Ex situ normothermic machine perfusion of the liver

Amelia J. Hessheimer, MD, PhD, FEBS in HPB & Transplant Surgery
Hospital Universitario La Paz
IdiPAZ, CIBERehd
Madrid, Spain

Disclosures

- Research funding:
  - Instituto de Salud Carlos III
  - Guanguong Shunde Innovative Design Institute

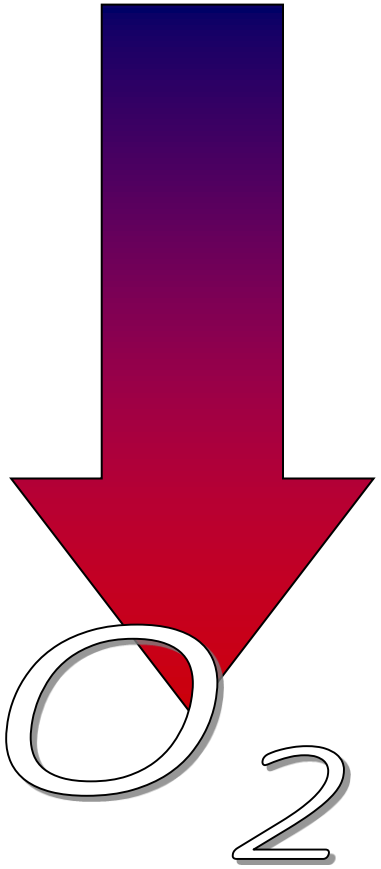
Learning objectives

- Understand:
  - Principles of *ex situ* NMP of the liver
  - Clinical application in different types of liver grafts
  - Limitations & areas for future research

Perfusion Strategies

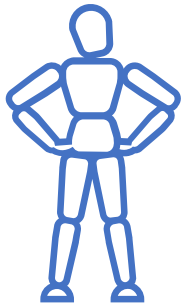
- Hypothermic:
  - 0-12 ºC
- Midthermic:
  - 13-24 ºC
- Subnormothermic:
  - 25-34 ºC
- Normothermic:
  - 35-38 ºC

"CONTROLLED REWARMING"

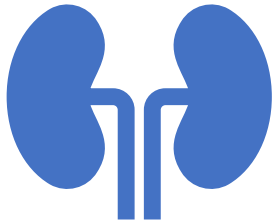


Karangwa Am J Transplant 2016.

Normothermic perfusion preservation



Organ fully metabolically active

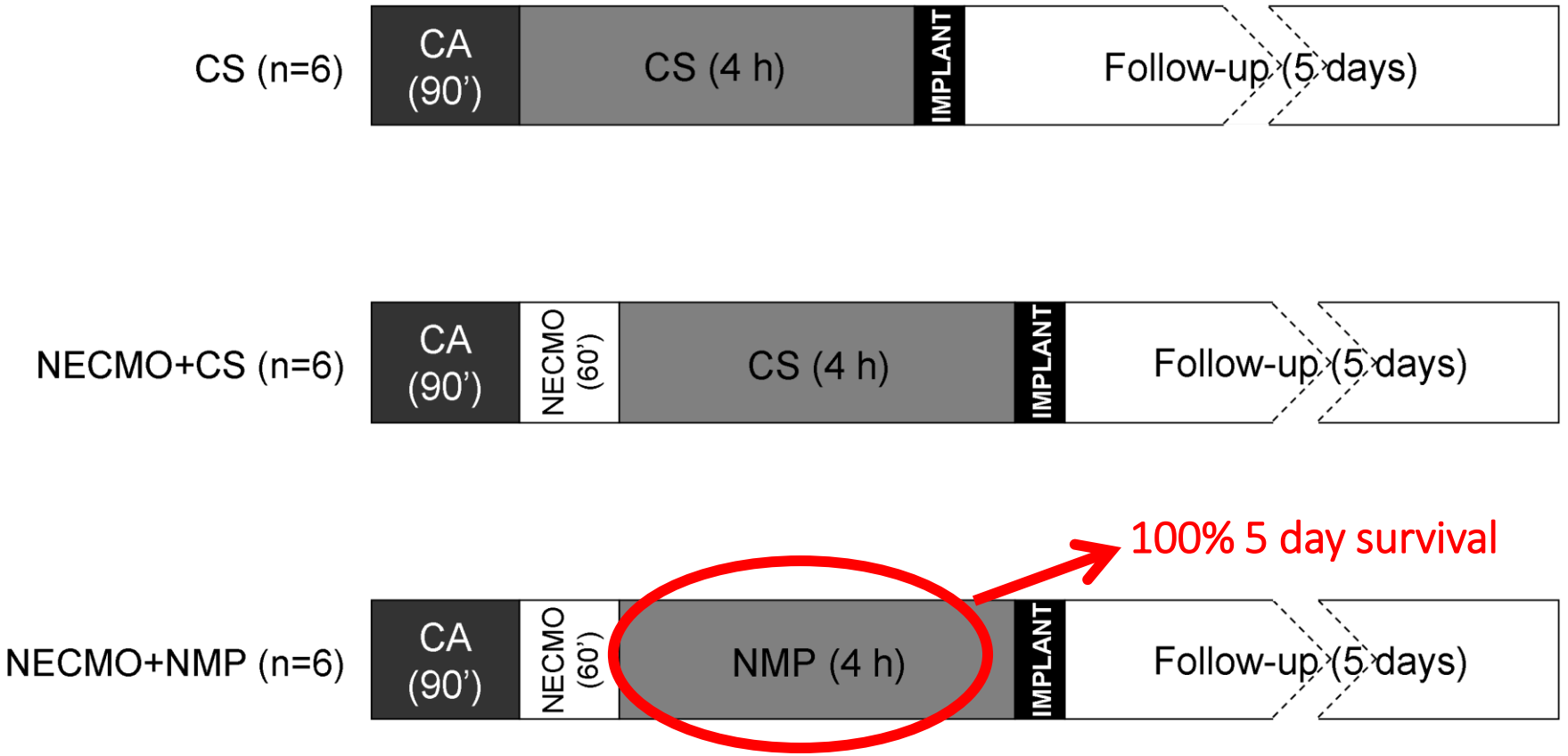


Ideally recreates *in situ* physiological conditions for the organ in the *ex situ* setting

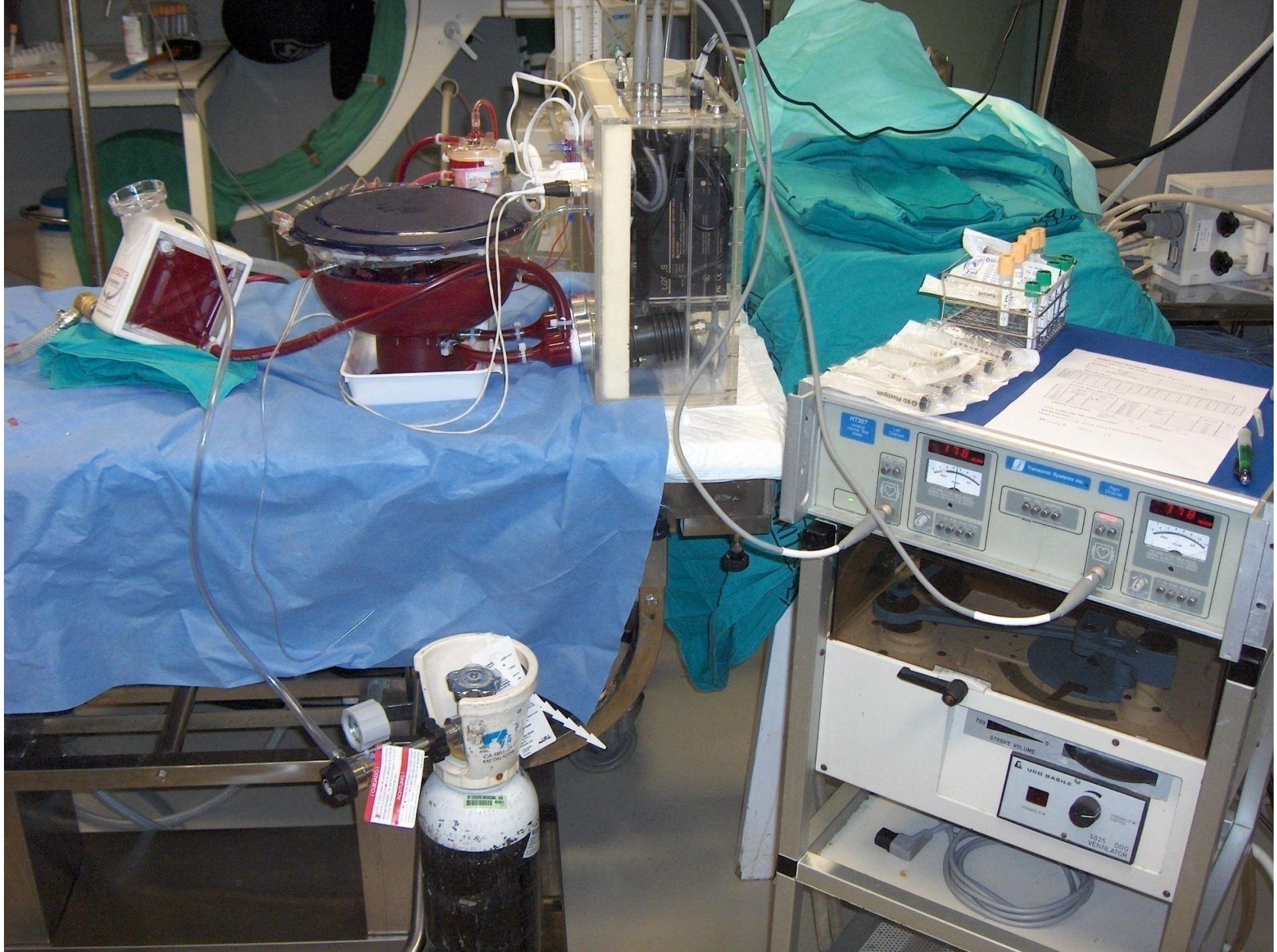
Maintain homeostasis

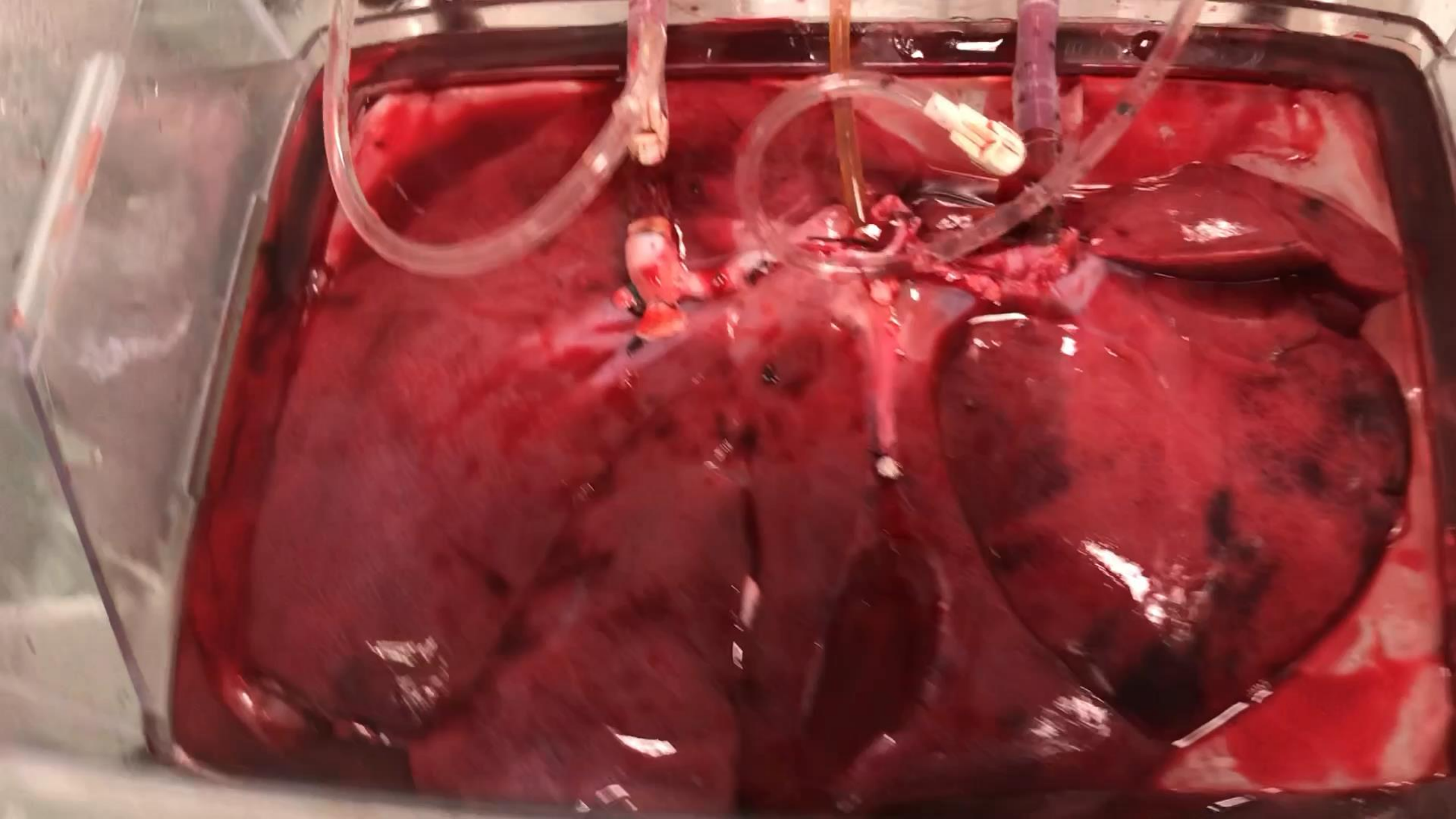
Initiate processes of regeneration & repair

Normothermic Machine Perfusion Experimental Protocol



Fondevila Ann Surg 2011.


HT207
Transonic Systems Inc.
STROKE VOLUME
UGO BASILE
5025 DOG VENTILATOR



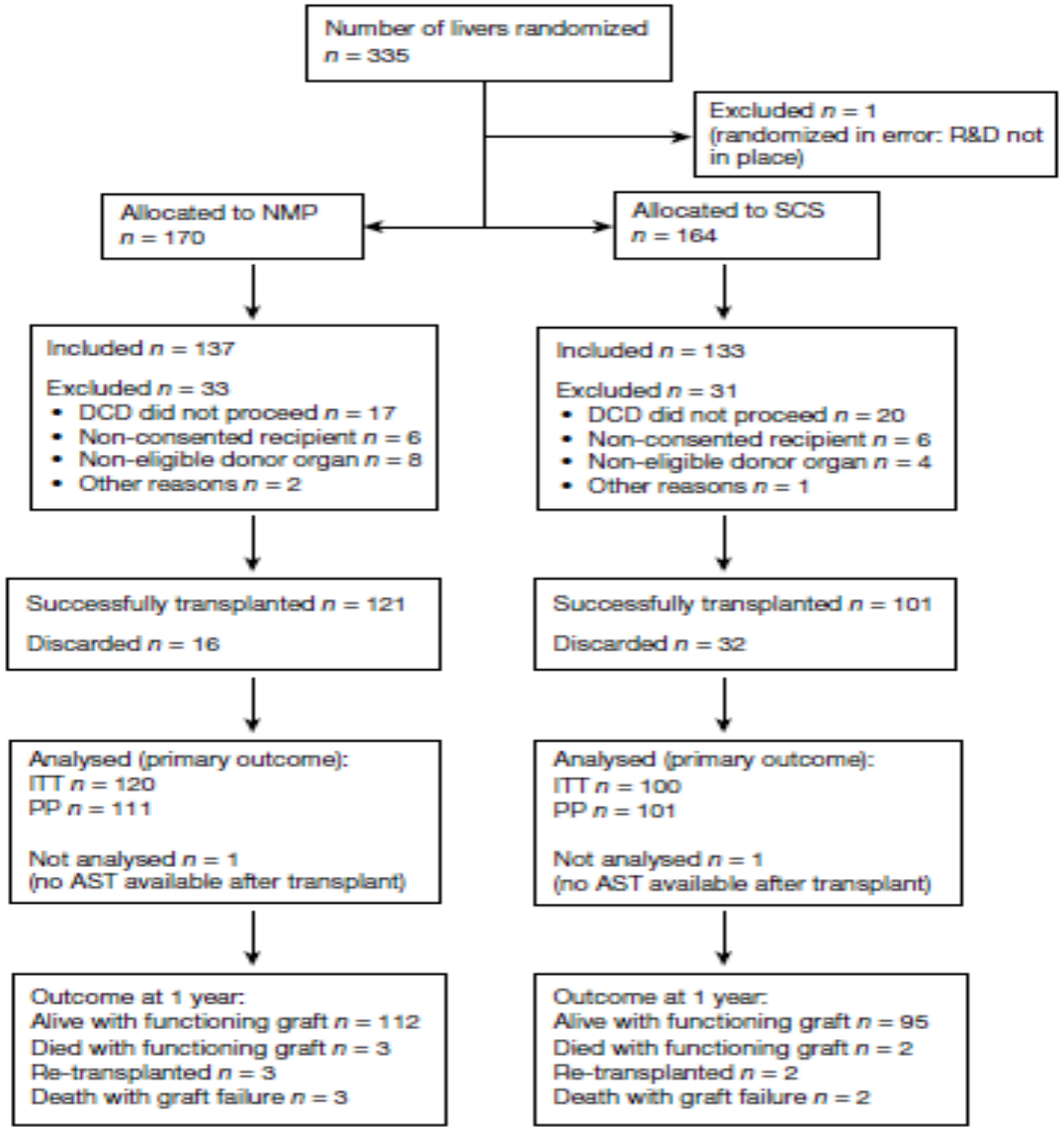
How has NMP been applied clinically?

Standard Livers

Study	Modality	Graft type	N	CIT (h)	Duration (h)	PNF (%)	ITBL (%)	6-mo. graft survival
Ravikumar 2016	NMP	DBD DCD	16 4	NR	9.3 (3.5-18.5)	0	0	100%
Selzner 2016	NMP	DBD DCD	8 2	NR	9.8 (3.7-12.2)	0	0	NR
Bral 2016	NMP	DBD DCD	6 3	3.1 (1.6-4.9)	11.5 (3.3-22.5)	0	0	80%[1]
Nasralla 2018	NMP	DBD DCD	87 34	2.1 (1.8-2.4)	9.1 (6.2-11.8)	0.8	0.8[2]	95%[3]
Markmann 2022	NMP	DBD DCD	123 28	2.9±0.7	4.6±2.0	?	3	99%

[1]Based on intention-to-treat and including one graft that was lost during NMP due to twisting of the portal vein.
[2]Cholangiographic imaging performed in 81 recipients demonstrated a 9% rate of non-anastomotic biliary strictures.
[3]One-year graft survival.

Standard Livers



- Major finding (NMP):
  - Significant reduction in peak AST after transplantation
  - No differences in any major measure of outcome (survival, biliary complications, etc.)

Nasralla Nature 2018.

Standard Livers…?

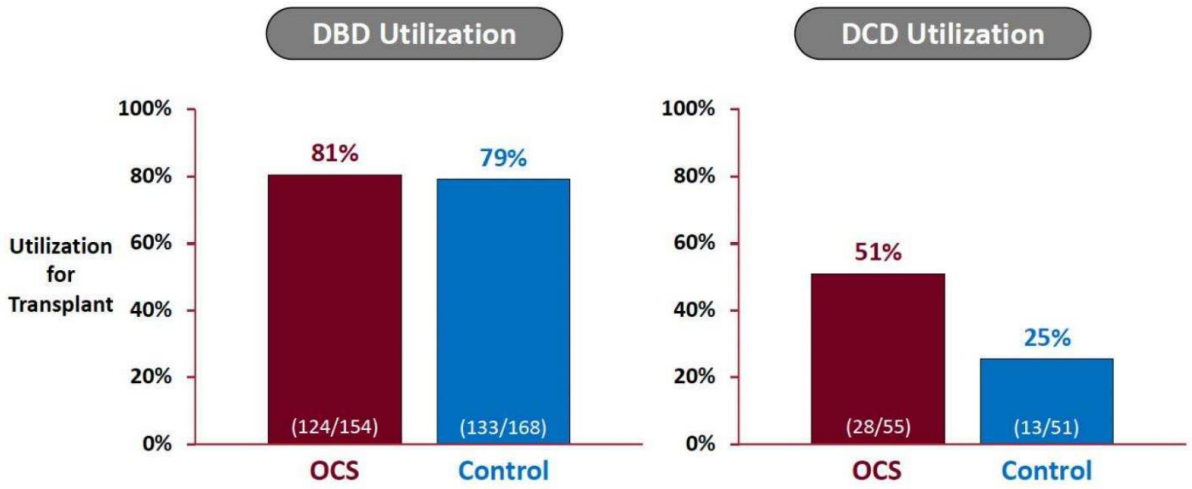
Extended Data Table 1 | Detailed breakdown of reasons for discard of NMP livers

Discarded Liver No	Device Error	Device User Error	Poor Perfusion Parameters	Donor Malignancy	Donor Cirrhosis	Poor In-situ Perfusion	Prolonged Donor Warm Ischaemia	Liver Size	Steatosis	Further Details
1	N	Y	N	N	N	N	N	N	Y	Poor perfusion due to IVC cannula positioning. Safely converted to cold storage and diiscarded due to steatosis.
2	N	N	N	N	Y	N	N	N	Y	Appearances consistent with cirrhosis in donor with known hepatitis C.
3	N	N	Y	N	N	N	N	N	N	Poor hepatic artery flow during NMP with increasing lactate.
4	N	N	N	Y	N	N	N	N	N	Incidental lung tumour found at retrieval
5	N	N	N	N	N	N	Y	N	Y	Warm ischaemia time greater than 30 minutes in DCD donor.
6	N	N	N	N	N	Y	Y	N	Y	Warm ischaemia time greater than 30 minutes in DCD donor. Poor in situ cold perfusion.
7	N	N	Y	N	N	N	N	N	Y	Persistently raised lactate >6mmol after 6 hours NMP.
8	N	N	N	Y	N	N	N	N	Y	Colonic tumour found at retrieval.
9	N	N	N	N	N	N	N	N	Y	60% steatosis on biopsy.
10	N	N	Y	N	N	N	N	N	N	Persistent acidosis with lactate >6mmol after 8hours NMP.
11	N	N	N	N	N	N	N	Y	Y	Large steatotic liver, no size-matched recipient found.
12	N	N	Y	N	N	N	N	N	Y	Persistently raised lactate >3mmol with acidosis.
13	N	N	N	N	N	N	N	N	Y	Moderate steatosis on biopsy, surgeon decision to discard.
14	N	N	Y	N	N	N	N	N	Y	Poor hepatic artery and portal vein flow during NMP in a steatotic liver.
15	N	Y	N	N	N	N	N	N	Y	Excessive bleeding during NMP from phrenic veins and hepatic artery in a steatotic liver. Safely converted to cold storage and declined due to steatosis.
16	Y	N	N	N	N	N	N	N	Y	See Supplementary Information for narrative description of device error.

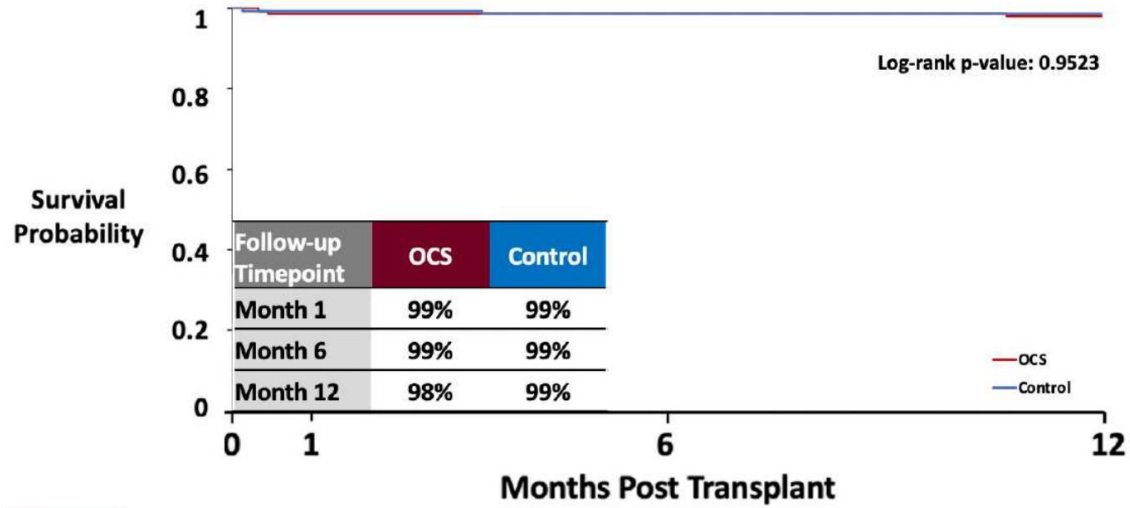
Nasralla Nature 2018.

Standard Livers

Utilization of DCD and DBD Donors in PROTECT



Graft Survival



Follow-up Timepoint	OCS	Control
Month 1	99%	99%
Month 6	99%	99%
Month 12	98%	99%

OCS	151	148	145	104
Control	142	140	136	105

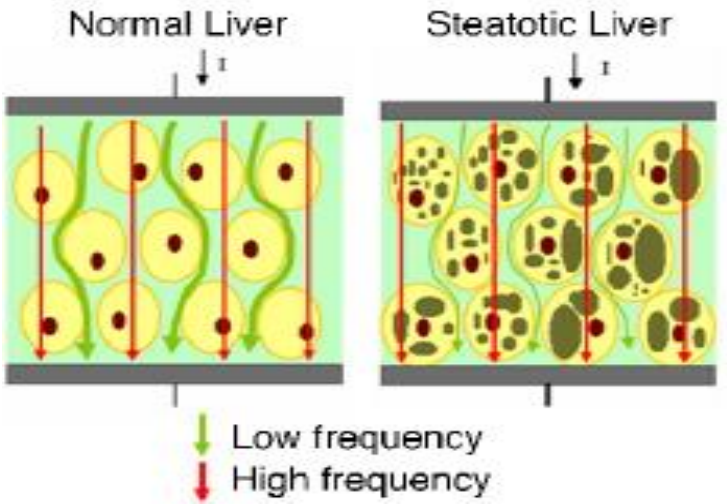
Markmann JAMA Surg 2022.

Steatotic Livers

- Macrovesicular steatosis is a major determinant of graft outcomes:

- Cold ischemia very detrimental:
  - Impaired mitochondrial function + increased uncoupling of electron transport chain → Increased oxidative stress + activation of inflammatory response

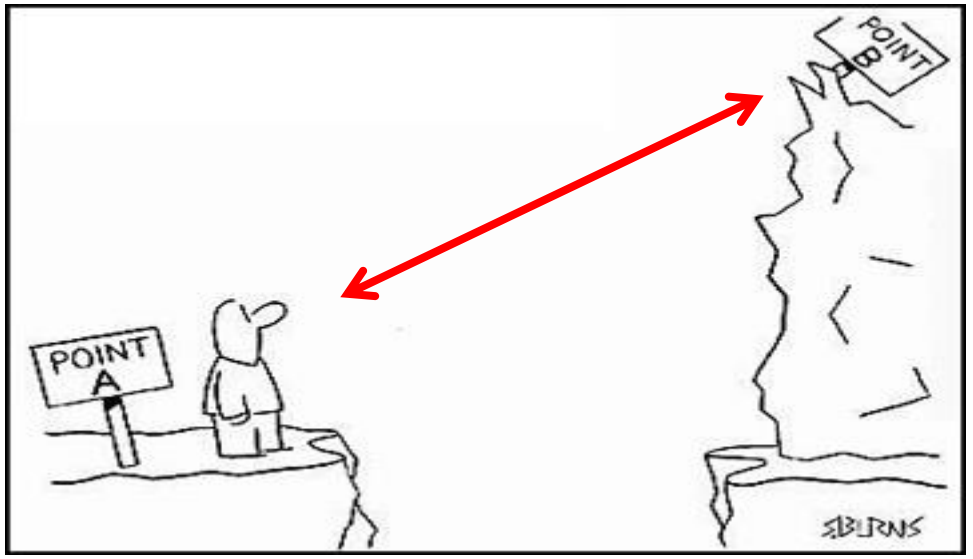
- Exacerbated by microcirculatory disturbances:



Hessheimer Transplantation 2009; Boteon Am J Transplant 2018.

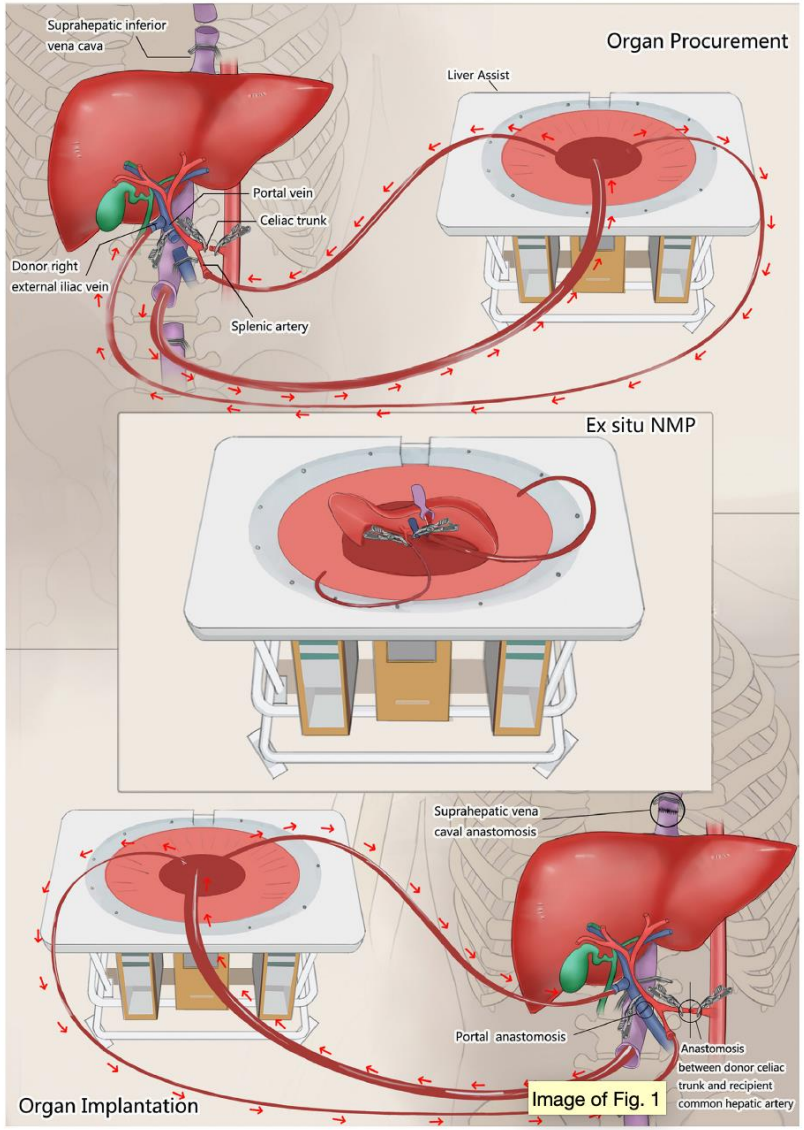
Steatotic Livers

- Function well in the donor prior to cold preservation and recovery
- Can function well in the recipient if cold ischemic period is limited
  - Steatosis can reverse (to a certain degree) upon transplantation



Boteon Am J Transplant 2018.

“Ischemia-free” LT



Guo Lancet Reg Health West Pac 2021; Guo Clin Transl Med 2022:

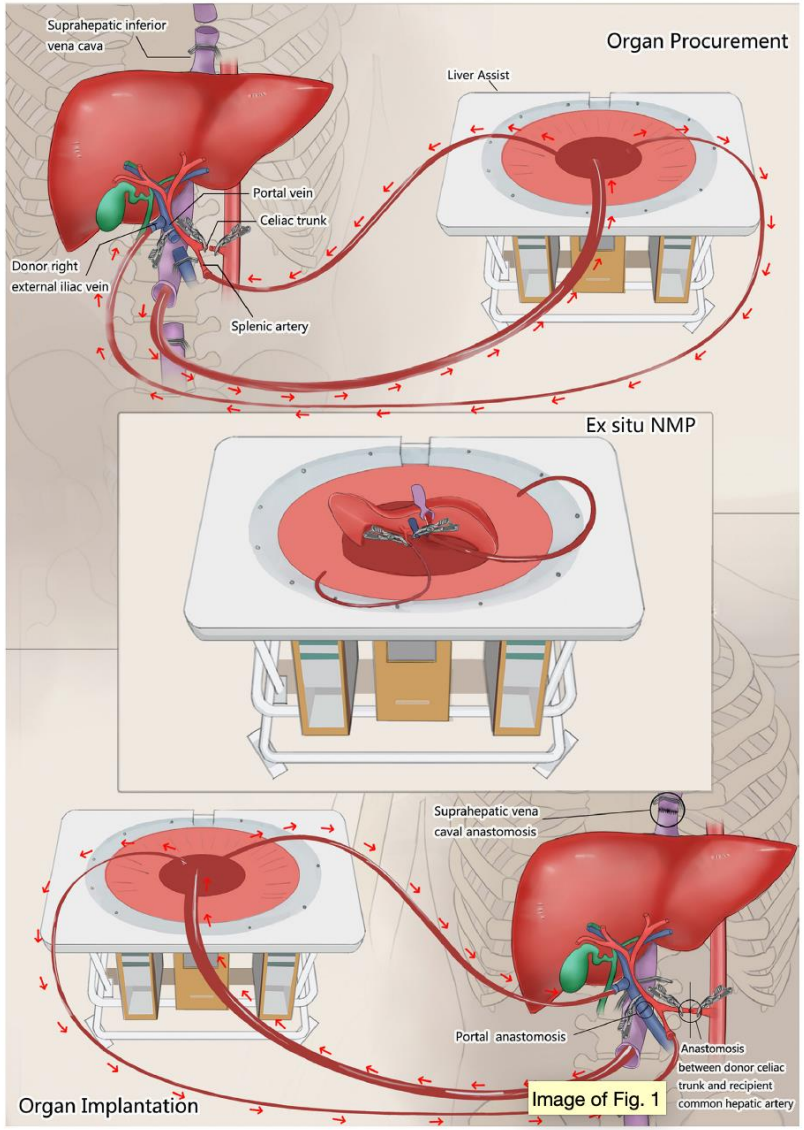
42 cases reported (ILTS Toronto 2019 – Guo O-079, He O-087)

38 cases published (Guo 2021 & 2022):

- Absence of typical histological changes associated with IRI
- Stable metabolism throughout preservation and transplantation
- Minimal changes in gene transcription
- Minimal-to-no inflammation
- Stable hemodynamic parameters and core body temperatures in recipients
- Two cases of EAD (5.3%)

Loss of “bystander” organs?

“Ischemia-free” LT



Guo Transplantation 2023.

Stable arterial and venous flows, blood gas parameters, transaminase release, and lactate clearance during 6 hours *ex situ* NMP

Metabolomic analysis (2 hours after in situ → ex situ transition):

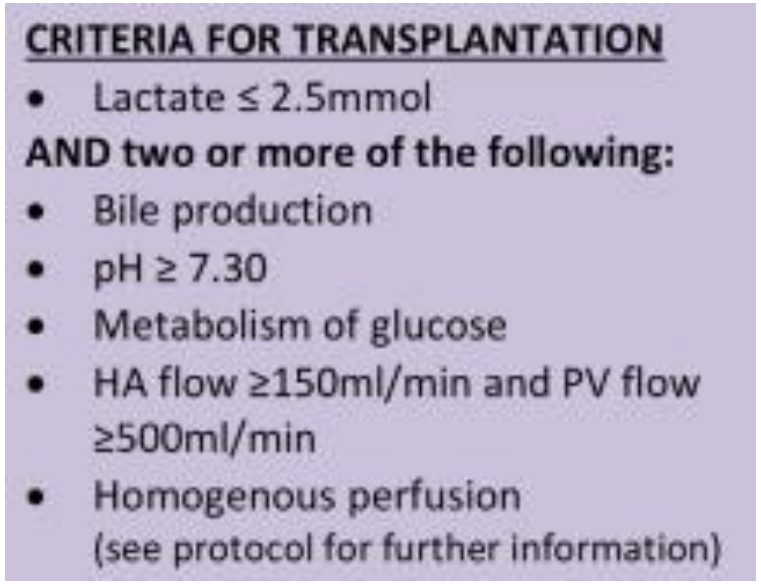
- Reduced metabolic and synthetic function
- Urea cycle dysfunction

Viability Assessment: Livers Initially Rejected for Transplantation

Study	Modality	Graft type	DWIT (min)	N	CIT (h)	Duration (h)	PNF (%)	ITBL (%)	6-mo. graft survival
Mergental 2016	NMP	DBD DCD	-- 19-109	1 4	7.0 (6.5-7.9)	5.8 (5.1-9.4)	0	0	100%
Watson 2018	NMP	DBD DCD	-- 16-160	6 16	6.4 (5.5-7.4)	NR	5	18	86%
Mergental 2020	NMP	DBD DCD	-- 19-35	12 10	7.5 (6.5-10)	9.8 (7.5-11.8)	0	14	95%
Quintini 2022	NMP	DBD DCD	-- 20±10	4 11	4.9±1.7	7.3±1.5	0	7	NR

Transplantation of discarded livers following viability testing with normothermic machine perfusion

Hynek Mergental[1,2,3,11✉], Richard W. Laing[1,2,3,11], Amanda J. Kirkham[4], M. Thamara P. R. Perera[1], Yuri L. Boteon[1,2,3], Joseph Attard[1,2,3], Darren Barton[5], Stuart Curbishley[2,3], Manpreet Wilkhu[5], Desley A. H. Neil[2,3,6], Stefan G. Hübscher[2,3,6], Paolo Muiesan[1], John R. Isaac[1], Keith J. Roberts[1,3], Manuel Abradelo[1], Andrea Schlegel[1,3], James Ferguson[1,2], Hentie Cilliers[1], Julian Bion[7], David H. Adams[1,2,3], Chris Morris[8], Peter J. Friend[8,9], Christina Yap[4,10,11], Simon C. Afford[2,3,11✉] & Darius F. Mirza[1,2,3,11✉]



- 126 livers suitable for trial consideration
- 31 livers undergoing viability assessment in 1.5 years (24%)
  → 22 ultimately transplanted (17%)
- 12 DBD
- 10 DCD

Outcomes:

- 0 PNF
- 100% 90-day patients survival (primary outcome)
- ITBL 30% among DCD grafts

Nat Comm 2020.

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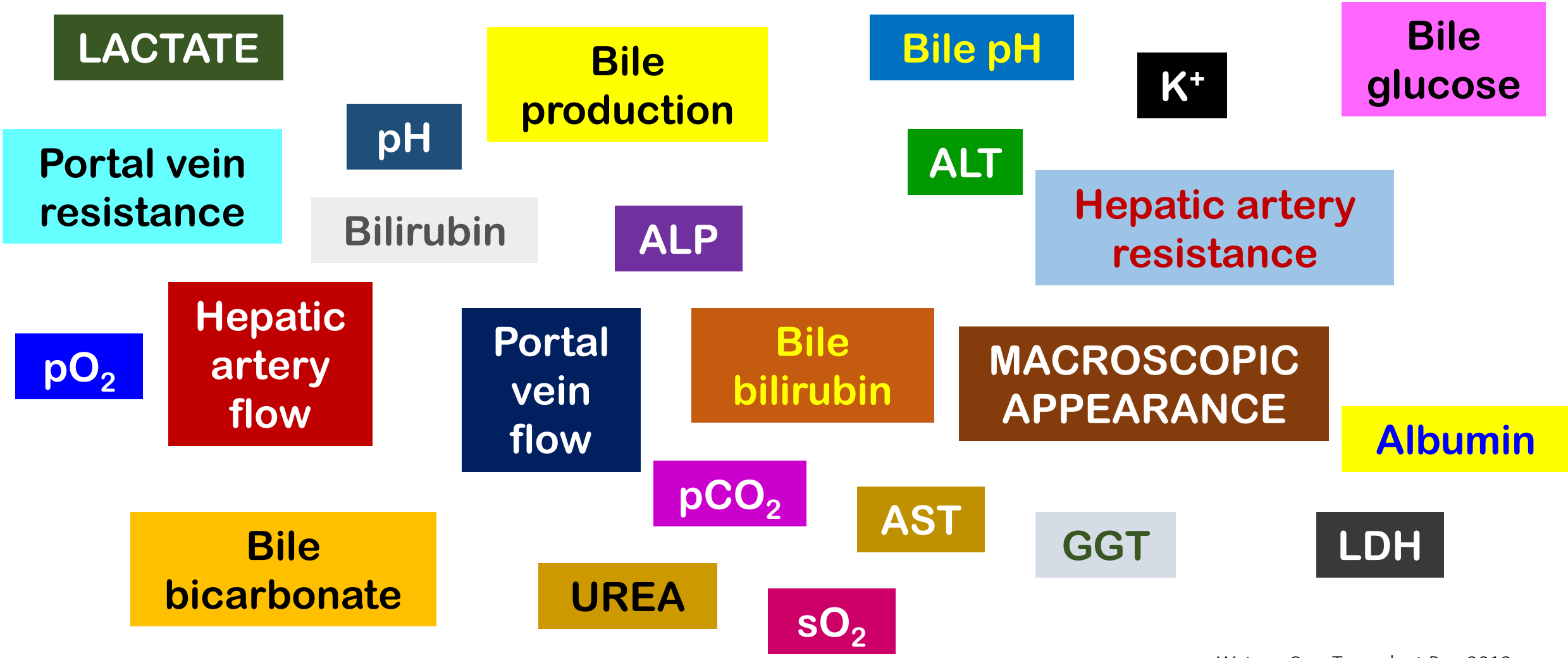
Quintini 2022	NMP	DBD DCD	-- 20±10	4 11	4.9±1.7	7.3±1.5	0	7	NR
van Leeuwen 2022	60’ DHOPE + 60’ COR + >150’ NMP	DCD	30 (25-34)	34	4.7 (4.3-5.0)	NR	0	3	97%

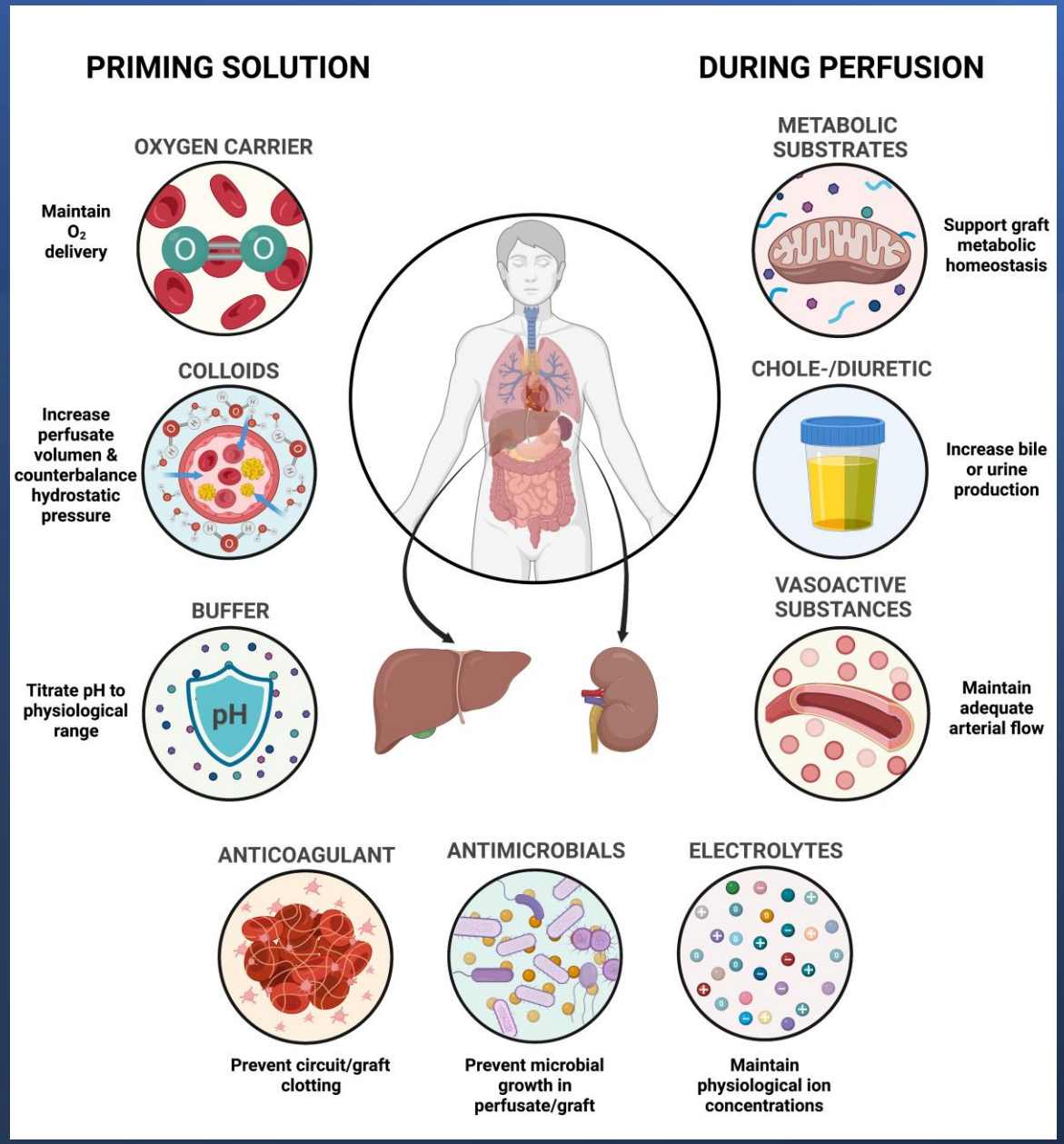
van Leeuwen 2022:

- 54 cDCD livers perfused → 34 ultimately transplanted in approx. 4-year period
  - Roughly 8 additional livers/year

NMP Liver Viability Markers



Watson Curr Transplant Rep 2018.



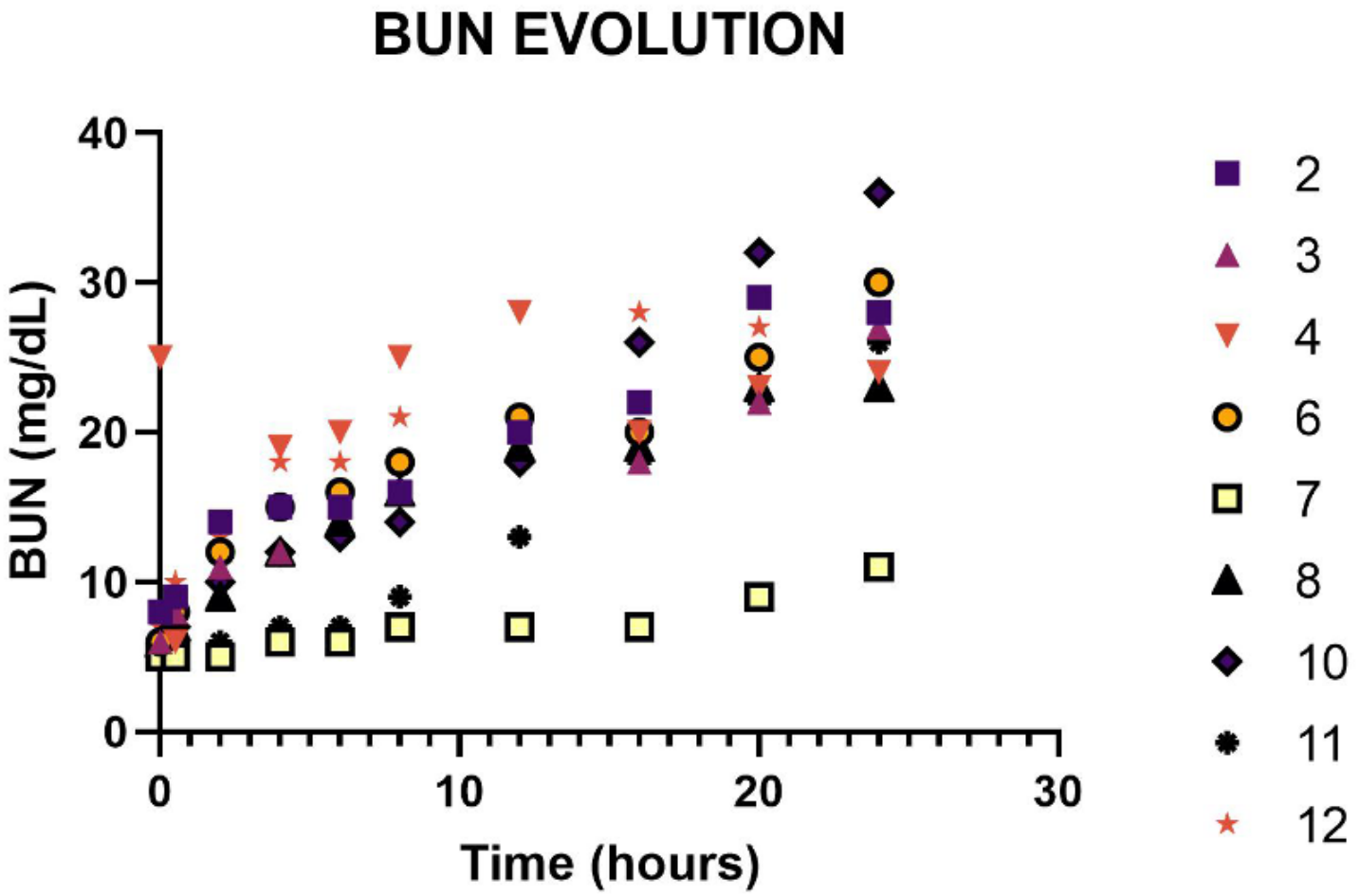
Ramos Transplantation 2022.

Common characteristics & compositions of solutions used for *ex situ* NMP

	Liver NMP	Kidney NMP
Oxygen carrier	PRBCs or HBOC	PRBCs or HBOC
Colloid	Albumin +/- succinylated gelatin or FFP	Albumin or succinylated gelatin
Anticoagulant	Heparin	Heparin
Antimicrobial	Antibiotic +/- antifungal	Antibiotic
Buffer	Bicarbonate (priming solution)	Bicarbonate (priming solution)
Electrolytes	Calcium +/- magnesium	Calcium +/- magnesium
Vasoactive substances	Epoprostenol +/- vasoconstrictor	Epoprostenol or verapamil
Maintenance of excretory function	Sodium taurocholate or UDCA	Mannitol & urine replacement
Metabolic substrates	Amino acids, glucose, insulin +/- MV, TE	Amino acids & glucose +/- insulin, MV
Other additives	Methylprednisolone	Dexamethasone

Ramos Transplantation 2022.

Prolonged *ex situ* liver NMP



Hessheimer et al. ESOT Milan 2021.

nature biotechnology

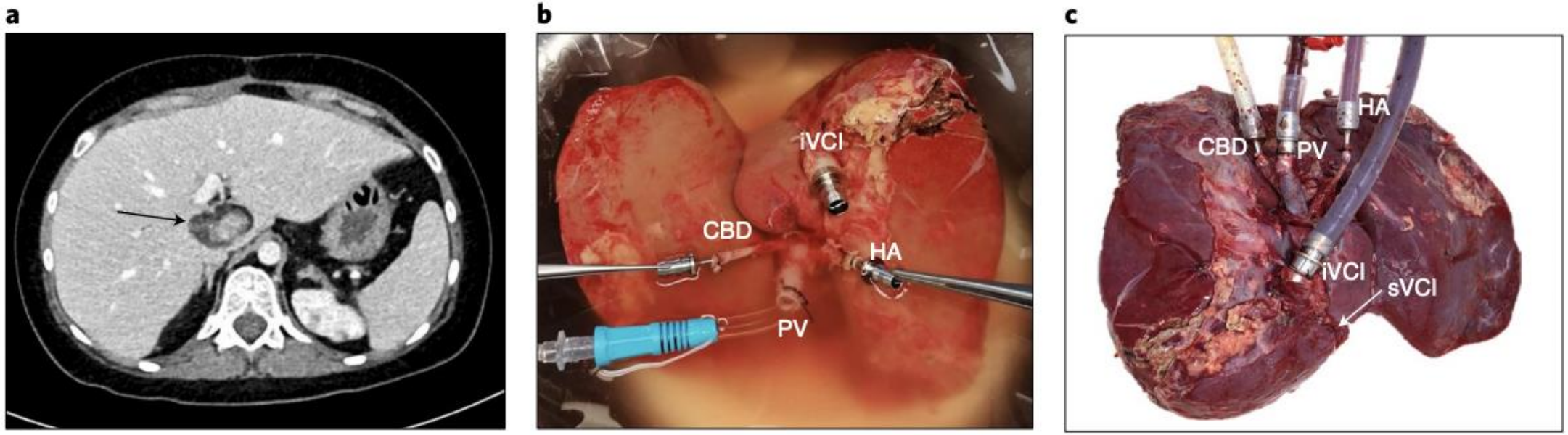
ARTICLES

https://doi.org/10.1038/s41587-022-01354-7

Check for updates

Transplantation of a human liver following 3 days of ex situ normothermic preservation

Pierre-Alain Clavien[1,2] ✉, Philipp Dutkowski[1], Matteo Mueller[1,2], Dilmurodjon Eshmuminov[1,2], Lucia Bautista Borrego[1,2], Achim Weber[3], Beat Muellhaupt[4], Richard X. Sousa Da Silva[1,2], Brian R. Burg[2,5,6], Philipp Rudolf von Rohr[2,5], Martin J. Schuler[2,5], Dustin Becker[2,5], Max Hefti[2,5] and Mark W. Tibbitt[2,5]



Prolonged *ex situ* liver NMP

Commonly administered:

- Oxygen carrier
- Plasma and/or other colloids
- Electrolytes
- Bicarbonate buffer (priming solution)
- Continuous infusion of amino acids, glucose, insulin, MV, TE
- Single bile acid
- Anticoagulant
- Broad spectrum antimicrobials
- Vasoactive substances
- Methylprednisolone

Commonly missing but important:

- Dialysis
- Glucagon
- Lipids
- Circadian variation in infusion of nutrients

May be administered in excess:

- Glucose
- Insulin
- Oxygen
- Bicarbonate

Potentially important (area for future research):

- Range of bile acids
- Platelets
- Leukocytes
- Gut microbe-derived metabolites (gut-liver axis)
- Bone marrow-derived progenitor cells (EC regeneration)

Hessheimer, Vengohechea & Fondevila Transplantation 2023.

Ex situ NMP: Final remarks

- Improves surrogate markers of graft function and IRI
- Offers an opportunity to assess some aspects of graft function prior to transplantation
  - Greater confidence to transplant more livers
- As yet, no evidence of any improvement in major clinical outcome measures
- Greater cost & complexity
- May lead to graft loss if performed improperly
- *NOT* physiological
  - Ongoing need for research on ideal perfusate composition and variation and perfusion conditions

THANK YOU
감사 해요
GRACIAS
谢谢你
BEDANKT
MERCI
DANKE SCHÖN
धन्यवाद
GRAZIE

ありがとうございました
TAKK SKAL DU HA
OBRIGADO
СПАСИБО
TEŞEKKÜRLER
БЛАГОДАРЯ ТИ
ขอบคุณ
DĚKUJI
ДЯКУЮ