Managing fluid, salt, K+ and creatinine in heart failure or cardiorenal syndrome

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Consulting Fees/Honoraria:
- Novartis, AstraZeneca, Janssen, Servier, Amgen, Sanofi

Clinical Trials:
- Novartis, Amgen
Learning objectives

Following this session, participants will be better able to:

• Understand the interaction of diabetes, kidney disease and HF
• Review the management of potassium, the "forgotten ion"
• Understand established & new modalities for the treatment of potassium disorders
Electrolyte and Fluid Disturbances in Congestive Heart Failure

November 22, 1951
HFREF = heart failure with reduced ejection fraction; HeFNEF = heart failure with normal ejection fraction; LV = left ventricular.
Mechanisms of Sodium and Water Retention in Heart Failure

Chronic Decrease in Cardiac Output
Or Decrease in Peripheral Vascular Resistance

- Increased Cardiac Filling Pressures
  - Water Retention
  - V2 Receptors Stimulation
  - Nonosmotic AVP Release

- Increased Sodium and Water Retention
  - Resistance to Natriuretic Peptides
  - Failure to Escape From Aldosterone
  - Reduced Distal Delivery of Sodium

- Decrease Fullness of The Arterial Circulation
  - Baroreceptor Desensitization
  - Decreased Renal Perfusion Pressure
  - Renal Vasoconstriction

- Increased SNS Activity
- Increased RAAS Activity
- Increased Water and Sodium Reabsorption in the Proximal Tubule

- Decreased GFR

Adapted from Schrier RW: J Am Coll Cardiol 2006; 47:1-8
Normal Physiology
Myocardial Injury

Decreased Cardiac Output, Arterial Under-Filling

HF Physiology
Figure 4. Paradigm of interstitial and intravascular volume expansion in chronic heart failure. BP indicates blood pressure; and CO, cardiac output.
Figure 3. Frequency distribution of measured total blood volume, red blood cell mass, and plasma volume at hospital admission in patients with decompensated chronic heart failure. Percent deviation from normal expected volumes.
Clinical Evaluation of HF

Figure 7. Lack of correlation between central venous pressure and measured total blood volume. Pressure is not volume. Reprinted from Shippy et al\textsuperscript{33} with permission of the publisher. Copyright ©1984, Wolters Kluwer Health.
Sodium and HF
Edema and Sodium
Hyponatremia signs and symptoms may include:

- Nausea and vomiting
- Headache
- Confusion
- Loss of energy, drowsiness and fatigue
- Restlessness and irritability
- Muscle weakness, spasms or cramps
- Seizures
- Coma
Correction of hyponatremia
## Correction of Hyponatremia

<table>
<thead>
<tr>
<th>Hyponatremia Type</th>
<th>Treatment Regimen</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Acute symptomatic</td>
<td>Serum sodium concentration should be increased by 2 mmol/L per hr until symptoms subside; may be used with or without loop diuretics such as furosemide</td>
<td>Correction should be limited to 8 mmol/L per 24 hr to avoid the risk of adverse neurologic outcomes</td>
</tr>
<tr>
<td>Chronic symptomatic</td>
<td>Rate of correction should be 0.5 to 1 mmol/L. Therapy should be discontinued when serum sodium concentrations are raised by 10% or when symptoms subside; may be used with or without loop diuretics such as furosemide</td>
<td>Correction should be limited to 25 mmol/L per 48 hr to avoid the risk of adverse neurologic outcomes</td>
</tr>
<tr>
<td>Chronic asymptomatic</td>
<td>Restrict fluid intake; use other pharmacologic agents</td>
<td>Loop diuretics may exacerbate hyponatremia</td>
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### Therapeutic Options for Hyponatremia Due to Congestive Heart Failure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Fluid restriction</td>
<td>Decreases total body water volume, increasing ratio of sodium to water</td>
<td>Treatment adherence issues</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>Increase ratio of sodium to water; may be used with furosemide to avoid fluid overload</td>
<td>Careful monitoring required; rapid correction can lead to neurologic damage</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Increase rate of urine flow</td>
<td>Promote excretion of sodium, exacerbating hyponatremia</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Inhibit aldosterone-mediated water retention</td>
<td>Promote excretion of sodium, exacerbating hyponatremia</td>
</tr>
<tr>
<td>Demeclocycline</td>
<td>Inhibits antidiuretic actions of AVP by inducing nephrogenic diabetes insipidus</td>
<td>Potential for nephrotoxicity</td>
</tr>
<tr>
<td>Lithium</td>
<td>Reduces antidiuretic activity of AVP by reducing V₂⁻ receptor-mediated stimulation of adenyl cyclase</td>
<td>Slow onset of action; CNS side effects, cardiotoxicity, and GI disturbances</td>
</tr>
<tr>
<td>Urea</td>
<td>Increases the osmolality of the plasma and tubular fluid</td>
<td>Nonpalatable; contraindicated in impaired renal function, intracranial bleeding, and liver failure</td>
</tr>
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</table>

AVP = arginine vasopressin; CNS = central nervous system; GI = gastrointestinal.
Symptoms of hypernatremia

- Non-specific,
- Restlessness,
- Irritability,
- Muscular twitching,
- Hyperreflexia,
- Spasticity, and
- Seizures
- With hypotonic losses - signs of volume loss
- Tachycardia,
- Hypotension,
- Decreased JVP,
- Dry mucosa,
- Reduced skin turgor and
- Thick doughy skin
Treatment recommendations for symptomatic hypernatremia

Recommendations are as follows:

• Establish documented onset (acute, < 24 h; chronic, >24h)
• In acute hypernatremia, correct the serum sodium at an initial rate of 2-3 mEq/L/h (for 2-3 h) (maximum total, 12 mEq/L/d).
• Measure serum and urine electrolytes every 1-2 hours
• Perform serial neurologic examinations and decrease the rate of correction with improvement in symptoms
• Chronic hypernatremia with no or mild symptoms should be corrected at a rate not to exceed 0.5 mEq/L/h and a total of 8-10 mEq/d (eg, 160 mEq/L to 152 mEq/L in 24 h).
• If a volume deficit and hypernatremia are present, intravascular volume should be restored with isotonic sodium chloride prior to free-water administration.
Distribution of Total Body $K^+$

**Intracellular fluid**
- 3,500 mEq (140-150 mEq/L)
  - Muscle: 2,700 mEq
  - Liver: 250 mEq
  - Erythrocytes: 250 mEq
  - Bone: 300 mEq

**Extracellular fluid**
- 70 mEq (3.5-5.5 mEq/L)
Heart Failure and Potassium

Fig. 2

Hypokalemia in heart failure. RAAS renin–angiotensin–aldosterone system
Homeostasis - controlled by EXCRETION

Kidney plays the most important role

- 90% is of K+ is resorbed before the distal tubule and collecting duct-
  - In distal tubule and collecting duct- K+ absorbed and secreted
  - Tubular secretion that regulates the amount of K+ in the urine
  - Regulating hormone- aldosterone (↑ in hyperkalemia)
    - Acts on cortical collecting duct
    - Moves sodium into cells
    - Creates a negative charge in the lumen → K+ excretion.
    - ↑ intracellular Na+ stimulates the basolateral Na+, K+-ATPase
      - Moves K+ into cells lining the cortical collecting duct from blood side.

- Glucocorticoids, ADH, high urine flow, and high Na+ delivery to the distal nephron also ↑ urine K+.
- Alkalosis ↑ urine K+.
- Acidosis ↓ urine K+.

- Excretion is decreased by insulin, catecholamines, and urine ammonia
Hypokalemia in CHF

**Causes:**
- Medication
- Increased losses: extrarenal and renal
- Transcellular shifts
- Decreased intake
- *Lab error- spurious
Treatment- Hypokalemia

Severe, symptomatic hypokalemia requires aggressive treatment.

Because of the risk of hyperkalemia, use IV potassium cautiously:
0.5–1 mEq/kg, usually given over 1 hr. The adult maximum dose is 40 mEq.

Oral potassium is safer.
- Potassium chloride is the usual choice for supplementation.
- Potassium acetate or potassium citrate for patients with acidosis and hypokalemia.
- Potassium phosphate if hypophosphatemia is present.

Potassium-sparing diuretics-
- ACE – Inhibitors/ARB
Hyperkalemia is routinely defined as a serum potassium level >5 mmol/L.

The PARADIGM-HF trial suggests the incidence of hyperkalemia was ≈16% over a median follow-up time of 27 months, despite a highly selected and carefully monitored clinical trial population.
Hyperkalemia in CHF

“One of the few things one can die from without any symptoms…”

Causes
Medications
Spurious
Increased Intake
Decreased Excretion
Transcellular shifts
RASi (i.e. ACE-I and ARB) in heart failure patients

Initiate with caution in patients with: Renal dysfunction (creatinine >3mg/dl), high potassium >5.0 mmol/L or bilateral renal artery stenosis.

Check potassium and renal function

1-2 weeks
Every 3-6 months

Discontinue or dose decrease for potassium >5.5mmol/L. Carefully reintroduce as soon as possible.

MRA in heart failure patients

Initiate with caution in patients with: Renal dysfunction (creatinine ≥2.5 mg/dL or GFR <30 mL/min/1.73 m²), high potassium >5.0mmol/L.

Check potassium and renal function

1 week
4 weeks
Every 3-6 months

Discontinue or dose decrease for potassium >5.5mmol/L. Carefully reintroduce as soon as possible.
WRF: Worsening renal function
Poor Sensitivity and Specificity of ECG as Diagnostic Test for Hyperkalemia

- In 127 patients with serum K$^+$ between 6-9.3 mEq/L, only 46% of ECGs noted to have changes$^1$

- In 90 cases, only 24 noted to have characteristic T-wave changes as read by a cardiologist$^2$

- Only 1/14 who presented with arrhythmias or arrest had strict criteria$^2$

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ECG, electrocardiogram.
Goals of Therapy to Treat Acute Hyperkalemia

Membrane Stabilization

- Antagonize the Effects of K⁺ on Excitable Cell Membranes

K⁺ Redistribution

- Redistribute Extracellular K⁺ Into Cells

K⁺ Elimination

- Enhance the Elimination of K⁺ From the Body

Therapies to Treat Acute Hyperkalemia

Membrane Stabilization\(^1,2\)

- **Calcium gluconate salt**
  - ↓ threshold potential of cardiac myocytes\(^1\)

- **Hypertonic solution**
  - ↑ action potential rising velocity of cardiac myocytes in hyponatremic, hyperkalemic patients\(^3\)

K\(^+\) Redistribution\(^1,2\)

- **Insulin**
  - Activates the Na\(^+\)/K\(^+\)-ATPase pump\(^1\)

- **β-adrenoceptor agonists**
  - MOA unknown\(^1\)

K\(^+\) Elimination\(^1,2\)

- **Sodium bicarbonate**
  - Alkalinizes the urine, thereby enhancing urinary K\(^+\) excretion\(^1\)

- **Loop diuretics**
  - Enhance urinary K\(^+\) excretion\(^2\)

- **SPS/CPS**
  - Enhance K\(^+\) removal through the colon\(^3\)

- **Hemodialysis**
  - Removal of K\(^+\) from blood\(^1\)

CPS, calcium polystyrene sulfonate; MOA, mechanism of action; SPS, sodium polystyrene sulfonate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sodium Polystyrene Sulfonate</th>
<th>Patiromersorbitex Calcium</th>
<th>Sodium Zirconium Cyclosilicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>Approved as Kayexalate</td>
<td>Approved as Veltassa Lokelma</td>
<td>Under review CADTH</td>
</tr>
<tr>
<td>Structure</td>
<td>Benzene, diethenyl-polymer, with ethenylbenzene, sulfonated, sodium salt, organic polymer</td>
<td>100-µm bead, organic polymer</td>
<td>Octahedral, micropore ring 3Å diameter, inorganic crystal</td>
</tr>
<tr>
<td>Administration</td>
<td>15–60 g, up to 4 times daily (85)</td>
<td>8.4 g once daily and can be advanced to 16.8 g to 25.2 g at weekly intervals</td>
<td>5–15 g, once daily, oral (71)</td>
</tr>
<tr>
<td>Normalize serum K⁺</td>
<td>Variable and not known</td>
<td>48 to 72 h (60)</td>
<td>2.2 h (mean) AstraZeneca</td>
</tr>
</tbody>
</table>
**NEW TREATMENTS FOR HYPERKALEMIA:**
**Patiromer (RLY5016) and Sodium zirconium cyclosilicate (ZS-9)**

<table>
<thead>
<tr>
<th>Positive effects:</th>
<th>Side Effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normalizes and maintains potassium levels</td>
<td>• Drug-drug interactions</td>
</tr>
<tr>
<td>• Efficacy in heart failure</td>
<td>• Edema (at high doses of ZS-9)</td>
</tr>
<tr>
<td>• Reduces aldosterone levels and blood pressure</td>
<td>• Constipation, diarrhea, flatulence, nausea</td>
</tr>
<tr>
<td></td>
<td>• Hypomagnesemia</td>
</tr>
<tr>
<td></td>
<td>• Hypokalemia</td>
</tr>
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**Evidence gaps:**

- *Prevention* of hyperkalemia
- Limitation of RAASi optimization due to hypotension or worsening renal function
- **Safety and efficacy of RAASi optimization** in patients excluded from previous trials
- **Safety and efficacy of RAASi use at higher doses than used in previous trials**
Hyperkalemia Is a Major Reason for Discontinuation of MRA

- 134 HF patients followed in a Portuguese HF clinic
- Spironolactone use in patients with SCr ≤2.5 mg/dL and K+ ≤5 mEq/L
- 25% of patients withdrew from spironolactone therapy (19/76)

Severe hyperkalemia (≥6 mEq/L) occurred in 7 patients who withdrew from spironolactone therapy (9.2%).

**Reason for spironolactone suspension (%)**

- Hyperkalemia: 17.1%
- Renal function decline: 14.5%
- Gynecomastia: 5.3%
- Other: 1.3%

Severe hyperkalemia (≥6 mEq/L) occurred in 7 patients who withdrew from spironolactone therapy (9.2%).

HF, heart failure; MRA, mineralocorticoid receptor antagonist; SCr, serum creatinine.
Serum Potassium Levels During the Randomized Phase (Days 8–29) According to Study Group

![Graph showing mean serum potassium levels by zirconium cyclosilicate dose levels](image)

Serum Potassium Levels During the Open-Label Phase (48 hours)

Potassium Levels with Sodium Zirconium Cyclosilicate 10 g Once-Daily During Phase 2

From “Sodium Zirconium Cyclosilicate in Hyperkalemia”, David K. Packham, 352, 3, 222-231 copyright © NEJM, Reprinted with permission from Massachusetts Medical Society
Effect of Patiromer on Serum Potassium Level: AMETHYST-DN (52 weeks)

Strategies to Overcome Cardiorenal Syndrome

- Avoid Hypotension
- Avoid “over diuresis” and allow adequate time for circulatory “refill”
- Addition of thiazide-type diuretics should be considered when a progressive decrease in loop diuretic efficacy is observed; Add to block distal tubule
- Reduce CVP and TR
- Improve RV function when possible: reduce PVR, support RV function
- MRA: use natriuretic dose (> 25 mg spironolactone). Peak effect 48 hours; use with loop diuretic
- Reduce Intra abdominal pressure: paracentesis
Pathogenesis and effects of hypomagnesemia in CHF. RAAS renin–angiotensin–aldosterone system.
Prognosis

- Hyponatremia is an independent predictor of morbidity and mortality in CHF
- Hypokalemia is an independent predictor of sudden cardiac death
- Hyperkaliemia is more prevalent than usually thought and often associated with disease modifying drug withdrawal
- Serum magnesium is not an independent risk factor of death in patients with moderate to severe CHF
Thank you!