Hemodynamic Consequences of Hemodialysis

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Outline

- Tour of the battlefield
- Injury is interconnected
- Making it better
- What we know is very limited
- Future approaches
- Conclusions
First direct study of HD-induced cardiac ischemia
Cardiac MRI during hemodialysis

Global function

Coronary flow

Segmental function

Myocardial perfusion

Nadir MAP (mmHg)

Number of stunned segments

UF rate (L/hour)

Number of stunned sections

Longer term effects of recurrent cardiac injury - Heart failure

<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>0.007</td>
</tr>
<tr>
<td>UF volume during HD of 1.5L</td>
<td>11.6</td>
<td></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>
</tr>
<tr>
<td>Max SBP reduction during HD of 30 mmHg</td>
<td>6.0</td>
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</tr>
</tbody>
</table>

Impact of Myocardial Stunning on 1-year Mortality

Children on dialysis- Uremia *without* classical CAD

Myocardial stunning occurs during intermittent haemodialysis for acute kidney injury

Huda Mahmoud, Lui G. Forni, Christopher W. McIntyre and Nicholas M. Selby

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Importance of tissue perfusion patterns- beyond HF

Renal Failure, 30:701–709, 2008
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CLINICAL STUDY

Hemodialysis-Induced Left Ventricular Dysfunction Is Associated with an Increase in Ventricular Arrhythmias
Dying to Feel Better: The Central Role of Dialysis–Induced Tissue Hypoxia

Christopher McIntyre and Lisa Crowley

HD- associated brain injury

- Universal
- Functionally significant
- Progressive
- Directly proportional to white matter changes
- Independently associated to hemodynamic instability

McIntyre CW, Goldsmith DJ. Kidney Int. 2015 Jun;87(6):1109-15
Eldehni MT, McIntyre CW. Semin Dial. 2012 May;25(3):253-6
Acute effects of HD on brain- PET/MR imaging
Toxic neurotransmitter release and Inflammation

Pre hemodialysis

Peak hemodialysis stress
Microglia are recruited and activated - with memory

This aggravates neurological injury
Gut derived endotoxin in CKD

Harrison LEA, McIntyre CW. Nephron 2014
Circulating Bacterial Fragments as Cardiovascular Risk Factors in CKD

Cheuk-Chun Szeto,¹ Christopher William McIntyre,² and Philip Kam-Tao Li¹
HD effects on hepatic perfusion - the selfish liver

Grant CA, McIntyre CW. Seminars in Dialysis 2019
RCT of dialysate cooling to improve hepatic and GIT perfusion during HD

<table>
<thead>
<tr>
<th></th>
<th>Standard HD</th>
<th></th>
<th>Cooled HD</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 hrs into HD</td>
<td>Baseline</td>
<td>3 hrs into HD</td>
</tr>
<tr>
<td>TLBF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HABF</td>
<td></td>
<td></td>
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<tr>
<td>PVBF</td>
<td></td>
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</tbody>
</table>

ICG Clearance Rate at 3 hr into HD as % of Baseline

Qirjazi E, Marants R, Li TY, McIntyre CW. TH-PO0355 ASN 2018
‘Kidney stunning’- recurrent dialysis induced AKI

Marants R, Grant CA, Lee T, McIntyre CW. TH-PO341 ASN 2018
HD-induced organ injury- Interconnected and horrible
Cooled dialysate- application to cardiovascular protection
Cardiac and neuro-protection with cooling


Eldehni MT, Odudu A, McIntyre CW. JASN 2014
Remote ischemic preconditioning (RIPC)

Four cycles of 5 min of limb ischaemia and 5 min reperfusion

Systemic release of circulating preconditioning substance(s)

Receptor

Intracellular kinase pathways

Mitochondria

Opening of ATP-dependent potassium channel
Closure of permeability pore

Protection

Decreased neutrophil pro-inflammatory gene expression and adhesion

Decreased myocardial infarction, reduced ischaemic pain, improved function

Evidence for multiorgan protection during cardiac and non-cardiac surgery


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Can RIPC protect against HD induced myocardial stunning in prevalent HD patients?

**Excluded**
- Older age (≥60 yrs) or mild to moderate systolic dysfunction (EF ≥ 50%)
- Simultaneous use of drugs that affect the renin-angiotensin-aldosterone system
- Taking anticoagulant
- Taking potassium channel opening or blocking drugs

**Baseline visit 1**
Confirm reproducibility of RWMAs

**Intervention visit 2**
Assessment for early phase benefit of RIPC

**Final visit 4**
To assess if benefit of RIPC is sustained

**Standard HD day 1**
Screening visit (Echo only) Screen for RWMAs

**Standard HD day 3** (estimated n=50) 1:1 Randomisation stratified by diabetes status

**Standard HD day 10**
RIPC applied

**Standard HD day 10**
Sham RIPC applied

**Standard HD day 12**

**Standard HD day 28**

**Primary outcome**
Percentage change in number of new stress RWMAs across all participants at day 10

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Crowley L, Odudu A. McIntyre CW. ASN 2014

Salerno F, Tommassi T Penny J, McIntyre CW. SA-P0858 ASN 2018
Exercise pre-conditioning to protect against HD-induced cardiac injury

Penny J, Bohm C, McIntyre CW. Nephrol Dialysis and Transplant 2019
Impact of daily dialysis on HD-induced cardiac injury

Jefferies HJ, Schiller B, Moran J, McIntyre CW. CJASN 2011
Tissue sodium deposition - $^{23}$Na MRI in CKD patients

Qirjazi E, Akbari A, Scholl T, McIntyre CW. SA-OR033 ASN 2018
Myocardial Na deposition - cardiotoxic

Increased myocardial sodium signal intensity in Conn's syndrome detected by $^{23}$Na magnetic resonance imaging

Martin Christa 1,2, Andreas M. Weng 2, Bettina Geier 3, Caroline Wörmann 1, Anne Scheffler 3, Leane Lehmann 4, Johannes Oberberger 1,2, Bettina J. Kraus 1,2, Stefanie Hahner 1, Stefan Störrk 1,2, Thorsten Klink 5, Wolfgang R. Bauer 1,2, Fabian Hammer 1,2, and Herbert Köstler 1,2

TH-PO512
Detection of Na+ Stores in the Myocardium and Skeletal Muscle of DOCA Treated Mice Using 23Na-MRI
We need to do better- **Precise and timely**

- Can only detect when harm has been evidenced
- No adequate biomarkers
- No feasible epidemiologically based approach
- No window for intervention or refinement before irreversible harm (HF or SCD)
Virtual cardiac physiology laboratory - VCPL

VCPL

PERSONALIZATION

OUTPUT

segmented cardiac imaging
porcine coronary vasculature
morphometry

mathematically generated
functional arterial tree

cardiac morphometry and coronary imaging
hemodynamics, HR, blood viscosity

Myocardial blood flow
BP, HR, electrolytes, ATP, drugs

segmented cardiac imaging
myocardial microstructure

Ionic cell model

MYOCARDIAL PERFUSION

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EP ACTIVITY

VCPLp

SUPER COMPUTER

VCPL Ep

SUPER COMPUTER

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Virtual cardiac physiology laboratory - Patient specific simulation of uremic heart

**VCPL\(_p\)**

**Patient specific data**

**VCPL\(_{EP}\)**

A. Effect of number of IZs on DF and tips increasing perfusion heterogeneity

B. Evolution of tips over time

Frames from re-entrant wave simulation

Kharche S, McIntyre CW. Frontiers in Physiol. 2018

Kharche SR et al. PLOS ONE 2017
So what does this all actually look like?

Current VCPL validation

Patient recruitment → Cardiac CT during HD → Non invasive EP mapping → Insertion of implantable loop recorder → Continuous monitoring of ILR (12 months)

Perfusion simulation → EP simulation

Iterative EP simulations

Patient Specific data

VCPL

Simulated CV HD response

Simulated CV HD response

MODIFY VIRTUAL TREATMENT

Current VCPL validation

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Conclusion and Controversy