Intradialytic Hypotension and Outcomes: What Does the Evidence Tell Us?

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Overview

• Hemodynamic Response to Dialysis
  – Proposed Pathophysiology
  – Complicating Factors
• Effects of Intradialytic Hypotension on Individual Organ Systems
• Associations Between Intradialytic Hypotension and Mortality
• Proposed Strategies to Limit Intradialytic Hypotension
Dialysis induces a 2-slope decrease in blood pressure that is partly dependent on ultrafiltration

Adapted from Dinesh et al. *Am J Kidney Dis* 2011; 58: 794
Intradialytic blood pressure decreases and intradialytic hypotension are associated with pre-dialysis serum osmolarity.


### Odds of Intradialytic Hypotension Per Change in Individual Lab Value

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Per 1 mmol/L increase in serum sodium</th>
<th>Per 2.8 mg/dL increase in SUN</th>
<th>Per 18 mg/dL increase in serum glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td>0.99 (0.98-1.00); p=0.2</td>
<td>1.02 (1.01-1.02); p&lt;0.001</td>
<td>1.03 (1.02-1.04); p&lt;0.001</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td>0.98 (0.97-0.99); p=0.01</td>
<td>1.02 (1.02-1.03); p&lt;0.001</td>
<td>1.02 (1.00-1.03); p=0.01</td>
</tr>
<tr>
<td><strong>Model 2A</strong></td>
<td>0.98 (0.96-0.99); p=0.01</td>
<td>1.02 (1.01-1.03); p&lt;0.001</td>
<td>1.00 (0.96-1.05); p=0.9</td>
</tr>
</tbody>
</table>
Differences in intradialytic changes in osmolarity related to vasopressin may influence intradialytic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Intradialytic Blood Pressure Decreases</th>
<th>Intradialytic Hypertension</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Dialysis Blood Urea Nitrogen</td>
<td>61 (16)</td>
<td>47 (13)</td>
<td>0.008</td>
</tr>
<tr>
<td>Pre-Dialysis Plasma Sodium (mmol/L)</td>
<td>136 (6)</td>
<td>138 (8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Post-Dialysis Plasma Sodium (mmol/L)</td>
<td>137 (6)</td>
<td>135 (4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Dialysate Sodium (mmol/L)</td>
<td>138 (0)</td>
<td>138 (0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pre-Dialysis Plasma Osmolarity (mOsm/kg)</td>
<td>320 (6)</td>
<td>315 (4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Post-Dialysis Plasma Osmolarity (mOsm/kg)</td>
<td>299 (3)</td>
<td>302 (9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Change in Plasma Osmolarity (mOsm/kg)</td>
<td>-21 (5)</td>
<td>-13 (10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in Systolic Blood Pressure (mmHg)</td>
<td>-31.2 (30)</td>
<td>+ 7 (24)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Adapted from Van Buren et al. *Kidney Blood Pressure Research* 2016; 41: 802
Ultimately, ultrafiltration remains a significant determinant of intradialytic blood pressure change.
There are physiologic mechanisms in place to compensate for ultrafiltration induced reductions in plasma volume

- Intravascular refill from the interstitium
- Increased cardiac output
  - Venoconstriction=increased preload
  - Increased myocardial contractility
- Increased total peripheral resistance
  - Vasoconstriction
Abnormalities in intradialytic blood pressure response are not homogeneous

- Decreased cardiac index (35%)
  - Intravascular volume depletion (UF exceeds refill)
  - Acute on chronic systolic or diastolic dysfunction
- Decreased vascular resistance (37%)
- Simultaneous Decrease in both! (23%)

Levin et al. *Nephrology Dialysis Transplantation*, Volume 33, Issue 9, September 2018, Pages 1643–1649,
There are epidemiologic risk factors for intradialytic hypotension

• Patient Demographic/Comorbidity Factors
  – Older Age
  – Female Sex
  – Diabetes
  – Coronary Artery Disease
  – Systolic or Diastolic Dysfunction
  – Hyperphosphatemia
  – Hypoalbuminemia
  – Higher BMI

• Behavioral Factors
  – Large IDWG

• Prescription Factors
  – High UF rates
  – Treatment time < 4 hours

Chou et al. Seminars in Dialysis 2017; 30: 473
What are the adverse effects of intradialytic hypotension?

- Heart
- GI Tract
- Brain
- Kidney
- Mortality!
Intradialytic hypotension is associated with end-organ damage: Myocardial stunning

<table>
<thead>
<tr>
<th>Ultrafiltration Volume During Dialysis</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 L</td>
<td>5.1</td>
<td>0.007</td>
</tr>
<tr>
<td>1.5 L</td>
<td>11.6</td>
<td></td>
</tr>
<tr>
<td>2 L</td>
<td>26.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maximum Systolic Blood Pressure Reduction During Dialysis</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mmHg</td>
<td>1.8</td>
<td>0.002</td>
</tr>
<tr>
<td>20 mmHg</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>30 mmHg</td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

Selby et al. AJKD 2006; 47: 830-841
Burton et al, CJASN 4: 914-920
Intradialytic Hypotension is associated with end-organ damage

$r^2=0.4$, $p=0.001$

(intradialytic SBP decrease with RWMA)
Intradialytic Hypotension is associated with end-organ damage-GI tract

- GI tract
  - Mesenteric Ischemia
  - Endotoxinemia

- Brain

- Kidney Function
What are the associations with intradialytic hypotension and mortality?
First, intradialytic hypotension is defined as…

- Absolute Blood Pressure Changes
  - KDQOI
    - Systolic blood pressure decrease of 20 mmHg
    - Mean arterial blood pressure decrease of 10 mmHg AND
    - Intradialytic symptoms
- Lowest blood pressure during dialysis
- Consider addition of interventions to treat such as crystalloids, colloids, UF reduction/cessation
Historic associations of intradialytic hypotension and mortality were inconsistent

Lowest intradialytic systolic blood pressure (by 20 mmHg increments):
OR 0.79 (0.033)
Historic associations of intradialytic hypotension and mortality were inconsistent.
More recent analysis has identified intradialytic systolic blood pressure nadir as the definition that best associates with mortality.

Nadir systolic blood pressure of <100 mmHg was most strongly associated with mortality if pre-dialysis systolic blood pressure >160 mmHg.

Flythe et al. JASN 2015; 26: 724-734
There is an incremental increase in mortality with increasing frequency of intradialytic hypotension.

Flythe et al.  *JASN* 2015; 26: 724-734
There is an incremental increase in mortality with increasing frequency of intradialytic hypotension

Chou et al. *NDT* 2018; 33: 149-159
There is an incremental increase in mortality with increasing frequency of intradialytic hypotension

Chou et al NDT 2018; 33: 149-159
Intradialytic Hypotension and Mortality Summary

- Frequent occurrences of low systolic blood pressure nadir increase mortality risk
  - Nadir 90 vs 100 mmHg?
  - Is the critical threshold 10%, 20%, 30%?
- There are mixed results regarding the effect of absolute reduction in blood pressure
  - Inability to eliminate confounding variables
  - Different studies with different sample sizes and different patient population had different findings in adjusted analyses
  - It is difficult to make conclusions on effect of symptoms/interventions
Can we stop intradialytic hypotension?
Can we stop intradialytic hypotension: Initial thoughts

• Exclude treatable pathology
  – Echocardiogram
    • Is there an effusion?
    • Is there a valve disease?
    • Is there ischemic cardiomyopathy?

• Eliminate complicating factors
  – Avoid eating during dialysis
Can we stop intradialytic hypotension?

- Limit ultrafiltration rates
  - Longer dialysis time
  - Limitation of interdialytic weight gain
    - Address skipped treatments
    - Limitation of dietary sodium intake and fluid intake
      - Address hyperglycemia
  - Diuretics
Physiologic Interventions-dialysate modification

• High calcium and dialysate sodium profiling
  – Risks inappropriately positive calcium balance and sodium balance with associated long term risks

• Lowering of dialysate sodium
  – Can lower interdialytic weight gain
  – But can promote intradialytic hypotension
  – May be appropriate for patients who IDWG and rapid UF rate is the main problems
Physiologic Interventions-dialysate temperature modification

- **Dialysate Cooling**
  - Definitions Vary
  - Trials Are Small
  - Meta Analyses show reduced risk of intradialytic hypotension
    - However, there may be a compromise of patient comfort and clearance

<table>
<thead>
<tr>
<th>Source</th>
<th>Intervention</th>
<th>Cool Dialysis</th>
<th>Standard Dialysis</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayoub 2004</td>
<td>Fixed 35 C</td>
<td>0 / 30</td>
<td>0 / 30</td>
<td>1.00 [0.92, 1.09]</td>
</tr>
<tr>
<td>Beerhout 2004</td>
<td>BTM 35.2 C</td>
<td>0 / 12</td>
<td>0 / 12</td>
<td>1.00 [0.89, 1.13]</td>
</tr>
<tr>
<td>Chesterton 2009</td>
<td>Fixed 35 C</td>
<td>1 / 9</td>
<td>2 / 9</td>
<td>0.90 [0.65, 1.24]</td>
</tr>
<tr>
<td>Cruz 1999</td>
<td>Fixed 35.5 C</td>
<td>6 / 99</td>
<td>29 / 99</td>
<td>0.21 [0.09, 0.47]</td>
</tr>
<tr>
<td>Dheenan 2001</td>
<td>Fixed 35 C</td>
<td>0.075 / 30</td>
<td>0.093 / 30</td>
<td>0.40 [0.12, 1.32]</td>
</tr>
<tr>
<td>Jost 1993</td>
<td>Fixed 35 C</td>
<td>0 / 12</td>
<td>18 / 12</td>
<td>0.03 [0.01, 0.46]</td>
</tr>
<tr>
<td>Kaufman 1998</td>
<td>BTM 35.7 C</td>
<td>5 / 15</td>
<td>10 / 15</td>
<td>0.50 [0.17, 1.46]</td>
</tr>
<tr>
<td>Setby 2006</td>
<td>Fixed 35 C</td>
<td>1 / 9</td>
<td>1 / 9</td>
<td>1.00 [0.46, 2.22]</td>
</tr>
<tr>
<td>van der Sande 1999</td>
<td>Fixed 35.5 C</td>
<td>0 / 9</td>
<td>1 / 9</td>
<td>0.33 [0.01, 1.54]</td>
</tr>
<tr>
<td>van der Sande 2009</td>
<td>BTM 0.5°C below body temperature</td>
<td>1 / 21</td>
<td>3 / 21</td>
<td>0.33 [0.03, 3.32]</td>
</tr>
<tr>
<td>Yu 1985</td>
<td>Fixed 35 C</td>
<td>0 / 18</td>
<td>0 / 18</td>
<td>1.00 [0.42, 2.40]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.32 [0.18, 0.56]</td>
</tr>
</tbody>
</table>

Test for heterogeneity for pooled Rate Ratio: Chi² = 6.35, df = 10 (P=0.78), P=0%
Physiologic Interventions

- Midodrine - particularly important for autonomic dysfunction
- Avoidance of eating during dialysis
- Consideration of withholding antihypertensives before HD
- More frequent HD: must balance out risk of absolute vs relative risk of hypotension per treatment

Cruz et al. *Am J Kidney Dis* 1999: 33; 920-926
Other Considerations

• Relative Blood Volume Monitoring?
The ultimate challenge:

1. Hypertension AND Extracellular Volume Overload remain independent mortality risk factors

2. Intervention trials to address these introduce further risk for intradialytic hypotension

- DRIP trial: increased incidence of intradialytic hypotension
- BP in HD Trial: increased incidence of recurrent intradialytic hypotension, nausea, and cramps

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Zoccali et al. JASN 2017; 28: 2491
Summary

- Intradialytic blood pressure decreases are the typical physiologic response to dialysis and ultrafiltration
  - Osmotic Changes
  - Ultrafiltration induced reductions in intravascular volume
- Intradialytic hypotension is frequent and reflects an inadequate physiologic compensation
  - Insufficient venous return
  - Insufficient vascular resistance
- Intradialytic hypotension affects cardiac performance, cerebral perfusion, GI perfusion, and renal perfusion
Summary

• Intradialytic hypotension increases mortality
  – The current data identifies a systolic blood pressure nadir of 90-100 mmHg as a critical threshold
  – **There is an incremental mortality risk as frequency increases**
• Prevention of intradialytic hypotension requires assessment of the likely etiology, but further prospective studies are required to establish evidence-based guidelines
• **We must ultimately find a way to balance out the risk of hypertension and extracellular volume overload with the risk of intradialytic hypotension**
Thank You