Cardiovascular Impact of Hemodialysis
Outline

• Tour of the battlefield
• Injury is interconnected
• Making it better
• Future approaches
• Conclusions
First direct study of HD-induced cardiac ischemia

McIntyre CW. Acute cardiac effects of haemodialysis. Kidney Int 2009
Longer term effects of recurrent cardiac injury - Heart failure

**Factor associated with development of myocardial stunning**

<table>
<thead>
<tr>
<th>Factor</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>
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<tr>
<td>UF volume during HD of 2L</td>
<td>26.2</td>
<td></td>
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<tr>
<td>Max SBP reduction during HD of 10 mmHg</td>
<td>1.8</td>
<td></td>
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<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>
<td></td>
</tr>
</tbody>
</table>

Impact of Myocardial Stunning on 1-year Mortality

Cardiac MRI during hemodialysis

Global function

Coronary flow

Segmental function

Myocardial perfusion

Number of stunned segments

Nadir MAP (mmHg)

UF rate (L/hour)

Number of stunned sections

\[ r = -0.813 \]

\[ r = 0.838 \]
Children on dialysis- Uremia \textit{without} classical CAD

HD induced diastolic dysfunction

Davies JE et al. Circulation 2006
Assa S, Frannsen C. AJKD 2013
Hothi D, Rees L, McIntyre CW, Marek T. Nephron 2013
Using CO₂ manipulation to study vasoregulation.
Grossly defective autoregulation in HD patients

Healthy

HD patient 09

HD patient 10

PO2 (mmHg) PCO2 (mmHg)

MCAv (cm/s)

PO2 (mmHg)

PetCO2 (mmHg)
Functional and structural defects in microcirculation

Bushroffa A, O'Sullivan S, McIntyre CW. PlosOne 2015
Microparticles released from distressed circulation

Gomes J, Qirjazi E, Leong H, McIntyre CW. FR-PO750 ASN 2018
Gomes J, Lucien F, McIntyre CW, Leong HS. Thromb Haemost. 2018 Sep;118(9):1612-1624
Myocardial stunning occurs during intermittent haemodialysis for acute kidney injury

Huda Mahmoud1,2, Lui G. Forni2, Christopher W. McIntyre3 and Nicholas M. Selby1,2
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

Pre-HD

Peak stress-HD
Toxic neurotransmitter release and Inflammation

Pre hemodialysis

Peak hemodialysis stress

Healthy Controls
Microglia are recruited and activated— with memory

This aggravates neurological injury
Gut derived endotoxin in CKD

Harrison LEA, McIntyre CW. Nephron 2014
Liver- organ of last resort

Circulating Bacterial Fragments as Cardiovascular Risk Factors in CKD

Cheuk Chun Soeto,¹ Christopher William McIntyre,² and Philip Kam-Tao Li¹

SYSTEMIC CIRCULATION

PORTAL CIRCULATION
HD effects on hepatic perfusion - the selfish liver

A B

Grant CA, McIntyre CW. Seminars in Dialysis 2019
‘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

Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter

Mohamed T. Eldawal, Aghofor Osuji, and Christopher W. McIntrye

Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, United Kingdom

ABSTRACT

Hemodialysis is associated with significant circulatory stress that could produce recurrent and cumulative ischemic insults to multiple organs, such as the brain. We aimed to characterize hemodialysis-induced ischemic brain injury by longitudinally studying the effects of hemodialysis on brain and dissecting mechanisms and further examine if the use of cooled dialysate could provide protection against hemodialysis-associated brain injury. In total, 73 patients on incident hemodialysis starting within 6 months were randomized to dialyze with a dialysate temperature of either 29°C or 0.5°C below the core body temperature and followed up for 1 year. Brain white matter integrity was studied by diffusion tensor magnetic resonance imaging at baseline and follow-up (all patients available for parent analysis). Intracranial hemodynamic stress was quantified using the extrema points analysis model. Patients on hemodialysis exhibited a pattern of ischemic brain injury (increased fractional anisotropy and reduced radial diffusivity). Cooled dialysate improved hemodynamic tolerability, and changes in brain white matter were associated with hemodynamic instability. Higher mean arterial pressure, systolic blood pressure, and lower radial diffusivity was associated with 1-year survival rate (0.483, P = 0.039) and lower radial diffusivity (P = 0.020). Patients who dialyzed at 0.5°C below core body temperature maintained complete protection against white matter atrophy at 1 year. Our data suggest that hemodialysis results in significant brain injury and that improvement in hemodynamic tolerability achieved by using cooled dialysate is effective at mitigating these effects. This intervention can be delivered without additional cost and is universally applicable.

Individual Intradialytic Neurocognitive and Neurochemical Changes After Hemodialysis-Induced Myocardial Stun, without Compromising Tolerability

Nicholas M. Selby and Christopher W. McIntrye


By a factor of 2.5 during HD, urea and BUN levels were doubled but creatinine was only increased by 1.5-fold. Blood pressure was higher during HD, with a higher peak pressure and time under the higher pressure threshold and no significant change in mean pressure. The decrease in mean pressure was accompanied by a more significant increase in radial diffusivity, as measured by diffusion tensor magnetic resonance imaging (DTI). This suggests that the decrease in mean pressure was more significant and important in the setting of hemodialysis.

Nicholas M. Selby and Christopher W. McIntrye

On the face of it, the results of this study do not indicate a reduction in mean pressure. However, this is likely due to the selection of patients with normal radial diffusivity at baseline, which suggests that the results are not applicable to all patients.
Cardiac and neuro-protection with cooling


Eldehni MT, Odudu A, McIntyre CW. JASN 2014
MY TEMP Trial- cluster RCT

Associations between Hemodialysis Facility Practices to Manage Fluid Volume and Intradialytic Hypotension and Patient Outcomes

Indranil Dargiepaila,1,2 G. Neill Thomas,3 Joanna Clarinav, Alice Shick,1,3 James Martin,3 Brian Bieber,4 Manfred Hecking,4 Angelo Karabian,5 Ronald Pyron,6 Friedrich Port,6 Bruce Robinson,7 and Hugh Rayner8

CJASN ePress. Published on February 5, 2019 as doi: 10.2215/CJN.08240718

Article
Remote ischemic preconditioning (RIPC)

RIPC effect on dialysis induced cardiac injury

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

Jefferies HJ, Schiller B, Moran J, McIntyre CW. CJASN 2011

Harrison LEA, McIntyre CW. Nephron 2014
Biology is really complex!
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 @, Andreas M. Weng @, Bettina Geier @, Caroline Wörmann @, Anne Scheffler @, Leane Lehmann @, Johannes Oberberger @, Bettina J. Kraus @, Stefanie Hahner @, Stefan Störk @, Thorsten Klink @, Wolfgang R. Bauer @, Fabian Hammer @, and Herbert Kostler @

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

MYOCARDIAL PERFUSION

EP ACTIVITY
Virtual cardiac physiology laboratory - **Patient specific** simulation of uremic heart

**VCPL_p**

Patient specific data

**VCPL_EP**

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)

Iterative EP simulations

Patient Specific data

VCPL

Simulated CV HD response

Simulated CV HD response

MODIFY VIRTUAL TREATMENT
Conclusion