Blood, Cells and Organs
Exploring Transfusion in Transplantation

21st November 2019
NHSBT

Stephen Large ma ms mrep fres(cth) frcs mba pae(rcp)
on behalf of the PIT
Papworth intra-thoracic transplant team
Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2014)

Median survival (years):

All pair-wise comparisons were significant at p < 0.05.
Long-term patient survival after first adult heart only transplant from donors after brain death, 1 January 2005 – 31 December 2017

Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant
Adult Heart Transplants
Functional Status of Surviving Recipients by Karnofsky Score (Follow-ups: January 2009 – June 2015)
Number of deceased and living donors in the UK, 1 April 2009 - 31 March 2019

Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant
Donation and transplantation rates of organs from DBD organ donors in the UK, 1 April 2018 – 31 March 2019

Transplanted:

- Kidney: 82%
- Liver: 79%
- Pancreas: 17%
- Bowel: 15%
- Heart: 13%
- Lungs: 21%

1 Hearts – in addition to age criteria, donors who died due to myocardial infarction are excluded
Bowels – in addition to age criteria, donors who weigh >=80kg are excluded

Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant
Heart Transplantation in UK: Demand vs Supply

Figure 7.1  Deceased donor heart programme in the UK, 1 April 2008 - 31 March 2018,
Number of donors, transplants and patients on the active transplant list at 31 March

www:NHSBT/report 2017-2018
Is DCD heart transplantation possible?

Recent NHSBT update: probably 135 more donor/year

The size of the pool:

3089 POTENTIAL DCD DONORS

CONSENT

YES (3034)

AGE < 50 YEARS

YES (974)

NO (2115)

PROCEEDED TO DONATE

YES (448)

NO (471)

FWIT < 30 MINS

YES (400)

NO (48)

CARDIAC ARREST

YES (182)

NO (218)

CARDIAC CAUSE OF DEATH

YES (2)

NO (216)

CARDIAC RISK FACTORS

YES (32)

NO (184)

CARDIOVASCULAR DISEASE

YES (3)

NO (181)

INOTROPIC SUPPORT

YES (13)

NO

168 SUITABLE DCD DONORS
Method for modelling DCD (rat and pig): Circulatory determined brain death DCD

Tolerance of ischaemia (*rat*):

Text-figure 4—The percent of severely damaged cells in hearts subjected to 30 to 55 minutes of anoxia and then reoxygenated for a total of 120 minutes of perfusion was estimated by direct counts from four equally spaced light microscopic sections of each heart. The percent of damaged cells correlated linearly by regression analysis (*r* = 0.861, *P* < 0.001) with duration of anoxic perfusion between 30 and 55 minutes.
Catecholamine concentrations after brainstem death and in the NHBD donor

Hearts from DCD donors display acceptable biventricular function after heart transplantation.

DCD heart transplantation: How tolerant the heart to normothermic ischaemia?

Looks to be largely an ischaemic insult

Hearts from DCD donors display acceptable biventricular function after heart transplantation.

OK! So clinically?
Is it Possible?

• First Successful human heart transplant Barnard December 3rd 1967

• Survived for 18 days succumbing to pneumonia
The Code Of Practice For
The Diagnosis & Confirmation Of Death

• After **5 minutes of continued** cardiorespiratory arrest, the absence of pupillary responses to light, of corneal reflexes, and of motor response to supra-orbital pressure is confirmed.

• Diagnosing death in this situation requires confirmation that there has been **irreversible damage to the vital centres in the brain-stem** due to the length of time in which the circulation to the brain has been absent.

• **Cerebral perfusion should not be restored** after death has been confirmed.

Timings following identification of futile treatment & consent for DCD organ donation:

Withdrawal of life support (WLST)
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- Withdrawal of life support (WLST)
- Functional warm ischaemia (FWIT)
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- Withdrawal of life support (WLST)
- Loss of pulse = asystole
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Timings following identification of futile treatment & consent for DCD organ donation:

- **Withdrawal of life support (WLST)**
- **Loss of pulse = asystole**
  - Functional warm ischaemia (FWIT)
  - + 5mins confirmation of DCD death
Timings following identification of futile treatment & consent for DCD organ donation:

- Withdrawal of life support (WLST)
- Loss of pulse = asystole
- Functional warm ischaemia (FWIT)
- + 5mins confirmation of DCD death
- Method of organ protection following insults
Direct Procurement
Timings following identification of futile treatment & consent for DCD organ donation:

- Withdrawal of life support (WLST)
- Loss of pulse = asystole
- Method of organ protection following insults
  - Functional warm ischaemia (FWIT)
  - + 5mins confirmation of DCD death
Normo-thermic Regional Perfusion (NRP)
Timings following identification of futile treatment & consent for DCD organ donation:

- Withdrawal of life support (WLST)
- Loss of pulse = asystole
- Method of organ protection following insults
- Functional warm ischaemia (FWIT)
- + 5mins confirmation of DCD death
- Transportation of organ to recipient hospital
Timings following identification of futile treatment & consent for DCD organ donation:

- Withdrawal of life support (WLST)
- Loss of pulse = asystole
- Method of organ protection following insults
- Transportation of organ to recipient hospital

Functional warm ischaemia (FWIT) + 5mins confirmation of DCD death
## Donor Demographics

<table>
<thead>
<tr>
<th></th>
<th>DCD n=75</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Med(IQR)</strong></td>
<td>36 (30-43)</td>
</tr>
<tr>
<td><strong>Male n (%)</strong></td>
<td>61 (82)</td>
</tr>
<tr>
<td><strong>Height cm</strong></td>
<td>175 (171-180)</td>
</tr>
<tr>
<td><strong>NRP/DPP</strong></td>
<td>23/52</td>
</tr>
<tr>
<td><strong>OCS/CS</strong></td>
<td>73/2</td>
</tr>
<tr>
<td><strong>Cause of Death</strong></td>
<td></td>
</tr>
<tr>
<td><strong>HBI n (%)</strong></td>
<td>42%</td>
</tr>
<tr>
<td><strong>ICH n (%)</strong></td>
<td>22%</td>
</tr>
<tr>
<td><strong>TBI n (%)</strong></td>
<td>18%</td>
</tr>
<tr>
<td><strong>Other n (%)</strong></td>
<td>18%</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td><strong>DCD n=75</strong></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
</tr>
<tr>
<td>30 day survival n (%)</td>
<td>100%</td>
</tr>
<tr>
<td>90 Day survival n (%)</td>
<td>95%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Mechanical Support</strong></td>
<td></td>
</tr>
<tr>
<td>IABP n (%)</td>
<td>20%</td>
</tr>
<tr>
<td>VA-ECMO n (%)</td>
<td>10%</td>
</tr>
<tr>
<td>VAD n (%)</td>
<td>4%</td>
</tr>
</tbody>
</table>
DBD v DCD survival

Figure 2  Kaplan-Meier survival of donation after circulatory-determined death (DCD) and donation after brain death (DBD) heart transplantation.
## Ischaemic Timings NRP/DPP

<table>
<thead>
<tr>
<th>Time</th>
<th>NRP n=17</th>
<th>DPP n=27</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal to death (mins) Med(IQR)</td>
<td>17 (13-21)</td>
<td>18 (14-25)</td>
<td>ns</td>
</tr>
<tr>
<td>Donation Withdrawal Ischaemic Time (mins)</td>
<td>24 (21-28)</td>
<td>36 (30-41)</td>
<td>0.005</td>
</tr>
<tr>
<td>Functional Warm Ischaemic Time (mins)</td>
<td>18 (16-22)</td>
<td>25 (23-30)</td>
<td>0.003</td>
</tr>
<tr>
<td>NRP Duration (mins)</td>
<td>39 (32-52)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OCS Perfusion Time (mins)</td>
<td>173 (140-186)</td>
<td>243(210-280)</td>
<td>0.003</td>
</tr>
<tr>
<td>Starting A lactate (mmol/L)</td>
<td>6.34 (3.49-6.83)</td>
<td>7.33 (6.39-9.25)</td>
<td>ns</td>
</tr>
<tr>
<td>Final A lactate (mmol/L)</td>
<td>4.25 (3.48-6.98)</td>
<td>5.5 (4.05-6.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Implant Duration (mins)</td>
<td>32 (31-39)</td>
<td>42 (35-51)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Issues with NRP/DPP

• Organ assessment
Serum lactate levels in the blood based perfusate of the DCD donor heart on donor NRP and OCS or ECMS (extra corporeal machine perfusion)
(Messer S 2016 by kind permission)
Issues with NRP/DPP

• Organ assessment

• Organ usage
DCD Clinical Program

- Set up February 2015
- Early Outcomes
  - Comparable allograft function, hospital stay, treated rejection episodes.
  - 90 day survival DCD 92% DBD 96% (p = 1.0)

**Early Outcomes after Heart Transplantation from DCD donors**

<table>
<thead>
<tr>
<th></th>
<th>DCD (n=26)</th>
<th>DBD (n=26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac output L/min</strong></td>
<td>4.9 (4.0-5.2)</td>
<td>3.9 (3.2-4.4)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Cardiac index L/min/m²</strong></td>
<td>2.5 (2.1-2.7)</td>
<td>2.0 (1.8-2.4)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Ejection fraction %</strong></td>
<td>63 (58-63)</td>
<td>63 (62-63)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Length of stay, days</strong></td>
<td>20 (17-28)</td>
<td>27 (21-34)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Treated rejection</strong></td>
<td>9 (35)</td>
<td>15 (58)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>90 day survival %</strong></td>
<td>92 (24)</td>
<td>96 (25)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Renal Function at One Year

No patients on renal replacement therapy

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73m²)</th>
<th>DCD</th>
<th>DBD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>53%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>30-60</td>
<td>47%</td>
<td>38%</td>
<td>0.59</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0%</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac Performance. Echocardiography

**DCD**
- Normal EF (>55%): 79% (15)
- Mild impairment (EF 45-54%): 21% (4)

**DBD**
- Normal EF (>55%): 86% (18)
- Mild impairment (EF 45-54%): 5% (1)
- Moderate impairment (EF 36-44%): 5% (1)
- Severe impairment (EF <35%): 5% (1)

$p$ value = 0.2
Issues with NRP/DPP

- Organ assessment
- Organ usage
- Does NRP upset other organ procurement?
Other solid organ usage with DCD heart Tx:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Donor organ utilisation</th>
<th>Papworth DCD heart donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>N/A</td>
<td>83 %</td>
</tr>
<tr>
<td>Lung</td>
<td>7 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Kidney</td>
<td>84 %</td>
<td>78 %</td>
</tr>
<tr>
<td>Liver</td>
<td>36 %</td>
<td>47 %</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22 %</td>
<td>26 %</td>
</tr>
</tbody>
</table>
Normothermic Regional Perfusion of Donors Following Circulatory Death Improves Outcomes in Liver Transplantation.

E. Mowlem, L. Randle, C. Fear, K. Crick, S. Messer, S. Large, A. Butler, C. Watson.

1 Cambridge Transplant Unit, Addenbrookes Hospital, Cambridge, United Kingdom
2 OrganOx Ltd, Oxford, United Kingdom
3 Dept of Surgery, University of Cambridge, Cambridge, United Kingdom
4 Papworth Hospital, Cambridge, United Kingdom

Meeting: 2017 American Transplant Congress

<table>
<thead>
<tr>
<th></th>
<th>NRP livers (n=20)</th>
<th>non-NRP livers (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1y actuarial graft survival (censored for death)</td>
<td>100%</td>
<td>87%</td>
</tr>
<tr>
<td>1 year actuarial patient survival</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>1y actuarial graft survival (not death censored)</td>
<td>93%</td>
<td>81%</td>
</tr>
<tr>
<td>Peak ALT (iu/L) in week one (median (IQR))</td>
<td>480 (349-1016)</td>
<td>840 (437-1443)</td>
</tr>
<tr>
<td>Biliary anastomotic leaks</td>
<td>6% (n=17)</td>
<td>5%</td>
</tr>
<tr>
<td>Biliary anastomotic strictures</td>
<td>12% (n=17)</td>
<td>5%</td>
</tr>
<tr>
<td>Ischaemic cholangiopathy</td>
<td>0 (n=17)</td>
<td>15%</td>
</tr>
</tbody>
</table>
Issues with NRP/DPP

• Organ assessment

• Organ usage

• Does NRP upset other organ procurement?

• Concerns about intra-cranial blood flow
Concerns about intra-cranial blood flow

- Canadian DCD summit 2018
- What risk: intra-cranial blood flow?
Concerns about intra-cranial blood flow

- Ligation of arch vessels
- and drainage of blood within arch vessels
- but concerns over ischaemic insult
Concerns about intra-cranial blood flow

• Ligation of arch vessels

• and drainage of blood within arch vessels

• but concerns over ischaemic insult

• Leading to the speediest solution: *Messer technique*
8 take home points

1. NRP probably offers earliest replenishment of energy stores within all organs
8 take home points

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2. .... a chance to assess cardiac function after death.
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2. … a chance to assess cardiac function after death.

3. … a chance to review the heart in terms of coronary disease and
8 take home points

1. NRP probably offers earliest replenishment of energy stores within all organs,

2. …. a chance to assess cardiac function after death.

3. …. a chance to review the heart in terms of coronary disease and

4. …. a chance to assess the donor to exclude malignancy
5. We believe that the size of this new donor group may be as high as 100 patients/year for our 65 million population (1.54 donors pmp, which has the potential to raise our transplant activity by 50%).

8 take home points
8 take home points

5. We believe that the size of this new donor group may be as high as 100 patients/year for our 65 million population (1.54 donors pmp. which has the potential to raise our transplant activity by 50%).

6. A chance to transport with cold storage as the Barnard brothers did in 1967.
5. We believe that the size of this new donor group may be as high as 100 patients/year for our 65 million population (1.54 donors pmp. which has the potential to raise our transplant activity by 50%).

6. A chance to transport with cold storage as the Barnard brothers did in 1967.

7. Heart donation from individuals dying of circulatory determined death (DCD) has led to heart transplantation in some 120 pts world-wide 75 of which procured by by RPH 29% using NRP and 74 Tx by RPH (2 as nrp-cold storage and 1 as a DCD heart & lung Tx).
8+ take home points

8. DCD heart transplantation has delivered the same early and midterm outcomes as heart transplantation from heart donors after brain death
8+ take home points

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9. although NRP has 100% survival of recipients
   i. We believe that the size of this new donor group may be as high as 100 patients/year for our 65million population (extra 1.54 donors pmp. So far 75 lives saved at RPH since 2015 = 16 lives/yr
   ii. which has the potential to raise our transplant activity by 40%)
   ....with a technique now has international acceptance.
8+ take home points

10. I believe we can support a heart for an extended period (72hrs) opening opportunity for “repair in perfusion” on ex-situ perfusion:

i. An increased use of DBD hearts perhaps:
   through recovery of function

ii. Through “pumping to perfection” organ banking on ex-situ machines
just may be?

“Picked one you like yet?”