Transplantasjon og organdonasjon

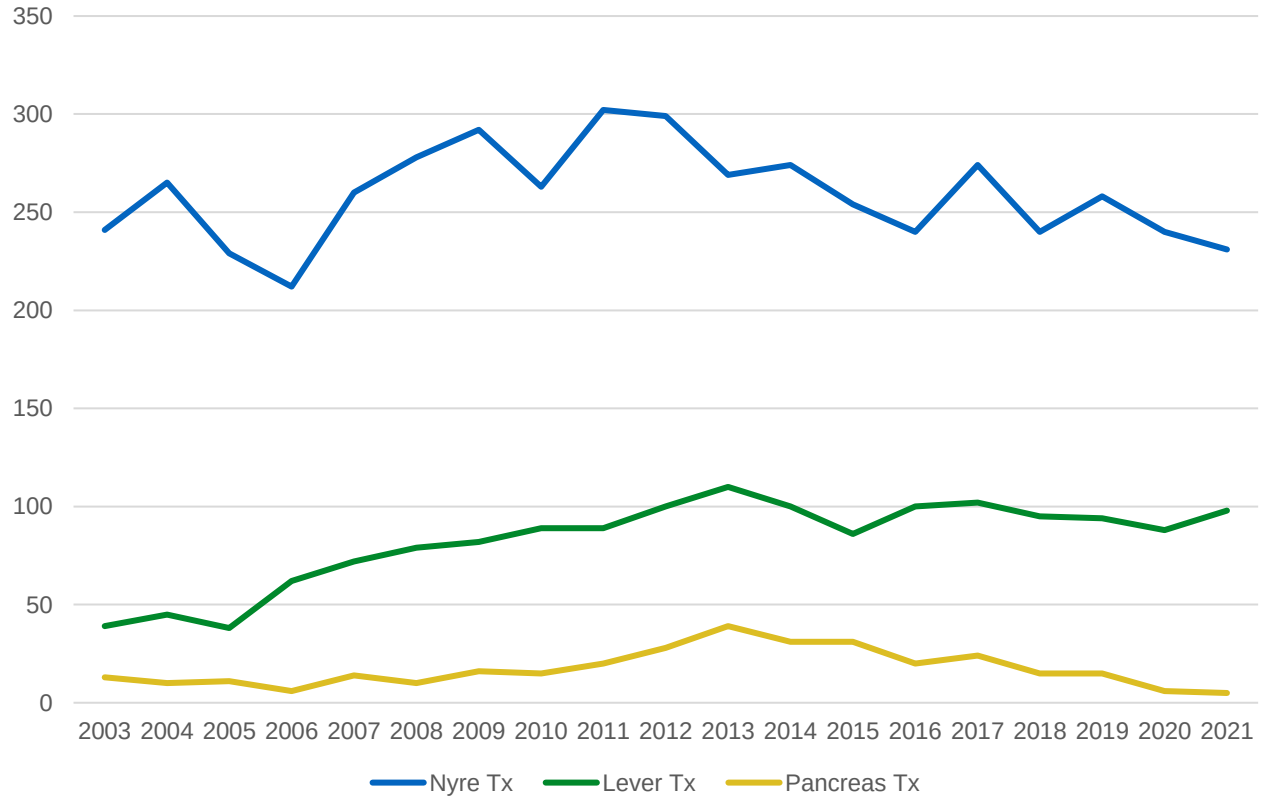
Nåtid og fremtid

Pål-Dag Line

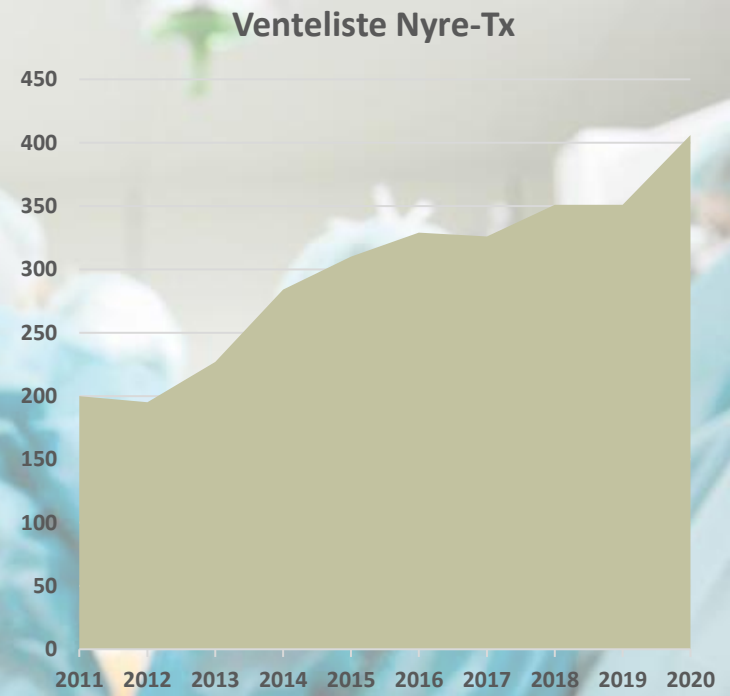
Avdeling for Transplanasjonsmedisin

Oslo universitetssykehus

Adominal organtransplantasjon Rikhospitalet 2003-2021



Trends in transplantation :



- Increasing waiting lists
- Increasing donor age
- Reduced donor organ quality
  (Extended criteria donors)

Consequences……

LIVER TRANSPLANTATION 21:1040–1050, 2015

ORIGINAL ARTICLE

Declining Liver Graft Quality Threatens the Future of Liver Transplantation in the United States

Eric S. Orman,[1,3] Maria E. Mayorga,[4] Stephanie B. Wheeler,[2] Rachel M. Townsley,[4] Hector H. Toro-Diaz,[5] Paul H. Hayashi,[1] and A. Sidney Barritt IV[1]

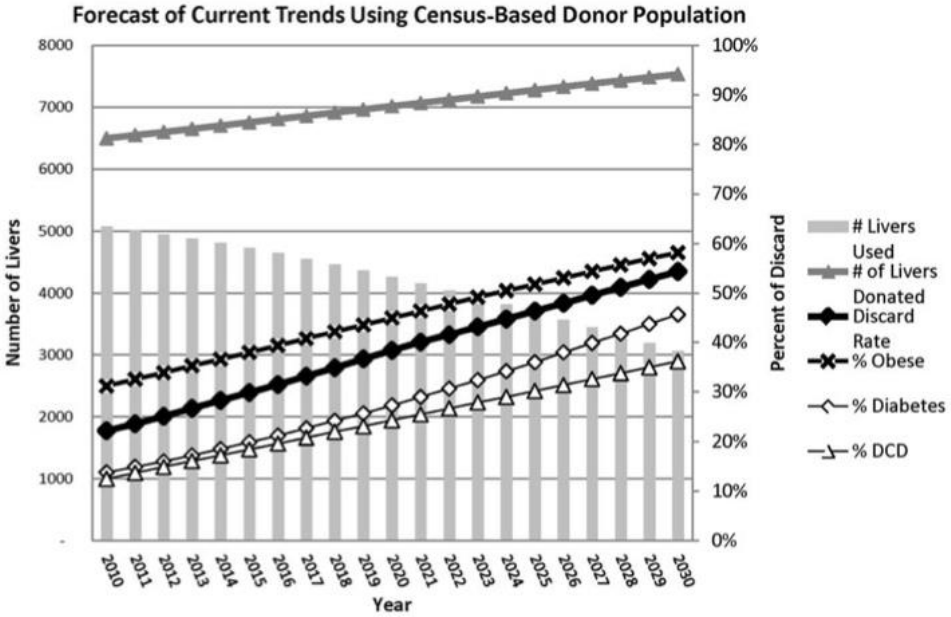
Department of [1]Medicine, and [2] Health Policy and Management, University of North Carolina, Chapel Hill, NC; [3]Department of Medicine, School of Medicine, Indiana University, Indianapolis, IN; [4]Department of Industrial and Systems Engineering, North Carolina State University, Raleigh, NC; and [5]Department of Industrial Engineering, Clemson University, Clemson, SC

- Decrements in organ quality are expected to continue over the next 2 decades
- 20-year discrete event simulation estimating LT volume from 2010 to 2030 based on UNOS donor data from 2000-2009

TABLE 2. Selected Attributes of Liver Donor Population 2010 to 2030

Year	Male	Age ≥50 Years	White	Black	Hispanic	Alcohol Use	Obese, BMI > 30 kg/m^2	Diabetic	DCD	Abnormal ALT, >40 U/L
2010	58.8	39.2	68.2	16.9	14.9	18.8	31.2	13.8	12.5	44.5
2015	58.8	40.3	63.8	19.8	16.5	18.9	38.0	19.7	18.4	48.7
2020	58.7	41.3	59.4	22.5	18.1	18.9	45.0	27.2	24.3	52.8
2025	58.7	42.6	55.0	25.3	19.7	19.0	51.8	36.1	30.2	56.9
2030	58.7	43.7	50.7	28.0	21.3	19.0	58.2	45.7	36.1	60.9

NOTE: All data are given as percentages.

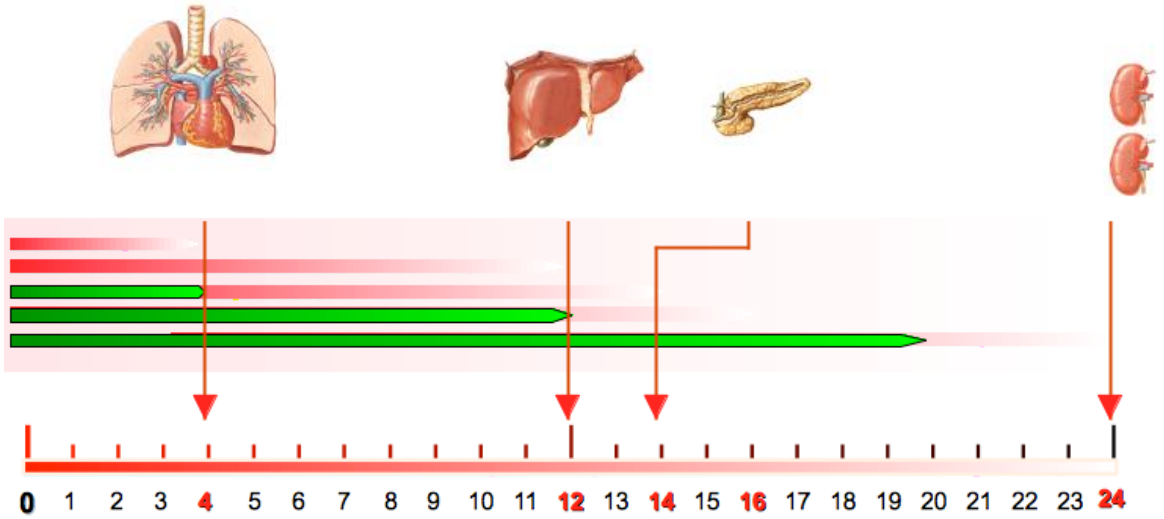


Orman ES et al. LIVER TRANSPLANTATION 21:1040–

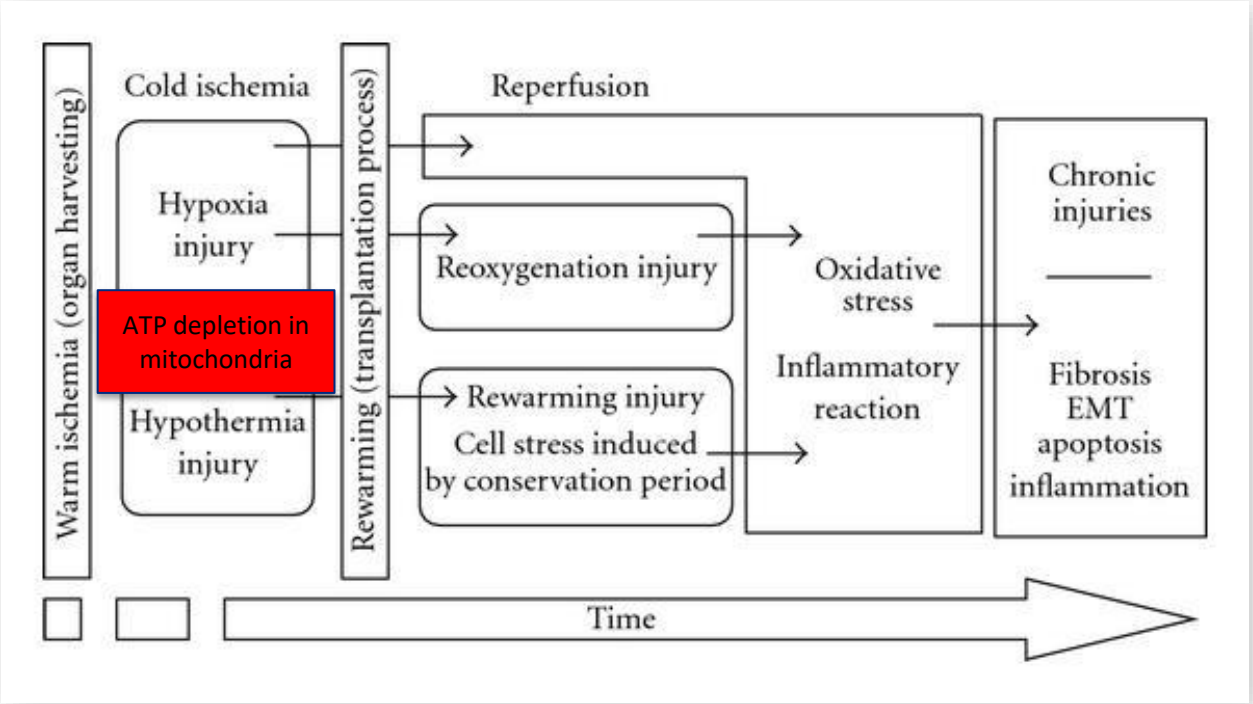
When every minute counts....

Basic principles for organ preservation

- Replacing blood to avoid intravascular coagulation
- Cell protective solutions
- Cooling to minimize energy/oxygen demand



The sequence of problems…..



Machine perfusion in kidney transplantation

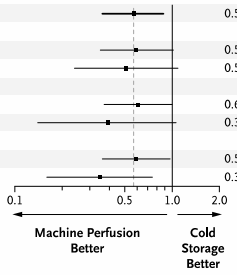
The NEW ENGLAND JOURNAL of MEDICINE

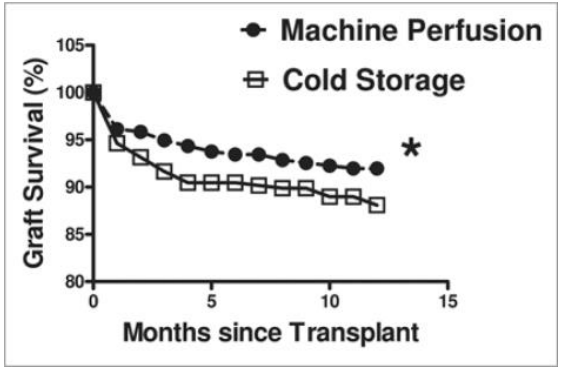
ESTABLISHED IN 1812 JANUARY 1, 2009 VOL. 360 NO. 1

Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation

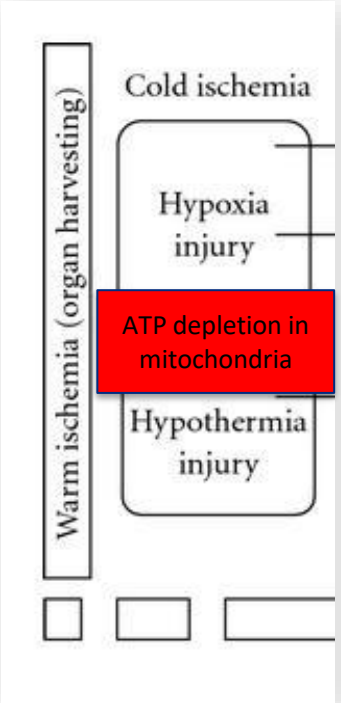
Cyril Moers, M.D., Jacqueline M. Smits, M.D., Ph.D., Mark-Hugo J. Maathuis, M.D., Ph.D., Jürgen Treckmann, M.D., Frank van Gelder, Bogdan P. Napieralski, Margitta van Kasterop-Kutz, Jaap J. Homan van der Heide, M.D., Ph.D., Jean-Paul Squifflet, M.D., Ph.D., Ernest van Heurn, M.D., Ph.D., Günter R. Kirste, 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.*

Subgroup	No. of Patients (%)	Machine-Perfusion Group	Cold-Storage Group	Adjusted Odds Ratio (95% CI)	P Value
		no. of events (%)			
Overall	672 (100)	70 (21)	89 (27)	0.57 (0.36–0.88)	
Donor criteria					0.75
Standard-criteria donation	484 (72)	48 (20)	60 (25)	0.59 (0.35–1.02)	
Expanded-criteria donation	188 (28)	22 (23)	29 (31)	0.51 (0.24–1.09)	
Donation procedure (main data set)					0.42
Donation after brain death	588 (88)	48 (16)	61 (21)	0.61 (0.37–1.00)	
Donation after cardiocirculatory death	84 (13)	22 (52)	28 (67)	0.39 (0.14–1.06)	
Donation procedure (extended data set)					0.26
Donation after brain death	588 (78)	48 (16)	61 (21)	0.59 (0.36–0.97)	
Donation after cardiocirculatory death	164 (22)	44 (54)	57 (70)	0.35 (0.16–0.75)	



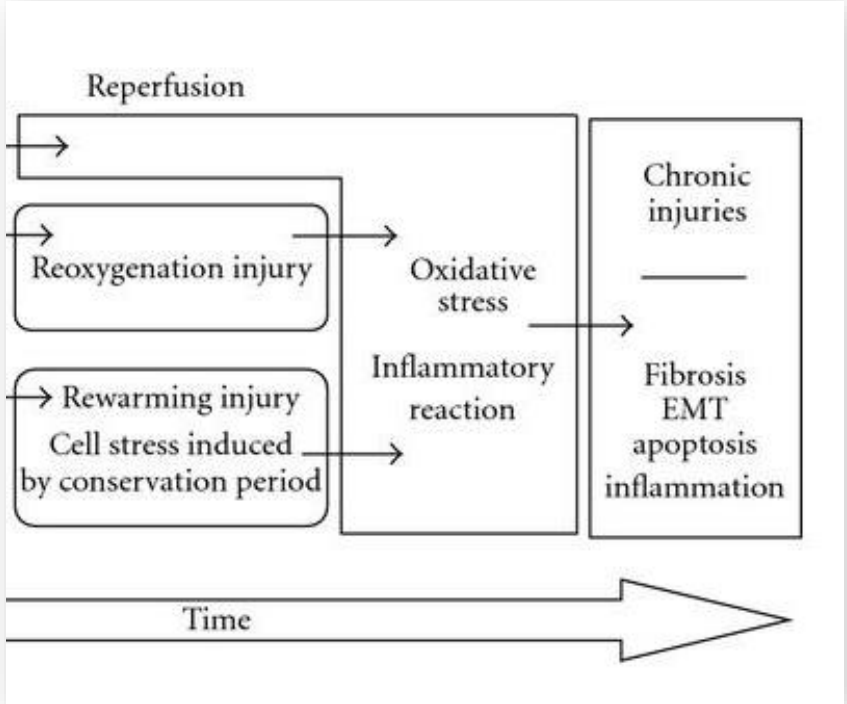


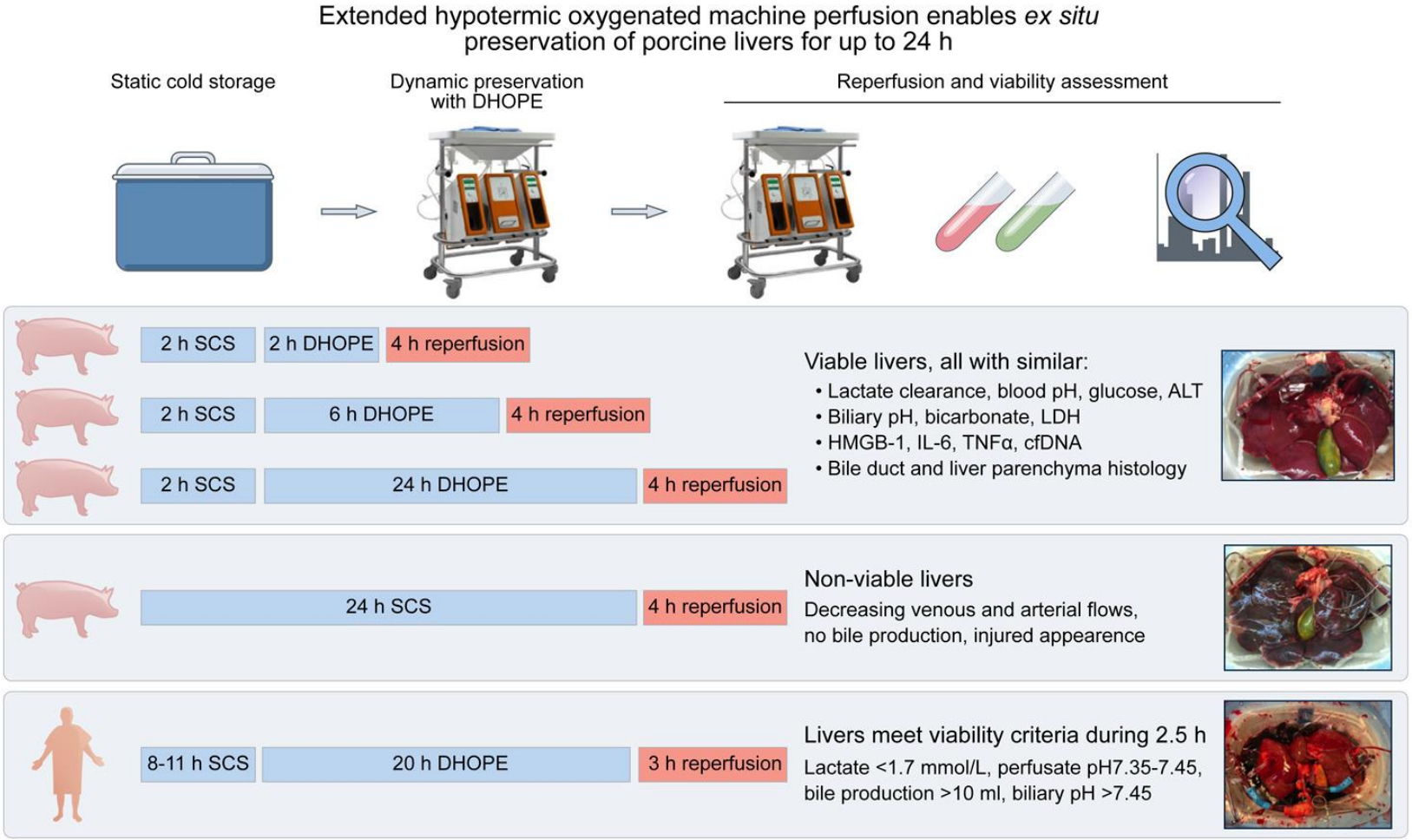
Reducing the organ preservation insult



Hypotermic Oxygenated machine perfusion (HOPE)

ATP accumulation in mitochondria





Brüggenwirth, I. M. A. *et al.* Extended hypothermic oxygenated machine perfusion enables ex situ preservation of porcine livers for up to 24 hours. *Jhep Reports* **2**, 100092 (2020).

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*

SECONDARY END-POINT MEASURES

Intraoperatively, the postreperfusion syndrome, which was defined as a decrease of more than 30% in the mean arterial blood pressure, occurred less frequently in recipients of a machine-perfused liver than in those in the control group (12% vs. 27%; adjusted risk ratio, 0.43; 95% CI, 0.20 to 0.91). This difference remained when we included increased inotropic support in the definition (Table 2). In line with this, the mean (±SD) serum potassium levels immediately after transplantation were lower in the machine-perfusion group than in the control group (4.1±0.7 mmol per liter vs. 4.4±1.1 mmol per liter; mean difference, −0.4 mmol per liter; 95% CI, −0.1 to −0.6).

Early allograft dysfunction occurred in 20 machine-perfused livers (26% of the patients), as

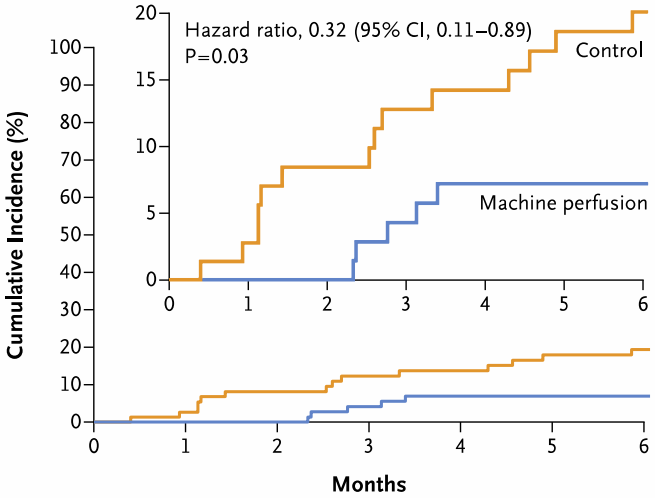
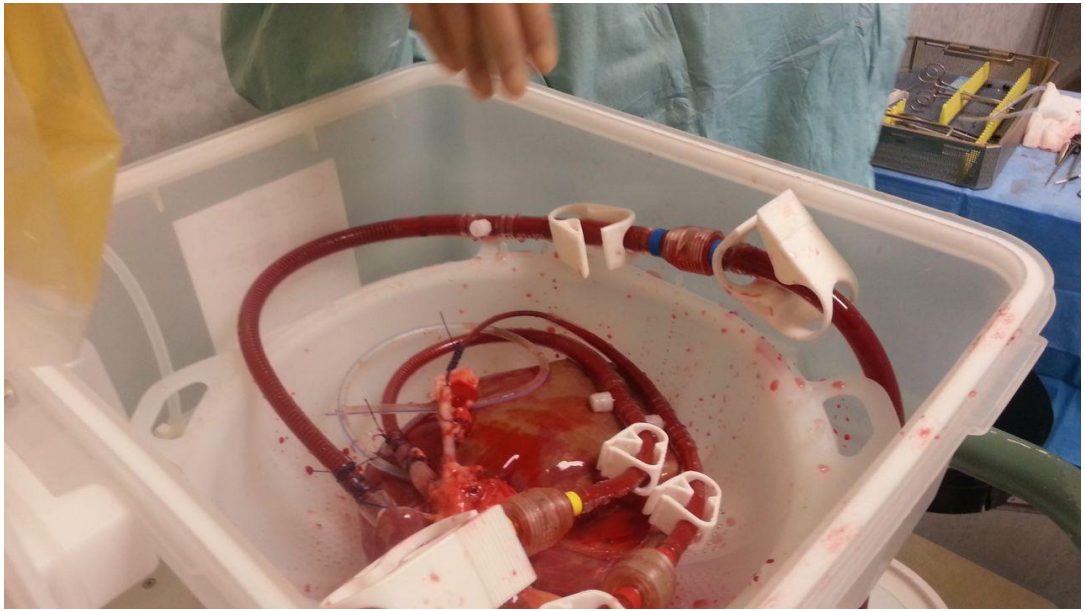


Figure 1. Cumulative Incidence of Symptomatic Nonanastomotic Biliary Strictures.

Shown are the time-to-event Kaplan–Meier curves for symptomatic nonanastomotic biliary strictures within 6 months after liver transplantation (primary end point). The hazard ratio was adjusted for stratification factors (transplantation center and primary sclerosing cholangitis) and for prespecified, established donor risk factors (donor warm-ischemia time and donor risk index); the P value is from a Cox regression analysis. P=0.03 also by the log-rank test. The inset shows the same data on an enlarged y axis.

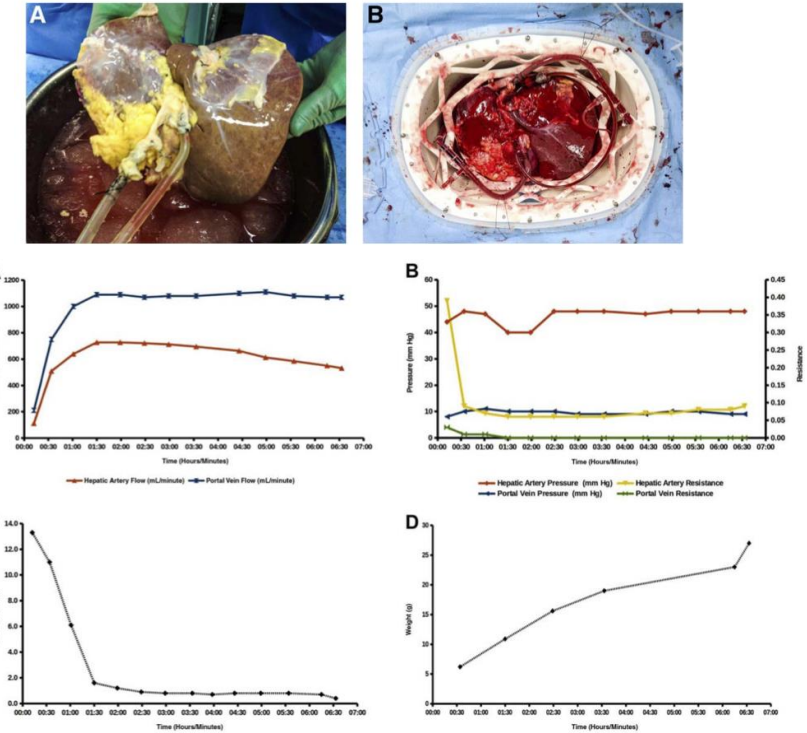
Normoterm leverperfusjon



LETTERS FROM THE FRONTLINE

First Human Liver Transplantation Using a Marginal Allograft Resuscitated by Normothermic Machine Perfusion

Received May 9, 2015; accepted October 14, 2015.



- 28 year old male DCD donor
- 109 min. warm ischaemia
- 422 min. cold ischaemia

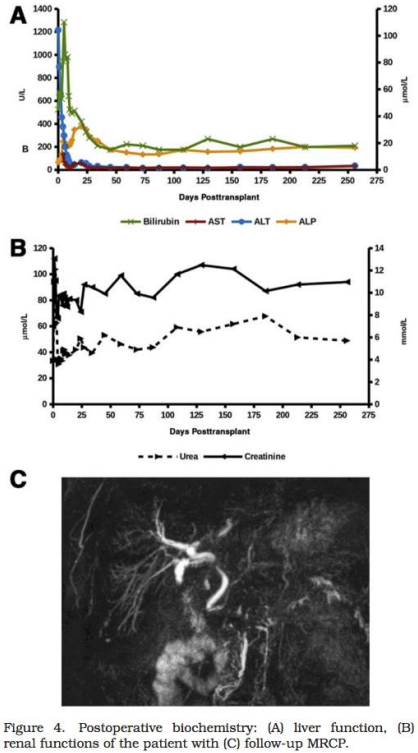


Figure 4. Postoperative biochemistry: (A) liver function, (B) renal functions of the patient with (C) follow-up MRCP.

nature biotechnology

ARTICLES

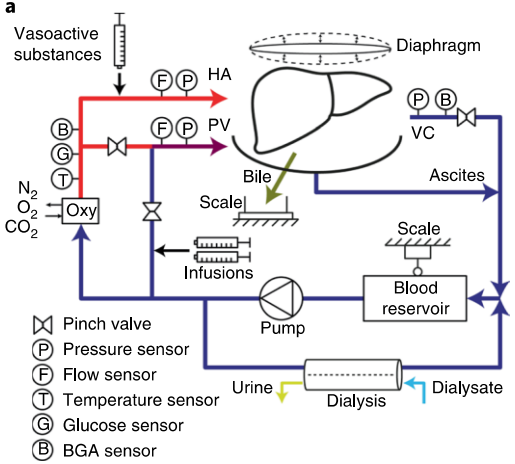
https://doi.org/10.1038/s41587-019-0374-x

An integrated perfusion machine preserves injured human livers for 1 week

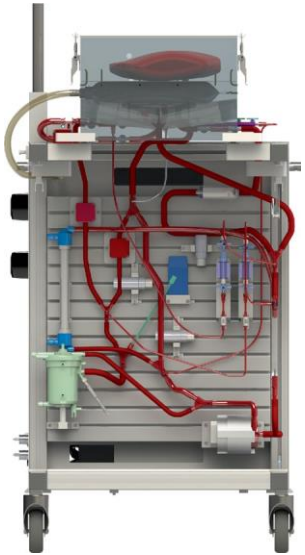
Dilmurodjon Eshmuminov[1,2,6], Dustin Becker[2,3,6], Lucia Bautista Borrego[1,2], Max Hefti[2,3], Martin J. Schuler[2,3], Catherine Hagedorn[1,2], Xavier Muller[1,2], Matteo Mueller[1,2], Christopher Onder[2,4], Rolf Graf[1,2], Achim Weber[5], Philipp Dutkowski[1,2], Philipp Rudolf von Rohr[2,3,7] and Pierre-Alain Clavien[1,2,7*]

The ability to preserve metabolically active livers ex vivo for 1 week or more could allow repair of poor-quality livers that would otherwise be declined for transplantation. Current approaches for normothermic perfusion can preserve human livers for only 24 h. Here we report a liver perfusion machine that integrates multiple core physiological functions, including automated management of glucose levels and oxygenation, waste-product removal and hematocrit control. We developed the machine in a stepwise fashion using pig livers. Study of multiple ex vivo parameters and early phase reperfusion in vivo demonstrated the viability of pig livers perfused for 1 week without the need for additional blood products or perfusate exchange. We tested the approach on ten injured human livers that had been declined for transplantation by all European centers. After a 7-d perfusion, six of the human livers showed preserved function as indicated by bile production, synthesis of coagulation factors, maintained cellular energy (ATP) and intact liver structure.

a



b



h

	Commercial perfusion machines	LIVER4LIFE Long term perfusion machine	
Liver chamber	X	X	Safe liver storage
Pump Continuous flow in PV Pulsatile flow in HA	 X X	 X X	Wave and pulse shape of flow and pressure of commercial machines not reported
Pressure/flow sensors HA PV Vena cava	 X X X	 X X X	Continuous pressure and flow monitoring
Oxygenator Gas supply Heat exchange Individual gas-supply for pH control in blood	 X X	 X X X	pH control with individual O_2, N_2, and CO_2 gas supply to oxygenator
Blood gas analysis HA PV Vena cava	X	 X X X	Monitoring of blood gases and other critical parameters during long term perfusion
Physiologic PV saturation with one oxygenator		X	Prevention of hyperoxygenation Reduction of vasoconstriction
Online glucose sensor		X	Real-time glucose monitoring
Feedback controlled infusions Insulin/glucagon		X	Automated correction of blood glucose level within predefined limits
Feedback controlled dialysis system		X	Metabolic waste removal Acid-base balance Control of sodium & electrolytes Hematocrit control
Liver movement		X	Prevention of pressure necrosis
Continuous response evaluation to vasoactiva, insulin and glucagon		X	Continuous viability assessment

nature biotechnology

ARTICLES

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

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]

Current organ preservation methods provide a narrow window (usually <12 hours) to assess, transport and implant donor grafts for human transplantation. Here we report the transplantation of a human liver discarded by all centers, which could be preserved for several days using ex situ normothermic machine perfusion. The transplanted liver exhibited normal function, with minimal reperfusion injury and the need for only a minimal immunosuppressive regimen. The patient rapidly recovered a normal quality of life without any signs of liver damage, such as rejection or injury to the bile ducts, according to a 1-year follow up. This inaugural clinical success opens new horizons in clinical research and promises an extended time window of up to 10 days for assessment of viability of donor organs as well as converting an urgent and highly demanding surgery into an elective procedure.

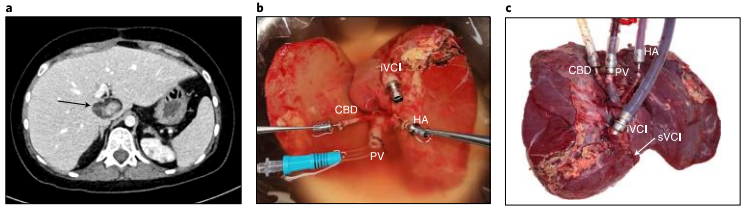


Fig. 1 | Donor liver shown on a preoperative CT scan, on the back table and during perfusion. a, CT scan of the donor liver displaying the tumor of unknown dignity (benign/malignant) in segment 1 (arrow). **b**, Donor liver on the back table. Flushing cannula in the portal vein (PV) during hypothermic perfusion with oxygenated MPS solution. Additional cannulas were placed in the hepatic artery (HA), the infrahepatic vena cava inferior (iVCI) and the common bile duct (CBD). **c**, Donor liver during ex situ normothermic machine perfusion. Cannulas were placed in the PV, the HA, the iVCI and the CBD. The suprahepatic vena cava inferior (sVCI) was temporarily sutured.

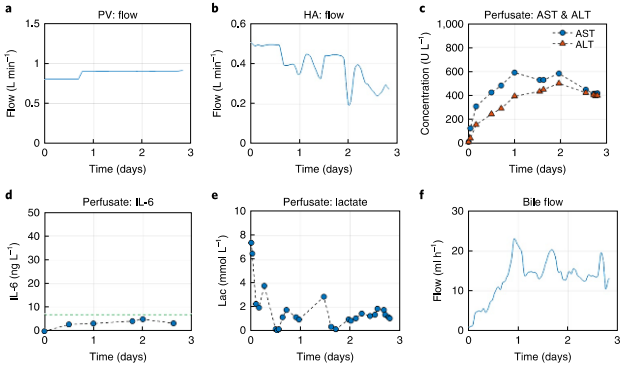
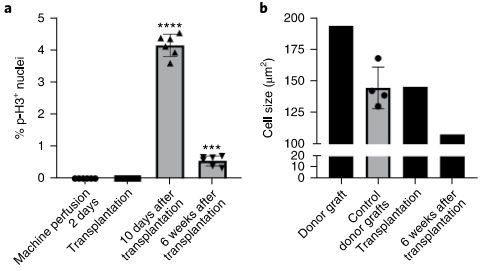
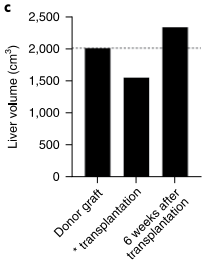
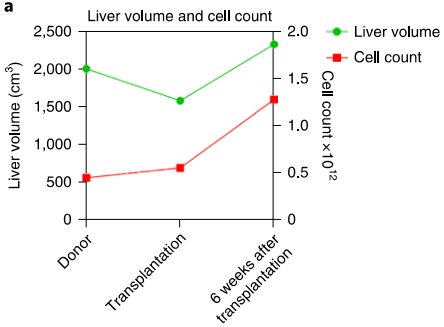
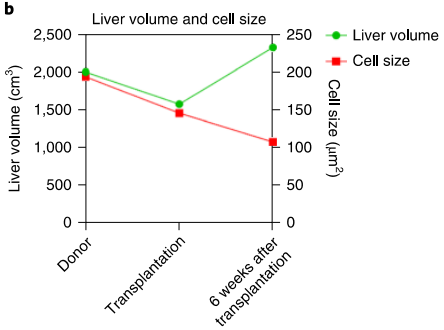


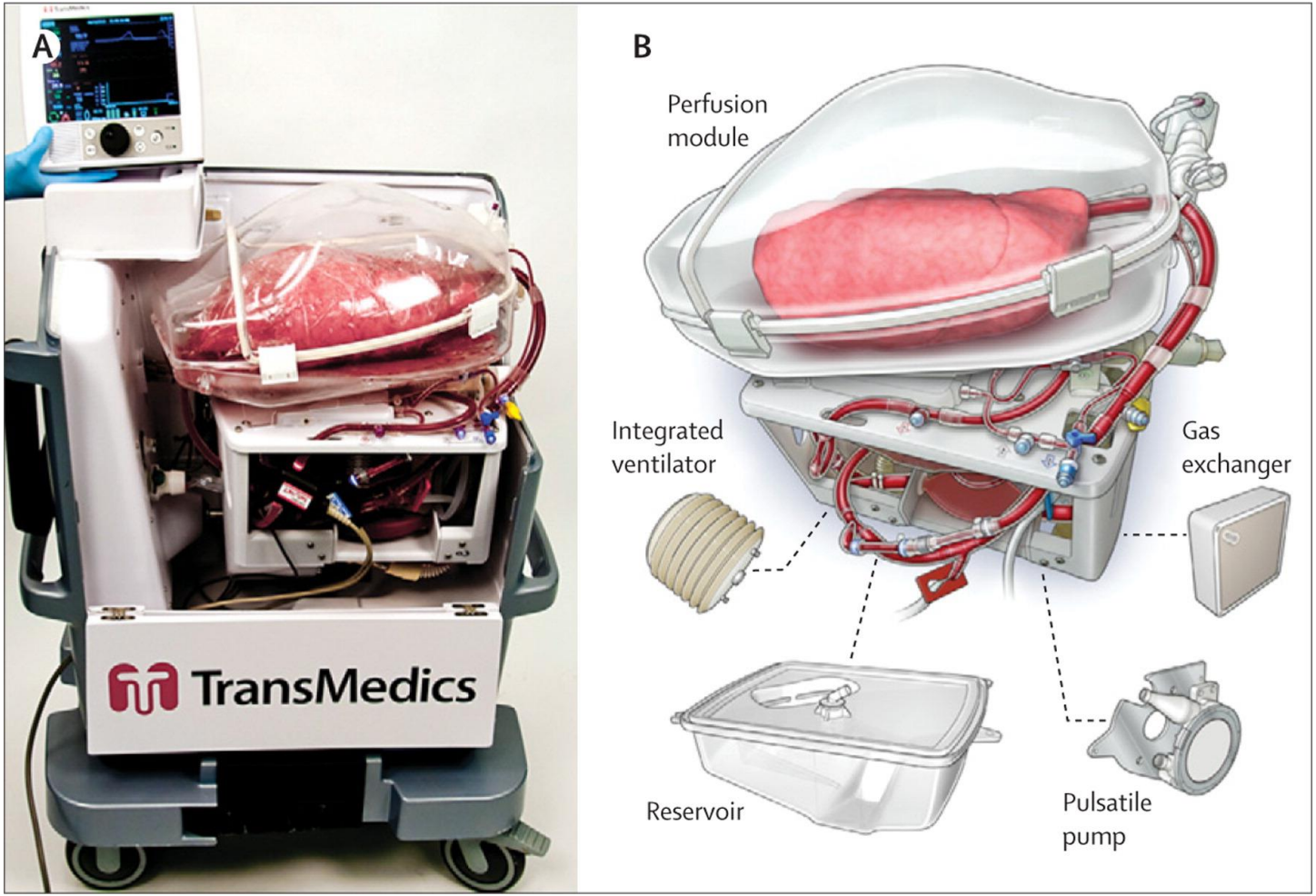
Fig. 2 | Liver performance parameters during ex situ normothermic machine perfusion. a, Steady PV flow maintained between 0.8 L min^{-1} and 0.9 L min^{-1}, resulting in a pressure between 10 mmHg and 12 mmHg. **b**, HA flow starting at 0.5 L min^{-1}, due to initial vasoplegia upon reperfusion, and decreasing to a physiologic value of 0.2 L min^{-1}. **c**, Course of AST and ALT with a relative slow increase—peak AST of 791 U L^{-1} and peak ALT of 587 U L^{-1}. **d**, Course of IL-6 as a marker of inflammation after ischemia reperfusion injury. Levels stayed low during all time points. Green dashed line shows the reference level (<7 ng L^{-1}). **e**, Lactate was maintained at a low level, demonstrating the capacity of the liver to clear lactate. **f**, Bile flow was nearly constant throughout the whole ex situ normothermic machine perfusion and at a high level.





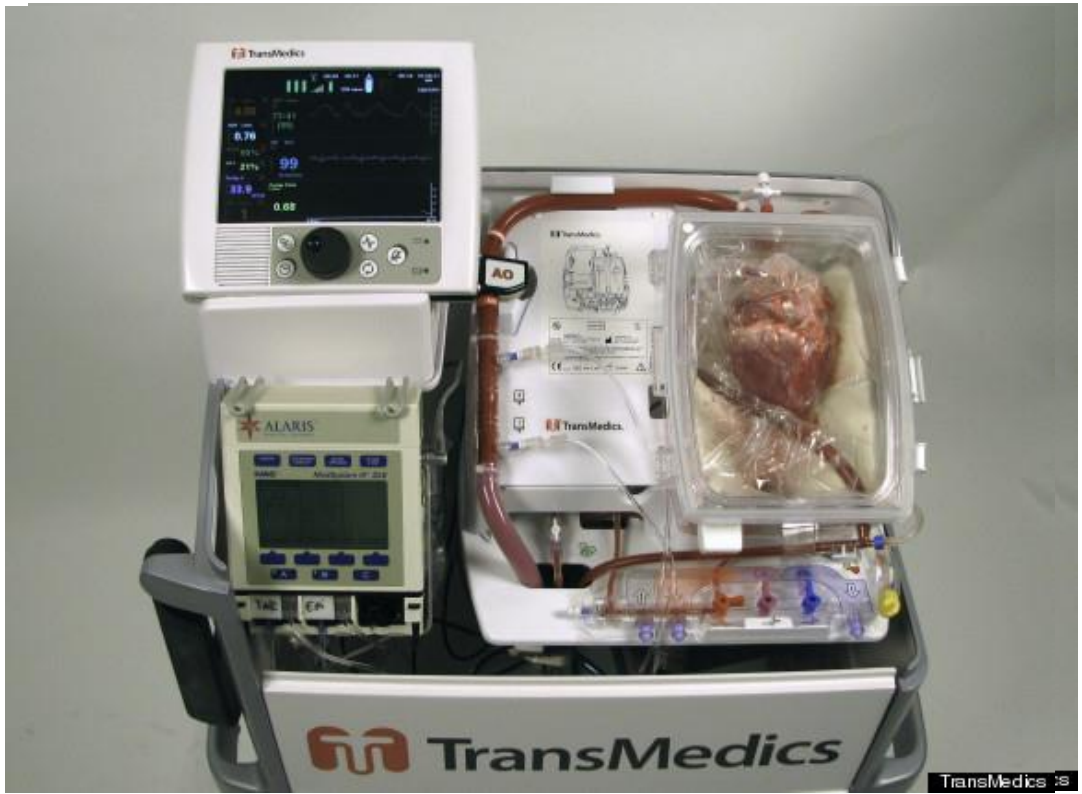




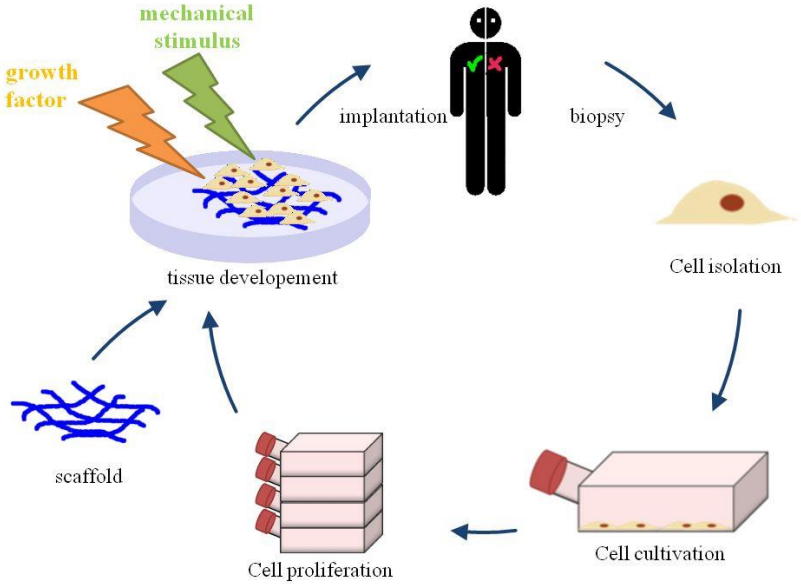

A
TransMedics
B
Perfusion module
Integrated ventilator
Gas exchanger
Reservoir
Pulsatile pump

Recovery of donor hearts after circulatory death with normothermic extracorporeal machine perfusion†

Herman Tolboom[a,*], Asya Makhro[b], Barbara A. Rosser[c], Markus J. Wilhelm[a], Anna Bogdanova[b] and Volkmar Falk[a]



- Tissue engineering



Acta Oto-Laryngologica, 2011; 131: 645–652

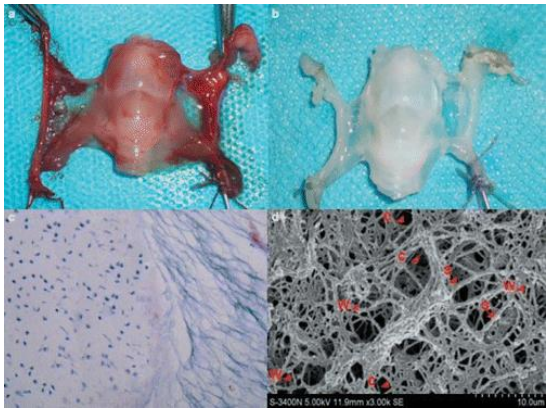
informa
healthcare

ORIGINAL ARTICLE

Tissue-engineered larynx using perfusion-decellularized technique and mesenchymal stem cells in a rabbit model

NAN HOU[1], PENGCHENG CUI[2], JIASHENG LUO[2], RUINA MA[2] & LI ZHU[1]

[1]*Department of Otorhinolaryngology Head and Neck Surgery, First Affiliated Hospital, Chengdu Medical College, Chengdu, Sichuan Province and* [2]*Department of Otorhinolaryngology Head and Neck Surgery, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shaanxi Province, PR China*

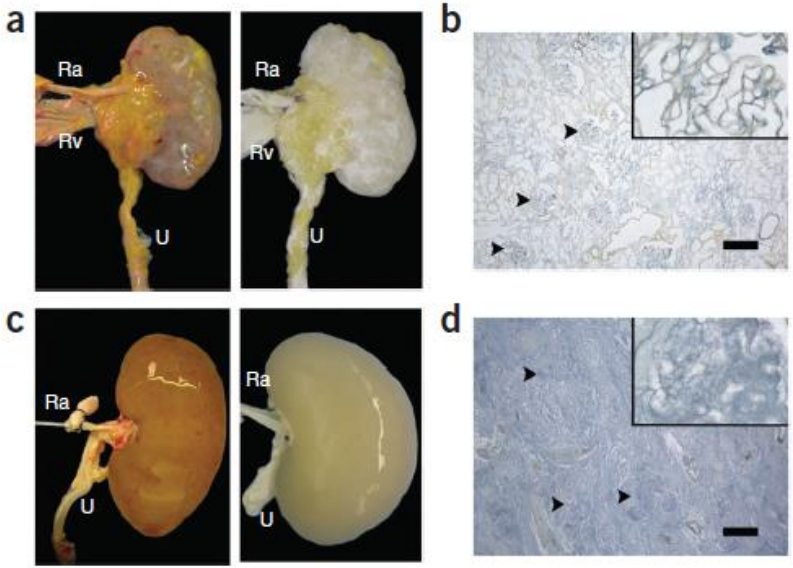


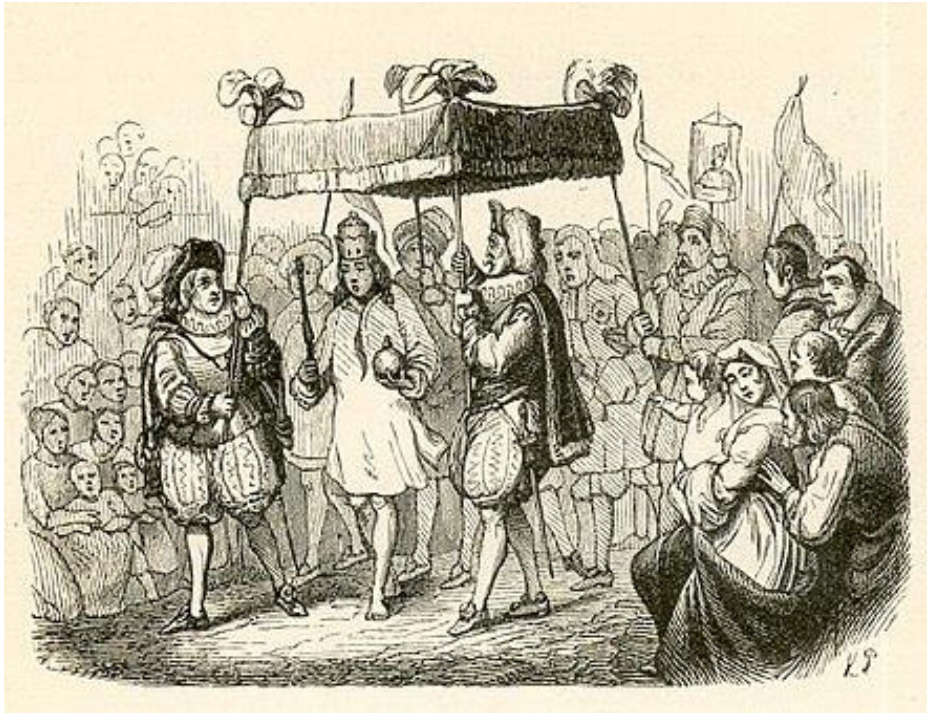
Stamcelleteknologi kommer til å påvirke transplantasjonsfeltet og reksonstruktiv kirurgi
•Celletransplantasjon
•Graft

nature medicine

Regeneration and experimental orthotopic transplantation of a bioengineered kidney

Jeremy J Song[1,2], Jacques P Guyette[1,2], Sarah E Gilpin[1,2], Gabriel Gonzalez[1,2], Joseph P Vacanti[1–3] & Harald C Ott[1,2,4]





FALLET MACCHIARINI

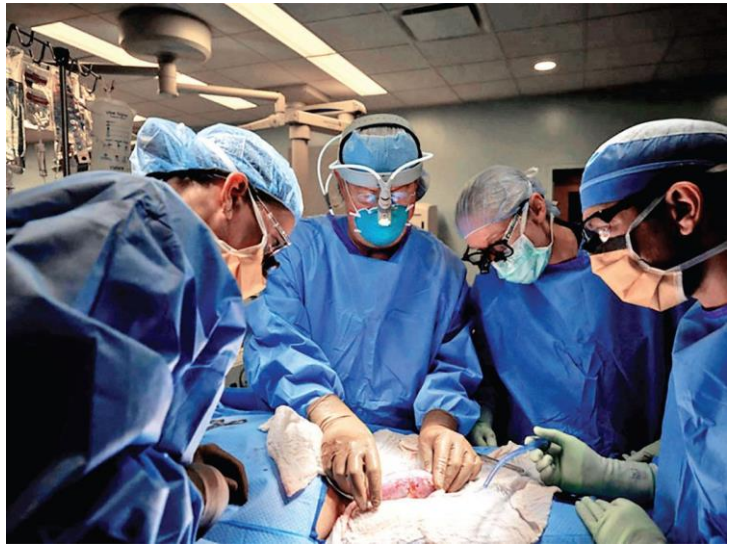
Utredning av verksamheten med transplantationer av syntetiska luftstrupar vid Karolinska Universitetssjukhuset

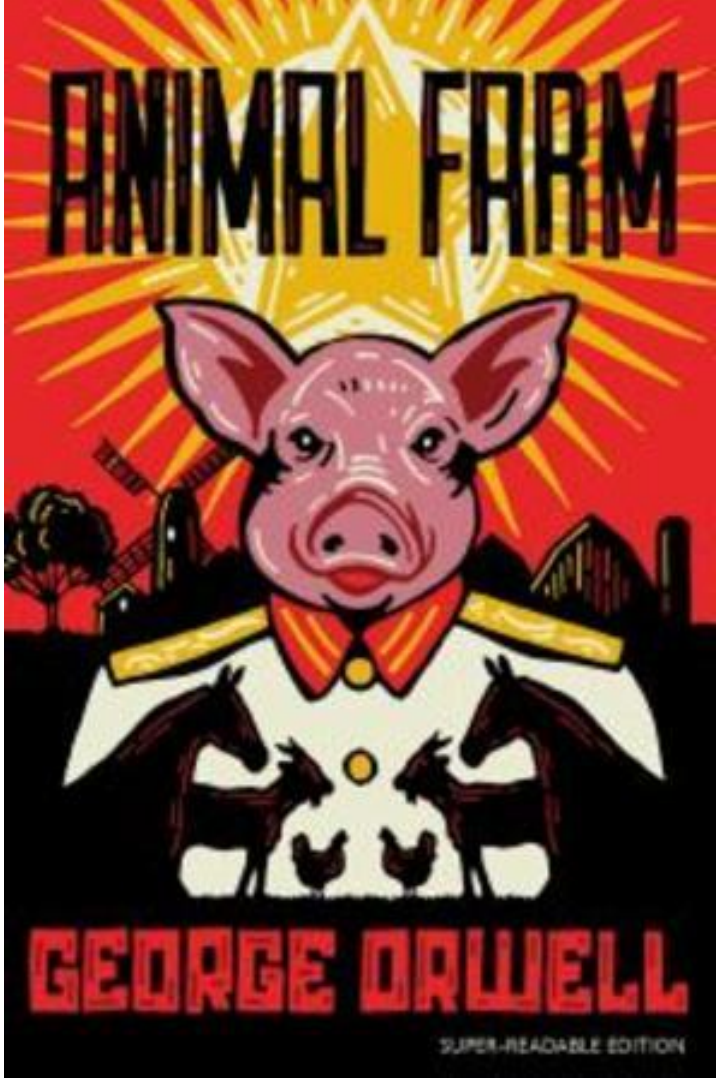
Man gets genetically-modified pig heart in world-first transplant

11 January

Kidneys From a Genetically Altered Pig Are Implanted in a Brain-Dead Patient

Surgeons at the University of Alabama at Birmingham said they hoped to start clinical trials with kidney patients later this year.





UNIVERSITETET I OSLO
Det medisinske fakultet

Cand. med. Pål-Dag Line

født 10. mars 1960 har i høstsemesteret 1996 oppnådd graden

doctor medicinae

Institutt — **Instituttgruppe for Oslo kommunale sykehus**
Kirurgisk avdeling B, Rikshospitalet

Prøveforelesningene
Oppgitt emne: ***Bruk av dyreorganer i bioimplantater og transplantasjonskirurgien***

Prøveforelesningene
Oppgitt emne: ***Bruk av dyreorganer i bioimplantater og transplantasjonskirurgien***

Selvvalgt emne: ***Sirkulasjonsundersøkelser i lever og nyretransplantater. Nåtid og fremtid.***

På grunnlag av innstillingen fra den oppnevnte bedømmelseskomitéen og fra De
medisinske fakultet har Det akademiske kollegium kreert cand. med.
Pål-Dag Line
til doctor medicinae den 5. desember 1996.

Takk for oppmerksomheten!