Intradialytic stunning
The role of systemic circulatory stress in uraemic complications

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Cardiac risk factors in dialysis patients

- Intra-dialytic hypotension
- Inter-dialytic weight gain
- Inflammation
- Fluid/electrolyte shifts (arrhythmia risk)
- Impaired baroreflex sensitivity
- Vascular calcification
- LVH
- LVSD
- Impaired CV risk
- ‘Traditional’ risk
  - Blood pressure
  - Cholesterol
  - Diabetes
  - Smoking
  - Anaemia

Odudu A, McIntyre CW. J Ren Care 2010
Systemic circulatory stress in HD
-Effects of HD on ScVO$_2$

ScVO$_2$ Pre HD 63.5 ±1 3%, post HD 56.4 ± 8% (p=0.04)*

*Harrison L, Selby NM, McIntyre CW. BRS/RA 2010
Repetitive cardiac injury - Hibernation and heart failure

- Enzyme induction
- Repetitive Ischaemia and Stunning
  - Metabolic adaptations
    - Functional hibernation
      - TIME
        - Oncogene expression
          - Structural hibernation
          - Cell death

- Proportion Abnormalities
  - Altered gene expression/transcription
    - Cell de-differentiation
      (Glycogen increase with loss of contractile proteins etc)
Assessing stress response to HD. Regional Wall Motion Analysis

- Semi-automated software
- Wall motion is calculated over 10 regions and expressed as %SF
- RWMA is defined as reduction in SF of >20% between baseline and peak images
- More than 2 RWMAs are significant
HD induced RWMA – prevalence and cTnT levels

- The higher the cTnT, the greater the reduction in SF

Troponin release dose not require myocardial necrosis

- Blebs develop on myocyte surface

- Prolonged ischemia → bleb rupture, necrosis & prolonged troponin release

- Shorter periods of ischemia → bleb release without rupture, shorter period of troponin release

Hickman et al. *Clinica Chimica Acta* 2010
Factors associated with the presence of RWMAs

- Factors associated with development of >2 RWMAs ($r^2=0.602$)

<table>
<thead>
<tr>
<th>Factor associated with development of myocardial stunning</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF volume during HD of 1L</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>UF volume during HD of 1.5L</td>
<td>11.6</td>
<td>0.007</td>
</tr>
<tr>
<td>UF volume during HD of 2L</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>Max SBP reduction during HD of 10 mmHg</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Max SBP reduction during HD of 20 mmHg</td>
<td>3.3</td>
<td>0.002</td>
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<tr>
<td>Max SBP reduction during HD of 30 mmHg</td>
<td>6.0</td>
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</tr>
<tr>
<td>cTnT</td>
<td>1.26</td>
<td>1.04 – 1.54</td>
</tr>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.01 – 1.128</td>
</tr>
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</table>

HD Induced Myocardial Stunning Lead to Myocardial Hibernation and Reduction in Overall Systolic Function

- Hibernation of segments co-localised with stress induced RWMAs

- Reduction in LVEF ~ 10% (absolute)
  - At rest
  - At peak stress on HD

Other significant associations of Dialysis induced myocardial stunning

- **Inflammation***
  - Increased levels of IL-6 and hs-CRP

- **Markers of volume status**
  - Increased TBW (deuterium based)
  - Increased levels of NT-proBNP

- **Ventricular arrhythmias***
  - 12 lead 24 hr Holter (intra and post dialytic monitoring)
  - complex ventricular arrhythmias (CVA) in 61% of patients

- **Elevated LAV****

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*Jefferies HJ, McIntyre CW. EDTA 2008**

**Jefferies HJ, McIntyre CW. RA/BRS 2008**

***Burton JO, Korsheed S, McIntyre CW. Renal Failure 2008***

****Haq I, Jefferies HJ, Burton JO, McIntyre CW.ASN 2009****
Mortality and time to CV event

Impact of Myocardial Stunning on 1-year Mortality

Impact of Myocardial Stunning on Mortality or First Cardiovascular Event

Intradialytic segmental myocardial perfusion - using cardiac water PET

McIntyre CW. Acute cardiac effects of haemodialysis. Kidney Int 2009
Effect of HD on global and segmental Myocardial Blood Flow

Uraemic effects on normal cardiac function

<table>
<thead>
<tr>
<th>Segment</th>
<th>Basal</th>
<th>Mid</th>
<th>Apical</th>
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<tr>
<td>HD Pts</td>
<td>Controls</td>
<td>HD Pts</td>
<td>Controls</td>
</tr>
<tr>
<td>Anterior</td>
<td>-22±2</td>
<td>-23±2</td>
<td>-27±2</td>
</tr>
<tr>
<td>Antero-septal</td>
<td>-19±2</td>
<td>-21±2</td>
<td>-24±2</td>
</tr>
<tr>
<td>Infero-septal</td>
<td>-18±1</td>
<td>-20±3</td>
<td>-21±4</td>
</tr>
<tr>
<td>Inferior</td>
<td>-16±2</td>
<td>-18±2</td>
<td>-25±3</td>
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<tr>
<td>Postero-Lateral</td>
<td>-21±2</td>
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<tr>
<td>Antero-Lateral</td>
<td>-21±2</td>
<td>-24±3</td>
<td></td>
</tr>
</tbody>
</table>

Odudu A, Eldehni MT, McIntyre CW. ISBP 2010
LV Strain studies- 2D Speckle tracing

- predisposition to longitudinal axis dysfunction
- predisposition to LV mechanical asynchrony

Hothi D, Rees L, McIntyre CW, Marek T. ASN 2009
## Children on dialysis-uraemia without epicardial CAD

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Months on Dialysis</th>
<th>Months on HD</th>
<th>Cause of ESRF AV fistula</th>
<th>LV septum [Z-score]</th>
<th>LV Posterior wall [Z-score]</th>
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<tr>
<td>1</td>
<td>5.7</td>
<td>4</td>
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<td>2</td>
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<td>cystinosis yes</td>
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<td>3</td>
<td>15.7</td>
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<td>FSGS yes</td>
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<td>4</td>
<td>15.0</td>
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<td>renal dysplasia yes</td>
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<td>0.2</td>
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<tr>
<td>5</td>
<td>15.7</td>
<td>32</td>
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<td>FSGS yes</td>
<td>2.6</td>
<td>1.9</td>
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<tr>
<td>6</td>
<td>13.8</td>
<td>7</td>
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<td>6.3</td>
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<td>7</td>
<td>11.2</td>
<td>41</td>
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<td>renal dysplasia yes</td>
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<td>-0.6</td>
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<td>8</td>
<td>13.6</td>
<td>15</td>
<td>15</td>
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<td>-1.1</td>
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<tr>
<td>9</td>
<td>2.2</td>
<td>7</td>
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<td>glomerulocystic no</td>
<td>1.5</td>
<td>1.7</td>
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<td>10</td>
<td>17.0</td>
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<td>12</td>
<td>bilateral VUR yes</td>
<td>1.9</td>
<td>1.7</td>
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<td>11</td>
<td>7.6</td>
<td>62</td>
<td>62</td>
<td>ARPKD yes</td>
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<td>0.3</td>
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<tr>
<td>12</td>
<td>14.6</td>
<td>23</td>
<td>6</td>
<td>cystic dysplasia yes</td>
<td>2.6</td>
<td>1.2</td>
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Recurrent HD induced myocardial stunning in children

<table>
<thead>
<tr>
<th>Proportion stunning</th>
<th>11/12</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>12.4 (2-17)</td>
</tr>
<tr>
<td>UF volume (L)</td>
<td>1.2 ± 0.79</td>
</tr>
<tr>
<td>Delta BP (mmHg)</td>
<td>25.5 ± 9</td>
</tr>
<tr>
<td>Pre HD LVEF (%)</td>
<td>55 ± 8.3</td>
</tr>
<tr>
<td>Post HD LVEF (%)</td>
<td>54.6 ± 7.5</td>
</tr>
</tbody>
</table>

PAPP-A in HD patients
Combined study with Finland

• Strongly associated with ACS and outcomes*

• NO ASSOCIATION WITH HD INDUCED ACUTE CARDIAC INJURY**

*Risto T, Clin Chemistry 2009
**Jefferies HJ, Risto T, Whitforth S, McIntyre CW. ASN 2009
How can aortic compliance induce myocardial ischaemia?

ECG changes

- 3-4 mm ST depression
- at rest and stressed

Myocardial perfusion

Watanabe et al. J Am Coll Cardiol 1993;21:1497-1506
Microcirculatory disturbance in HD and vascular calcification

Myographic ex-vivo arterial assessment

Responses of resistance arteries to (A) KPSS, (B) BK and (C) non-CKD vs. HAEMODIALYSIS.

Figure 14. Differences between artery and vein.

Bushroffa A, Odudu A, Ehehni MT, O'Sullivan S, McIntyre CW. Unpublished data.
Reduction in HD induced circulatory stress ameliorates myocardial stunning

**a) standard dialysis vs. biofeedback**

<table>
<thead>
<tr>
<th></th>
<th>HD baseline</th>
<th>HD 240min</th>
<th>HD post</th>
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</thead>
<tbody>
<tr>
<td>RWMA</td>
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<td></td>
</tr>
<tr>
<td>Resolution</td>
<td></td>
<td></td>
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**b) standard dialysis vs. cooled dialysis**

<table>
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</tr>
<tr>
<td>Resolution</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N Selby, S Lambie, C Baker, P Camici, C McIntyre. AJKD 2006
Daily dialysis impact on UF and BP

Weight change Pre-dialysis to Peak stress

Change in Systolic BP, Pre-dialysis to Peak stress

Patients fully matched for age, sex, history of IHD and dialysis vintage

Jefferies HJ, Schiller B, Moran J, McIntyre CW. Accepted for publication CJASN 2010
Impact of dialysis schedule - Intradialytic cardiac stunning

Number of RWMAs by Dialysis Regimen

- CHD3
- CSD
- HSD
- HN

Weight loss rate vs. Number of stunned segments

- $r=-0.409$, $p=0.0048$

Jefferies HJ, Schiller B, Moran J, McIntyre CW. Accepted for publication CJASN 2010
Peritoneal dialysis is not associated with myocardial stunning

Limited evidence (<5% of segments during drain/fill cycle)

Studied during drain/fill and at peak ultrafiltration
Patients studied had little structural cardiac disease

Selby NM, McIntyre CW. PDI 2010
Endotoxin and heart failure

- Bacterial endotoxin is a lipopolysaccharide (LPS) comprising over 70% of the total bacteria in the human gut.

- Stimulus for immune activation in the pro-inflammatory state of congestive heart failure (CHF)\(^*\)

- ET enters the circulation via bacterial translocation from the gut:
  - bowel oedema
  - hypoperfusion

- Endotoxinaemia reduces with
  - Reduction in venous congestion
  - Selective gut detoxification

Endotoxaemia in CKD 3-5D

Effect of haemodialysis related factors on Endotoxaemia

Endotoxinaemia and inflammation in daily dialysis patients

Pre-dialysis hsCRP (pg/ml)

CHD3  CSD  HSD  HN

Pre-dialysis EU/ml

SDHD  NHD
Dialysis hurts hearts- and a whole lot more besides

ENDOTOXIN
Interventional studies are great.....but make sure you’re testing the right one