The Value Of Thyroid Hormone, Corticosteroids, Hypothermia and Other Means to Maintain/Improve Donor Heart Function

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Conflict of Interest Disclosure

• I have received consulting fees and clinical trial support from Thoratec, Inc.
Organ Donor

Myocardial Dysfunction

- **Sympathetic Surge**: Myocardial necrosis secondary to catecholamines
- **Hormone Depletion**: Low circulating levels thyroid and cortisol impair function
- **Coronary Perfusion**: Decreased coronary perfusion pressure precipitates ischemia impairing myocardial function
Endocrine Failure After Brain Injury

- Anterior pituitary dysfunction prevalence 30%\textsuperscript{1}
- Abnormal function in one anterior pituitary axis in 53%\textsuperscript{2}
- Estimated incidence hormonal reduction in TBI\textsuperscript{3}
  - Adrenal 15%  
  - Thyroid 5 - 15%  
  - Growth Hormone 18%  
  - Vasopressin 3% - 37%  
  - Gonadal 25% - 80%

- Associations
  - Impaired aerobic metabolism
  - Increased anaerobic metabolism
  - Increased lactate production
  - Depletion high energy phosphates

\textsuperscript{1} Schneider J Neurotrauma 2005; 22: 937-946. 
\textsuperscript{2} Dimopoulou Int Care Med 2004; 30: 1051-1057. 
\textsuperscript{3} Powner Neurocritical Care 2006; 5: 61-70.
Hemodynamic Effects of T3

- Mediated by up-regulation of sarco-endoplasmic reticulum Ca2+ ATPase (SERCA).
- Independent of the beta-adrenergic signaling pathway.
- Ameliorates post-ischemic cardiac dysfunction.
- Improves contractile performance after excessive catecholamine stimulation.

Glucocorticoids

- Membrane stabilizer
- Block up-regulation of inflammatory cytokines
- Maintains cardiac contractility – LV pre-load recruitable stroke work (PRSW)

**Figure 1.** TNF-α levels in serum at baseline, 60 minutes and 360 minutes after brain death. \(^a\)p < 0.05 compared with Group 1; \(^b\)p < 0.05 compared with Group 2.

Hemodynamic Effects of Hormone Resuscitation

Pre-Brain Death (Baseline)

Control

Hormone Resuscitation

6.25 h Post Brain Death Induction

Control

Hormone Resuscitation

Hemodynamic Effects of Hormone Resuscitation

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Heart rate (bpm)</th>
<th>Cardiac output (L/min)</th>
<th>Stroke work (mL.mmHg)</th>
<th>LAD flow (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-brain death (CON)</td>
<td>64 ± 18</td>
<td>99 ± 26</td>
<td>4.7 ± 1.1</td>
<td>3146 ± 1087</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>Pre-brain death (HR)</td>
<td>59 ± 13</td>
<td>91 ± 12</td>
<td>4.1 ± 0.5</td>
<td>2916 ± 473</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>3 h post-brain death (CON)</td>
<td>63 ± 9</td>
<td>161 ± 25</td>
<td>5.6 ± 0.9</td>
<td>3356 ± 724</td>
<td>35 ± 14</td>
</tr>
<tr>
<td>3 h post-brain death (HR)</td>
<td>61 ± 7</td>
<td>166 ± 27</td>
<td>4.6 ± 1.4</td>
<td>2634 ± 903</td>
<td>44 ± 17</td>
</tr>
<tr>
<td>6 h post-brain death (CON)</td>
<td>54 ± 15</td>
<td>186 ± 41</td>
<td>5.1 ± 1.9</td>
<td>2980 ± 1528</td>
<td>47 ± 23</td>
</tr>
<tr>
<td>6 h post-brain death (HR)</td>
<td>74 ± 17(^\d)</td>
<td>157 ± 19</td>
<td>5.3 ± 2.2</td>
<td>3224 ± 1158</td>
<td>45 ± 25</td>
</tr>
<tr>
<td>6.25 h post-brain death* (CON)</td>
<td>38 ± 11</td>
<td>155 ± 25</td>
<td>3.2 ± 1.2</td>
<td>1536 ± 702</td>
<td>31 ± 14</td>
</tr>
<tr>
<td>6.25 h post-brain death* (HR)</td>
<td>72 ± 21(^\d)</td>
<td>156 ± 15</td>
<td>5.8 ± 1.4(^\d)</td>
<td>3640 ± 1083(^\d)</td>
<td>51 ± 15</td>
</tr>
</tbody>
</table>

*Norepinephrine infusion fixed at 3.3 μg/min.
\(^\d\) p < 0.05.
\(^\d\) p < 0.005.
LAD = left anterior descending coronary artery.

<table>
<thead>
<tr>
<th></th>
<th>Standard (26)</th>
<th>Hormone (21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsuitable TXP</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Dopamine ug/Kg/min</td>
<td>14 → 19</td>
<td>27 → 13</td>
</tr>
<tr>
<td>CV Fxn</td>
<td>→</td>
<td>↑ 2x Cardiac output</td>
</tr>
<tr>
<td>EKG abnormal</td>
<td>Persisted</td>
<td>Improved</td>
</tr>
<tr>
<td>MAP</td>
<td>→</td>
<td>56mmHg → 86mmHg</td>
</tr>
<tr>
<td>CVP</td>
<td>→</td>
<td>11mmHg → 7mmHg (↓ 35%)</td>
</tr>
<tr>
<td>HR</td>
<td>→</td>
<td>67 → 91 (↑ 35%)</td>
</tr>
<tr>
<td>HCO₃ Required</td>
<td>↑ 100%</td>
<td>↓ 95%</td>
</tr>
<tr>
<td>Lactate</td>
<td>NR</td>
<td>5.1 → 2.4 (↓ 52%)</td>
</tr>
<tr>
<td>Temp</td>
<td>→</td>
<td>33⁰ → 36⁰</td>
</tr>
</tbody>
</table>

Novitzky Transplantation 1987; 43:852-854
T3: 4 g bolus + infusion at 3 g/hour
Vasopressin: 1 unit bolus + infusion at 0.5-4 units/hour (titrate to SVR 800-1200)
Methylprednisolone: 15 mg/kg bolus
Insulin: 1 unit/hour minimum (titrate to BS 120-180 mg/dL)

CONSORT: Hormone Resuscitation

Total number of zonal donors during study period (250)

Total number of donors approached (116)

Excluded from study [according to exclusion criteria (134)]
- Age (<16, >65)-22
- Chest trauma-2
- Myocardial infarction-2
- Distance >100 miles-29
- Donors within 24h period-32
- Non-unit participation-47

No consent to study (36)

Trial donors (randomized) (80)

Placebo (21) T3 (20) MP (19) T3 and MP (20)

CONSORT: Hormone Resuscitation and Cardiac Output

CONSORT: No effect of HR on CO

### Meta Analysis of Hormone Resuscitation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>T3 Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goarin [9]</td>
<td>3.9</td>
<td>1.5</td>
<td>19</td>
<td>3.9</td>
<td>1.5</td>
<td>18</td>
<td>11.5%</td>
<td>0.00 [-0.97, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Mariot [24]</td>
<td>3.1</td>
<td>0.9</td>
<td>20</td>
<td>3.1</td>
<td>0.9</td>
<td>20</td>
<td>34.4%</td>
<td>0.00 [-0.56, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Perez-Blanco [40]</td>
<td>4.4</td>
<td>2.2</td>
<td>29</td>
<td>4.7</td>
<td>1.7</td>
<td>23</td>
<td>9.5%</td>
<td>-0.30 [-1.36, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Venkateswaran [47]</td>
<td>4.2</td>
<td>1.3</td>
<td>40</td>
<td>3.8</td>
<td>0.9</td>
<td>40</td>
<td>44.6%</td>
<td>0.40 [-0.09, 0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>108</strong></td>
<td></td>
<td><strong>101</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.15 [-0.18, 0.48]</strong></td>
<td><strong>Favours T3</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \ Chi^2 = 2.06, df = 3 \) (\( P = 0.56 \)); \( I^2 = 0% \)
Test for overall effect: \( Z = 0.90 \) (\( P = 0.37 \))

Figure 2. Forest plot comparing the effect of triiodothyronine (T3) vs. placebo on cardiac index at the end of study drug administration. \( CI \), confidence interval; \( IV \), intravenous. Number in brackets indicates reference number.

- 16 Case series
- 7 Randomized trials
  - 4 Placebo controlled

Thyroid Hormone

# Increased Procurement

<table>
<thead>
<tr>
<th>Organs</th>
<th>Group A (T$_3$/T$_4$) (donors, n=23,022)</th>
<th>Group B (no T$_3$/T$_4$) (donors, n=17,102)</th>
<th>Statistical significance A vs. B (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. organs transplanted</td>
<td>Percentage of donors</td>
<td>No. organs transplanted</td>
</tr>
<tr>
<td>Hearts</td>
<td>8,055</td>
<td>34.99</td>
<td>4,406</td>
</tr>
<tr>
<td>Both lungs</td>
<td>8,070</td>
<td>17.53</td>
<td>4,278</td>
</tr>
<tr>
<td>Single lung</td>
<td>798</td>
<td>3.47</td>
<td>442</td>
</tr>
<tr>
<td>Both kidneys</td>
<td>33,722</td>
<td>73.24</td>
<td>22,018</td>
</tr>
<tr>
<td>Single kidney</td>
<td>1,566</td>
<td>6.80</td>
<td>1,234</td>
</tr>
<tr>
<td>Livers$^b$</td>
<td>18,461</td>
<td>80.26</td>
<td>13,642</td>
</tr>
<tr>
<td>Pancreas$^c$</td>
<td>4,914</td>
<td>21.35</td>
<td>2,681</td>
</tr>
<tr>
<td>Intestine$^d$</td>
<td>597</td>
<td>2.59</td>
<td>400</td>
</tr>
<tr>
<td>Total</td>
<td>76,183$^e$</td>
<td>49,101$^e$</td>
<td>3.31±1.78$^e$</td>
</tr>
</tbody>
</table>

Thyroid Hormone

Donor Resuscitation

Hemodynamic Management

STABILITY AND ECHOCARDIOGRAPHIC ASSESSMENT
- Mean Arterial Pressure ≥ 60 mmHg AND Vasoactive Requirement ≤ 10 μg/kg/min AND Urine Output ≥ 1.0 cc/kg/hr AND Left Ventricular Ejection Fraction ≥ 45%

PULMONARY ARTERY CATHETER ASSESSMENT

CAPACITANCE VOLUME
- GOALS
  - PCWP 8-12 mmHg
  - CVP 6-9 mmHg
- INITIAL SPECIFIC TREATMENT
- FLUIDS
- INOTROPES

HYDRAULIC PUMP
- CI = 2.4 L/min
- LVSWI = 15 gram-meters/m²
- SVR = 800-1200 dyne·sec·cm⁻⁵
- UO ≥ 1.0 cc/kg/hr

RESISTANCE
- MAP ≥ 60 mmHg

MONITOR AWAITING PROCUREMENT
- YES
- NO

HORMONE REPLACEMENT THERAPY

MONITOR AWAITING PROCUREMENT
- YES
- NO

FLUIDS
- INOTROPES
- VASOPRESSORS

- Goals met and stability obtained with Vasopressor/Inotropic Requirements ≤ 10 μg/kg/min AND Left Ventricular Ejection Fraction ≥ 45%
Donor Resuscitation

Hemodynamic Management

**HORMONE REPLACEMENT THERAPY**

<table>
<thead>
<tr>
<th></th>
<th>Bolus</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-iodothyronine (T3) or Thyroxine (T4) and Methylprednisolone</td>
<td>4.0 μg</td>
<td>3.0 μg/hr</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>20 μg</td>
<td>10 μg/hour</td>
</tr>
<tr>
<td>Insulin</td>
<td>15 mg/kg</td>
<td>Repeat in 24 hours</td>
</tr>
<tr>
<td></td>
<td>1 u</td>
<td>0.5 – 4.0 u/hr</td>
</tr>
<tr>
<td></td>
<td>10u/50% Dextrose</td>
<td>150 mg/dl maintain 80 mg/dl glucose minimum 1u/hour</td>
</tr>
</tbody>
</table>

- REASSESS GOALS AND STABILITY
- DEFINE ORGANS APPROPRIATE FOR PROCUREMENT
Hypothermia

Cardiac transplantation with a donor heart rescued from deep hypothermia

Luca Botta, MD, Stefano Branzoli, MD, and Luigi Martinelli, MD

Table 1  Blood Gas Analyses of Donor With Accidental Deep Hypothermia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arterial gas&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Venous gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.89</td>
<td>6.65</td>
</tr>
<tr>
<td>P&lt;sub&gt;CO&lt;/sub&gt;&lt;sub&gt;2&lt;/sub&gt;, mm Hg</td>
<td>53.7</td>
<td>75</td>
</tr>
<tr>
<td>P&lt;sub&gt;O&lt;/sub&gt;&lt;sub&gt;2&lt;/sub&gt;, mm Hg</td>
<td>525</td>
<td>96.8</td>
</tr>
<tr>
<td>HCO&lt;sub&gt;3&lt;/sub&gt;, mmol/L</td>
<td>N/A</td>
<td>4.6</td>
</tr>
<tr>
<td>Base excess</td>
<td>−20.6</td>
<td>−25.2</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>K&lt;sup&gt;+&lt;/sup&gt;, mmol/L</td>
<td>N/A</td>
<td>5.5</td>
</tr>
</tbody>
</table>

NA, not available; P<sub>CO</sub>2, partial pressure of carbon dioxide; P<sub>O</sub>2, partial pressure of oxygen.

<sup>a</sup>Venous gas analysis was performed at intensive care unit admission, and arterial analysis was done 1 to 10 minutes later. Both examinations had a fraction of inspired oxygen of 100%.

*J Heart Lung Transplant 2011;30:1203-4.*
Hypothermia

Other Means
Conclusions

• Cardiac dysfunction is common following brain death
• Hemodynamic-guided resuscitation of the brain dead donor increases organ recovery independent of hormone therapy
• Role of HR in hemodynamically stable donors is uncertain
• Vasopressin rather than NE is the agent of choice
Effect of CVP on OTPD

<table>
<thead>
<tr>
<th></th>
<th>Final CVP ≥10</th>
<th>Final CVP &lt;10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 73)</td>
<td>(N = 146)</td>
<td></td>
</tr>
<tr>
<td>OTPD</td>
<td>3.38</td>
<td>4.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart/donor</td>
<td>0.39</td>
<td>0.56</td>
<td>0.019</td>
</tr>
<tr>
<td>Lungs/donor</td>
<td>0.19</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver/donor</td>
<td>0.83</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Kidneys/donor</td>
<td>1.68</td>
<td>1.90</td>
<td>0.010</td>
</tr>
<tr>
<td>Pancreas/donor</td>
<td>0.29</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

CVP, central venous pressure.

Outline
1. Hormone depletion is a consequence of brain death
2. Endocrine failure is common & associated with adverse biologic effects
3. Several lines of evidence that HR should be beneficial
   1. Hemodynamic effects of Thyroid hormone – look up
   2. Hemodynamic effects of corticosteroids – look up Lyons, look up McLean
4. Animal studies
5. Human study – Novitzky
6. Crystal City consensus
7. Prospective clinical trials
8. Meta analysis look up Randell trial possibly harmful
9. Large database analysis
10. Current protocols
11. Hypothermia – case
12. Moderate hypothermia in DCD