Machines de perfusion hépatique : Indications et perspectives

Dr Michel Rayar

CHU Rennes

Absence de conflit d'intérêts en lien avec la présentation

Petit rappel historique …

Concept ancien !

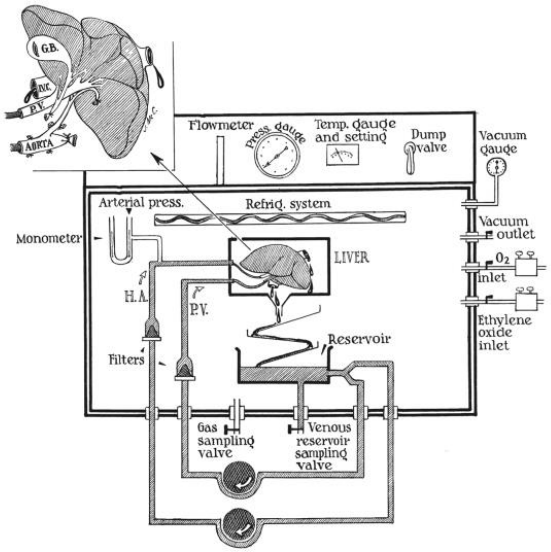
- Alexis Carrel 1912
- Charles Lindberg 1935

Application clinique

- Thomas Starzl 1967

Puis abandon du concept

- Complexité
- Conservation statique 1971



Mécanismes ischémie/reperfusion

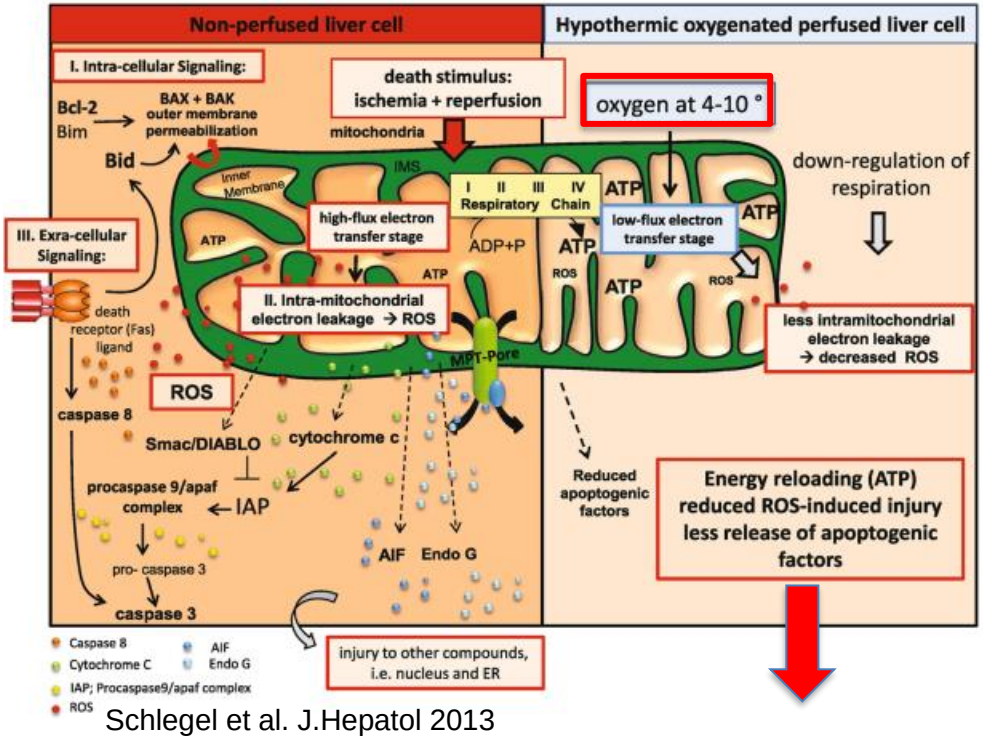
Ischémie (4°C) :
- baisse du métabolisme cellulaire (mais persiste !)
- métabolisme anaérobie (production lactate, baisse synthèse ATP, accumulation e-)

Reperfusion : Apport O2
- production ion O2-

⇒ Altération membrane

⇒ Accentué par déficit ATP

Lésion I/R :
- Destruction mitochondrie
- Libération Ca+
- Activation enzymes
- Destruction cellulaire
- Activation cellule Kupffer
- Emballement réaction immunitaire



Schlegel et al. J.Hepatol 2013

Apport O2 pdt phase conservation:
- Maintient activité mitochondriale
- Maintient production ATP
- Baisse production radicaux libre

⇒ Diminution lésion d'I/R

Objectif de la perfusion hépatique : apporter de l'O2 pendant la conservation !

Perfuser: oui! mais comment ?

Délai d'initiation ?

Dès le prélèvement ?

Dans le centre de greffe ?

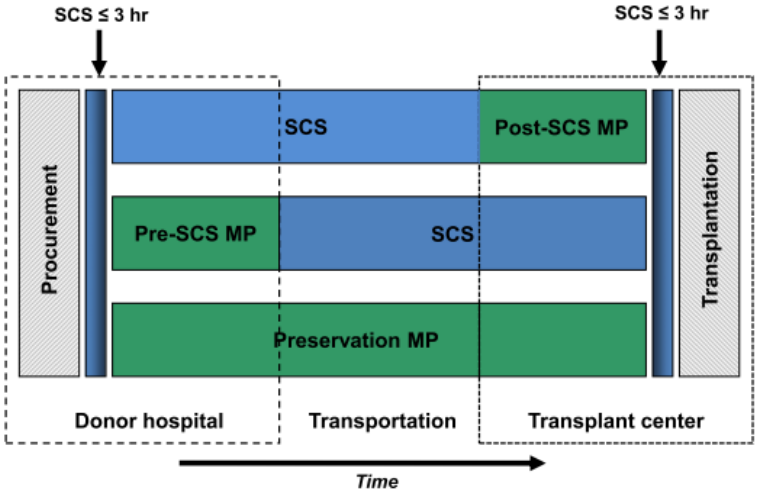
Par quelle voie ?

V. porte seule ? Artère+ V.porte ?

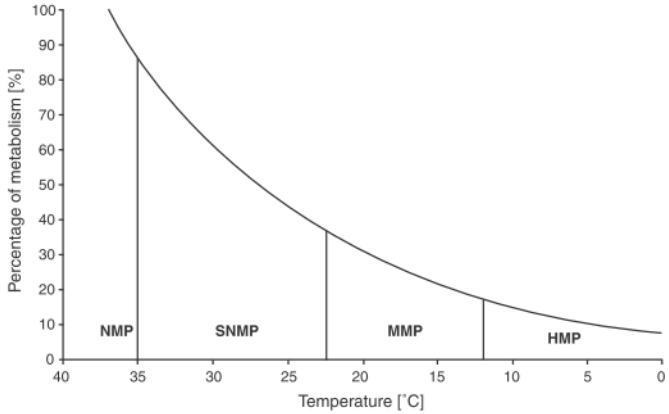
A quelle température ?

Hypothermique? Normothermique? Subnormothermique ?

Combinaison de plusieurs ?



Karanga et al, AJT 2016



Multiples possibilités…

Les techniques :

2 principales méthodes :

Hypothermie (HOPE)

NORMOTHERMIE (NMP)

HOPE

Hypothermique Oxygenated PErfusion

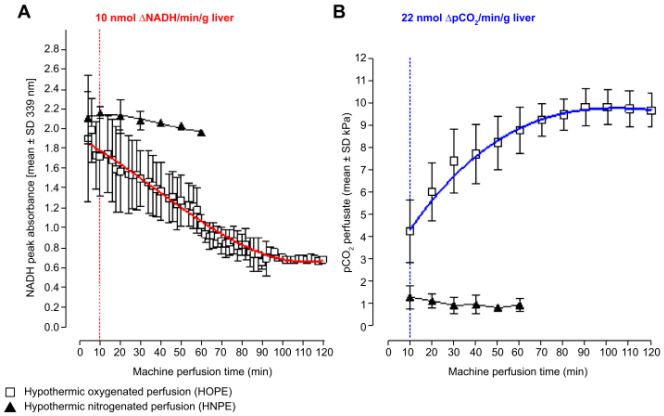
Après conservation statique initiale

1-2h de HOPE (avant la greffe)

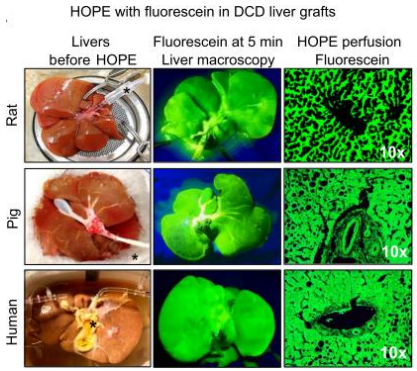
Perfusion portale (/ Dual perfusion)

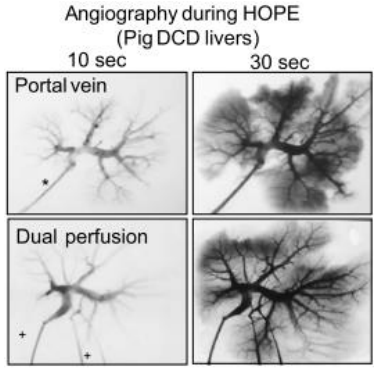
Logistique plus simple, couts ++

(Avantage de l'hypothermie si problème !)



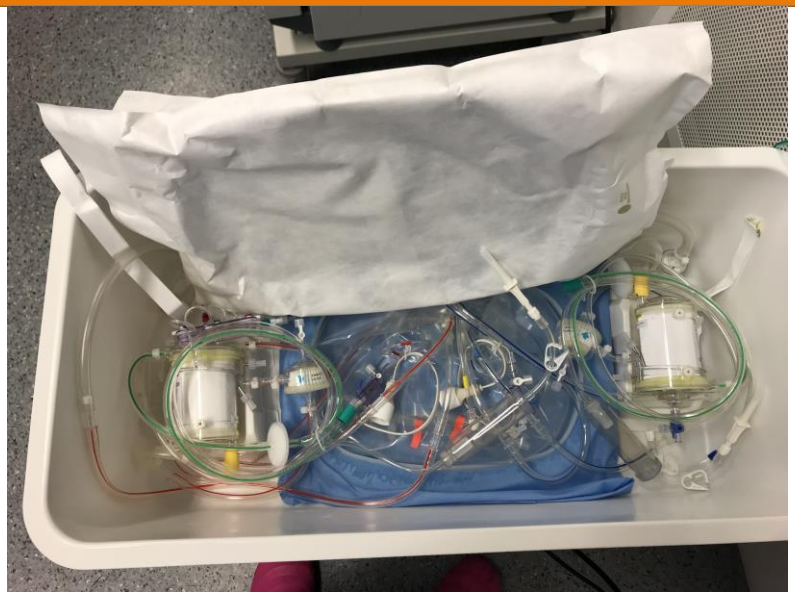
Schlegel et al, J.Hepatol 2013

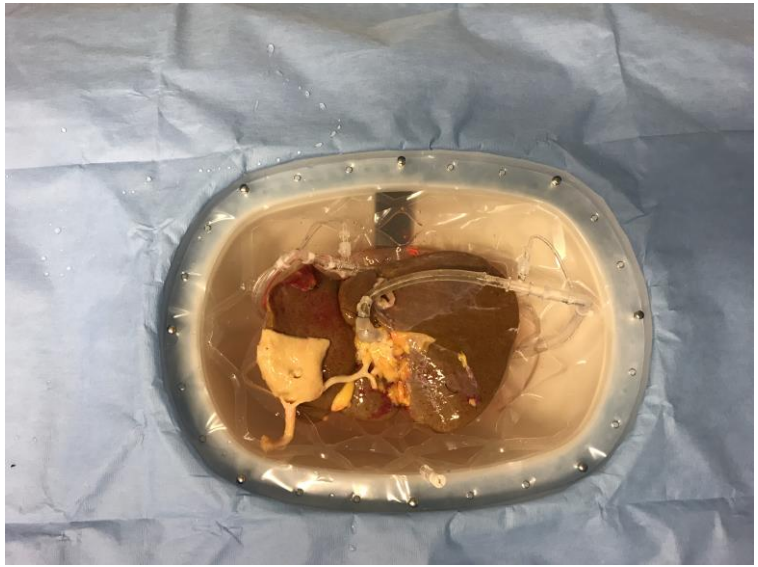




Schlegel et al, J.Hepatol 2016

En pratique





Normothermie

Perfusion en situation physiologique

- Perfusion à 37°
- Liquide de perfusat : sang (le plus souvent)

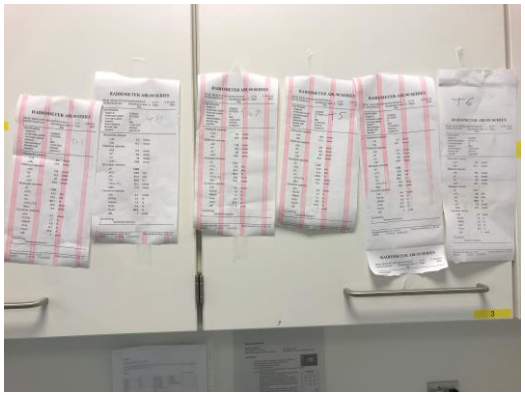
Complexité ++

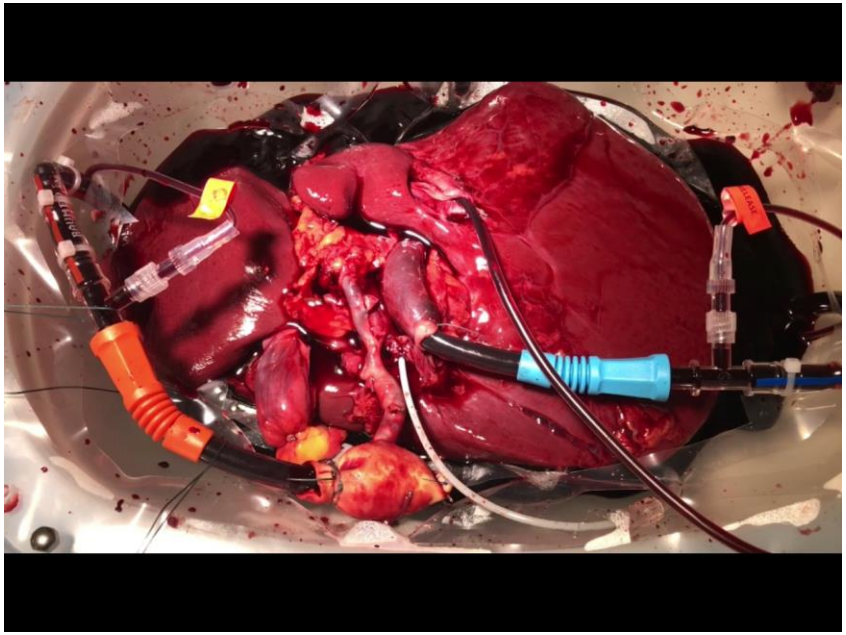
Cout +++

Si problème machine … risque perte greffon

⇒ Permet évaluer fonction du greffon

En pratique

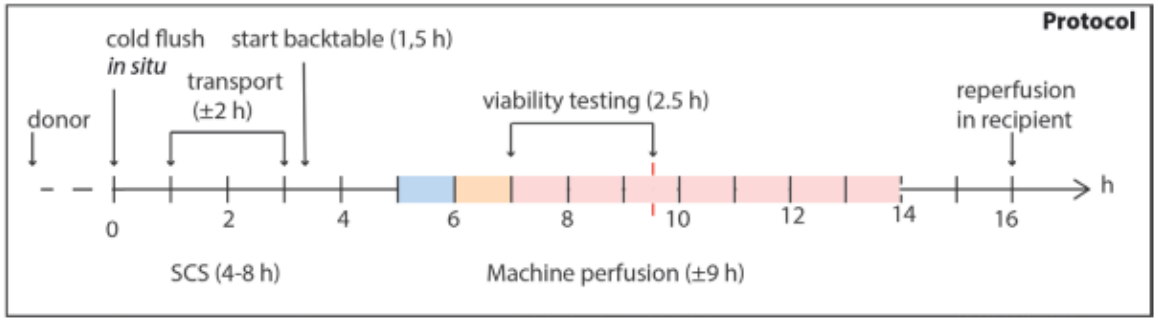




Une 3ème méthode : DHOPE-COR-NMP

Combinaison HYPO + NORMO

1 seule équipe à réaliser cette méthode



Transplantation of High-risk Donor Livers After Ex Situ Resuscitation and Assessment Using Combined Hypo- and Normothermic Machine Perfusion

A Prospective Clinical Trial

Otto B. van Leeuwen, BSc, Yvonne de Vries, MD,* Masato Fujiyoshi, MD, PhD,* Maarten W. N. Nijsten, MD, PhD,† Rinse Ubbink, MSc,‡ Gert Jan Pelgrim, PhD,‡ Maureen J. M. Werner, MD,* Koen M. E. M. Reyntjens, MD,§ Aad P. van den Berg, MD, PhD,|| Marieke T. de Boer, MD, PhD,* Ruben H. J. de Kleine, MD,* Ton Lisman, PhD,¶ Vincent E. de Meijer, MD, PhD,* and Robert J. Porte, MD, PhD*✉*

(*Ann Surg* 2019;270:906–914)

Sequential Hypothermic and Normothermic Machine Perfusion Enables Safe Transplantation of High-risk Donor Livers

Otto B. van Leeuwen[1], Silke B. Bodewes[1], Veerle A. Lantinga[1], Martijn P.D. Haring[1], Adam M. Thorne[1], Isabel M.A. Brüggenwirth[1], Aad P. van den Berg[2], Marieke T. de Boer[1], Ruben H.J. de Kleine[1], Bianca Lascaris[1], Maarten W.N. Nijsten[4], Koen M.E.M. Reyntjens[5], Vincent E. de Meijer[1], Robert J. Porte[1]

AJT 2022

Principales indications

Améliorer la qualité de la conservation

Hypothermie >> Normothermie

Augmenter la durée de la conservation

Hypothermie > Normothermie

Evaluer la transplantabilité

Normothermie >>>>> Hypothermie

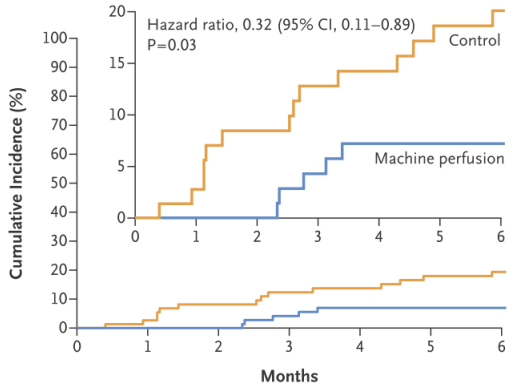
Transport d’organes

Amélioration conservation

Hypothermic Machine Perfusion in Liver Transplantation — A Randomized Trial

The NEW ENGLAND JOURNAL of MEDICINE

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*



No. at Risk							
Control	78	71	66	63	61	58	57
Machine perfusion	78	74	73	68	66	66	66

Gold standart pour utilisation greffon M3 (sans CRN) depuis 2021

En France : si transa > 4N

Amélioration qualité de la conservation

Etude pilote sur perfusion greffon ECD

25 greffons
Objectif : amélioration conservation
⇒ Reprise de fonction du greffon

Hypothermie
- Simplicité
- Cout

Résultats

Variable	Perfusion (n=25)	Contrôles-appariés (n= 69)
ASAT max	722 [184 ; 6673]	1301 [236 ; 10979]
ALAT max	493 [132 ; 4353]	722 [169 ; 5754]
Complications graves	20%	37,7%
Réa (jours)	3	5
Hospitalisation (jours)	15	20
RRF	28%	43,5%
Survie greffon à 1 an	88%	89%
Survie patient à 1 an	91%	91%

Absence de surcouts liés à l'utilisation de la machine:

Surcout par greffe : 5298 € ; compensée par réduction hospitalisation

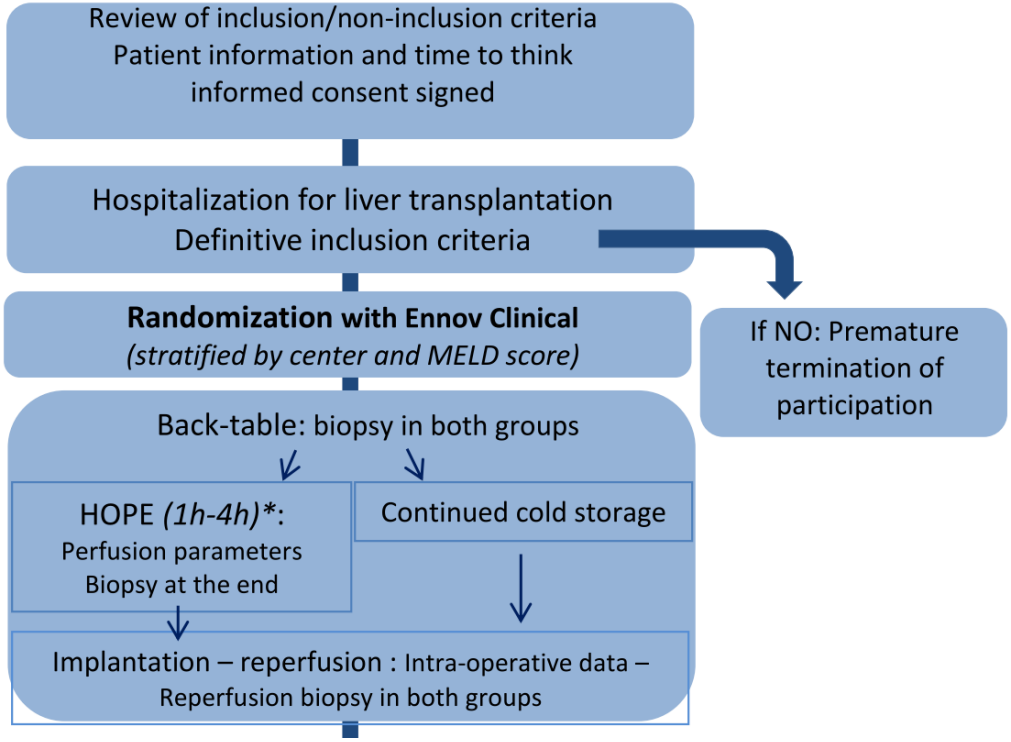
Rayar et al, Liver Transplantation 2021

Amélioration qualité de la conservation

Etude HOPExt

Terminée en 2022

Résultats en 2024

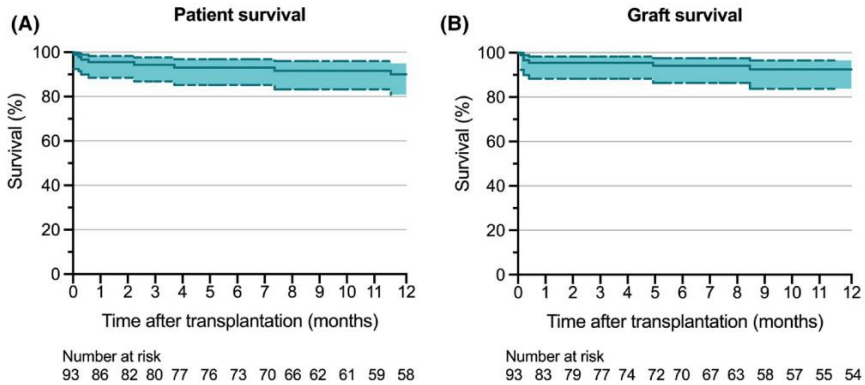


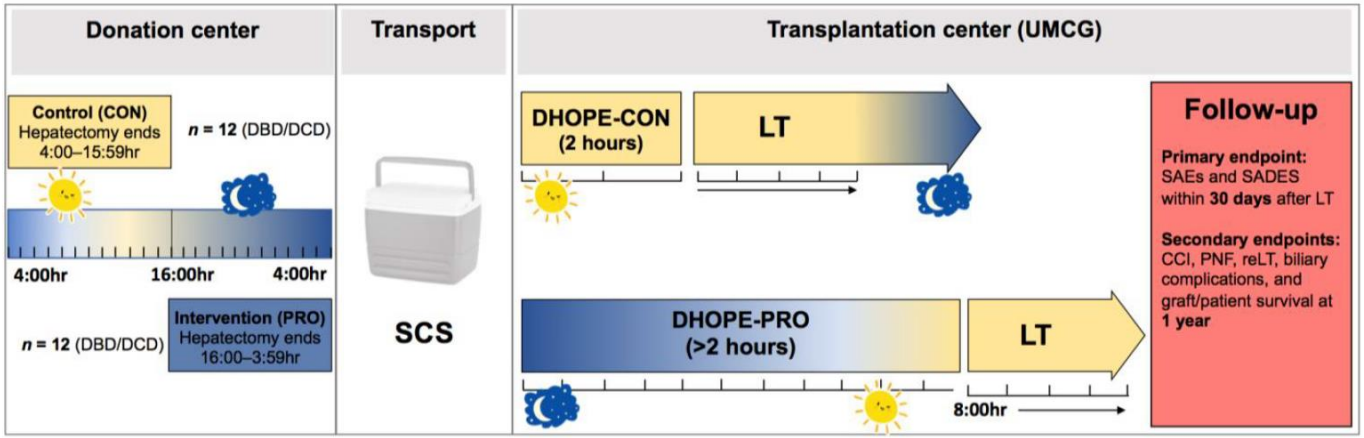
Utilisation en pratique courante ?

Augmentation durée conservation

Prolonged preservation by hypothermic machine perfusion facilitates logistics in liver transplantation: A European observational cohort study

Brüggenwirth et al, AJT 2022



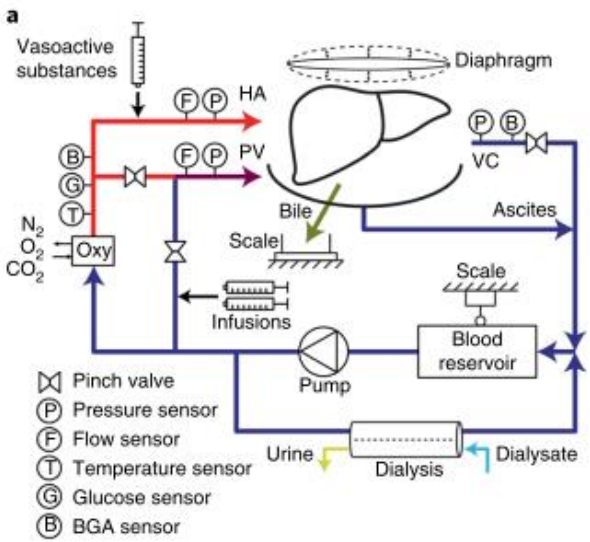


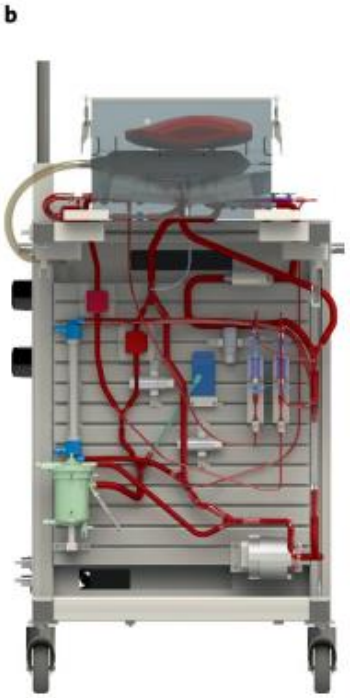
Brüggenwirth et al, BMJ open 2022

Augmentation durée conservation

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 Weber[5], Philipp Dutkowski[1,2], Philipp Rudolf von Rohr[2,3,7] and Pierre-Alain Clavien[1,2,7]*





Evaluer la transplantabilité ++++

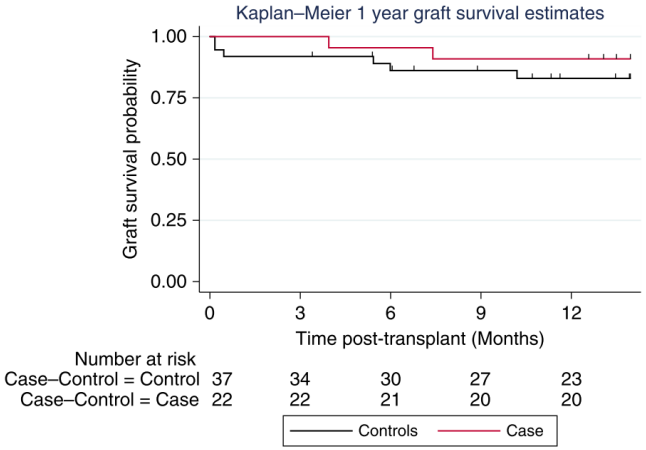
Transplantation of discarded livers following viability testing with normothermic machine perfusion

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]

NATURE COMMUNICATIONS | (2020)

1. Lactate ≤ 2.5 mmol/L
2. AND two or more of the following within 4 h of starting perfusion

- Evidence of bile production
- pH ≥ 7.30
- Metabolism of glucose
- HA flow ≥ 150 mL/min and PV flow ≥ 500 mL/min
- Homogenous perfusion



1-year graft survival—*n* (%)[a]	19 (86.4)
1-year patient survival—*n* (%)[d]	22 (100)

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AJT 2022

	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
	Perfusate pH	7.35 – 7.45	7.25 to 7.35	< 7.25
Cholangiocytes	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

Variable	All livers (n=34)
Post-transplant outcomes	
Actuarial graft survival	
3-months	97%
6-months	97%
12-months	94%
Retransplantation for	
Chronic rejection	1 (3%)
Venous outflow tract obstruction	1 (3%)
Actuarial patient survival	
12-months	100%

Transport d'organes

Impact of Portable Normothermic Blood-Based Machine Perfusion on Outcomes of Liver Transplant

The OCS Liver PROTECT Randomized Clinical Trial

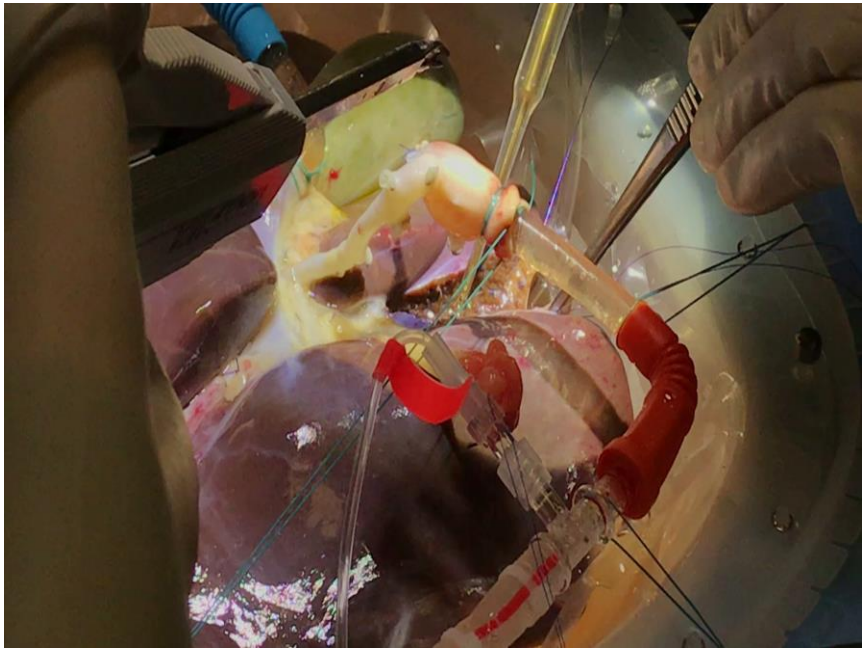
Markman et al JAMA surg 2022

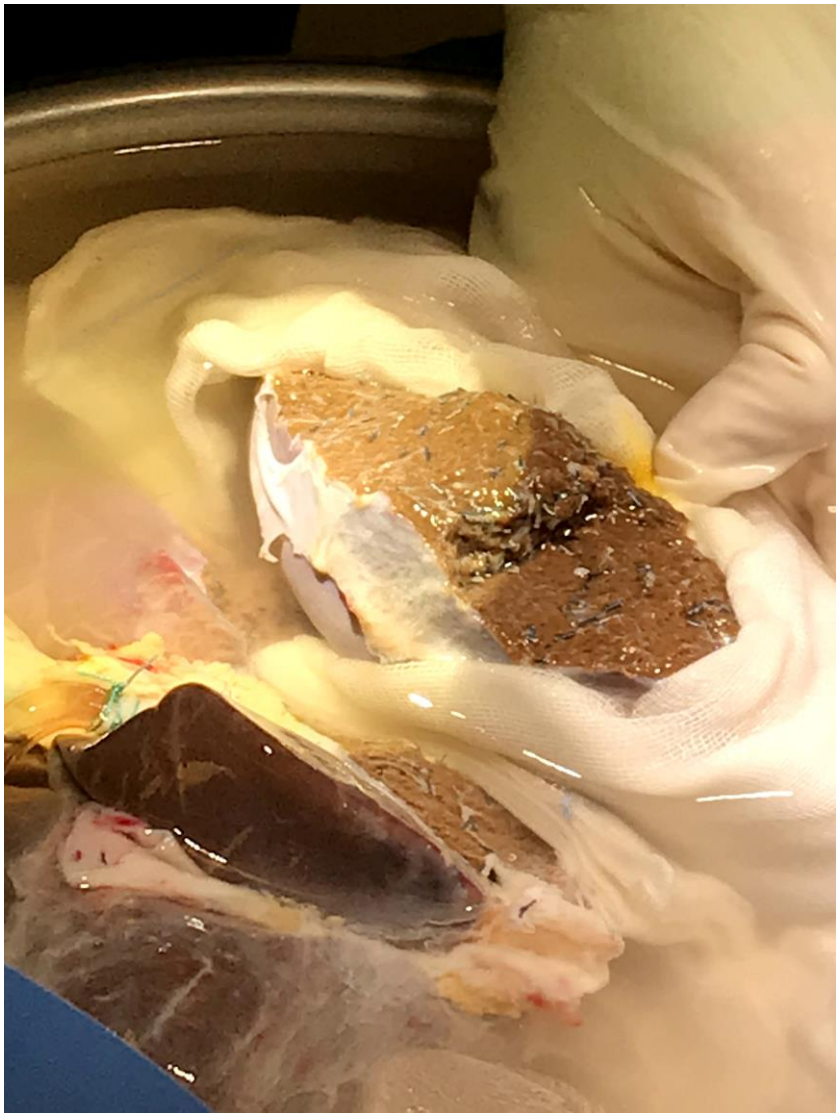
Perspectives

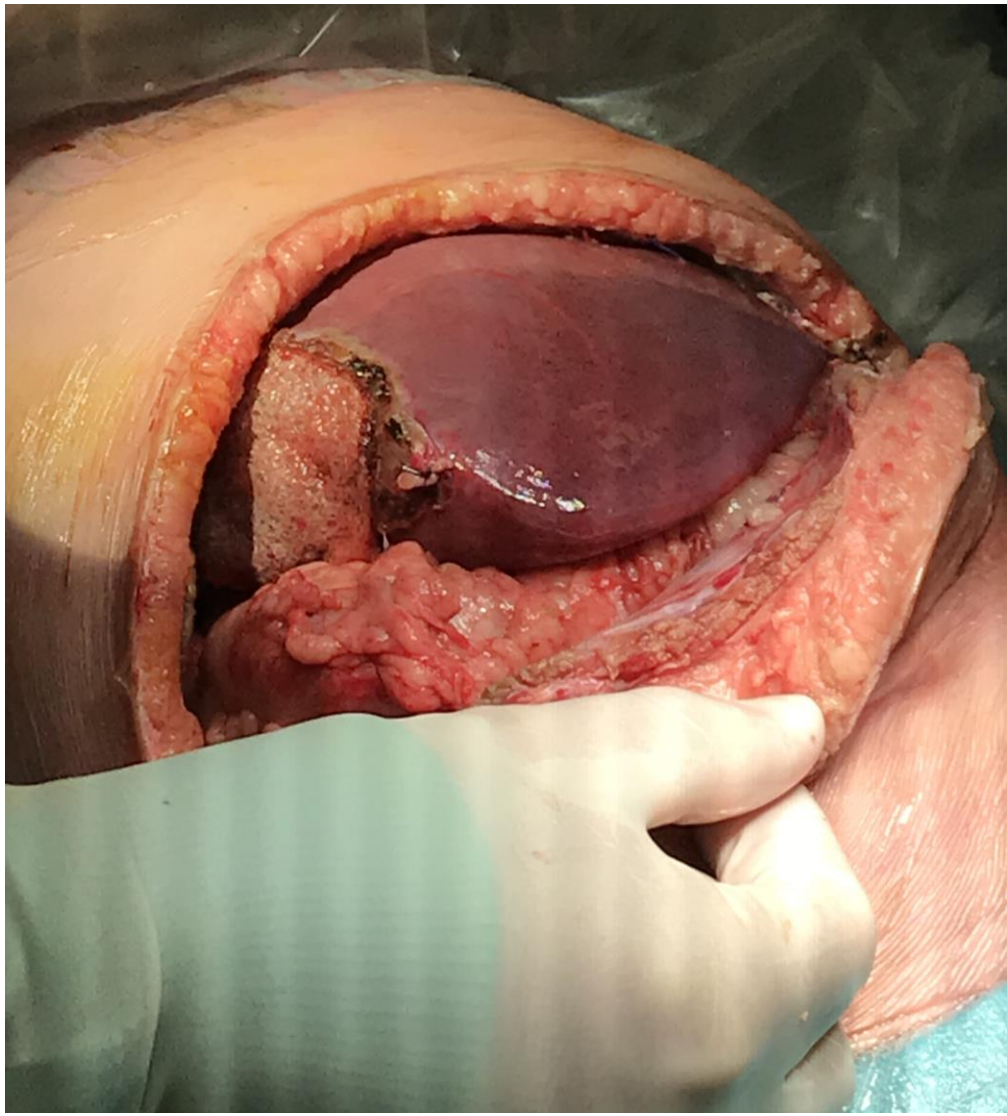
Bipartition sur la machine

Ex Situ Dual Hypothermic Oxygenated Machine Perfusion for Human Split Liver Transplantation

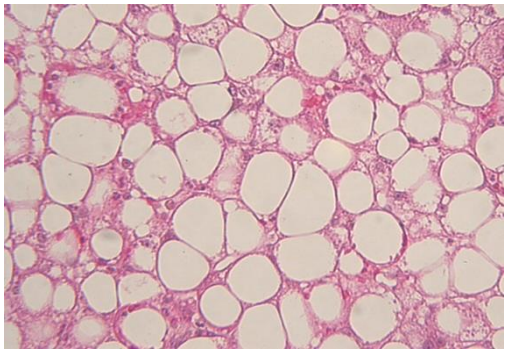
Adam M. Thorne, BSc,[1] Veerle Lantinga, BSc,[1] Silke Bodewes, BSc,[1] Ruben H. J. de Kleine, MD,[1] Maarten W. Nijkamp, MD, PhD,[1] Joost Sprakel, MD,[1] Hermien Hartog, MD, PhD,[2] Wojciech G. Polak, MD, PhD,[2] Robert J. Porte, MD, PhD,[1] and Vincent E. de Meijer, MD, PhD[1]







« Défatting » ?



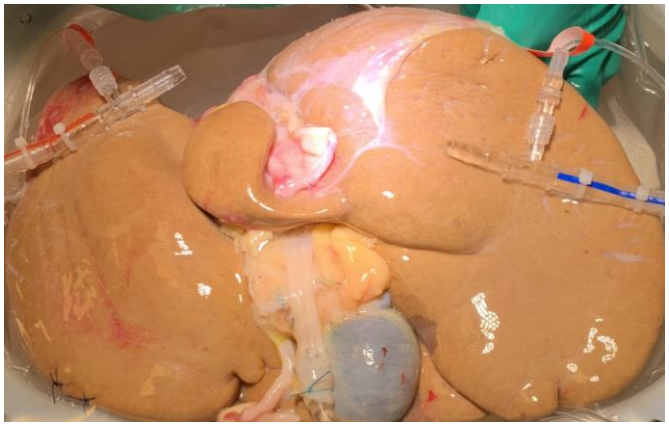
Stéatose

Gravité :

- –légère : < 30%
- –modéré: 30-60%
- –sévère: > 60%

Risque de non function du greffon

- 1.5%-3% = greffon normal
- 3%-15% = risque majeur
- >50% = risque important



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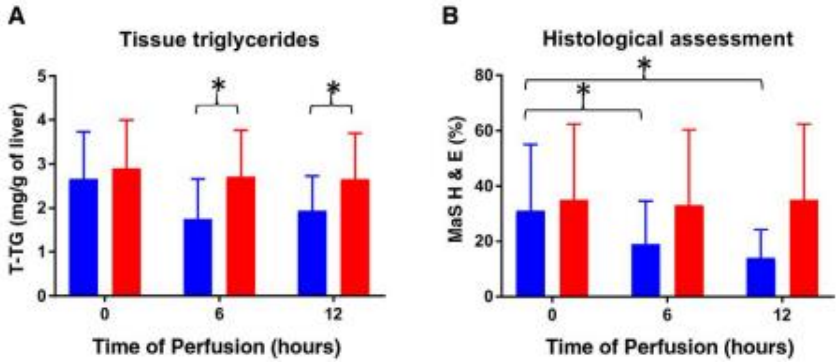
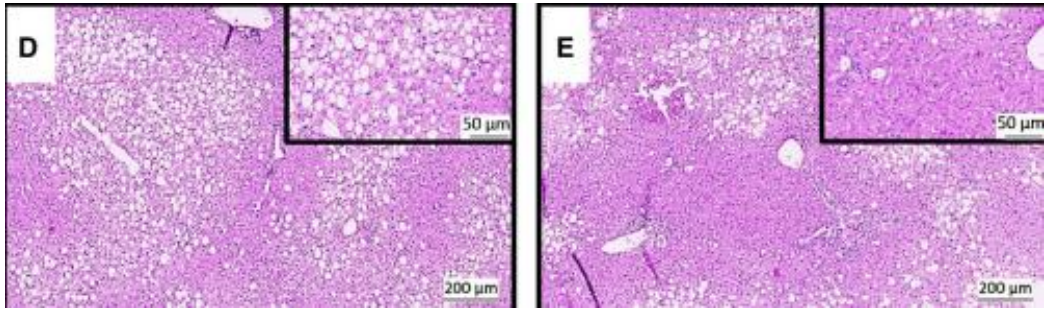
Manipulation of Lipid Metabolism During Normothermic Machine Perfusion: Effect of Defatting Therapies on Donor Liver Functional Recovery

Yuri L. Boteon,[1,3,4] Joseph Attard,[1,3,4] Amanda P. C. S. Boteon,[1] Lorraine Wallace,[3,4] Gary Reynolds,[3,4] Stefan Hubscher,[1,2] Darius F. Mirza,[1,3,4] Hynek Mergental,[1,3,4] Ricky H. Bhogal,[5] and Simon C. Afford[3,4]



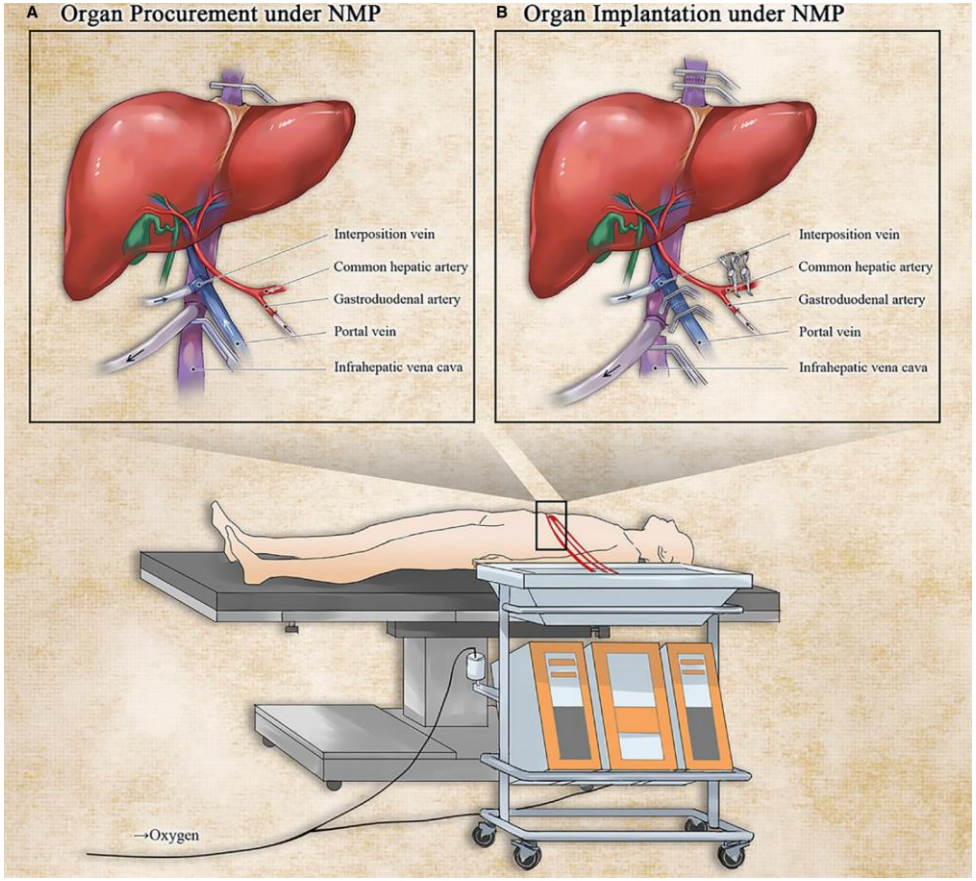


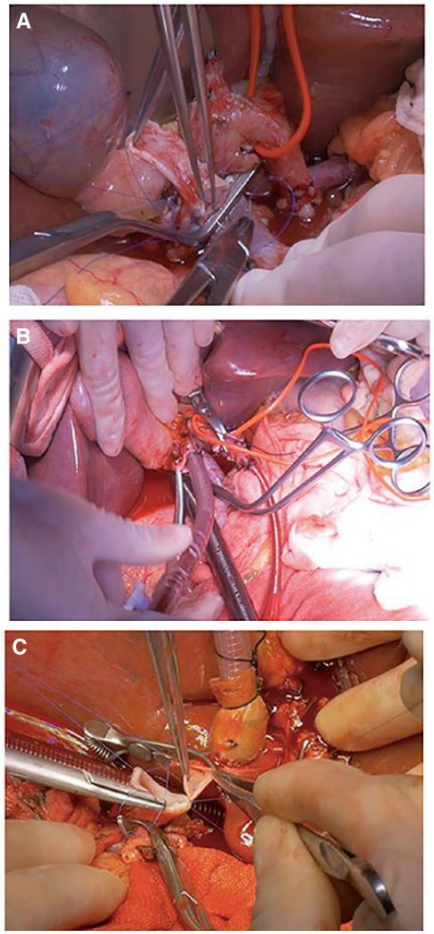
Ischemia free

American Journal of TRANSPLANTATION

He et al, AJT 2017

The first case of ischemia-free organ transplantation in humans: A proof of concept





Conclusions

Innovation technologique majeure

- Indications précises
- Coûteuse mais rentable

Changement pratiques et concepts de la TH

- Performance de la greffe
- Crainte de l’ischémie
- Augmentation « pool » de greffons

Merci de votre attention