

NORMOTHERMIC LIVER PERFUSION

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D'où vient-t-on?

Conservation
Statique froide

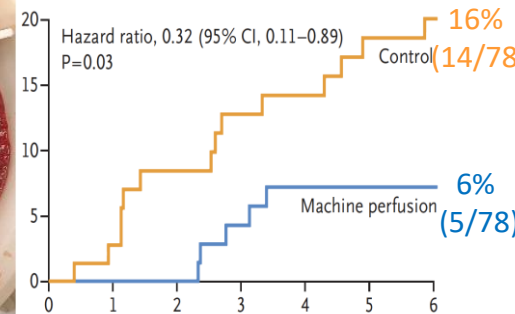
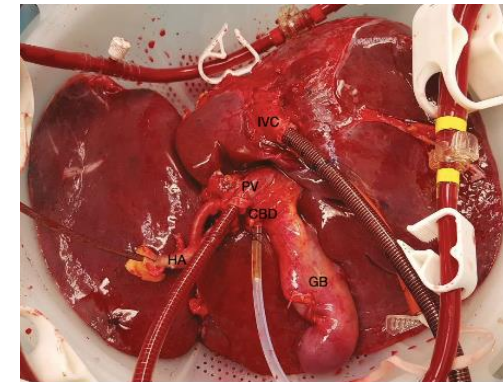
Perfusion en
Transpl. rénale

Essai randomisé
Normo vs. Statique

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 Hoel, 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*



nature



The **NEW ENGLAND**
JOURNAL of MEDICINE

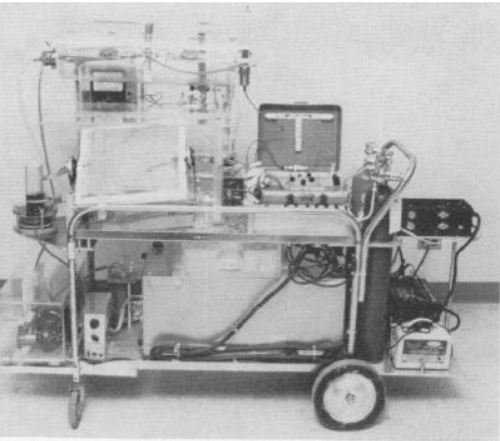
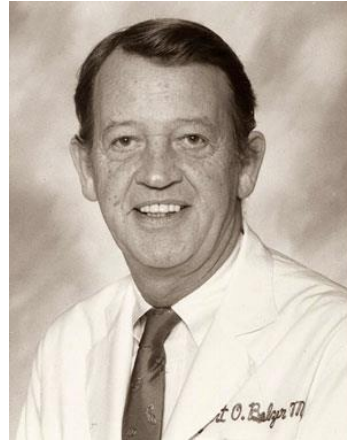


FIG. 3. Photograph of transportable renal preservation unit.

1968

80-90's

2009

2018

2021

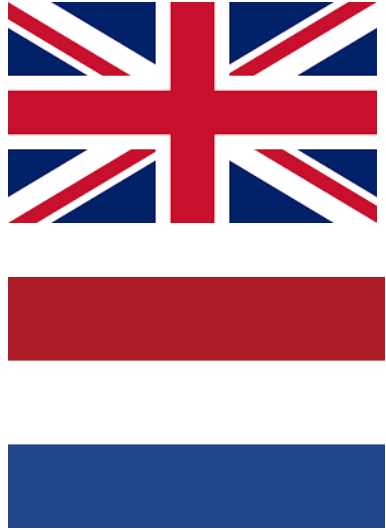
Belzer et al, *Ann Surg* 1968

Moers et al, *NEJM* 2009

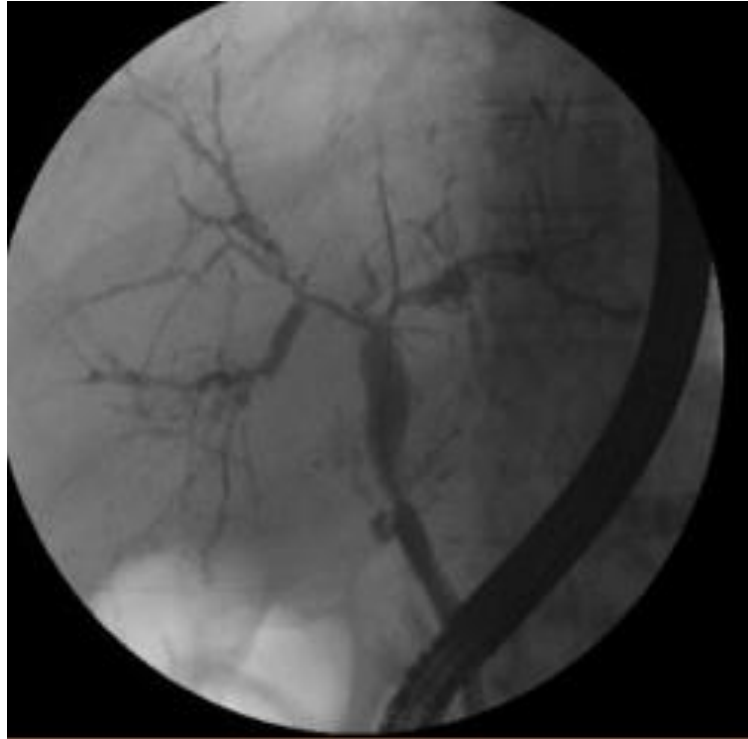
Nasralla et al, *Nature* 2018

Van de Rijn et al, *NEJM* 2021

Rationnel de la perfusion normothermique



Donneur DCD (30 – 50% du pool...)
Cholangiopathie post-TH (ischémie chaude)

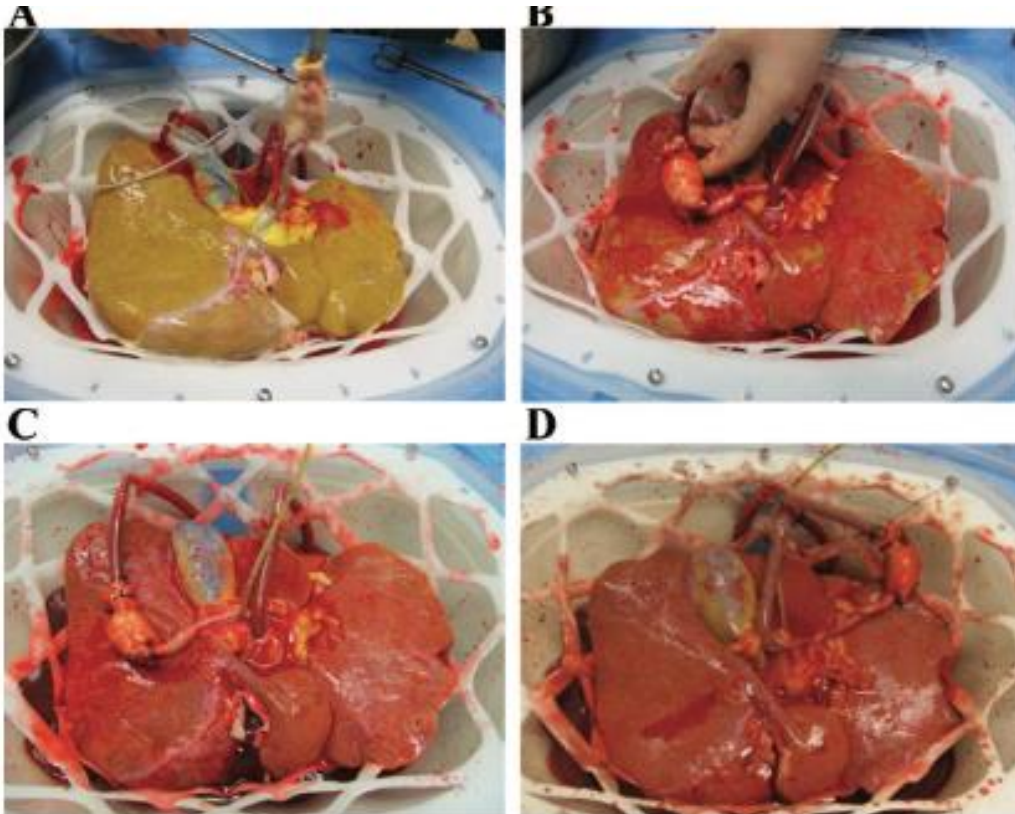


Objectif : améliorer la préservation des greffons
pour diminuer l'incidence des cholangiopathies

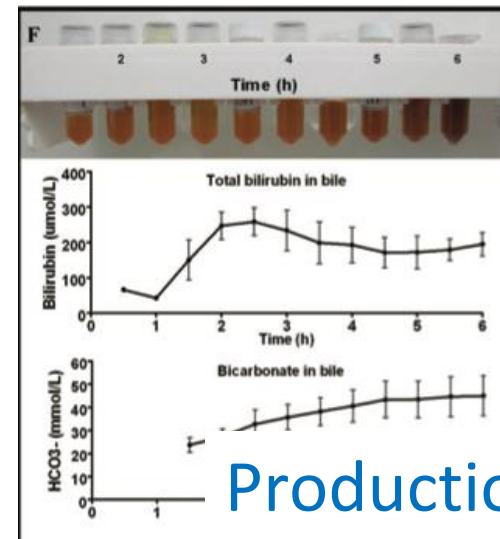
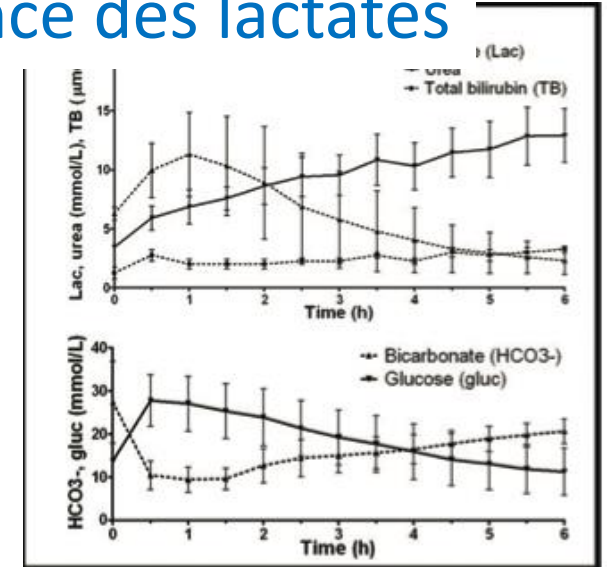
Un outil de sélection pour les greffons marginaux

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

Op Den Dries, Am J Transpl 2013



Clairance des lactates



Production et qualité de la bile

Potentiel pour « récupérer » des greffons marginaux

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. V. Virginia Chiochia^{6,7}, Susan J. Dutton⁸, Juan Carlos García-Valdecasas⁹, Nigel Heaton¹⁰, Charles Imber¹¹, Wayne Ina Jochmans^{12,13}, John Karani^{10,14}, Simon R. Knight^{1,15}, Peri Kocabayoglu¹⁶, Massimo Malagò¹¹, Darius M. Arvind Pallan¹⁷, Andreas Paul¹⁶, Mihai Pavel⁹, M. Thamara P. R. Perera³, Jacques Pirenne^{12,13}, Reena P. Sara Upponi¹⁹, Chris J. E. Watson^{5,20}, Annemarie Weissenbacher¹, Rutger J. Ploeg¹, Peter J. Friend¹⁸, Liver Organ Preservation in Europe

	Cold storage (n=121)	Normothermic Perfusion (n=121)	P
Peak AST	488	488	<0.0001
PNF	0 (0%)	1 (0.8%)	NS
Early Dysfunction	29(29.9%)	12 (10%)	0.0002
Discard rates	32 (24.1%)	16 (11.7%)	0.008

Diminue le taux de greffons récusés de 50%!

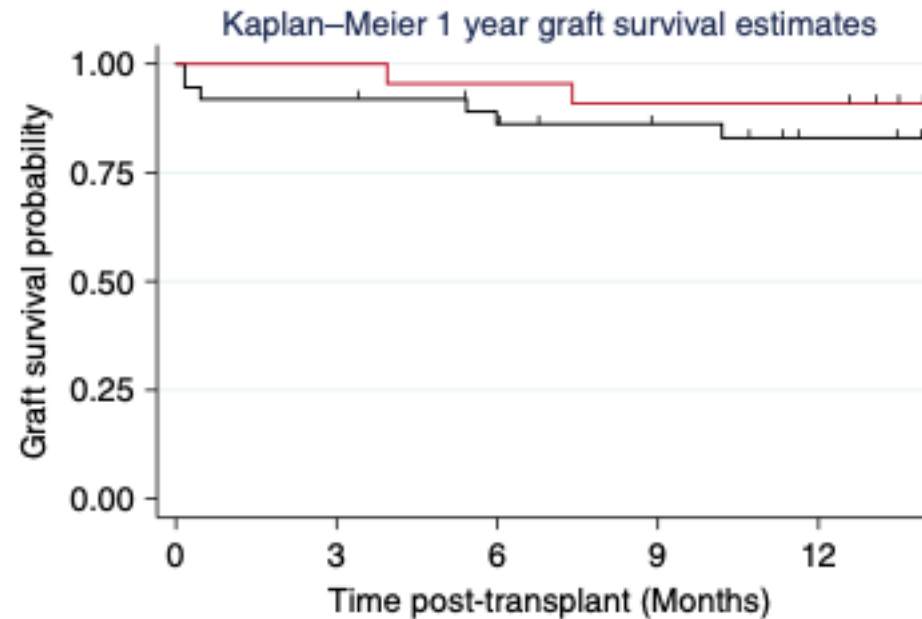
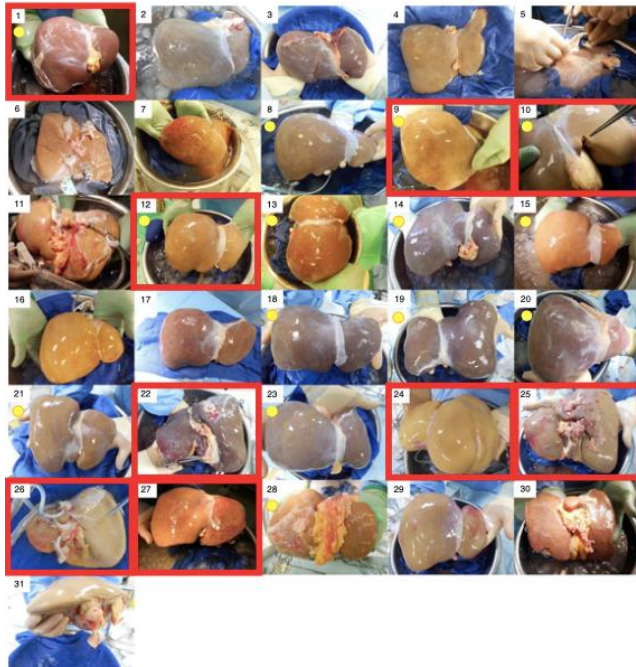
Plateforme de perfusion pour greffons « orphelins »

Transplantation of discarded livers following viability testing with normothermic machine perfusion

Mergental et al, Nature Comm 2020



31 Foies perfusés normo. = > 22 Transplantés



Number at risk						
Case-Control = Control	37	34	30	27	23	
Case-Control = Case	22	22	21	20	20	

— Controls — Case

Préservation longue pour des impératifs logistiques

Clinical Implementation of Prolonged Liver Preservation and Monitoring Through Normothermic Machine Perfusion in Liver Transplantation

Transplantation 2020



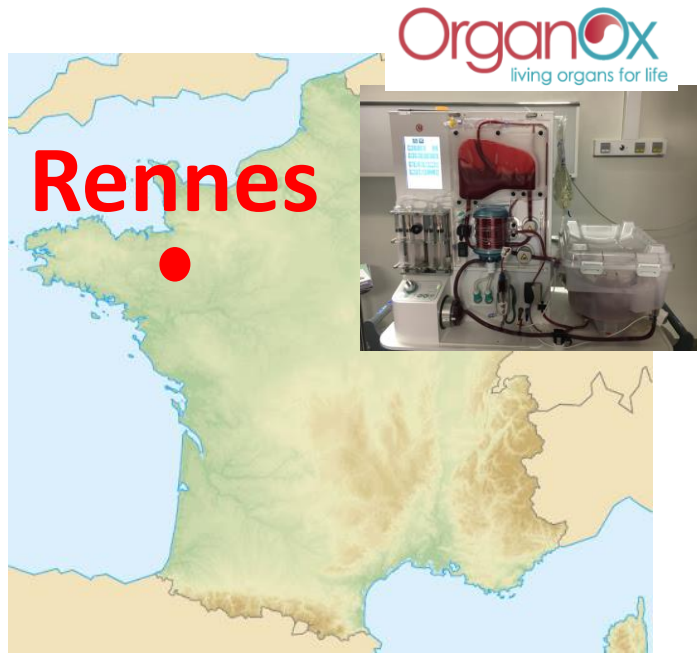
Un avantage logistique chez 16/25 greffons !

sons for decline). The main reasons to opt for NMP in the 25 transplanted cases were marginal donor organ in 9 patients, **logistics** in 6 patients (multiple organ transplantation such as heart, lung, or kidney pancreas transplantations), the combination of marginal donor quality and **logistics** in 5 patients, the combination of **logistics** and surgically complex recipients in 2 cases as well as the combination of marginal organ quality, and **logistics** as well as surgically complex recipient in 3 cases

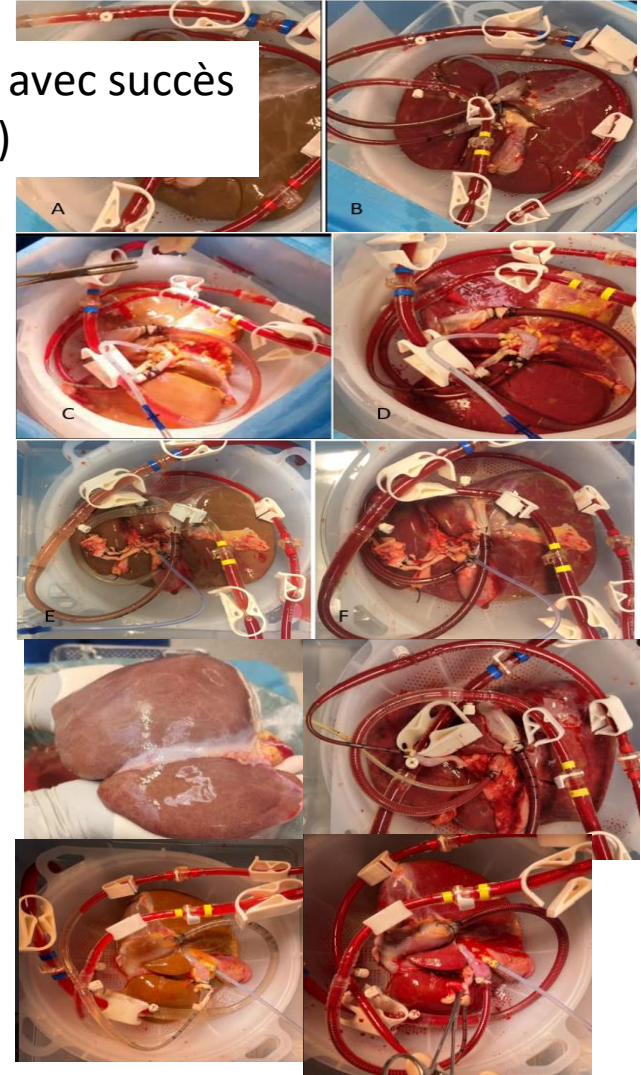
Durée moyenne Perf Normo : 13,6 Heures

- Intervention de jour !
- **Evite les annulations** de chir. élective
- Diminution des listes d'astreintes
- Evite l'ischémie froide prolongée

Préservation longue pour des impératifs logistiques



5 foies perfusés et transplantés avec succès
Perfusion 11h57 (7h58 – 16h02)



Objectif : pas de greffe la nuit !

En pratique : perfusion des greffons clampés
entre 15h et 22h.

Incision du receveur le lendemain matin

Financement : CHU de Rennes

25 Kits (projet innovation)

Courtesy from H. Jeddou, K. Boudjema

Machine de perfusion normothermique

Liver Assist (In Vivo)



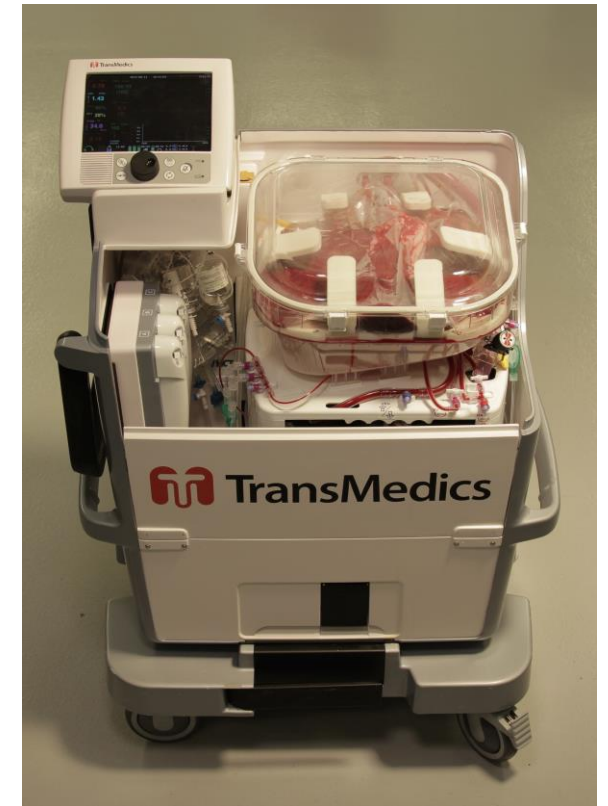
Non Transportable
De 8 à 37°C

Organox Metra



Transportable
Normothermie exclusive

TransMedics



Machine de perfusion normothermique

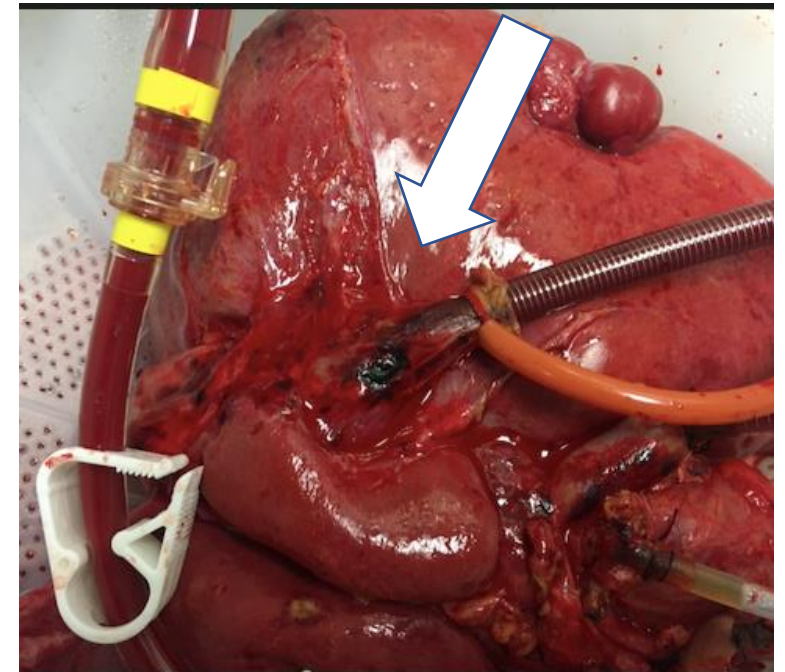


Machine de perfusion normothermique



Inconvénients de la normothermie

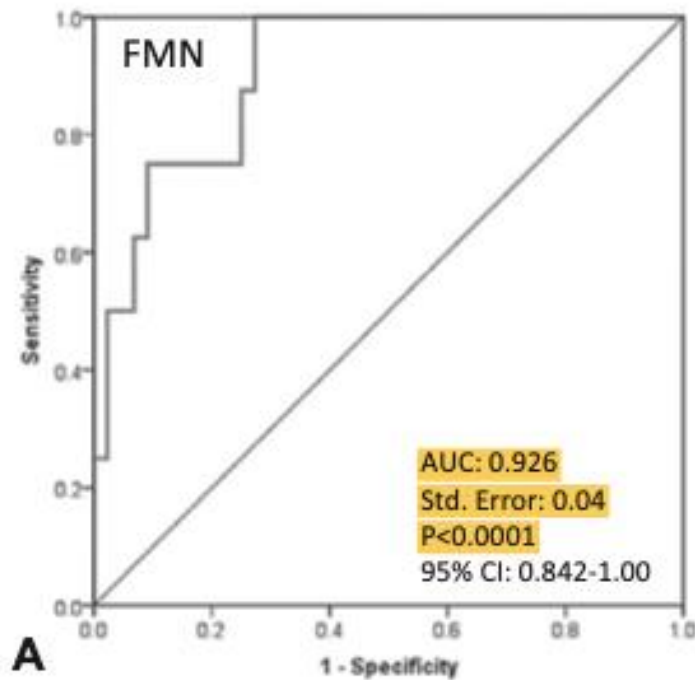
$$\begin{aligned} f(u) &= \int f(x) e^{-\frac{1}{2} \frac{u^2}{\sigma^2}} \frac{1}{\sigma \sqrt{2\pi}} dx \\ p(\frac{\partial v}{\partial t} + v \nabla v) &= \nabla p \cdot \nabla T \cdot l \\ H &= \sum p(x) \log p(x) \\ TC(Q, q, m) &= \sum_{i=1}^n \left[\frac{1}{2} S_i + c_i D_i + \frac{H_i}{2} \left(u(1 - \frac{D_i}{P_i}) - 1 \cdot \frac{D_i}{P_i} \right) \right] \\ \left[\frac{d \Delta p(s, \phi)}{ds} \right] &= \begin{bmatrix} \tilde{J} - \tilde{L} \\ \tilde{P} \ 0 \end{bmatrix} \begin{bmatrix} \Delta p(s, \phi) \\ \Delta M(s, \phi) \end{bmatrix} \\ \int_0^1 \log \sin x \, dx &= -\int_0^1 \log \cos x \, dx = -\frac{\pi}{2} \end{aligned}$$



HOPE pour sélection et perfusion longue!

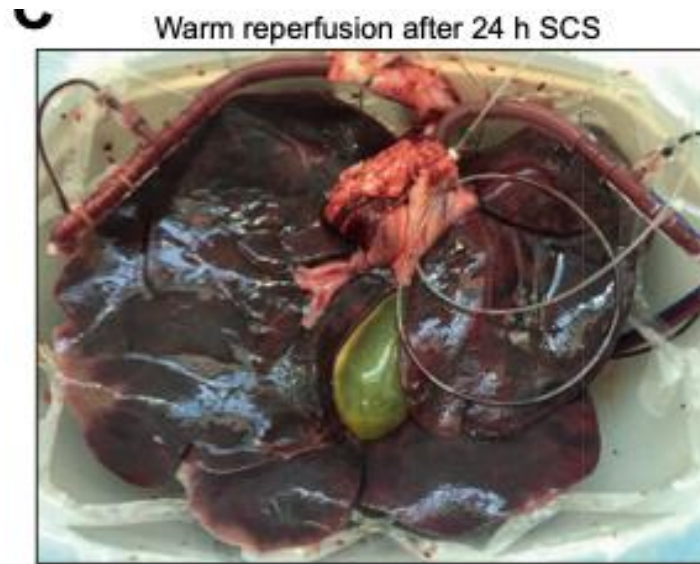
Flavine Mono-Nucléotide

Novel Real-time Prediction of Liver Graft Function During Hypothermic Oxygenated Machine Perfusion Before Liver Transplantation



Muller et al, Ann Surg 2019

24 H de Conservation statique



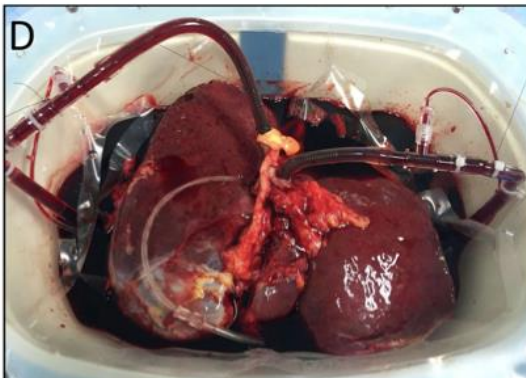
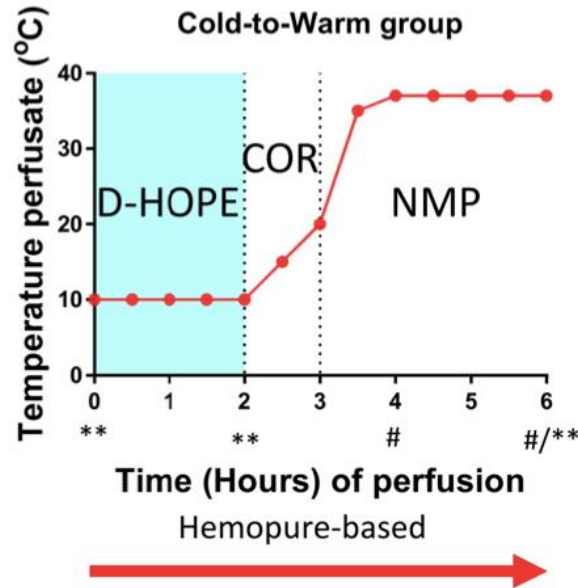
24 H de D-HOPE



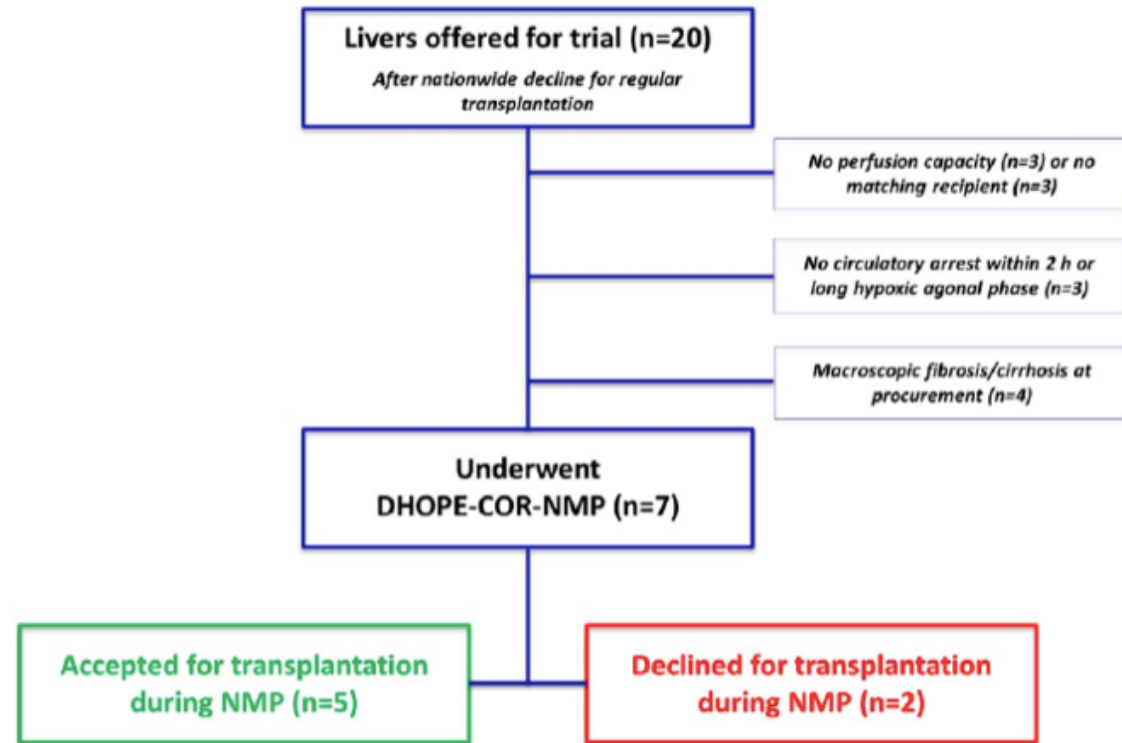
Bruggenwirth et al, JHEP REPORT 2021

HOPE avant Normothermie !

10 discarded livers (5 NMP vs 5 HOPE + NMP)
Liver Assist et HBOC-201 (Hemopure)



DHOPE-COR-NMP Dutch TRIAL avec HBOC1
(Dual HOPE + Controlled oxyg. rewarming + NMP)



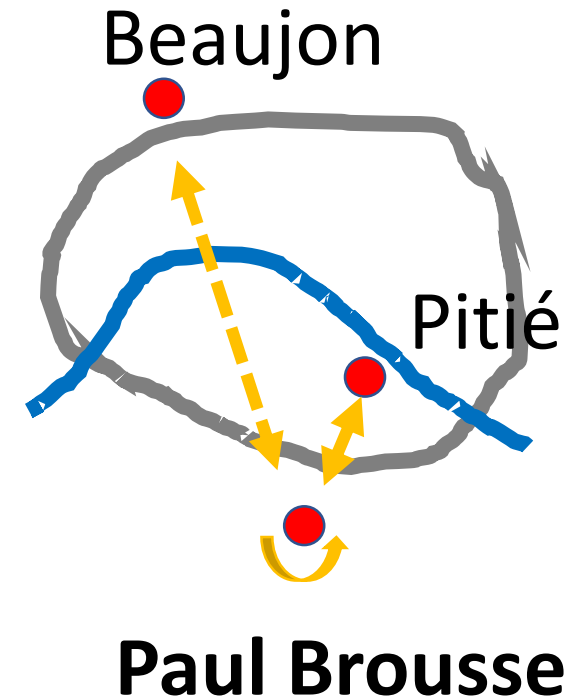
Boteon et al, Liver Transpl 2018
Boteon et al, PloSone 2019
De Vries et al, Am J Transplant 2019

Ischémie froide courte pour greffons « très » marginaux

PENOFOR - Plateforme AP-HP de perfusion normothermique de greffons stéatosiques



- Forfait innovation APHP
- 20 greffons stéatosiques
- Receveur Child A- CHC
- Ischémie froide < 8 heures



Préservations « très » longues

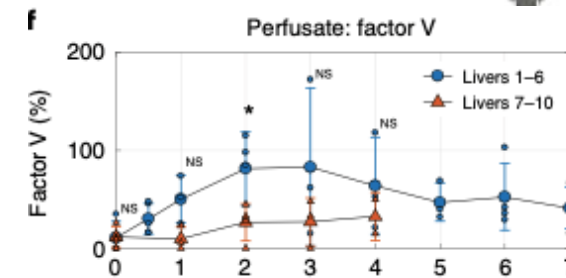
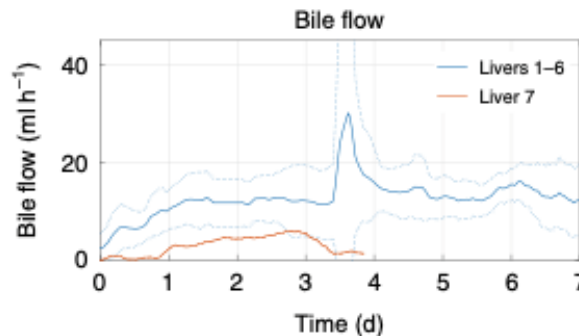
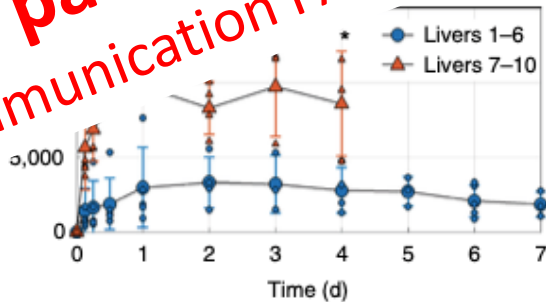
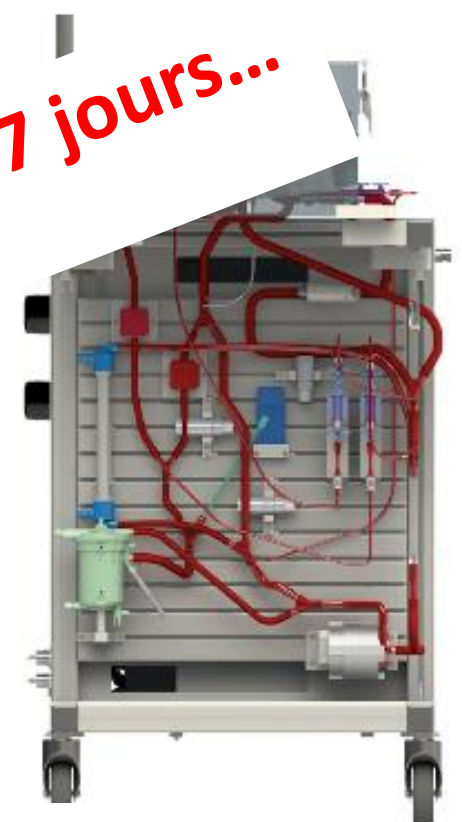
An integrated perfusion machine preserves injured human livers for 1 week

nature
biotechnology

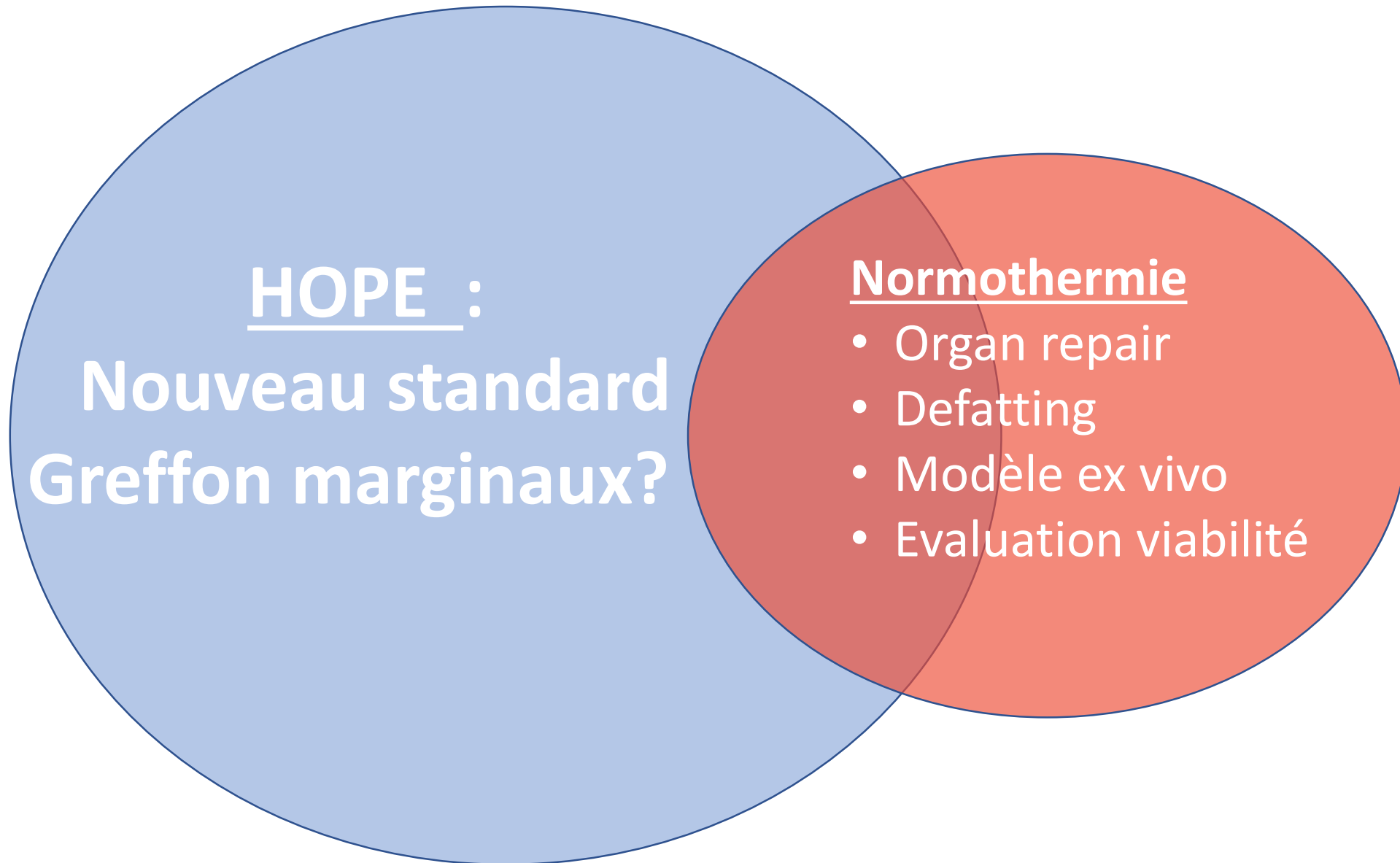
Eshmuminov et.. Clavien 2020

1. Monitoring automatisé et continu de la glycémie
2. Limiter l'hémolyse (prévention par une seule pompe et caractère non pulsatile de la perfusion 60bpm)
3. Contrôle de la balance électrolyte (m)
4. Maintien d'une saturation (cyst porte (evite l'hyperoxygenation de la fonction artérielle))
5. Mouvement (compression)

Une patiente transplantée avec succès après perfusion de 7 jours...
Communication PA Clavien, Nov 2021



L'avenir de la normothermie?



Conclusion

- Expérience débutante en France (10 patients transplantés après normothermie...)
- 2 indications : sélection et logistique
- Courbe d'apprentissage
- Moyens financiers et humains
- Besoin de travaux collaboratifs et multicentriques
- « Perfusioniste de greffon » un nouveau métier ?