Department of Visceral, Transplant and Thoracic Surgery
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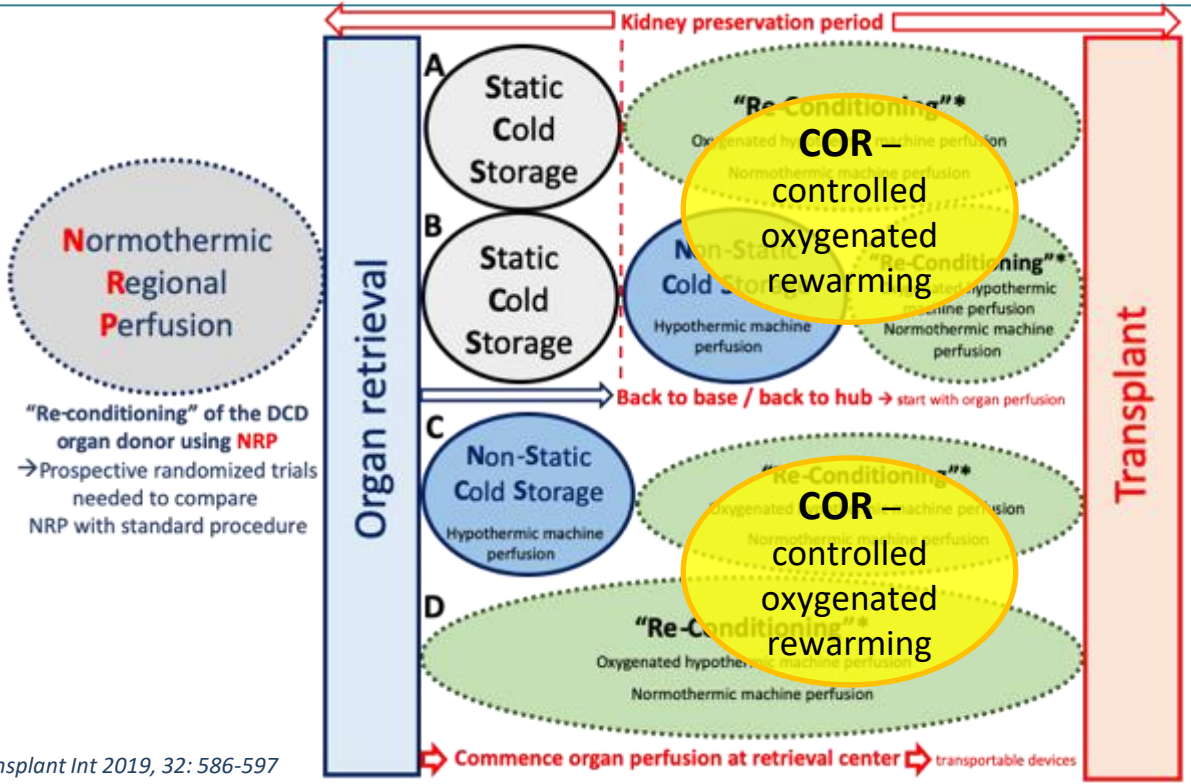
Perfusion – Ex situ machines in SOT

Renal and liver transplantation

17º CONGRESO SCT BCN BARCELONA 22-24 marzo 2023
SOCIETAT CATALANA DE TRASPLANTAMENT

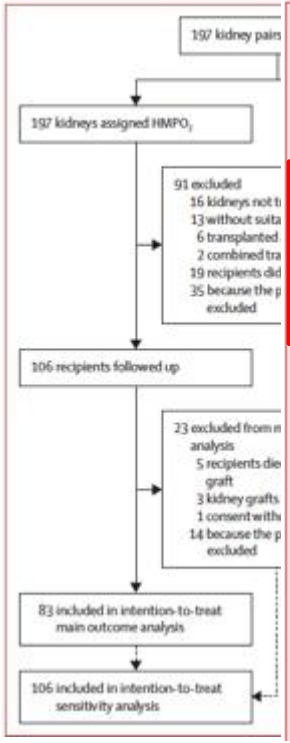
Annemarie Weißenbacher | 22nd March 2023

PRESERVATION REVISITED



- *Weissenbacher et al., Transplant Int 2019, 32: 586-597*

OXYGENATED HMP VS SCS IN DCD KIDNEY TX



	HMPO$_2$ mean	HMP mean	Mean or risk difference*	p value†
Primary endpoint‡				
Primary comparison (n=83)	50·5 (19·3)	46·7 (17·1)	3·7 (−1·0 to 8·4)	0·12
Sensitivity analysis (n=106)	47·6 (20·1)	42·6 (20·3)	5·0 (0·4 to 9·7)	0·035
Secondary endpoints				
Primary non-function (n=106)	3 (3%)	5 (5%)	−2 (−7 to 3)	0·48
Delayed graft function (n=106)	38 (36%)	38 (36%)	0 (−14 to 14)	0·99
Functional delayed graft function (n=106)	76 (72%)	76 (72%)	0 (−13 to 11)	0·99
Acute rejection shown by a biopsy (n=106)	15 (14%)	27 (26%)	−11 (−22 to −0·01)	0·040
Renal function post-transplant				
GFR at 3 months (mL/min per 1·73 m²)				
CKD-EPI equation (n=88)	46·5 (18·2)	45·0 (16·9)	1·5 (−3·2 to 6·3)	0·53
MDRD equation (n=89)	44·8 (15·7)	44·3 (23·8)	0·5 (−5·2 to 6·1)	0·87
GFR at 6 months (mL/min per 1·73 m²)				
CKD-EPI equation (n=83)	50·1 (18·5)	47·1 (19·6)	3·0 (−1·8 to 7·7)	0·22
MDRD equation (n=85)	48·1 (17·7)	44·7 (17·9)	3·4 (−1·2 to 8·0)	0·15
GFR at 12 months (mL/min per 1·73 m²)				
MDRD equation (mL/min per 1·73m²) primary comparison (n=83)	48·8 (19·5)	44·4 (15·4)	4·4 (−0·2 to 9·1)	0·062
MDRD equation (mL/min per 1·73 m²) sensitivity analysis (n=106)	46·1 (19·9)	40·7 (18·8)	5·4 (0·8 to 10·0)	0·021
Creatinine clearance in 24 h urine collection (mL/min) (n=77)	58·2 (21·4)	51·1 (21·9)	7·1 (1·1 to 13·0)	0·021

6)	HMP (n=106)
3·0)	58·0 (54·0–63·0)
	40 (38%)
	66 (62%)
	25 (23–28)
	16 (15%)
	42 (40%)
	39 (37%)
	9 (9%)
	44 (42%)
	61 (58%)
	1 (1%)
	29 (27%)
)	0·7 (0·6–0·9)
	28·5 (22–36)

machine perfusion.
n. *Six records missing.
intention-to-treat

- *Jochmans I, Brat A, Davis L, et al. Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE): a randomised , double-blind, paired, phase-3 trial. Lancet 2020;396:1653-1662.*

Oxygenated End-Hypothermic Kidney Perfusion

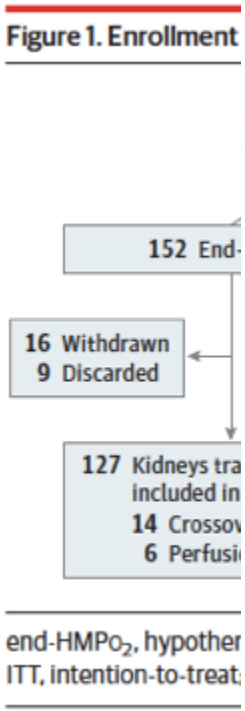


Table 2. Primary and Secondary End Points

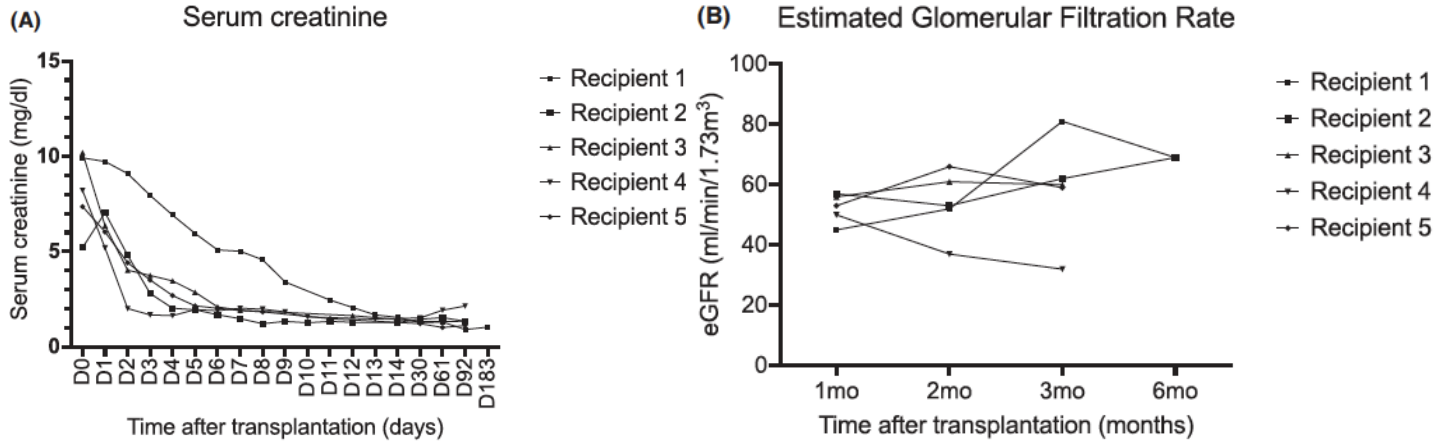
Variable	No. (%) End-HMPO$_2$ (n = 127)	No. (%) SCS (n = 135)	Risk difference (95% CI)	P value
Primary end point				
Graft survival at 1 y	117 (92.1)	126 (93.3)	−1.2 (−7.5 to 5.1)	.71
Secondary end points				
Posttransplant estimated GFR, MDRD equation, mean (SD), mL/min/1.73m^2				
7 d	27.1 (16.2)	26.0 (17.6)	1.08 (−3.38 to 5.55)	.63
3 mo	38.1 (13.9)	39.8 (15.8)	−1.74 (−5.44 to 1.96)	.36
6 mo	38.0 (13.3)	39.6 (15.4)	−1.61 (−5.21 to 2.00)	.38
1 y	39.9 (14.4)	41.2 (17.1)	−1.31 (−5.36 to 2.75)	.53
Delayed graft function	30 (23.6)	38 (28.1)	−4.5 (−15.1 to 6.1)	.40
Functional delayed graft function	76 (59.8)	93 (68.9)	−9.9 (−22.5 to 2.7)	.13
Primary nonfunction	8 (6.3)	8 (5.9)	0.4 (−5.4 to 6.2)	.90
Patient death	9 (7.1)	2 (1.5)	5.6 (0.07 to 10.5)	.03[a]
Biopsy-proven acute rejection episodes	23 (18.1)	18 (13.3)	4.8 (−4.0 to 13.6)	.29

- *Husen P, Boffa C, Jochmans I, et al. Oxygenated end-hypothermic machine perfusion in expanded criteria donor kidney transplant: a randomized clinical trial. JAMA Surg 2021*

BUBBLE SURFACE OXYGENATION IN DCD KIDNEY HMP

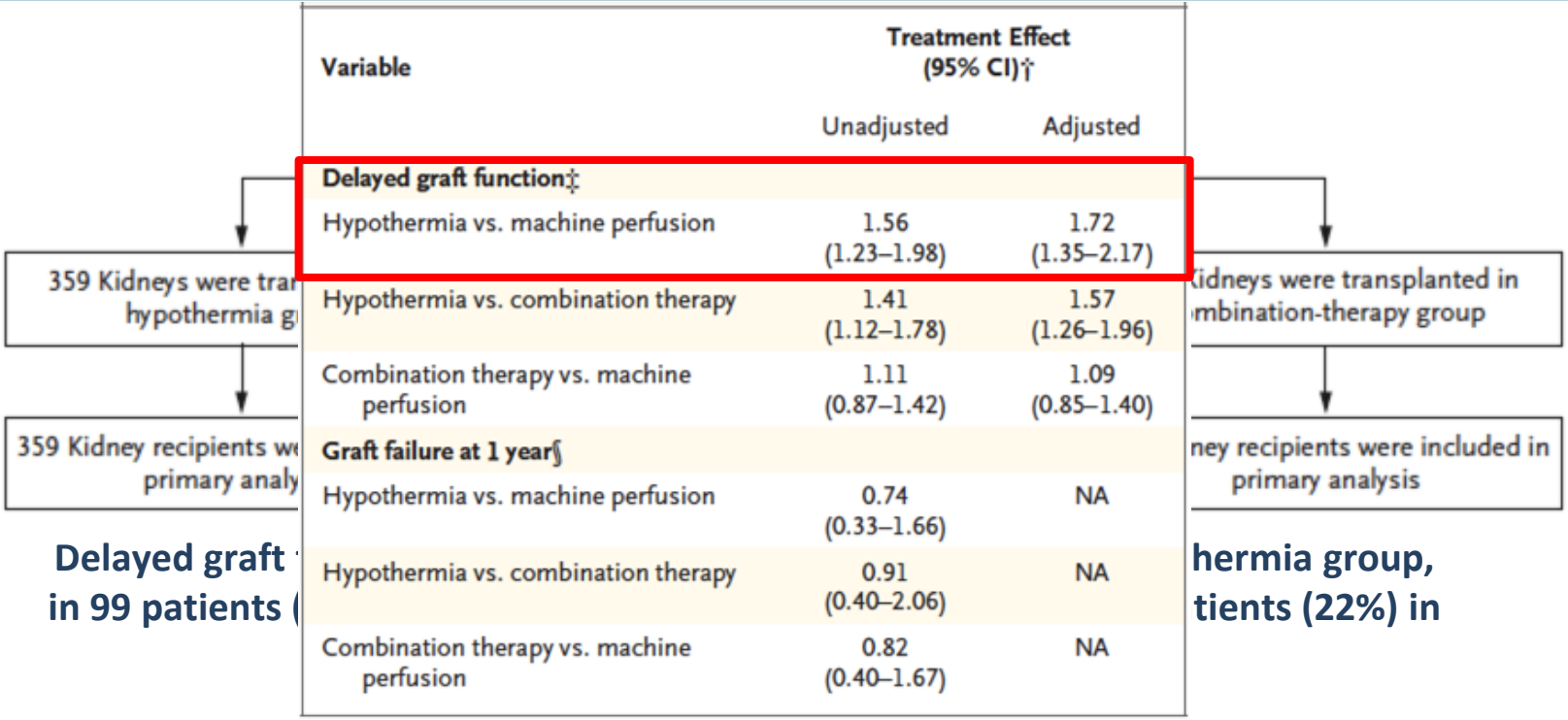
Machine perfusion characteristics

Study group: continuous versus intermittent surface oxygenation	Continuous surface O_2	Intermittent surface O_2	Continuous surface O_2	Continuous surface O_2	Intermittent surface O_2
Time of bubble oxygenation, min	58	48	59	73	65



- *Darius T, Devresse A, Buemi A, Kanaan N, De Meyer M, Mourad M. First kidneys transplanted in man after brief bubble and subsequent surface oxygenation as alternative for membrane oxygenation during hypothermic machine perfusion. Artif Organs. 2022;*

HYPOTHERMIA 34-35°C OR HMP IN DBD?



359 Kidneys were tran… hypothermia g…

359 Kidney recipients w… primary analy…

…idneys were transplanted in …mbination-therapy group

…ney recipients were included in primary analysis

Variable	Treatment Effect (95% CI)†	
	Unadjusted	Adjusted
Delayed graft function‡		
Hypothermia vs. machine perfusion	1.56 (1.23–1.98)	1.72 (1.35–2.17)
Hypothermia vs. combination therapy	1.41 (1.12–1.78)	1.57 (1.26–1.96)
Combination therapy vs. machine perfusion	1.11 (0.87–1.42)	1.09 (0.85–1.40)
Graft failure at 1 year§		
Hypothermia vs. machine perfusion	0.74 (0.33–1.66)	NA
Hypothermia vs. combination therapy	0.91 (0.40–2.06)	NA
Combination therapy vs. machine perfusion	0.82 (0.40–1.67)	NA

Delayed graft … in 99 patients (…

…hermia group, …tients (22%) in …

- *Malinoski D, Saunders C, Swain S, Groat T, Wood PR, Reese J, et al. Hypothermia or Machine Perfusion in Kidney Donors. N Engl J Med. 2023;388:418–26.*

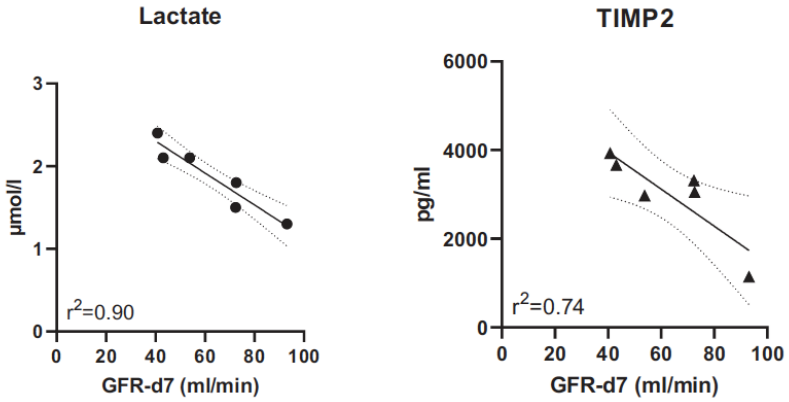
CLINICAL USE OF COR – A PILOT STUDY

Characteristic	Control ($N = 6$)	COR ($N = 6$)	p-value
Donor			
Age (years)	64.8 ± 10.2	56.7 ± 3.7	.130
Last Creatinine (mg/dl)	1.25 ± 0.71	1.17 ± 0.64	.738
KDRI	1.567 ± 0.4008	1.358 ± 0.1514	.217
Preservation			
Total ischaemic time (hours)	12.57 ± 6.54	11.83 ± 2.48	.999
WIT (min)	26.0 ± 7.2	20.2 ± 4.5	.095
Recipient			
Age (years)	59.3 ± 13.6	45.0 ± 14.6	.1212
Sex, (m/f)	3(3)	1(5)	.5455
Last Creatinine (mg/dl)	7.46 ± 2.72	7.90 ± 3.29	.9372
Before transplantation			
Disease recipient	PCKD, 2 × RPGN 2 × IgA-Nephropathy 1 × unknown	DM nephropathy Alport-syndrome IgA-nephropathy Conn-syndrome PSH IgA-nephritis	
Duration of dialysis (years)	4.7 ± 1.08	5.6 ± 1.43	.6099
Previous Transplants	0/6 (0%)	1/6 patients (17%)	

- *Zlatev H, von Horn C, Kaths M, Paul A, Minor T. Clinical use of controlled oxygenated rewarming of kidney grafts prior to transplantation by ex vivo machine perfusion. A pilot study. Eur J clin Invest 2022;52:e13691.*

CLINICAL USE OF COR – A PILOT STUDY

Perfusate parameter



Outcome parameter

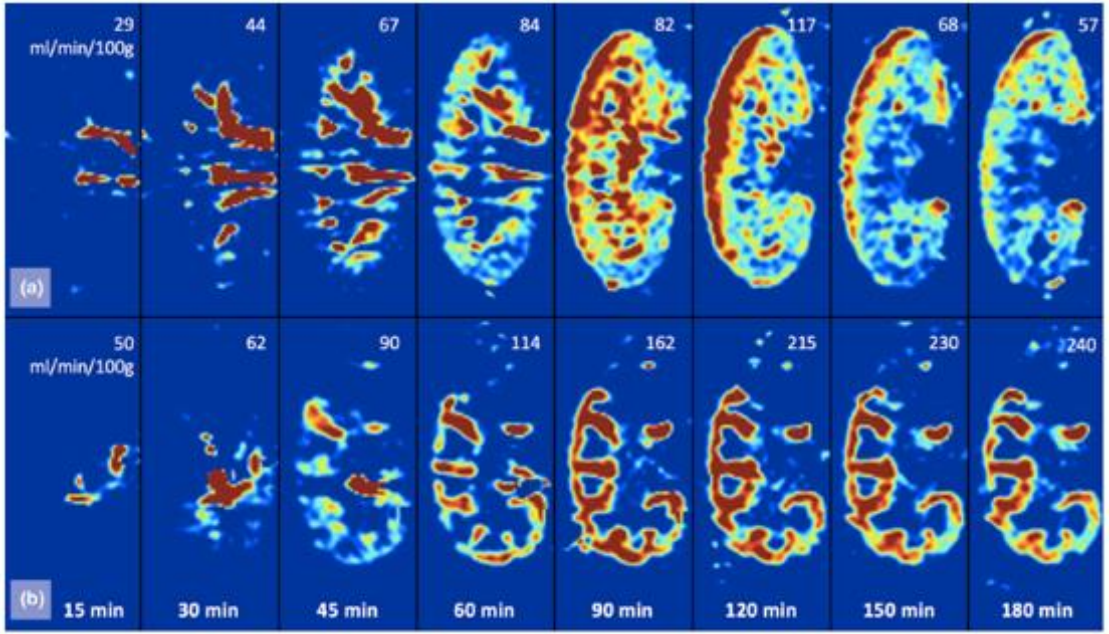
	Control ($N = 6$)	COR ($N = 6$)	p-value
Creatinine clearance POD7 (ml/min)	27.0 ± 12.7	66.1 ± 19.1	.004
FE Na+ (%)	4.7 ± 2.6	1.8 ± 0.8	.026
PNF	1/6 (17%)	0/6 (0%)	.999
DGF	2/6 (33%)	0/6 (0%)	.333
Hospital stay (days)	16.6 ± 5.0	17.8 ± 6.6	.924
3-month graft survival	5/6 (83%)	6/6 (100%)	.999
3-month GFR (ml/min)	45 ± 19	70 ± 13	.023
Adverse events (≥Clavien-Dindo 3b)	1/6 (17%)	2/6 (33%)	.999

- *Zlatev H, von Horn C, Kaths M, Paul A, Minor T. Clinical use of controlled oxygenated rewarming of kidney grafts prior to transplantation by ex vivo machine perfusion. A pilot study. Eur J clin Invest 2022;52:e13691.*

MRI ASSESSMENT OF RENAL FLOW DISTRIBUTION

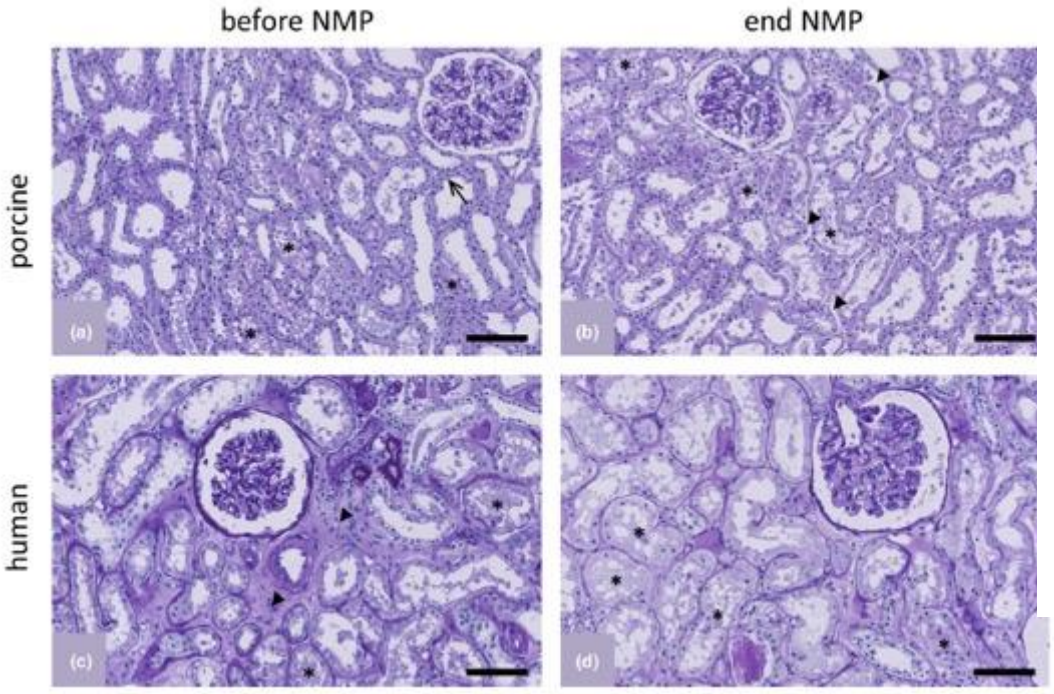
Table 1. Baseline characteristics, externally measured total flow, and ASL perfusion-derived corticomedullary (CM) ratio of porcine and human discarded kidneys.

	Porcine kidney $n = 9$ Mean (SD)	Human kidney $n = 4$ Mean (SD)
Weight prior to NMP (g)	291 (±42)	224 (±69)
Warm ischemia time (min)	21 (±2)	22 (±13)
Total cold ischemia time (min)	695 (±19)	896 (±399)
Externally measured flow (ml/min/100g)		
30 min	83 (±39)	143 (±66)
60 min	117 (±31)	185 (±99)
120 min	129 (±51)	226 (±68)
180 min	116 (±46)	244 (±50)
ASL-derived perfusion signal intensity (CM ratio)		
30 min	2.1 (±2.1)	1.2 (±1.0)
60 min	5.0 (±5.0)	3.0 (±1.1)
120 min	6.5 (±6.4)	4.5 (±1.0)
180 min	5.3 (±3.7)	6.6 (±2.8)



- *Schutter R et al. Magnetic resonance imaging assessment of renal flow distribution patterns during ex vivo normothermic machine perfusion in porcine and human kidneys. Transplant Int 2021; 34:1643-1655*

MRI ASSESSMENT OF RENAL FLOW DISTRIBUTION

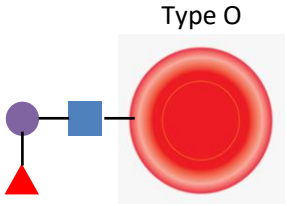


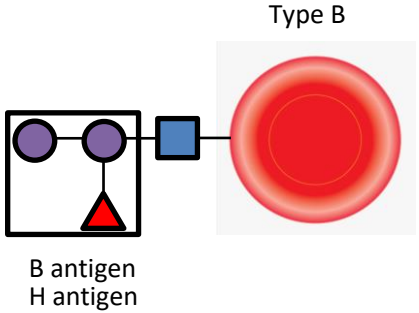
Conclusion

This study found that intrarenal flow distribution changes after the start of *warm* ex vivo perfusion and it takes 1 to 2 h before an adequate, in vivo like cortical perfusion is achieved. Since the majority of nephrons are located in the renal cortex, renal function may not recover at the same rate as total renal blood flow does during NMP. Quality assessment markers measured early after the start of NMP should therefore be interpreted cautiously. Given the rapidly increasing popularity of renal NMP, our study suggests that imaging can help to better characterize ex vivo kidney physiology and stresses the importance of studies which unravel ex vivo renal autoregulation and metabolism in order to develop relevant quality assessment strategies.

- *Schutter R et al. Magnetic resonance imaging assessment of renal flow distribution patterns during ex vivo normothermic machine perfusion in porcine and human kidneys. Transplant Int 2021; 34:1643-1655*

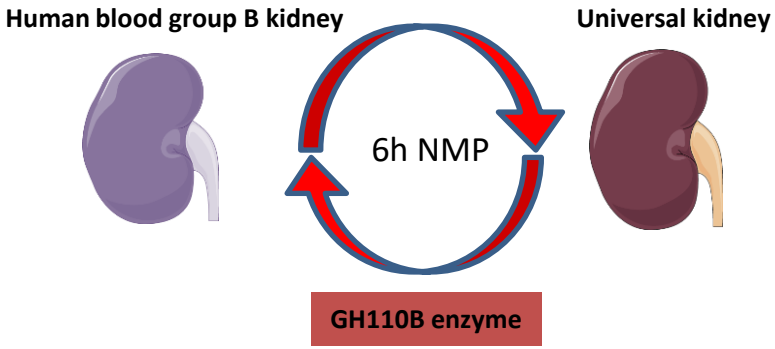
Enzymatic conversion of blood group B donor kidneys



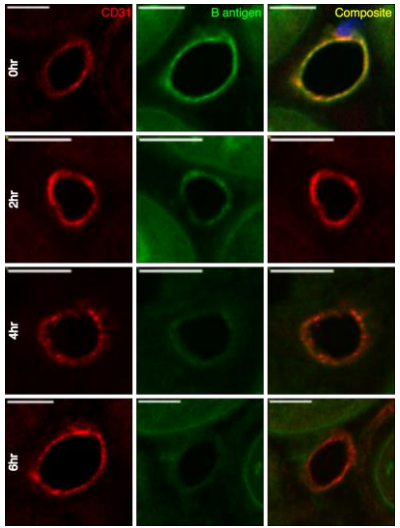


Courtesy of Prof M Nicholson & Dr S Hosgood, University of Cambridge
MacMillan S, Hosgood SA, Nicholson ML. Enzymatic blood group conversion of human kidneys during ex vivo normothermic machine perfusion. Br J Surg. 2023;110:133–7.

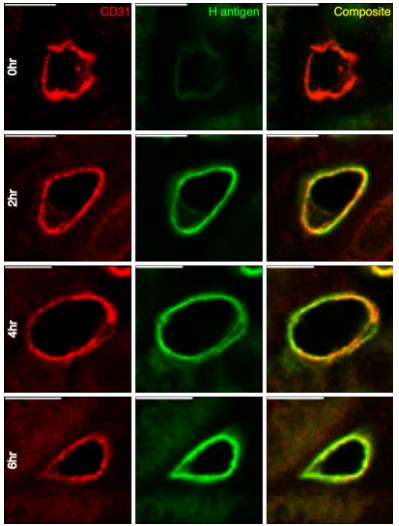
Normothermic machine perfusion



Removal of B antigen



Emergence of H antigen



URINE RECIRCULATION FOR LONG TERM NMP

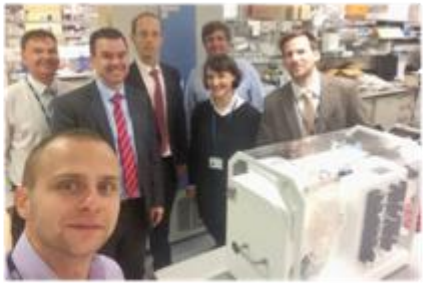
DOI: 10.1111/ajt.14932

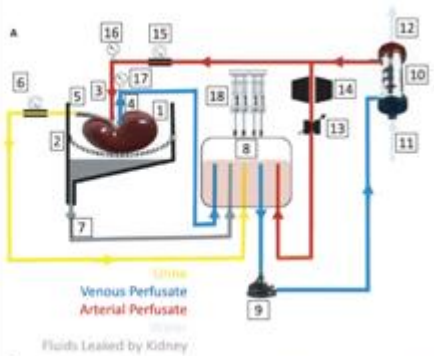
ORIGINAL ARTICLE

AJT

Twenty-four–hour normothermic perfusion of discarded human kidneys with urine recirculation

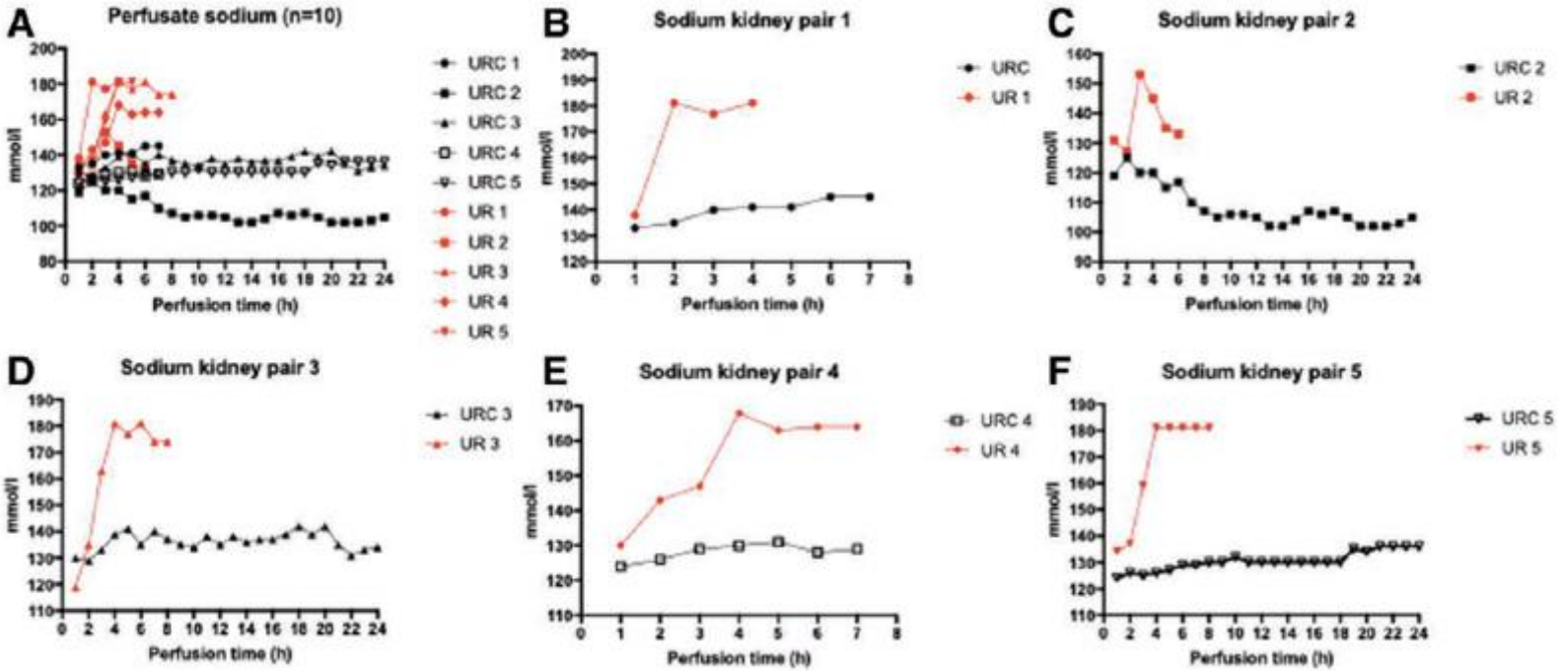
Annemarie Weissenbacher[1] | Letizia Lo Faro[1] | Olga Boubriak[2] | Maria F. Soares[3] | Ian S. Roberts[3] | James P. Hunter[1] | Daniel Voyce[4] | Nikolay Mikov[4] | Andrew Cook[4] | Rutger J. Ploeg[1] | Constantin C. Coussios[2] | Peter J. Friend[1]





- *Weissenbacher A, Lo Faro L, Boubriak O, et al. Twenty-four-hour normothermic perfusion of discarded human kidneys with urine recirculation. Am J Transplant. 2019;19:178-192.*
- *Weissenbacher A, Voyce D, Ceresa CDL, et al. Urine recirculation improves hemodynamics and enhances function in normothermic kidney perfusion. Transplant Direct. 2020;6:e541.*

URINE RECIRCULATION ENABLES 24 HOURS NMP



- *Weissenbacher A, Lo Faro L, Boubriak O, et al. Twenty-four-hour normothermic perfusion of discarded human kidneys with urine recirculation. Am J Transplant. 2019;19:178-192.*
- *Weissenbacher A, Voyce D, Ceresa CDL, et al. Urine recirculation improves hemodynamics and enhances function in normothermic kidney perfusion. Transplant Direct. 2020;6:e541.*

OXFORD KIDNEY NMP – PHASE I CLINICAL TRIAL

M07: Prolonged duration normothermic perfusion of the kidney prior to transplantation – preliminary data from a phase 1 clinical trial

Mr Richard Dumbill[1,2], Mr Simon Knight[1,2], Mr James Hunter[1,2], Mr John Fallon[1,2], Mr Daniel Voyce[3,4], Mr Jacob Barrett[4], Mr Matt Ellen[4], Ms Annemarie Weissenbacher[5], Professor Rutger Ploeg[1,2], Professor Constantin Coussios[3,4], Professor Peter Friend[1,2,4]

[1]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom. [2]Oxford Transplant Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom. [3]Oxford Institute of Biomedical Engineering, University of Oxford, Oxford, United Kingdom. [4]OrganOx Ltd., Oxford, United Kingdom. [5]Medical University of Innsbruck, Innsbruck, Austria

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NUFFIELD DEPARTMENT OF SURGICAL SCIENCES
Medical Sciences Division
Oxford University Hospitals NHS
NHS Foundation Trust

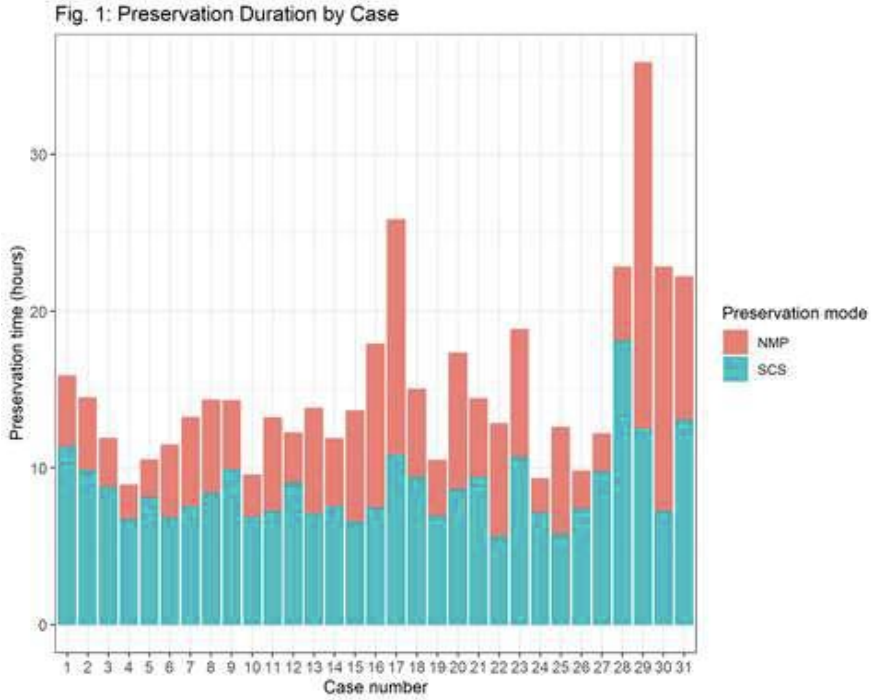
- *BTS NHSBT Joint Congress 2023 [Internet]. British Transplantation Society. Available from: https://bts.org.uk/events-meetings/bts-nhsbt-joint-congress-2023/*

OXFORD KIDNEY NMP – PHASE I CLINICAL TRIAL

- **NKP1 is single centre trial investigating the safety and feasibility of prolonged duration NMP-K following SCS, using an automated mobile system (OrganOx, UK) designed for 24-hour perfusion**
- **Transplant data of 31/36 target NMP-transplants available**
- **Min NMP time with URC 2h11min, max NMP time with URC 23h22min**
- **Total preservation time (CIT+NMP) was 9h45min to 37h19min**
- **25 patients reached 30-day follow-up with 100% dialysis independence**
- **No adverse events to the NMP technique**
- **Early graft function comparable to a control cohort matched on CIT**

- *BTS NHSBT Joint Congress 2023 [Internet]. British Transplantation Society. Available from: https://bts.org.uk/events-meetings/bts-nhsbt-joint-congress-2023/*

OXFORD KIDNEY NMP – PHASE I CLINICAL TRIAL



	NKP1 (n=31)	Controls (n=62)
Matching criteria		
CIT, hh:mm, mean (sd)	08:47 (02:33)	09:15 (02:25)
DRI, mean (sd)	1.42 (0.62)	1.36 (0.57)
Induction agent	22 Alemtuzumab 9 Basiliximab	44 Alemtuzumab 18 Basiliximab
Donor type, DCD, n (%)	12 (38.7)	24 (38.7)
Outcomes		
DGF (dialysis in first 7 days)	11 (35.5)	25 (40.3)
Day 2 creatinine reduction ratio, mean (sd)	0.35 (22)	0.18 (0.30)
30-day eGFR, mean (sd)	46.1 (15.6)	44.7 (22.0)
3-month eGFR, mean (sd)	49.8 (16.0)	49.9 (20.5)

- *BTS NHSBT Joint Congress 2023 [Internet]. British Transplantation Society. Available from: https://bts.org.uk/events-meetings/bts-nhsbt-joint-congress-2023/*

DYNAMIC LIVER PRESERVATION – A CLINICAL REALITY

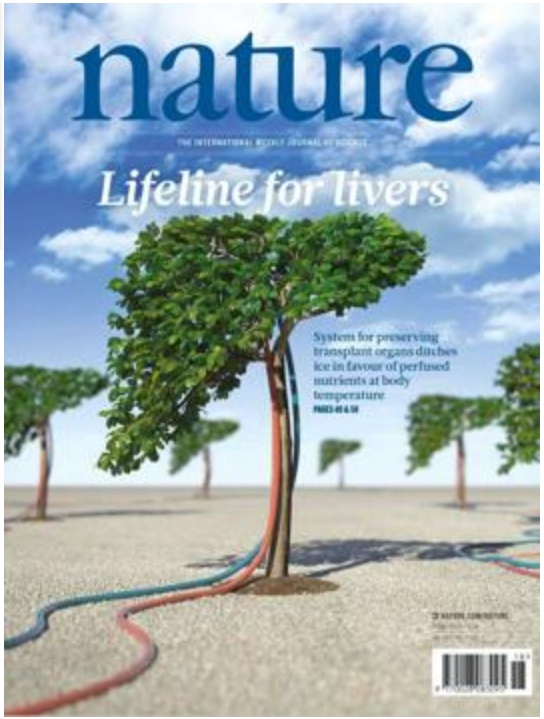
- **Prospective randomized trials available for hypothermic and normothermic liver NMP**
- **Clinically used at several (all Austrian) Tx institutions**
- **Liver NMP officially commissioned in the UK**
  - Clinical governance, shared decision making
  - NMP at all UK liver Tx centres
- **Uncertain status of legislation in regards to HMP/HOPE**

- *Nasralla D et al. A randomized trial of normothermic preservation in liver transplantation. Nature 2018;557:50-56.*
- *Van Rijn R et al. Hypothermic machine perfusion in liver transplantation – a randomized trial. N Engl J Med 2021;384:1391-1401.*

RCT I

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.

- 50% lower level of graft injury, ↓ peak AST
- 50% lower rate of organ discard
- 54% longer mean preservation time



- *Nasralla et al. A randomized trial of normothermic preservation in liver transplantation. Nature 2018;557:50-56.*

RCT II

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 15, 2021 VOL. 384 NO. 15

Hypothermic Machine Perfusion in Liver Transplantation — A Randomized Trial

R. van Rijn, I.J. Schurink, Y. de Vries, A.P. van den Berg, M. Cortes Cerisuelo, S. Darwish Murad, J.I. Erdmann, N. Gilbo, R.J. de Haas, N. Heaton, B. van Hoek, V.A.L. Huurman, I. Jochmans, O.B. van Leeuwen, V.E. de Meijer, D. Monbaliu, W.G. Polak, J.J.G. Slangen, R.I. Troisi, A. Vanlander, J. de Jonge, and R.J. Porte, for the DHOPE-DCD Trial Investigators*

- *Van Rijn R et al. Hypothermic machine perfusion in liver transplantation – a randomized trial. N Engl J Med 2021;384:1391-1401.*

Table 2. Primary and Secondary End Points.*

Outcome	Machine Perfusion (N=78)	Control (N=78)	Treatment Effect (95% CI)	P Value
Primary end point†				
Nonanastomotic biliary strictures — no. (%)	5 (6)	14 (18)		0.03
Unadjusted risk ratio			0.36 (0.14 to 0.94)	0.03
Adjusted risk ratio			0.35 (0.14 to 0.92)	0.03
Secondary end points				
Postreperfusion syndrome				
>30% decrease in systemic mean arterial pressure — no./total no. (%)	9/72 (12)	19/70 (27)	0.43 (0.20 to 0.91)‡	
>30% decrease in systemic mean arterial pressure or ≥100% increase in norepinephrine dose — no./total no. (%)	20/72 (28)	33/72 (46)	0.59 (0.38 to 0.92)‡	
Serum potassium after reperfusion — mmol/liter§	4.1±0.7	4.4±1.1	−0.4 (−0.1 to −0.6)	
Graft-related complication — no. (%)				
Early allograft dysfunction¶	20 (26)	31 (40)	0.61 (0.39 to 0.96)	
Primary nonfunction	0	1 (1)	NA	
Hepatic-artery thrombosis	2 (3)	2 (3)	0.94 (0.12 to 7.19)‡	
Portal-vein thrombosis	0	2 (3)	NA	
Biliary anastomotic stricture	23 (29)	22 (28)	1.07 (0.52 to 2.20)‡	
Biliary anastomotic leakage	6 (8)	8 (10)	0.69 (0.22 to 2.13)‡	
Renal failure leading to dialysis — no. (%)	7 (9)	7 (9)	0.79 (0.27 to 2.34)‡	
Median duration of stay (interquartile range) — days				
In the intensive care unit	2 (2 to 5)	2 (1 to 4)	NA	
In the hospital	15 (12 to 20)	15 (12 to 26)	NA	
Retransplantation within 6 mo — no. (%)	3 (4)	6 (8)	0.49 (0.12 to 1.94)‖	
Primary nonfunction — no.	0	1		
Hepatic-artery thrombosis — no.	2	1		

- *Van Rijn R et al. Hypothermic machine perfusion in liver transplantation – a randomized trial. N Engl J Med 2021;384:1391-1401.*

RCT III

JAMA Surgery

RCT: Impact of Portable Normothermic Blood-Based Perfusion vs Ischemic Cold Storage on Outcomes of Liver Transplant

POPULATION

202 Men, 97 Women

Patients ≥18 y listed for liver transplant on the United Network of Organ Sharing national waiting list

Median age: 57.8 y (IQR, 19.5-77.8 y)

INTERVENTION

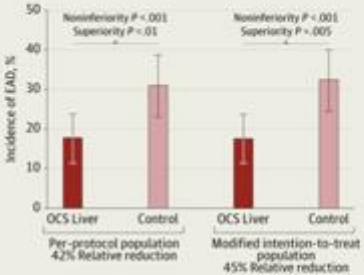
392 Patients randomized
300 Patients analyzed

153 Portable normothermic machine liver perfusion (PNMP)
Normothermic deceased donor liver preservation via portable Organ Care System (OCS)

147 Ischemic cold storage (ICS) of donor liver
Deceased donor liver preservation initiated at donor with conventional ICS

FINDINGS

Liver grafts preserved by PNMP using OCS resulted in significantly reduced incidence of EAD compared with ICS. The mean number of LGRSAEs in the OCS group was noninferior to that in the ICS group.



Incidence of EAD:
PNMP with OCS,18.0%
ICS, 31.2%
(*P* = .01)

Mean number of LGRSAEs:
PNMP with OCS, 0.046
ICS, 0.075
(noninferiority *P* < .001)

SETTINGS / LOCATIONS

20 Major US academic liver transplant centers

PRIMARY OUTCOME

Primary effectiveness end point was incidence of early allograft dysfunction (EAD) by postoperative day 7. Primary safety end point was mean number of liver graft-related severe adverse events (LGRSAEs) by 30 d.

Markmann JF, Abouljoud MS, Ghobrial RM, et al. Impact of portable normothermic blood-based machine perfusion on outcomes of liver transplant: the OCS Liver PROTECT randomized clinical trial. *JAMA Surg*. Published online January 5, 2022. doi:10.1001/jamasurg.2021.6781

RCT IV

Randomized controlled trial in DBD liver grafts:
Cold storage (control) *vs.* cold storage with HOPE (HOPE) before transplantation
Primary endpoint: number of patients with one or more Clavien ≥III complication within 12 months after liver transplantation

Highlights

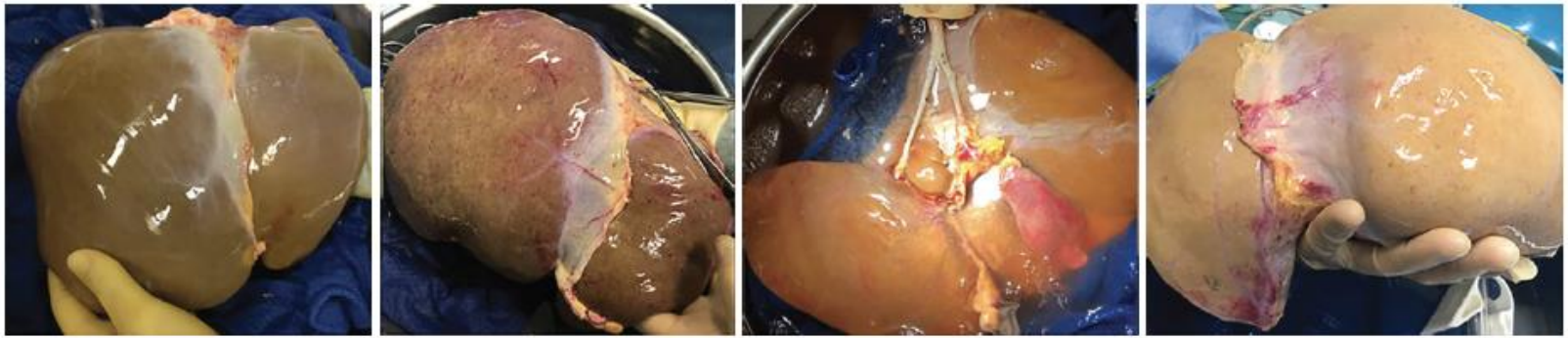
- The number of patients with at least one Clavien ≥III complication was not significantly different between groups.
- Severe post-transplant complications (Clavien grade IIIb or more), occurred less frequently in the HOPE-group.
- This was caused by a 3.7-fold lower number of liver-related Clavien ≥IIIb complications per patient in the HOPE-group.
- Graft failure due to liver-related complications did not occur in the HOPE-group but occurred in 7% in the control-group.

Impact and implications

This randomized controlled phase III trial is the first to investigate the impact of hypothermic oxygenated perfusion (HOPE) on cumulative complications within a 12-month period after liver transplantation. Compared to conventional cold storage, HOPE did not have a significant effect on the number of patients with at least one Clavien ≥III complication. However, we believe that HOPE may have a beneficial effect on the quantity of complications per patient, based on its application leading to fewer severe liver graft-related complications, and to a lower risk of liver-related graft loss. The HOPE approach can be applied easily after organ transport during recipient hepatectomy. This appears fundamental for wide acceptance since concurring perfusion technologies need either perfusion at donor sites or continuous perfusion during organ transport, which are much costlier and more laborious. We conclude therefore that the *post hoc* findings of this trial should be further validated in future studies.

- *Schlegel A, Mueller M, Muller X, Eden J, Panconesi R, von Felten S, et al. A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. J Hepatol. 2023;78:783–93.*

NAPLES Study – NMP for Liver ReTx



Non-steatotic	Mild steatosis	Moderate steatosis	Severe steatosis
Graft features: Donor ALT of 2180 units/L. Coagulative necrosis (10%) but no macrovesicular steatosis on biopsy	**Graft features:** Donor diabetic with BMI of 40 kg/m². Biopsy confirmed 5–10% macrovesicular steatosis	**Graft features:** Donor history of excessive alcohol consumption and ALT 2600 units/L at time of organ donation	**Graft features:** Severe steatosis on visual assessment. Graft not transplanted as it failed to attain viability criteria. Perfusate lactate 5.4 mmol/l after 4 h of perfusion
Recipient: 30-year-old man undergoing retransplant for ITBL	**Recipient:** 44-year-old woman with recurrence of primary sclerosing cholangitis	**Recipient:** 27-year-old woman undergoing retransplant for ITBL	

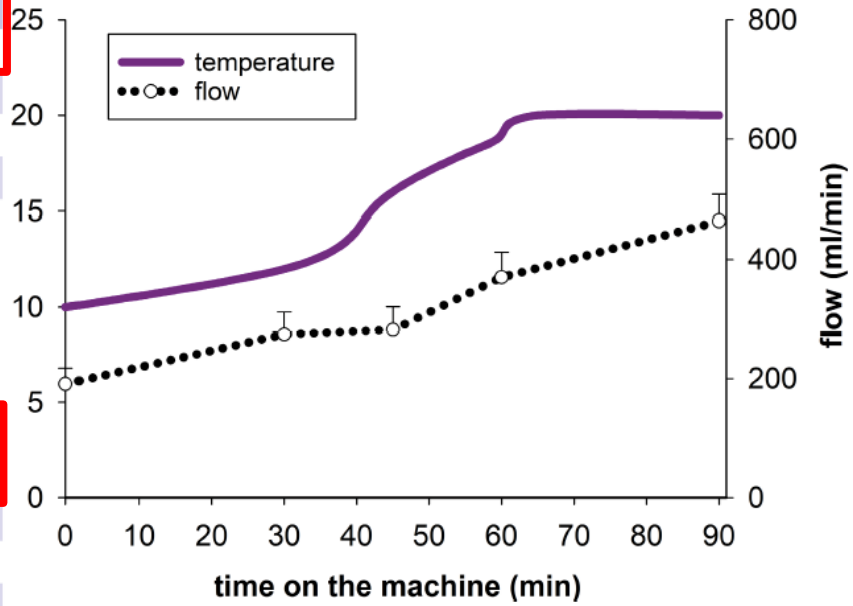
Fig. 2 Macroscopic assessment of liver allograft steatosis

Macroscopic appearance of grafts with varying severity of steatosis. Examples of grafts transplanted in the normothermic machine perfusion (NMP) cohort. The graft with severe steatosis was not transplanted owing to its failure to attain the major criterion of a perfusate lactate level below 2.5 mmol/l after 4 h of NMP. ALT, alanine aminotransferase; ITBL, ischaemic-type biliary lesions.

- *Hann A, Lembach H, Nutu A, Dassanayake B, Tillakaratne S, McKay SC, et al. Outcomes of normothermic machine perfusion of liver grafts in repeat liver transplantation (NAPLES initiative). Br J Surg. 2022;109:372–80.*

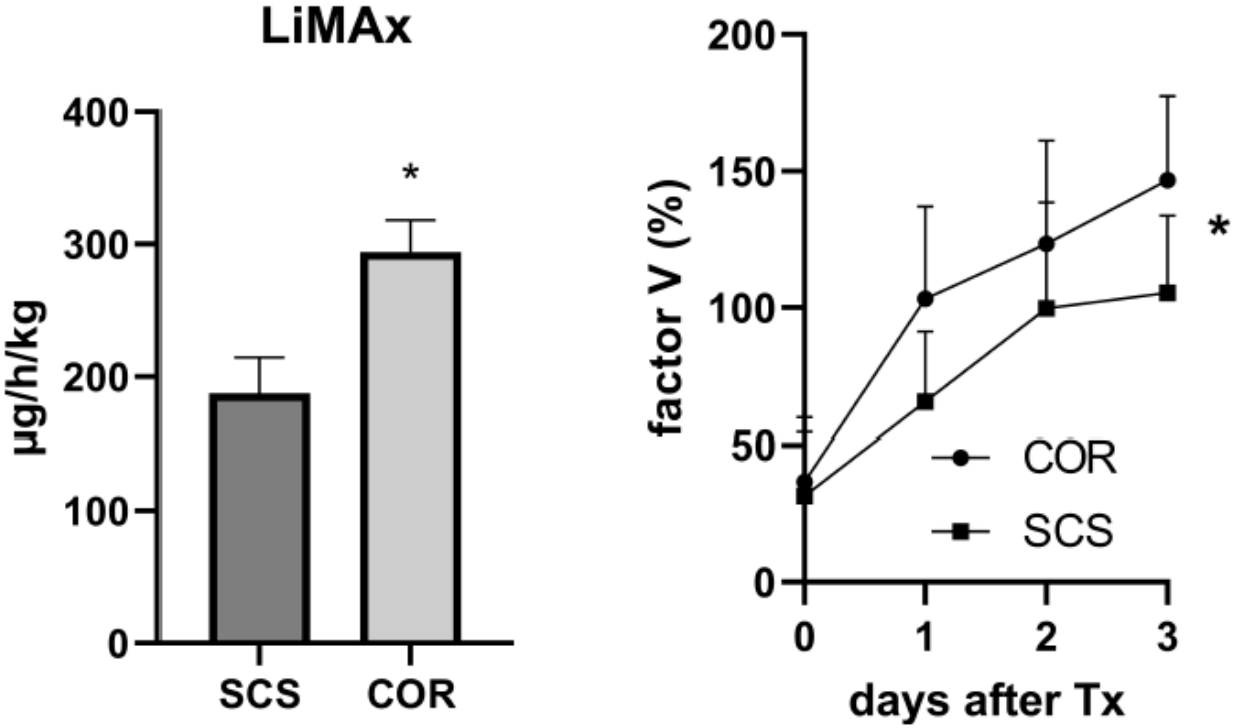
Controlled Oxygenated Rewarming – Liver Tx

Donor characteristics	COR ($n = 20$)	SCS ($n = 20$)	Total
Donor age, years	63.65 ± 12.75	63.50 ± 16.18	63.58 ± 14.38
Donor gender, M/F (%)	9/20 (45.0)	5/20 (25.0)	14/40 (35.0)
Donor BMI, kg/m^2	27.15 ± 3.96	27.91 ± 6.13	27.53 ± 5.11
Donor ICU stay, days	5.70 ± 4.54	4.90 ± 4.09	5.30 ± 4.29
Donor cause of death *n* (%)			
Cerebrovascular	16/20 (80.0)	12/20 (60.0)	28/40 (70.0)
Hypoxia	3/20 (15.0)	6/20 (30.0)	9/40 (22.5)
Trauma	1/20 (5.0)	1/20 (5.0)	2/40 (5.0)
Others	0/20 (0.0)	1/20 (5.0)	1/40 (2.5)
Donor risk index	1.80 ± 0.31	1.90 ± 0.29	1.85 ± 0.37
Macrosteatosis (≥20%)	15/20 (75)	14/20 (70)	29/40 (72.5)
Storage solution HTK/UW, *n*	20/0	20/0	40/0
Cold ischemia time, min	485 ± 82	454 ± 83	469 ± 81
Warm ischemia time, min	29.5 ± 5.3	27.1 ± 6.3	28.3 ± 5.9



- *Minor T, von Horn C, Zlatev H, Saner F, Grawe M, Lüer B, et al. Controlled oxygenated rewarming as novel end-ischemic therapy for cold stored liver grafts. A randomized controlled trial. Clin Transl Sci. 2022;15:2918–27.*

Controlled Oxygenated Rewarming – Liver Tx



- *Minor T, von Horn C, Zlatev H, Saner F, Grawe M, Lüer B, et al. Controlled oxygenated rewarming as novel end-ischemic therapy for cold stored liver grafts. A randomized controlled trial. Clin Transl Sci. 2022;15:2918–27.*

PREDICTIVE MARKERS FOR EAD DURING NMP

- EAD was more likely in livers with lower perfusate pH
- Number of platelets in perfusate correlated with CIT and indicative for occurrence of EAD
- vWF antigen was significantly higher in perfusates of EAD livers
- Perfusate transaminases, AP and LDH correlated with MEAF score
- Perfusate parameters measured at hour 6 after NMP start equivalent to overall analyses
- CIT </>6 hours, NMP </> 12 hours and overall preservation </> 18 hours did not impact postoperative liver function

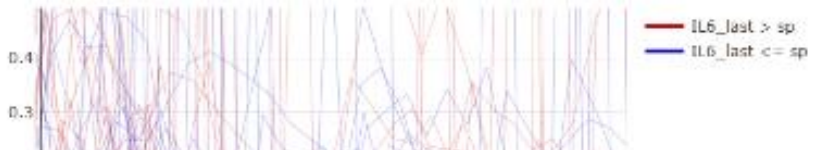
- *Weissenbacher et al. Perfusate enzymes and platelets indicate early allograft dysfunction after transplantation of normothermically preserved livers. Transplantation 2021*

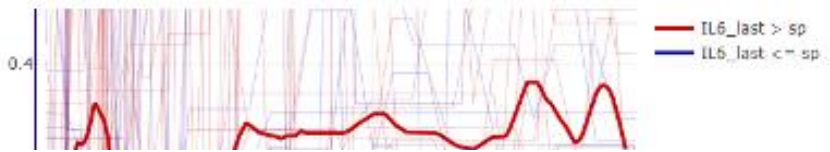
Interleukin-6 and Reperfusion syndrome

- Clinical observation
- Hypothesis: IL6 in perfusates of livers resulting in reperfusion syndrome is higher
- 77 transplanted NMP livers investigated
- 15 DCD, median donor age 61; median recipient age 60
- Median CIT 6.2 hrs, NMP 17.6 hrs, overall 23.6 hrs
- Median (IQR) IL6 in perfusate 52 (175), 278 (674) and 174 (2171) ng/L
- CIT and NMP time do not correlate with perfusate IL6
- IL6 does not correlate with occurrence of EAD

- *Angelico R, Perera MTPR, Ravikumar R, et al. Normothermic machine perfusion of deceased donor liver grafts is associated with improved postreperfusion hemodynamics. Transplant Direct 2016;2:e97*
- *Weissenbacher A, Mathis S, et al, unpublished*

Interleukin-6 und Reperfusion syndrome





NMP liver recipients with perfusate-IL6 higher than median IL6, have significant lower MAP (20% decrease from baseline) despite significant higher catecholamine dosage (25% increase from baseline) up to 30 minutes post reperfusion

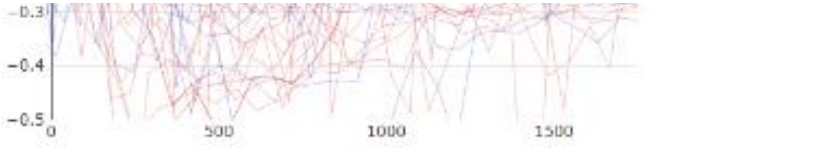


Figure 1A) MAP compared to baseline

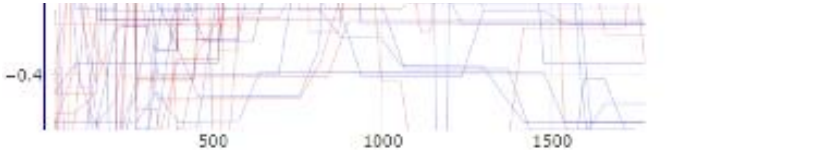


Figure 1B) Catecholamine demand compared to baseline

- *Weissenbacher A, Mathis S et al, unpublished*

PLUS – Perfused Liver Utilisation Study

- Utilisation of normothermic machine preservation in extended criteria livers - a national threshold-crossing study
- To assess whether normothermic machine preservation (NMP) can increase the availability of livers for transplantation without compromising the outcome
- The primary endpoint will be the proportion of organs transplanted with function at 12 months

- To provide the evidence needed to determine whether NMP should be adopted for routine use, and help to inform the pricing model and adoption strategy required to make this possible
- NIHR funded; June 2020 – December 2023

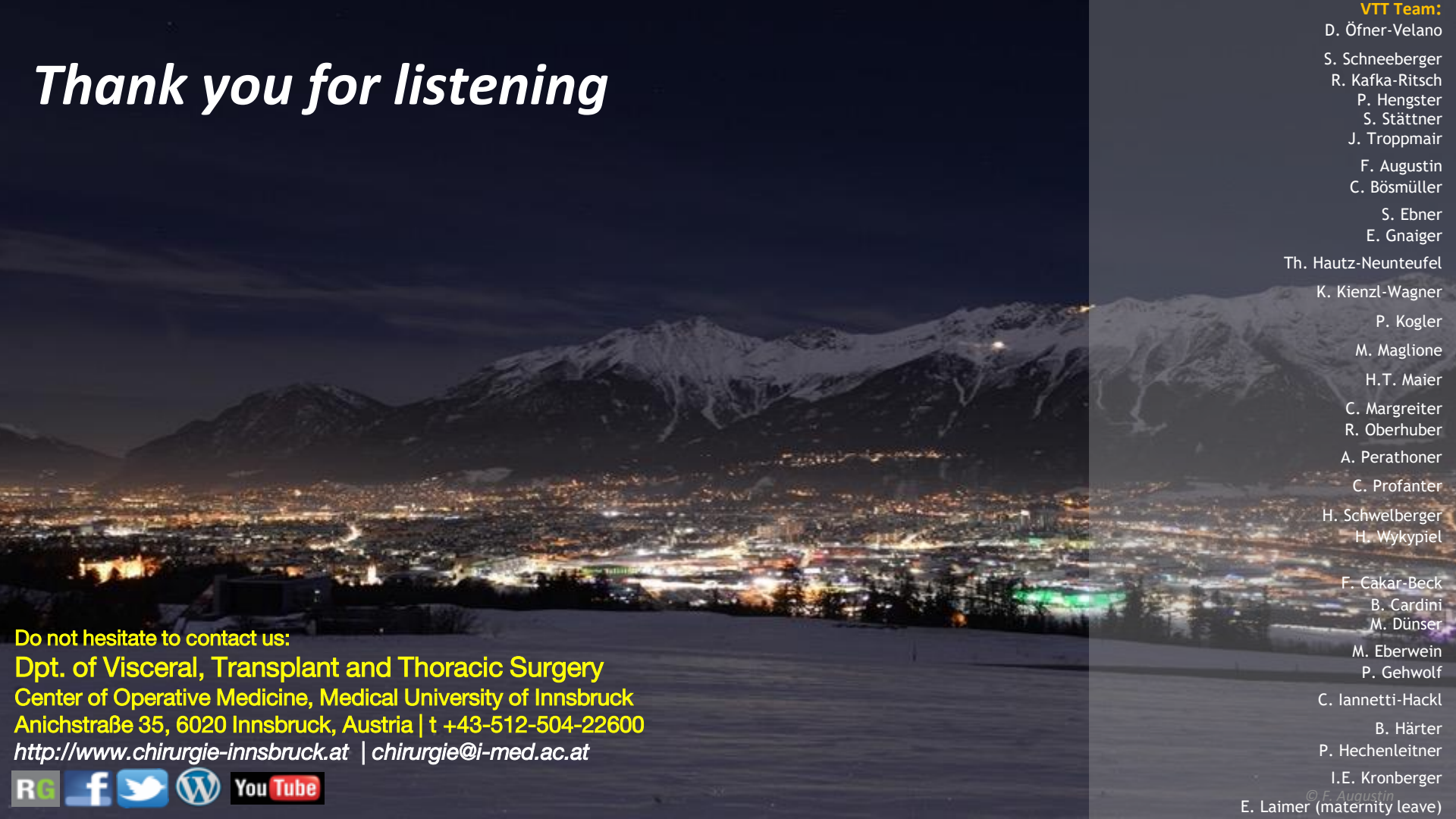
DEFATTING DONOR LIVERS DURING NMP

- **Defatting during NMP will allow more steatotic livers to be transplanted with improved outcomes**
- **Randomly assign 60 livers from donors with a high-risk of hepatic steatosis to either NMP alone or NMP with defatting interventions**
- **Primary endpoint will be the proportion of livers that achieve predefined functional criteria during perfusion and indicate potential suitability for Tx**
- **First study to deliver an ex-situ intervention during NMP with subsequent Tx**
- **If intervention proves effective, safe transplantation of livers that are currently very likely to be discarded**
- **NIHR funded; April 2021 – April 2024**

CONCLUSIONS

- **Ex situ preservation feasible + safe**
- **Viability assessment is on the horizon**
- **More sensitive perfusate markers are required**
  - Prediction of IRI currently imperfect
- **Data published stop short of transplant survival-based studies**
  - Crucial before progressing further with NMP?
  - Impossible? Too late?
- **Short term vs long term- what are the real-world challenges?**
  - Technical tour de force or real clinical advance
  - Organ repair and reconditioning
- **Transportable devices are needed – issues of usability**

Thank you for listening



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