Liver Preservation: Current Status and Future Directions

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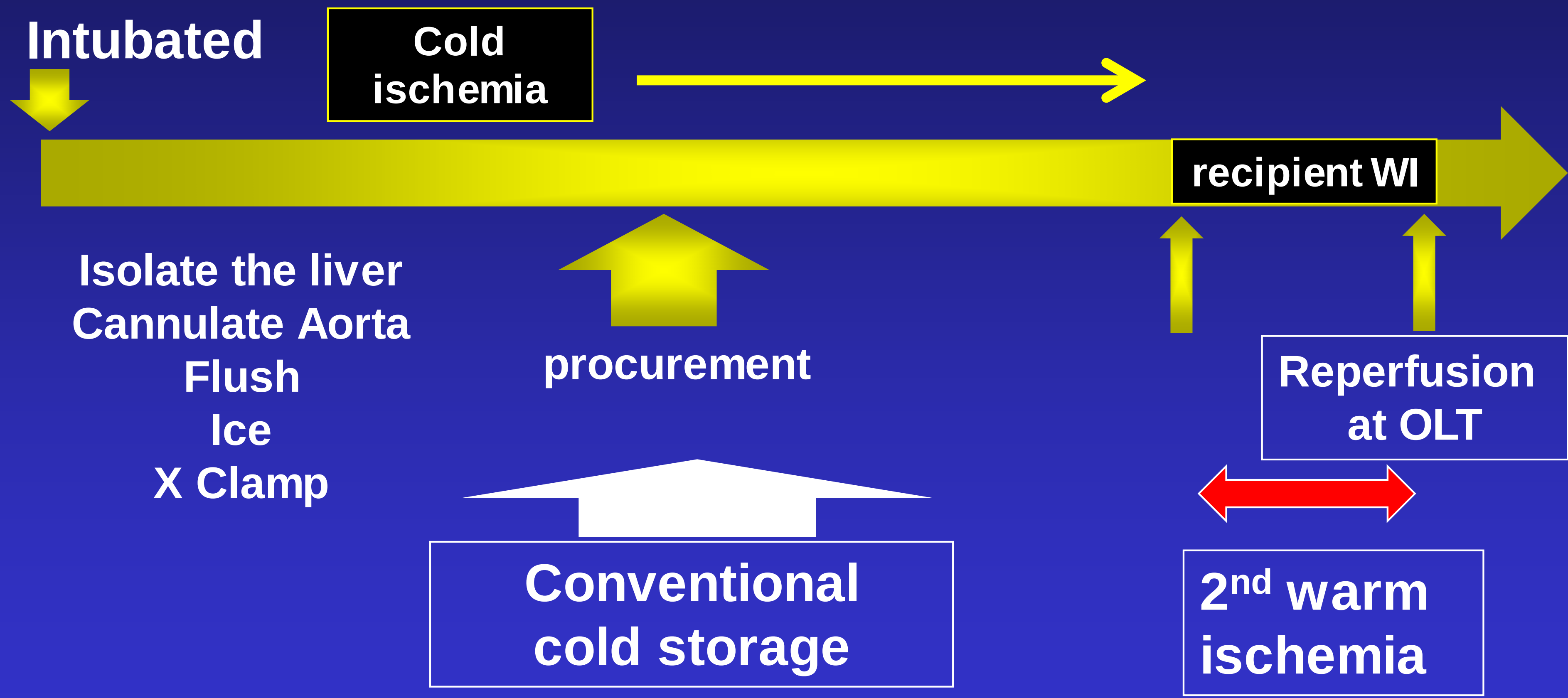
Houston Methodist Hospital

Machine Perfusion

- Introduction and definitions
- Normothermic regional perfusion
- Normothermic machine
- Hypothermic machine perfusion

Conventional Preservation and DBD Liver Allografts



Shapey M and Muiesan, Liver Transplantation 2013

Cold Static Preservation

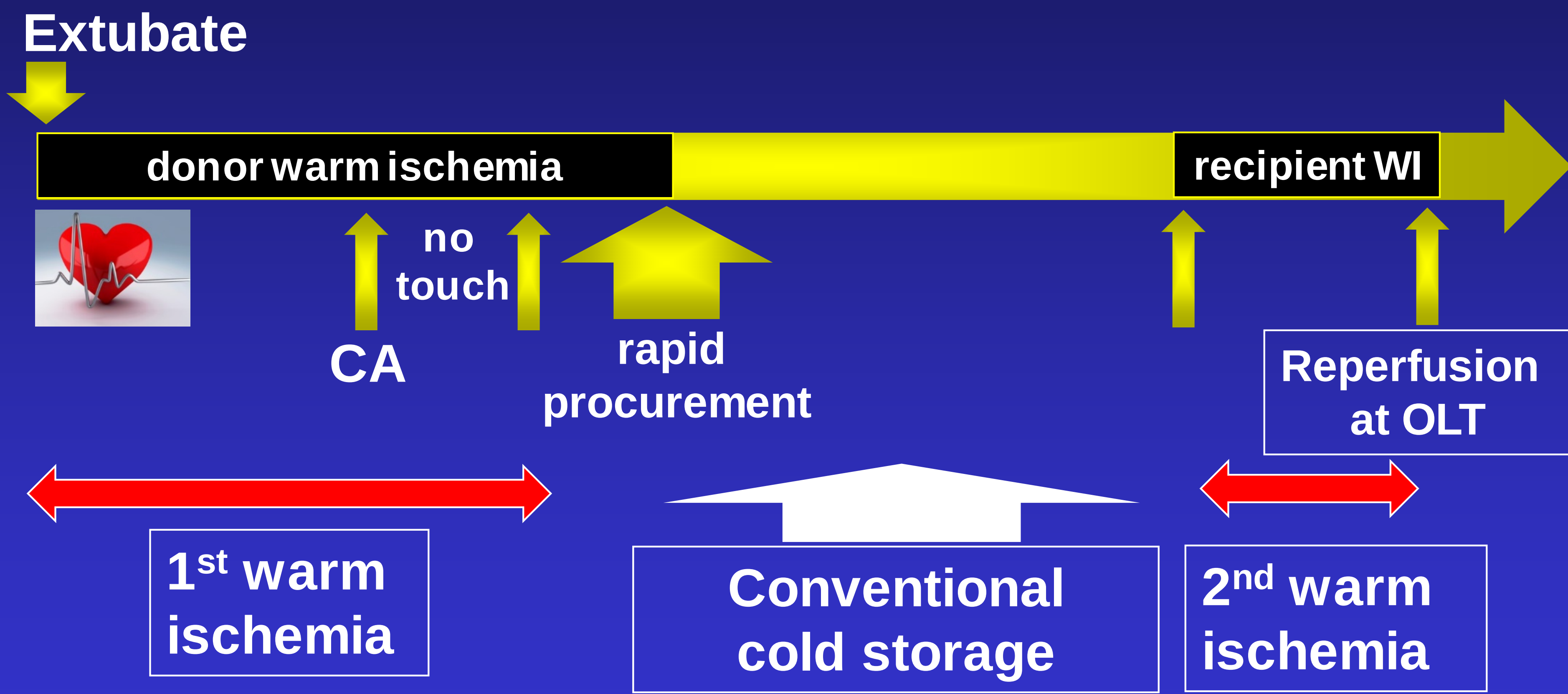
- Easy to perform
- Low costs
- Effective for “good grafts”

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

Factors Affecting Graft Surviavl

- Donor Age
- Fat content 30%
- Cold Ischemia time CIT
- Warm ischemia time WIT
- Visualization
- Method of procurement DBD vs DCD

DCD Allografts Suffer More Injury than DBD Livers After Conventional Preservation



Shapey M and Muiesan, Liver Transplantation 2013

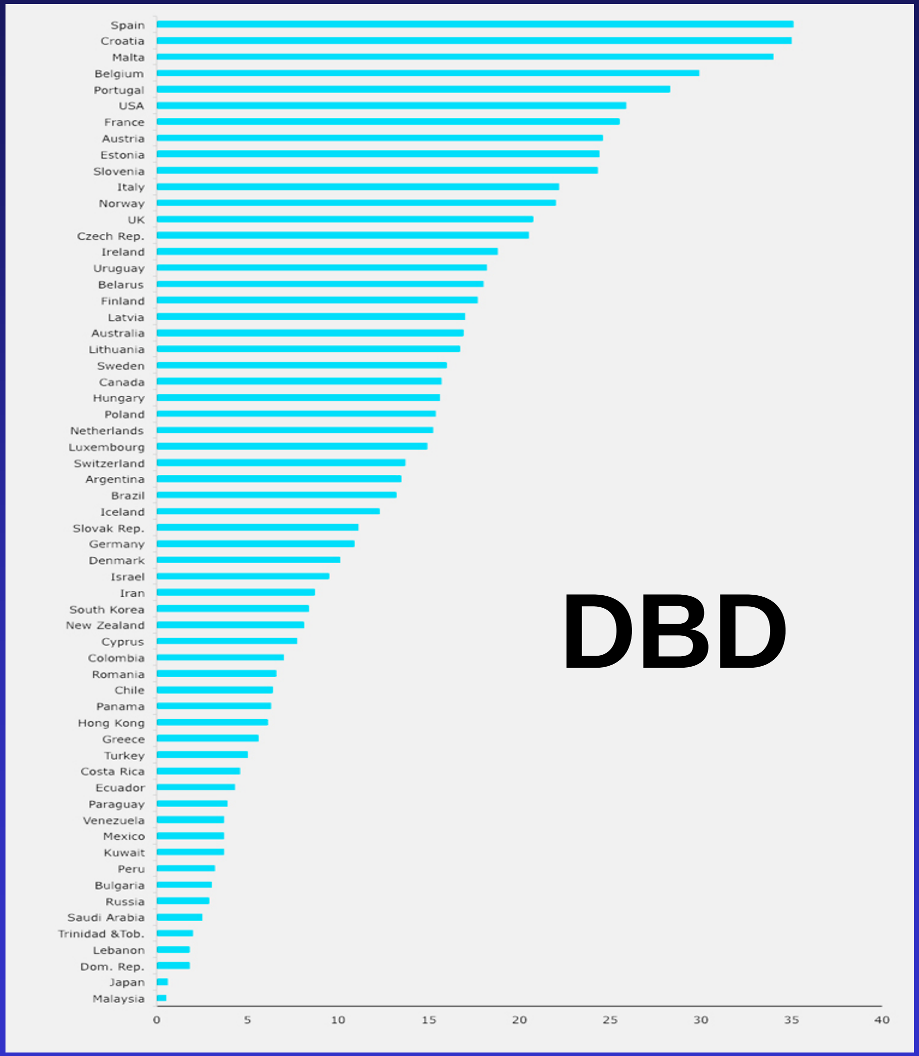
Categories of Non-Heart-Beating Donors
Donors After Cardiac Death
Maastricht Classification - Netherlands

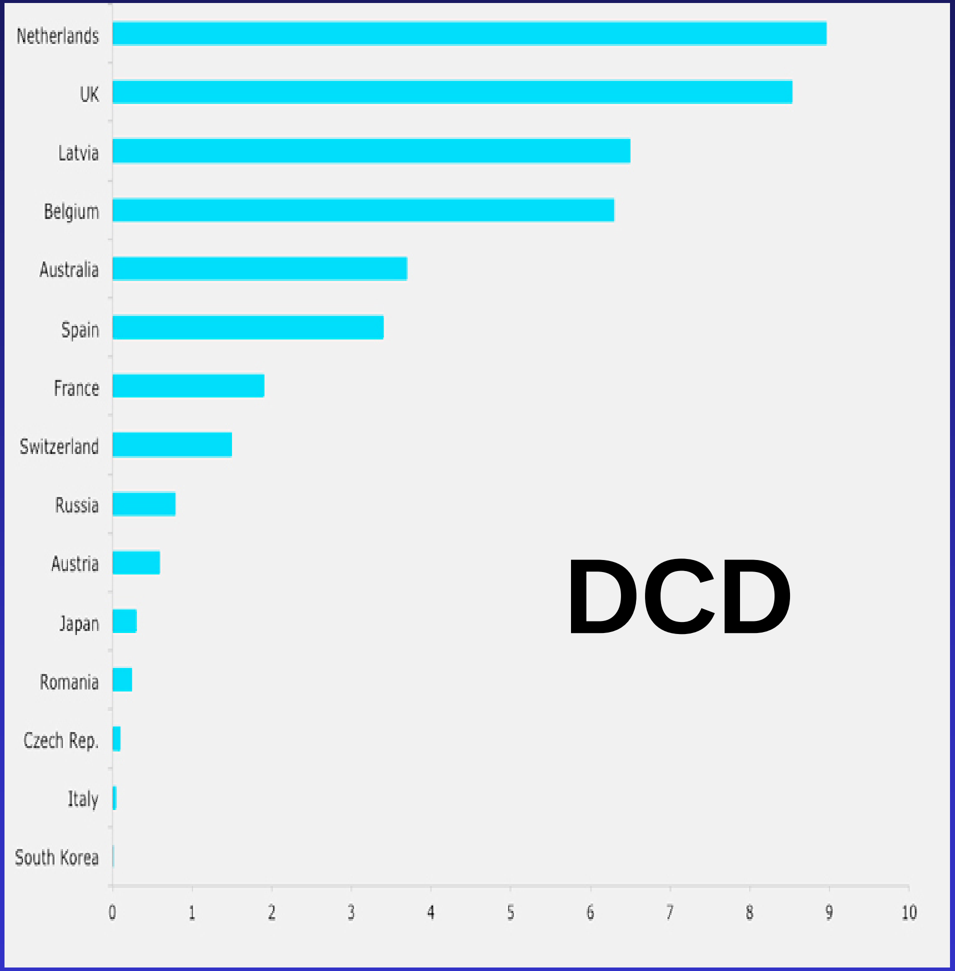
I	Brought in dead	Irreversible on the street	**Uncontrolled uDCD**
II	Unsuccessful resuscitation	Resuscitation in ambulance	
III	Awaiting cardiac arrest		**Controlled cDCD**
IV	Cardiac arrest after brain-stem death	Insufficient evidence for brain death	**Uncontrolled uDCD**
V	Unexpected Cardiac arrest in a hospital inpatient		**uncontrolled** (added in 2000)

Kootstra G, Daemen JH, Oomen AP, Transplantation Proceedings 1995

Sánchez-Fructuoso A I et al, J Am Soc of Nephrol 2000

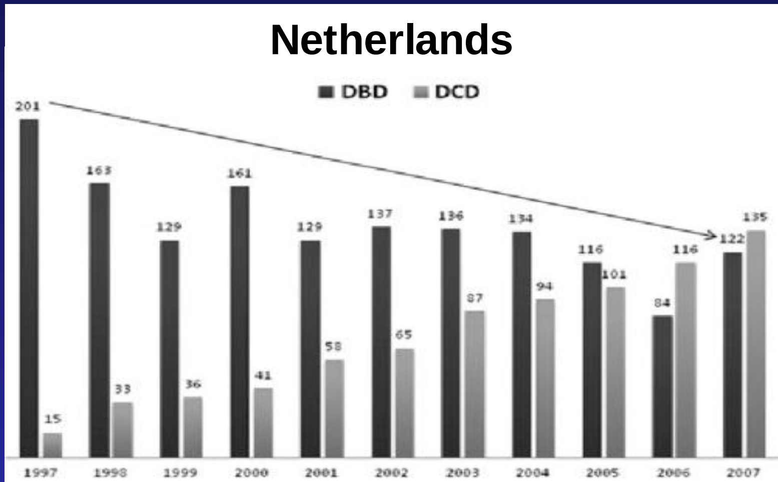
Worldwide DCD Donors (PMP)

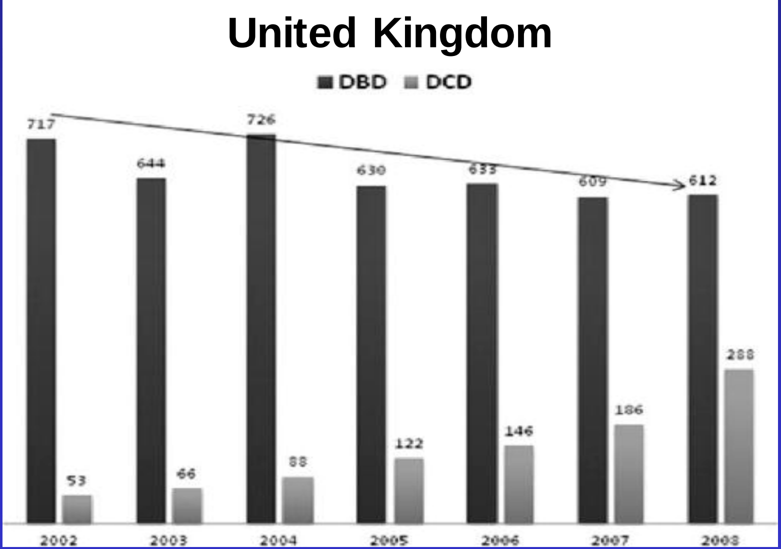


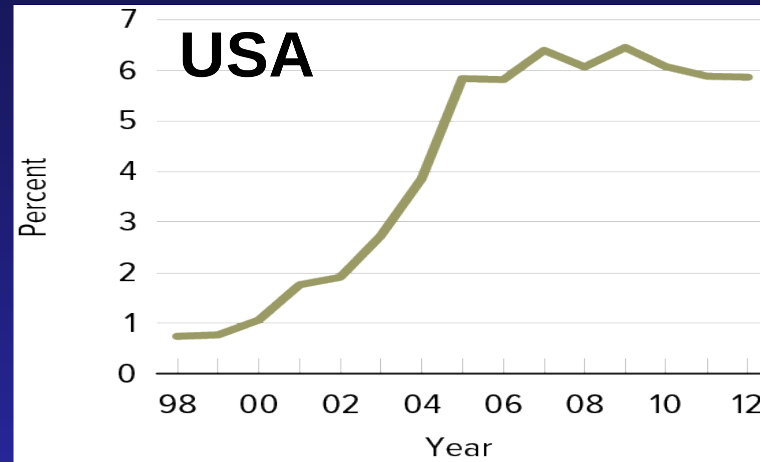


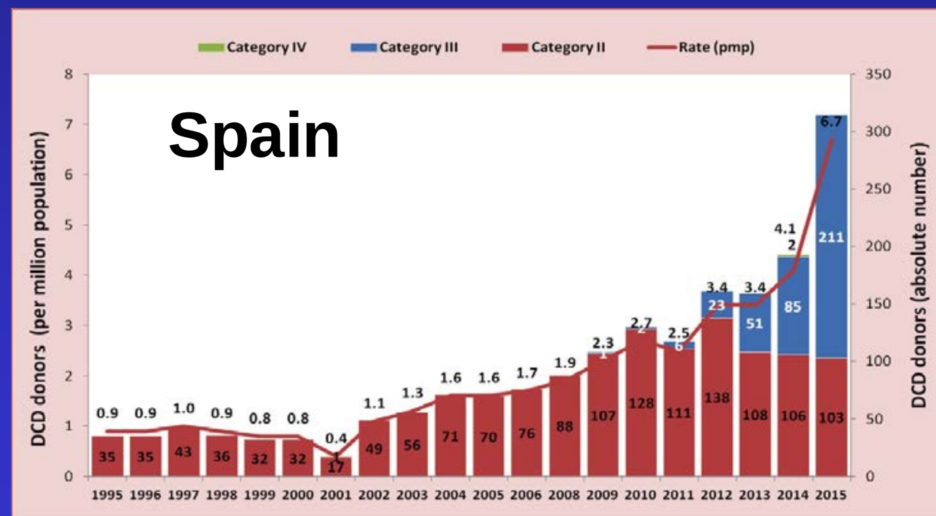
International Registry for Organ Donation and Transplantation (IRODaT), 2013

Increased DCD Utilization









DeOliveira ML, Ann Surg 2012

Fondevila C et al, AJT 2016
SRTR, 2012 Annual Data Report

Meta Analysis of Ischemic Cholangiopathy after cDCD Liver Transplantation

- 489 DCD and 4455 DBD
- 2.4 times increased odds of biliary complications
- 10.8 times odds for ischemic cholangiopathy
- 1.6 times and 2.1 times higher odds for recipient mortality and graft failure

Jay CL et al, Ann Surg 2011

Machine Perfusion

- Repairing putative organ injuries and increase utilization of DCD livers

- Offers the opportunity to test organ quality and test organ function

STEVEN SPIELBERG PRESENTS

BACK TO THE FUTURE™

A ROBERT ZEMECKIS FILM

Surgery, 1963; 54:900-911

Extracorporeal perfusion for obtaining postmortem homografts

T. L. MARCHIORO, M.D.*, **R. T. HUNTLEY, B.S.**, **W. R. WADDELL, M.D.**, and **T. E. STARZL, M.D., Ph.D.****
Department of Surgery, University of Colorado School of Medicine, and the Denver Veterans Administration Hospital

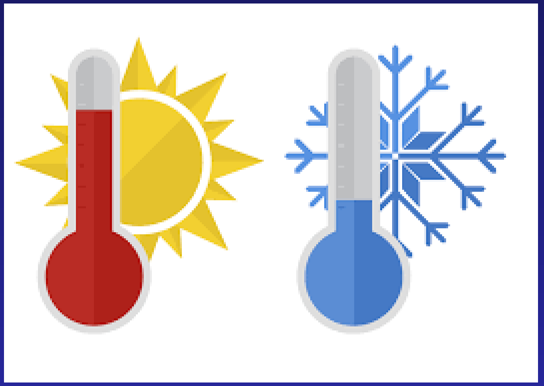
Transplantation. 1967 July ; 5: 790–803

HOMOTRANSPLANTATION OF THE LIVER

Thomas E. Starzl, **Thomas L. Marchioro**, **K. A. Porter**, and **Lawrence Brettschneider**
Department of Surgery, University of Colorado School of Medicine, Denver, Colo., and St. Mary's Hospital and Medical School, London, England

Immediately after death, efforts were made not only to cool but to perfuse the liver in situ by means of an extracorporeal pump oxygenator into which a heat exchanger had been incorporated.

Machine Perfusion

Normothermic  Hypothermic

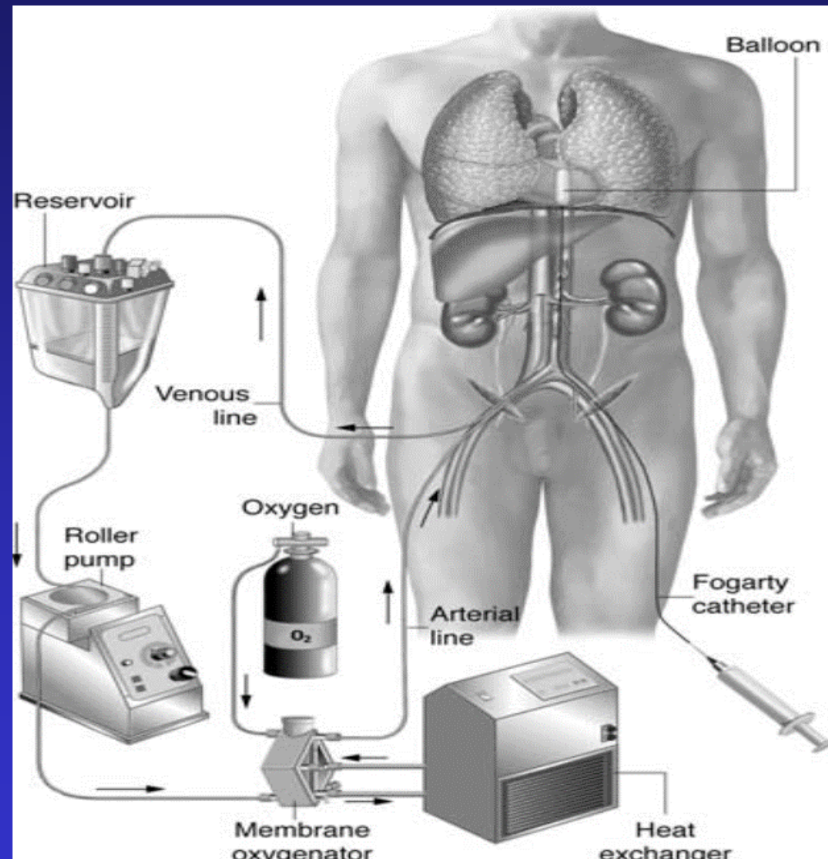
- **Perfusion with blood at normothermic conditions**
- **Minimize cold storage**

***In Situ* regional perfusion**

***Ex Situ* during or after organ transfer**

Strategies to Improve DCD Quality
In Situ Dynamic Preservation by ARP

- **Abdominal regional perfusion applies extracorporeal membrane oxygenation to deliver oxygen**
- **Hypothermic RP (HRP) reduces metabolic requirements**
- **Normothermic RP (NRP) physiologically restores cellular function**



Fondevila C et al, AJT 2012

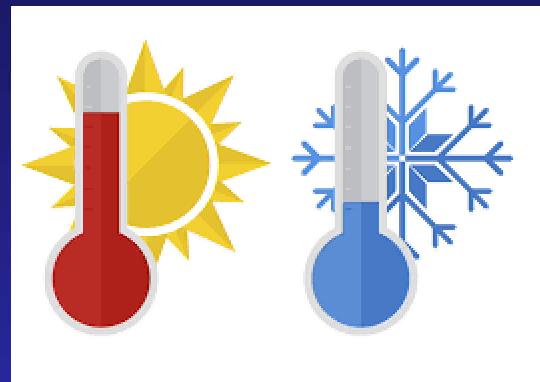
Jochmans I, AJT 2016

Advantages of Abdominal Regional Perfusion

- Experimental results show improved transplantation outcomes compared to cold storage
- Normothermic oxygen delivery to tissues allows for regeneration of ATP, NAD and prevents accumulation of toxic metabolites
- Improves the concentration of antioxidants
- Converts a "rapid recovery" rush into a controlled procurement that allows donor liver evaluation

Machine Perfusion

Normothermic



Hypothermic

- **Hypothermic oxygenated perfusion (HOPE)**
- **Dual hypothermic oxygenated perfusion (D-HOPE)**

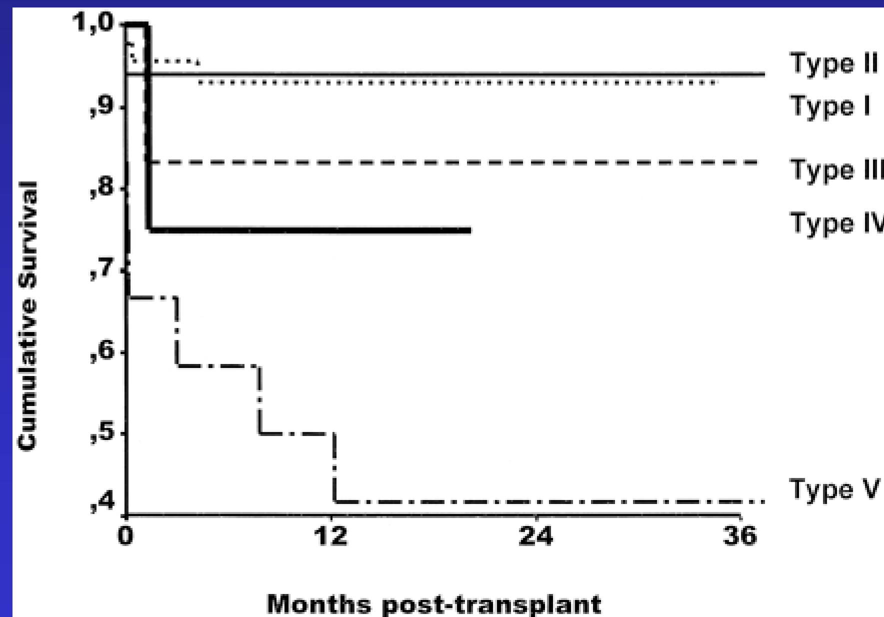
Performed *after* cold storage prior to implantation

Renal Transplantation from Non-Heart Beating Donors: A Promising Alternative to Enlarge the Donor Pool

ANA I. SANCHEZ-FRUCTUOSO,* DOLORES PRATS,* JAIME TORRENTE,*
M. JESU´ S PEREZ-CONT´IN,‡ CRISTINA FERNA´ NDEZ,† JOAQU´IN ALVAREZ,§ and ALBERTO BARRIENTOS*
*Departments of *Nephrology, †Preventive Medicine, and ‡Surgery, and §Transplant Coordination, Hospital Clinico San Carlos, Madrid, Spain.*
J Am Soc Nephrol 11: 350-358, 2000

In 1989, kidneys procured from NHBD, donors were maintained - from cardiac arrest to procurement - on cardiopulmonary bypass: extracorporeal circulation, external oxygenator and intense hypothermia

95 of 144 kidneys were transplanted: PNF 6%, 94% successful, DGF 61%,



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Liver Transplantation from Maastricht Category 2 - uNHBD

La Coruna and Madrid – Spain 2003

1. Cardiac arrest (CA)
2. CPR time followed
3. 5 min after declaration of death,
   Cardiopulmonary Support (CPS): combined mechanical chest and abdominal compression, PaO_2 100, MAP 100, pH > 7.10
4. WIT: CA to CPS

1. Cardiac arrest (CA)
2. CPR time followed
3. 5 min after declaration of death,
   Cardiopulmonary Bypass (CPB)/ECMO is started
4. WIT: CA to ECMO

Otero et al, Transplantation 2003

Liver Transplantation from Maastricht Category 2 – uNHBD

La Coruna and Madrid - Spain

- **Cardiopulmonary support (CPS)** **n=6**
- **Cardiopulmonary bypass (CPB, ECMO)**
  - **- Hypothermic perfusion (HR) at 15-20 ^{O}C** **n=7**
  - **- Normothermic perfusion (NRP) at 37 ^{O}C** **n=7**

Otero et al, Transplantation 2003

Liver Transplantation from Maastricht Category 2 – uNHBD

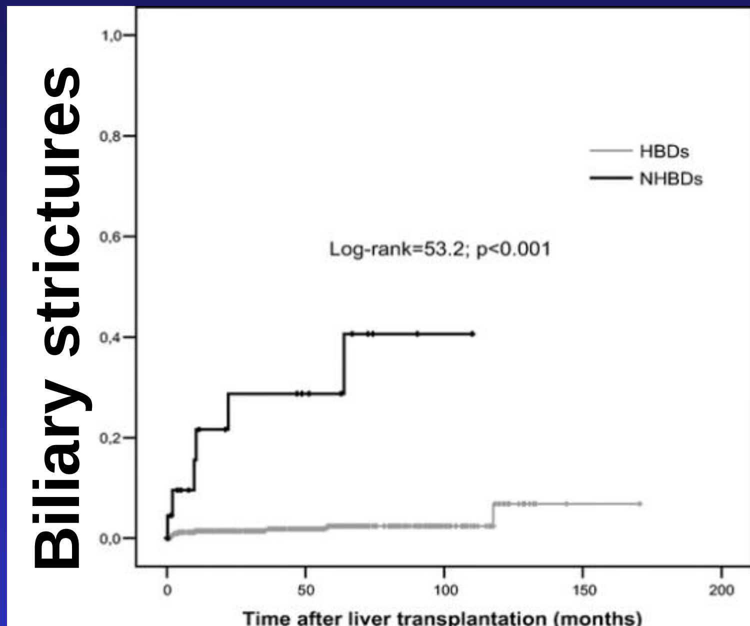
La Coruna and Madrid - Spain

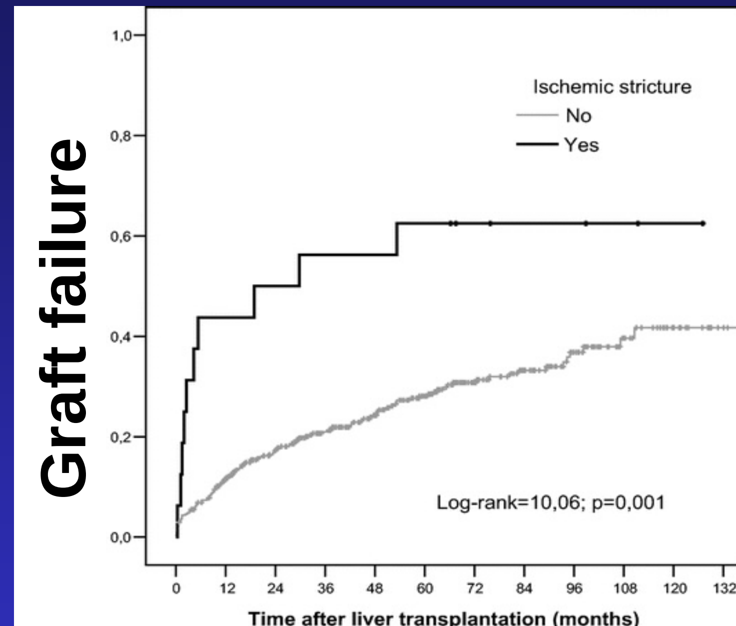
	CPS n=6	CPB/ECMO n=14
Pt survival	100 %	71 %
Graft survival	83 %	43 %
PNF	1 (16%)	4 (28%)

- CPS, if efficient, is better than CPB and should not exceed 130 min
- CPB/ECMO can provide an additional 150 min
- No livers failed if CPB <150 min
- No difference between hypothermic and normothermic perfusion

Otero et al, Transplantation 2003

Biliary Complications in Maastricht Category 2 - uNHBD





Multivariate Analysis		
	P value	Relative Risk
NHBD	0.002	47.1
HAT	<0.001	98.7

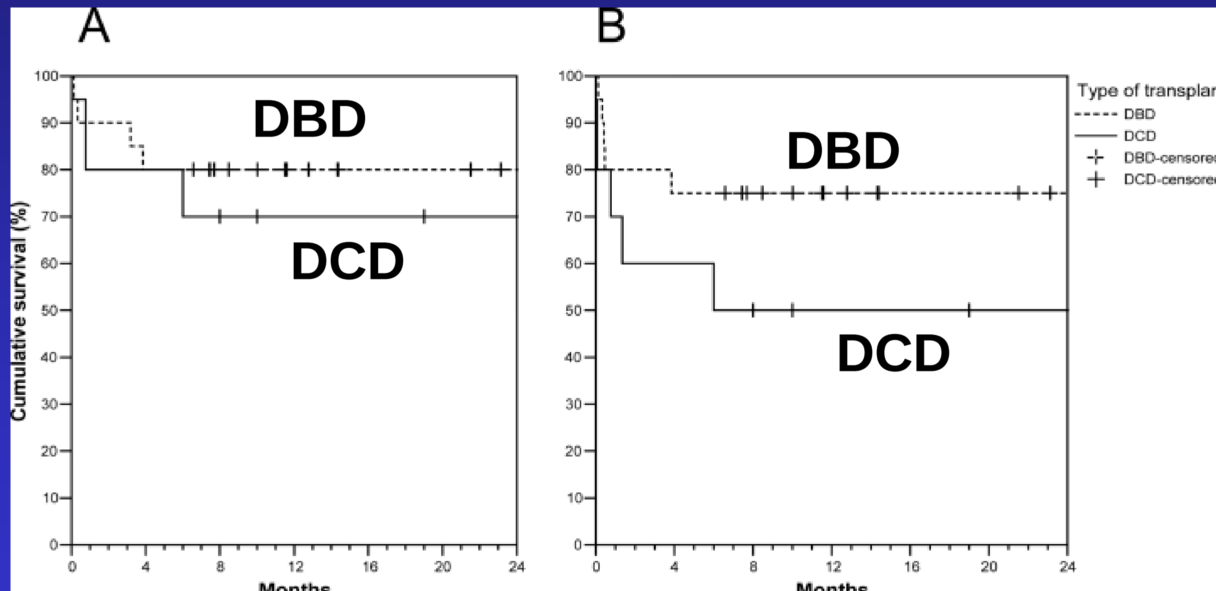
Suarez F et al, Transplantation 2003

Liver Transplant Using Donors After Unexpected Cardiac Death: Novel Preservation Protocol and Acceptance Criteria

C Fondevila et al, *AJT 2007; 1849-1855*

NECMO - NRP

- **10 of 40 uDCD livers were transplanted**
- **Only 1 of 10 with biliary anastomotic stricture and 1 HAT**



Fondevila C et al, AJT 2007

Single Center Experience for Abdominal Regional Perfusion using NECMO in uDCD

Group period	Pump flow L/min	Perfusion time (min)	N	PNF %	Ischemic biliary lesion %	1-yr graft survival %
Barcelona 2015 [1]	1.7	195 (184-230)	43	9	12	74
Madrid 2009 [2]	3.3±0.6	174 ± 46	20	10	5	80
Paris 2015 [3]	2-3	240 (209-319)	13	23	7	69

[1] *Fondevila C et al, AJT 2012*

[2] *Jimenez-Galanes, Liver Transplantation 2009*

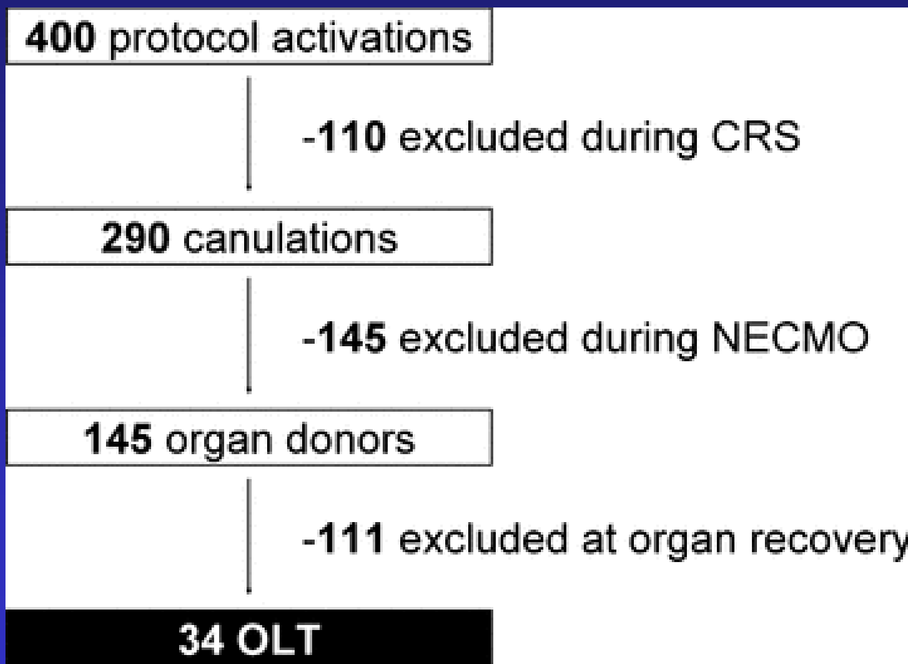
[3] *Savier E, Liver Transplantation 2015*

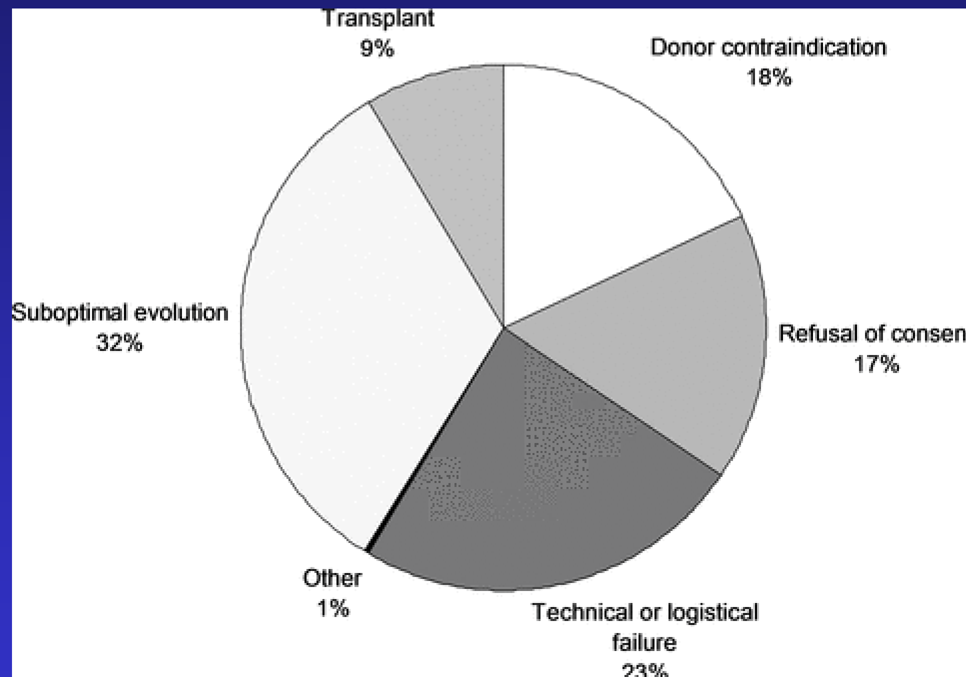
Parameters for Donor Utilization in Maastricht Category 2 - uDCD

- Time limits: <15 min cardiac arrest without CPR
  <150 min advanced cardiorespiratory support
  < 4 hr NECMO
- Pump parameters: 1.7 l/min, temp 35.5 -37.7 ºC
- Most common contraindications to donate:
  age > 65
  poor venous return
  Elevated enzymes > 3x normal
  Macro appearance of allograft
  History of alcohol or liver disease
  Judicial refusal

Fondevila C et al, AJT 2012

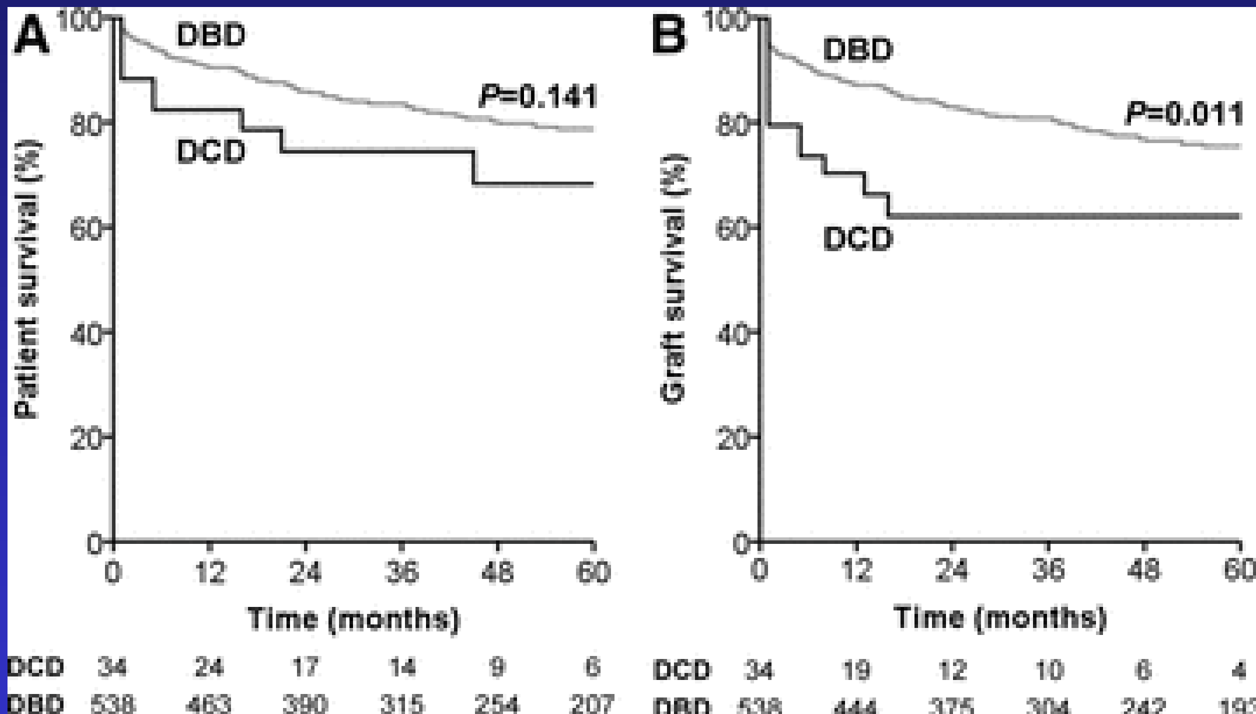
Logistical Analysis of Activation of uDCD Donation Protocol





Fondevila C et al, AJT 2012

Patient and Graft Survival of uDCD Recipients



Fondevila C et al, AJT 2012

Perioperative Care of uDCD Recipients

	uDCD (n = 40)	DBD (n = 80)	p
EAD (%)	20 (50)	16 (20)	0.001
PNF (%)	2 (5)	1 (1)	0.215
Surgical reintervention (%)	21 (53)	11 (14)	<0.001
Renal replacement therapy (%)	6 (15)	2 (3)	0.010
Mechanical ventilation (h)	58 (7–120)	7 (5–24)	0.001
ICU stay (days)	7 (4–11)	5 (3–6)	0.005
Hospital stay (days)	22 (16–42)	16 (13–21)	0.003
Retransplantation (%)	6 (15)	1 (1)	0.002

Fondevila C et al, AJT 2016

Utilization of uDCD – Lessons Learned

- Potential donors can be increased by thousands
- Despite logistical challenges, uDCD maybe only option in some countries where DBD donors are not utilized
- Application of Ex Vivo RP have resulted in good patient survival but reduced graft survival rates
- Although some European countries and only New York City have adopted protocols for uDCD, most donor increases have come from cDCD

Magliocca JF, AJT 2016

Hessheimer AJ et al, AJT 2016

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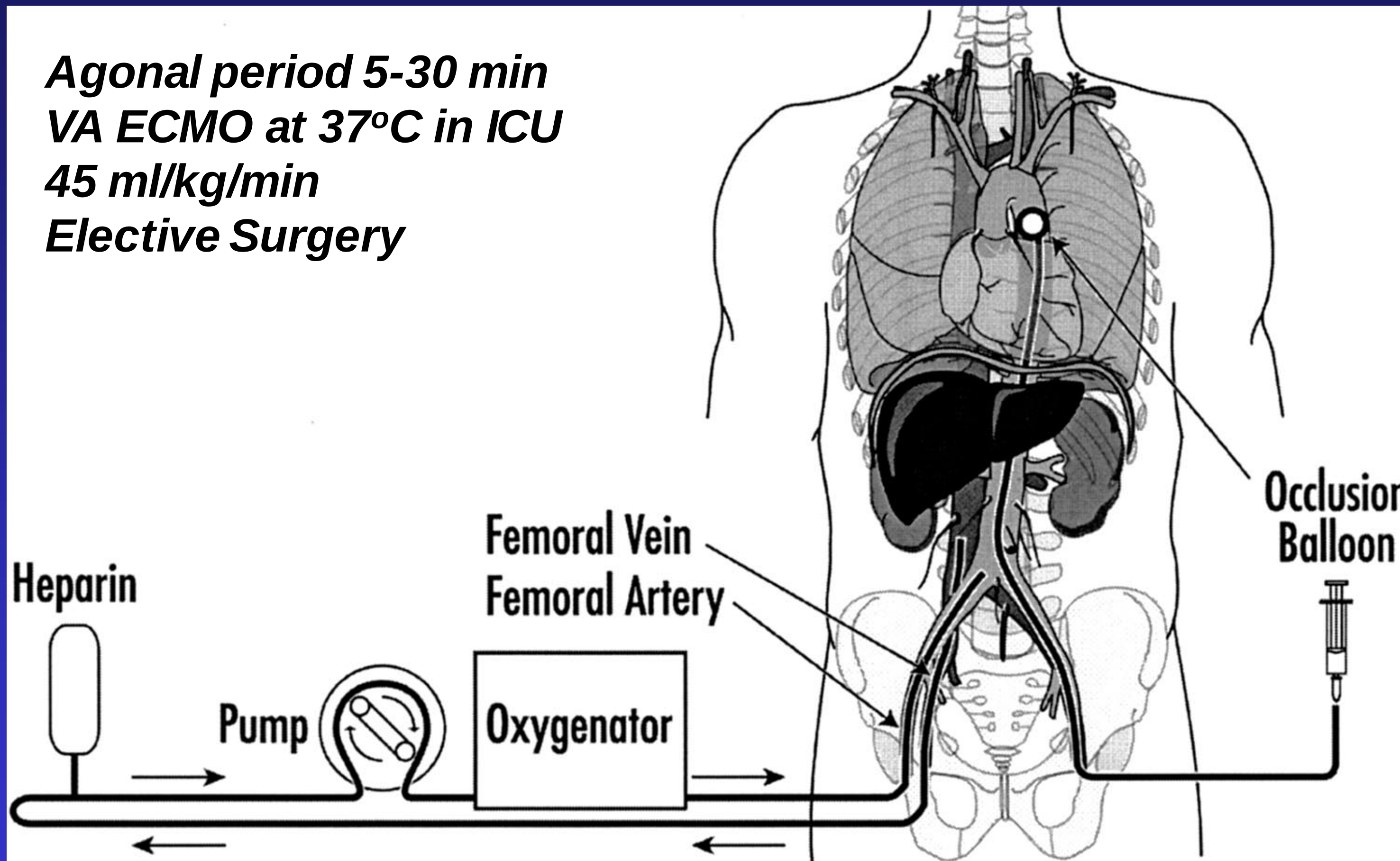
The University of Michigan Experience



Rojas-Pena, Clin Transl Res 2014

ECMO Utilization in Recovery in cDCD: Comparison to Cold Storage

	Rapid Recovery Cold Storage	E-DCDD
Organs donated	Kidneys/occasional livers	All except heart
Goal	Deep cooling/ decrease metabolism	Restore warm circulation and oxygenation/normal metabolism
Time to procurement	Urgent	Elective
Cold Storage	Routine followed by pump perfusion	Pump perfusion not necessary
Organ Assessment	During pump perfusion	At recovery and pump perfusion
Post Tx Function	40-60% DGF	8-30% DGF

Rojas-Pena, Clin Transl Res 2014

Logistical Analysis of Activation of cDCD Donation Protocol

37 donors, 38.7 (9-65) yrs, 79.5 (30-143.6) Kg

	Kidneys	Livers	Pancreas	ORPD
Recovered	73	21	2	2.59
Transplanted	48	13	1	1.68

Rojas-Pena, Clin Transl Res 2014

Change of Arterial Blood Gases with ECMO

Variable	At Initiation	At Termination
pH	7.09 ± 0.02	7.28 ± 0.02
SVO_2	45.5 ± 3.6	67.0 ± 3.2
PaO_2	304.8 ± 39.2	373.3 ± 41.3
$PaCO_2$	55.5 ± 8.4	34.5 ± 2.4
SaO_2 %	84.4 ± 3.5	90.4 ± 34
K^+	6.1 ± 0.8	4.9 ± 0.5

Rojas-Pena, Clin Transl Res 2014

Single Center Experience for Abdominal Regional Perfusion using NECMO in cDCD

Group period	Pump flow L/min	Perfusion time (min)	N	PNF %	Ischemic biliary lesion %	1-yr graft survival %
Michigan 2014 [1,2]	3.5	86 ± 5	13	0	7	86
UK 2009 [2]	1.7 - 4	120 (34-156)	11	9	0	NR

[1] Rojas-Pena, Clin Transl Res 2014
[2] Magliocca et al, J Trauma 2005
[3] Oniscu GC, AJT 2014

Can ECMO be improved ?

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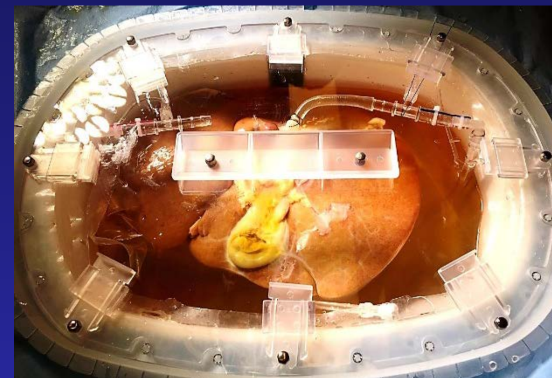
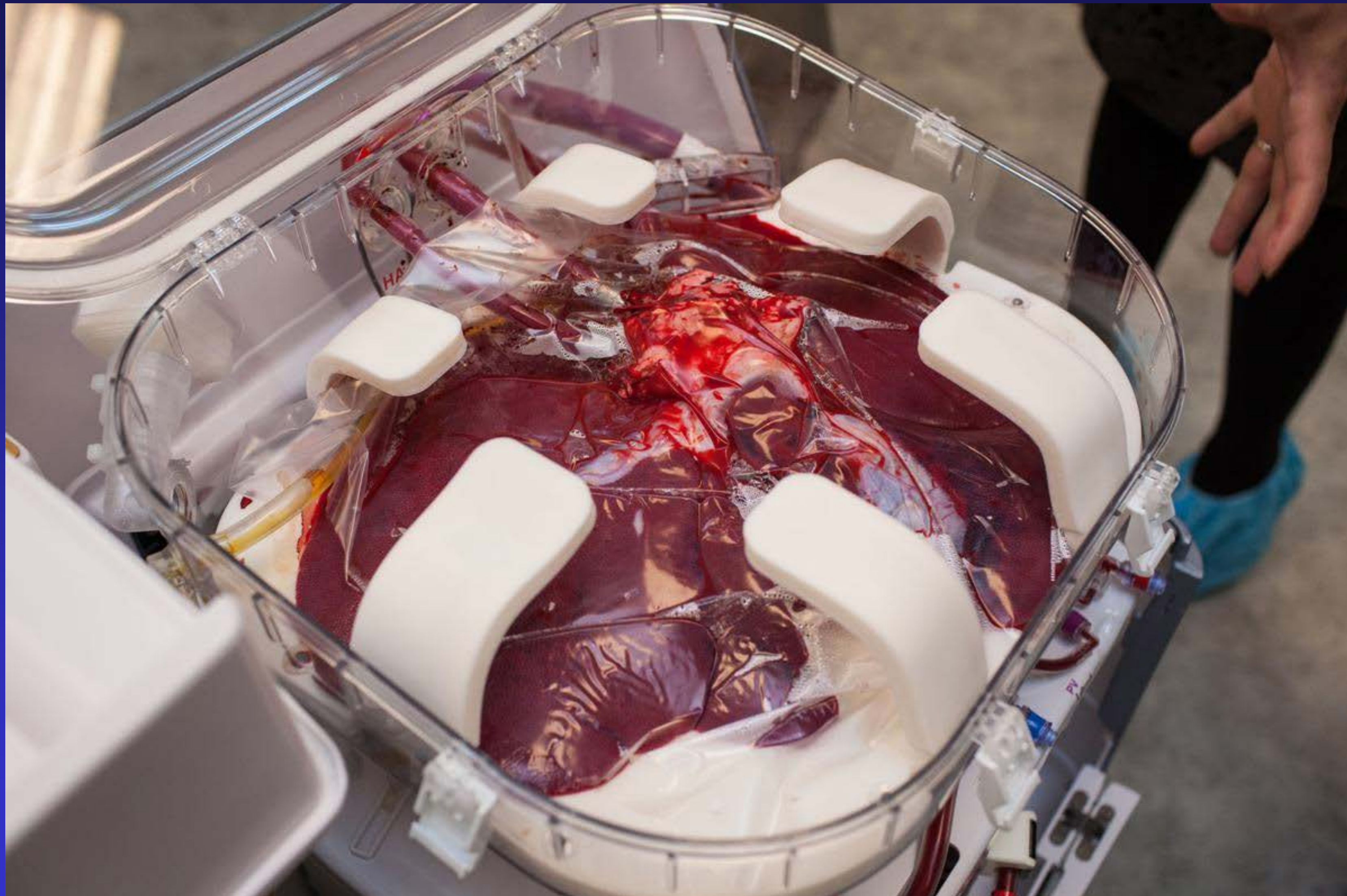
Machine Perfusion Devices





A randomized trial of normothermic preservation in liver transplantation

David Nasralla[1]*, Constantin C. Coussios[2]*, Hynek Mergental[3], M. Zeeshan Akhtar[1,4], Andrew J. Butler[5,20], Carlo D. L. Ceresa[1], Virginia Chiocchia[6,7], Susan J. Dutton[8], Juan Carlos García-Valdecasas[9], Nigel Heaton[10], Charles Imber[11], Wayel Jassem[10], Ina Jochmans[12,13], John Karani[10,14], Simon R. Knight[1,15], Peri Kocabayoglu[16], Massimo Malagò[11], Darius Mirza[3], Peter J. Morris[1,15], Arvind Pallan[17], Andreas Paul[16], Mihai Pavel[9], M. Thamara P. R. Perera[3], Jacques Pirenne[12,13], Reena Ravikumar[1], Leslie Russell[18], Sara Upponi[19], Chris J. E. Watson[5,20], Annemarie Weissenbacher[1], Rutger J. Ploeg[1], Peter J. Friend[1]* for the Consortium for Organ Preservation in Europe

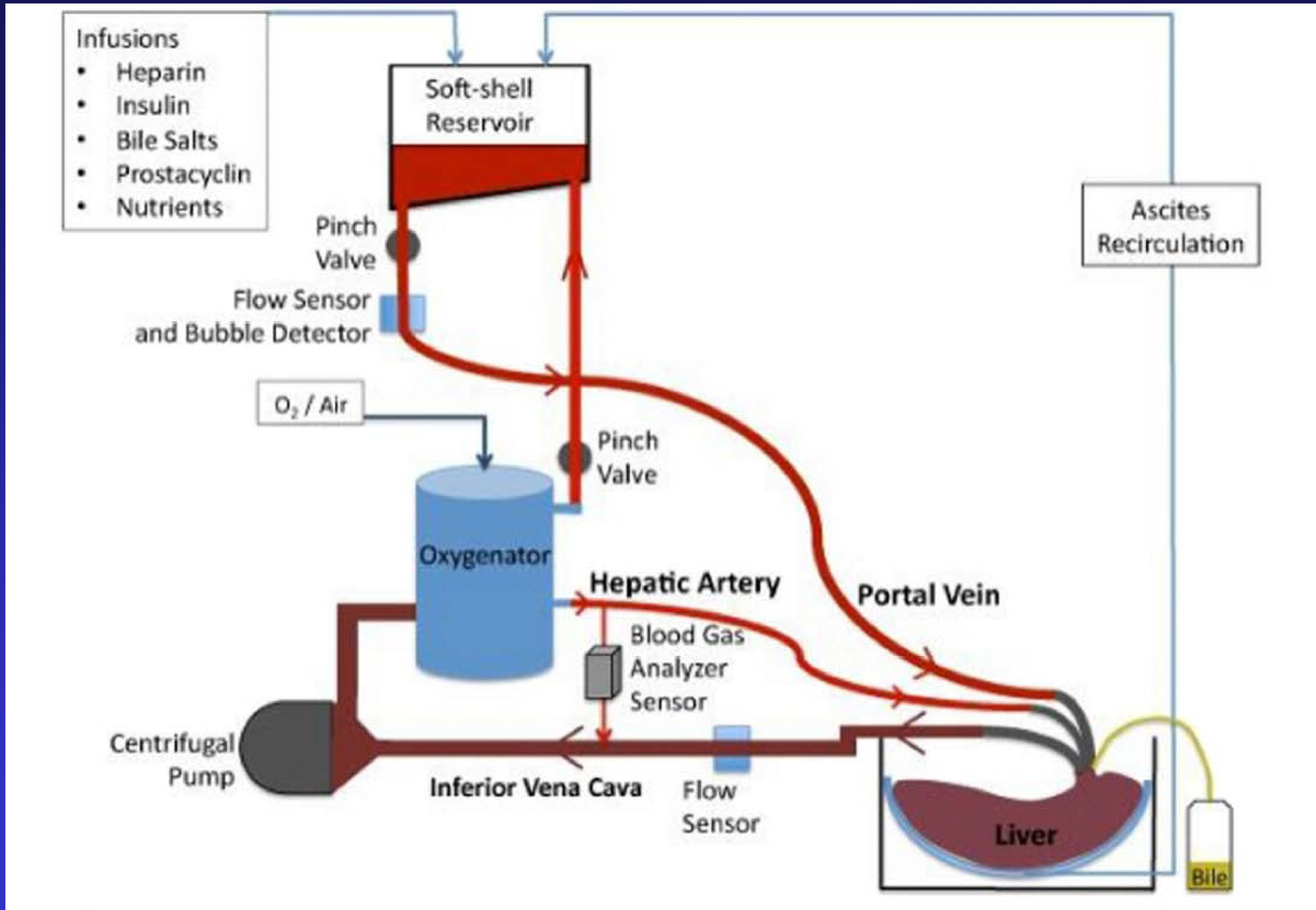
Liver transplantation is a highly successful treatment, but is severely limited by the shortage in donor organs. However, many potential donor organs cannot be used; this is because sub-optimal livers do not tolerate conventional cold storage and there is no reliable way to assess organ viability preoperatively. Normothermic machine perfusion maintains the liver in a physiological state, avoids cooling and allows recovery and functional testing. Here we show that, in a randomized trial with 220 liver transplantations, compared to conventional static cold storage, normothermic preservation is associated with a 50% lower level of graft injury, measured by hepatocellular enzyme release, despite a 50% lower rate of organ discard and a 54% longer mean preservation time. There was no significant difference in bile duct complications, graft survival or survival of the patient. If translated to clinical practice, these results would have a major impact on liver transplant outcomes and waiting list mortality.

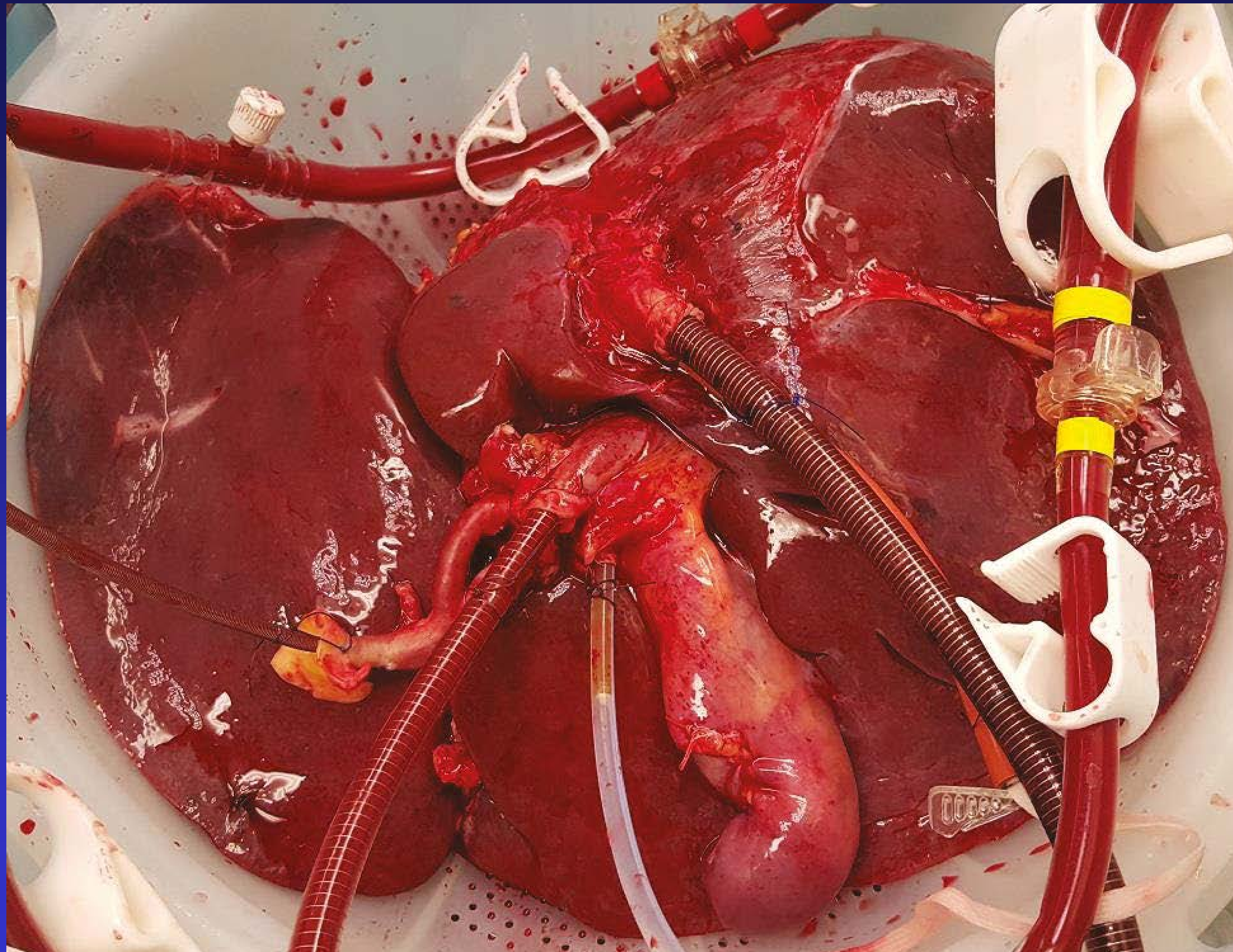
Randomized Controlled trial
NEsLP vs Cold Storage

NEsLP (n=121/ DCD=34) vs SCS (n=101/DCD=21)

- Portable perfusion, Metra device
- Acceptable for transplantation

Nasralla, Nature 2018; 557(7703):50-56


Infusions
• Heparin
• Insulin
• Bile Salts
• Prostacyclin
• Nutrients
Soft-shell Reservoir
Pinch Valve
Flow Sensor and Bubble Detector
O_2 / Air
Pinch Valve
Oxygenator
Hepatic Artery
Portal Vein
Blood Gas Analyzer Sensor
Centrifugal Pump
Inferior Vena Cava
Flow Sensor
Ascites Recirculation
Liver
Bile

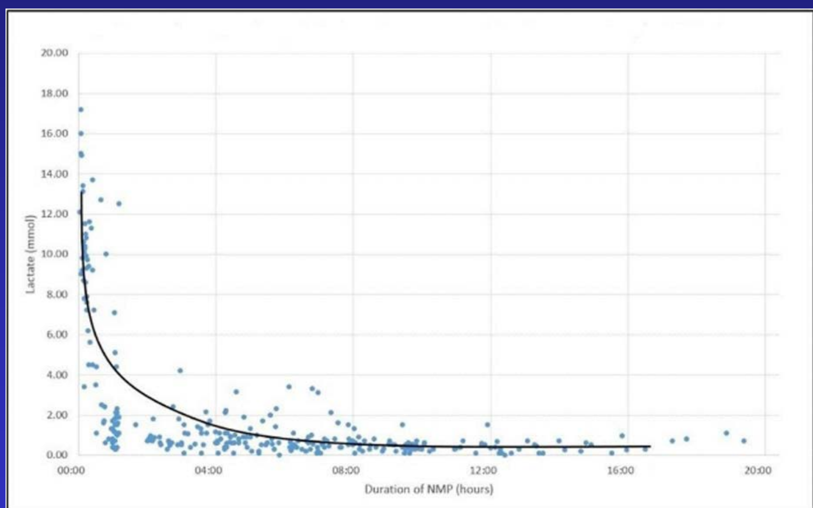


Nasralla, Nature 2018; 557(7703):50-56

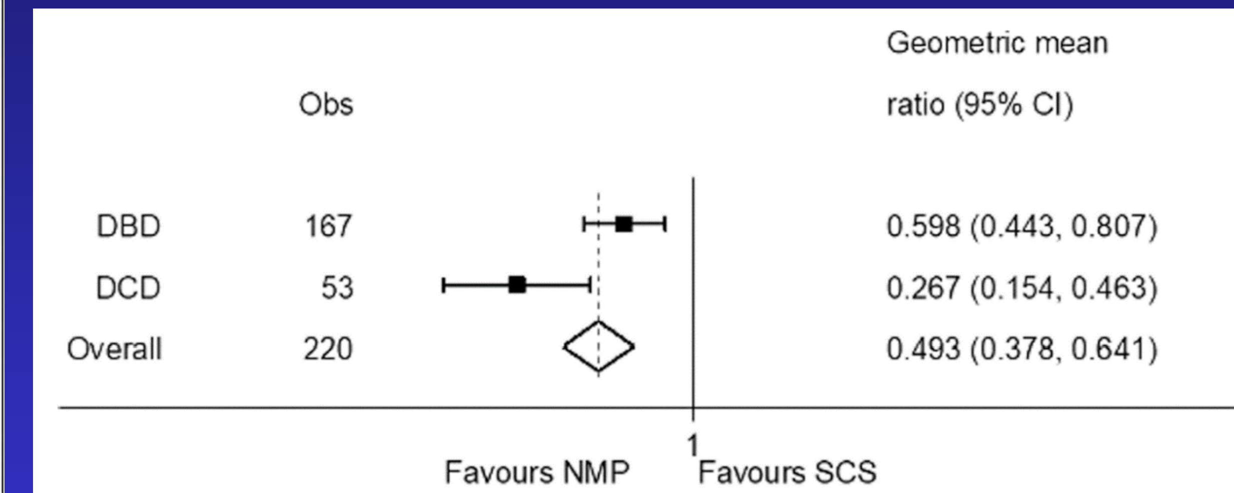
Randomized Control Trial NEsLP vs SCS (Outcomes)

	NMP ($n=121$)[a]	SCS ($n=101$)[a]	Effect (95% CI)[b]	*P* value
Peak AST				
ITT[c]				
Adjusted	488.1 (408.9–582.8)	964.9 (794.5–1,172.0)	0.5 (0.4–0.7)	0.0000
Unadjusted	484.5 (406.4–577.6)	973.7 (795.2–1,192.3)	0.5 (0.4–0.6)	0.0000
Test for interaction by donor type				0.012
Subgroup analysis by donor type				
DBD	526.2 (427.3–647.9)	880.2 (708.5–1,093.5)	40.2% (19.3–55.7%)	0.0009
DCD	389.7 (278.0–546.4)	1,458.1 (944.7–2,250.5)	73.3% (53.7–84.6%)	0.0000
PP analysis	498.6 (414.8–599.4)	982.9 (810.4–1,192.2)	0.5 (0.4–0.7)	0.0000
Secondary outcomes				
Discard rates[d]	16 (11.7%)	32 (24.1%)	−12.4% (−21.4 to −3.3%)	0.008
Primary non-function[e]	1 (0.8%)	0 (0.0%)	NA	NA
Post-reperfusion syndrome	15 (12.4%)	32 (33.0%)	−20.6% (−31.6 to −9.6%)	0.0002
Post-reperfusion lactate[f]	3.6 (2.6–4.2)	4.1 (3.2–5.0)		0.018
Early allograft dysfunction	12 (10.1%)	29 (29.9%)	0.263 (0.126–0.550)	0.0002

Randomized Control
Trial NEsLP vs SCS (Outcomes)



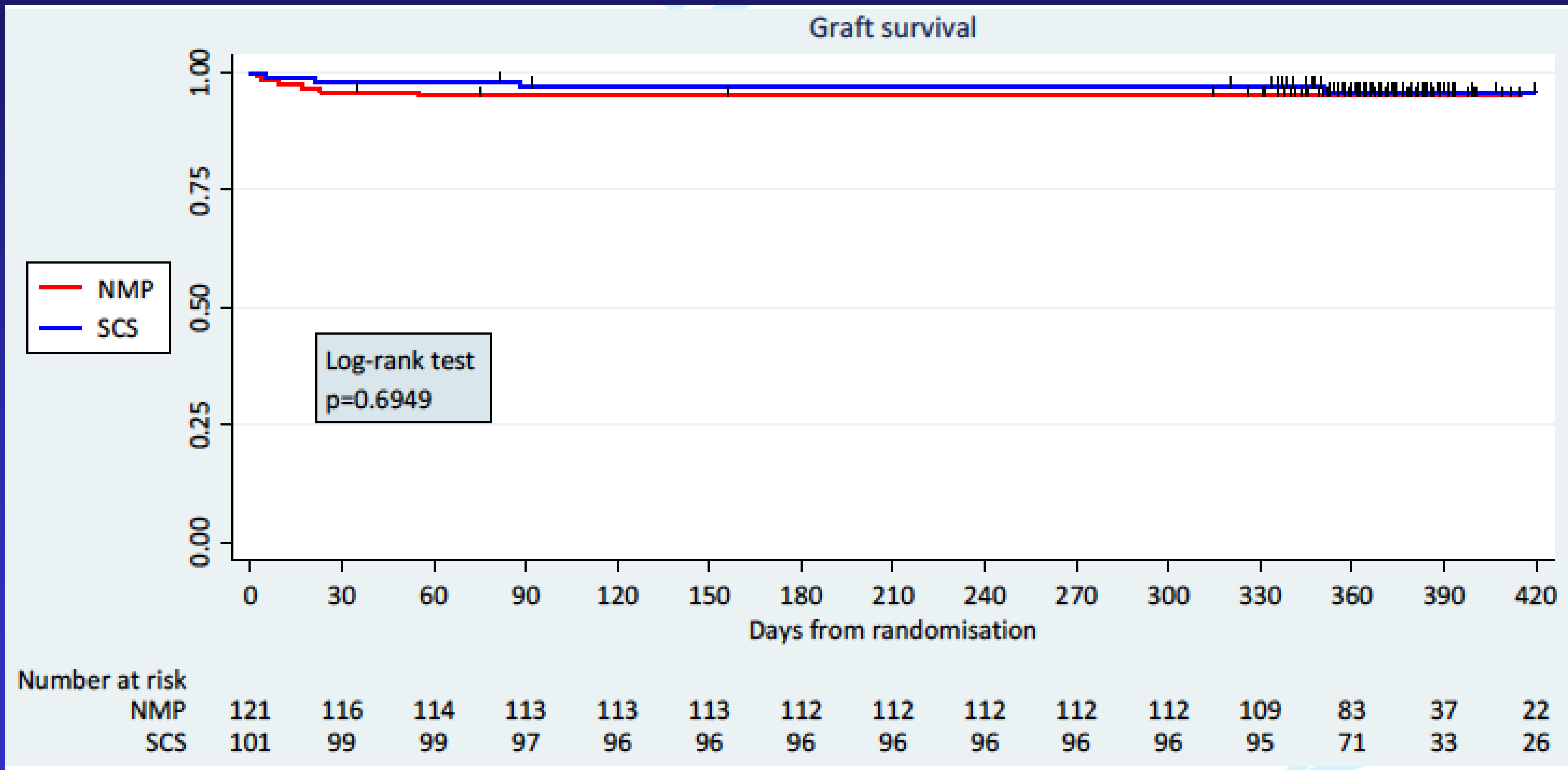
Perfusate lactate levels during NMP



Subgroup analysis

Nasralla, Nature 2018; 557(7703):50-56

Graft Survival

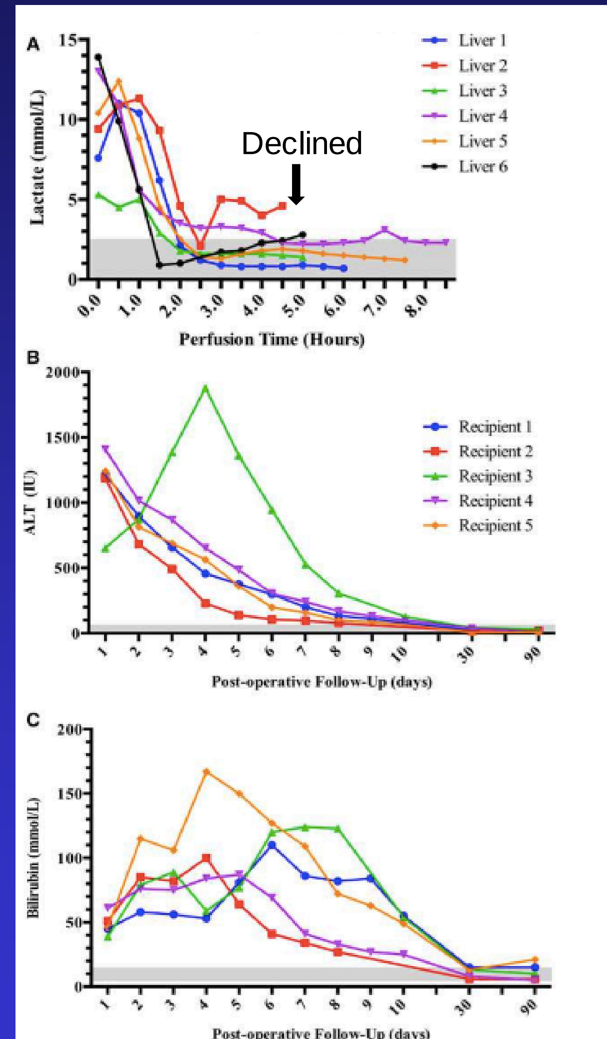


Nasralla, Nature 2018; 557(7703):50-56

- **All usable livers**
- **How does normothermic MP perform with extended criteria livers**

Transplantation of Rejected Liver Grafts After NEsLP

- 6 rejected livers (4 DCD/ 2 HBD)
- DCD organs rejected due to prolonged WIT
- HBD organs rejected due to high LFTs



Outcomes:
- Median Hospital stay was 10 days
- The mean for ALT peak was 1386 IU/L
- No EAD
- No Ischemic cholangiopathy at 7 months (median) after transplant

Mergental H, et al. Am J Transplant. 2016; 16(11):3235-3245

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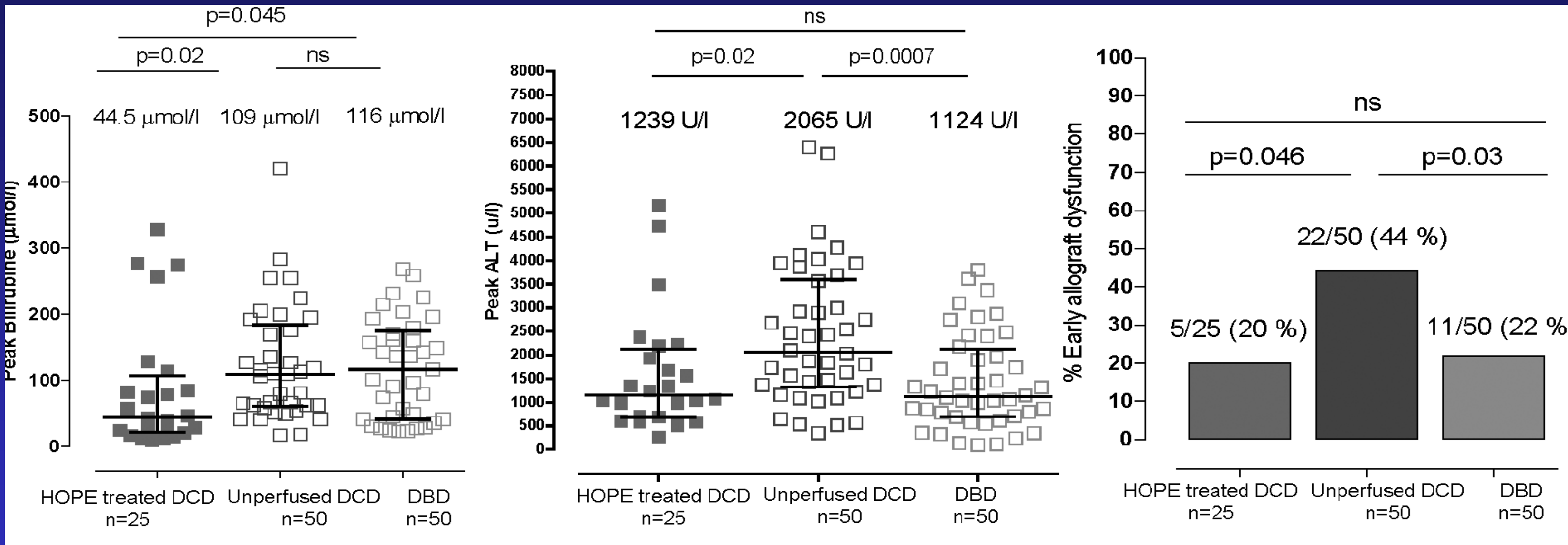
First Comparison of Hypothermic Oxygenated PErfusion Versus Static Cold Storage of Human Donation After Cardiac Death Liver Transplants

An International-matched Case Analysis

Philipp Dutkowski, MD, Wojciech G. Polak, MD, PhD,† Paolo Muiesan, MD,‡ Andrea Schlegel, MD,* Cornelia J. Verhoeven,† Irene Scalera, MD,‡ Michelle L. DeOliveira, MD,* Philipp Kron, MD,* and Pierre-Alain Clavien, MD, PhD, FACS (Hon)**

Hypothermic Oxygenated Machine Perfusion (HOPE-PV)

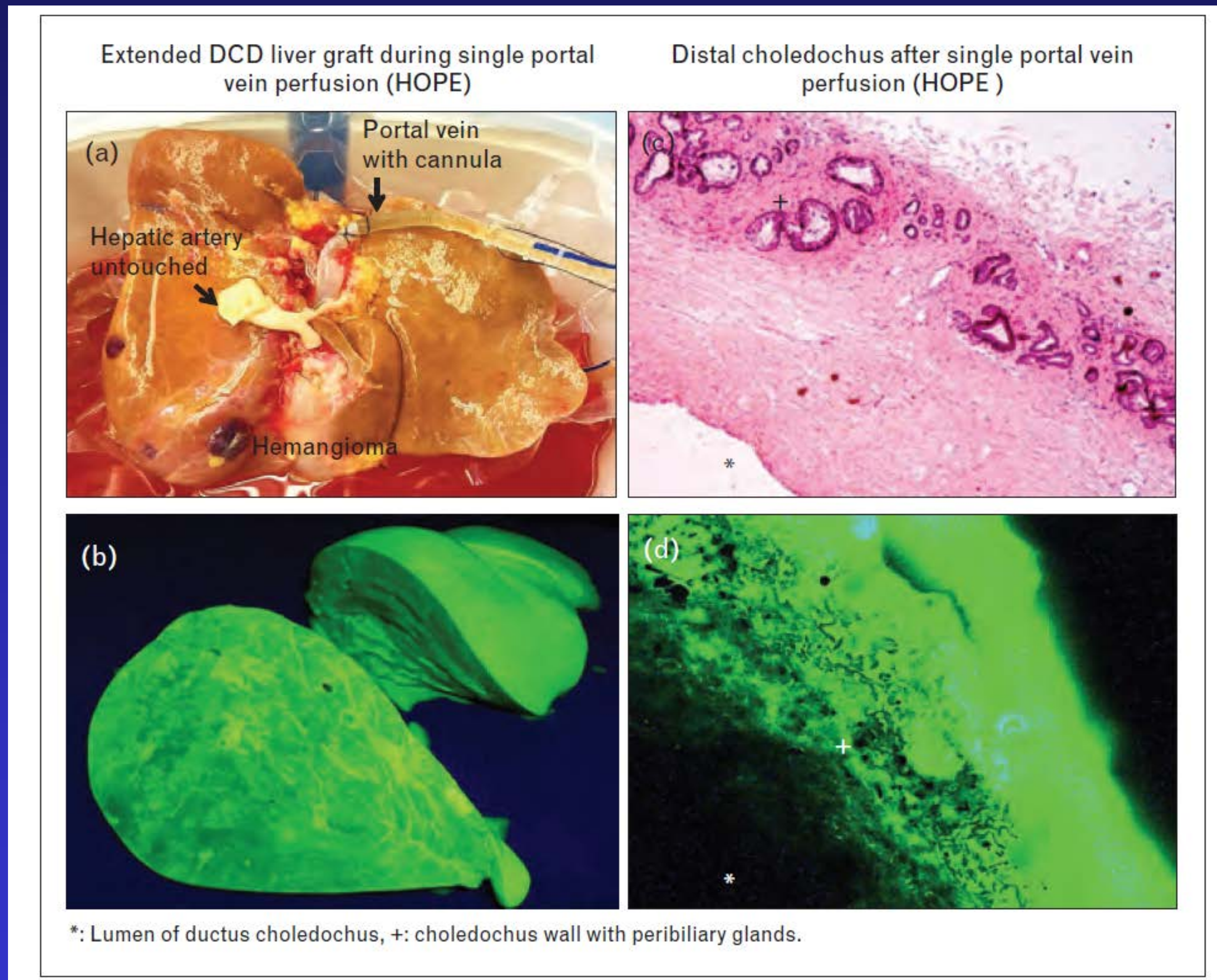


- **First comparison of HOPE-PV (n=25) vs SCS (n=50) in DCD livers**

- **Decrease in peak ALT** (HOPE-PV:1239U/L vs SCS:2065U/L; *P*=0.02)
- **Less intrahepatic cholangiopathy** (HOPE-PV:0% vs SCS:22%; *P*=0.015)
- **Decrease in EAD** (HOPE-PV: 20% vs SCS: 44%; *P*=0.046)
- **Improved 1 year graft survival** (HOPE-PV: 90% vs SCS: 69%; *P*=0.035)

Dutkowski P, Ann Surg. 2015;262(5):764-770

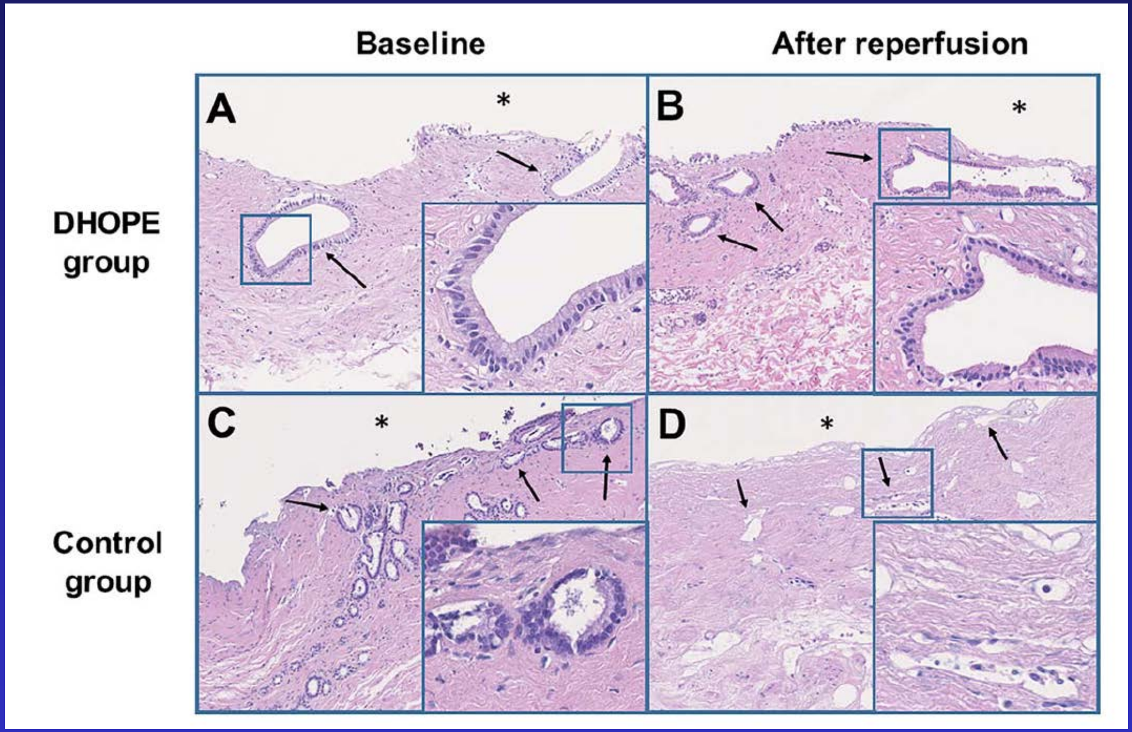
HOPE in Human DCD Allograft



Schlegel A, Kron P, and Dutkowski P Curr Opin Organ Transplant 2016, 21:308-314

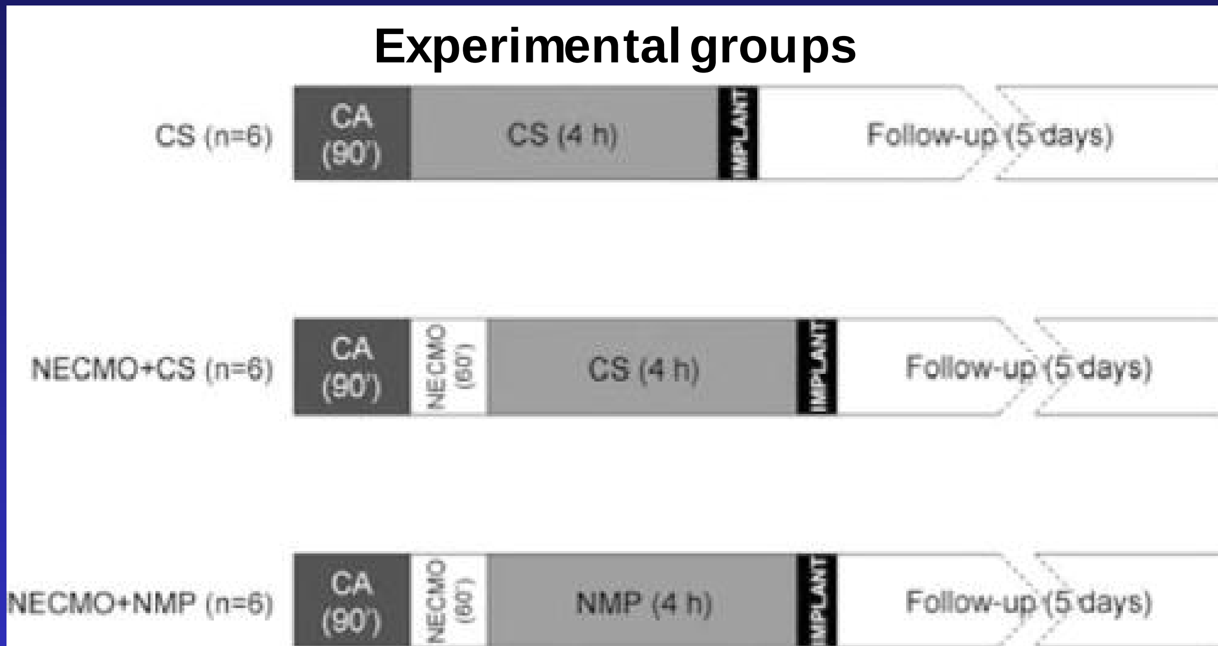
Hypothermic oxygenated machine perfusion (HOPE-D)

- DCD livers [HOPE-D: 10 livers vs SCS : 20 livers]
- Less stroma necrosis (p=0.002) and injury of the deep peribiliary glands (PBG) (p=0.02)in HOPE-D compared to the baseline in the SCS group



van Rijn R, et al. Liver Transpl. 2018;24(5):655-664

Superior Preservation of DCD Livers With Normothermic Perfusion



Survival
0
83%
100 %

NECMO + NMP resulted in superior survival, reduced pro-inflammatory responses, hsitological injury and endothelial activation

Fondevila et al et al, Ann Surg 2011

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 Clinic

None

Search Continues for Optimal Preservation Technique

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

Acknowledgment

Dr Nazia Selzer
Toronto General Hospiatal

Conclusions

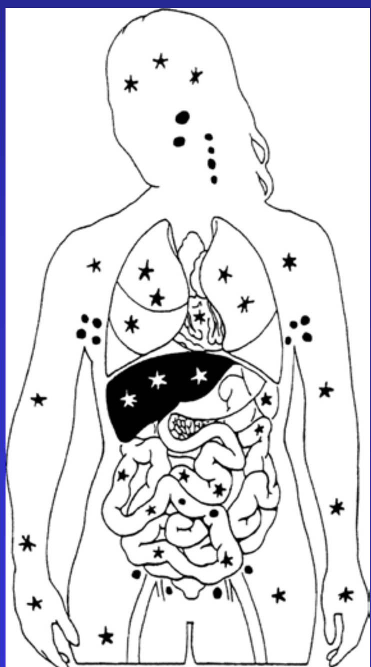
- Machine perfusion is in the early phase of development
- Perfusion technologies provide a great potential to influence allograft function
- It is not clear which type of perfusion would salvage extended criteria and DCD allografts
- Ongoing randomized controlled trials may clear the path for clinical utilization


RISE OF THE
MACHINES
CNBC
PRIME

Lancet. 1992 June 27; 339(8809): 1579–1582.

Cell migration, chimerism, and graft acceptance

Thomas E. Starzl, **Anthony J. Demetris**, **Noriko Murase**, **Suzanne Ildstad**, **Camillo Ricordi**, and **Massimo Trucco**
Pittsburgh Transplant Institute and the Departments of Surgery (T. E. Starzl, MD, N. Murase, MD, S. Ildstad, MD, C. Ricordi, MD), Pathology (A. J. Demetris, MD), and Pediatrics (M. Trucco, MD), University of Pittsburgh Health Science Center, Pittsburgh, Pennsylvania 15213, USA.



SUCCESSFUL EMERGENCY TRANSPLANTATION OF A LIVER ALLOGRAFT FROM A DONOR MAINTAINED ON EXTRACORPOREAL MEMBRANE OXYGENATION

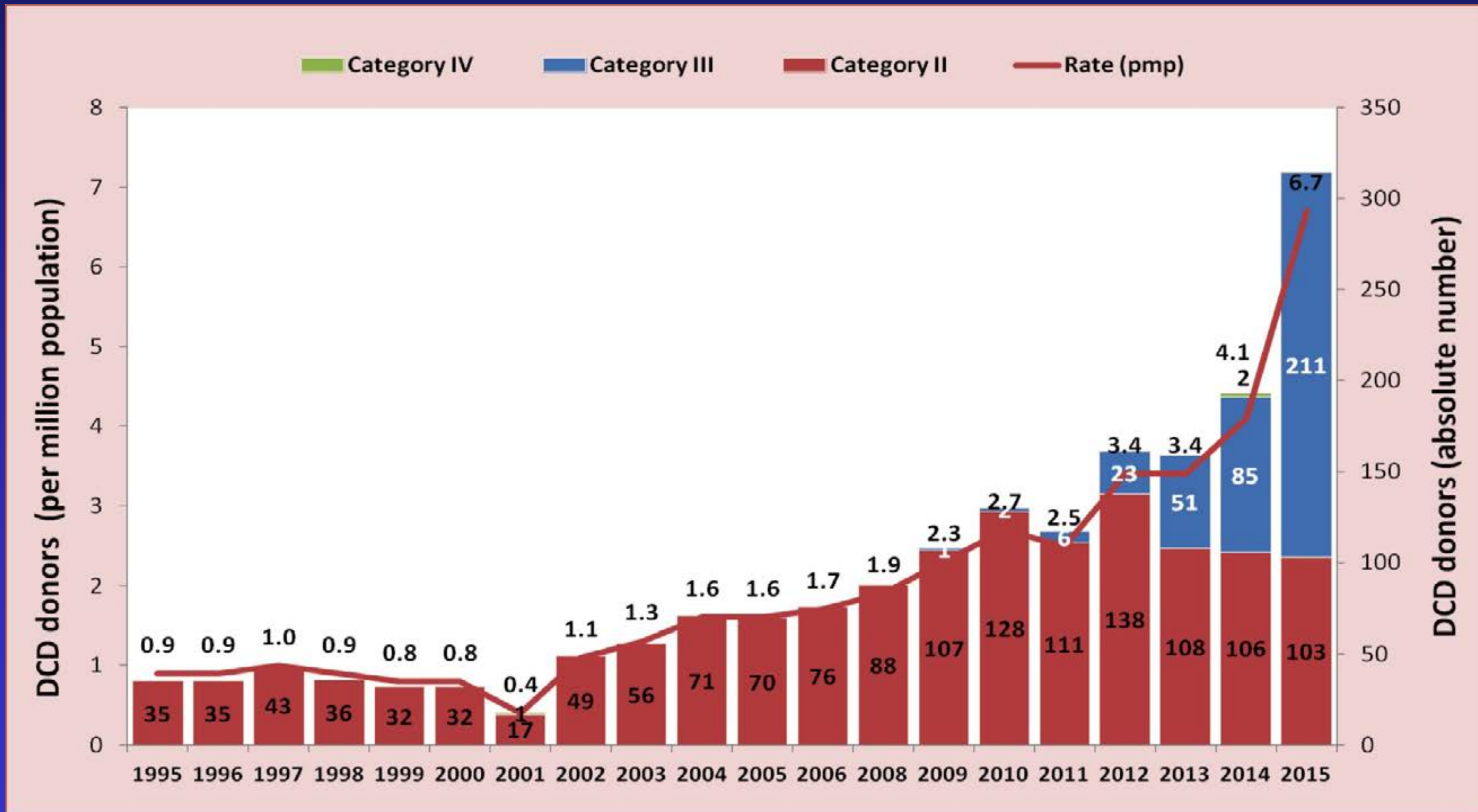
Johnson, Lynt B.; Plotkin, Jeffrey S.; Howell, Charles D.; Njoku, Mary J.; Kuo, Paul C.; Bartlett, Stephen T.

Departments of Surgery, Anesthesia, and Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201

Transplantation 63(6): 910-911, 1997

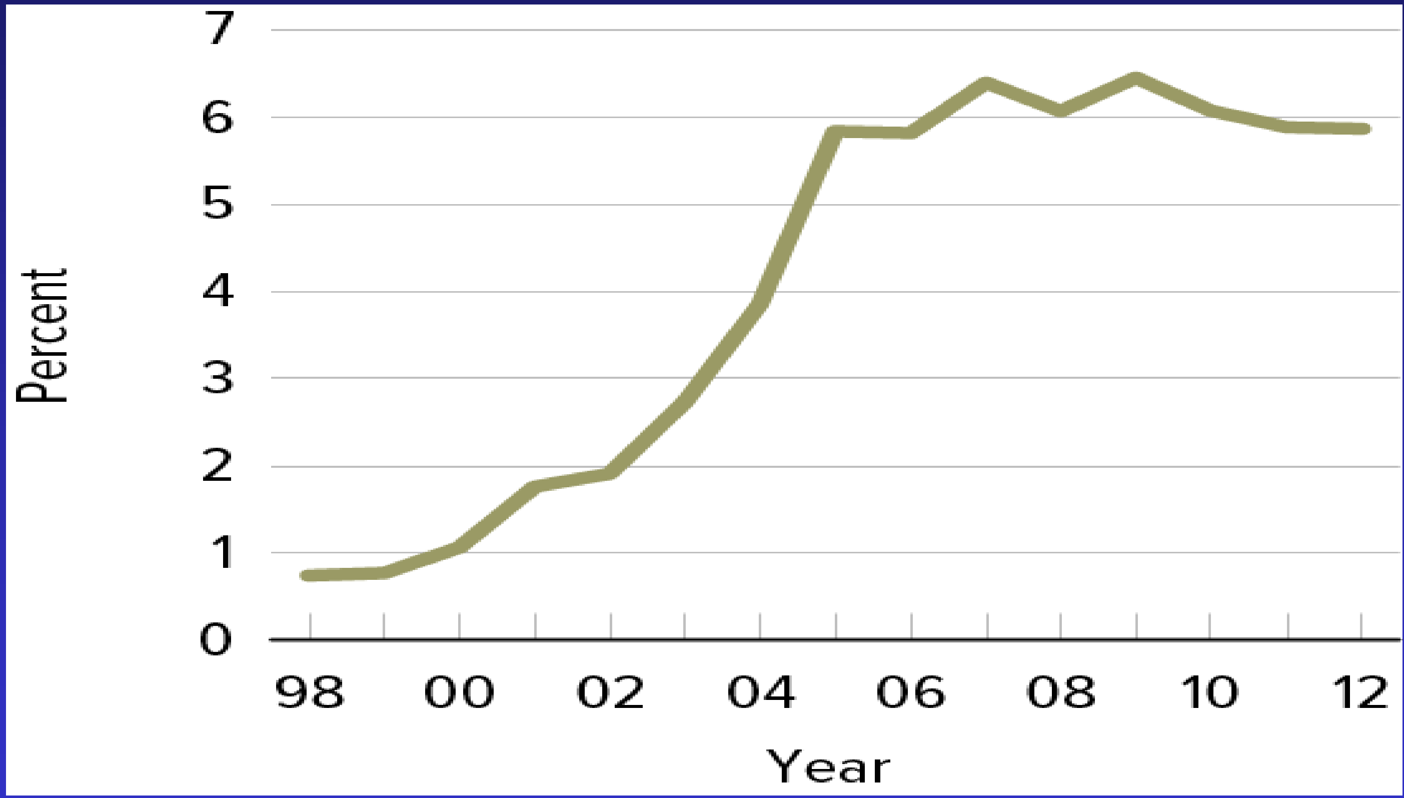
A liver allograft from a donor whose oxygen delivery was maintained by extracorporeal membrane oxygenation (ECMO) for 29 days before suffering an anoxic brain injury from ECMO dysfunction. Liver transplantation was successfully performed in a patient with fulminant hepatic failure.

DCD Activity in Spain According to Maastricht Categories

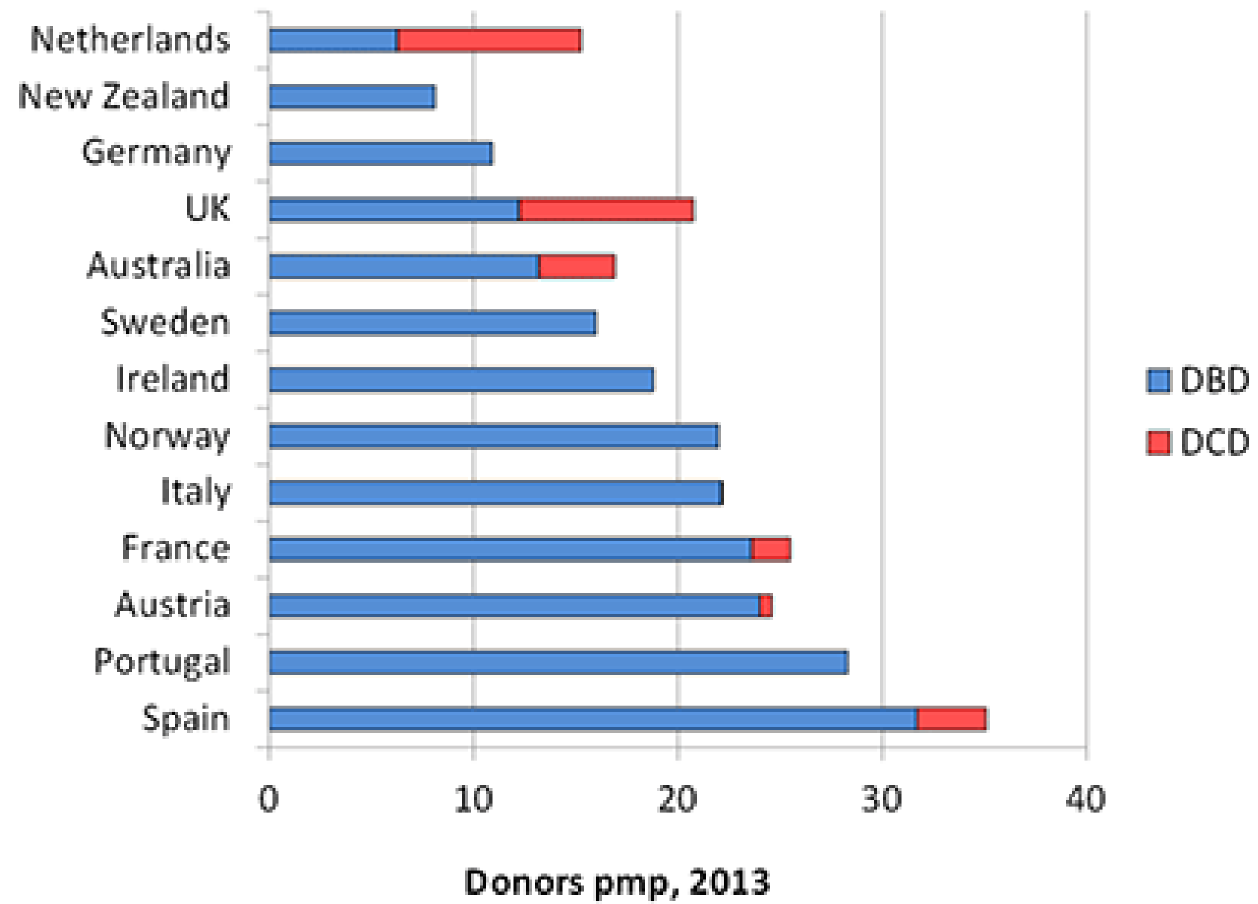


Fondevila C et al, AJT 2016

DCD Liver Utilization in the U.S



SRTR, 2012 Annual Data Report



Netherlands
New Zealand
Germany
UK
Australia
Sweden
Ireland
Norway
Italy
France
Austria
Portugal
Spain
0
10
20
30
40
Donors pmp, 2013
DBD
DCD

Surgery, 1963; 54:900-911

Extracorporeal perfusion for obtaining postmortem homografts

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