Improving transplant outcomes:

The use of new technologies

Colin Wilson

20:20 Vision
The Future of Transfusion
Wednesday 13th October 2021
Introduction

• Organ perfusion
  – Defatting livers, repairing bile ducts
  – Identifying organs for transplant (6 gene signature)
• Artificial Intelligence
• Novel communication tools
• Advanced therapeutics
• Novel blood substitutes

• (Stem cells)
Organs are not being transplanted

170 kidneys in 2010

410 kidneys in 2020

Source: Annual report on kidney Transplantation 2019/20, NHSBT
Figure 4.4  Percentage of livers retrieved that were not transplanted from deceased organ donors in the UK, 1 April 2011 - 31 March 2021

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-2012</td>
<td>783</td>
</tr>
<tr>
<td>2012-2013</td>
<td>825</td>
</tr>
<tr>
<td>2013-2014</td>
<td>932</td>
</tr>
<tr>
<td>2014-2015</td>
<td>924</td>
</tr>
<tr>
<td>2015-2016</td>
<td>1011</td>
</tr>
<tr>
<td>2016-2017</td>
<td>1041</td>
</tr>
<tr>
<td>2017-2018</td>
<td>1148</td>
</tr>
<tr>
<td>2018-2019</td>
<td>1113</td>
</tr>
<tr>
<td>2019-2020</td>
<td>1126</td>
</tr>
<tr>
<td>2020-2021</td>
<td>870</td>
</tr>
</tbody>
</table>

Source: Annual report on Liver Transplantation 2020/21, NHSBT
Normothermic perfusion (EVNP)

- Red cells
- Nutrients
- Oxygen
Ex vivo normothermic perfusion (EVNP) of deceased donor kidneys – current studies

Colin Wilson, Chris Callaghan, Gabi Oniscu, Sarah Hosgood, Mike Nicholson
KRUK-funded studies (1)

- RCT comparing EVNP with standard treatment (SCS) in DCD kidney transplantation (ISRCTN 15821205)
  - Open label
  - 4 sites (Cambridge, Guy’s, Newcastle, Edinburgh)
  - Aim: determine if EVNP improves initial graft function in DCD kidney transplantation
  - Primary outcome: DGF (any dialysis in first week)
  - Secondary outcomes: PNF, DGF duration, fDGF, LOS, BPAR, 12m eGFR, PS, DCGS
KRUK-funded studies (1)

- RCT comparing EVNP with standard treatment (SCS) in DCD kidney transplantation (ISRCTN 15821205)
  - Duration of follow-up: one and 5 years
  - Sample size: 400 patients (30% relative reduction in DGF, from 50% to 35%, with a power of 80% and significance of 0.05)
  - Interim analyses (ITT) at 125 patients enrolled (7 days), and 250 patients enrolled (7 days)
  - Recruitment terminated at 306 - Covid awaiting results
KRUK-funded studies (2)

• Quality Assessment Study (QAS)
  – Open label, non-randomised
  – 3 sites (Cambridge, Newcastle, Guy’s)
  – Aim: to increase the number of kidneys for transplantation by using EVNP to assess quality of organs declined by other centres that would otherwise have been discarded
KRUK-funded studies (2)

- Quality Assessment Study (QAS)
  - Scoring system

**Table 1** *Ex vivo normothermic perfusion assessment score*

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroscopic assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Grade I: excellent perfusion (global pink appearance)</td>
<td>1</td>
</tr>
<tr>
<td>Grade II: moderate perfusion (patchy appearance)</td>
<td>2</td>
</tr>
<tr>
<td>Grade III: poor perfusion (global mottled and purple/black appearance)</td>
<td>3</td>
</tr>
<tr>
<td>Renal blood flow (ml per min per 100 g)</td>
<td></td>
</tr>
<tr>
<td>Threshold &gt; 50</td>
<td>0</td>
</tr>
<tr>
<td>Threshold &lt; 50</td>
<td>1</td>
</tr>
<tr>
<td>Total urine output</td>
<td></td>
</tr>
<tr>
<td>Threshold &gt; 43</td>
<td>0</td>
</tr>
<tr>
<td>Threshold &lt; 43</td>
<td>1</td>
</tr>
</tbody>
</table>

1 – Best
5 – Worst
KRUK-funded studies (2)

- Quality Assessment Study (QAS)
  - Open label, non-randomised
  - 3 sites (Cambridge, Newcastle, Guy’s)
  - Aim: to increase the number of kidneys for transplantation by using EVNP to assess quality of organs declined by other centres that would otherwise have been discarded
  - Outcome measures: PNF, DGF, DGF duration, fDGF, LOS, BPAR, 12m eGFR, PS, DCGS, quality of life, pump parameters
  - Duration of follow-up: one year
KRUK-funded studies (2)

- Quality Assessment Study (QAS)
  - Pathway
    - >100 kidneys offered
    - 14 kidneys perfused with EVNP
Quality assessment
Lower pole artery injury
<table>
<thead>
<tr>
<th>Kidney ID</th>
<th>Donor Age (y)</th>
<th>Reason for Decline</th>
<th>Cold Ischaemia (h. min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QAS 01</td>
<td>35</td>
<td>Poor in-situ flush</td>
<td>17.24</td>
</tr>
<tr>
<td>QAS 02</td>
<td>35</td>
<td>Poor in-situ flush</td>
<td>19.44</td>
</tr>
<tr>
<td>QAS 05</td>
<td>53</td>
<td>Poor in-situ flush + stripped ureter</td>
<td>18.55</td>
</tr>
<tr>
<td>QAS 08</td>
<td>51</td>
<td>Poor in-situ flush</td>
<td>7.49</td>
</tr>
<tr>
<td>QAS 09</td>
<td>51</td>
<td>Poor in-situ flush</td>
<td>9.27</td>
</tr>
<tr>
<td>QAS 03</td>
<td>75</td>
<td>Poor in-situ flush</td>
<td>14.04</td>
</tr>
<tr>
<td>QAS 04</td>
<td>36</td>
<td>Poor in-situ flush</td>
<td>15.27</td>
</tr>
<tr>
<td>QAS 06</td>
<td>78</td>
<td>Older donor</td>
<td>12.30</td>
</tr>
<tr>
<td>QAS 07</td>
<td>78</td>
<td>Older donor</td>
<td>14.27</td>
</tr>
<tr>
<td>QAS 10</td>
<td>60</td>
<td>Poor in-situ flush</td>
<td>17.14</td>
</tr>
</tbody>
</table>
Non Transplanted Kidneys

<table>
<thead>
<tr>
<th>Unused kidneys</th>
<th>QAS Score</th>
<th>Declined</th>
</tr>
</thead>
<tbody>
<tr>
<td>QAS 03</td>
<td>3</td>
<td>Logistics – prolonged CI after NP</td>
</tr>
<tr>
<td>QAS 04</td>
<td>3</td>
<td>Poor function/integrity of microcirculation</td>
</tr>
<tr>
<td>QAS 06</td>
<td>1</td>
<td>High Remuzzi score (chronic injury)</td>
</tr>
<tr>
<td>QAS 07</td>
<td>4</td>
<td>QAS score and high Remuzzi score</td>
</tr>
<tr>
<td>QAS 10</td>
<td>4</td>
<td>QAS score</td>
</tr>
</tbody>
</table>
Perfusion Parameters

Renal Blood Flow

P < 0.05

Total Urine Output

P = 0.008
1. Capture images of donor organ, combine with clinical data and store the information in a secure database that can be accessed via the internet.

2. Provide rapid, point-of-use assessment of donor organ quality based upon image analysis of the organ's macroscopic appearance. Simple and intuitive stand-alone system that can be used by SNOD without the need for any other equipment. Aims to provide a numerical score that mimics expert clinical judgement and which can be rapidly communicated within NHS-BT. Information synced to database when convenient.

3. AI/ machine learning. Longer term (but potentially more powerful) system for predicting transplant outcomes based upon analysis of the database.
Log in and record image assay data using iPad App

- The app is fully secure, only registered users can log in and access. After log-in the user can start a new image assay or manage previous ones, allowing you to work wholly offline and then sync with the central server later.
ORQA – Current functionality

1. Capture & sync Images
2. Calibrate Images
3. Analyse Image & colour space
4. Provide qualitative score

- Capture & sync using the iPad APP

NIHR | Blood and Transplant Research Unit in Organ Donation and Transplantation at Cambridge and Newcastle Universities
ORQA – Current functionality

5. Capture & Sync Images
6. Central management of assay via Web browser

ORQA

List of assays

Filter Results:

<table>
<thead>
<tr>
<th>User</th>
<th>Hospital</th>
<th>Organ type</th>
<th>Date</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradford Admin User</td>
<td>Test hospital 1</td>
<td>Liver</td>
<td>12/6/2020</td>
<td>View</td>
</tr>
<tr>
<td>Bradford Admin User</td>
<td>Test hospital 1</td>
<td>Liver</td>
<td>12/6/2020</td>
<td>View</td>
</tr>
<tr>
<td>Bradford Admin User</td>
<td>Test hospital 1</td>
<td>Kidney</td>
<td>12/6/2020</td>
<td>View</td>
</tr>
<tr>
<td>Bradford Admin User</td>
<td>Test hospital 1</td>
<td>Liver</td>
<td>12/6/2020</td>
<td>View</td>
</tr>
</tbody>
</table>

ORQA

Assay detail screen

- Date of assay: 28/02/2021
- Donor gender: Male
- Hospital: Test hospital 1
- ID number: 635275
- Donor: DBD
- Transplantable: Yes
- Texture: Good
- Arterial O2 on Inhale: 92%

Images:

Comments:
- All comments are timestamped and show who posted it.
- Users can add comments here to add additional details to the assay.
VIABILITY ASSESSMENT DURING D-HOPE LIVER PERFUSION
How to discriminate?

• Took samples from 9 excellent livers and 9 very bad livers
• Microarray to separate out all the proteins at different time points
Combined Scoring System

- All discard livers ≥ 6
- All clinical livers ≤ 3
  - 6 proteins at 20 minutes perfusion

- $p < 0.0001$
Possibilities

• Now patented
  – Psyros/ Bridge to Life collaboration

• Move into other organs/ warm temperatures
  – Thanks to Chris Watson, Philip Dutkowski

• Personalised transplantation
  – Target certain organs for certain recipients
  – HCC
Sam Tingle
Academic Clinical Fellow in Transplantation
Newcastle upon Tyne
2,4-Dinitrophenol for steatotic human livers; pharmacological considerations for NMP therapeutics
DNP displays one-phase decay when delivered during NMP:
- **Half Life** = 7.703 hours (95% CI = 5.076-15.97)
- **Exponential Decay Constant** = 0.08999/hr (0.0434 - 0.1366)
- 15mg/kg bolus, an infusion at 1.35 mg/kg/hour should maintain steady perfusate DNP concentration
• Experiments on discard livers

• Levels of complement component in machine perfused livers - comparing DCD with DBD livers

• Deposition of complement within the tissue architecture
Complement system

- Proteins made in the liver
- Important for defence
- Can attack own cells
C3 production over time

- DCD vs DBD
- Normal range 80-160mg/ml
Red cell aggregates during normothermic machine perfusion of human livers

- Series of research livers undergoing normothermic machine perfusion: 2 DCD, 5 DBD; mean age 48yrs; mean CIT 15hrs 27mins
- No RBC aggregates following cold storage, but every liver accumulated aggregates during NMP
- RBC aggregates form in sinusoids and in the portal tract capillaries which supply ischaemia-sensitive bile ducts.
- Future research should investigate the use of agents which could prevent this ‘aggregative microangiopathy’ and clear the microcirculation
Haemopure

- Hemopure is a hemoglobin-based oxygen carrier (HBOC) ready for immediate infusion, that transports and delivers oxygen from the plasma and expands the circulating volume. The product is supplied in sterile, flexible infusion bags with a fill volume of 250mL. Consisting of 32.5 g purified, glutaraldehyde-polymerized, bovine hemoglobin (Hb) in an iso-oncotic balanced modified Ringer's lactate, it can be stored at room temperature for at least three years.
Too much Oxygen...

The reduction of methaemoglobin by methylthioninium chloride

Methaemoglobin (Fe³⁺)  
Methylthioninium chloride (oxidised)

NADPH, reduced form of nicotinamide-adenine dinucleotide phosphate.

The reduction of methaemoglobin by methylthioninium chloride

Methaemoglobin (Fe³⁺)  
Methylthioninium chloride (oxidised)

NADPH, reduced form of nicotinamide-adenine dinucleotide phosphate.

NIHR
Blood and Transplant Research Unit
in Organ Donation and Transplantation
at Cambridge and Newcastle Universities
Prolonged perfusion

Perfusate (32°C) MAP 65mmHg
- Ringer’s solution
- Human serum albumin 20%
- Dexamethasone
- Sodium bicarbonate 8.4%
- Mannitol 10%
- 10ml Calcium gluconate 10%
- 95% oxygen/5% carbon dioxide 0.1L/min
- Prostacyclin, GTN, verapamil
- Nutrients, glucose

Oxygen 95%
60-70kPA
Perfusion parameters

Renal Flow

<table>
<thead>
<tr>
<th></th>
<th>AP01 (24h)</th>
<th>AP02 (18h)</th>
<th>AP03 (24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean flow (ml/min/100g)</td>
<td>121</td>
<td>104</td>
<td>148</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>31.8</td>
<td>31.8</td>
<td>31.9</td>
</tr>
<tr>
<td>Arterial Pressure (mmHg)</td>
<td>64</td>
<td>59</td>
<td>62.2</td>
</tr>
<tr>
<td>Total urine output (ml)</td>
<td>360</td>
<td>414</td>
<td>163</td>
</tr>
</tbody>
</table>
Reperfusion

AP03
67y DCD kidney (WIT 16min)
Rejected for transplant
CIT 20h

24h perfusion 32°C

2h reperfusion RBC 36°C

Renal blood flow

RBF (ml/min/100g)
Total U/O 34ml
Thank you to the Donors and their families.

- IoT Transplant Team
- NHSBT and NIHR BTRU support
- All the staff