Organ preservation & transplantation: newest insights & perspectives

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KU Leuven, Belgium
1. Expand the donor pool
2. Optimal **preservation & resuscitation**
3. Organ **bioengineering & regeneration**
1. Can we ‘resuscitate’ organs?
1. Can we ‘resuscitate’ organs?

- **protect**
  - stop ischaemic injury
  - repair possible
- **pedict**
  - viability
  - quality
- **prolong** preservation time
Continuous machine perfusion (MP)

Retrieve 

Optimise 

Transplant

Pre-ischaemic MP 

Intermediate MP 

End-ischaemic MP 

HMP – hypothermic MP (4-10°C)

SMP – subnormothermic MP (20-25°C)

NMP – normothermic MP (35-37°C)

Potential benefits 

Complexity
1935 1st concept of machine perfusion
1936 1st successful kidney transplantation
1953 1st human to human kidney transplantation
1962 1st cadaveric kidney transplantation
1964 Construction and clinical use of machine perfusion
1971 1st report on long-term cold storage preservation
First liver transplant Belgium (18/02/1969)

Kestens, Surgery 1961
Kestens et al, Bull Soc Int Chir 1966
Squifflet JP, Acta Chirg Belg 2003
Preservation solution (e.g. Collins, UW, ...)

Change donor population

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Status of the legal definition of death.
Selby R, Selby MT.

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Machine Perfusion
Cold Storage

Usage

Time
Principle of simple cold storage is ... simple

hypothermia (0-4°C)

\[ \text{decreased metabolism} \]

50% with each 10°C

\[ \text{decreased ischemic injury} \]

Work of Belzer, Southard, Collins
Changing donor profile

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Criteria Donor (SCD)</td>
<td>Donation after circulatory death (DCD)</td>
</tr>
<tr>
<td>Expanded Criteria Donor (ECD)</td>
<td></td>
</tr>
</tbody>
</table>
Simple cold storage might be ... too simple

Renewed interest in MP
- Donors ↑ susceptibility IRI
- Simple cold storage reached limits
- Better preservation is needed
Hypothermic MP of kidney

Pulsatile flow
- cold
- acellular fluid
- non oxygenated
- re-circulates

25-30 mmHg
Meta-analyses HMP vs. Cold Storage

HMP in kidney transplantation

• Reduces Delayed Graft Function

• Too little data on
  – Primary non-function
  – Graft function
  – Graft survival

Jiao et al. PLOS one 2013
Deng et al. PLOS one 2013
O’Callaghan et al. BJS 2013
Bathini et al. J Urol 2013
More studies starting

Effect of $\text{O}_2$ during HMP

- **ECD**
  - Cold Storage vs. end-ischemic HMP+$\text{O}_2$
  - $n=262$ to be included – ISRCTN63852508

- **DCD**
  - continuous HMP+$\text{O}_2$ vs. HMP
  - $n=166$ to be included – ISRCTN32967929

**Consortium for Organ Preservation in Europe**

www.cope-eu.org
Does HMP predict viability / quality?

Renal Resistance

- Independently associated with
  - Delayed Graft Function & Graft survival
  - Primary non-function

Perfusate injury markers

- Independently associated with
  - Delayed Graft Function
  - Primary non-function

- Accuracy too low to predict reliably
Can HMP repair?

Low temperature, likely limited options but,

• siRNA ↓ caspase-3 expression prox tub cells

• curcumin in CS solution pig Tx model
  – ↑ kidney function
  – ↓ fibrosis

Yang et al. J Cell Biochem 2011
Thuillier et al. AJT 2014
Normothermic MP of Kidney

- **Arterial**
- **Venous**

**Flow probe**

**Pressure line**

**Centrifugal Pump**

**Infusion Pumps**

**Nutrition** - lipid free TPN

**Vasodilator** - prostacyclin

**Antibiotic**

70-75 mmHg

- **Venous reservoir**

- **Oxygenator/heater**

- **Urine collection**

- **packed RBC**

- **crystalloids**

- **no WBC**

- **acellular**

- **O2 carrier**

Brasile et al.

Hosgood et al.

Nasser et al.

Courtesy S. Hosgood
End-ischaemic NMP - experimental

Different large animal set ups

- feasible & safe
- ↑ function
- ↓ injury
- ATP replenished

Hosgood et al. Brasile et al. (pig Tx model)

Hosgood et al. BJS 2011
End-ischaemic NMP - clinical

18 ECD kidneys NMP vs. matched controls

<table>
<thead>
<tr>
<th></th>
<th>NMP (n=18)</th>
<th>CS (n=49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Graft Function</td>
<td>5.6%</td>
<td>36.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary non-function</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Graft survival</td>
<td>100%</td>
<td>98%</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Nicholson et al. AJT 2013
Does NMP predict viability / quality?
Can NMP repair?

• Gaseous molecules (e.g. NO)  Hosgood et al. BJS 2008
• Drugs (e.g. growth factors)  Brasile et al. AJT 2005
• Gene therapy
  – siRNA
• Cell therapy – stem cells
Hypothermic MP of Liver

- ↓ hepatocyte injury vs. Cold Storage histology
- ↓ Kupffer activation & endothelial injury
- ↑ ATP
- poor survival

(pig DCD Tx model) 60’ WIT + 7h CS

Schlegel et al. J Hepatol 2013
End-ischaemic HMP - clinically

20 DBD HMP livers compared vs. matched controls

<table>
<thead>
<tr>
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<th>HMP (n=20)</th>
<th>CS (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early allograft dysfunction</td>
<td>5%</td>
<td>25%</td>
<td>0.08</td>
</tr>
<tr>
<td>PNF</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Biliary strictures</td>
<td>1</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Graft survival</td>
<td>90%</td>
<td>90%</td>
<td>-</td>
</tr>
</tbody>
</table>

Guarrera et al. AJT 2010
End-ischaemic HMP - clinically

Single perfusion Belzer MP
pv <3 mmHg
pO₂ >500 mmHg
1-2h after 2,5h CS

8 DCD HMP livers vs. DBD controls

<table>
<thead>
<tr>
<th></th>
<th>HMP (n=8) - DCD</th>
<th>CS (n=8) - DBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early allograft dysfunction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PNF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biliary complications</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Graft survival @ 6mo</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Dutkowski et al. J Hepatol 2014
More studies ongoing

- **ECD**
  - phase 2 trial, non-randomised
  - n=24 to date – [NTC01274520](#)

- **DCD**
  - non-randomised
  - n=20 to date

- **DBD**
  - RCT “HOPE” vs. CS
  - n=170 to be included
  - Peak ALT - [NCT01317342](#)
Normothermic MP of Liver

- ha: 90-95 mmHg
- packed RBC colloid no WBC
- pv: 10 mmHg gravity

Courtesy P. Friend
Continuous NMP – experimental

improved survival in extreme Tx models - 20h storage time

(pig Tx model with 20h of storage)
Continuous NMP – clinical

- Phase I – Feasible & Safe
- Phase II – RCT started

Start
After 60s

Courtesy P. Friend
Normothermic MP of Lung

Cold storage

Ex vivo lung perfusion
EVLP

Courtesy D. Van Raemdonck
Normothermic MP of Heart

First transplant of a DCD heart on 24/10/2014 after normothermic preservation in Sydney
2. Can we ‘grow’ organs?
1. Bioreactor
2. Scaffold
3. Cells
Bioreactor

Badylak et al, Lancet 2012
Scaffold – synthetic and biodegradable
Scaffold – extracellular matrix

**Decellularization:**
During this phase, the cellular compartment is cleared with detergent-based solutions. Clearance of ≥95% of the cellular/nuclear content is the target outcome.

- Green circle = Growth factors
- Red ellipse = Native animal cells destined to be removed

**Recellularization:**
Cells are delivered through intravascular or transmural injection. The main objectives of this phase are the reconstitution of the endothelium to allow implantation and of the organ-specific cellular compartment, namely parenchymal cells.

- Blue circle = Patient's autologous cells

Orlando et al, Reg Med 2013
Decellularised rat heart
Decellularised rat lungs
Decellularised pig lungs

Cortiella et al, Regenerative Medicine, 2013
Decellularised human lungs

Cortiella et al, Regenerative Medicine, 2013
Decellularised human heart
Decellularised pig kidneys that were transplanted

Orlando et al, Ann Surg 2012
Decellularised pig kidneys

Decellularised human kidneys

Song et al, Nature Medicine 2013
Cells - reseeding

Reseeding of rat kidneys

Song et al, Nature Medicine 2013
Transplantation of reseeded rat kidneys with (imperfect) function,