ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM
Intradialytic Hypotension and Hypertension: Salt and Water Balance

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History Lesson in Hemodialysis

1940’s - Kolff 1st successful dialysis in humans

1960’s - Salt and water removed mostly by diffusion/osmosis. Low sodium diet. Dialysate sodium of 126 meq/L. 70-90% of pts BP controlled

1970’s - improved dialyzer’s and machines allowed hydrostatic driven ultrafiltration. Development of “dialysis dysequilibrium” thought from osmotic dysequilibria or tonicity gradient between plasma and dialysate

1980’s - High-sodium bicarbonate dialysis introduced and improved patient comfort. kt/v introduced and dialysis adequacy based on urea removal. Dialysis treatment times reduced to 4-5 hrs 3x/week.

1990’s - average dialysate sodium rose from 132 to 140-145

2000’s - prevalence of HTN is 70-90%, mortality rates remain high
The Balancing Act

Hypotonic “low” sodium dialysate
• lower incidence of hypertension
• higher patient discomfort
• intradialytic hypotension

Isotonic/hypertonic “high” sodium dialysate
• higher incidence of hypertension
• lower patient discomfort
• intradialytic hypertension
Higher Sodium Dialysis

Higher pOsm

Mobilization IC and EC

Removal of Fluid from both IC and EC

Fewer Episodes of IDH, better dialysis compliance

Higher pOsm

Thirst

IDWG

Interdialytic BP
Overview - Sodium Balance

- Sodium is the most abundant cation in human extracellular fluid.
- Tight regulation of plasma osmolarity and sodium in all terrestrial mammals.
- Total body sodium determines extracellular fluid volume.
Plasma osmolality

THIRST ADH-Renal

Hypothalamic Osmotic Sensor

Pituitary

Baroreceptor

Normal Range

270  280  290  300

Plasma osmolality

THIRST

ADH-Renal
Sodium Intake

Recommended salt (NaCl) intake is < 5 gm/day
- Na intake of 2 g/day or 85 mmol/day

Salt intake will raise osmolality and stimulate thirst
- 8 gm salt = 3 g Na = 139 mmol Na = 1 L intake
- Weight gain of ~0.65 kg/day if limit to 5 gm salt (NaCl) /day

1.5 grams of sodium included

139 mmol Na+

1 Liter water

Na+
Sodium Flux During HD

UF volume is set into machines regardless of sodium gradient

Removal of Na during HD
• mostly due to convection (based on prescribed UF with Na removed from filtered plasma)
  • 3L UF = 408 mmols sodium (9 gms sodium removed)
• partially due to diffusion (based on the gradient between plasma and the dialysate)

Dialysate to patient sodium gradient
• activity Na = activity coefficient Na x concentration sodium
• Diffusion of Na is driven by the difference between activity Na blood vs activity Na dialysate
Serum Sodium Activity Vs Dialysate Sodium Activity

Serum sodium activity
- Serum Na of 140 meq/L fails to take into consideration ~6% of plasma is colloidal protein/lipid
- 140 meq/L in 0.94L plasma water = plasma water sodium concentration 149 meq/L

Dialysis sieving
- Protein-induced transport asymmetry restricts sodium from isotonic flow across the dialysis membrane
- This Gibbs-Donnan effect results in hypotonic ultrafiltrate
- Donnan effect predicts isonatric dialysis will occur only if dialysate Na activity is 5-10 mmol less than plasma water sodium activity
Gibbs-Donnan Membrane Equilibrium

Blood  |  Dialysate

protein anion (10)
sodium cation (10)

Blood  |  Dialysate

protein anion (10)

\[ \text{Na}^+ \quad 18 \]
\[ \text{Cl}^- \quad 8 \]
\[ \text{Na}^+ \quad 12 \]
\[ \text{Cl}^- \quad 12 \]
Higher interdialytic weight gain (driven by high sodium intake and high serum sodium) increases systolic BP

eg, 5% interdialytic weight gain (3.5 kg) = 5 mmHg increase in prediaylsis SBP

*Adjusted for comorbid conditions, demographics, lab variables, medical compliance, and antihypertensive medications.

Dialysate Sodium and BP in Dialysis

Obtaining adequate sodium balance and ECFV control are essential for BP control

Crossover study of 11 HD patients assigned to 3 different dialysate Na prescriptions: time average sodium 138 meq/L vs 140 meq/L vs 147 meq/L

- Higher time average NA resulted in stepwise increase in thirst scores, interdialytic weight gain and ambulatory blood pressure in the interdialytic period
  - 136/82 with Time-average Na 138 meq/L
  - 139/81 with Time-average Na 140 meq/L
  - 147/84 with Time-average Na 147 meq/L

Song et al, AJ KD. 40:291, 2002
# Trials of Effect of Changing Dialysate Na on BP

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Dialysate Na Change</th>
<th>BP effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krautzig</td>
<td>8</td>
<td>140 → 135 meq/L</td>
<td>Decreased</td>
<td>Also dietary Na restriction and fixed Na decrease</td>
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<tr>
<td>Farmer</td>
<td>10</td>
<td>138-140 → 133-135 meq/L</td>
<td>Decreased</td>
<td>Fixed decrease in Na, ABP measured</td>
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<td>Kooman</td>
<td>6</td>
<td>140 → 136 meq/L</td>
<td>NS</td>
<td>Fixed decrease in Na</td>
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<td>Ferraboli</td>
<td>14</td>
<td>140→135 meq/L</td>
<td>Decreased</td>
<td>Fixed decrease in Na</td>
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<tr>
<td>De Paula</td>
<td>27</td>
<td>138→135</td>
<td>Decreased</td>
<td>Tailored decrease in Na</td>
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<tr>
<td>Lambie</td>
<td>16</td>
<td>136→variable</td>
<td>Decreased</td>
<td>Progressive titration in Na based on dialysate conductivity</td>
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<tr>
<td>Sayarlioglu</td>
<td>18</td>
<td>Variable based on preHD NA</td>
<td>Decreased</td>
<td>Decreased IVC diameter</td>
</tr>
</tbody>
</table>

Effect of High Plasma Na

Potential pro-hypertensive effects of high Na independent of volemia

- In a study of young dahl-sensitive rats, increasing plasma sodium increased central sympathetic outflow1
- Increased brain sodium and osmolality increased ANGII levels and increased sympathetic outflow2
- In vitro, high medium sodium concentrations results in hypertrophy of cardiomyocytes and vascular smooth muscle3
- Increased sodium concentration (from 135-145) in endothelial cell culture medium produced significant endothelial cell stiffness and decreased NO release in the presence of aldosterone4

Every 1 mmol/L increase in plasma sodium was associated with a 1.91 mmHg increase in systolic BP, p<0.05

Adapted from Suckling et al. 81:407, 2012
Higher sodium impairs NO release and increases endothelial cell stiffness

Adapted from Oberleithner et al. Proc Natl Acad Sci USA 2007. 104:16281
Pathophysiology of BP changes during HD

Hypotension during HD

Drop in plasma osmolality

• Comparison of HD vs UF vs hypertonic mannitol HD vs isotonic mannitol HD
  • UF alone (with no change in osm) and hypertonic mannitol HD avoided postdialysis hypotension

Impaired sympathetic response

Poor cardiac reserve

Rapid ultrafiltration rates with impaired vascular reactivity

Dialysate to plasma tonicity gradient and ultrafiltration/plasma refilling

Hypertension during HD

• Volume overload
• Sodium loading
• Sympathetic over-activity
• Activation of the renin-angiotensin aldosterone system
• Endothelial cell dysfunction
• Dialysis-specific factors
  - net sodium gain
  - high ionized calcium
  - hypokalemia
• Medications
  - Erythropoietin stimulating agent
  - Removal of antihypertensive medications
• Vascular stiffness

1 Henrich, KI:18:480, 1980

Inrig, AJKD, 55:580, 2010
Causes of Intradialytic Hypotension

**DROP IN ECFV**
- UFR too high (exceeds refill rate)
- low target weight
- low dialysate Na (drop in osmolality)
- acetate dialysate

**LACK OF VASOCONSTRICTION**
- warm dialysis solution
- splanchnic vasodilation
  - tissue ischemia
- autonomic neuropathy
- antihypertensive medications

**CARDIAC FACTORS**
- low cardiac output
- failure to increase HR
- low dialysate calcium

Hypotension
Ultrafiltration Rates

- The greater the gap between ultrafiltration and plasma refill from the interstitium, the greater the risk for hemodynamic complications.

- Ultrafiltration rates that exceed the plasma refill rate (PRR) will increase the risk of hypotension, blood pressure instability, and complications during HD.
Intradialytic hypotension defined by a nadir intradialytic systolic BP of <90 mmHg associated with higher mortality

- Post-hoc analysis of HEMO Study
- (+) IDH characterized as meeting specified IDH definition in at least 30% of baseline treatments
- Nadir systolic BP <90 mmHg was most potently associated with mortality. Other definitions were not associated with mortality.

Flythe et al. JASN, 9/30/2014, doi: 10.168
How Common is Hemodynamic Instability During HD?

- **No Nursing Intervention**: 45%
- **Hypotension Needing Nursing Intervention**: 24%
- **Cramping**: 14%
- **Lightheadedness**: 12%
Summary - Management of Intradialytic Hypotension

• Intradialytic hypotension occurs in up to 30% of hemodialysis sessions
• Intradialytic hypotension is associated with increased morbidity and mortality
• Sequential UF is not routinely effective at preventing intradialytic hypotension
• Avoid hypertonic saline and sodium modeling due to risk of sodium excess
• Use other therapies for long-term management of intradialytic hypotension: cooler temperature, longer dialysis sessions, extra UF session, midodrine
Causes of Intradialytic Hypertension

- Excess Extracellular Volume
- High Dialysate Na
- Endothelial Cell Dysfunction
- RAAS Overactivity
- Medications - ESA - dialyzability of antihypertensives
- High Endothelin-1 & Low Nitric Oxide
- High Dialysate Ca+
- SNS overactivity

Hypertension
Intradialytic Hypertension is Associated With Increased Morbidity and Mortality

6 Month Hospitalization or Mortality

<table>
<thead>
<tr>
<th>SBP Increase e10 mmHg</th>
<th>2.17</th>
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<tbody>
<tr>
<td>SBP Decrease e10 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

Reference

Inrig et al. KI, 71: 454-461, 2007

2-year Survival

Log rank p-value=0.01

Systolic BP decreased > 10 mmHg

Systolic BP unchanged (+/- 10 mmHg)

Systolic BP increased > 10 mmHg (intradialytic HTN)

Inrig et al. AJKD. 54:881-890, 2009
Intradialytic Hypertension affects >20% of Hemodialysis Sessions

Systolic Blood Pressure Patterns Over 6 Months (n=22,955 treatments)

- 26.7% Systolic Blood Pressure Decrease >10 mmHg
- 21.3% Systolic Blood Pressure Increase >10 mmHg
- 52.0% Systolic Blood Pressure Decrease >10 mmHg

HYPERTENSIVE = Systolic BP >140 mmHg pre HD
Or >130 mmHg post-HD

Van Buren et al. IJ AO, 35:1031, 2012
Carvedilol improves Intradialytic Hypertension

The frequency of intradialytic hypertension declined from 77% (4.6/6) at baseline to 28% (1.7/6) of HD sessions at study end (p<0.0001)

Baseline                  After Carvedilol

Systolic BP (mmHg)

ΔSBP - 3.8 mmHg

ΔSBP +15.0 mmHg

Inrig et al, cJ ASN, 7:1300, 2012
Summary - Management of Intradialytic Hypertension

• Intradialytic hypertension occurs in >20% of hemodialysis sessions
• Intradialytic hypertension is associated with increased morbidity and mortality
• First step in managing intradialytic hypertension is reduction in dry weight
• Avoid high dialysate-to-plasma sodium gradients as it may case vasoconstriction and contribute to intradialytic hypertension
• Consider use of carvedilol for management of intradialytic hypertension
Conclusion

Patients should be educated to minimize sodium intake between treatments (<2 gm/day)

Adequate sodium solute removal during HD is critical for BP control

Inadequate sodium solute removal can contribute to higher thirst, larger interdialytic weight gains, and higher interdialytic BP burden

Both intradialytic hypotension and intradialytic hypertension are associated with higher mortality

There are many cause of both intradialytic hypotension and hypertension
  • Intradialytic hypotension is dependent on UF, while intradialytic hypertension is not

Treatment options for intradialytic hypotension:
  • Extend treatment times, low dietary sodium intake, cool dialysate, midodrine

Treatment options for intradialytic hypertension:
  • Reduce dry weight, low dietary sodium intake, review dialyzable medications, consider carvedilol, consider lowering dialysate sodium