Hyperkalemia – a silent killer?

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Mr. Hyper K. Lemia
charged with serial murder
**Internal and external $K^+$-balance**

From: Giebisch et al. In: Medical Physiology 2017

**Plasma:** 20 mmol

**Total body $K^+$:**
- 98% intracellular
- 2% extracellular

**Normal extracellular K:**
- $3.5 – 4.5$ mmol/l

**Range:** $6-900$ mmol/d
Mechanisms leading to hyperkalemia

**Excess potassium intake**
- Nutrition
- Potassium supplements

**Reduced potassium excretion**
- Impaired renal function
- Impaired aldosterone secretion or action:
  - Renin-angiotensin-aldosterone system (RAAS) inhibitors
- Adrenal insufficiency
- Pseudohypoaldosteronism
- Hyporeninemic hypoaldosteronism
- Low distal Na⁺ delivery

**Potassium redistribution**
- Acidosis
- Insulin deficiency or resistance
- Drugs
- Strenuous exercise
- Tissue breakdown (tumor lysis, rhabdomyolysis...)
- Hemolysis
Consequences of hyperkalemia

- Clinical consequences of hyperkalemia are caused by alterations in membrane excitability.
- These consequences may be life-threatening, but symptoms are unspecific and often absent:
  - Neuromuscular: fatigue, weakness, muscle pain or tightness, paresthesias
  - Gastrointestinal: nausea, vomiting
  - Cardiac: palpitations
Serum-$K^+$ and mortality

Predialysis $K^+$ and mortality in HD

Time-averaged $K^+$ and mortality in PD

$K^+$ and mortality in CKD

Mean in-hospital $K^+$ and mortality after MI

Community-based $K^+$ and mortality

Kovesdy, CJASN 2007

Torlen, CJASN 2012


Einhorn, Arch Int Med 2009

Goyal, JAMA 2012

Hughes-Austin, CJASN 2017
Serum-$K^+$ and mortality

- Hyperkalemia is associated with higher mortality across a spectrum of diseases
- But: association = causality?
- Clinical consequences of hyperkalemia depend not only on the $K^+$-level, but:
  - rapidity of onset
  - presence of concomitant electrolyte abnormalities
  - Medications
  - other comorbidities

$\rightarrow$ Hence, there is no clear cut off for a „critically elevated“ and also no upper limit for a „safe“ $K^+$-level!
Consequences of hyperkalemia

<table>
<thead>
<tr>
<th>Serum Potassium</th>
<th>Typical ECG Appearance</th>
<th>Possible ECG Abnormalities</th>
</tr>
</thead>
</table>
| Mild (5.5-6.5 mEq/L) | ![Typical ECG Appearance](image1) | Peaked T waves  
Prolonged PR segment |
| Moderate (6.5-8.0 mEq/L) | ![Typical ECG Appearance](image2) | Loss of P wave  
Prolonged QRS complex  
Flattened T waves |
| Severe (> 8.0 mEq/L) | ![Typical ECG Appearance](image3) | |

**Frequency of ECG changes**

![Bar Chart](image4)

Montague, CJASN 2008

Figure from McCullough PA, et al. Rev Cardiol 2008
Hyperkalemia: a double-edged sword

Direct, potentially deleterious cardiac and neuromuscular effects

Hyperkalemia prompts the discontinuation of important medications and healthy nutrition
<table>
<thead>
<tr>
<th>Disease state</th>
<th>Recommendation</th>
<th>Source of recommendation</th>
<th>Level of recommendation</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with reduced ejection fraction</td>
<td>In patients with history of MI and reduced EF, ACEIs or ARBs should be used to prevent HF. ACEIs are recommended in patients with HFpEF (LVEF ≤40%) and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended in patients with HFpEF with current or prior symptoms who are ACEI-intolerant, unless contraindicated, to reduce morbidity and mortality. Addition of an ARB may be considered in persistently symptomatic patients with HFpEF who are already being treated with an ACEI and a beta-blocker in whom an aldosterone antagonist is not indicated or tolerated. MRAs are recommended in patients with NYHA class II to IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. MRAs are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF ≤40% who develop HF symptoms or who have a history of DM, unless contraindicated.</td>
<td>ACC/AHA&lt;sup&gt;18&lt;/sup&gt;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>For prevention of CKD progression, suggest an ARB or ACEI be used in diabetic adults with CKD and UAE &gt; 300 mg/24 h. For prevention of CKD progression, recommend an ARB or ACEI be used in both diabetic and nondiabetic adults with CKD and UAE &gt; 300 mg/24 h. Do not routinely discontinue RAASI (ACEI, ARB, MRA, direct renin inhibitor) in people with GFR &lt; 30 ml/min/1.73 m&lt;sup&gt;2&lt;/sup&gt; as they remain nephroprotective. In the population ≥18 years of age with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status</td>
<td>KDIGO&lt;sup&gt;20,21&lt;/sup&gt;</td>
<td>2</td>
<td>D</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Pharmacological therapy for patients with DM and HTN should comprise a regimen that includes either an ACEI or an ARB. Either an ACEI or ARB is suggested for the treatment of diabetic nephropathy patients with moderately elevated UAE (30–299 mg/day) and is recommended for those with UAE &gt; 300 mg/day.</td>
<td>ADA&lt;sup&gt;26&lt;/sup&gt;</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Resistant hypertension</td>
<td>MRAs should be considered, if no contraindication exists.</td>
<td>ESH/ESC&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>

ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction; ESC, European Society of Cardiology; ESH, European Society of Hypertension; GFR, glomerular filtration rate; HF, heart failure; HFpEF, HF with reduced EF; HTN, hypertension; JNC, Joint National Committee; KDIGO, Kidney Disease Improving Global Outcomes; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NYHA, New York Heart Association; RAASI, renin-angiotensin-aldosterone system inhibitor; UAE, urine albumin excretion.

<sup>*</sup>Recent data suggest ACEIs are possibly superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD.®
**RAASi use in the real world setting**

- Several studies have shown underutilization of RAASi compared to guideline recommendations
- When RAASi are prescribed, they are often used in submaximal doses
Reasons for withholding RAASi therapy

Ironically, patients with risk factors for hyperkalemia are also those who receive the greatest absolute benefit from RAASi.
Hyperkalemia, subsequent RAASi adaptation and mortality

**Figure 2A.** Among Patients on RAAS Inhibitor at Maximum Dose

<table>
<thead>
<tr>
<th>Condition</th>
<th>Maintained Dose</th>
<th>Down-titrated Dose</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Hyperkalemia (Potassium 5.1-5.4 mEq/L)</td>
<td>52%</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>Moderate-to-Severe Hyperkalemia (Potassium ≥5.5 mEq/L)</td>
<td>41%</td>
<td>20%</td>
<td>39%</td>
</tr>
</tbody>
</table>

**Figure 2B.** Among Patients on RAAS Inhibitor at Submaximum Dose

<table>
<thead>
<tr>
<th>Condition</th>
<th>Maintained Dose</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Hyperkalemia (Potassium 2.5-2.9 mEq/L)</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>Moderate-to-Severe Hyperkalemia (Potassium ≥3.0 mEq/L)</td>
<td>55%</td>
<td>45%</td>
</tr>
</tbody>
</table>

**Figure 4.** Percent Mortality by Prior RAAS Inhibitor Dose

<table>
<thead>
<tr>
<th>Condition</th>
<th>Maximum Dose</th>
<th>Submaximum Dose</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stages 3-4</td>
<td>9.8%</td>
<td>25.3%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>13.7%</td>
<td>27.7%</td>
<td>30.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.0%</td>
<td>10.1%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Total Population</td>
<td>4.1%</td>
<td>8.2%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

RAAS indicates renin-angiotensin-aldosterone system.
Hyperkalemia – really of concern?

Juurlink, NEJM 2004
Current management of hyperkalemia

- **Potassium redistribution**: Insulin – Glucose, Beta-agonists, Bicarbonate
- **Facilitate renal potassium excretion**: Reduce / stop RAASi, Loop diuretics, Rehydration if volume depleted / less sodium restriction, Fludrocortisone
- **Restrict potassium intake**: Nutritional restrictions
- **Facilitate intestinal potassium excretion**: Potassium binders
- **Extracorporeal removal**: Dialysis
## Potassium-binders available and under evaluation

<table>
<thead>
<tr>
<th>Potassium Binders</th>
<th>Exchange Ion</th>
<th>Onset of action</th>
<th>Effect duration</th>
<th>Preparation and administration</th>
<th>Dosing</th>
<th>Setting</th>
<th>Clinical studies performed</th>
<th>Safety profile</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium polystyrene sulfonate (SPS), Resonium®</td>
<td>Na⁺</td>
<td>variable, 2 – 6 hours&lt;sup&gt;1&lt;/sup&gt;</td>
<td>variable, 6 – 24 hours&lt;sup&gt;1&lt;/sup&gt;</td>
<td>powder, 15g in 100mL water&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3 – 4 x daily&lt;sup&gt;2&lt;/sup&gt;</td>
<td>sub-acute (contraindicated at serum K⁺ &lt; 5.0 mmol/L)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1961: observational study&lt;sup&gt;12&lt;/sup&gt; 2014: randomized, single-blind, SPS vs. CPS (3d)&lt;sup&gt;13&lt;/sup&gt; 2015: randomized, double-blind, placebo-controlled (7d)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>hypomagnesemia, anemia, edema, nausea, vomiting, constipation, diarrhea, GI tract ulceration or necrosis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>US: approved since 1958 France: 1980</td>
</tr>
<tr>
<td>Patiomer Calcium Sorbitex, Veltassa®</td>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>7 hours&lt;sup&gt;3&lt;/sup&gt;</td>
<td>12 – 24 hours&lt;sup&gt;3&lt;/sup&gt;</td>
<td>powder, 8.4/16.8 g in 80mL water, apple juice, cranberry juice&lt;sup&gt;15&lt;/sup&gt;</td>
<td>chronic: 1 x daily with meal&lt;sup&gt;15&lt;/sup&gt;</td>
<td>chronic (should not replace emergency treatment)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>RLY5016-103: Onset of action (12d)&lt;sup&gt;3&lt;/sup&gt; RLY5016-201: HD patients (1w)&lt;sup&gt;4&lt;/sup&gt; RLY5016-202: PEARL (4w)&lt;sup&gt;5&lt;/sup&gt; RLY5016-205: AMETHYST (52w)&lt;sup&gt;6&lt;/sup&gt; RLY5016-301: OPAL (12w)&lt;sup&gt;7&lt;/sup&gt; RLY5016-401: TOURMALINE(4w)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>common: hypomagnesemia, constipation, diarrhea, abdominal pain, flatulence uncommon: nausea, vomiting&lt;sup&gt;15&lt;/sup&gt;</td>
<td>US: approved since October 2015 EU: approved since July 2017 CH: under review</td>
</tr>
<tr>
<td>Sodium zirconium cyclosilicate, ZS-9</td>
<td>Na⁺</td>
<td>1 – 6 hours&lt;sup&gt;1&lt;/sup&gt;</td>
<td>unclear, 4 – 12 hours&lt;sup&gt;1&lt;/sup&gt;</td>
<td>powder, 5/10/15 g in 240mL water&lt;sup&gt;1&lt;/sup&gt;</td>
<td>subacute: 3 x daily with meal&lt;sup&gt;1&lt;/sup&gt; chronic: 1 x daily with meal&lt;sup&gt;1&lt;/sup&gt;</td>
<td>subacute or chronic&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ZS-002: Phase II (2/4d) ZS-003: Phase III (3w)&lt;sup&gt;9&lt;/sup&gt; ZS-004: HARMONIZE (4w)&lt;sup&gt;10&lt;/sup&gt; ZS-005: long-term (52w)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>hypertension, peripheral edema, urinary tract infection, nausea, constipation, anemia, upper respiratory tract infection&lt;sup&gt;11&lt;/sup&gt;</td>
<td>US: under review EU: under review</td>
</tr>
</tbody>
</table>

Conclusions

• Hyperkalemia is consistently associated with mortality across a wide range of clinical situations
• Other factors modulate the „cardiac toxicity“ of hyperkalemia and there is no threshold for mortality risk
• Apart from its direct potentially fatal consequences, hyperkalemia is often responsible for underprescription of RAASi
Thank you for your attention

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Physiological role of K⁺

intracellular
- Cell volume
- pH
- Enzymatic functions

extracellular
- Resting membrane potential
  → Neuromuscular function
  → Cardiac rhythm
  → Vascular tone
Mechanisms leading to hyperkalemia

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  - Nutrition
  - Potassium supplements

- **Potassium redistribution**
  - Acidosis
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  - Drugs
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