Potassium metabolism and (mis)adventures in acquired hypokalemia

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Rules about K\(^+\)-Balance

Daily intake (EU): 50-120 mmol/24 h
(Kykuyu in Africa 3 times that much)

The mechanisms (‘of defense’) for K homeostasis:

**Cellular movements**

**Renal excretion** (regulates ~90% Urine)

A direct “feed forward” mechanism for immediate renal elimination is discussed but imperfectly defined.

**GI losses** (weak and regulates about ~10% Feces, can be more in ESRD)
Powers responsible for K disposition
(Meds, Hormones, [H], Osmolarity, Cell destruction)

Physiological:
- Na-K-ATPase
- Catecholamines - α und β agonists
- Insulin
- Plasma K+
- Bodily activity

Pathological:
- Meds
- Chronic illness
- Extracellular pH-[H]
- Hyperosmolality
- Cell destruction

Cell membrane
4 mmol/l
ECF total 70 mmol

140 mmol/l
ICF 3700 mmol
Renal K\(^+\)-regulation

**Filtration**

(\(~800\) mmol/24 h)

**Reabsorption**

(PT)

(LOH)

100%

10%

**Secretion**

(CCD)

\(~20-180\%\)

**Reabsorption**

(MCD)

**EXCRETION**

(~100 mmol/d)

Low K ~2%; <20 mmol/24 h

High K ~10-150%; >200 mmol/24 h

FEK about 10%
Cortical collecting duct (CCD)

Na$^+$

Amiloride

3Na$^+$

ENaC

2K$^+$

ROMK

Chief cell (CCD)

-70mV

Lumen (-ve p.d.)

Barium

Blood

K$^+$

Ouabain (yellow oleander)

Barium
Transcellular movement

2% total body K⁺ in ECF

= ~65 mmol/l (= 2 „Curry“ sausages or 1 Big Mac!)

Therefore, we need very fast protection against hyperkalemia:

- **Insulin** (Na⁺,K⁺-ATPase/Na⁺-H⁺) – increases after chow!

(*Insulin is as important for K⁺-Homeostasis as it is for blood sugar regulation.*

- **Sympathics** - β₂ (+Intake) vs. α (-Brake)
Regulation of K-transcellular movement

- **Blocked:** Ouabain
- **Activated:** Aldo, TSH

**Osmole**

**Acid-Base**

**NHE**

**Insulin receptor**

**ATPase**

**Insulin**

**Phosphodiesterase**

**3′-5′ cAMP**

**β2-AR**

**Adrenalin etc.**

**5′ AMP**

**Theophylline/caffeine I**

**5′ AMP**
Resting potential is also influenced by Na, Ca, Phos, and other products.
Hypokalemia because of Cell-shifts

• Alkalosis – not much

• Barium (carbonate, not sulfate) poisoning – Inhibits K inward rectifier current and causes hypokalemia from intracellular shifts. There are hundreds of cases in the literature. Chloroquin does this too.

• Rapid cell recovery (or growth) – Anabolism (e.g. PA/B₁₂, Post-DKA)

• Hypokalemic periodic paralysis – loss-of-function mutations on skeletal muscle K, Na, or Ca channels CACNA1S, SCN4A, KCNE3. Patients (oriental) with hyperthyroidism. These patients do NOT have an acid-base disturbance. Provoked by carbohydrate meals.
41 year-old Scot visits Berlin and while watching a soccer match develops palpitations, tachycardia, and profound weakness.

In ER BP 154/65 mm Hg, RR 20/min, HR irregular at 100/min. Na 140, Cl 111, K 1.6 (all mmol/L).

ABGs pH 7.43, PaCO₂ 35 mm Hg, PaO₂ 98 mm Hg, HCO₃ 24 mmol/L

labs revealed TSH <0.030, T3 391.1, Free T3 17.42 and Free T4 4.24.

Hypokalemic thyrotoxic periodic paralysis (TPP)

Note that no acid-base disturbances are present!

Kettritz, Luft, Kidney Int 2011
42 year-old woman with “panic attacks” over weeks. BP was always normal. Serum creatinine was 3 mg/dl; K was commonly <3 mmol/l

- She denied nausea, vomiting, diarrhea, medications etc.
- As a „Teenager“ she was once sent to a diet camp and lost 15 kg.
- She smoked like a chimney and admitted to occasionally enjoying one drink too many.
- She was enthusiastic about a “grape fruit” diet and ate about >30 grapefruits and lemons per week.
- Vital signs (volume status), examination (including backs of her teeth) was all normal.
Armed with this information, my next step would be:

1. NKCC, ROMK, Cl-channel, and Barttin mutations by sequencing
2. Arterial blood gases
3. K, Na, Cl, and creatinine in urine
4. Renin and aldosterone
5. Transtubular K-gradient

*If potassium is low or high (does not matter) always order ABGs*
What is the next step?

• pH 7.59, PaCO\textsubscript{2} 30 mm Hg, PaO\textsubscript{2} 100 mm Hg, HCO\textsubscript{3} 29 mmol/l
• Na 141, K 2.9, Cl 94, Ca 2.3, Mg 0.9 und Phos 1.4 (all mmol/l)
• Does TTKG = [Ku/(Uosm/Sosm)]/Ks help in patients with hypokalemia?
• I do TTKG with Hyperkalemia and hypokalemia, although I admit Urine-K is probably adequate

Always check and document A-B balance first!!!!!!!!!!!!
Extrarenal (GI) $K^+$ losses

- Urine-$K^+$ $< 20$ mmoles/day ($U_K/U_{Cr} < 2$)

- Diarrhea most common - GI $K^+$ losses

- Vomiting-associated Hypokalemia occurs via renal losses renal $K^+$ losses

Ogilvie Syndrome
(terminal flatulence)
Extrarenal K losses?

• Vasoactive intestinal Peptide (VIP) inhibits acid and could lead to watery diarrhea. Villous adenoma could cause a similar syndrome.

• Infectious and secretory diarrhea?

• Ogilvie Syndrome – secretory diarrhea, active K secretion (fecal K >100 mmol/l)

• Ureteral Diversion

• Acquired Chloridorrhea? “Down-regulated in adenoma” (*SLC26A3*; *DRA*) Cl-HCO₃ exchanger is the gene product

• Laxative abuse!
You may have ordered 24-h electrolyte excretion in this patient (24-h),

- UNaV 200 mmol
- UKV 97 mmol
- UCIV 97 mmol
- UCaV 0.45 mmol
- UMgV 4.6 mmol
- UPhosV 19 mmol
- UoxalateV 57 mg

Sodium excretion is high, chloride excretion does not fit.
Why was the creatinine level 3 mg/dl??

The von Kossa stain for calcium (and probably phosphate) shows crystals.
Renal $K^+$ -Loss

Diagnosis
- Urine-$K^+$ Excretion $>20$ mmol/24 h ($U_K/U_{Cr} >10$), FEK$>10$
- no Diarrhea

(not to forget laxative abuse!)

Primary $\uparrow$ Mineralocorticolism$^*$

versus

Primary $\uparrow$ distal-$Na^+$ delivery

(*ECV expansion)
(*BP increases)

(With chronic hypokalemia $K <2$ mmol/L, represents a loss of $\sim500$ mmol)
A primary increase in the distal Na\(^+\) delivery

- Diuretics, working proximal of the distal collecting duct
  -(Loop and Thiazides)

- Nonreabsorbable Anions (Vomiting/NG-Suction/Hippurates – Glue-sniffers)

- Mg\(^{2+}\)-deficiency (interferes with Na\(^+\) ‘Pump’ /inhibits ROMK )

- Bartter Syndrome

- Gitelman Syndrome

- Acidosis
Let's take another look at this urine!

- UNaV 200, UKV 97, UCIV 97
- Urine “anion gap“ = 200+97 - 97 = +200!
- 200 mmol Na disappear with some sort of unknown anion in our patient.
- What could this anion be?
- We measured the urine pH (7.9); the urine culture was negative

This crazy urine anion gap! Is it really good for something?
Wie did some very direct questioning (but no “water boarding”)

3000 mmol Na and HCO$_3^-$ per box

She was not using this stuff to clean the toilet!
Does hypokalemic nephropathy exist?


• Schwedler SB, Gröne EF, Luft FC. Chronic hypokalaemia and nephrocalcinosis. NDT-Plus 2009

• I actually am a non-believer, but Saban Elitok and I had a recent patient (Clin Kidney J 2016) that fits this rubric.
Patient #3  Does chronic hypokalemia cause CKD?

58 year-old woman from a wealthy middle-eastern country is referred because of “pain all over”. She was a frail, cachectic-looking woman. She was anemic (Hb 8.2 g/dl), Na 138, K 2.9, Ca 2.4, Phos 0.4 (all mmol/L). 25-OH vitamin D3 was low, PTH was normal, eGFR (cystatin C) 15 ml/min. pH 7.29, PaCO₂ 31, PaO₂ 75, HCO₃ 14 mmol/L.

24 H Urine Na 48, K 14, Phos 0.7 mmol/L.

Complete GI workup was “negative” with the exception of:

*Melanosis coli* are lipofuscin deposits from a laxative

“hypokalemic nephropathy” from “starvation”. Note the droplets in the tubular cells!
28 year-old man admitted because of severe chest and abdominal pain

- Ten days earlier he was treated for a „tooth abscess“
- He was given ibuprofen and took more than >5 g/day
- 48 h earlier, vomiting began.
- BP 100/70 mm Hg, HR 100/min; he was not able to stand
- Na 124, Cl 63, K 2.9, HCO$_3$ 41, Lactate 5 mmol/l
- Creatinine 674 µmol/l
His chest x-ray looked peculiar, so we ordered a CT. Shown is a high cut about apex level.
The CT is consistent with:

1. Boerhaave Syndrome
2. Pneumatodes intestinalis
3. Right-sided esophageal rupture
4. Mediastinal gas gangrene
5. *Echinococcus* cysts
The patient has severe metabolic alkalosis (renal K losses)

- Shock, metabolic alkalosis, renal failure, high lactate; so he also has concomitant metabolic acidosis
- Anion gap \([124 - (63+41)] = 20 \text{ mmol/l!}\)
- From the data given, can you reconstruct his ABGs
- How do his kidneys adjust to these problems?
- What should we do about his esophagus?
We can reconstruct his blood gases!

- \([H] = 24 \times \text{PaCO}_2/\text{HCO}_3\) (Henderson) ie
  - Compensated metabolic alkalosis 0.7 mm Hg per mmol increase in \(\text{HCO}_3\) (24 to 41 mmol/l; 17 mmol/l); so we would expect \(\text{PaCO}_2\) of 50 mm Hg
- \([H] = (24 \times 50)/41 = 29\) nmol/l; ie pH 7.51
- The values should be: pH 7.51, \(\text{PaCO}_2\) 50 mm Hg, \(\text{HCO}_3\) 41, Na 124, Cl 63, K 2.9, AG 20 mmol/l (and so they were!)
- Compensated metabolic alkalosis with a minor metabolic acidosis

\[
H = \frac{\text{PCO}_2}{\text{HCO}_3}
\]
Na 124, Cl 63, K 2.9, \(\text{HCO}_3\) 41, Lactate 5 mmol/l
**Na, K, and Cl = Dietary intake**

Filtered

- **Na**: 25
- **HCO₃⁻**: 25

- **Na**: 66
- **Cl**: 66

Filtered

- **Na**: 140
- **HCO₃⁻**: 104
- **Cl**: 25
- **K**: 4

Filtered

- **Na**: 47
- **HCO₃⁻**: 53
- **Cl**: 3

Filtered

- **Na**: 124
- **HCO₃⁻**: 63
- **Cl**: 2.7
- **K**: 4

UNa 9 mmol/l

UK 29

UCl 3

Cl = 3
What to do for this patient?

1. Thoracic surgeons

2. 4 L, 0.9% saline + 20 mmol/l KCl over 8 hours

3. 4 L, balanced electrolyte solution (Ionosteril) + 20 mmol KCl over 8 hours

4. Ceftriaxone

5. “Chest Tube” Drainage
Hypokalemia

Algorithm

$U_K \uparrow$ or $\downarrow$

<20 mmol/24 h ($U_K/U_{Cr} < 2$)

- GI - Diarrhoea

$\uparrow$

- Renin, Aldosterone

- RAAS
- Conn/adrenal Hyperplasia
- GRA
- Cushing‘s
- AME
- Liddle‘s

$\downarrow$

>20 mmol/24 h ($UK/U_{Cr} > 10$)

- BP, ECV

$\downarrow/\Rightarrow$

- ABG-Plasma [$HCO_3^-$]

$\downarrow$

- RTA

$\Rightarrow$

- Urine [$Cl^-$]

- Diuretics
- Mg$^{2+}$-deficiency
- Bartter‘s
- Gitelman’s

- Gastric vomiting
- NR Anion
How should this patient be treated?

- Boerhaave Syndrome >48 h, not septic, no effusion
- Esophagoscopy was done; no tear was seen, which is not uncommon
- Nasogastric tube, antibiotics (anaerobic coverage)
- After 8 h and saline infusion, pH 7.41, PaCO$_2$ 45, HCO$_3$ 28, creatinine 435 µmol/l
- He recovered rapidly and left us
Patient #5  Nonneurological tetraplegia

A 56-year-old patient was brought to our emergency department with profound weakness of his limbs to the point that he was unable to get up from a couch unassisted. A day earlier, he had been discharged from a neurology service where he had been because of similar complaints. An 8-day workup including computed tomography and magnetic resonance imaging of the head and spinal column, blood work, and lumbar puncture had not proved helpful. An electromyogram disclosed changes consistent with sensory motor demyelinizing polyneuropathy. A nutritional cause for the symptoms was presumed, and with thiamine administration and 8 days of hospital food, there was some improvement. Serum electrolyte levels were not evaluated.

<table>
<thead>
<tr>
<th>Sodium</th>
<th>145 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride</td>
<td>111 mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.5 mmol/l</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.44 mmol/l</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.86 mmol/l</td>
</tr>
<tr>
<td>Urine pH</td>
<td>7.0</td>
</tr>
<tr>
<td>Urine glucose</td>
<td>Negative</td>
</tr>
</tbody>
</table>

pH 7.39
PaCO₂ 24 mm Hg
PaO₂ 92 mm Hg
HCO₃ 14 mmol/L

Alcoholic-associated RTA
Kidney Int 2016
N Engl J Med 1993

Thank you for listening!