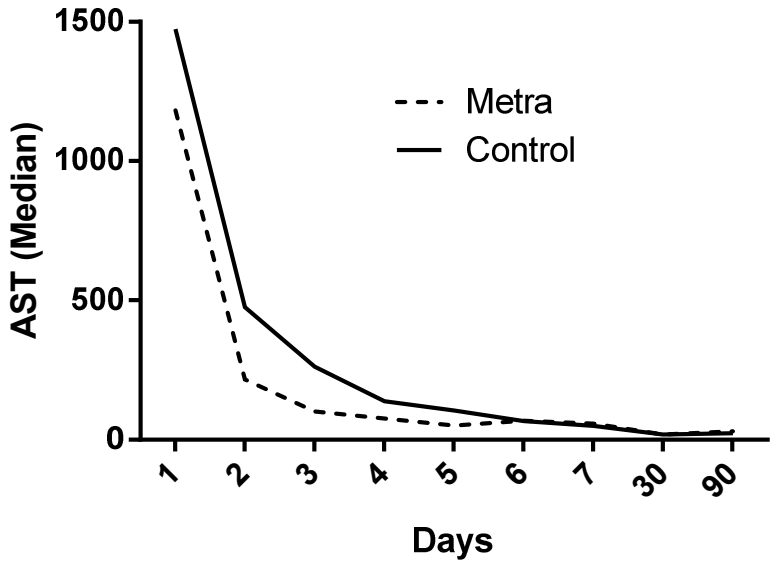
## Science | Health

**15 Mar 13**

**First human liver transplant with normothermic ex vivo perfused preservation**

# Reperfusion Injury After Transplantation



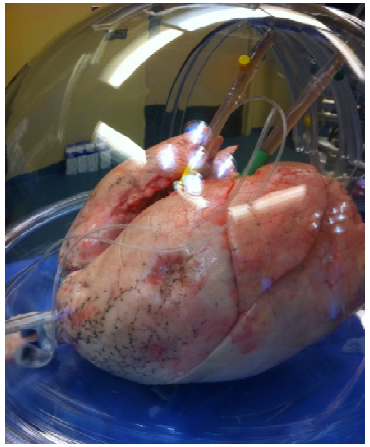



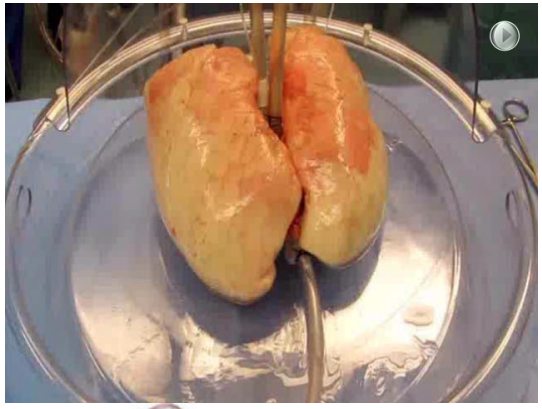

$p > 0.05$ at all time points

# Graft Function and Injury After Transplantation

| | NEVLP | CS | p-value |
|---|---|---|---|
| • ALT peak 48hr (U/L) | 619 (55-2858) | 949 (233-3073) | 0.55 |
| • INR peak | 2.6 (2-4.4) | 2.7 (1.7-5.8) | 0.61 |
| • INR 1 week | 1.1 (1-1.56) | 1.1 (1-1.3) | 0.47 |
| • INR 3 month | 1 (1-2) | 1 (1-2) | 0.91 |
| • Bilirubin day 7 (mg/dl) | 1.5 (1.0-7.7) | 2.78 (0.4-15) | 0.49 |
| • Bilirubin 3 month (mg/dl) | 0.4 (0.2-0.8) | 0.6 (0.2-18) | 0.21 |
| • Alk. Phos day 7 (U/L) | 202 (96-452) | 147 (87-456) | 0.21 |
| • Alk. Phos 3 month (U/L) | 111 (101-136) | 132 (54-657) | 0.33 |
| • Creatinine 1 week (mg/dl) | 1.0 (0.5-2.0) | 0.9 (0.5-2.3) | 0.76 |
| • Creatinine 3 month (mg/dl) | 1.1 (0.9-2.4) | 1.1 (0.3-1.8) | 0.53 |

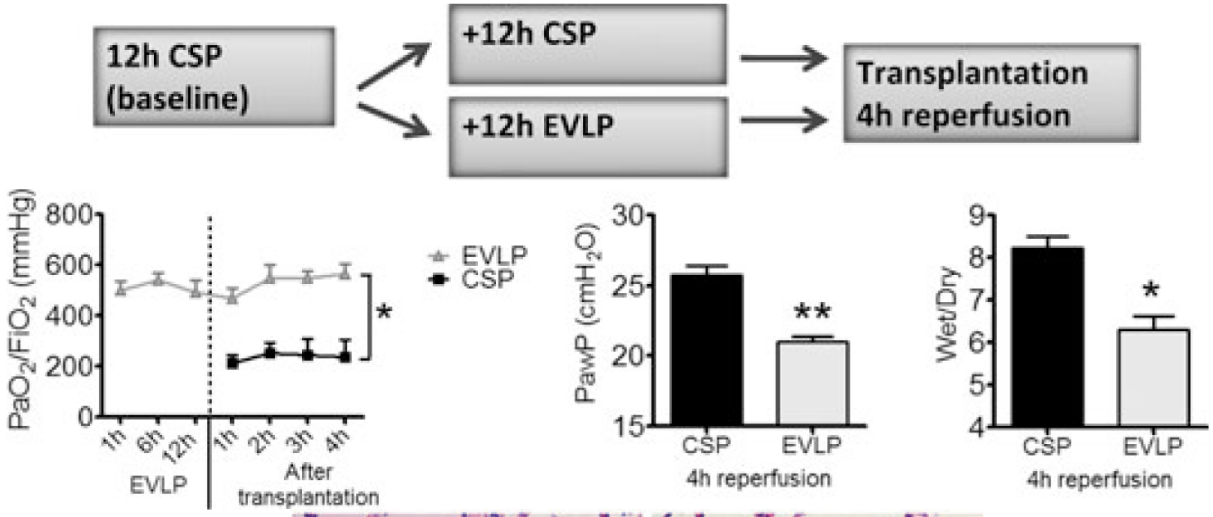
# Normothermic Ex Vivo Lung Perfusion

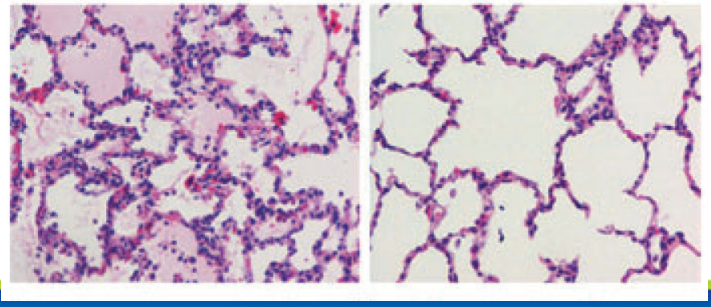




# Normothermic Ex Vivo Perfusion Interrupts Cold Ischemic Injury (24h)

Cypel/Keshavjee. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. *Am J Transplant*. 2009 Oct;9(10):2262-9



CS

EVLP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

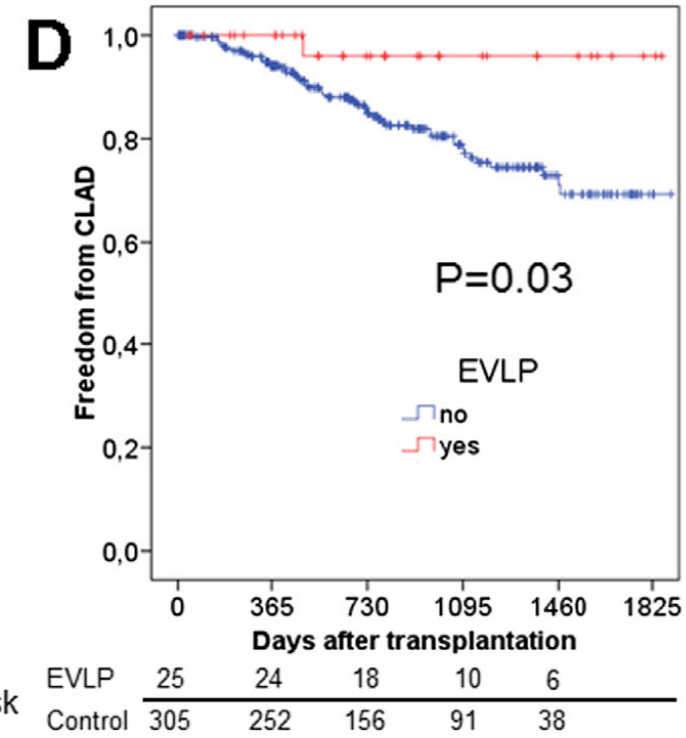
# Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.

NEJM, April 14th 2011, vol. 364, no. 15, pp. 1431-1440.

# Freedom from CLAD

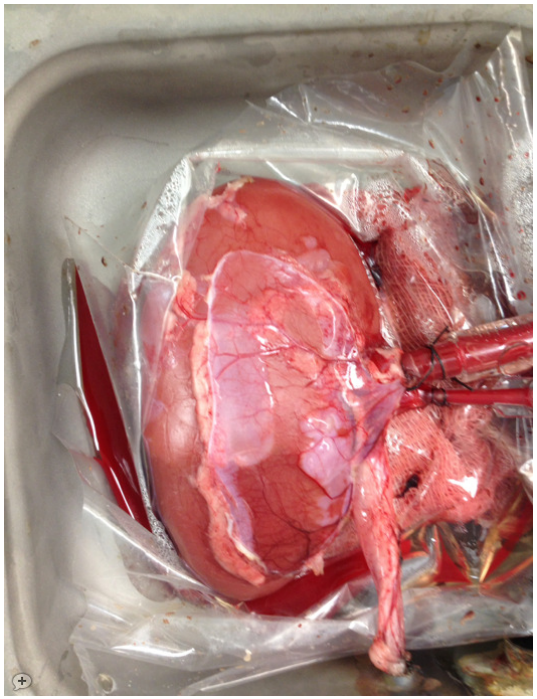
## (EVLP of high risk NDDs)




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| | EVLP | 25 | 24 | 18 | 10 | 6 |
| | Control | 305 | 252 | 156 | 91 | 38 |

Tikkanen JM . J Heart Lung Transplant. 2015 Apr;34(4):547-56

# Normothermic Ex Vivo Kidney Perfusion



# Normothermic Ex Vivo Kidney Perfusion in Pigs

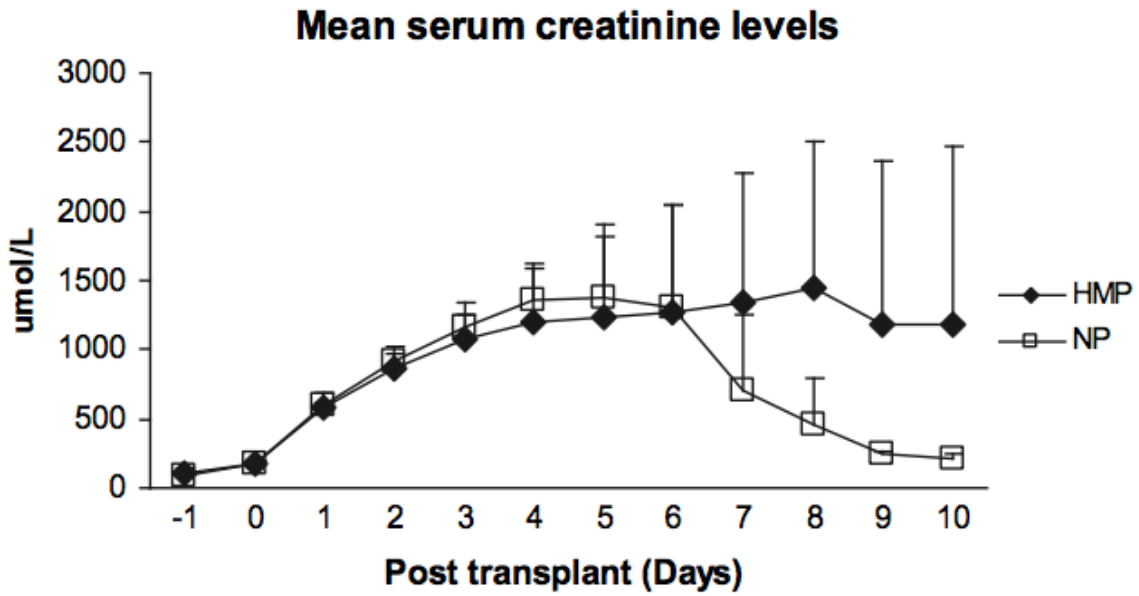
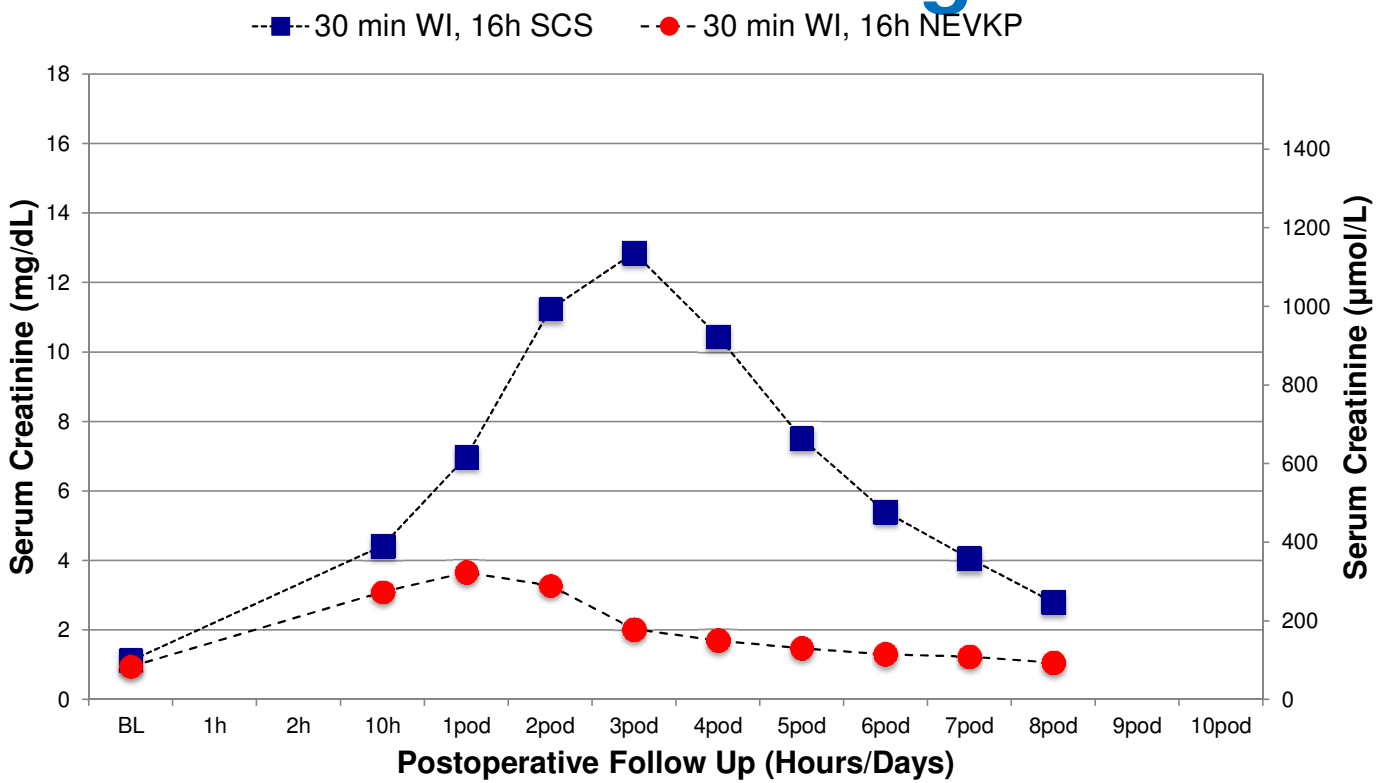



**FIG. 3.** The mean serum creatinine levels for hypothermic machine perfusion (HMP) normothermic perfusion (NP) groups over 10 d post-transplant.

DCD 30 min WIT, 22 HMP vs 20 HPM + 2hr NEVKP
Auto-transplantation

Hosgood, et al

# Continuous Normothermic Ex Vivo Kidney Perfusion in Pigs




DCD 30 min WIT, 16hrs preservation, auto-transplantation

# Renal Transplantation After *Ex Vivo* Normothermic Perfusion: The First Clinical Study

**Results:**

- Delayed graft function (defined as need of dialysis within first 7 days)
  - 1/18 patients in NEVKP group (5.6%)
  - 17/47 patients in SCS only group (36.2%) (p = 0.014)

- No difference in graft (p = 0.510) or patient survival (p = 1.000)

Nicholson, M. L., & Hosgood, S. A. (2013).
American Journal of Transplantation

# Graft Assessment

- Graft function maintained during normothermic ex vivo organ perfusion
- Assessment of graft injury during preservation period
- Decline grafts based on data not personal opinion

# Normothermic Ex Vivo Perfusion Characteristics During Human Ex Vivo Liver Perfusion Prior to Transplantation (n=10)

| | |
|---|---|
| • Perfusion time (min) | 480 (340 – 580) |
| • Peak AST (U/l) | 1647 (227 – 9200) |
| • Peak ALT (U/l) | 444 (152 – 1460) |
| • Bile production (ml) | 61 (14 – 146) |
| • first Lactate (mmol/l) | 6.5 (4.3-11.5) |
| • last Lactate (mmol/l) | 1.46 (0.56 – 1.74) |
| • pH | 7.26 (7.13-7.33) |
| • HA flow (cc/min) | 300 (200-400) |
| • PV flow (cc/min) | 1250 (1200-1300) |

# Assessment of DCD Liver Graft

- DCD, 29 male, 1hr 49min withdrawal time
- 4hr cold storage followed by 7hr Normothermic ex vivo machine perfusion
- Lactate clearance (13  2 mmol/l)
- Bile production
- Glucose consumption
- Low intrahepatic flow resistance

<u>Post Transplant Outcome</u>

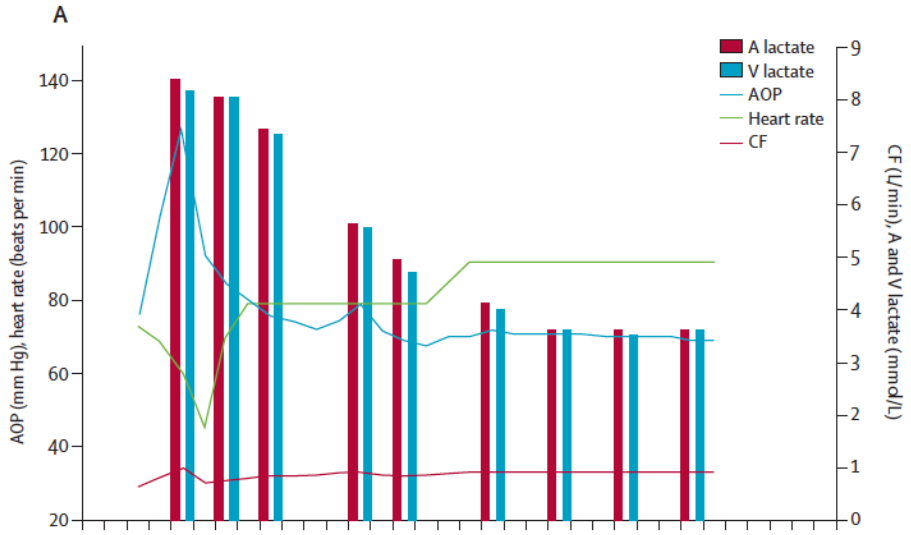
- Peak ALT 1215 U/L
- Discharge POD 10

Pererra et al Liver Transplantation 2015

# Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series

Kumud K Dhital, Arjun Iyer, Mark Connellan, Hong C Chew, Ling Gao, Aoife Doyle, Mark Hicks, Gayathri Kumarasinghe, Claude Soto, Andrew Dinale, Bruce Cartwright, Priya Nair, Emily Granger, Paul Jansz, Andrew Jabbour, Eugene Kotlyar, Anne Keogh, Christopher Hayward, Robert Graham, Phillip Spratt, Peter Macdonald

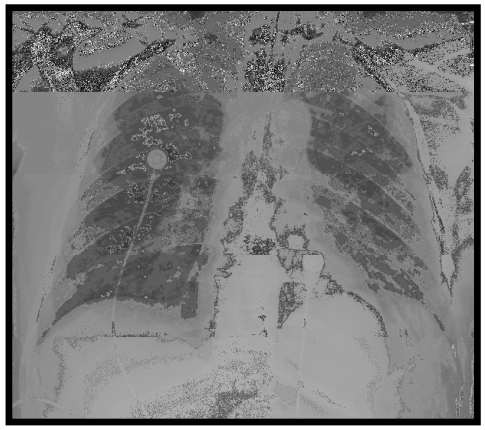
Case series of DCD heart donation
Four retrieved hearts → 3 transplants after Ex-Vivo assessment



# Graft Repair/Treatment

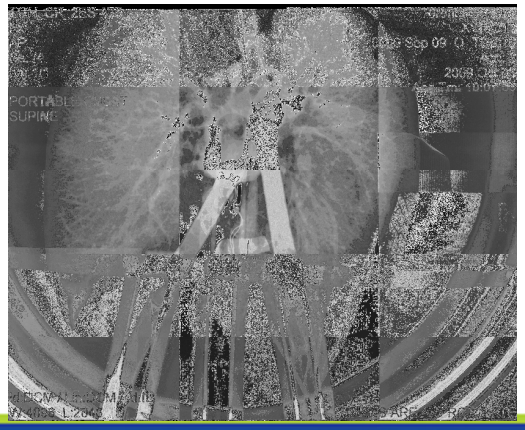
- Improve graft function during ex vivo perfusion
- Application of repair strategies

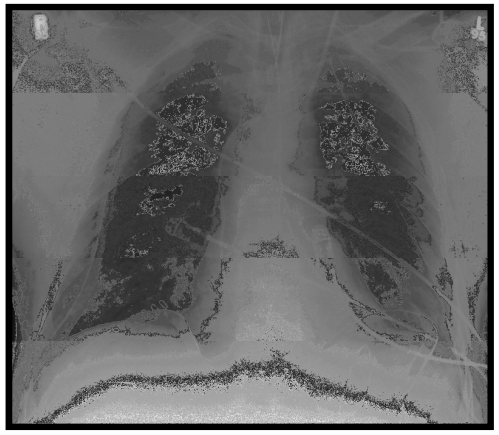
# Resolution of Pulmonary Edema During EVLP



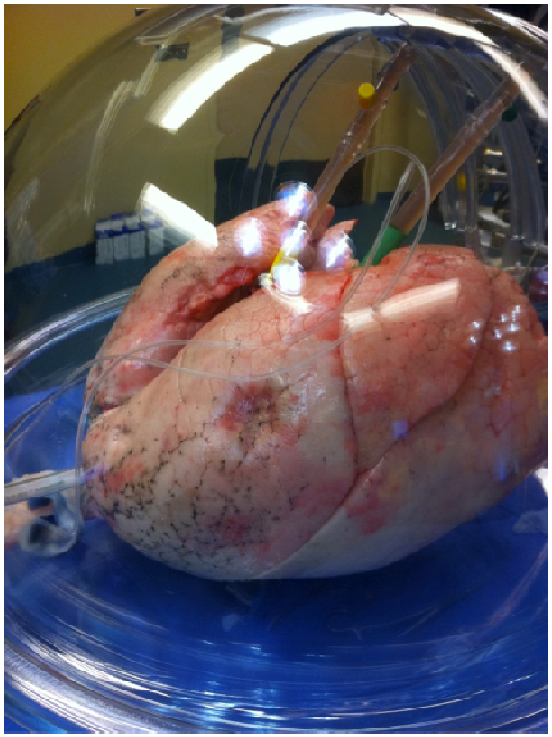
Recipient P/F 420


3h EVLP





# EVLP Assessment Confirms the In Vivo Findings



On initiation of EVLP: abnormal PA pressures even with low flows

**Persistent hemodynamic impairment in the ex vivo organ**

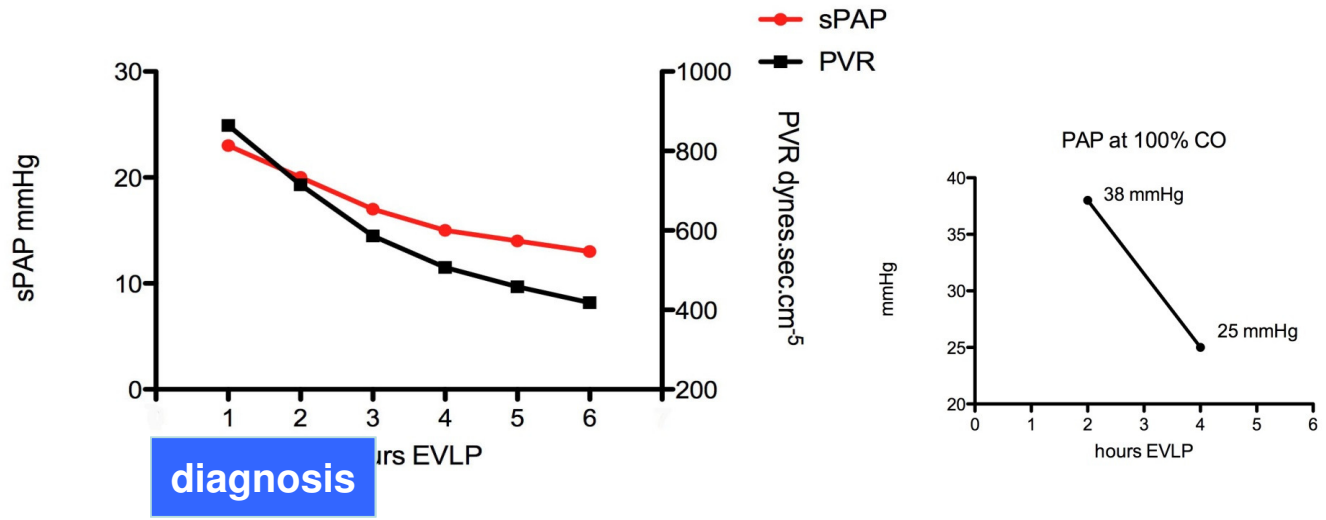
↓

**Apply similar diagnosis / treatment as in vivo treatment of massive PE**

↓

**ALTEPLASE 20 mg (reduced clearance)**

# Significant Improvement of Pulmonary Hemodynamics after Treatment







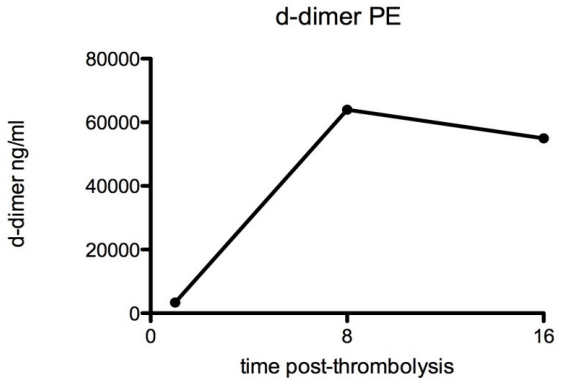
**diagnosis**

**treatment**

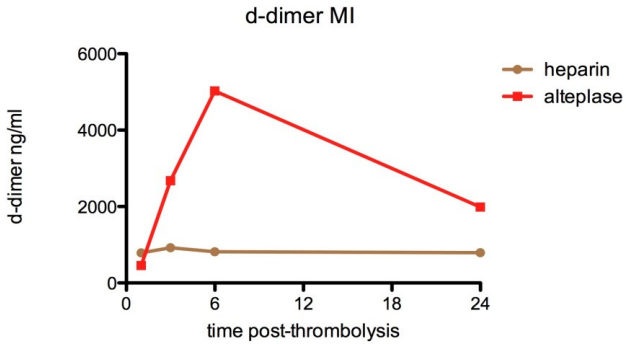
**Response monitoring**

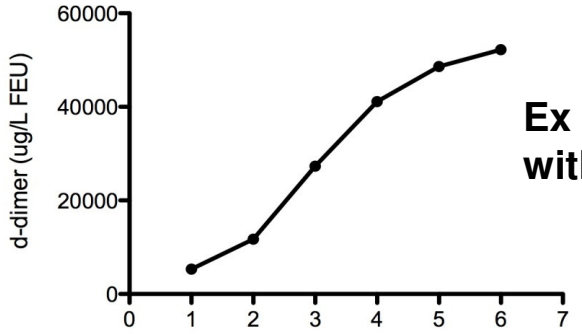
# D-dimer and Evidence of Thrombolysis

Knecht et al. PE + fibrinolysis
Thromb Res 1992




Brenner et al. MI + fibrinolysis
Circulation 1998

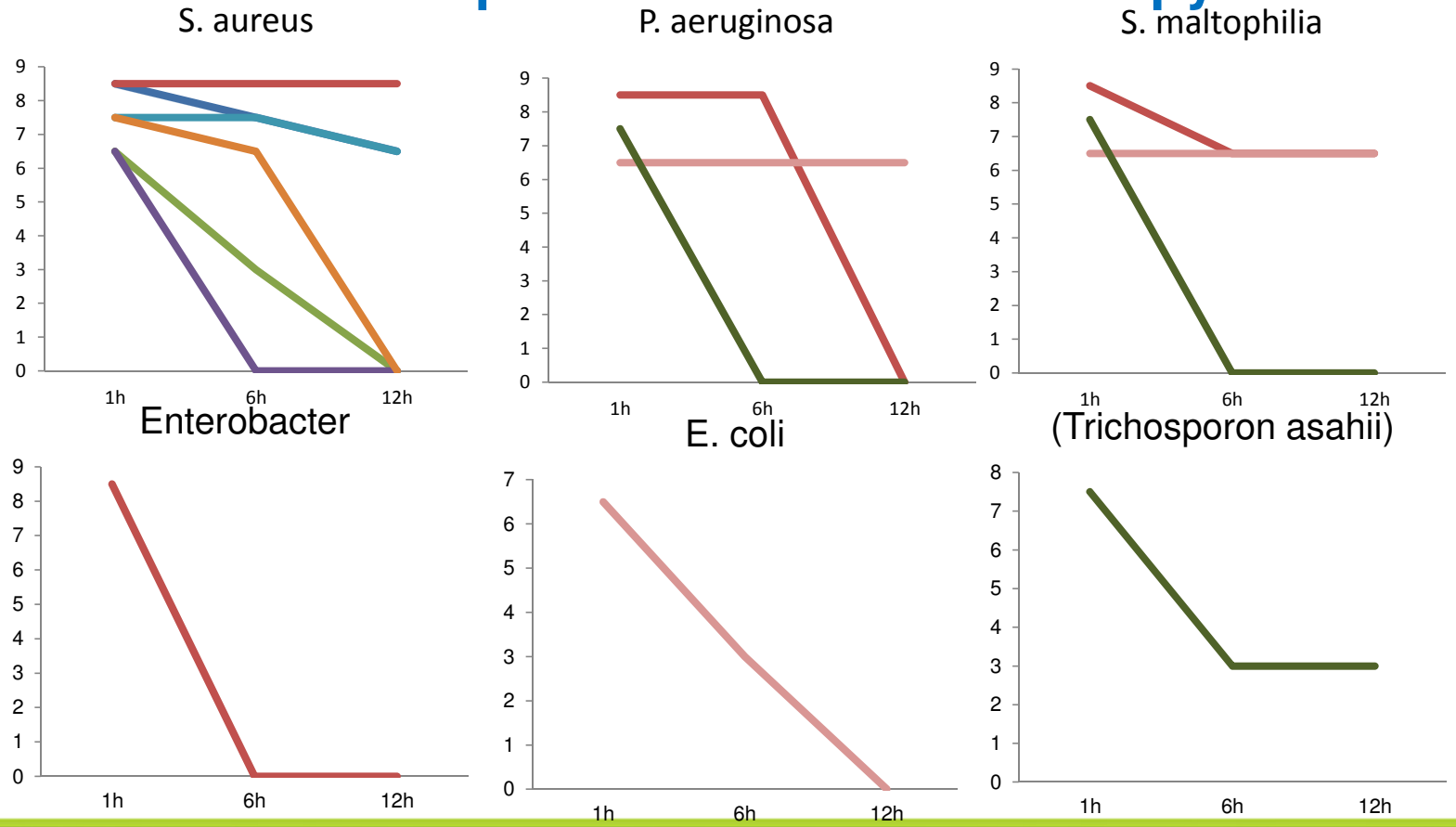



**Ex vivo treated lung with massive PE**

**11-fold increase**

# Bacteria ($log_{10}$ {cfu/L}), reduced with Ex Vivo Broad-Spectrum Antibiotic Therapy



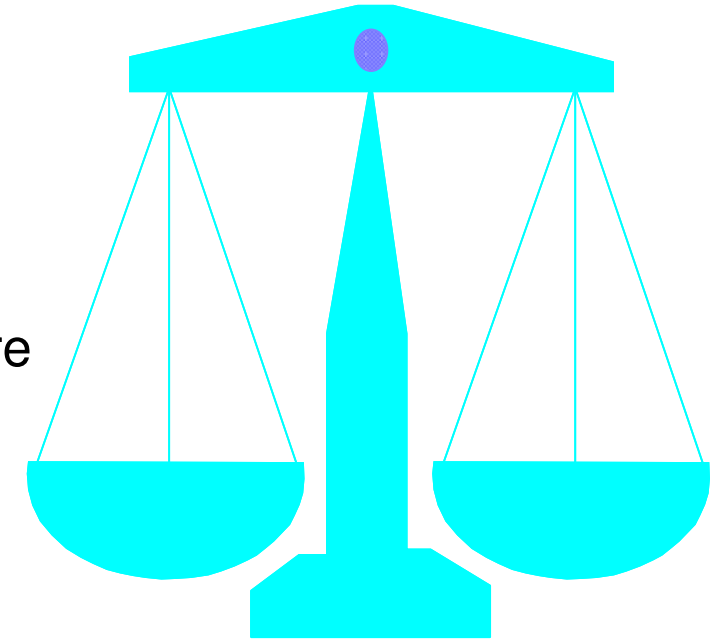
# Normothermic Perfused Organ Preservation

Increased costs

Difficult logistics

Possibility of machine failure

Prolonged organ retrieval



Less cold ischemic injury

Graft assessment

Graft repair

# Normothermic Perfused Organ Preservation

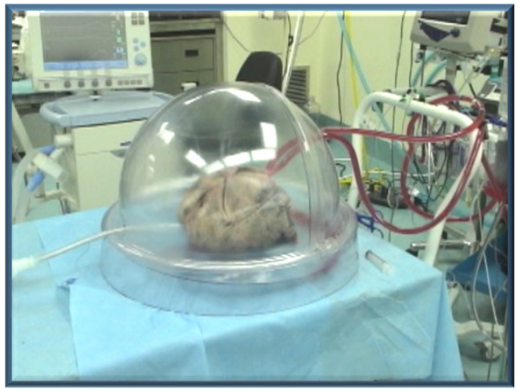
- Decreased graft injury in animal models of liver, kidney, lung, heart and transplantation
- No benefit demonstrated so far in human studies
- New opportunities for assessment and repair
- Identify the graft type that will benefit

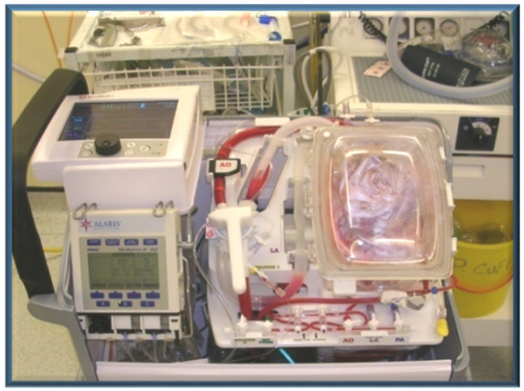

?

# The Organ Repair Center

# The Future of Organ Preservation…
# The "Organ Repair Center"

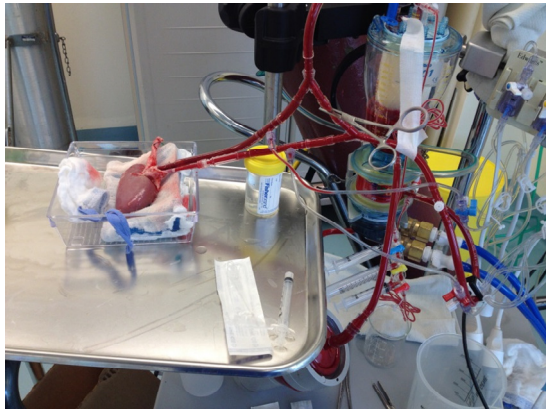
Lung





Heart

Liver



Kidney

# Thanks to…

- Marcelo Cypel
- Shaf Keshavjee

- Mitesh Badiwala
- Vivek Rao