6th INTERNATIONAL CONGRESS

INFECTIONS & TRANSPLANTATION

Varese, 18-20 Maggio 2017
ATA Hotel

PROGRAMMA SCIENTIFICO PRELIMINARE

Conservazione e trattamento degli organi destinati al trapianto

Sergio Vesconi
Coordinamento regionale trapianti Lombardia

Organ preservation

Static cold storage (SCS)

- Metabolic rate < 10% of normal, at 4°C

Preservation solutions

- minimize effects of prolonged ischemia and ischemia-reperfusion injury

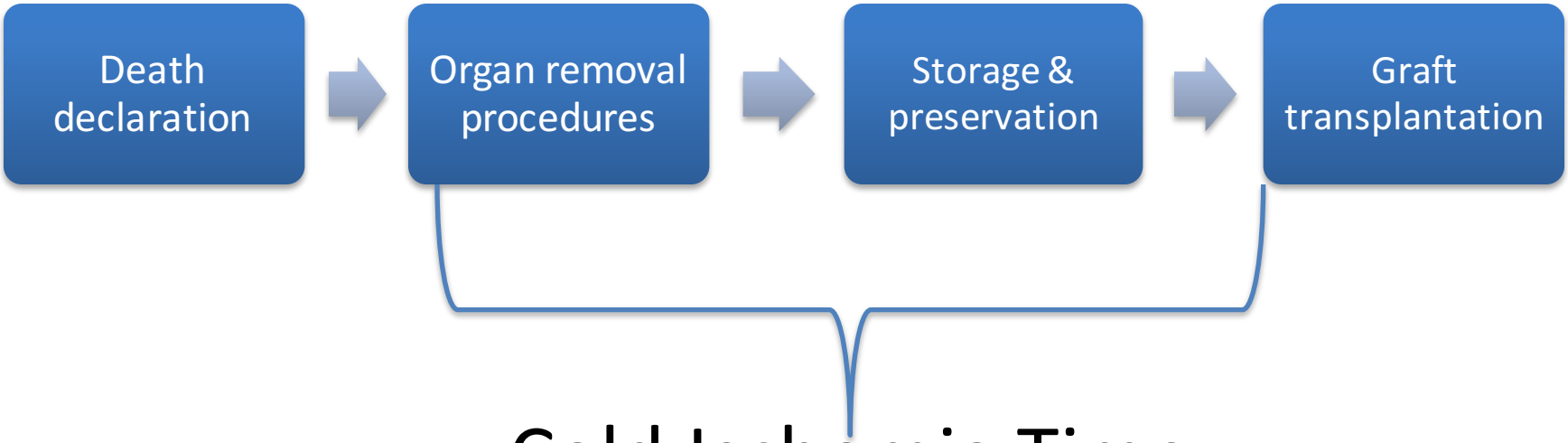
"Duration of CIT is one of the more significant variables in determinig outcome after TX and one of the only modifiable factors"

SCS limits & fitfalls

Current organ preservation by static cold storage (SCS) falls short in several aspects that are of particular importance for successful transplantation of extended criteria organs(ECD):

- Injury sustained during donor death and organ procurement is not reversed.
- Cold preservation causes itself time-dependent injury beyond that induced by ischemia.
- Viability of the organ cannot be assessed before transplantation.
- Preservation times are very limited.

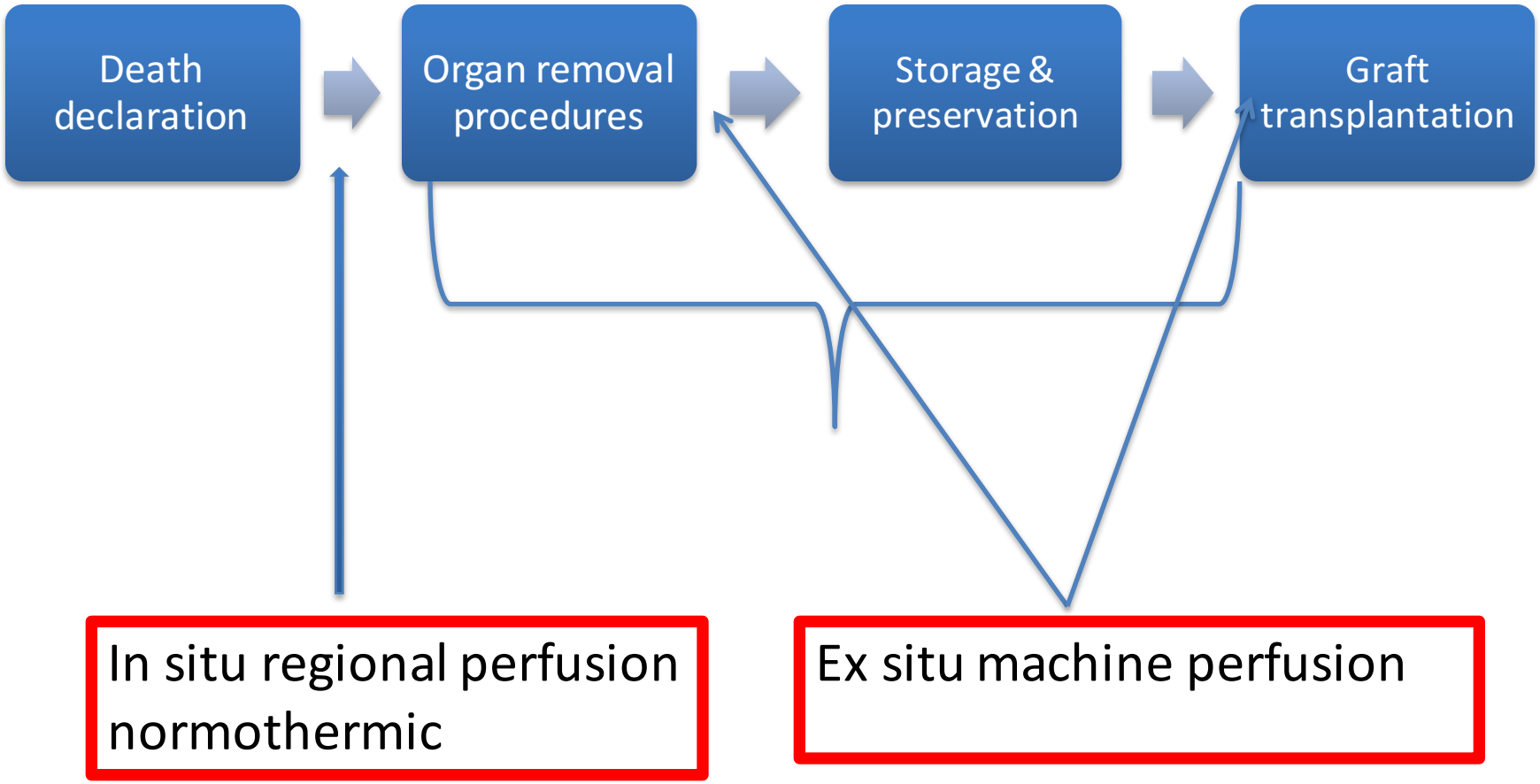
donation-transplantation (DBD)



Cold Ischemia Time

Heart	4 hrs
Lung	6
Liver	8
Pancreas	12
Small Bowel	12
Kidney	18

donation-transplantation



MP in DCD

LIVER TRANSPLANTATION 19:1292–1303, 2013

REVIEW

Regional Perfusion by Extracorporeal Membrane Oxygenation of Abdominal Organs From Donors After Circulatory Death: A Systematic Review

Iestyn M. Shapey[1] **and Paolo Muiesan**[2]
[1]*Department of Transplantation Surgery, Manchester Royal Infirmary, Manchester, United Kingdom; and* [2]*Department of Hepatobiliary and Transplantation Surgery, Queen Elizabeth Hospital, Birmingham, United Kingdom*

doi: 10.1111/ajt.

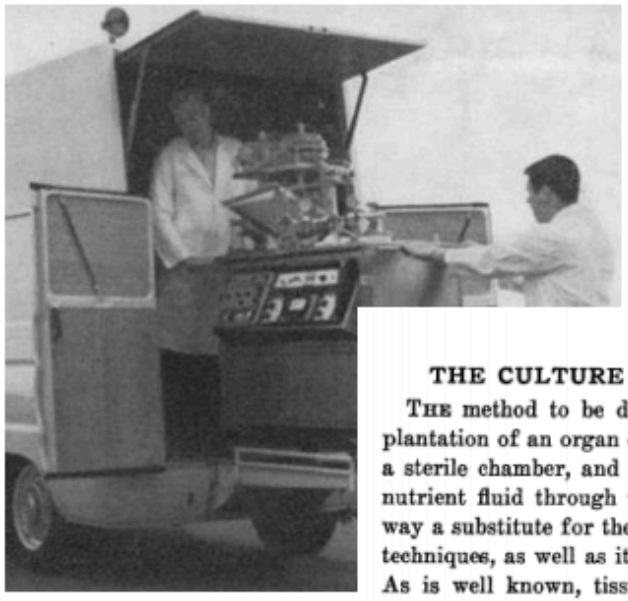
Special Article

Past, Present, and Future of Dynamic Kidney and Liver Preservation and Resuscitation

Jochmans I

American Journal of Transplantation 2016

Normothermic Graft Perfusion for Organ Preservation



SPECIAL ARTICLES

THE CULTURE OF WHOLE ORGANS

THE method to be described consists of the transplantation of an organ or of any part of the body into a sterile chamber, and of its artificial feeding with a nutrient fluid through the arteries. It is not in any way a substitute for the method of tissue culture. Its techniques, as well as its purposes, are quite different. As is well known, tissues and blood cells grow like bacteria in flasks containing appropriate media. The techniques for the cultivation of tissues are somewhat analogous to bacteriological techniques, although far more delicate. But it is through the employment of complex mechanical and surgical procedures that organs are enabled to live isolated from the body. Tissue culture deals with cells as units of bodily structures; the new method, with cellular societies as organic wholes. Its ultimate purposes are the manufacture *in vitro* of the secretions of endocrine glands, the isolation of the substances essential to the growth, differentiation and functional activity of those glands, the discovery of the laws of the association of organs, the production *in vitro* and the treatment of organic and arterial diseases, etc.

The idea of maintaining alive a portion of the body in order to study its functions is not new. In 1812, the physiologist Le Gallois wrote that, "if one could sub-

Lindbergh, *Science*, 1935

MACHINE PERFUSION: CONCEPT AND METHODS

Machine perfusion consists of creating a flow through the organ generated by a pump in a circuit to recirculate a preservative solution at various temperatures through the vasculature.

This continuous perfusion permits:

better penetration of preservation solutions within the organ,

delivery of oxygen and nutrients to the parenchyma (in case the perfusate is oxygenated),

removal of toxic metabolites (in case the perfusate is renewed or filtered).

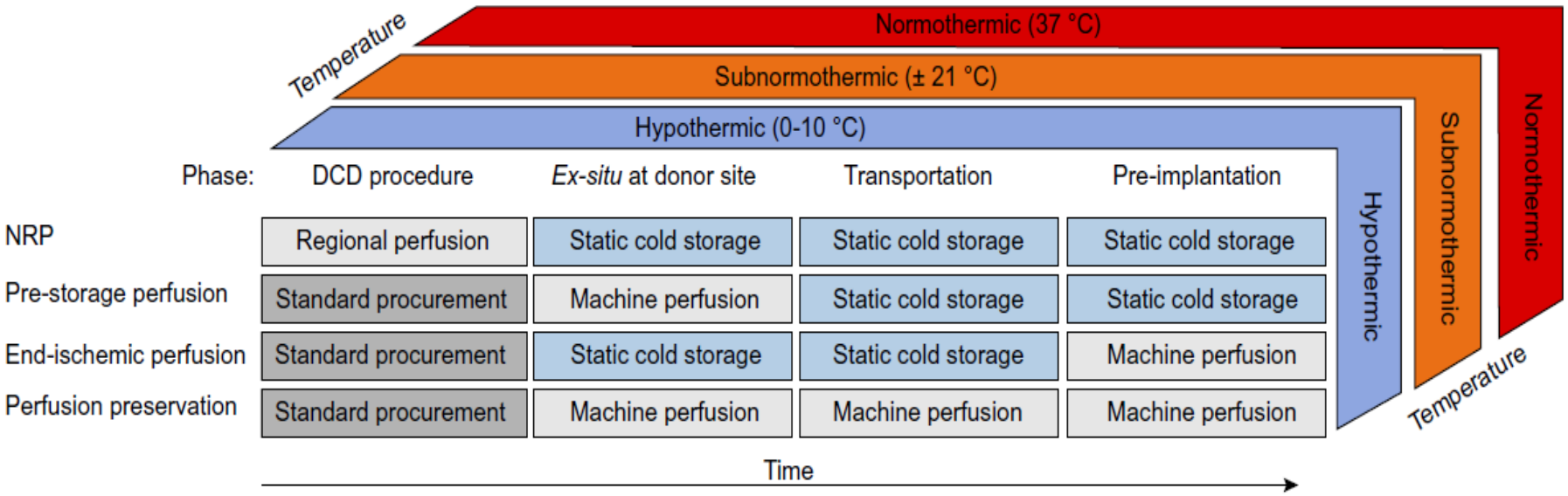
Machine perfusion: a spectrum of techniques

The term ‘machine perfusion’ is very broad; it covers a spectrum of techniques with mechanical perfusion as their common denominator.

Fundamentally, the configuration of machine perfusion depends on three parameters:

- the timing of its application
- the duration
- the perfusion temperature.

In order to prevent endothelial shear stress, pressure controlled perfusion is considered to be a safer method compared to flow controlled perfusion.


Temperature
Normothermic (37 °C)
Subnormothermic (± 21 °C)
Hypothermic (0-10 °C)
Phase:
DCD procedure
Ex-situ at donor site
Transportation
Pre-implantation
NRP
Regional perfusion
Static cold storage
Static cold storage
Static cold storage
Pre-storage perfusion
Standard procurement
Machine perfusion
Static cold storage
Static cold storage
End-ischemic perfusion
Standard procurement
Static cold storage
Static cold storage
Machine perfusion
Perfusion preservation
Standard procurement
Machine perfusion
Machine perfusion
Machine perfusion
Hypothermic
Subnormothermic
Normothermic
Temperature
Time

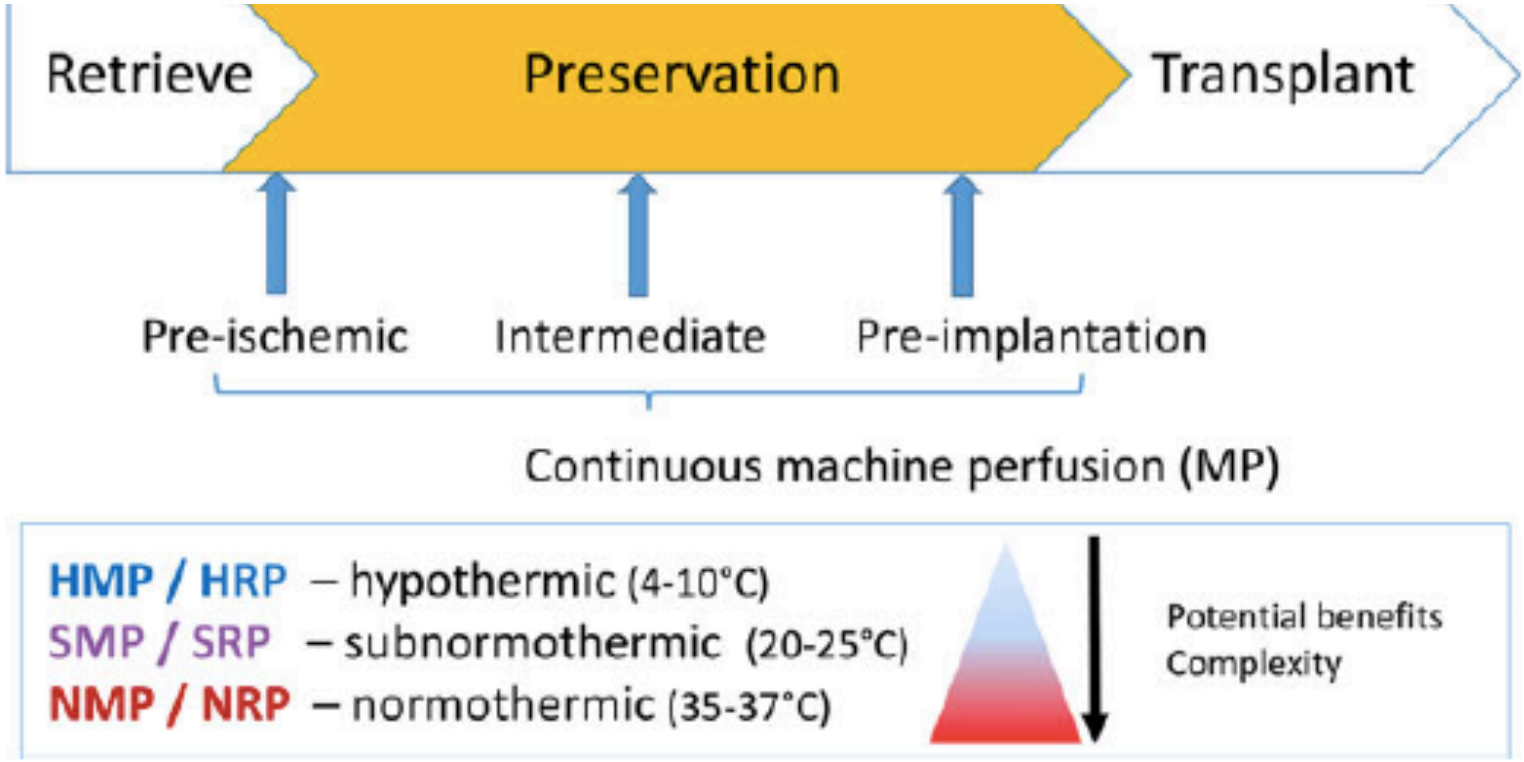


Figure 2: The different dynamic preservation strategies currently entering clinical practice with the different modalities of their use.

hypothermic regional perfusion; NMP, normothermic machine

revisiting organ preservation

use of perfusion techniques to improve outcome

In situ (before organ retrival)

- ✓ regional perfusion

Ex situ (before organ implantation)

- ✓ machine perfusion (MP)- ex vivo lung perfusion (EVLP)

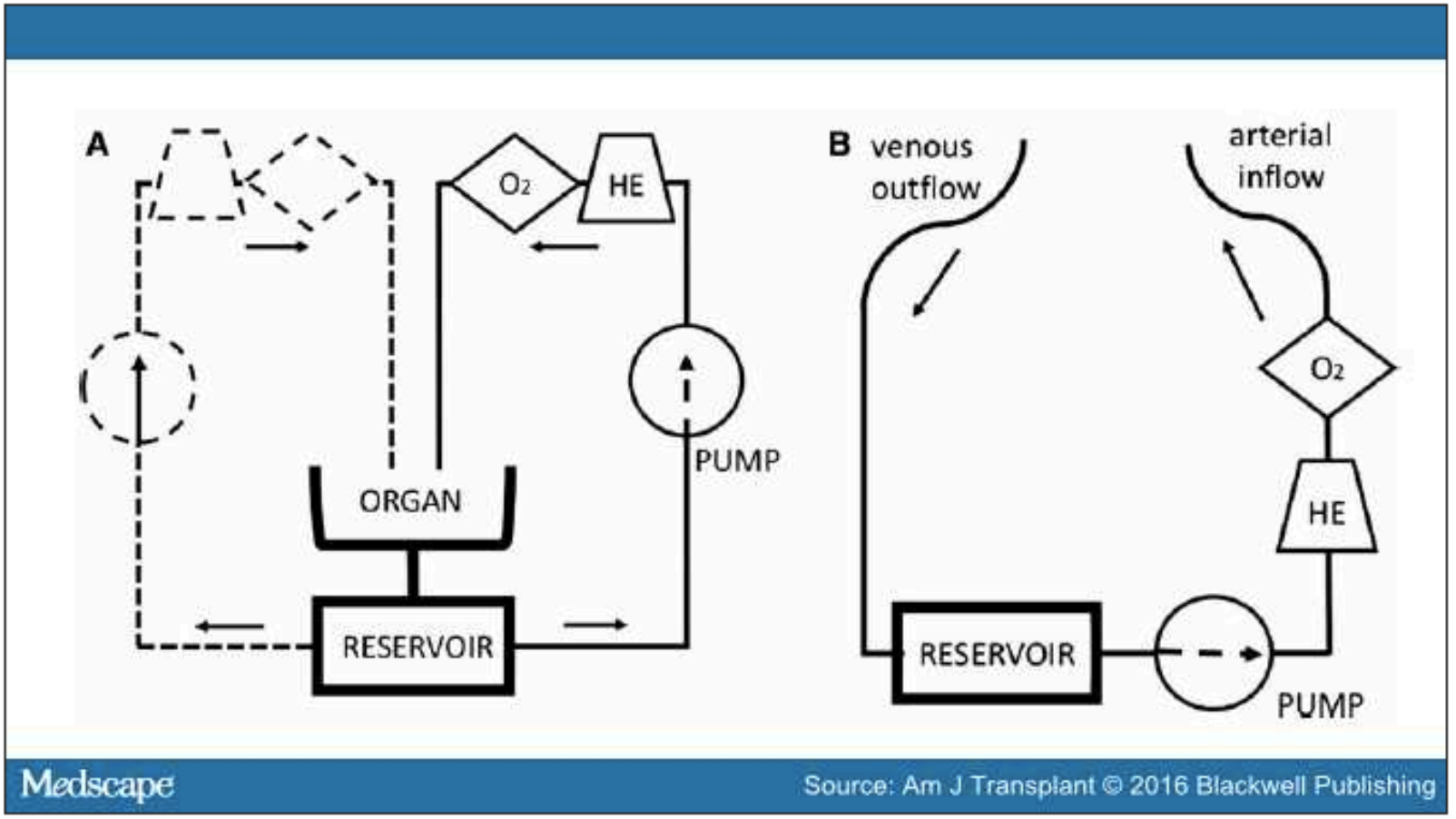


Figure 1

in situ

ex situ

MP: techniques-1

Different methods have been investigated experimentally.

Techniques may vary among solid organs.

Various ranges of **temperature** have been used from hypothermic perfusion at 4° C to normothermic perfusion at 37° C.

The former method is intended to preserve the organ in a low metabolic state, while the latter will keep the organ in a more physiologic and metabolically active state with the advantage that organ repair and reconditioning may become possible.

In addition to an improved preservation, machine perfusion may allow **real-time monitoring of functional and biochemical performance** of the graft prior to transplantation and may provide a tool to select ‘transplantable’ grafts, to improve their condition, to reduce the incidence of ischemia/reperfusion injury (IRI), and possibly to safely increase the preservation time.

MP techniques-2

Solutions used as perfusate vary among various organs from low potassium crystalloid solutions to blood-based solutions (full blood or packed red blood cells) mixed with colloids (dextran) and albumin. The power to circulate the perfusate through the vasculature is created by a roller pump (occlusive) or a centrifugal pump (nonocclusive) that delivers a continuous **flow** or a pulsatile flow mimicking the physiologic variations in systolic and diastolic pressure.

MP techniques-3

Organs can be preserved in **resting mode (preservation) or functioning mode (assessment).**

With normothermic perfusion organs will resume their function.

Kidneys will excrete urine and clear creatinine.

The liver will produce bile and coagulation factors and will clear metabolites.

Hearts can be perfused while fibrillating or beating building up pressures.

Lungs can be perfused in an atelectatic state or while ventilated, allowing gas exchange.

MP techniques-4

During machine perfusion, different physiological parameters specific to the organ can be measured and various biochemical markers released in the perfusate or excreted (in urine or bile) can be analyzed to assess the viability and the functional state of the graft.

The exact value of these **markers** to decide whether to accept or to decline an organ and to predict its functional performance after transplantation is not clear yet and needs to be further investigated.

MP techniques-5

For the kidney, vascular resistance correlates with delayed graft function, but the predictive value is low.

For the liver, the vascular resistance does not seem to correlate with viability.

In normothermic machine perfusion, the capacity of the liver to correct metabolic acidosis during machine perfusion correlates well with its function after transplant.

For the lung, oxygenation capacity taken alone may be misleading in assessing the ex-vivo lung. Other parameters like pulmonary vascular resistance, compliance, and airway pressures are equally important.

MP: impact in organ transplantation

- Preservation
  - longer (clinical, organization, safety)
  - improved (graft viability)
- Ex vivo organ assessment
- Reconditioning
- Immunomodulation
- Repair (surgery, drugs, MSC)

Reconditioning

Many organs are currently declined because of acute – albeit recoverable– injuries.

Potential grafts may get injured by several hits during the whole transplantation process in the transition phase from donor to recipient:

the initial insult leading to brain damage,

resuscitation maneuvers with intubation and ventilation,

autonomic storm and systemic inflammation following brain-stem death,

warm ischemia in donors after circulatory death,

organ manipulation and surgical trauma during procurement and organ extraction,

the cold preservation period, the implantation process, and finally

the reperfusion phase.

Altogether, organ damage may result fromdirect mechanical trauma and contusion, hemorrhage, inflammation, and infection.

Immunomodulation

MP may offer a tool for ex-vivo repair of the organs and improvement of their quality prior to transplantation and perhaps for

‘immunomodulation’ of these organs in order to protect them from innate immune responses (IRI) and adaptive immune responses (acute and chronic rejection) in the recipient.

Down-regulation of immuno-response

Repair

Research is ongoing for all organs to look for ways to administer agents with the potential to reduce the injury and to restore organ functionality.

The easiest strategy to deliver drugs directly to the organs is by including them into the perfusion solution or by injecting them into the afferent tubing running to the vasculature of the graft.

Theoretically, different drugs according to the type of injury or even a combination of them (cocktail approach) could be administered at intervals during machine perfusion: antibacterial, antiviral, and antifungal agents to treat infection, antiinflammatorymolecules to block proinflammatory responses, vasodilating agents to improve perfusion of the microvasculature, fibrinolytic agents to dissolve microthrombi, high osmotic agents to remove interstitial edema, etc.

Mesenchimal Stem Cells (MSC)

The use of mesenchymal stem cells to treat human diseases has gained much attention – in particular in the field of organ transplantation – because of their proregenerative, anti-inflammatory, and immunomodulatory properties.

Machine perfusion provides a unique tool to treat organs directly with mesenchymal stem cells ex vivo prior to transplantation and to study their mode of action.

FIGURE 3

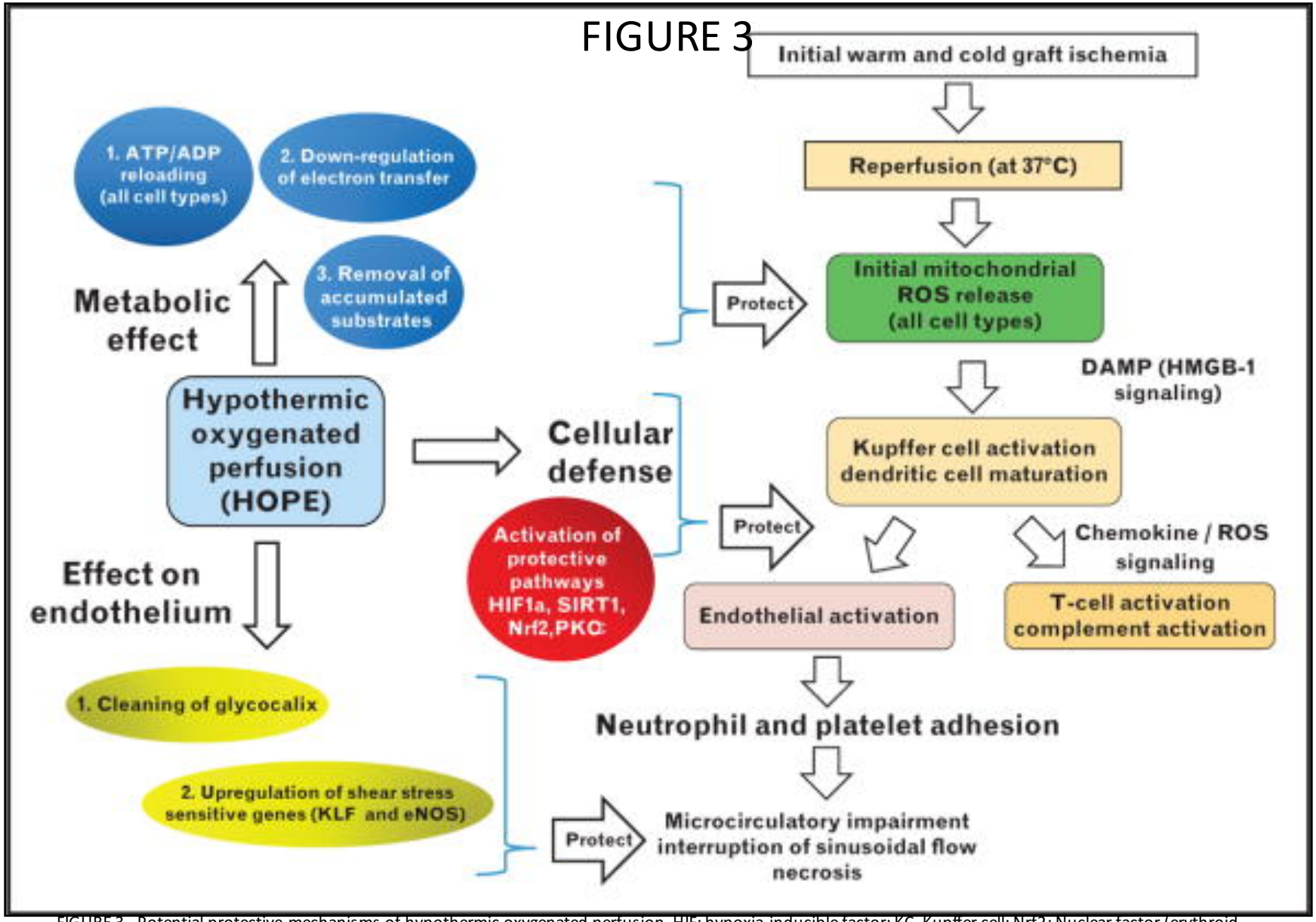
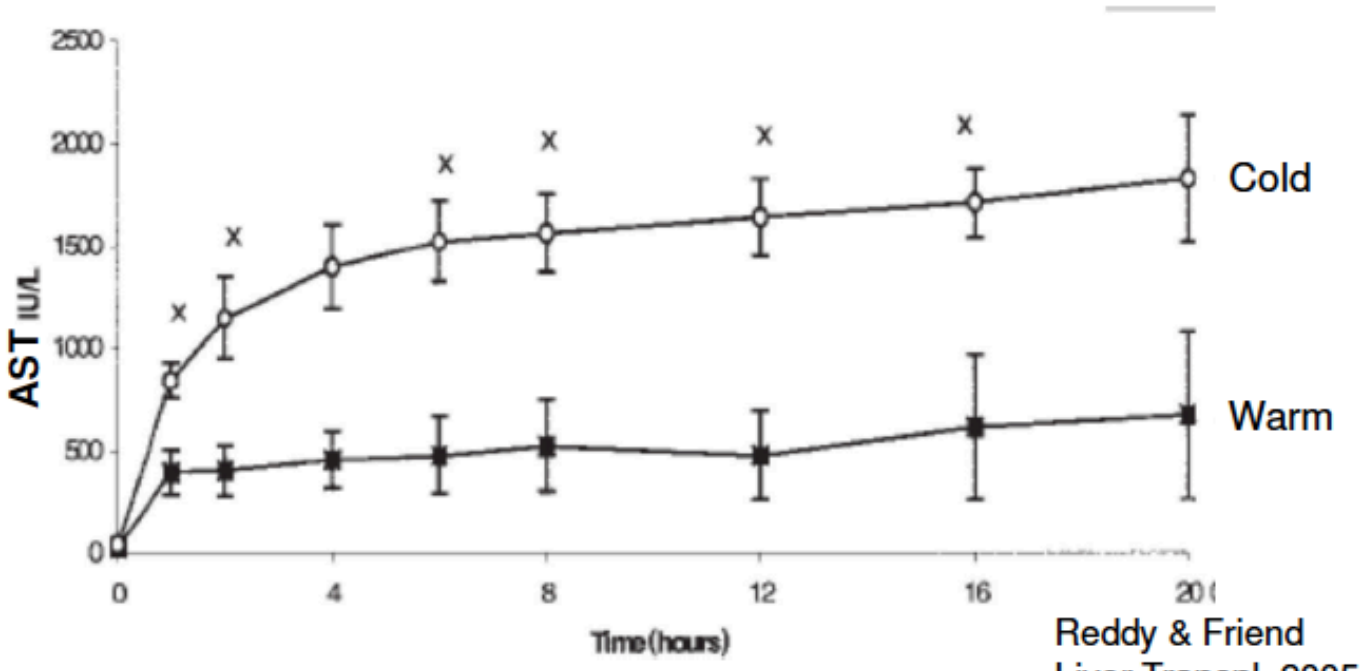


FIGURE 3 . Potential protective mechanisms of hypothermic oxygenated perfusion. HIF: hypoxia-inducible factor; KC, Kupffer cell; Nrf2: Nuclear factor (erythroid-derived 2)-like 2; PKC[epsilon]: protein kinase C epsilon; SIRT1: SIRT-1: gene of NAD-dependent deacetylase sirtuin-1.

Liver Injury During Perfusion



Reddy & Friend
Liver Transpl, 2005

Kidney TX

Standard technique: SCS

MP: hypothermic>>>normothermic)

- Maintenance of vascular bed patency
- Pressure-Flow-Resistance indices (predictive indices)
- Perfusate biomarkers

Current application: ECD, DCD

Cost effectiveness

Reduced DGD

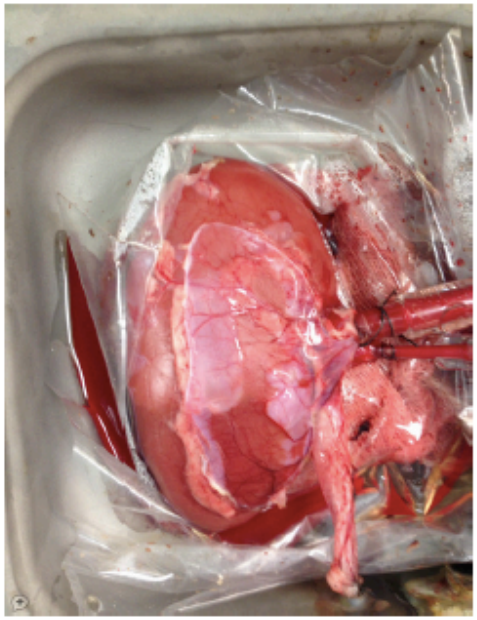
To Pump or Not to Pump: A Comparison of Machine Perfusion vs Cold Storage for Deceased Donor Kidney Transplantation

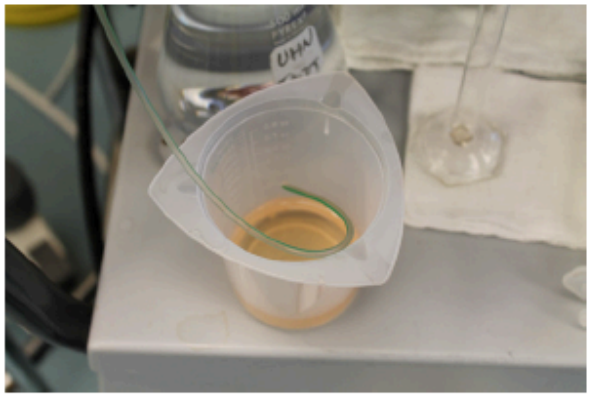
Robert M Cannon, MD, MS, Guy N Brock, PhD, R Neal Garrison, MD, FACS, Jason W Smith, MD, PhD, FACS, Michael R Marvin, MD, FACS, Glen A Franklin, MD, FACS

BACKGROUND: A recent multicenter European trial has demonstrated reduced rates of delayed graft function when kidneys undergo machine perfusion before transplantation. This study was undertaken to evaluate the impact of machine perfusion on early kidney transplant function in the United States.

CONCLUSIONS: Machine perfusion of deceased donor kidneys results in significantly decreased rates of DGF. (J Am Coll Surg 2013;216:625–634.

Normothermic Ex Vivo Kidney Perfusion





Liver TX

Normo-hypo-subnormothermic

Flow (single-double- continous-pulsatile)

Solutions

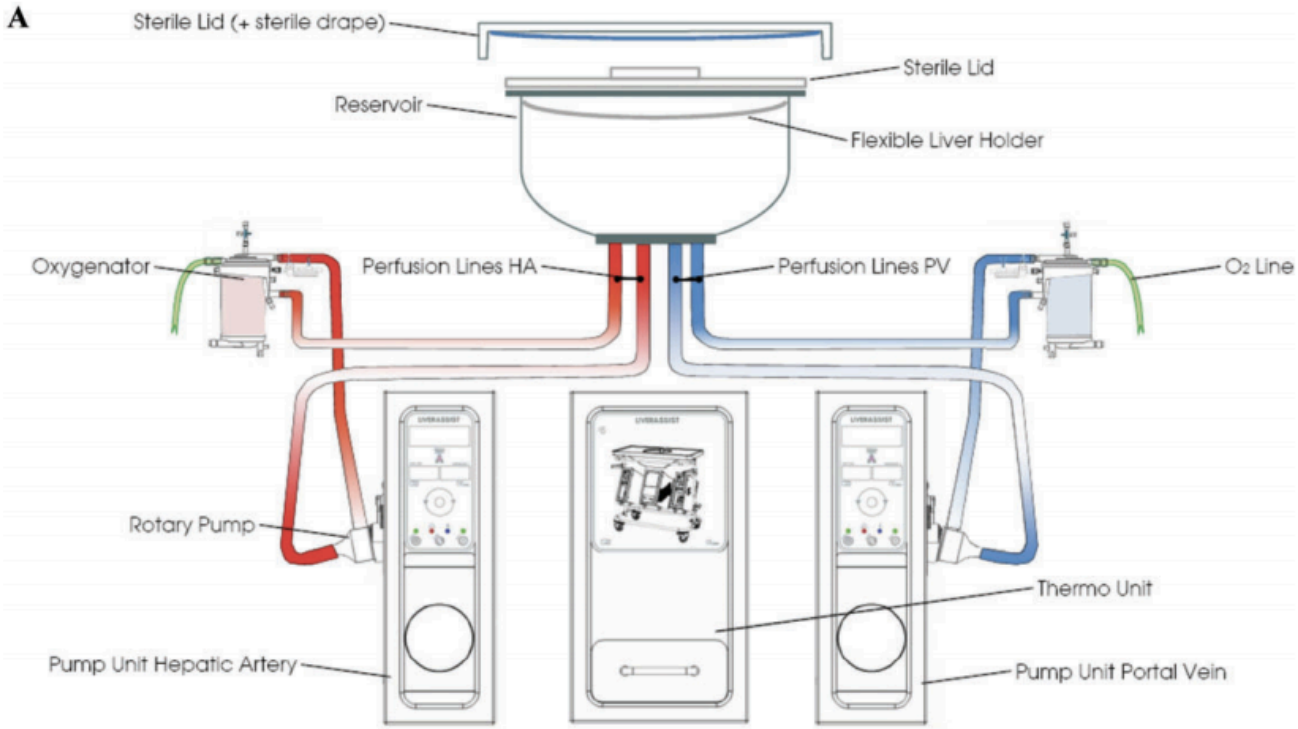
Clerance lactates, cytolitic enzymes, bile production

Biomarkers (more specific for liver damage)

Early allograft dysfunction, choledocic stenosis

Indications: ECD, DCD….

Normothermic Perfusion of Human Livers



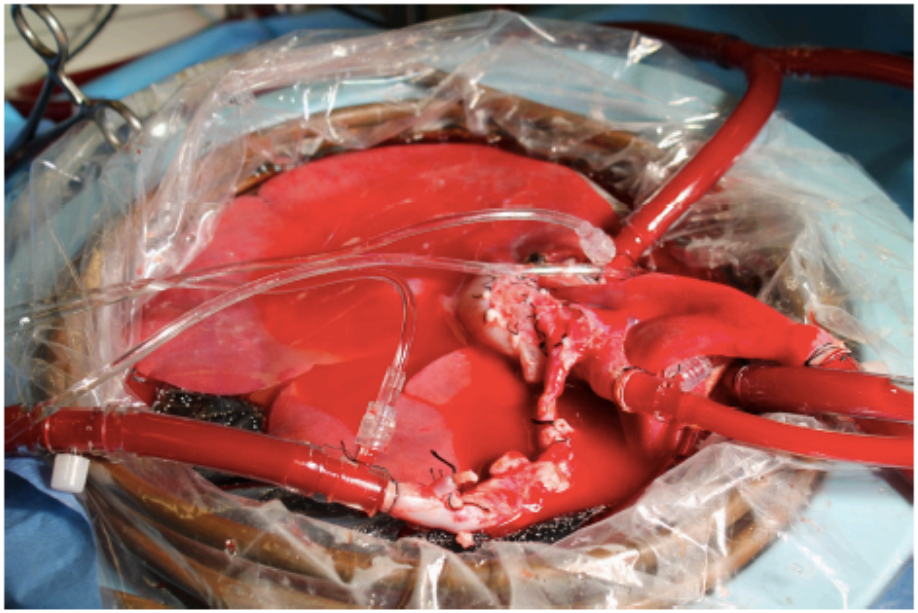
LIVER TRANSPLANTATION 18:S31-S33, 2012

SUPPLEMENT

Assist Devices: Machine Preservation of Extended Criteria Donors

James V. Guarrera
Center for Liver Disease and Transplantation, Columbia University College of Physicians and Surgeons, New York, NY

Normothermic Ex Vivo Liver Perfusion



Heart TX

CS:short interval for graft transplantation

Better postperfusion recovery

Less oxidative damage and energy depletion

MP portable, normothermic, oxygenated, solution (mimicking physiologic state)

Monitor enzymes

High technical skills

Costs

Indications: ECD, DCD, long CIT

TRANSPLANT
INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Normothermic donor heart perfusion: current clinical experience and the future

Simon Messer,[1] Abbas Ardehali[2] and Steven Tsui[1]

1 Transplant Unit, Papworth Hospital, Cambridgeshire, UK
2 Division of Cardiothoracic Surgery, Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Lung TX

CS >>>Ex Vivo Lung Perfusion

(ventilation &normothermic perfusion)

Pretransplant evaluation (blood gases, pressures)

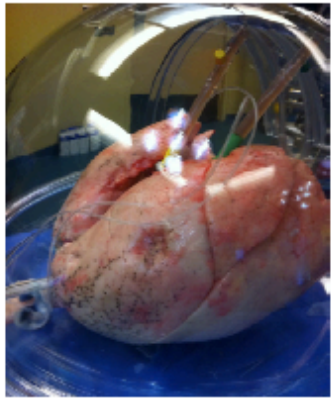
Increase preservation time, less preservation-induced damage

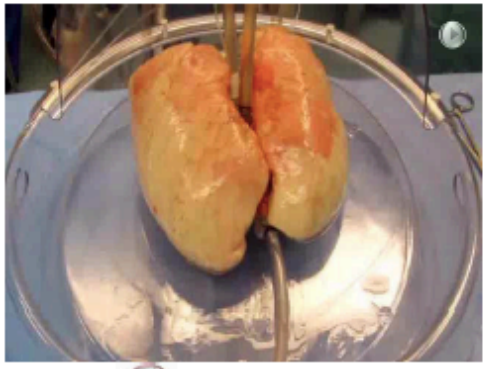
biormarkers: cytokines and substances in alveolar lavage

Indications: ECD, DCD

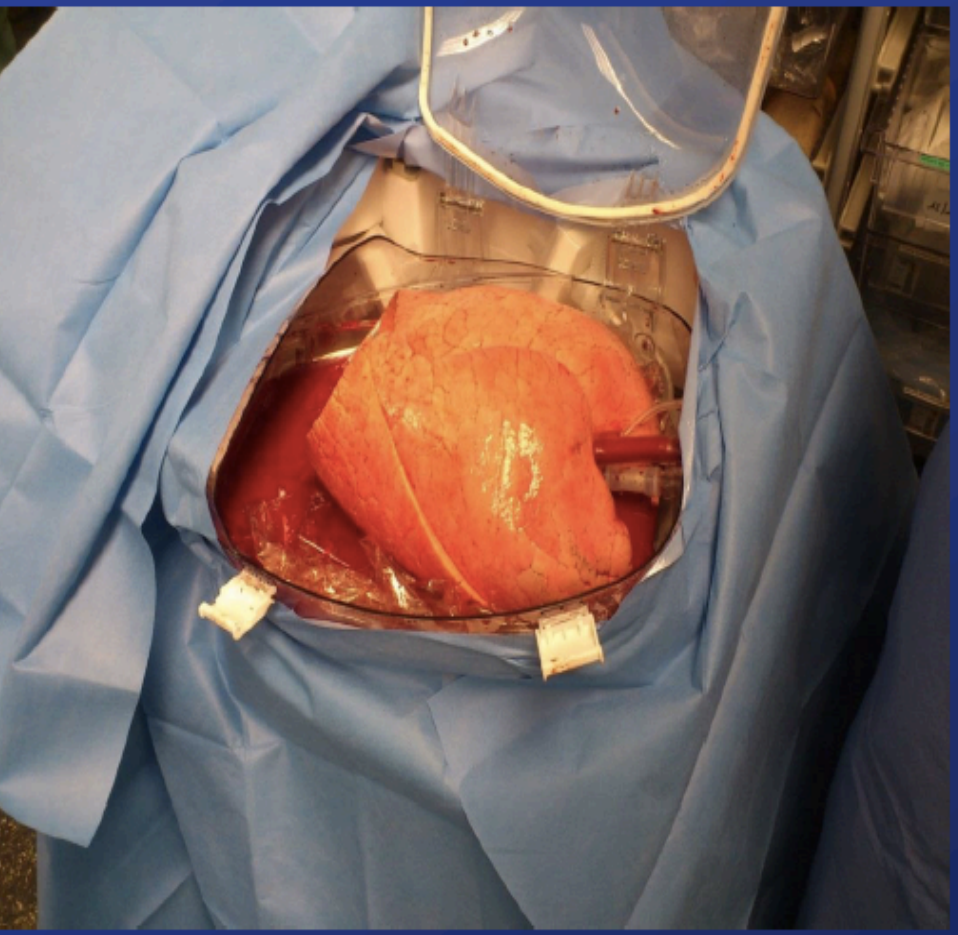
Reconditionig: correct injury secondary to retrival and improve graft quality

Normothermic Ex Vivo Lung Perfusion





EVLP = Platform for



- ✓ *Assessment*
- ✓ *Preservation*
- ✓ *Reconditioning*
- ✓ *(Immunomodulation)*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.

Pancreas TX

CS >> MP reduced organ ischemia

Low flow and pressure: incresed risk of mechanical organ damage (edema)

Beneficial in maintaining islet yeld, viability and function (insulin content) in organs with prolonged cold ischemia

Increase in organ suitable for tx

Langenbecks Arch Surg
DOI 10.1007/s00423-014-1161-2

REVIEW ARTICLE

Machine perfusion in solid organ transplantation: where is the benefit?

Helge Bruns · Peter Schemmer

Received: 16 July 2013 / Accepted: 1 January 2014

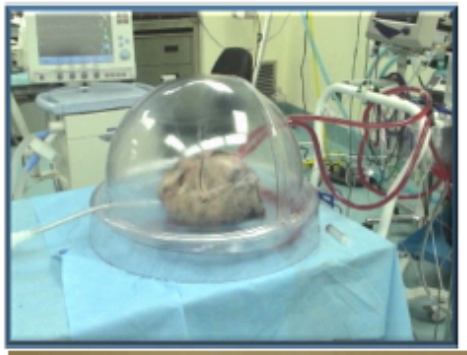
HTA
Cost-efficacy
Sustainability

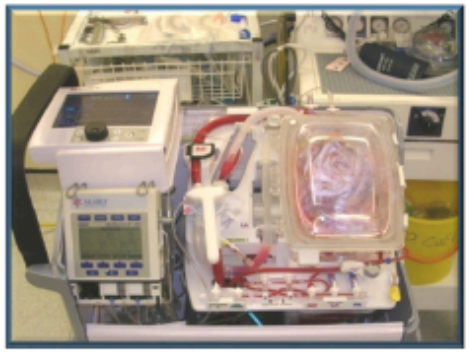

APPLE
COMPUTER

?

The Future of Organ Preservation…
The "Organ Repair Center"

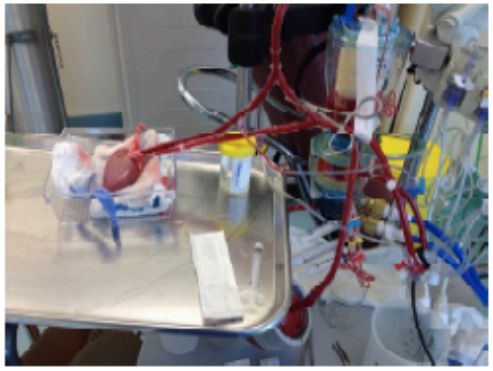
Lung





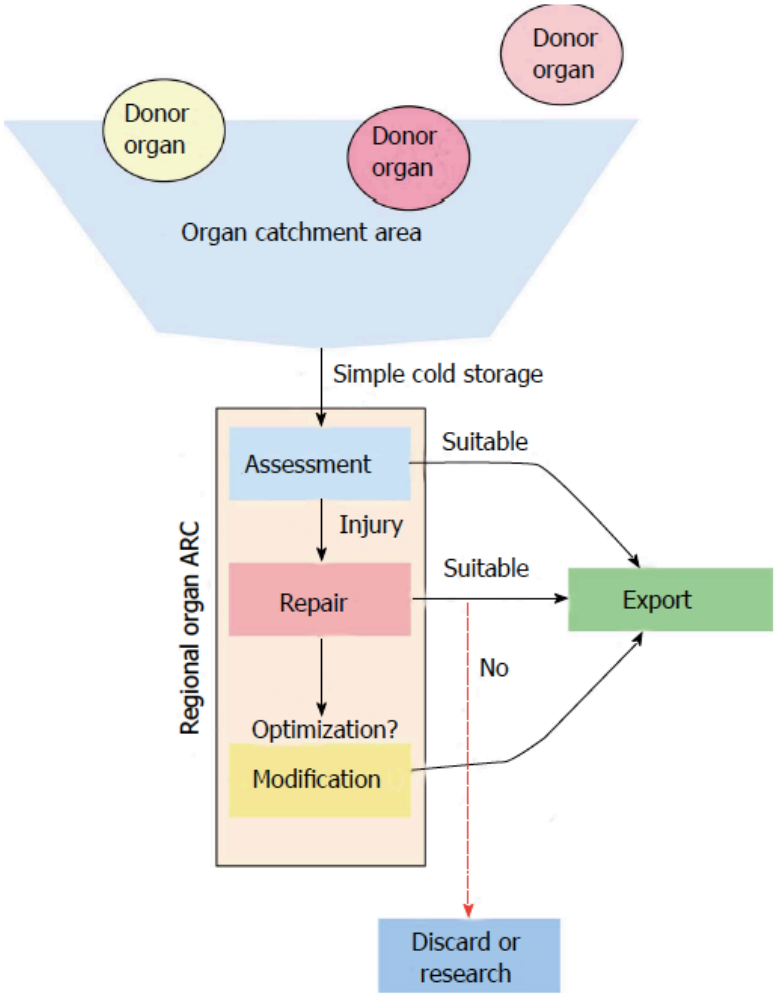
Heart

Liver



Kidney

the future: organ repair centers



The Organ Repair Center

6th INTERNATIONAL CONGRESS

INFECTIONS & TRANSPLANTATION

Varese, 18-20 Maggio 2017
ATA Hotel

PROGRAMMA SCIENTIFICO PRELIMINARE

grazie