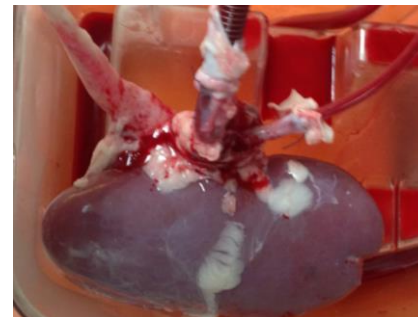


Machineperfusie van abdominale organen: *van donor tot ontvanger*

Intensivistendagen 2023

Dr. Volkert Huurman
Transplantatiechirurg
Leids Universitair Medisch Centrum

v.a.l.huurman@lumc.nl



Disclosure belangen spreker	
Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties	Projectsubsidie NRP Ministerie van VWS, no. 331958
<ul style="list-style-type: none"> • Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk... 	XVIVO, Göteborg, Sweden (in-kind research support)

Machineperfusie

Waarom en hoe

De nier

Het pancreas

De lever

De donor

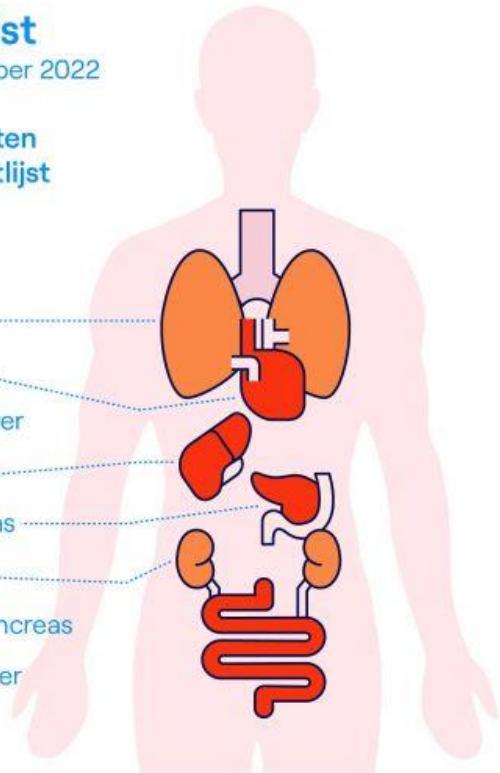
Machineperfusie? Hoezo?

Wachlijst

op 31 december 2022

1247 patiënten
op de wachtlijst

- 127 Long
- 127 Hart
- 1 Hart/lever
- 38 Lever
- 16 Pancreas
- 923 Nier
- 13 Nier/pancreas
- 2 Nier/lever



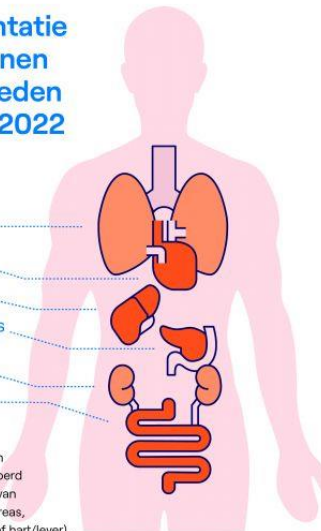
Voorlopige cijfers 2022 van de Nederlandse Transplantatie Stichting

Transplantatie met organen van overleden donoren 2022

- 122 Long
- 51 Hart
- 182 Lever
- 35 Pancreas
- 492 Nier
- 0 Darm

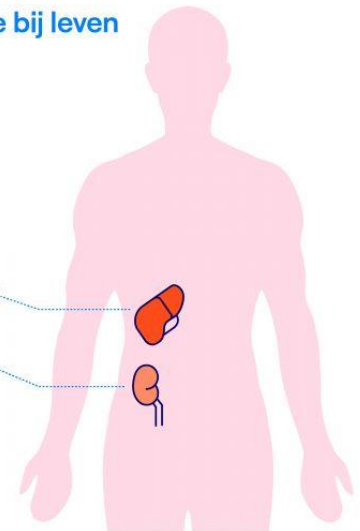
In 2022 is 25 keer een transplantatie uitgevoerd met een combinatie van 2 organen (nier/pancreas, nier/lever, hart/long of hart/lever).

Voorlopige cijfers 2022 van de Nederlandse Transplantatie Stichting, peildatum 10 januari 2023.



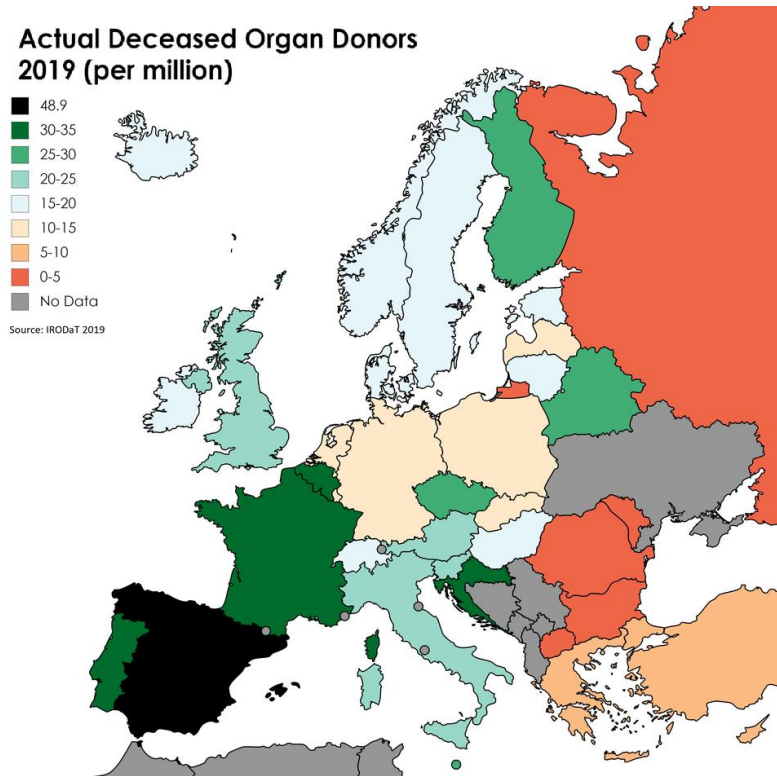
Donatie bij leven 2022

- 26 Lever
- 516 Nier

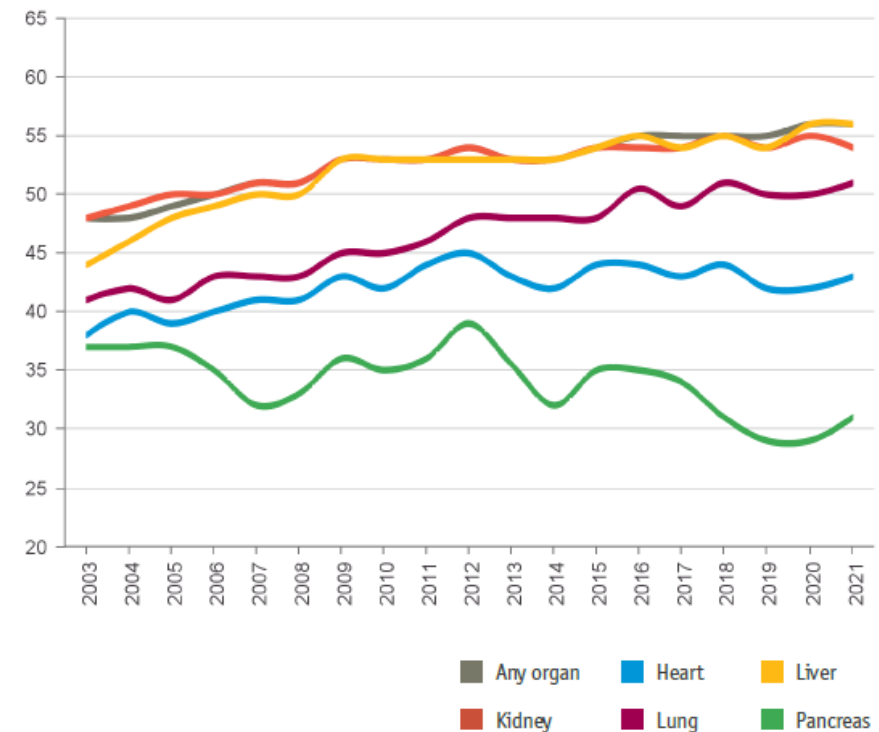


Voorlopige cijfers 2021 van de Nederlandse Transplantatie Stichting, peildatum 13 januari 2022.

Uitdagingen: donoraantal en -leeftijd



2.3.4 Median age (years) of deceased donors used for transplant in Eurotransplant, by organ

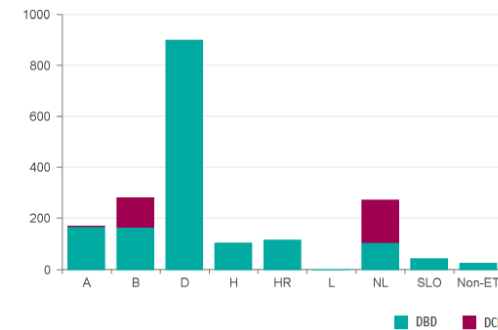


Uitdagingen (2): DCD donatie

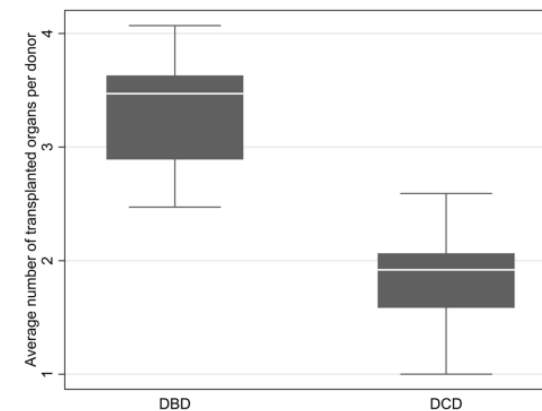
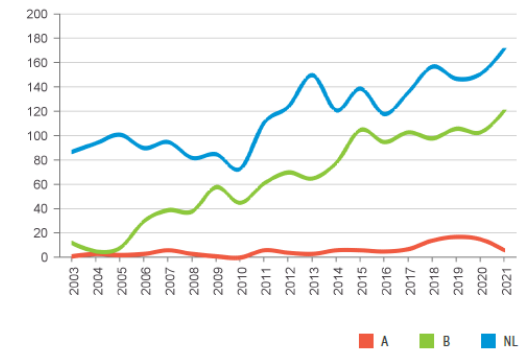


- Te weinig
- Te oud
- Te lage kwaliteit

2.4.1 DBD/DCD donors (any organ) used for transplant in Eurotransplant in 2021, by donor country



2.4.3 DCD donors (any organ) used for transplant in Eurotransplant, by donor country



Oplossingen



Meer donoren!

- Actieve donor registratie
- Levende donatie
- Xenotransplantatie ?



Verbeteren van uitgangssituatie

- Meer DBD – betere resultaten
- DCD: Pre-mortem interventies



Verbeteren orgaankwaliteit

- Tijdens uitname
- Tijdens preservatie

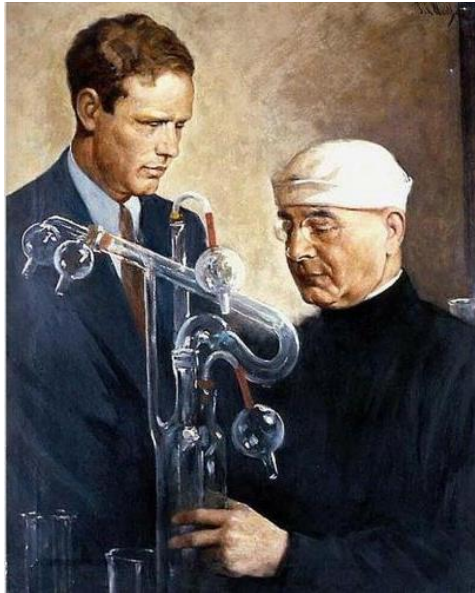


Machineperfusie!

De technische oplossing...



Een oud idee...



1938



1970



2023

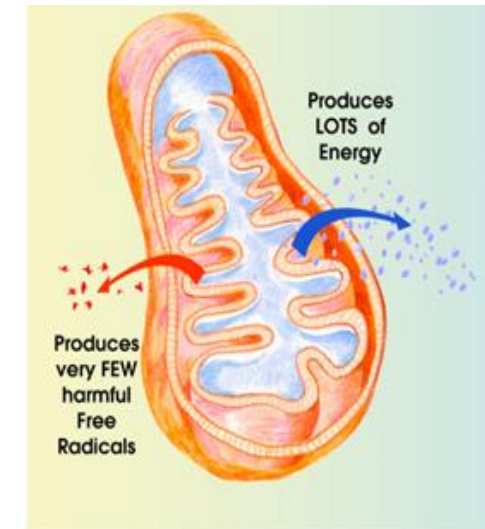
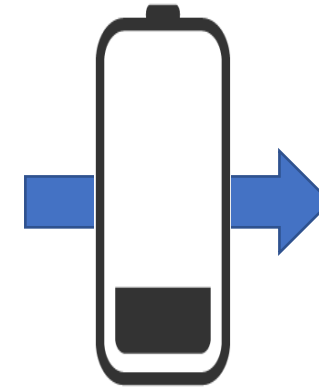
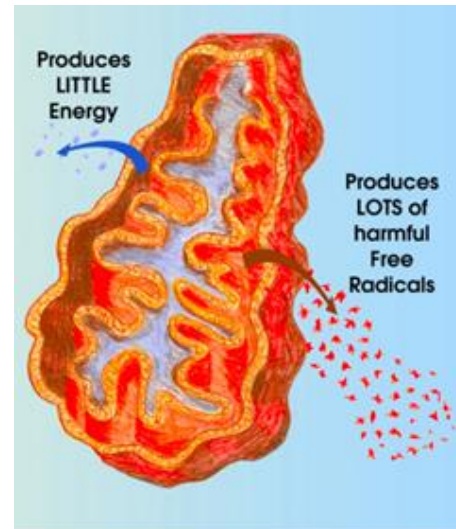
Mechanisme

Bestrijden van zuurstoftekort
in mitochondria

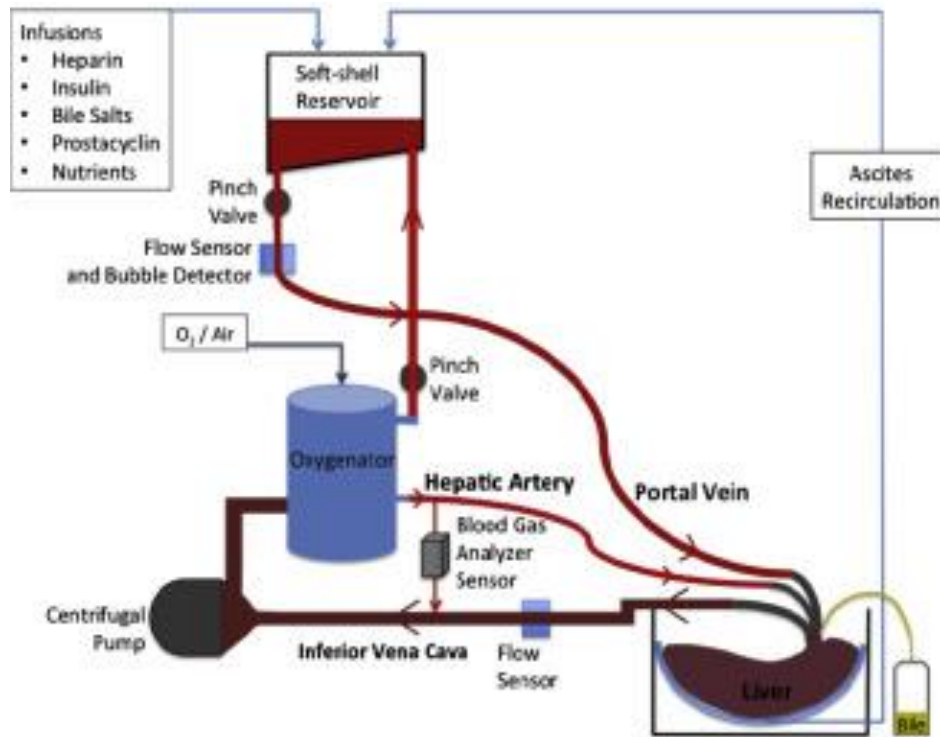
'Opladen van de batterij' ->
hoger ATP niveau

Mogelijkheid voor testen en
verbeteren organen

Logistiek voordeel



Techniek ≈ ECMO



Doelen van machineperfusie



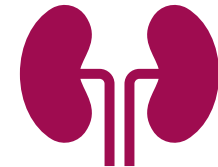
Verlagen PNF ratio

Voorkomen futiele transplantaties
(‘first do no harm’)



Verhogen orgaan utilisatie

Goede organen niet mislopen
Logistiek verbeteren



Orgaankwaliteit verbeteren

Beoordelen
Behandelen
Repareren

Meerdere opties...



- In de donor
- Tijdens transport
- Direct voor transplantatie



- Hypotherm
- Normotherm
- Met en zonder zuurstof



Nierperfusie: Nederland voorop



- RCT, n=252
- Hypotherme perfusie
- Zonder O2
- Tijdens gehele preservatieperiode

Effect:

- Minder delayed graft function
- Beter survival

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

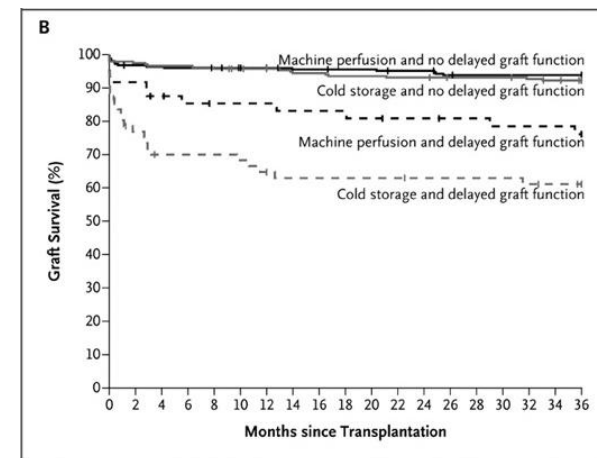
ESTABLISHED IN 1812

JANUARY 1, 2009

VOL. 360 NO. 1

Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation

Cyril Moers, M.D., Jacqueline M. Smits, M.D., Ph.D., Mark-Hugo J. Maathuis, M.D., Ph.D., Jürgen Treckmann, M.D., Frank van Gelder, Bogdan P. Napieralski, Margitta van Kasterop-Kutz, Jaap J. Homan van der Heide, M.D., Ph.D., Jean-Paul Squifflet, M.D., Ph.D., Ernest van Heurn, M.D., Ph.D., Günter R. Kirste, M.D., Ph.D., Axel Rahmel, M.D., Ph.D., Henri G.D. Leuvenink, Ph.D., Andreas Paul, M.D., Ph.D., Jacques Pirenne, M.D., Ph.D., and Rutger J. Ploeg, M.D., Ph.D.*



Nu standaard in heel NL

- January 11th 2016
- Standard preservation method
- All deceased donor kidneys



Hypothermic Machine Perfusion as a National Standard Preservation Method for Deceased Donor Kidneys

Aukje Brat, MD,¹ Kirsten M. de Vries, MSc,² Ernst W. E. van Heurn, MD, PhD,³ Volkert A. L. Huurman, MD, PhD,⁴ Wim de Jongh, BSc,⁵ Henri G. D. Leuvenink, PhD,¹ Arjan D. van Zuijlen, MD, PhD,⁶ Bernadette J. J. M. Haase-Kromwijk, MSc,² Jeroen de Jonge, MD, PhD,⁷ Stefan P. Berger, MD, PhD,⁸ and Sijbrand H. Hofker, MD¹

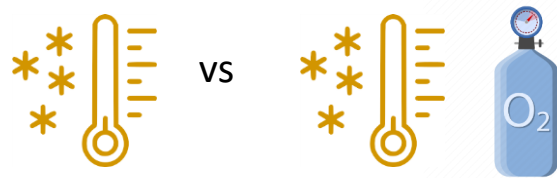
Figure 2: Forest plot of the effect of the implementation of non-oxygenated HMP on the prevalence on DGF in different donor subgroups

Subgroup	N	DGF historical cohort	N	DGF project cohort	p-value	Odds ratio (CI)	p-value
Overall	1812	43.7 (791)	681	38.2 (260)	<0.001*	0.69 (0.553 – 0.855)	0.001*
Donor type							
DBD	839	25.0 (210)	270	22.2 (60)	0.186	0.78 (0.539 – 1.112)	0.774
DCD	973	59.7 (581)	411	48.7 (200)	<0.001*	0.68 (0.513 – 0.896)	0.006*
Donor criteria							
SCD	455	20.7 (94)	146	17.8 (26)	0.426	0.83 (0.481 – 1.423)	0.493
ECD	384	30.2 (116)	124	27.4 (34)	0.284	0.72 (0.441 – 1.190)	0.203
DCD < 50	347	55.9 (194)	131	40.5 (53)	<0.001*	0.61 (0.369 – 1.004)	0.052
DCD ≥ 50	626	61.8 (387)	280	51.4 (147)	<0.001*	0.71 (0.506 – 1.001)	0.051

Preference HMP Preference CS

‘Real ‘life’ zelfde resultaten als in RCT

HMP 2.0: de COMPARE trial



Oxygenated versus standard cold perfusion preservation in kidney transplantation (COMPARE): a randomised, double-blind, paired, phase 3 trial

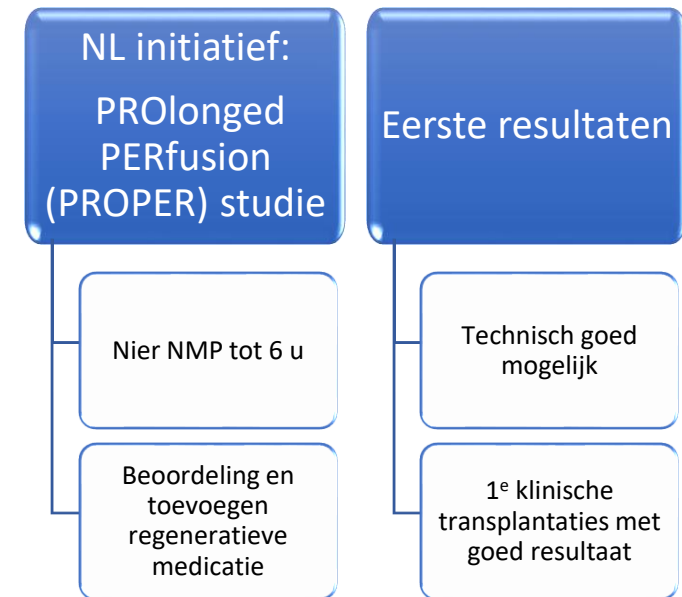
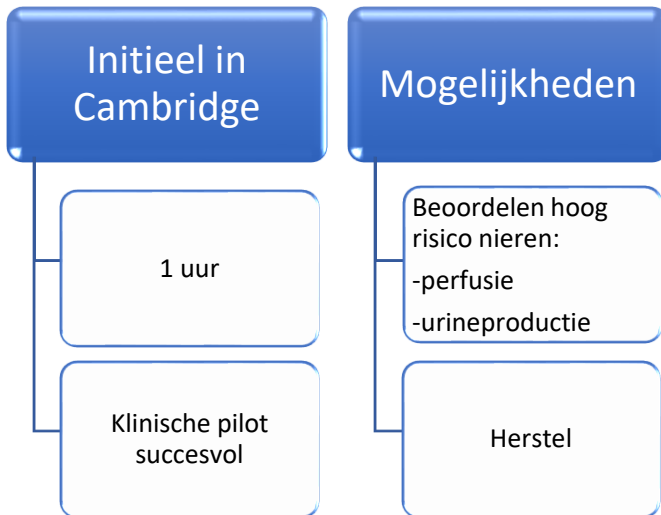
Ina Jochmans, Aukje Brat, Lucy Davies, H Sijbrand Hofker, Fenna E M van de Leemkolk, Henri G D Leuvenink, Simon R Knight, Jacques Pirenne*, Rutger J Ploeg*, on behalf of the COMPARE Trial Collaboration and Consortium for Organ Preservation in Europe (COPE)

Oxygenatie in DCD nieren leidt tot:

- Minder rejectie
- Betere overleving
- Betere nierfunctie na 1 jaar

	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
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 12 months (mL/min per 1.73 m ²)				
MDRD equation (mL/min per 1.73m ²) 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 m ²) 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

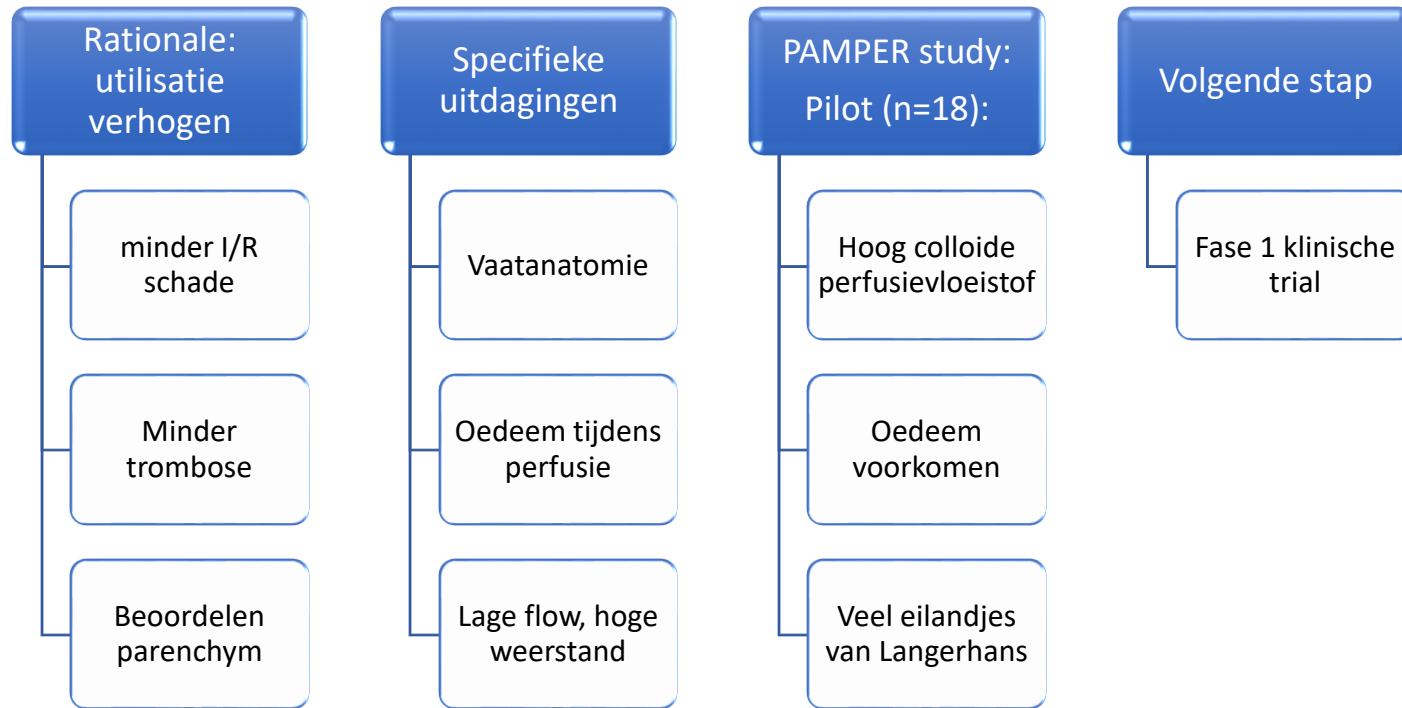
Toekomst: normotherme nierperfusie?



PROPER



Pancreasperfusie: experimenteel



Leverperfusie: opnieuw NL voorop!

- RCT n=160
- Hypotherm, Geoxygeneerd
- 2 uur, vlak voor implantatie

Effect:

- Minder early allograft dysfunctie
- Minder galwegschade / kans op retransplantatie
- Orgaan utilisatie hetzelfde

Bevestigd in 2e trial

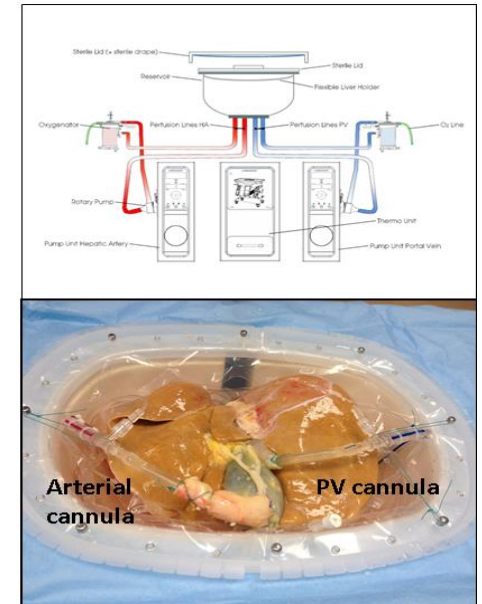
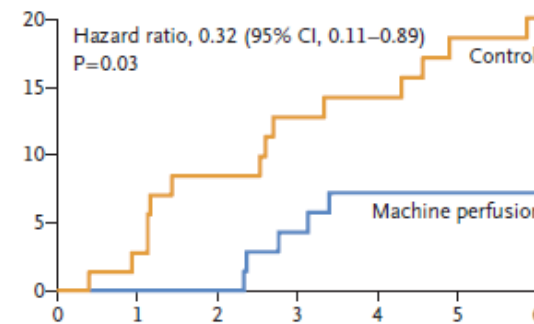


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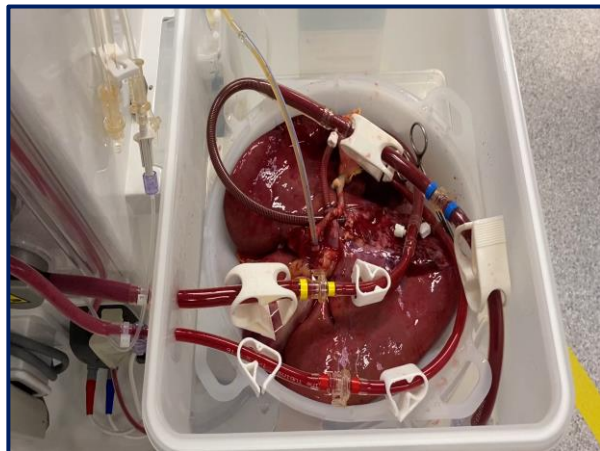
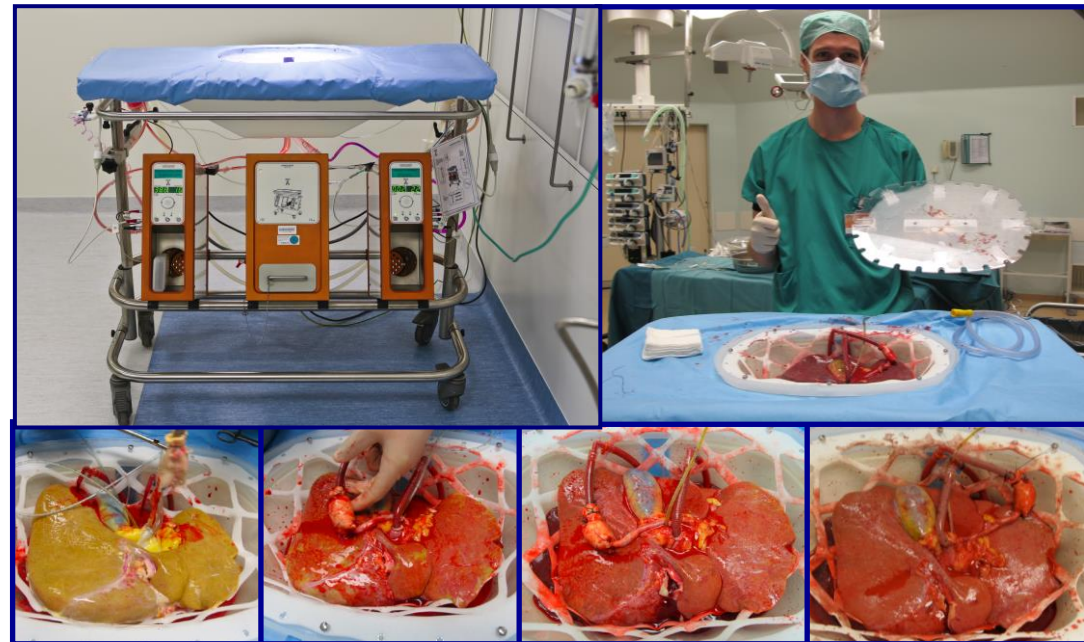
ORIGINAL ARTICLE

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. Hurman, 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*



Normotherme leverperfusie



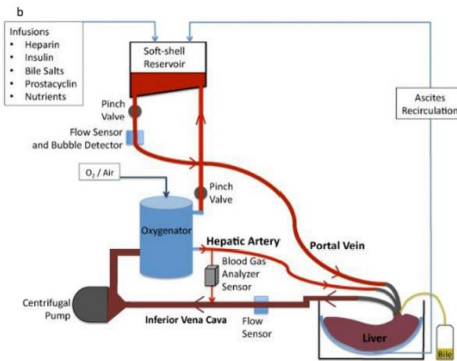
Normotherme leverperfusie

ARTICLE

<https://doi.org/10.1038/s41586-018-0047-9>

A randomized trial of normothermic preservation in liver transplantation

David Nasralla^{1*}, Constantin C. Coussios^{2*}, Hynek Mergental³, M. Zeeshan Akhtar^{1,4}, Andrew J. Butler^{5,20}, Carlo D. L. Ceresa¹, Virginia Chiochia^{6,7}, Susan J. Dutton⁸, Juan Carlos Garcia-Valdecasas⁹, Nigel Heaton¹⁰, Charles Imber¹¹, Wajal Jassem¹⁰, Ina Jochmans^{12,13}, John Karani^{10,14}, Simon R. Knight^{1,15}, Peri Kocabayoglu¹⁶, Massimo Malago¹¹, Darius Mirza³, Peter J. Morris^{1,15}, Arvind Pallan¹⁷, Andreas Paul¹⁶, Mihai Pavel⁹, M. Thamara P. R. Perera³, Jacques Pirenne^{12,13}, Reena Ravikumari¹, Leslie Russell¹⁸, Sara Upponi¹⁹, Chris J. E. Watson^{2,20}, Annemarie Weissenbacher¹, Rutger J. Ploegh³, Peter J. Friend²⁰ for the Consortium for Organ Preservation in Europe



Pilot, Open, Randomized, Prospective Trial for Normothermic Machine Perfusion Evaluation in Liver Transplantation From Older Donors

Davide Ghinolfi¹, Erion Reka¹, Vincenzo De Tata³, Maria Franzini³, Daniele Pezzati¹, Vanna Fierabracci³, Matilde Masini³, Andrea Cacciatoinsilla⁴, Maria Lucia Bindi², Lorella Marselli⁶, Valentina Mazzotti⁵, Riccardo Morganti⁵, Piero Marchetti⁶, Giandomenico Biancofiore², Daniela Campani⁴, Aldo Paolicchi³ and Paolo De Simone¹

Effect:

- Minder early allograft dysfunctie
- Galwegschade en survival onveranderd
- Toename orgaan utilisatie!

ORIGINAL ARTICLE

AJT

Sequential hypothermic and normothermic machine perfusion enables safe transplantation of high-risk donor livers

Otto B. van Leeuwen^{1,2}, Silke B. Bodewes¹, Veerle A. Lantinga¹, Martijn P.D. Haring¹, Adam M. Thorne¹, Isabel M.A. Brüggewirth¹, Aad P. van den Berg³, Marieke T. de Boer¹, Iris E.M. de Jong^{1,2}, Ruben H.J. de Kleine¹, Bianca Lascaris¹, Maarten W.N. Nijsten⁴, Koen M.E.M. Reyntjens⁵, Vincent E. de Meijer¹, Robert J. Porte¹

	Parameter	Green zone	Orange zone	Red zone
Hepatocytes	Bile production (ml)	≥ 10*	5 to 10	< 5
	Perfusate lactate (mmol/L)	< 1.7	1.7 to 4.0	> 4.0
Cholangiocytes	Perfusate pH	7.35-7.45	7.25 to 7.35	< 7.25
	Bile pH	> 7.45	7.40 to 7.45	< 7.40
	ΔpH	> 0.10	0.05 to 0.10	< 0.05
	ΔHCO ₃ ⁻ (mmol/L)	> 5.0	3.0 to 5.0	< 3.0
	ΔGlucose (mmol/L)	< -5.0	-3.0 to -5.0	> -3.0

Ontwikkelingen in 'ex-situ' leverperfusie

COR-NMP:

- Combinatie van koude en warme perfusie
- Minder galwegschade, meer utilisatie

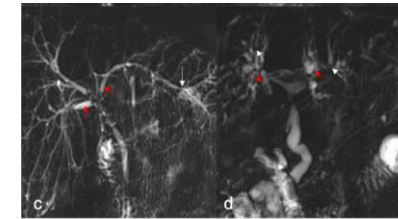
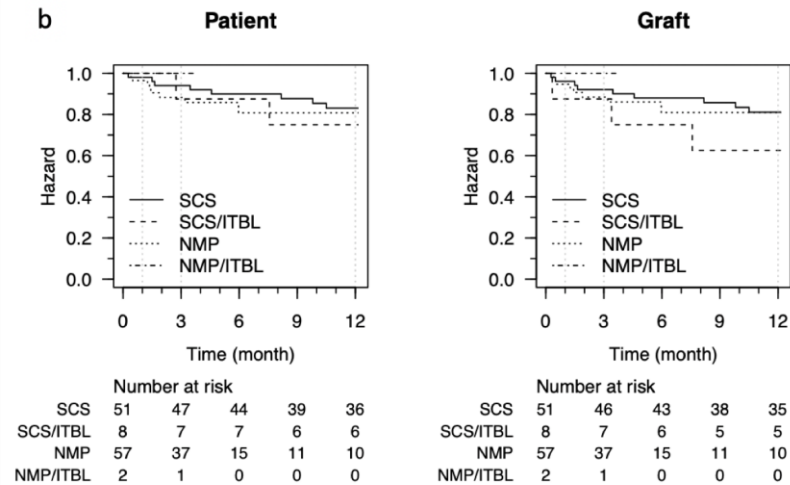
DHOPE-PRO (UMCG):

- Langdurige koude perfusie om logistieke redenen
- Transplantatie in daguren

Koude en warme leverperfusie vergoede zorg sinds 1/1/2022

Volgende stap: alleen nog overdag?

Superieur resultaat met lange perfusie!



Item	SCS		NMP		P value
	n	m	n	m	
Length Of Stay (Days)*	59	23 (21)	55	17 (12)	p=.006
Clavien Dindo Classification	59		57		p=.086
Ischemic Type Biliary Lesions (ITBL)	59	8 (14)	59	2 (3)	p=.047
ITBL grade	8		2		n.a
Mild		1 (12)		2 (100)	
Moderate		1 (12)		.	
Severe		6 (75)		.	
Intrahepatic Cast	25	3 (12)	17	.	p=.138
Extrahepatic Cast	25	6 (24)	17	.	p=.029
Cholangitis	59	11 (19)	59	4 (7)	p=.053

Fodor M et al, BJS 2021

Department of Visceral, Transplant und Thoracic Surgery | Daniel Swarovski Research Laboratory



Het kan altijd langer...

nature
biotechnology

ARTICLES

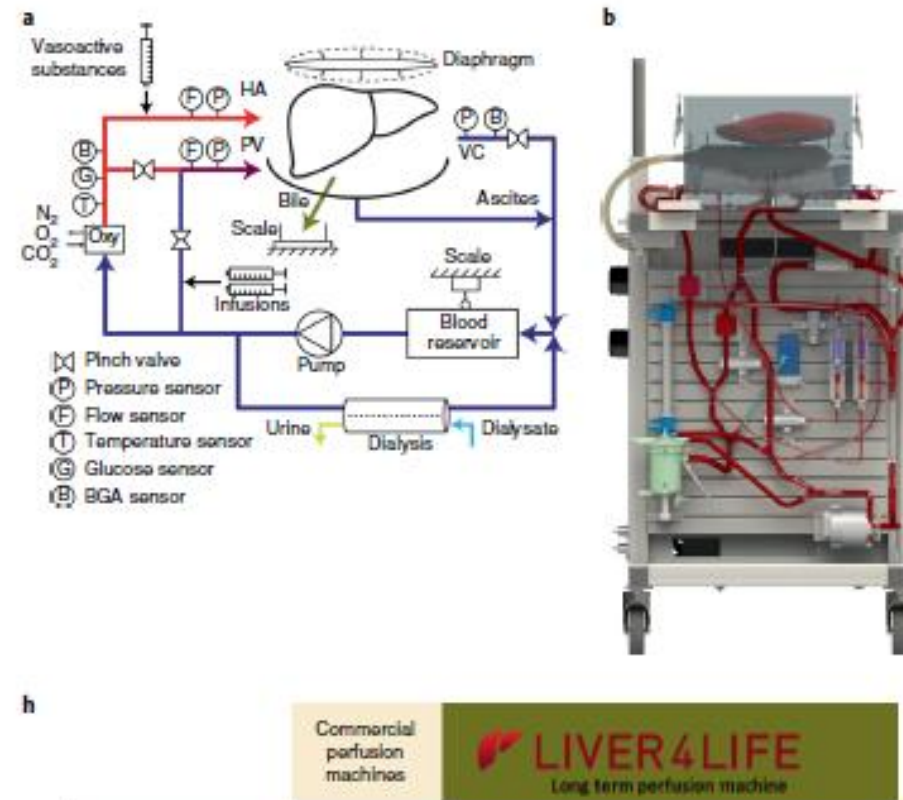
<https://doi.org/10.1038/s41587-019-0374-x>

An integrated perfusion machine preserves injured human livers for 1 week

Dilmurodjon Eshmuminov^{1,2,6}, Dustin Becker^{2,3,6}, Lucia Bautista Borrego^{1,2}, Max Hefti^{2,3}, Martin J. Schuler^{2,3}, Catherine Hagedorn^{1,2}, Xavier Muller^{1,2}, Matteo Mueller^{1,2}, Christopher Onder^{2,4}, Rolf Graf^{1,2}, Achim Weber⁵, Philipp Dutkowski^{1,2}, Philipp Rudolf von Rohr^{2,3,7} and Pierre-Alain Clavien^{1,2,7*}

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

Pierre-Alain Clavien^{1,2}, Philipp Dutkowski¹, Matteo Mueller^{1,2}, Dilmurodjon Eshmuminov^{1,2}, Lucia Bautista Borrego^{1,2}, Achim Weber³, Beat Muellhaupt⁴, 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}



Baas boven baas...

Ischemie-vrije levertransplantatie

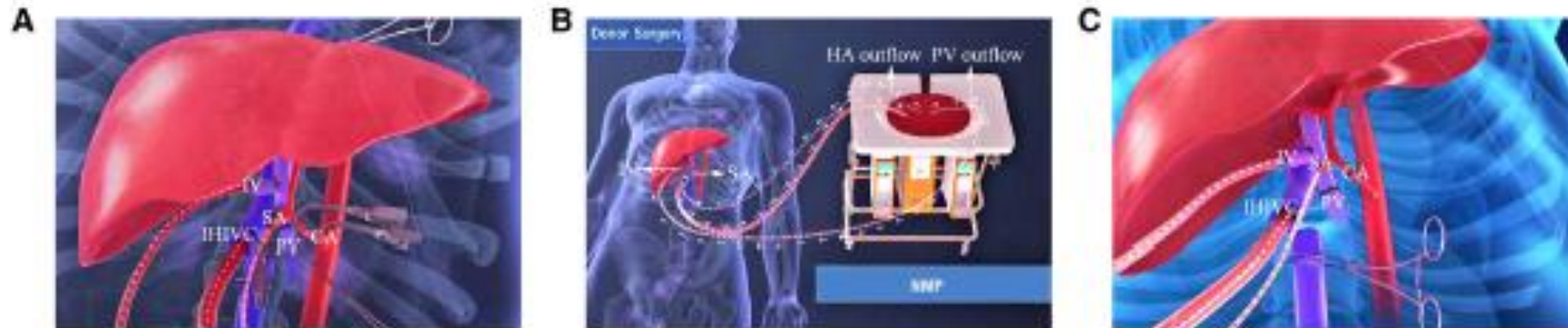
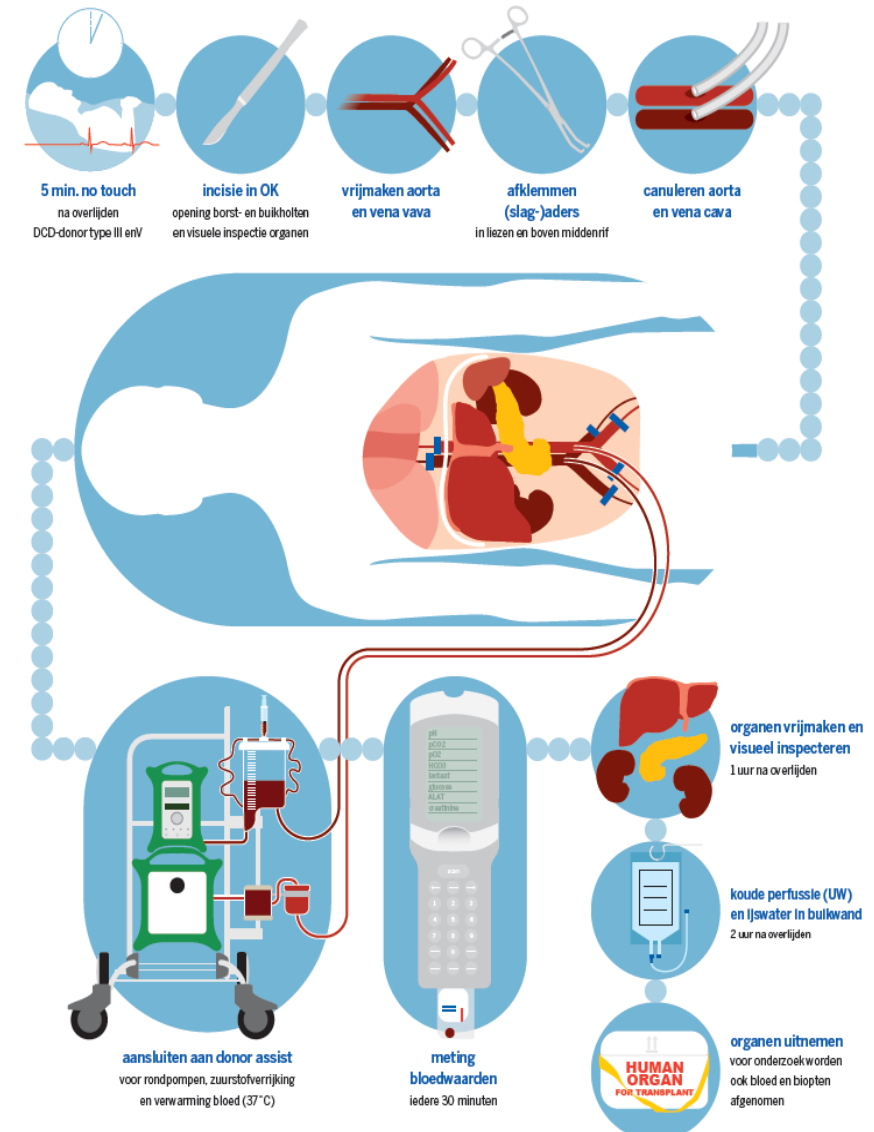


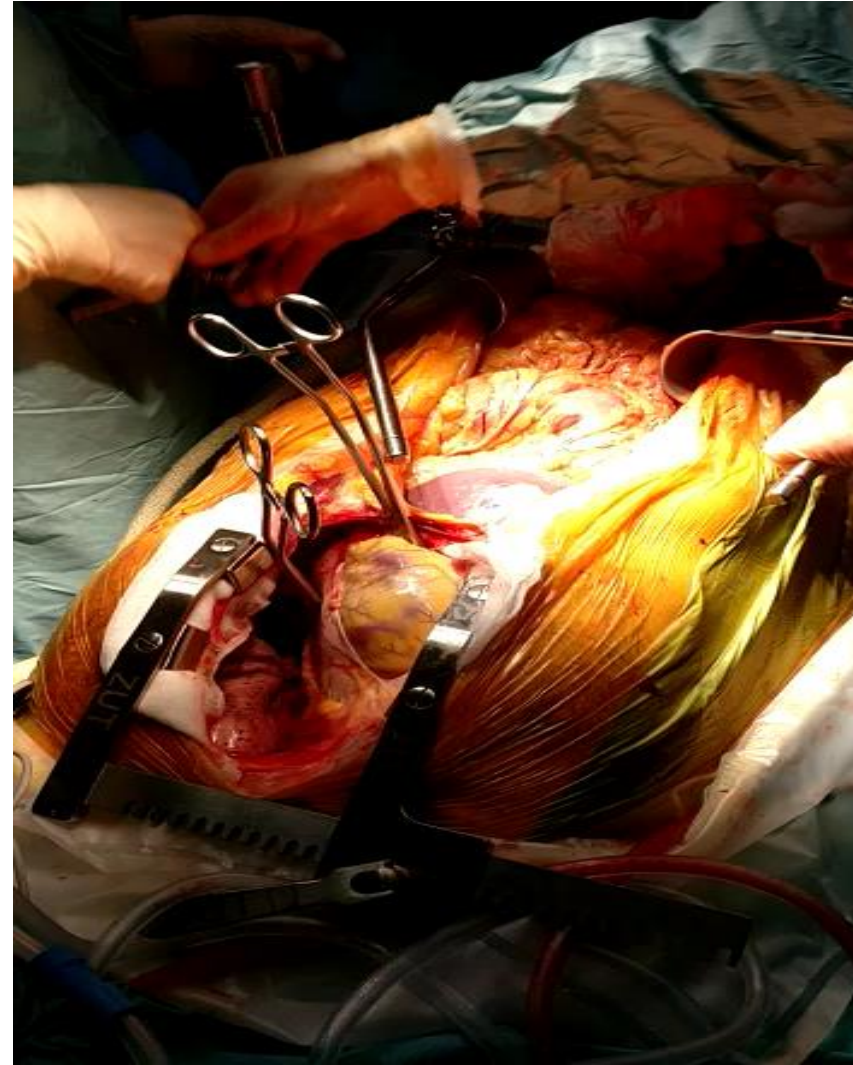
FIG. 1. The diagrams of IFLT procedure. (A) The in situ NMP. The portal and arterial cannulas are inserted into the IV and SA, respectively. PV and CA are blocked, and then PV and HA outflow ports of the NMP device supply the oxygenated perfusate to the liver through 2 extended tubes. Then, the SHIVC is blocked, and the perfusate flows into the reservoir through the cannula in the IHIVC. After in situ NMP is constructed, the work of harvesting the liver occurs. (B) The full view of in situ NMP (Liver Assist). (C) Organ implantation under NMP. When the liver is transferred from outside to inside the recipient under continuous NMP, the SHIVC is anastomosed first. The PV and CA are subsequently anastomosed. Then, the PV and CA are opened together with termination of NMP.

4. Normotherme Regionale Perfusie (NRP)

- 4 organen tegelijk
- Alleen DCD -- Herstel 'DBD' situatie
- Minder haast
- Functionele assessment
- Kan ook centraal (thoracaal)

- Verplicht in meerdere landen bij DCD
- Spanje/Belgie: cannulatie en start NRP op IC

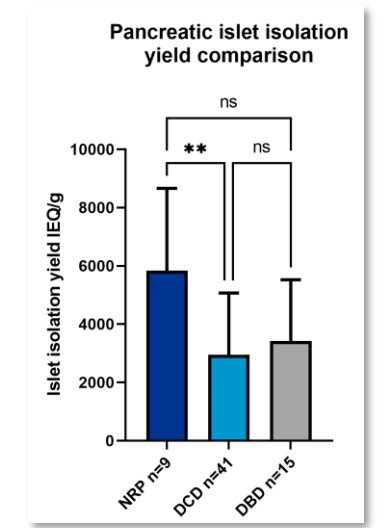
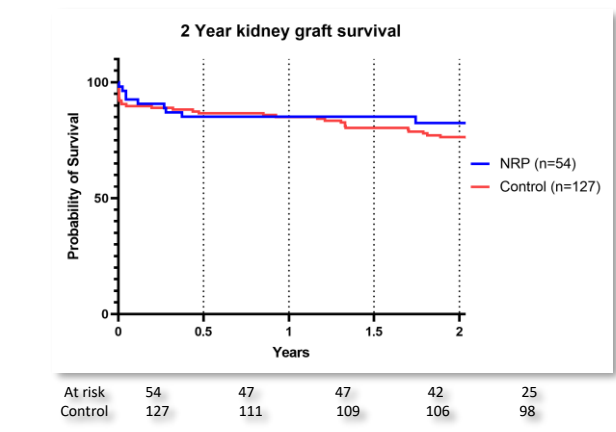
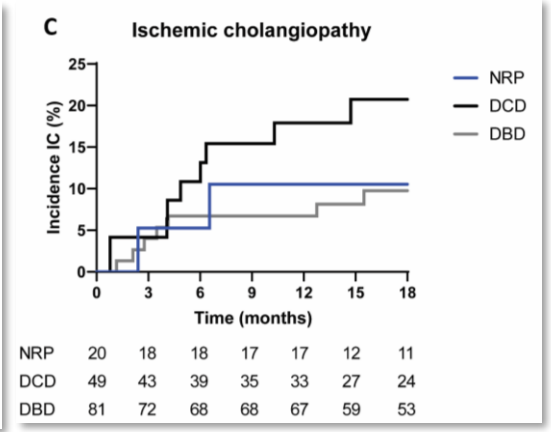
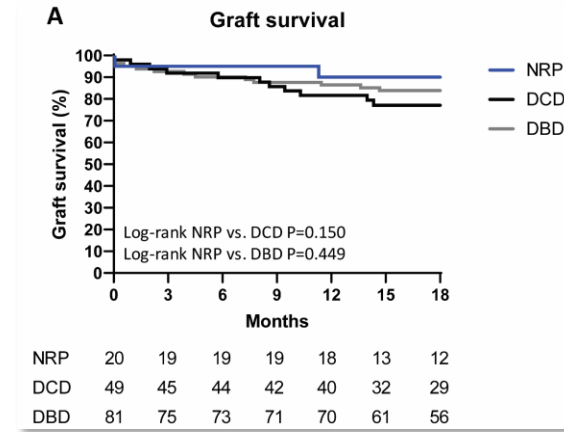




Resultaten in NL

- Sinds 2018
- Alleen >60 DCD (extended donoren)
- Zelfstandig Uitname Team West (Leiden/Rotterdam)

- 15% toename leverutilisatie
 - 39/57 van normaal geweigerde levers toch getransplanteerd
 - Survival en galwegschaade beter
- Nieroverleving gelijk
- Toename opbrengst eilandjesisolaties

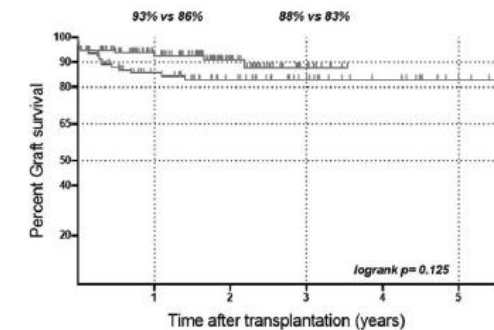


Maar...Wat is nou het best?

Hypothermic Oxygenated Perfusion Versus Normothermic Regional Perfusion in Liver Transplantation From Controlled Donation After Circulatory Death

First International Comparative Study

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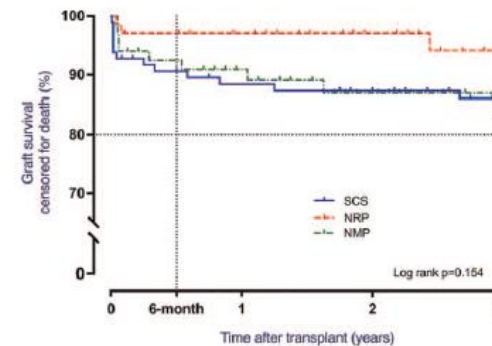
NRP	132	82	33	8	0	0
HOPE	93	67	48	33	24	14

- NRP en HMP geven gelijke overleving
- NRP assessment mogelijk

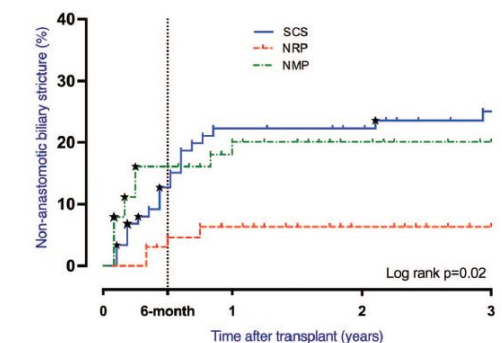
Liver Transplantation Outcomes From Controlled Circulatory Death Donors

SCS vs *in situ* NRP vs *ex situ* NMP

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At risk					
SCS	97	84	81	76	66
NRP	69	65	57	39	23
NMP	67	60	50	32	17



At risk					
SCS	88	74	65	60	50
NRP	66	62	53	37	22
NMP	63	50	40	28	16

- NRP en NMP beter dan cold storage
- NRP minder ischemische galwegschade

Conclusies machineperfusie

Machineperfusie is een antwoord op het orgaantekort

In gang gezet door grote aantal DCD donoren

Verbeterd resultaten

Leidt tot beter planbare en superieure transplantatiezorg

Toekomst?

Vergoeding voor alle typen perfusie

Grote vergelijkende studie 'in situ' NRP vs 'ex situ' HMP/NMP

Langere perfusie om logistieke redenen

Blijven streven naar meer DBD donatie!

Wat betekent dit voor de intensivist?



Perfusie als onderdeel van donatiezorg

Transplantaties beter planbaar?

NRP op de IC?

Langdurige perfusie: de machine als patient...

Dank voor uw aandacht



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NEDERLANDSE TRANSPLANTATIE STICHTING