Prospects of Liver Machine Perfusion

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UMC Groningen Transplant Center
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Disclosure

- I have no financial links with any commercial company
- Nor any other potential conflicts of interest

Prospects of Liver Machine Perfusion

- Why do we need machine perfusion?
- What do we know about machine perfusion?
  - *Timing and temperature: Nomenclature*
  - *Available devices*
- Clinical experience
  - *Hypothermic (oxygenated) machine perfusion (HMP)*
  - *Controlled oxygenated rewarming (COR)*
  - *Normothermic machine perfusion (NMP)*
- How to move forward?

The Incentive for Machine Perfusion

- Shortage of suitable donor livers
- Increased use of extended criteria donors (ECD) and donation after circulatory death (DCD) livers
- Conventional static cold storage does not provide optimal preservation of ECD and DCD liver grafts
  - *Early graft dysfunction*
  - *More (biliary) complications*
  - *Retransplantation*
  - *Underutilization of the current donor pool*

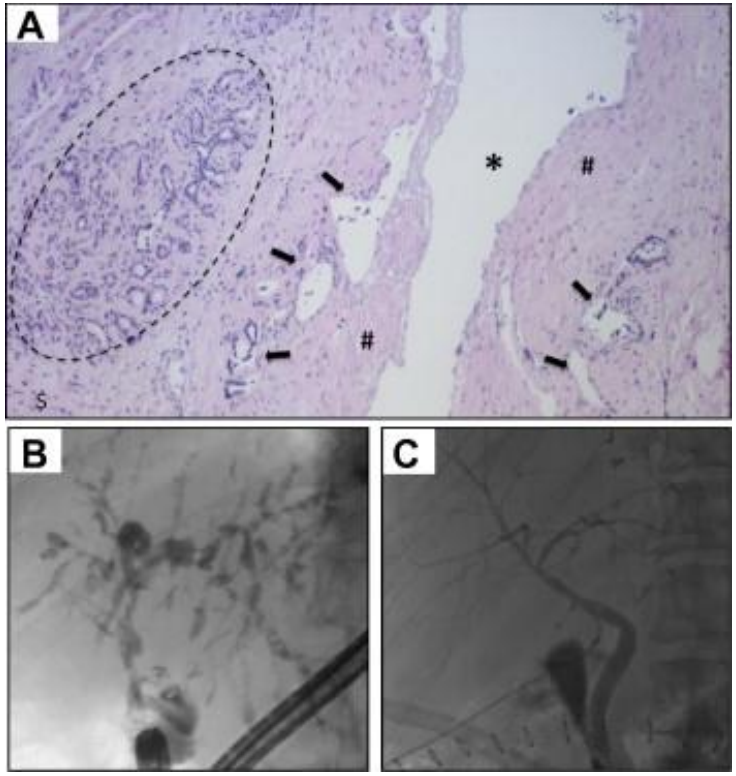
Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

J Hepatol 2014

Injury to peribiliary glands and vascular plexus before liver transplantation predicts formation of non-anastomotic biliary strictures

Sanna op den Dries[1,2], Andrie C. Westerkamp[1], Negin Karimian[1], Annette S.H. Gouw[3], Bote G. Bruinsma[4], James F. Markmann[2], Ton Lisman[1], Heidi Yeh[2], Korkut Uygun[4], Paulo N. Martins[2,†], Robert J. Porte[1,*,†]



At the time of transplantation (n=128):

- *Biliary epithelial lining of the large bile ducts is severely injured in >90% of the donor livers*

- *The degree of injury of the peribiliary glands and the peribiliary vasculature predicts the later development of biliary strictures*

Machine Preservation: An Alternative For Static Cold Storage

- Advantages:
  - Reduces ischemia / reperfusion injury
  - Prolonged preservation times
  - Better *ex situ* assessment of graft viability
  - Potential of (pharmacological) preconditioning
  - Potential to restore / regenerate damaged tissue
  - Increase in numbers and quality of donor organs

- Disadvantages:
  - More complex
  - More expensive than static cold storage

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Machine Perfusion of Livers

- Still Unanswered Questions -

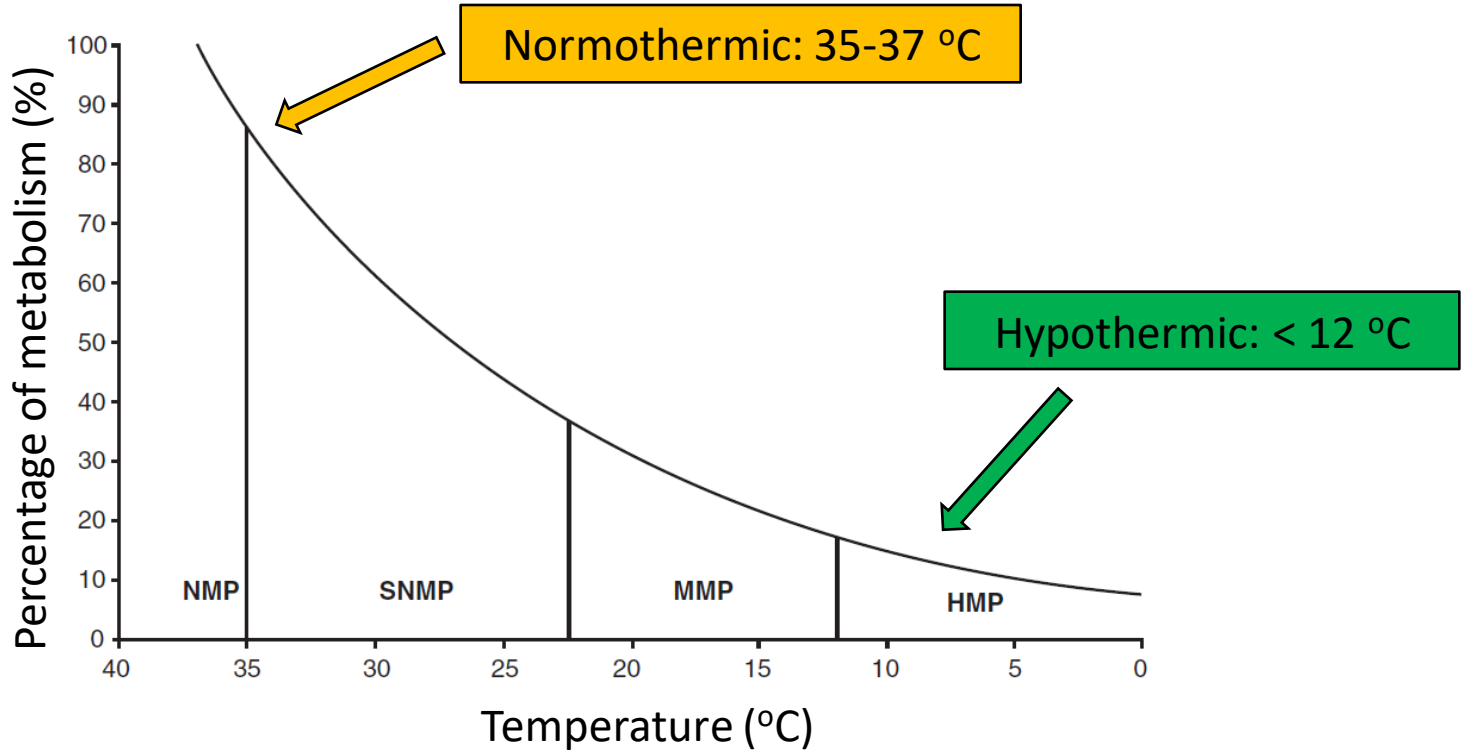
- What is the optimal temperature?
- Do we need to get rid of “the cold” completely?
- How long and when should we perfuse?
- What is the optimal perfusion pressure?
- What is the optimal oxygen carrier?
- What are good criteria for viability assessment?
  - Liver function
  - Bile duct viability

American Journal of Transplantation 2016; 16: 2932–2942
Wiley Periodicals Inc.

doi: 10.1111/ajt.13843

Machine Perfusion of Donor Livers for Transplantation: A Proposal for Standardized Nomenclature and Reporting Guidelines

S. A. Karangwa[1,2], P. Dutkowski[3], P. Fontes[4,5], P. J. Friend[6], J. V. Guarrera[7], J. F. Markmann[8], H. Mergental[9], T. Minor[10], C. Quintini[11], M. Selzner[12], K. Uygun[13], C. J. Watson[14] and R. J. Porte[1,*]



Type and Timing of Machine Perfusion

Procurement	Pre-transport	During Transport	Pre-implantation
Cold flush out	Cold storage	Cold transport	Cold

Liver Machine Perfusion Devices

Organ Recovery systems

- Hypothermic
- No active oxygenation

ORGAN ASSIST

LIVERASSIST

- Hypo- or normothermic (10 – 37 ºC)
- Controlled rewarming
- Oxygenation

- Normothermic

OrganOx
living organs for life

- Normothermic

TransMedics®
Bringing new life to organ transplant™

Prospect of Liver Machine Perfusion

- Why machine perfusion?
- What do we know?
- Timing and temperature: Nomenclature
- Available devices
- Clinical experience
  - *Hypothermic (oxygenated) machine perfusion (HMP)*
  - *Controlled oxygenated rewarming (COR)*
  - *Normothermic machine perfusion (NMP)*
- How to move forward?

Rationale for Hypothermic Oxygenated Machine Perfusion

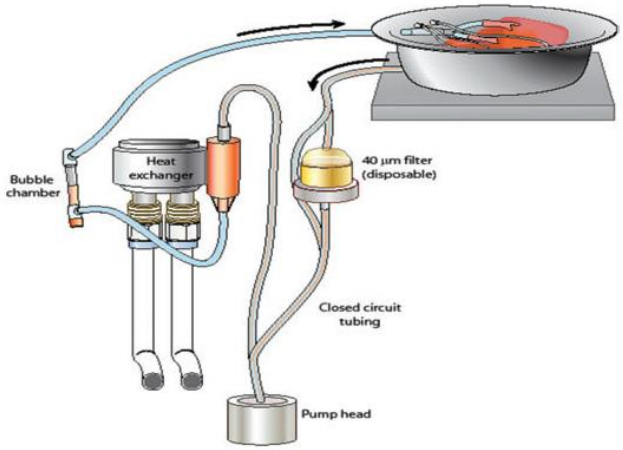
Procurement	Pre-transport	During Transport	Pre-implantation
	Cheap, simple, safe		Restoration of energy content Reducing of I/R injury
			
			
Cold flush out	Cold storage	Cold transport	Hypothermic Oxygenated MP

First Human Study of End-ischemic Machine Perfusion

Hypothermic Machine Preservation in Human Liver Transplantation: The First Clinical Series

J. V. Guarrera[a,*], S. D. Henry[a], B. Samstein[a], R. Odeh-Ramadan[a], M. Kinkhabwala[d], M. J. Goldstein[a], L. E. Ratner[a], J. F. Renz[c], H. T. Lee[b], R. S. Brown, Jr.[a] and J. C. Emond[a]

Am J Transplant 2010



<u>Non-oxygenated</u> Cold Perfusion

After Static Cold Storage and Transportation

Organ Recovery systems

Hypothermic *Oxygenated* Machine Perfusion

Research Article

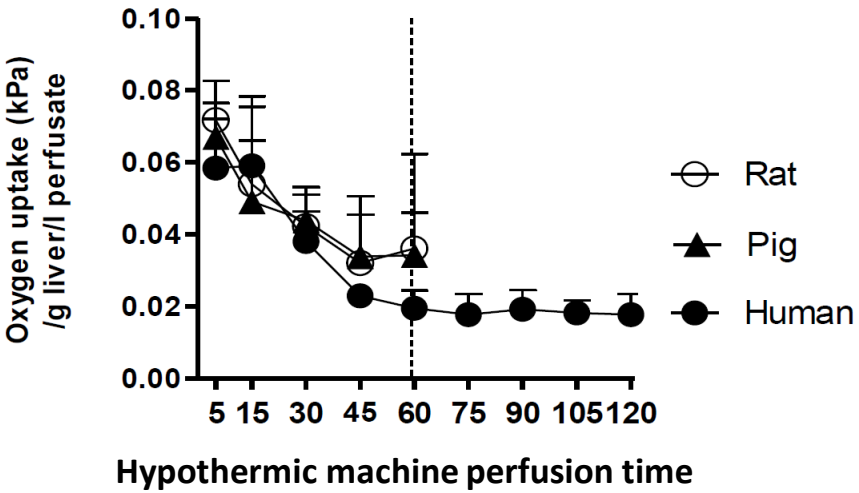
EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

HOPE for human liver grafts obtained from donors after cardiac death

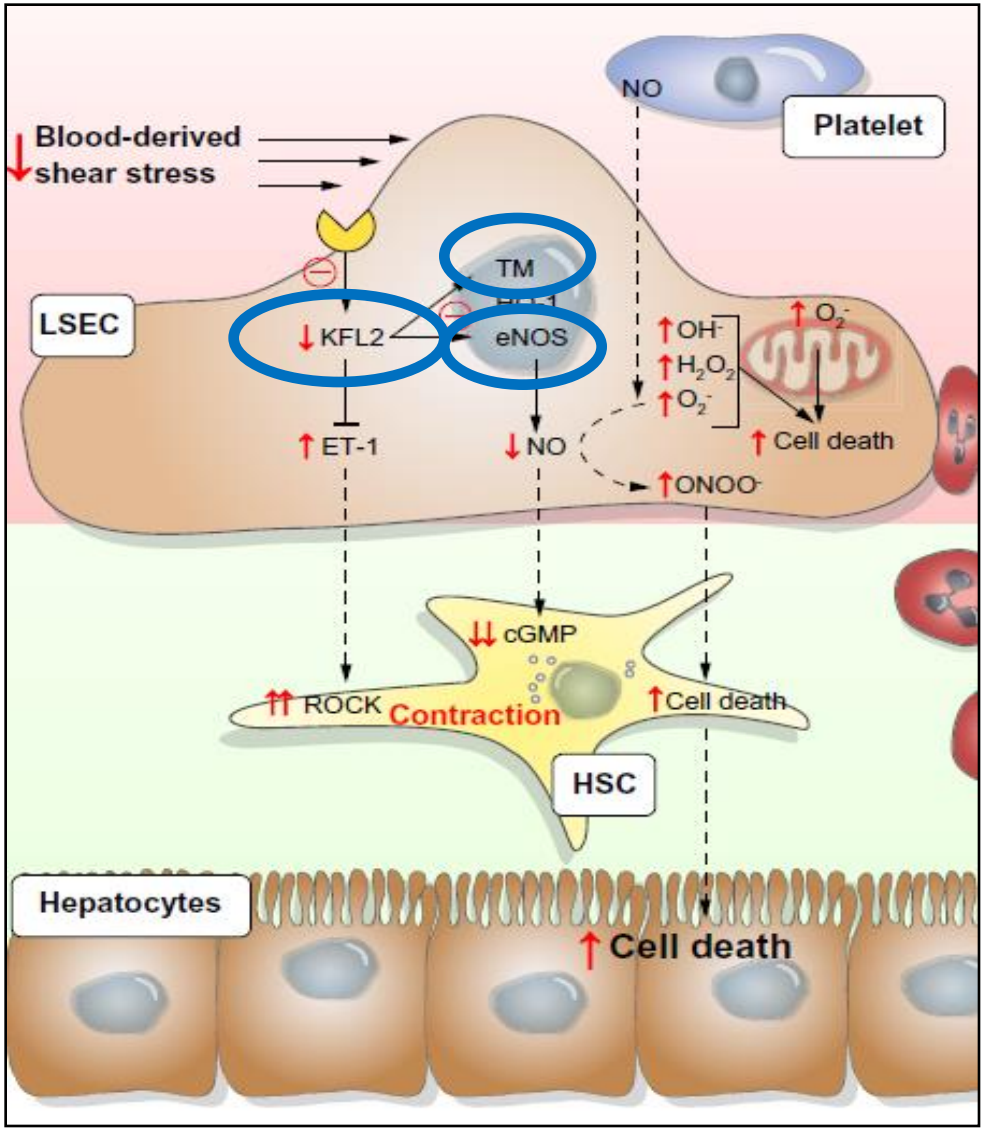
Philipp Dutkowski[1,†], Andrea Schlegel[1,†], Michelle de Oliveira[1], Beat Müllhaupt[2], Fabienne Neff[1], Pierre-Alain Clavien[1,*]

- Single portal perfusion (8ºC)
- Restores mitochondrial O_2 debt
- Reduced reperfusion injury:
  - *Less ROS production*
  - *Less apoptosis*
  - *Less nuclear injury*
  - *Less endothelial activation*
  - *Less Kupffer cell activation*

Oxygen uptake during HOPE (Δ pO2 inflow-outflow)



Biomechanical Stimulation of Endothelial Cells

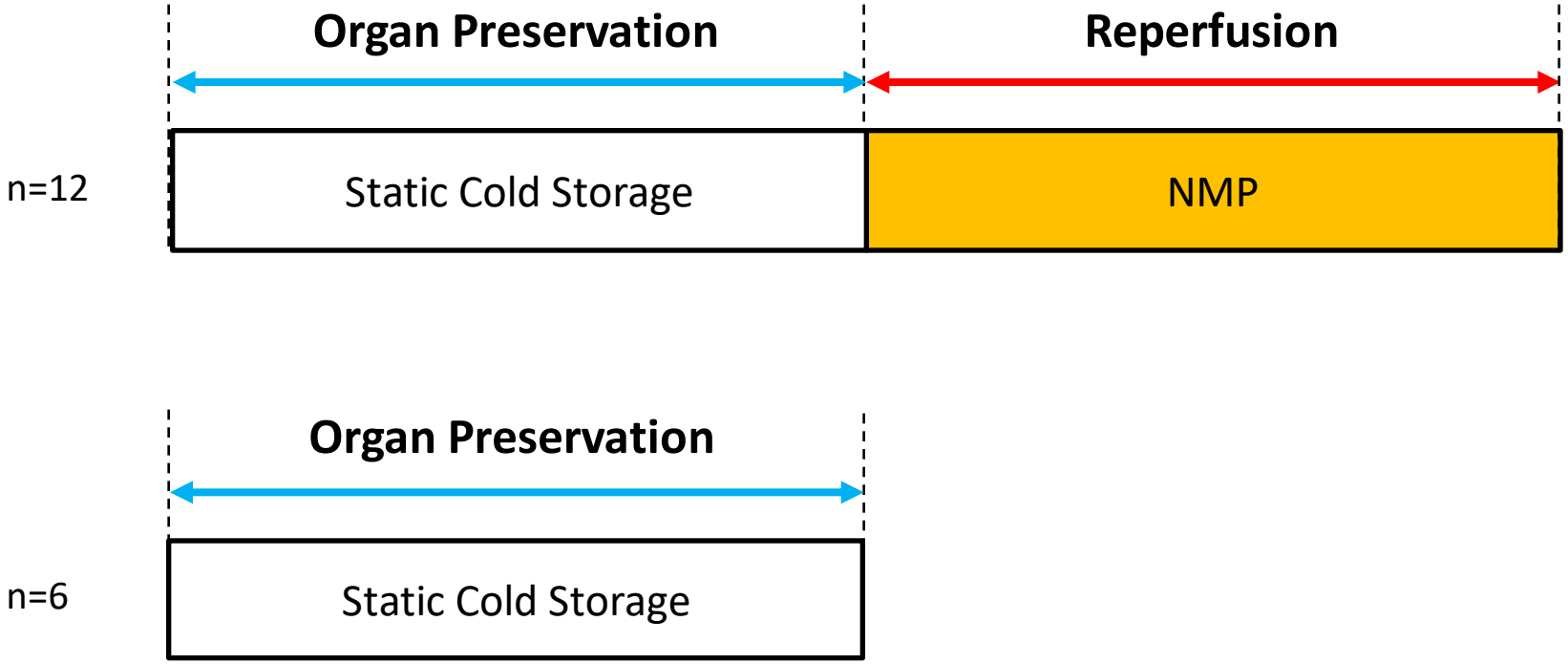


Liver Assist®
Oxygenated Dual Liver Perfusion

- Pressure controlled
- Temperature controlled (10 - 37°C)
- Pulsatile arterial flow
- Continuous portal flow
- Oxygenation

Hypothermic Oxygenated Machine Perfusion

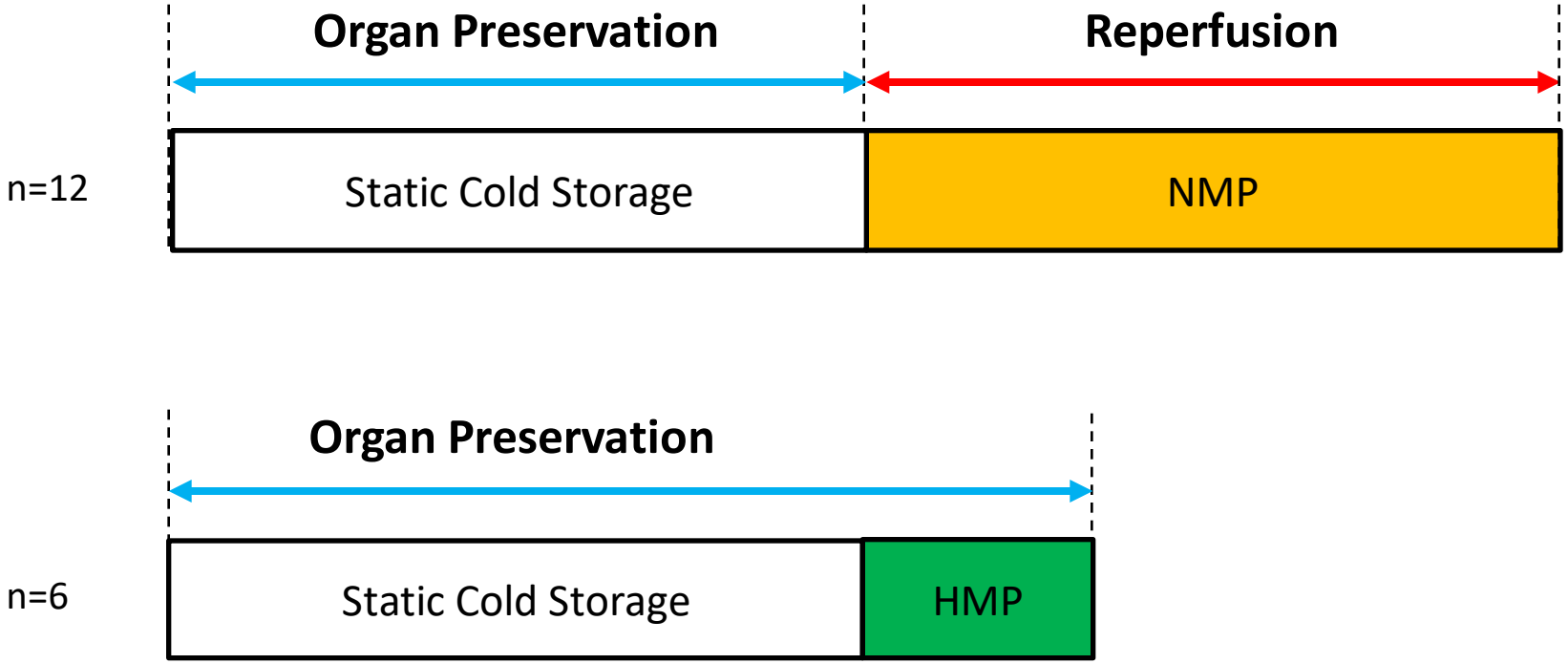
Human Discarded Livers



Westerkamp et al. Transplantation 2016

Hypothermic Oxygenated Machine Perfusion

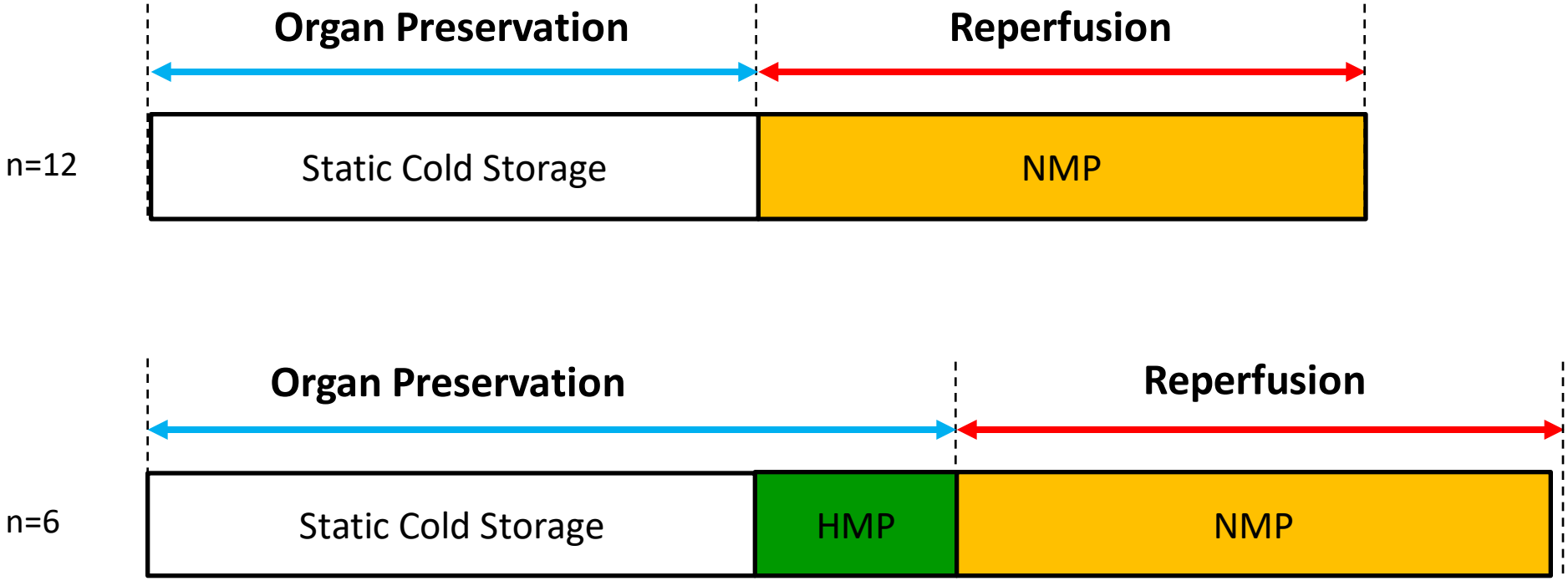
Human Discarded Livers



Westerkamp et al. Transplantation 2016

Hypothermic Oxygenated Machine Perfusion

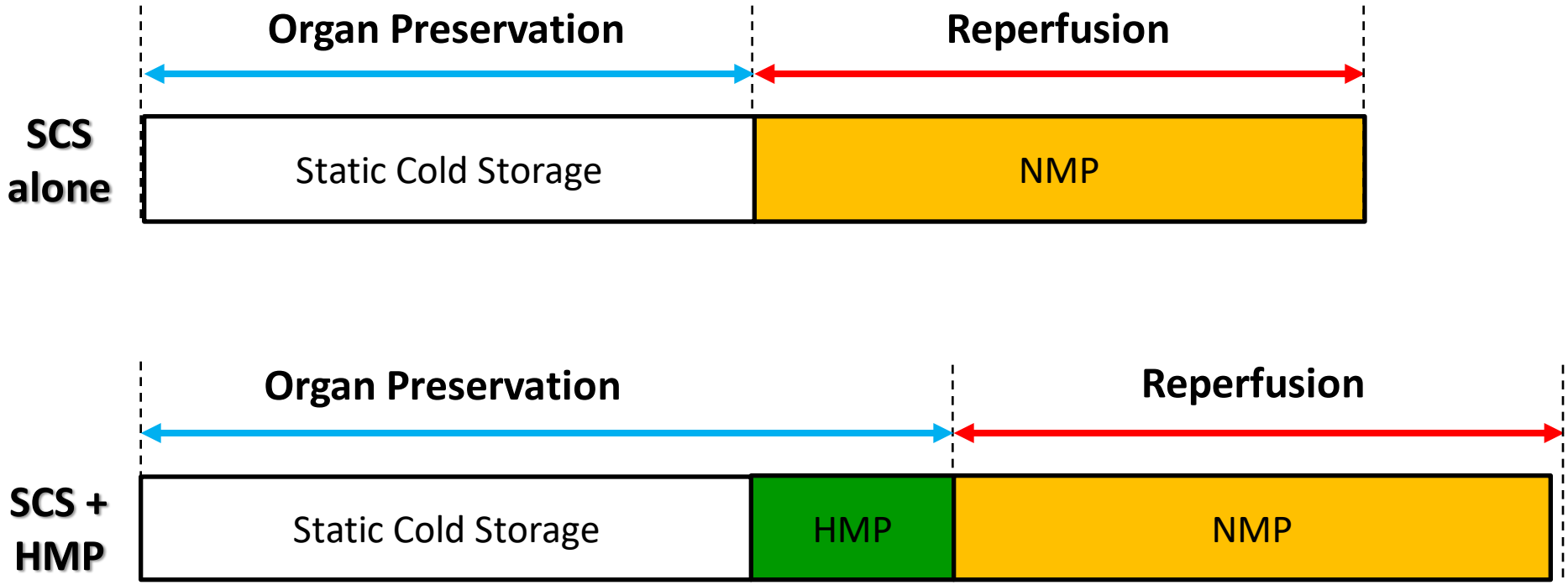
Human Discarded Livers



Westerkamp et al. Transplantation 2016

Hypothermic Oxygenated Machine Perfusion

Human Discarded Livers



Westerkamp et al. Transplantation 2016

Hypothermic Oxygenated Machine Perfusion

ATP Regeneration

6 hr Cold Storage

6 hr Cold

n = 12

n = 6

SCS + HMP

SCS only

AT

1 2

HMP (hrs)

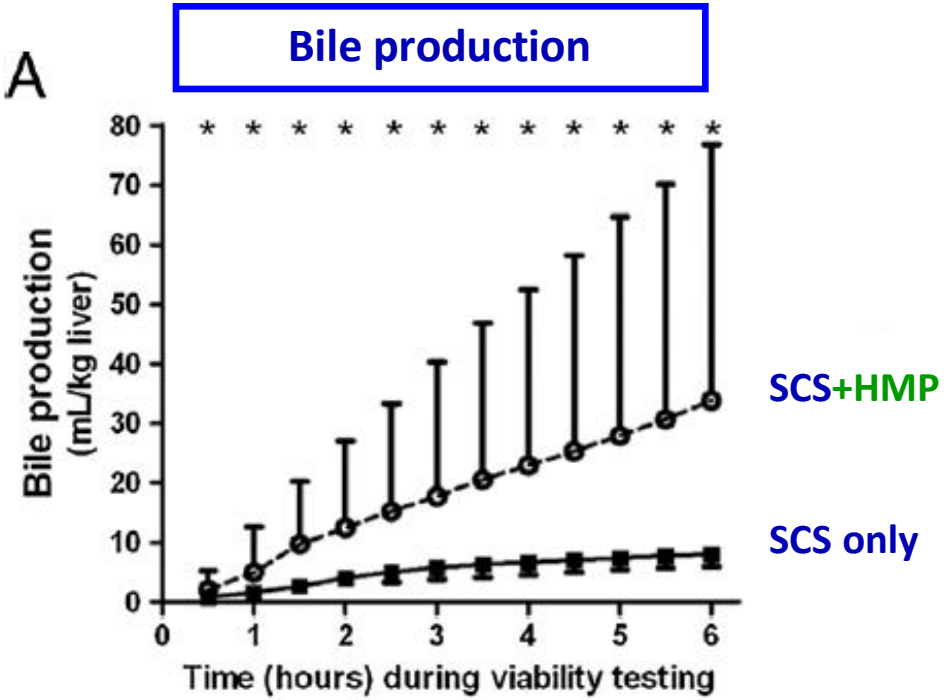
0 2 4 6

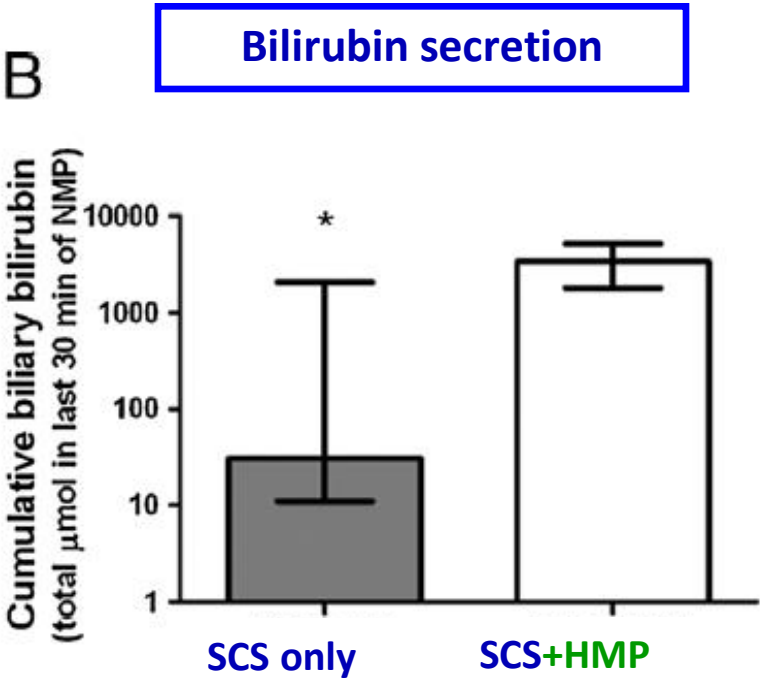
Viability testing (hrs)

Hypothermic Oxygenated Machine Perfusion

Study in 18 human DCD donor livers

Cumulative Bile Production

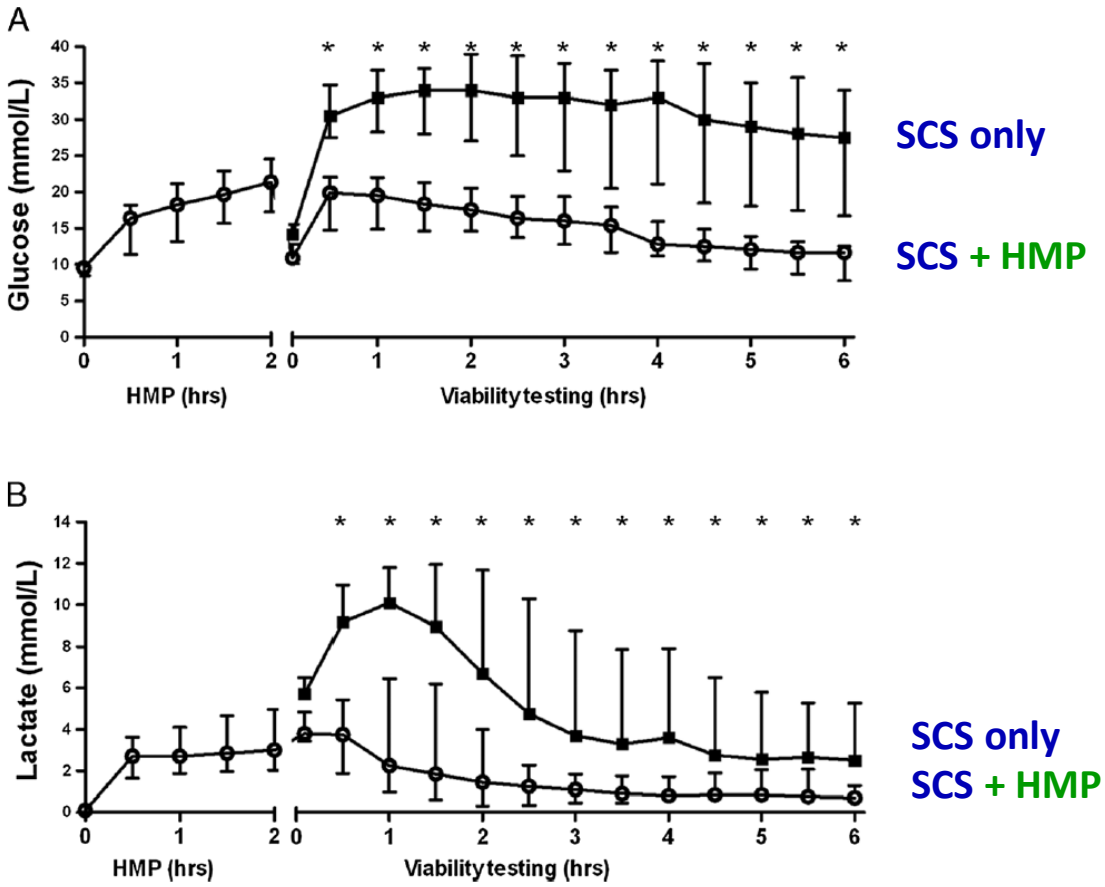




Westerkamp et al. Transplantation 2016

Hypothermic Oxygenated Machine Perfusion

Glucose and Lactate Concentration in Perfusate



Westerkamp et al. Transplantation 2016

DHOPE in DCD Liver Transplantation

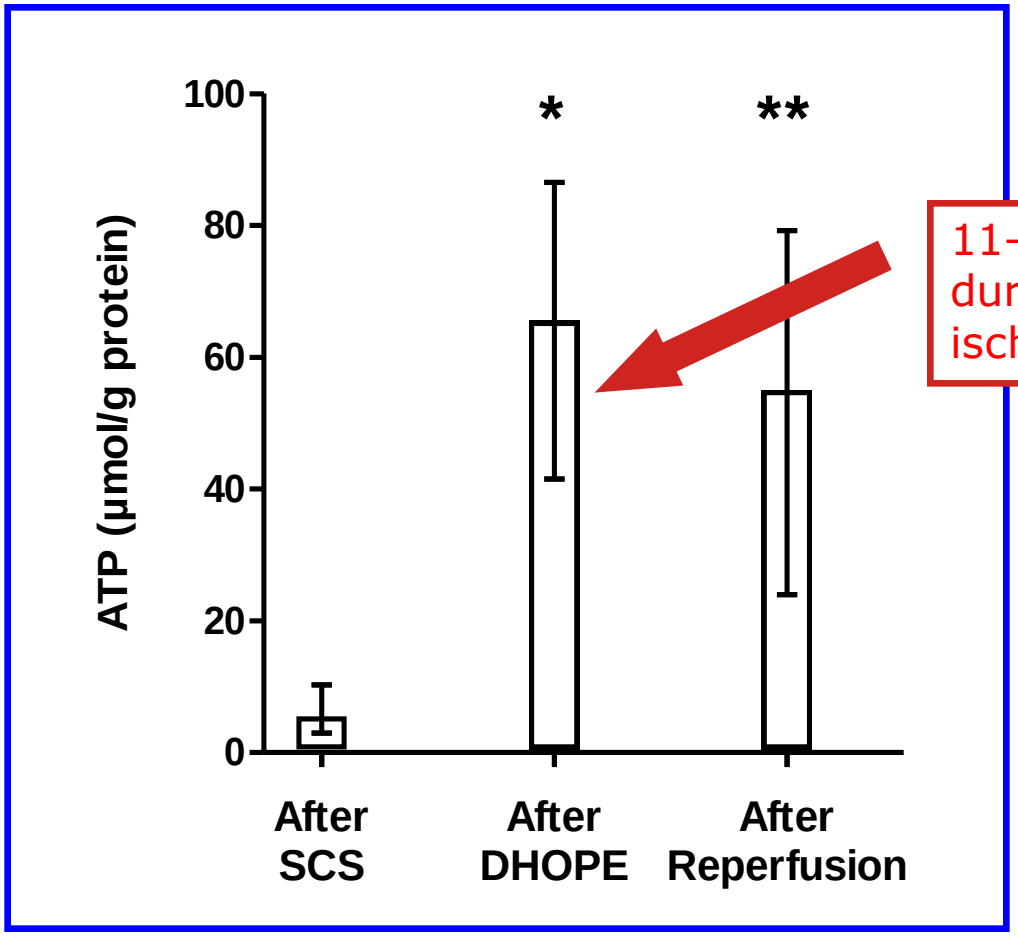
- First in Man Study -

- Aim: Safety and feasibility
- Intervention: DHOPE (dual hypothermic oxygenated perfusion)
- Inclusion: 10 consecutive DCD liver transplantations (2014)
- Controls: 20 previous DCD liver transplantations (2008-2014)

  Matched: donor age, MELD score, and asystole time
- Endpoints: Technical problems, microbiological tests, early graft function, complications, graft and patient survival

Van Rijn et al. Br J Surg 2017

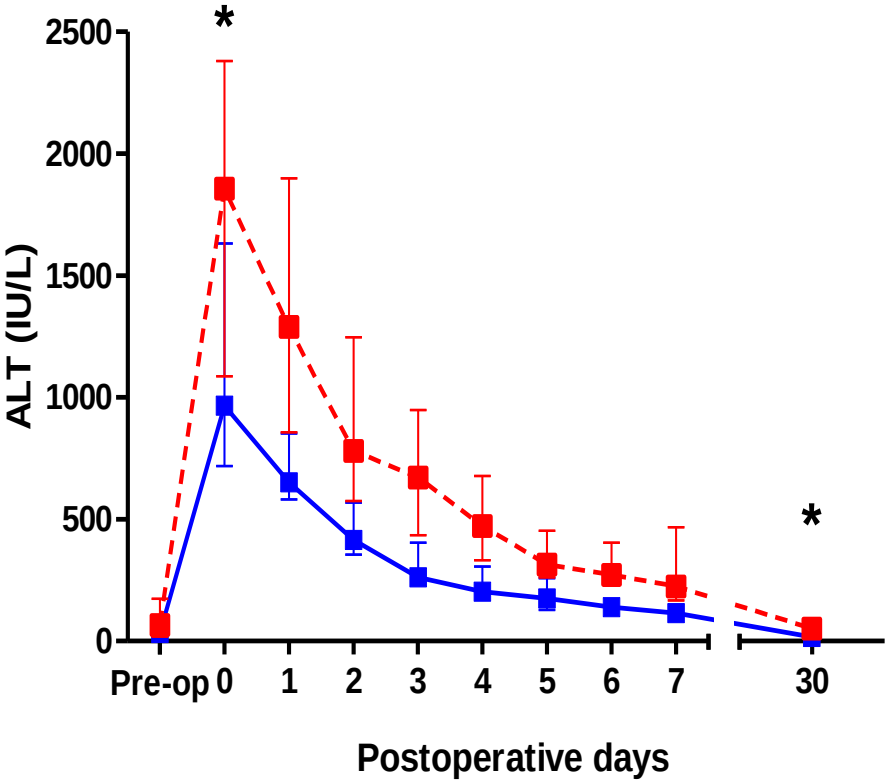
ATP Regeneration Before Transplantation During Hypothermic Oxygenated Machine Perfusion (DHOPE)

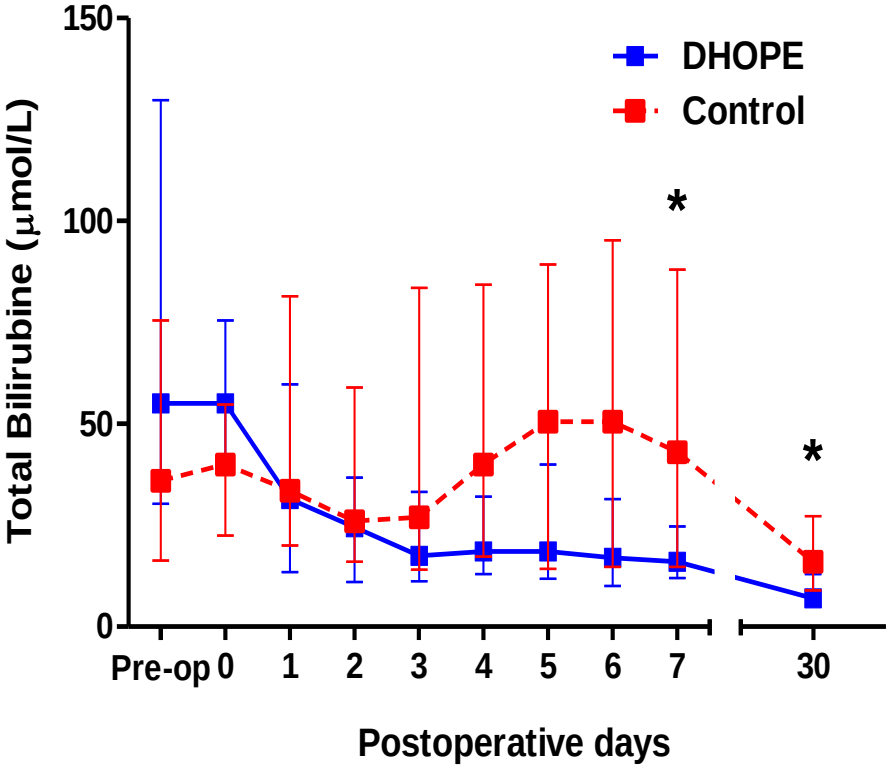


11-fold increase of ATP during 2hrs of end-ischemic DHOPE

Van Rijn et al. Br J Surg 2017

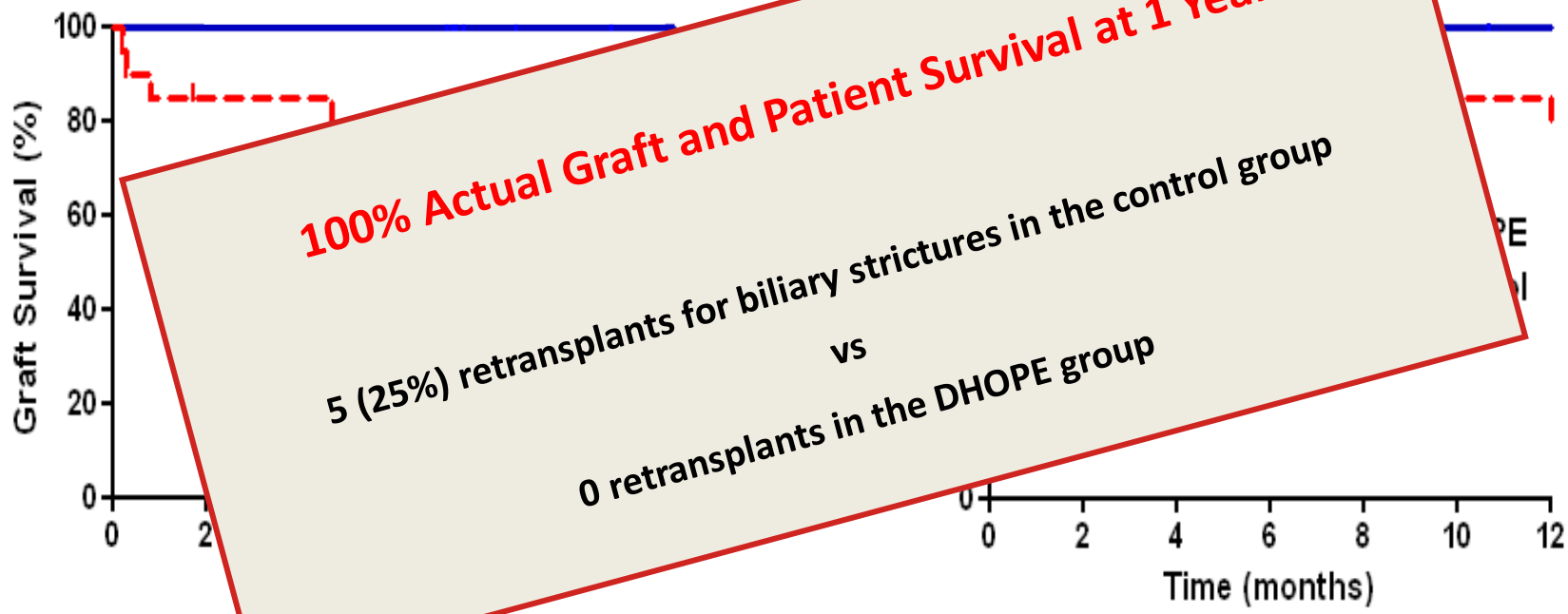
Postoperative Serum ALT and Bilirubin





Van Rijn et al. Br J Surg 2017

Graft and Patient Survival After DCD Liver Transplantati



100% Actual Graft and Patient Survival at 1 Year

5 (25%) retransplants for biliary strictures in the control group

vs

0 retransplants in the DHOPE group

Number at risk	Baseline	1 month	6 months	12 months
DHOPE	10	10	10	10
Control	20	16	15	12

Baseline	1 month	6 months	12 months
10	10	10	10
20	20	19	17

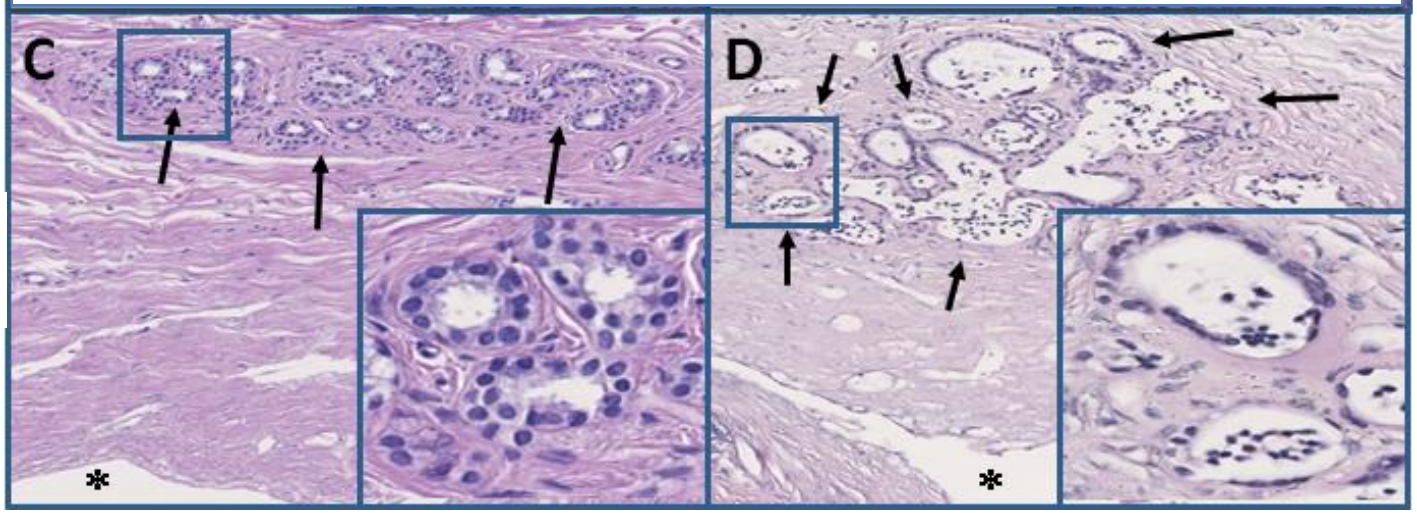
Van Rijn et al. Br J Surg 2017

Histology of Large Bile Ducts

BEFORE REPERFUSION AFTER REPERFUSION

DHOPE

CONTROL



Van Rijn, Gouw, Porte, et al. Unpublished data

Hypothermic Oxygenated Machine Perfusion

Clinical Trials in Europe

- **Pilot Studies (Zürich and Groningen)**
  - End-ischemic (after static cold storage) (dual) hypothermic oxygenated machine perfusion [(D)HOPE] of DCD livers

- **Multi-center Randomized Clinical Trials (*in progress*)**
  - ***HOPE-DBD Trial*** *(PI: Dutkowski)*
    - End-ischemic hypothermic oxygenated machine perfusion versus static cold storage alone of DBD livers
    - Primary endpoint: Composite complications
  - ***DHOPE-DCD Trial*** *(PI: Porte)*
    - End-ischemic dual hypothermic oxygenated machine perfusion versus static cold storage alone of DCD livers
    - Primary endpoint: biliary strictures

Prospect of Liver Machine Perfusion

- Why machine perfusion?
- What do we know?
- Timing and temperature: Nomenclature
- Available devices
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Controlled Oxygenated Rewarming

Procurement	Pre-transport	During Transport	Pre-implantation
	Cheap, simple, safe		Restoration of energy content Reducing of I/R injury
			
			
Cold flush out	Cold storage	Cold transport	Controlled oxygenated rewarming

Controlled Oxygenated Rewarming

Original Clinical Science—Liver

Transplantation 2016

Controlled Oxygenated Rewarming of Cold Stored Livers Prior to Transplantation: First Clinical Application of a New Concept

Dieter P. Hoyer, MD,[1] Zoltan Mathé, MD, PhD,[1] Anja Gallinat, MD,[1] Ali C. Canbay, MD,[2] Juergen W. Treckmann, MD,[1] Ursula Rauen, MD,[3] Andreas Paul, MD, MSc,[1] and Thomas Minor, MD[4]

- 6 ECD livers transplanted in Essen
- Machine-assisted slow oxygenated rewarming to 20ºC during 90 min
- 106 historical ECD controls

Results:

- 50% lower peak serum transaminases (AST and ALT)
- 6-months graft survival 100% vs 81% (p=0.24)

Prospect of Liver Machine Perfusion

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Two Types of Normothermic Machine Perfusion

Procurement	Pre-transport	During Transport	Pre-implantation
			
Cold flush out	Normothermic MP	Normothermic MP	Normothermic MP

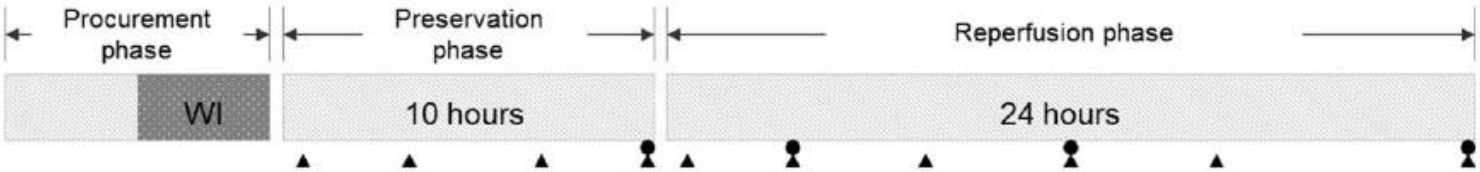
			
Cold flush out	Cold storage	Cold transport	Normothermic MP

LIVER TRANSPLANTATION 00:00–00, 2014

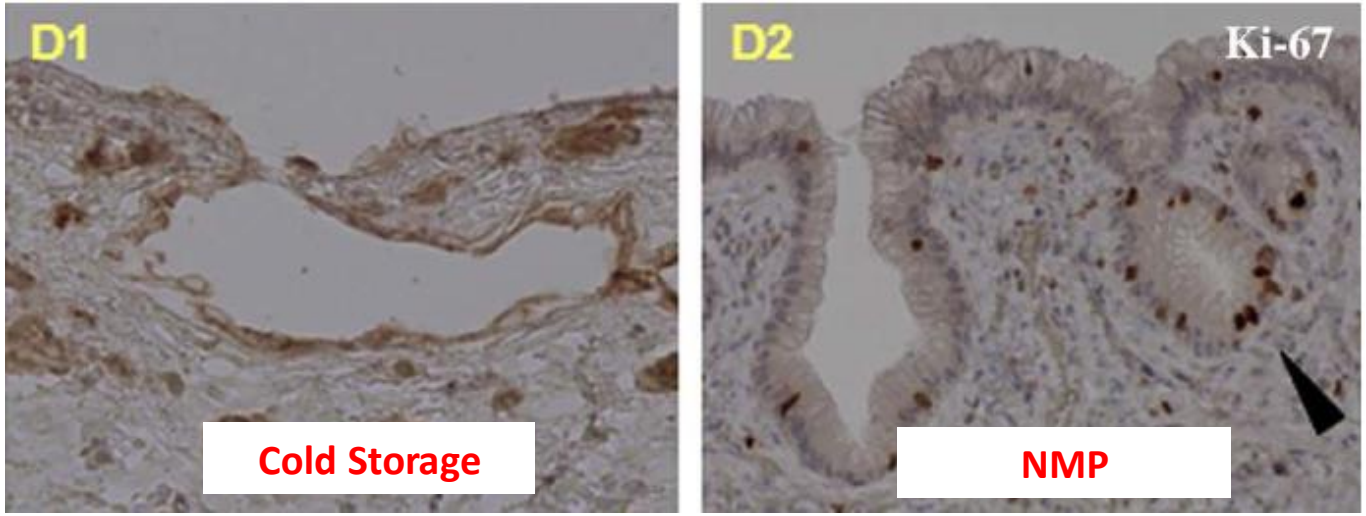
ORIGINAL ARTICLE

Sanguineous Normothermic Machine Perfusion Improves Hemodynamics and Biliary Epithelial Regeneration in Donation After Cardiac Death Porcine Livers

Qiang Liu,[1] Ahmed Nassar,[1] Kevin Farias,[1] Laura Buccini,[1] William Baldwin,[2] Martin Mangino,[3] Ana Bennett,[4] Colin O'Rourke,[1] Toshiro Okamoto,[1] Teresa Diago Uso,[1] John Fung,[1] Kareem Abu-Elmagd,[1] Charles Miller,[1] and Cristiano Quintini[1]



Bile Duct Histology



Normothermic Machine Preservation

Liver Transplantation After *Ex Vivo* Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial

R. Ravikumar[1,2,†], W. Jassem[3,†], H. Mergental[4], N. Heaton[3], D. Mirza[4], M. T. P. R. Perera[4], A. Quaglia[3], D. Holroyd[2], T. Vogel[1], C. C. Coussios[2] and P. J. Friend[1,*]

Am J Transplant 2016

- Normothermic machine perfusion <u>from donor to recipient</u>
- Organox Metra device
- 20 Liver transplants (Kings and Birmingham)
  - *16 DBD liver grafts*
  - *4 DCD liver grafts*
- Matched 1:2 with cold stored livers

Liver Transplantation After *Ex Vivo* Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial

R. Ravikumar[1,2,†], W. Jassem[3,†], H. Mergental[4], N. Heaton[3], D. Mirza[4], M. T. P. R. Perera[4], A. Quaglia[3], D. Holroyd[2], T. Vogel[1], C. C. Coussios[2] and P. J. Friend[1,*]

Am J Transplant 2016

Table 2: Clinical outcomes of normothermic machine perfusion (NMP) and control livers

	Total			
Outcomes	NMP (n = 20)	Control (n = 40)	Risk ratio/effect size (95% CI)	p-value
30-day graft survival, n (%)	20 (100)	39 (97.5)	1.03 (0.98–1.08) RR	1.00
PNF, n (%)	0	0		1.000
EAD, n (%)	3 (15)	9 (22.5)	0.67 (0.20–2.19) RR	0.734
Peak AST within 7 days (IU/L), median (range)	417 (84–4681)	902[1] (218–8786)	−0.44 (−0.98 to 0.11) ES	0.034
Bilirubin on day 7 (μmol/L), median (range)	25 (8–211)	30[1] (9–221)	−0.23 (−0.77 to 0.32) ES	0.203
INR on day 7, median (range)	1.05 (0.88–1.40)	1.03 (0.90–2.22)[1]	−0.16 (−0.70 to 0.38) ES	0.922
ALP on day 7 (U/L)	245 (81–568)	243 (76–743)[1]	−0.11 (−0.65 to 0.43) ES	0.798
ITU stay (days), median (range)	3 (1–8)	3 (1–41)[1]	−0.42 (−0.96 to 0.13) ES	0.459
Hospital stay (days), median (range)	12 (6–34)	14 (8–88)[1]	−0.44 (−0.98 to 0.11) ES	0.100
30-day mortality (%)	0 (0)	1 (2.5)		1.000
6-month survival, n (%)	20 (100)	39 (97.5)	1.03 (0.98–1.08) RR	1.000

End-ischemic Normothermic Machine Perfusion

American Journal of Transplantation
Wiley Periodicals Inc.

doi: 10.1111/ajt.12187

Brief Communication

Ex vivo Normothermic Machine Perfusion and Viability Testing of Discarded Human Donor Livers

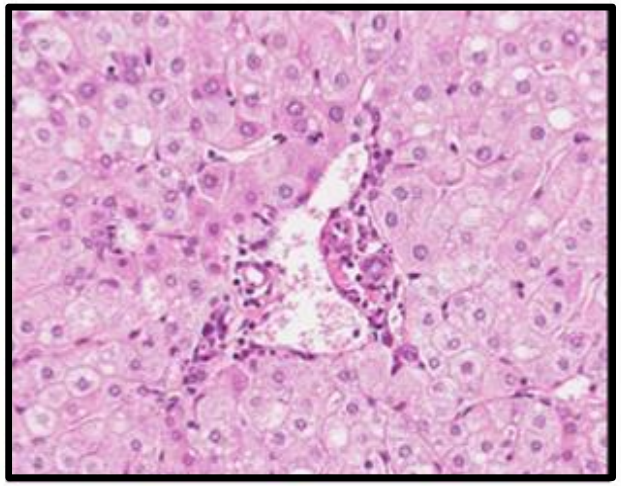
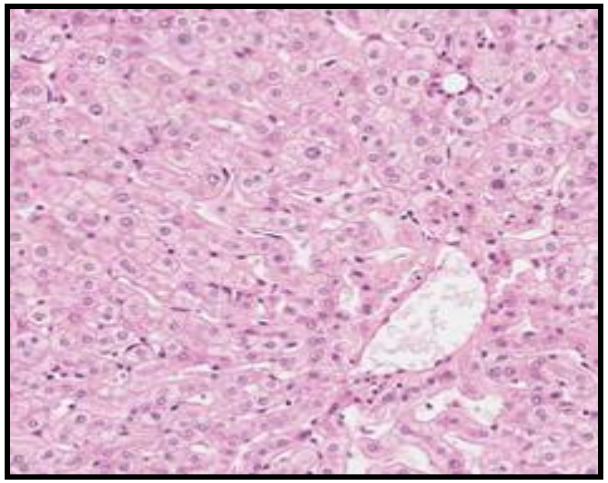
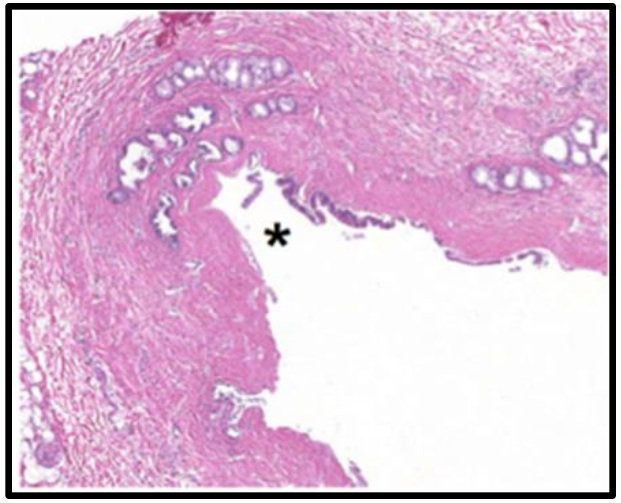
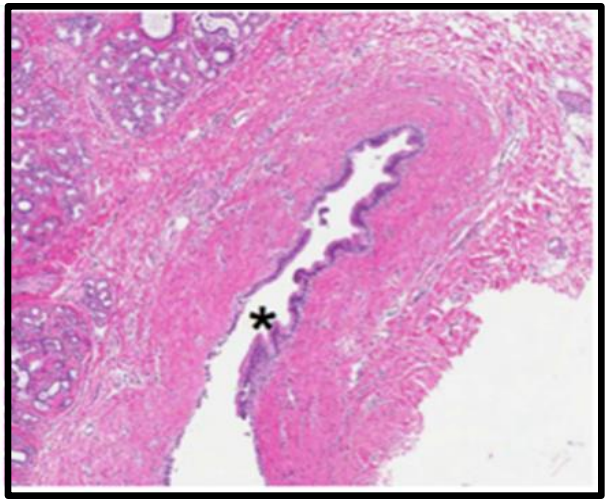
S. op den Dries[a,b], N. Karimian[a,b], M. E. Sutton[a,b], A. C. Westerkamp[a,b], M. W. N. Nijsten[c], A. S. H. Gouw[d], J. Wiersema-Buist[b], T. Lisman[a,b], H. G. D. Leuvenink[b] and R. J. Porte[a,*]

Am J Transplant 2013

- The first reported study on normothermic perfusion of human livers
- Proof of technical feasibility of NMP
- 6 hours of normothermic, oxygenated perfusion
- Perfusion fluid: RBC, FFP, nutrients, vitamins, trace elements, antibiotics

- Allows functional assessment of the liver before transplantation
- Potential: Therapeutic intervention and (re)conditioning

Histology After 6 hr of Normothermic Perfusion

	Before	After 6 hr of perfusion
Liver Parenchyma		
Extrahepatic Bile Duct		

End-ischemic Normothermic Machine Perfusion

American Journal of Transplantation 2016; 16: 353–357
Wiley Periodicals Inc.

doi: 10.1111/ajt.13448

Case Report

Preimplant Normothermic Liver Perfusion of a Suboptimal Liver Donated After Circulatory Death

C. J. E. Watson[1,*], V. Kosmoliaptsis[1], L. V. Randle[1], N. K. Russell[1], W. J. H. Griffiths[1], S. Davies[2], H. Mergental[3] and A. J. Butler[1]

Cambridge, UK

LIVER TRANSPLANTATION 22:120–124, 2016

LETTERS FROM THE FRONTLINE

First Human Liver Transplantation Using a Marginal Allograft Resuscitated by Normothermic Machine Perfusion

Perera T, Mergental H, et al.

Birmingham, UK

End-ischemic Normothermic Machine Perfusion

A Word of Caution

- NMP is complex and requires experience
- Both the Cambridge and Birmingham team have reported the loss of a patient due to PNF of a ECD liver that was transplanted after end-ischemic NMP
- A high percentage of biliary complications has been noted after transplantation of DCD livers that were treated with end-ischemic NMP
  - *Watson, oral communication at the Groningen Workshop on Liver Machine Perfusion 2015*

Normothermic Machine Preservation

- Single center report from Edmonton, Canada
- 10 patients
  - 4 DCD, 6 DBD
- Matched 1:3 with a control group of SCS livers
- Device: Organox Metra
- NMP from donor to recipient

Results:

- 6-month graft survival 80% in NMP group vs 100% in SCS group (p=0.01)
- ICU and hospital stays were significantly more prolonged in the NMP group
- One liver was lost (not transplanted) due a technical problem during NMP

Bral, et al. Am J Transpl 2016

Hypothermic versus Normothermic

- **Hypothermic Oxygenated Machine Perfusion**
  - Resuscitation of the mitochondria
  - Restoration of ATP, recovery of oxygen debt
  - Reduction of I/R injury
  - Relatively simple and safe
  - Relatively low costs

0-12°C

What Is The Best Strategy?

Procurement	Pre-transport	During Transport	Pre-implantation
Resolution of oxygen debt Restoration of cellular energy content in DCD donor livers		Cheap, simple, safe	Restoration of energy content Reducing of I/R injury Viability testing
 ECOPS system		 	 Liver Assist
Normothermic regional perfusion	Slow oxygenated cooling	Static cold storage and transport	Oxygenated HMP/ Controlled rewarming / NMP

The Groningen Organ Preservation & Resuscitation Unit

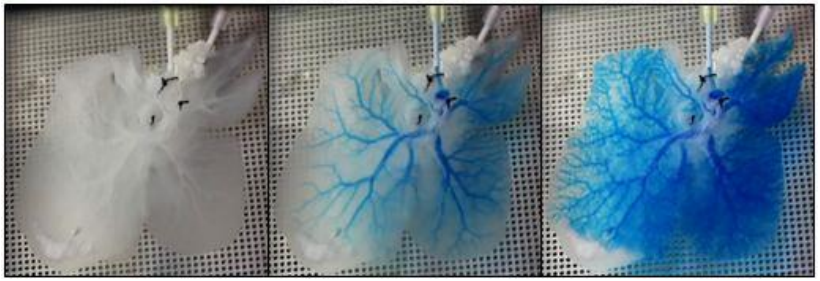
Central facility for:

- Back table preparation
- Simultaneous machine perfusion of: Lungs, liver, two kidneys

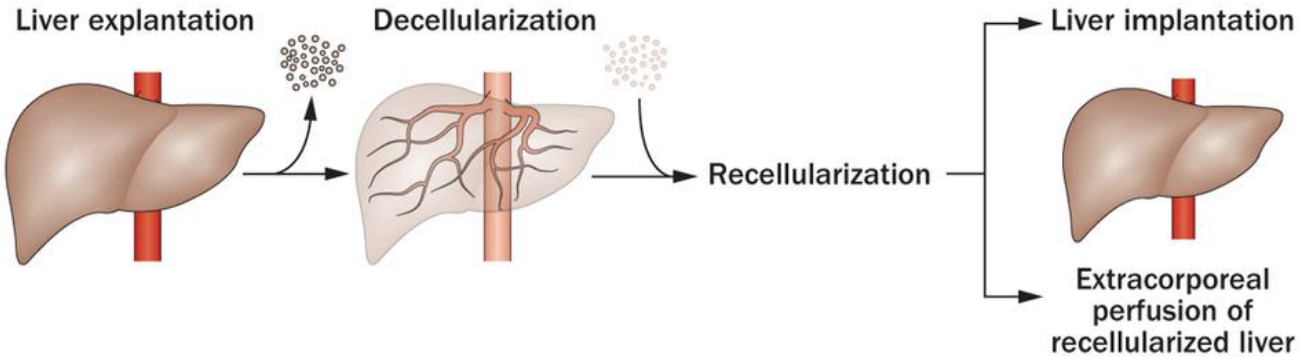
UMC Groningen Transplant Center
Shared care for shared organs®

Potential Future Applications of Normothermic Machine Perfusion

- Gen therapy
- Stem cell therapy
- Decellularization and development of a liver scaffold for creation of a new (autologous) organ



Decellularized liver scaffold



Summary - I

- Liver machine preservation techniques are rapidly developing and entering the clinical arena

- Clinical experience with liver machine perfusion
  - *Hypothermic (oxygenated) machine perfusion (HMP, HOPE, DHOPE)*
  - *Controlled oxygenated rewarming (COR)*
  - *Normothermic machine perfusion (NMP)*

- Hypothermic oxygenated MP and COR
  - Restore hepatic ATP content and reduce I/R injury
  - Relatively simple and safe
  - Can be performed after static cold storage in the transplant center

Summary - II

- Normothermic oxygenated machine perfusion
  1. *Normothermic Machine Perfusion Preservation*
     - *From donor to recipient*
  2. *End-ischemic Normothermic Machine Perfusion*
     - *After static cold storage and arrival at the transplant center*
- Expensive and potentially risky
- Preclinical experience is necessary!
- The only way to really increase the pool of donor livers?
  - Application of gene and stem cell therapies
- Optimal clinical application of machine perfusion technology may consist of a combination of different modalities?

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Machine Perfusion of Donor Livers for Transplantation: A Proposal for Standardized Nomenclature and Reporting Guidelines

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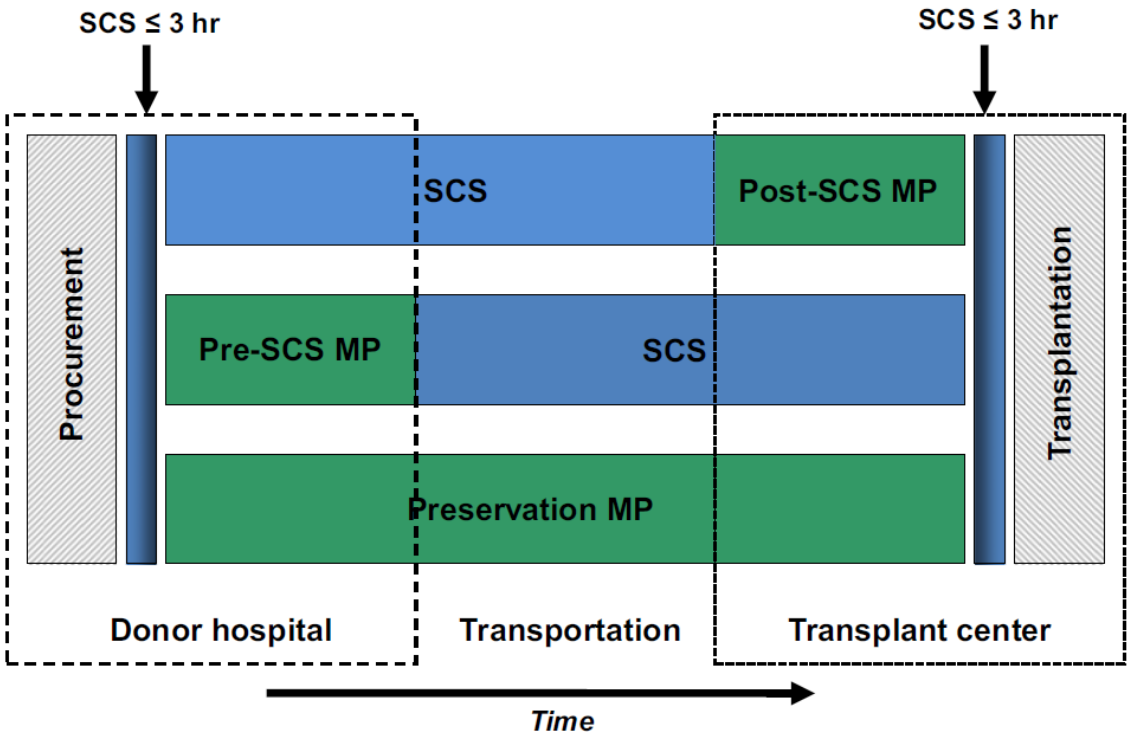

The Effect of Machine Preservation of Donor Livers