Heart Transplantation from Donation after Cardiocirculatory Death Donors: Future Research Directions

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Surgery, Physiology and Biomedical Engineering
Disclosure

• I am a cardiac surgeon/scientist
• I have received supplies from
  – XVIVO Perfusion
  – Medtronic
  – LivaNova (Sorin)
  – Getinge Group (Maquet)
  – Astellas Pharma Canada
• I am the founder of Tevosol, Inc
Organ Donation Process

NDD
- Withdrawal Life Support
- Circulatory Arrest
- Organ Procurement
- Organ Storage
- Organ Transplant

DCD
- Hypoxic Arrest
- Stand-Off Period
- Organ Storage
- Organ Transplant
Donation after circulatory death (DCD)

Withdrawal Life Support
Circulatory Arrest
Utilization of Hearts from DCD donors

• Historical aspects
  • The first heart transplant was performed with a donor after cardiocirculatory death was declared

  – The lack of success of heart transplant early on has been attributed in part to the use of hearts from DCD donors

  – Given the shortage of donor hearts, there is renewed interest in recovering hearts from DCD donors for transplantation, particularly in the pediatric population
Utilization of Hearts from DCD donors

• Concerns
  • Can viability of the heart be maintained through the DCD process?
  • How can the clinician be assured that the heart will regain sufficient function to allow successful transplantation?
  • What is the best way to resuscitate/preserve the heart for transplantation?
  • What effect will the warm ischemic period have on the development of CAV?
Myocardial ischemia

• Cessation of blood flow/oxygen delivery
  • Rapid reduction in oxidative metabolism
  • Depletion of ATP occurs over 15-20"
    • Poor correlation between ATP level and irreversible injury
• Progressive reduction in myocardial contractility
• Loss of mitochondrial membrane potential
• Ionic perturbations
Ionic changes during ischemia

Ionic changes during ischemia

Ionic changes during reperfusion

Ionic changes during reperfusion

Impact of intracellular calcium overload

Gottlieb JCPT 2011
Reperfusion

• Allows restoration of oxidative metabolism
• Normalization of pH

• Large burst of ROS
• Onset of apoptotic and necrotic cell death

• IR injury occurs predominately during reperfusion
  • Tremendous opportunity for intervention
  • Therapies must be administered at the point of reperfusion or within seconds
Therapeutic goals

• Facilitate restoration of ATP
• Facilitate restoration of ion homeostasis
• Minimize the effect of $[\text{Ca}^{2+}]_i$
• Control ROS
• Protect mitochondria
• Protect endothelium
Putative therapeutic targets

Murphy et al, Physiol Rev 2008
Standard myocardial preservation

• Crystalloid mixtures
  • St. Thomas
  • Celsior
  • HTK
  • UW
  • Del Nido

• All are delivered at profoundly hypothermic conditions
• All are hyperkalemic
• Varying $[\text{Ca}^{2+}]$ and $[\text{Mg}^{2+}]$
Organ preservation

- Hyperkalemia
  - no added beneficial effect over inducing asystole
  - coronary vasoconstriction, compromise cardioplegia delivery and distribution
  - damage endothelial cells and myocytes
  - promote myocardial electrical instability and arrhythmias
  - intracellular Na\(^+\) and Ca\(^{2+}\) loading and oxidative stress leading to mitochondrial impairment, necrosis and apoptosis
Limiting IR injury

- Better preservation techniques
  - pre/post/remote conditioning

- preservation solutions/additives
  - non-depolarizing cardioplegia
  - NHE inhibitors
  - NCX inhibitors
  - MPTP inhibitors (CsA)
  - growth factors
  - adenosine axis
  - PKC-ε inhibitors
Methods

• 60 kg female pigs
• Brain death control group
  • intracranial balloon inflation
• Donation after circulatory death group
  • hypoxic circulatory arrest (CVP = MAP)
  • 15 minutes stand-off period
  • reperfusion *in vivo* on cardiopulmonary bypass
    (normothermic regional perfusion, NRP)
  • Cold static storage until transplant
• invasive hemodynamic assessment
• magnetic resonance cardiac imaging and spectroscopy

Myocardial Energetics

<table>
<thead>
<tr>
<th>Orthotopic heart transplantation</th>
<th>DCD (n = 5)</th>
<th>BD (n = 5)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Load-independent measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ESPVR</td>
<td>1.77 (0.96)</td>
<td>1.04 (0.13)</td>
<td>0.43</td>
</tr>
<tr>
<td>LV PRSW</td>
<td>80 (26)</td>
<td>54 (19)</td>
<td>0.21</td>
</tr>
<tr>
<td>RV ESPVR*</td>
<td>0.90 (0.28)</td>
<td>0.42 (0.18)</td>
<td>0.32</td>
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<tr>
<td><strong>Load-dependent measurements</strong></td>
<td></td>
<td></td>
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<tr>
<td>MAP (mm Hg)</td>
<td>48.0 (8.0)</td>
<td>54.2 (8.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>115 (24)</td>
<td>101 (10)</td>
<td>0.31</td>
</tr>
<tr>
<td>Max LV systolic BP (mm Hg)</td>
<td>84 (16)</td>
<td>77 (15)</td>
<td>0.63</td>
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<tr>
<td>LV dP/Dt max (mm Hg/sec)</td>
<td>1585 (172)</td>
<td>1535 (421)</td>
<td>0.83</td>
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<tr>
<td>LV dP/Dt min (mm Hg/sec)</td>
<td>-1234 (231)</td>
<td>-1557 (477)</td>
<td>0.27</td>
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<td><strong>Diastolic function</strong></td>
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<tr>
<td>LV EDPVR</td>
<td>0.12 (0.04)</td>
<td>0.07 (0.02)</td>
<td>0.15</td>
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<tr>
<td>RV EDPVR*</td>
<td>0.04 (0.03)</td>
<td>0.05 (0.03)</td>
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<tr>
<td><strong>MRI measurements</strong></td>
<td></td>
<td></td>
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<tr>
<td>LVEDV (mL)</td>
<td>44 (13)</td>
<td>44 (13)</td>
<td>0.99</td>
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<tr>
<td>LVESV (mL)</td>
<td>18 (7)</td>
<td>23 (16)</td>
<td>0.73</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58 (9)</td>
<td>53 (26)</td>
<td>0.70</td>
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<tr>
<td>RVEDV (mL)*</td>
<td>53 (19)</td>
<td>64 (12)</td>
<td>0.27</td>
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<tr>
<td>RVESV (mL)*</td>
<td>43 (9)</td>
<td>39 (15)</td>
<td>0.30</td>
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<tr>
<td>RVEF (%)*</td>
<td>10 (11)</td>
<td>25 (10)</td>
<td>0.04</td>
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<tr>
<td>CO (L/min)</td>
<td>3 (0.8)</td>
<td>2.4 (0.6)</td>
<td>0.32</td>
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</tbody>
</table>
Summary

• The *in situ* resuscitated DCD heart
  • is viable with restoration of near normal energy state
  • demonstrates good contractile function

• Successful orthotopic transplantation of resuscitated DCD hearts with comparable hemodynamic performance to transplanted BD hearts
Towards controlled initial reperfusion

- Cardioplegic arrest in the donor
- \textit{ex vivo} perfusion/evaluation
- Transplantation
Methods

- 60 kg female pigs
- Donation after circulatory death
  - hypoxic circulatory arrest (CVP=MAP)*
  - 15 minutes stand-off period
- Initial reperfusion via the isolated aortic root
- Strategies:
  - 1: Initial reperfusion with standard hypothermic, hyperkalemic cardioplegia (Plegisol/blood); \textit{ex vivo} perfusion with STEEN Solution™/blood; cold ischemic period for mounting on the apparatus as well as transplant
  - 2: Initial reperfusion with tepid adenosine/lidocaine cardioplegia†; \textit{ex vivo} perfusion with STEEN Solution™/blood; continuous perfusion after mounting on the apparatus
- Orthotopic cardiac transplantation
- Invasive hemodynamic assessment
- Magnetic resonance cardiac imaging

*CMAJ, 2006; †JTCS 2010, 2007, 2004
Hypoxic Cardiac Arrest

Cold crystalloid/blood cardioplegia

Wean from CPB Post transplant functional assessment

Strategy 1

15 min

Mount on ex vivo perfusion apparatus

Ex vivo perfusion and assessment of function with STEEN Solution/blood

Transplant

Strategy 2

15 min

Mount on ex vivo perfusion apparatus

Ex vivo perfusion and assessment of function with STEEN Solution/blood

Transplant

Adenosine/Lidocaine cardioplegia
Myocardial edema and myocytolysis

Weight Gain (grams/hour)

<table>
<thead>
<tr>
<th>Strategy 1</th>
<th>Strategy 2</th>
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</thead>
<tbody>
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<td></td>
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$p = 0.008$

Tropinon I (ng/ml)

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<tr>
<th>Start ex vivo</th>
<th>End ex vivo</th>
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<tbody>
<tr>
<td>Strategy 1</td>
<td>Strategy 2</td>
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</table>

$p = 0.047$

$p = 0.014$

White et al, JHLT 2013
### Strategy 1

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<th>Compound</th>
<th>Log2FoldChange</th>
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<tr>
<td>4-oxo-butryl-PPC</td>
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<td>SGC</td>
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<td>Acetal-POVPC</td>
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<td>12-oxo-8,10-dodecadienoil-PPC</td>
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### Strategy 2

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<tr>
<th>Compound</th>
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<tr>
<td>SLPC-PPC</td>
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<td>PLPC-OOH,OH</td>
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<td>PLPC-diOH,epoxy</td>
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<td>IsoPG(A2,J2)-PPC</td>
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<td>PAPC-OOH</td>
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<td>SLC-P-epoxy,keto</td>
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<td>2,3-dinor-isoTxB2-PPC</td>
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<td>15-deoxy-Δ1Δ14-isoPGJ2-PPC</td>
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<td>SLC-P-epoxy</td>
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<td>SLC-PPC</td>
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<td>SLC-trioOH</td>
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<td>isoPG(A2,J2)-SC</td>
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<td>SLC-OH,keto</td>
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<td>isoPC[G2,J2,D2]-SC</td>
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<td>SLC-PPC</td>
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<td>SLC-trioOH</td>
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<td>isoPGF2α-SC</td>
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<td>SLC-OH,keto</td>
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<td>KODia-SFC</td>
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<td>SEPC</td>
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<td>isoPGF2α-SC</td>
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<tr>
<td>SLC-OH,keto</td>
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### White et al, JHLT 2013
## Post-transplant function

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<tr>
<th>Function</th>
<th>Baseline</th>
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<th>Post-Transplant</th>
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<tr>
<td></td>
<td>Strategy 1</td>
<td>Strategy 2</td>
<td>p value</td>
<td>Strategy 1</td>
</tr>
<tr>
<td>Systolic Function</td>
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<tr>
<td>dP/dt max (mmHg/s)</td>
<td>845 (120)</td>
<td>925 (126)</td>
<td>0.181</td>
<td>718 (156)</td>
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<td>ESPVR</td>
<td>1.36 (0.38)</td>
<td>1.35 (0.34)</td>
<td>0.981</td>
<td>4.50 (5.93)</td>
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<td>PRSW</td>
<td>36.7 (11.0)</td>
<td>37.6 (17.5)</td>
<td>0.892</td>
<td>19.7 (10.9)</td>
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<td>Diastolic Function</td>
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<tr>
<td>dP/dt min (mmHg/s)</td>
<td>-817 (162)</td>
<td>-955 (154)</td>
<td>0.084</td>
<td>-475 (201)</td>
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<td>EDPVR</td>
<td>0.14 (0.03)</td>
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<td>0.575</td>
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<td>Tau (ms)</td>
<td>38.6 (4.4)</td>
<td>42.7 (5.8)</td>
<td>0.108</td>
<td>65.2 (21.1)</td>
</tr>
</tbody>
</table>

White et al, JHLT 2013
Summary

- Controlled initial reperfusion with a strategy that avoids hypothermia and hyperkalemia resulted in improved function and outcomes
  - Beneficial effects of adenosine for preventing I/R injury
  - Avoidance of recurrent ischemia
Temperature and ATP production

5C   25C   35C

% Normal ATP Production

0  10  20  30  40  50  60  70  80  90  100

5C     25C   35C
Normothermic ex vivo heart perfusion

- **Standoff 15min**
- **Vent Off**
- **Death**
- **Procurement**
- **Reperfusion 5C**

*(N=6)*

Normothermic ex vivo heart perfusion

- **Standoff 15min**
- **Vent Off**
- **Death**
- **Procurement**
- **Reperfusion 25C**

*(N=5)*

Normothermic ex vivo heart perfusion

- **Standoff 15min**
- **Vent Off**
- **Death**
- **Procurement**
- **Reperfusion 35C**

*(N=7)*

Functional Assessment
Temperature and reperfusion of the DCD heart

White et al, AJT 2016
Endothelial integrity

White et al, AJT 2016
Histology - Electron Microscopy

Endothelial Injury

Myocyte Injury

Electron Microscopy Injury Score

$\text{5C}$

$\text{25C}$

$\text{35C}$

$p < 0.05$

$p = 0.07$

White et al, AJT 2016
Functional evaluation

![Graph showing dP/dt maximum and minimum across T1, T3, and T5 for 5C, 25C, and 35C conditions.]

- For dP/dt maximum, p < 0.05 for 25C and 35C compared to 5C.
- For dP/dt minimum, p < 0.05 for 25C and 35C compared to 5C.

White et al, AJT 2016
Summary

• Initial reperfusion conditions impact the severity of injury and functional recovery of DCD hearts

• Avoidance of profound hypothermia during initial reperfusion of DCD hearts
  • Minimizes injury
  • Improves functional recovery
Preservation/Cardioplegic solutions

• These are used at initial reperfusion
• They do not contemplate any specific IRI target nor allow ischemic postconditioning
• All are delivered at profoundly hypothermic conditions
• All are hyperkalemic
• Varying $[\text{Ca}^{2+}]$ and $[\text{Mg}^{2+}]$
Resuscitation of the DCD heart

Increasing the Tolerance of DCD Hearts to Warm Ischemia by Pharmacological Postconditioning
Adenosine-lidocaine cardioplegia

- Adapted from Dobson and Rudd

Adenosine
- Activates the reperfusion injury salvage kinase (RISK) pathway
- Up-regulates the anti-apoptotic protein Bcl-2
- Attenuates neutrophil infiltration into endothelial cells
- Inhibits the generation of reactive oxygen species

Lidocaine
- Inhibits sodium fast channels and produces a diastolic arrest
- Maintains a polarized membrane potential which may minimize calcium overload (in contrast to a hyperkalemic arrest)
Stepwise analysis of cardioplegia composition

Minimize Ca$^{2+}$ influx during initial reperfusion

Cardioplegic solution

- [Ca$^{2+}$] $\mu$mol/L: 50, 220, 500, 1250
- pH: 7.9, 7.4, 6.9, 6.4
15-minute Standoff

- Normothermic ex vivo heart perfusion (N=4)
  - 3-minute IR, $[\text{Ca}]=0.05$

- Normothermic ex vivo heart perfusion (N=9)
  - 3-minute IR, $[\text{Ca}]=0.22$

- Normothermic ex vivo heart perfusion (N=4)
  - 3-minute IR, $[\text{Ca}]=0.50$

- Normothermic ex vivo heart perfusion (N=5)
  - 3-minute IR, $[\text{Ca}]=1.25$

**Functional Assessment (Working Mode)**
- LAP=8, HR=100, Aortic diastolic pressure=40
Edema

Function

$\text{Ca}^{2+}$ 0.05 $\text{Ca}^{2+}$ 0.22 $\text{Ca}^{2+}$ 0.50 $\text{Ca}^{2+}$ 1.25

$0\text{.05}$ $0\text{.22}$ $0\text{.50}$ $1\text{.25}$

$\text{Cardiac Index} (\text{ml/min/gram})$

Initial reperfusion $[\text{Ca}^{2+}]$

Initial reperfusion $[\text{Ca}^{2+}]$

White et al, ATS 2016
Summary

• Initial normocalcemic reperfusion is detrimental
  • Promotes Na-Ca$^{2+}$ exchange and Ca$^{2+}$ overload

• Initial hypocalcemic reperfusion improves the functional recovery of DCD hearts
  • 220 µmol/L provides the best functional recovery

• Profoundly hypocalcemic reperfusion is detrimental
  • $\leq$ 50 µmol/L may promote the calcium paradox
• Acidosis?
• Intracellular sodium overload?
15-minute Standoff
Normothermic ex vivo heart perfusion (N=5)

3-minute IR pH=7.9

15-minute Standoff
Normothermic ex vivo heart perfusion (N=9)

3-minute IR pH=7.4

15-minute Standoff
Normothermic ex vivo heart perfusion (N=8)

3-minute IR pH=6.9

15-minute Standoff
Normothermic ex vivo heart perfusion (N=6)

3-minute IR pH=6.4

Warm ischemia
Initial Reperfusion
Ex vivo heart perfusion

Functional Assessment (Working Mode)
LAP=8, HR=100, Aortic diastolic pressure=40
Edema

Function

Initial reperfusion pH

Initial reperfusion pH

White et al, ATS 2016
Summary

• Initial alkalotic reperfusion is detrimental
  • Promotes $\text{Na}^+ - \text{H}^+$ exchange and worsens $\text{Na}^+$ and $\text{Ca}^{2+}$ overload

• Profound acidosis during initial reperfusion is detrimental
  • pH to extreme for necessary enzymatic function

• Mild acidosis during initial reperfusion may be beneficial
Effect of WLST on $O_2$ delivery

White et al, AJT 2016
Effect of WLST on ventricular distension

White et al, AJT 2016
Conclusion

• DCD organs are unique and must be treated differently

• DCD hearts can be resuscitated and transplanted

• Recovery of function can be optimized
  • Multiple therapeutic targets
  • Extrapolation of data from IR literature
Future Directions

- Defining the onset of myocardial stress during DCD
- Extending safe warm ischemic period
- Optimizing initial reperfusion solution
- Optimizing ex vivo heart perfusion protocols
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