Potassium metabolism and (mis)adventures

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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:

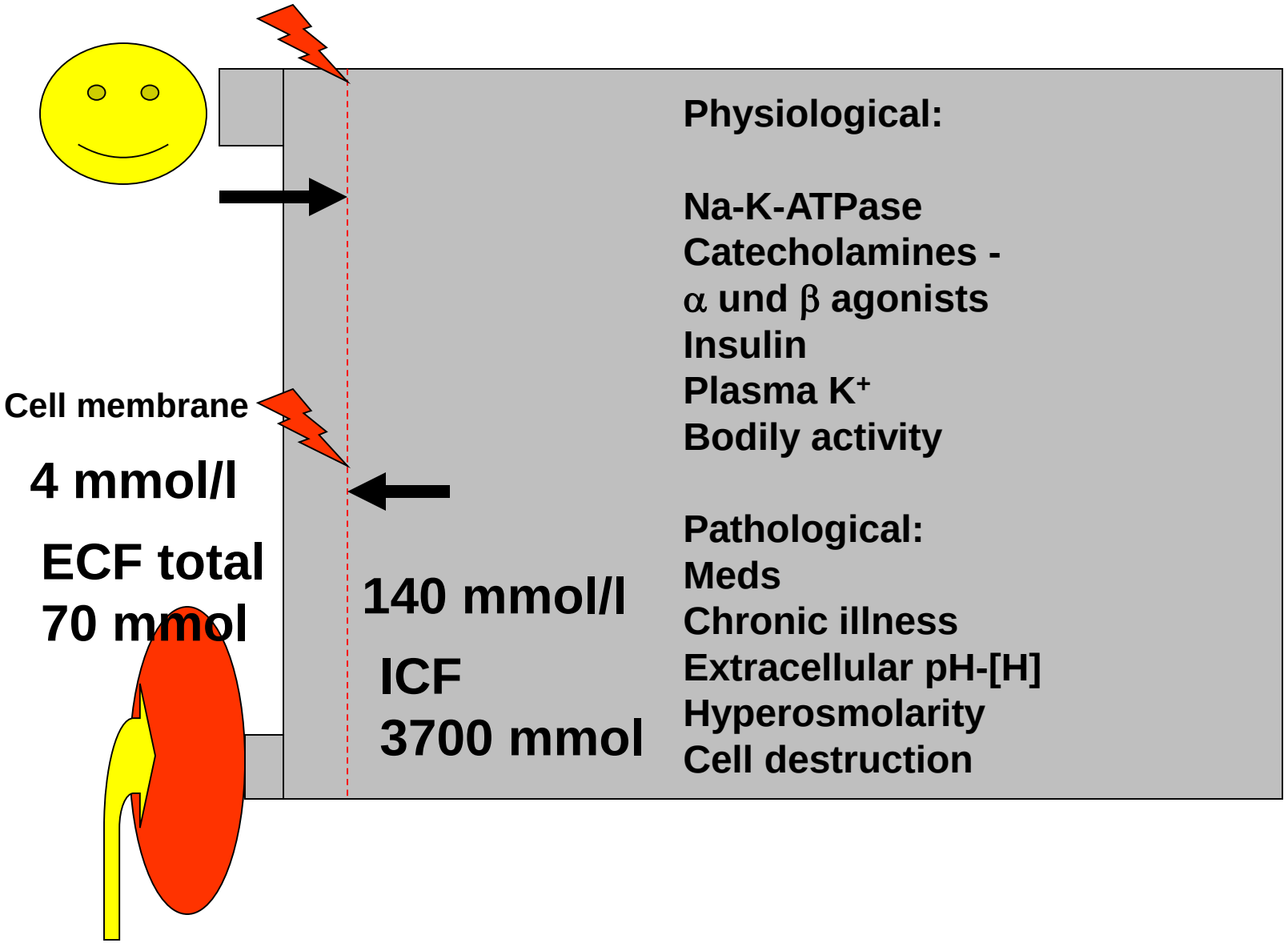
Cellular movements

Renal excretion (regulates ~90% Urine)

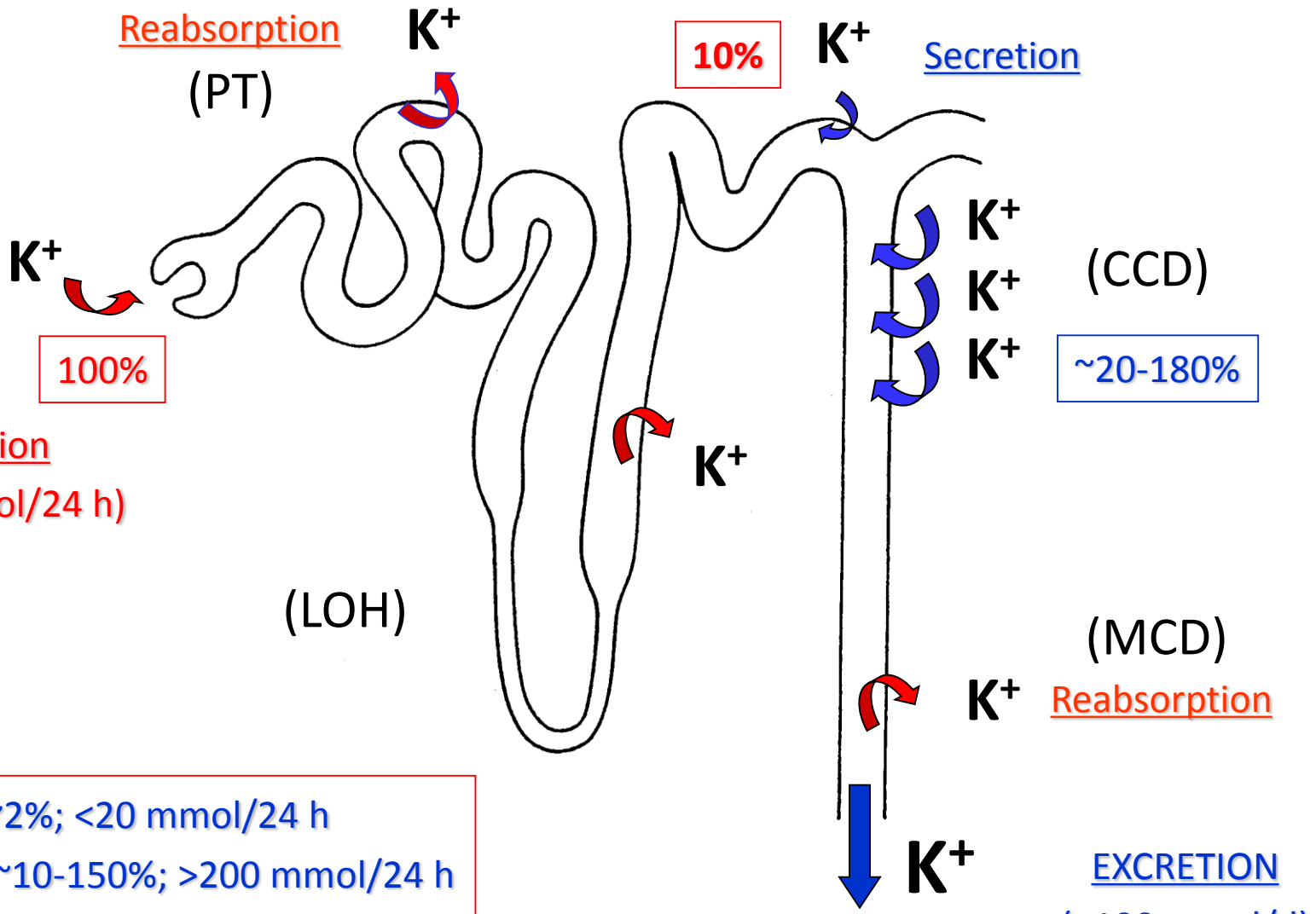
A direct “feed forward” mechanism for immediate renal elimination is discussed but imperfectly defined.

GI losses (weak and regulates about ~10% Feces, can be more in ESRD)

Powers responsible for K disposition (Meds, Hormones, [H], Osmolarity, Cell destruction)



Renal K^+-regulation (capacity is great)



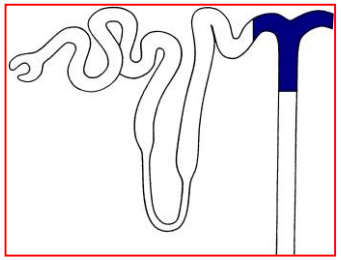
Low K ~2%; <20 mmol/24 h

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

FEK about 10%

Cortical collecting duct (CCD)

Dependent upon sodium delivery



Transcellular movement

2% total body K^+ in ECF

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

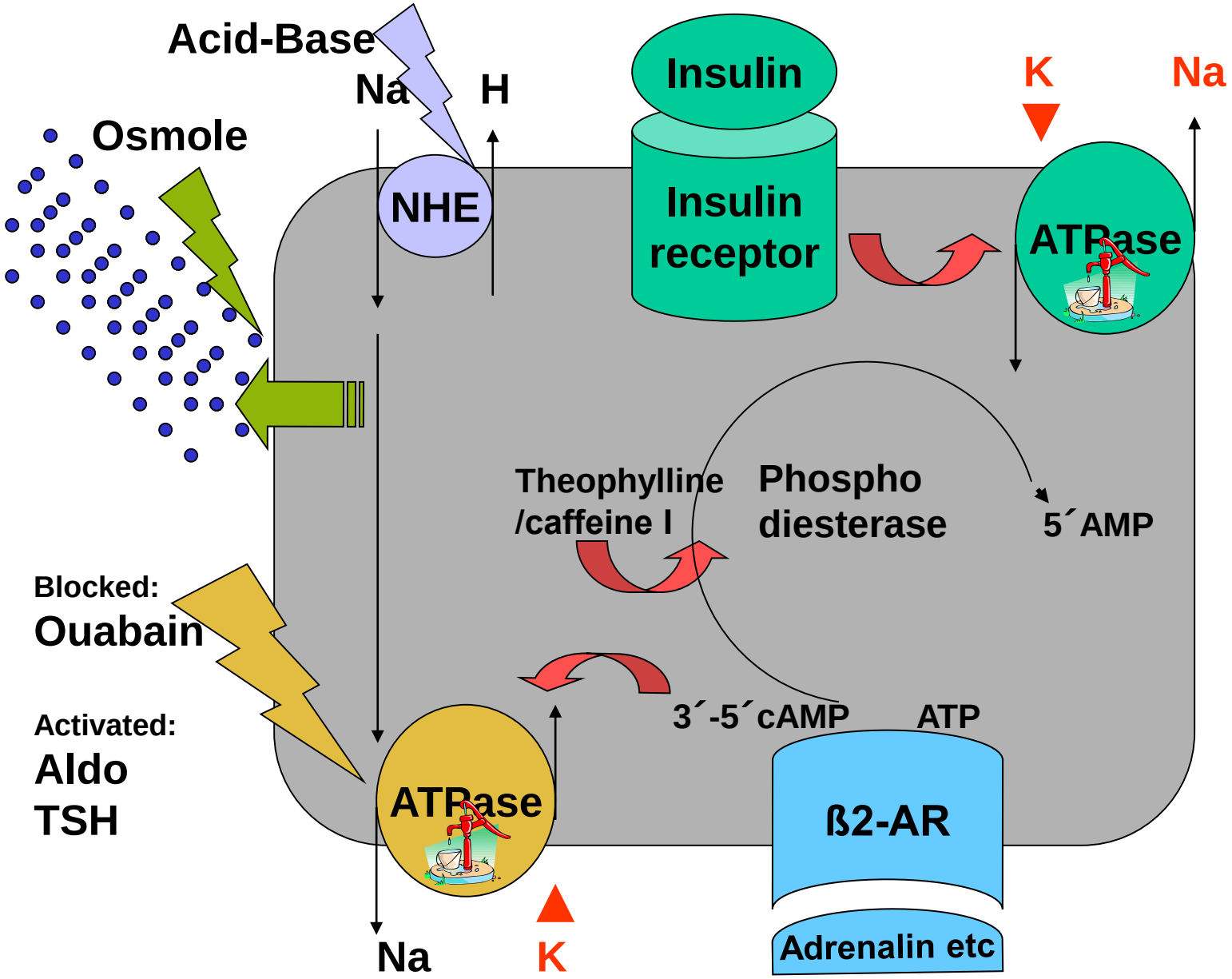
Therefore, we need very fast protection against hyperkalemia:

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

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

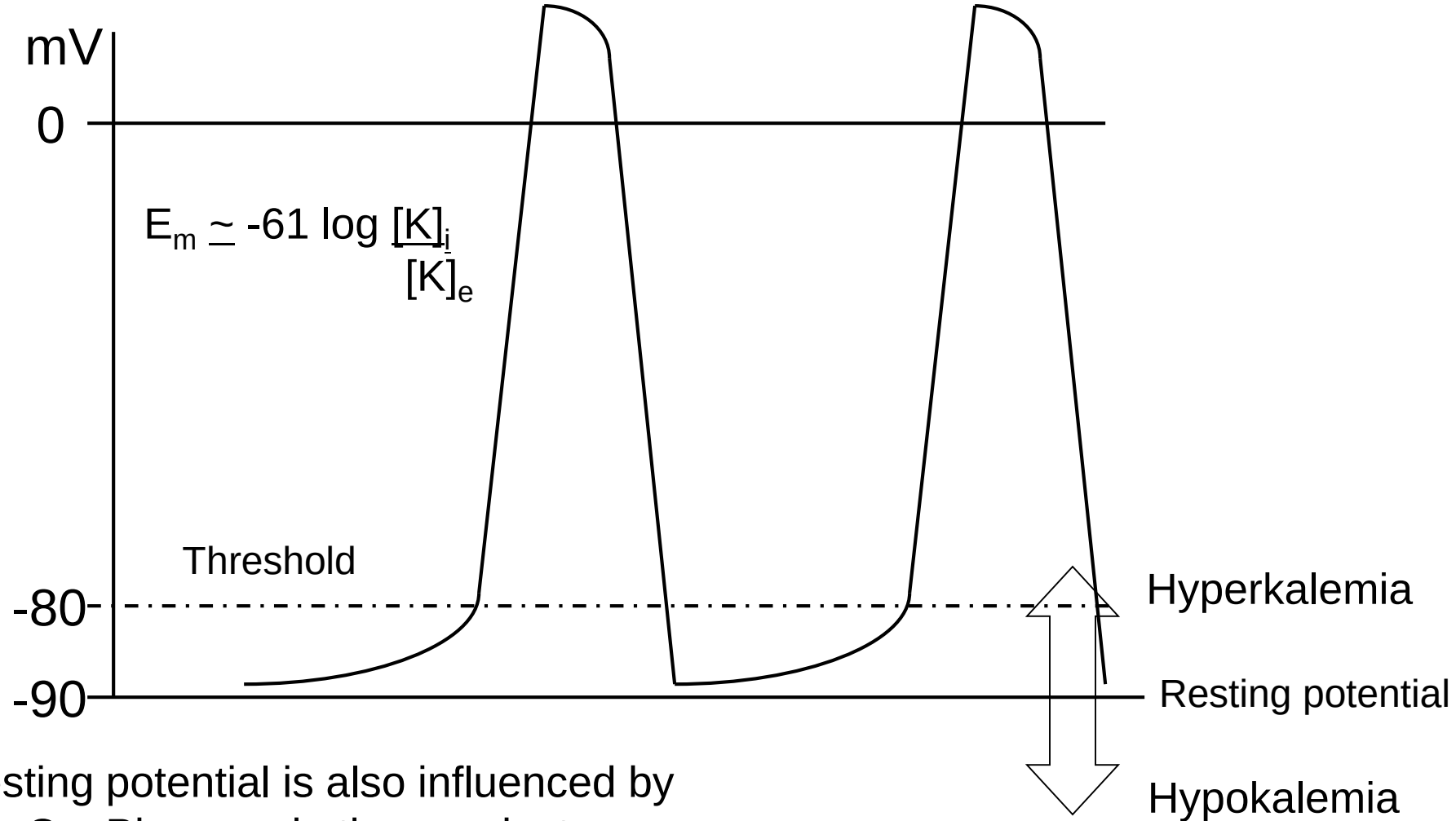
- **Sympathics** - β_2 (+**Intake**) *vs.* α (-**Brake**)

Regulation of K-transcellular movement



SA-node (a gross oversimplification)

$$E_m = -61 \log \frac{r[K]_i + 0.01\,[Na]_i}{r[K]_e + 0.01\,[Na]_e}$$

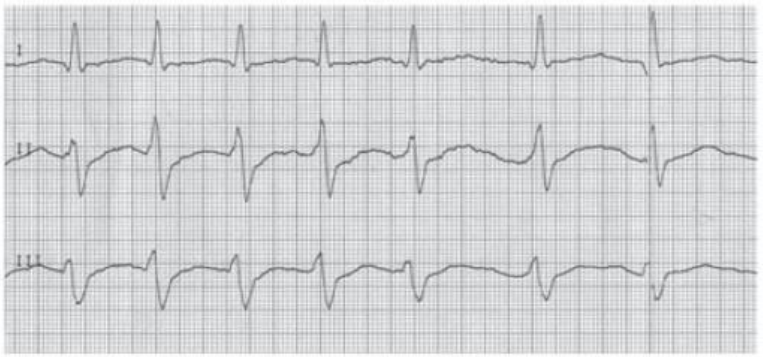


Resting potential is also influenced by
Na, Ca, Phos, and other products

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/B_{12}, 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.

Patient #1



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, $PaCO_2$ 35 mm Hg, PaO_2 98 mm Hg, HCO_3 24 mmol/L

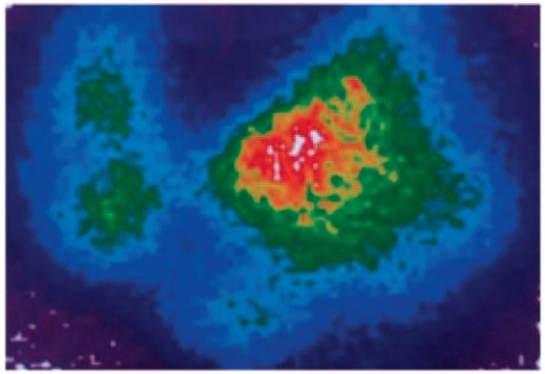


Figure 2 | Tc99 scintigraphy shows an active nodule in the left upper lobe of the thyroid gland.

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

Patient #2

A case of weakness, anemia, and dry eyes

30 year old lady reports feeling poorly and having
lost 7 kg in weight. She also has observed a dry mouth
and her physician reported the presence of anemia.
She denied joint pains, skin rash, or Raynaud phenomenon

Physical examination showed rhagades at the mouth angles.
The Schirmer test was positive. Laboratory disclosed anemia,
Rheumatoid factor present, total protein 98 g/l with globulin fraction 40 g/l.
Sediment: granular casts, 35 erys, 26 leukos, Pr 1.2 g/24 h.

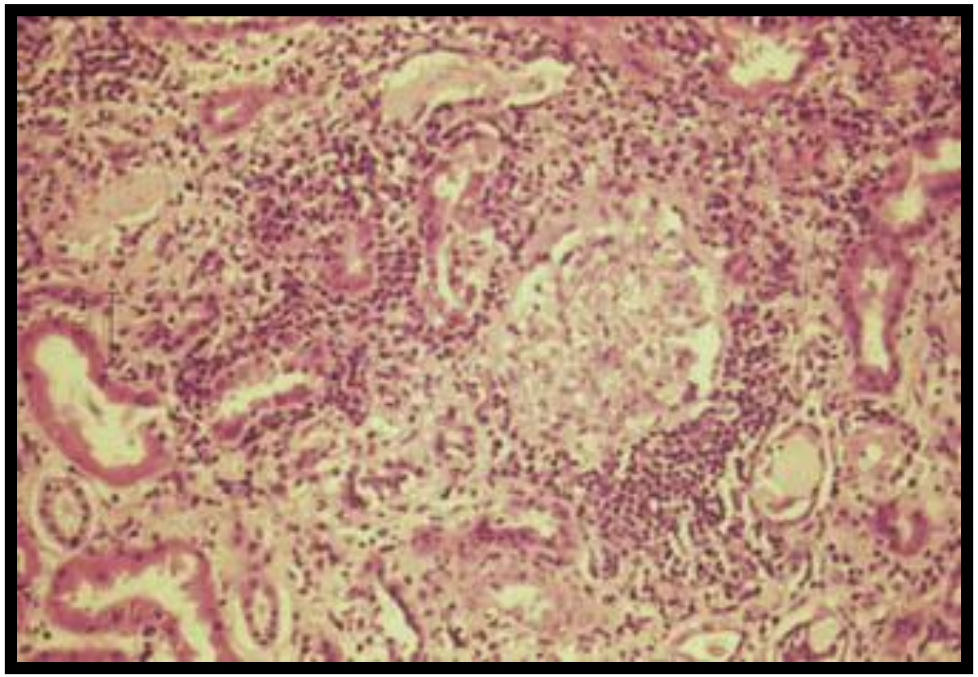
Creatinine clearance 48 ml/min, ANA 1:2560, UNa 43 mmol/l
UK 35 mmol/l, UCl 42 mmol/l. The citrate excretion was reduced.

pH 7.36, $PaCO_2$ 24 mm Hg, PaO_2 110 mmHg

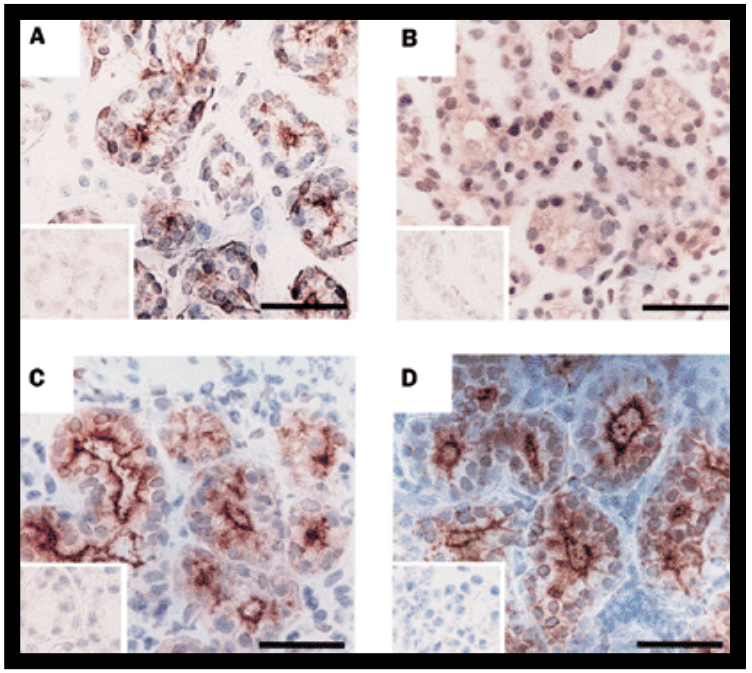
HCO_3 14 mmol/l, Na 139, K 2.7, Cl 115 mmol/l

What is the diagnosis here and why do these poor patients have dry eyes?

Renal biopsy, our patient



A=normal, B=Sjörgren´s
C=non-Sjörgren´s, D=Mikulicz´s



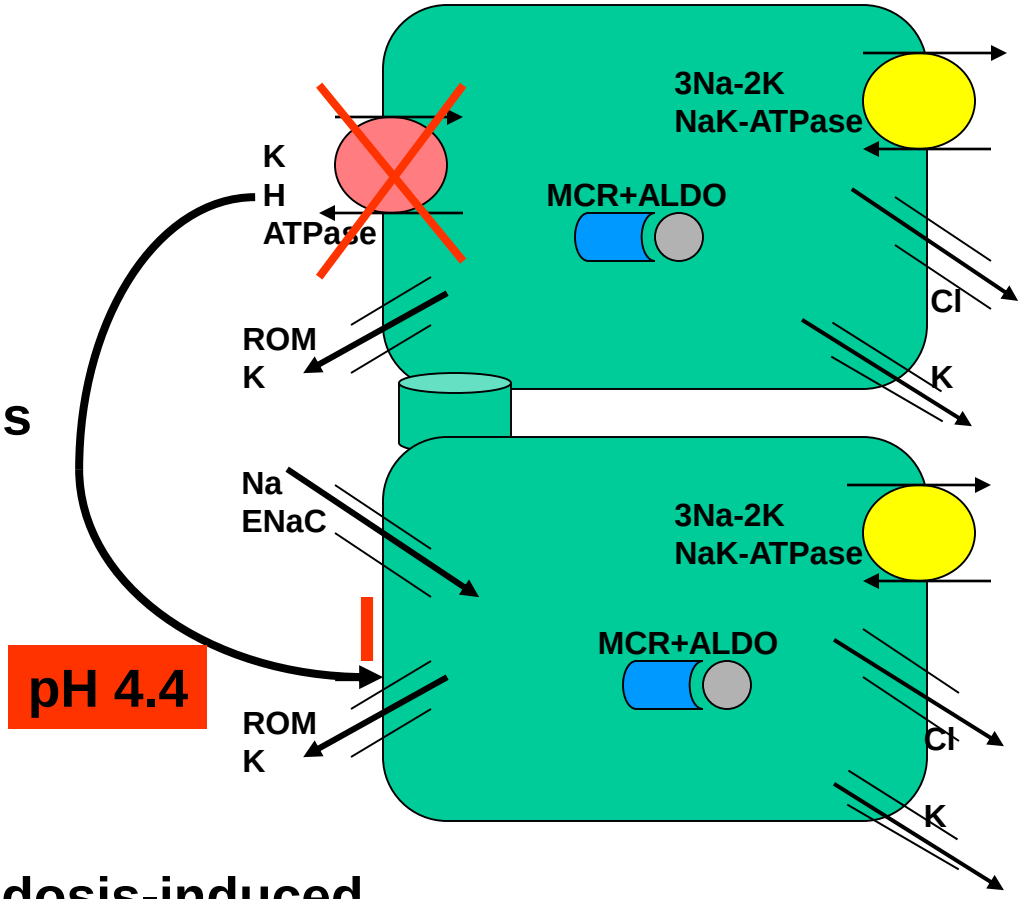
Massive interstitial infiltration;
She cannot place AQP5 into the apical surface of certain glands

Tsubota K et al.
Lancet 2001; 357: 688

Distal RTA, defect in K-H ATPase transporter or increased permeability of tubule to H (This condition is not too important either)

The features of classical RTA

1. **Narrow-gap metabolic acidosis**
2. **Urine pH >5.5 in face of acidosis**
3. **HYPO-kalemia**
4. **Nephrocalcinosis & stones**



Nephrocalcinosis is related to acidosis-induced hypercalciuria and decreased citrate excretion

Aside from the primary disorder, what to do for this patient?

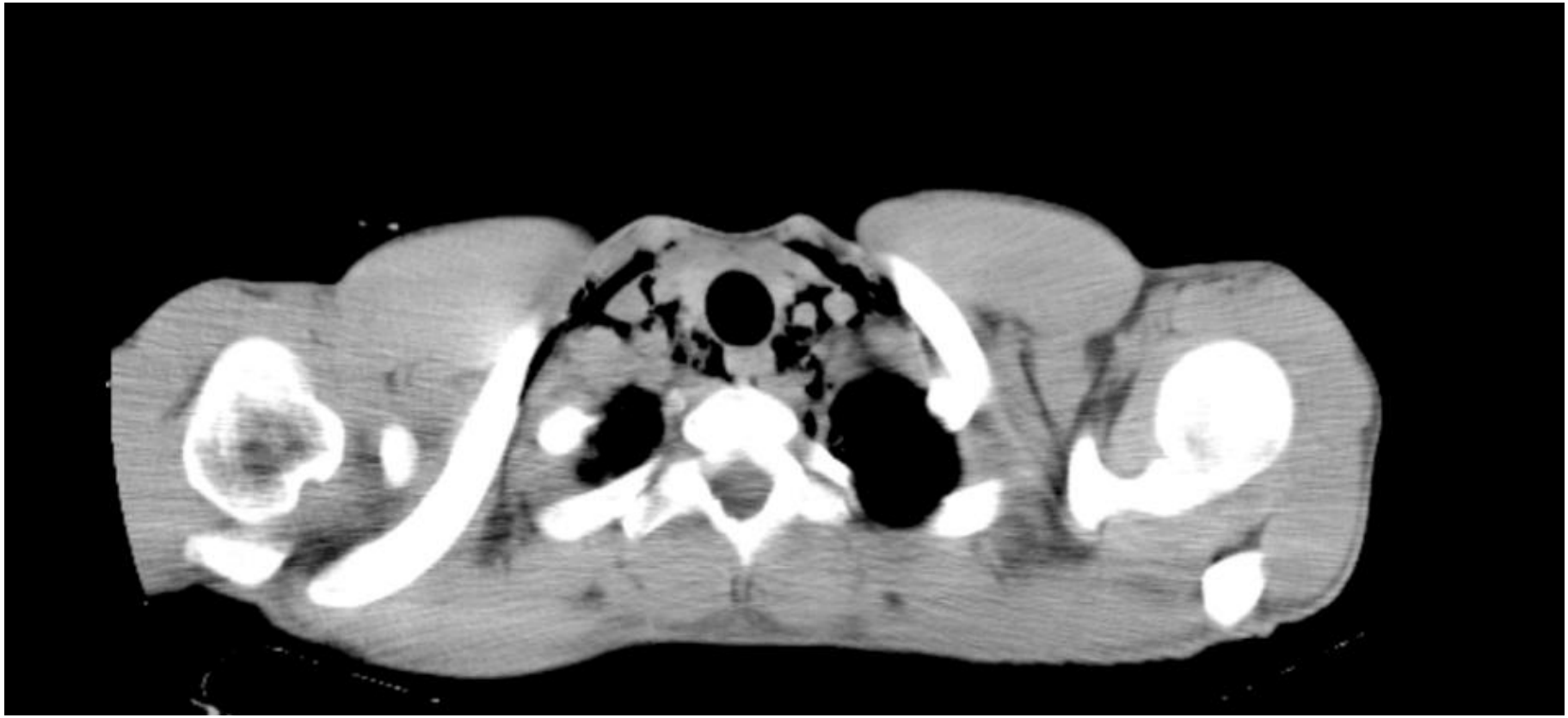
1. Potassium chloride tablets
2. Potassium citrate tablets (Kalinor Brause)
3. 4 L, balanced electrolyte solution (Ionosteril) + 20 mmol KCl over 8 hours
4. Bicarbonate tablets
5. Hydrochlorothiazide

Patient #3

28 year-old man admitted because of severe chest and abdominal pain

- Ten days earlier he was treated for a „tooth abcess“
- 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
- UNa 9, UCl 3, UK 29 (mmol/L)

His chest xray 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

1668-1738

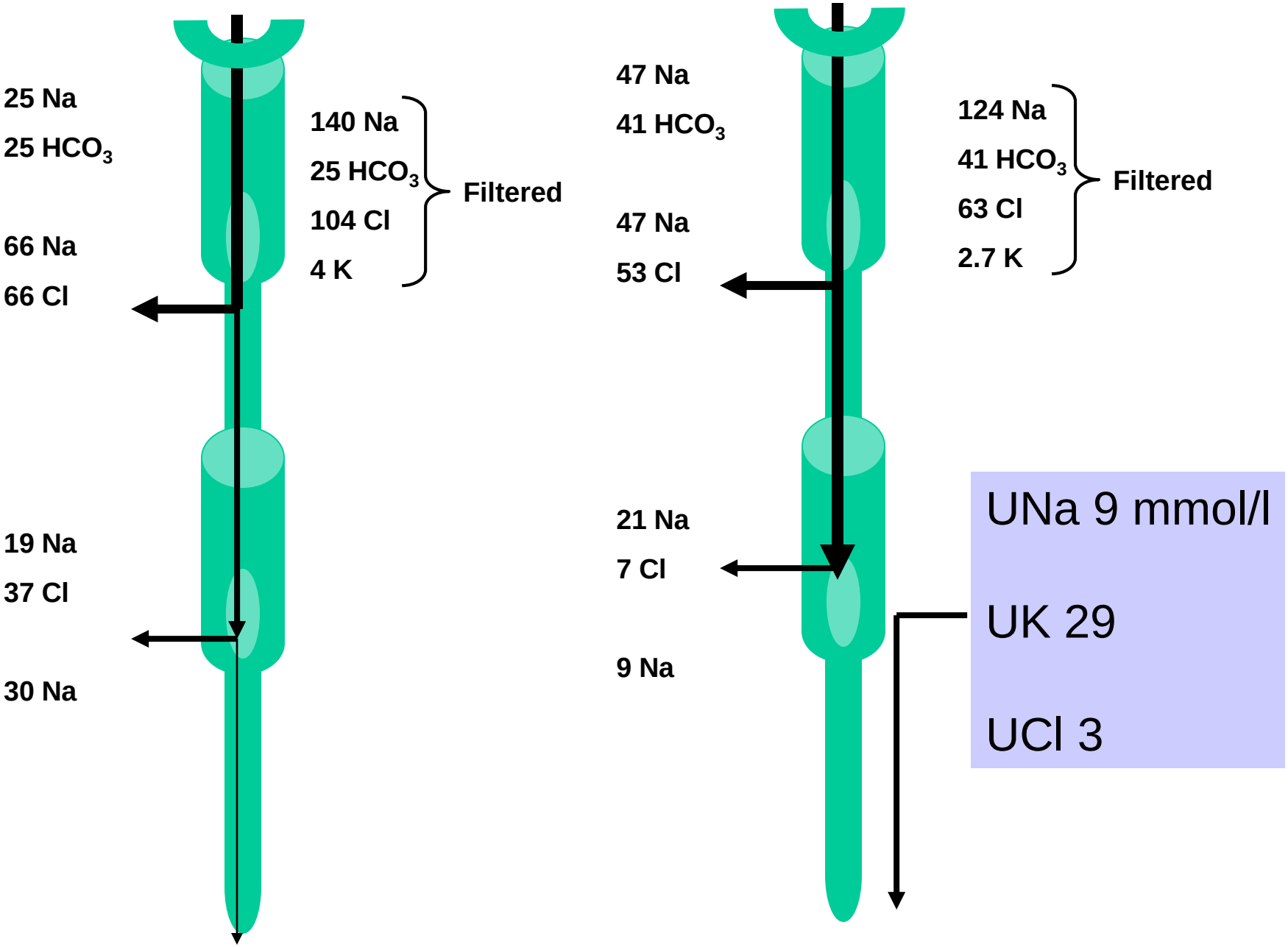
The patient has severe metabolic alkalosis (renal K losses)

- Shock, metabolic alkalosis, renal failure, high lactate; so he also has concomitant metabolic acidosis
- Anion gap [124 - (63+41)] = 20 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 x $PaCO_2/HCO_3$ (Henderson) ie Compensated metabolic alkalosis 0.7 mm Hg per mmol increase in HCO_3 (24 to 41 mmol/l;17 mmol/l); so we would expect $PaCO_2$ of 50 mm Hg
- [H] = (24x50)/41= 29 nmol/l; ie pH 7.51
- The values should be: pH 7.51, $PaCO_2$ 50 mm Hg, 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

$H = PCO_2/HCO_3$
Na 124, Cl 63, K 2.9, HCO_3 41, Lactate 5 mmol/l


25 Na
25 HCO3
66 Na
66 Cl
140 Na
25 HCO3
104 Cl
4 K
Filtered
19 Na
37 Cl
30 Na
Na, K, and Cl = Dietary intake
47 Na
41 HCO3
47 Na
53 Cl
124 Na
41 HCO3
63 Cl
2.7 K
Filtered
21 Na
7 Cl
9 Na
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

How should this patient be treated?

- Boerhaave Syndrome >48 h, not septic, no effusion
- Esophagoscopy was done; no tear was seen, which is not uncommom
- 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

Renal K^+ -Loss

Diagnosis

- Urine-K^+ Excretion >20 mmol/24 h (U_K/U_{Cr} >10), FEK>10%

- no Diarrhea

Secondary ⇑ Mineralocorticolism

Primary ⇑ Mineralocorticolism*

Versus

Secondary ⇑ distal-Na^+ delivery

Primary ⇑ distal-Na^+ delivery

(*ECV expansion)

(*BP increases)

(With chronic hypokalemia K <2 mmol/L, represents a loss of ~500 mmol)

Extrarenal (GI) K^+ losses

- **Urine-K^+ <20 mmoles/day (U_K/U_{Cr} <2)**
- **<u>Diarrhea</u> most common - *GI K^+ losses***
- **<u>Vomiting-associated</u> Hypokalemia occurs via renal losses *renal K^+ losses***

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-HCO_3 exchanger is the gene product
- Laxative abuse!

Secondary and primary increases 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

Does chronic hypokalemic nephropathy exist?

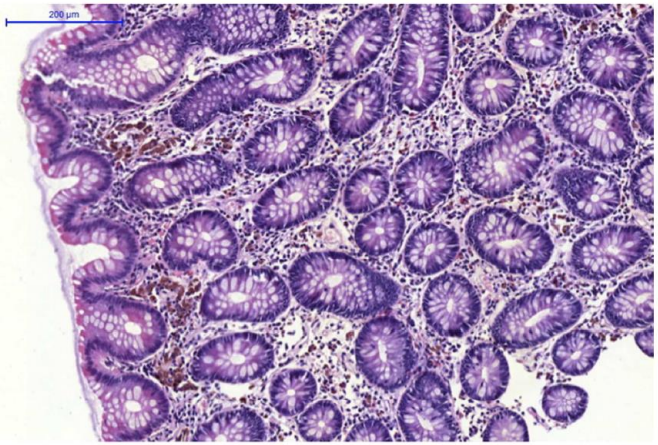
- Bock KD, Cremer W, Werner U. Chronic hypokalemic nephropathy: a clinical study. Klin Wochenschr. 1978;(56 Suppl 1):91-6.
- Riemenschneider T, Bohle A. Morphologic aspects of low-potassium and low-sodium nephropathy. Clin Nephrol. 1983;19:271-9.
- Schwedler SB, Gröne EF, Luft FC. Chronic hypokalaemia 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.

Does chronic hypokalemia cause CKD?

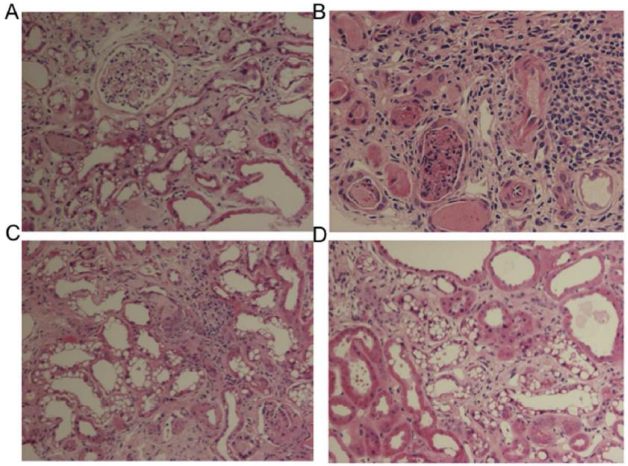
58 year-old woman from a wealthy middle-eastern country is referred because of “pain all over”. She was a frail, cachectic-looking woman.
She was anemic (Hb 8.2 g/dl), Na 138, K 2.9, Ca 2.4, Phos 0.4 (all mmol/L).
25-OH vitamin D3 was low, PTH was normal, eGFR (cystatin C) 15 ml/min.
pH 7.29, $PaCO_2$ 31, PaO_2 75, HCO_3 14 mmol/L.

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

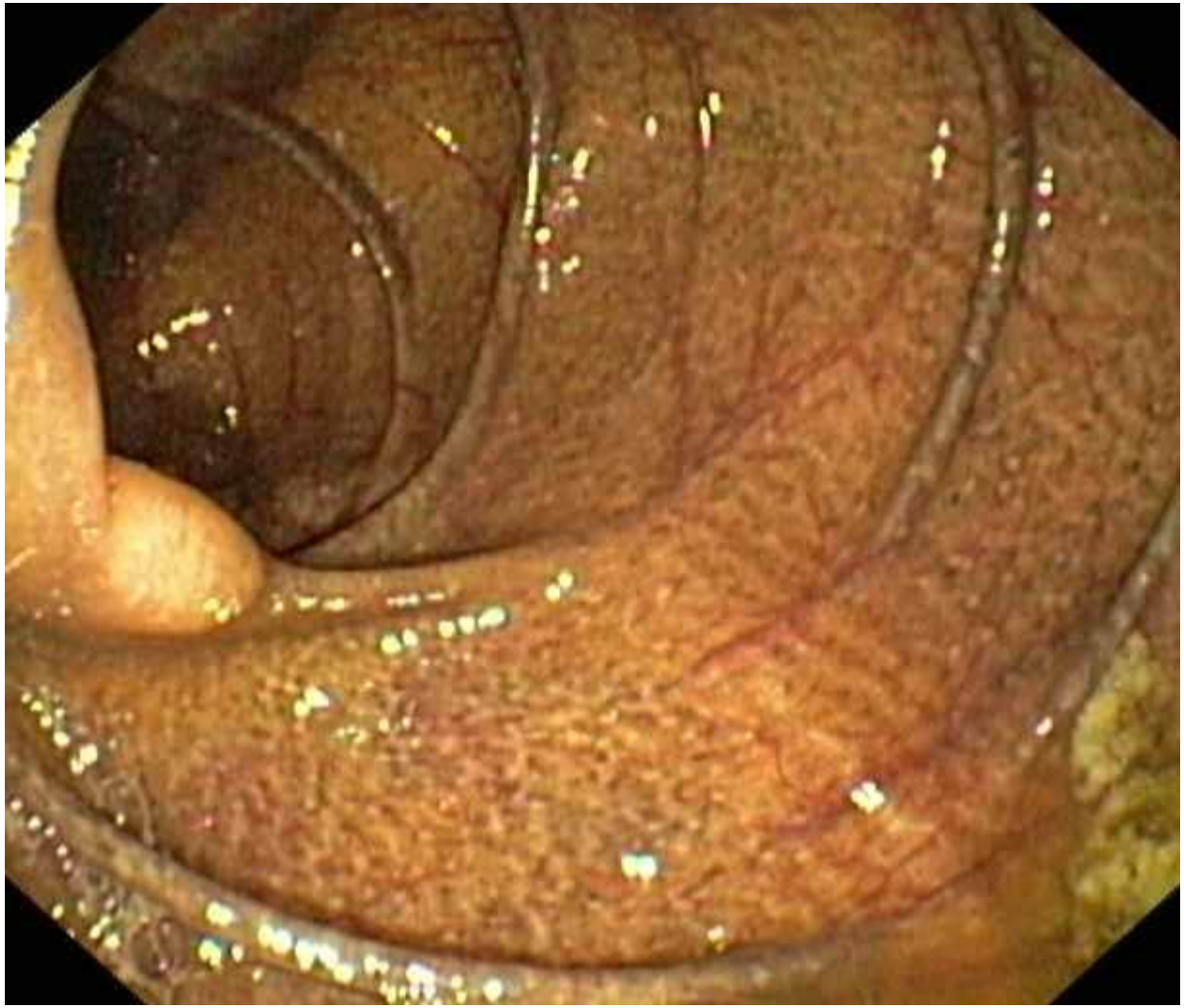
Complete GI workup was “negative” with the exception of:



Melanosis coli are lipofucsin deposits from a laxative



“hypokalemic nephropathy” from “starvation”. Note the droplets in the tubular cells!

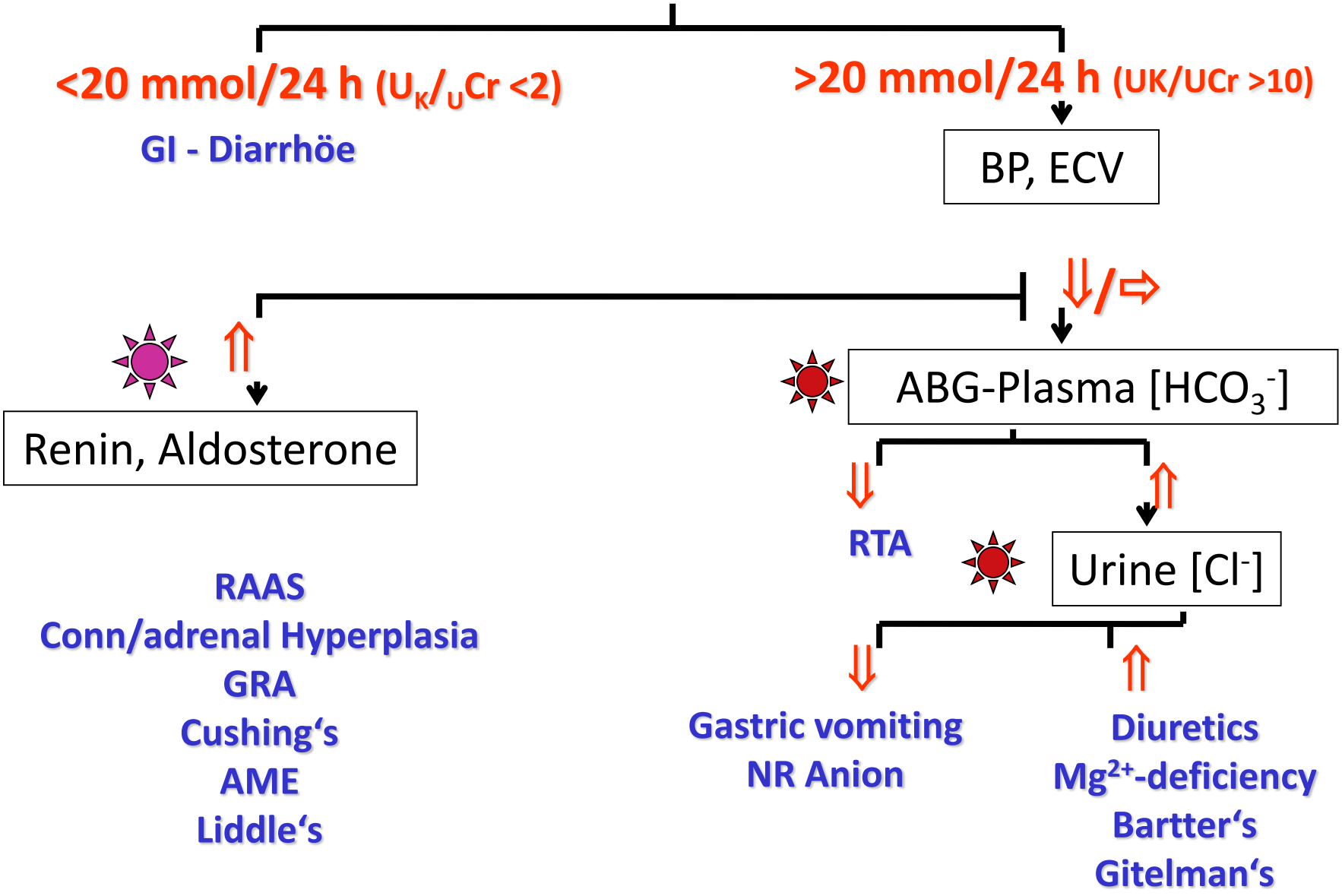


Colonoscopy

Elitok et al. Clin Kidney J 2016

Hypokalemia Algorithm

U_K ⇑ or ⇓



Hyperkalemia?!? In 1969, we did not dialyze persons >40 years and no-one with diabetes mellitus

We had a „God-Squad“ who decided whether or not ESRD patients received dialysis.

Older persons, persons without partners (home dialysis), and diabetics were excluded from dialysis.

I was assigned to care for the „control“ group.

I believe my patients did better than the „dialysis“ group.

I do not recall anyone ever dying from hyperkalemia.

Berlyne GM et al. Dangers of resonium A in the treatment of hyperkalemia in renal failure. Lancet 1966

Hyperkalemia

Medications

RAAS blockade

Inhibition of renin release
Beta blockers, NSAIDs, calcinuerin inhibitors

Inhibition of aldosterone release
Heparins, ketoconazole

MR blockade
Spironolactone, eplerinone, drospirenone

ENaC blockade
Amiloride, triamterene, trimethoprim

K supplements, salt substitutes, herbal remedies

Patient #5

38 year-old dialysis patient is operated upon for a perirectal abcess

Na 138, K 4.9, Cl 103, HCO3 21 (mmol/L)
Creatinine 9 mg/dL

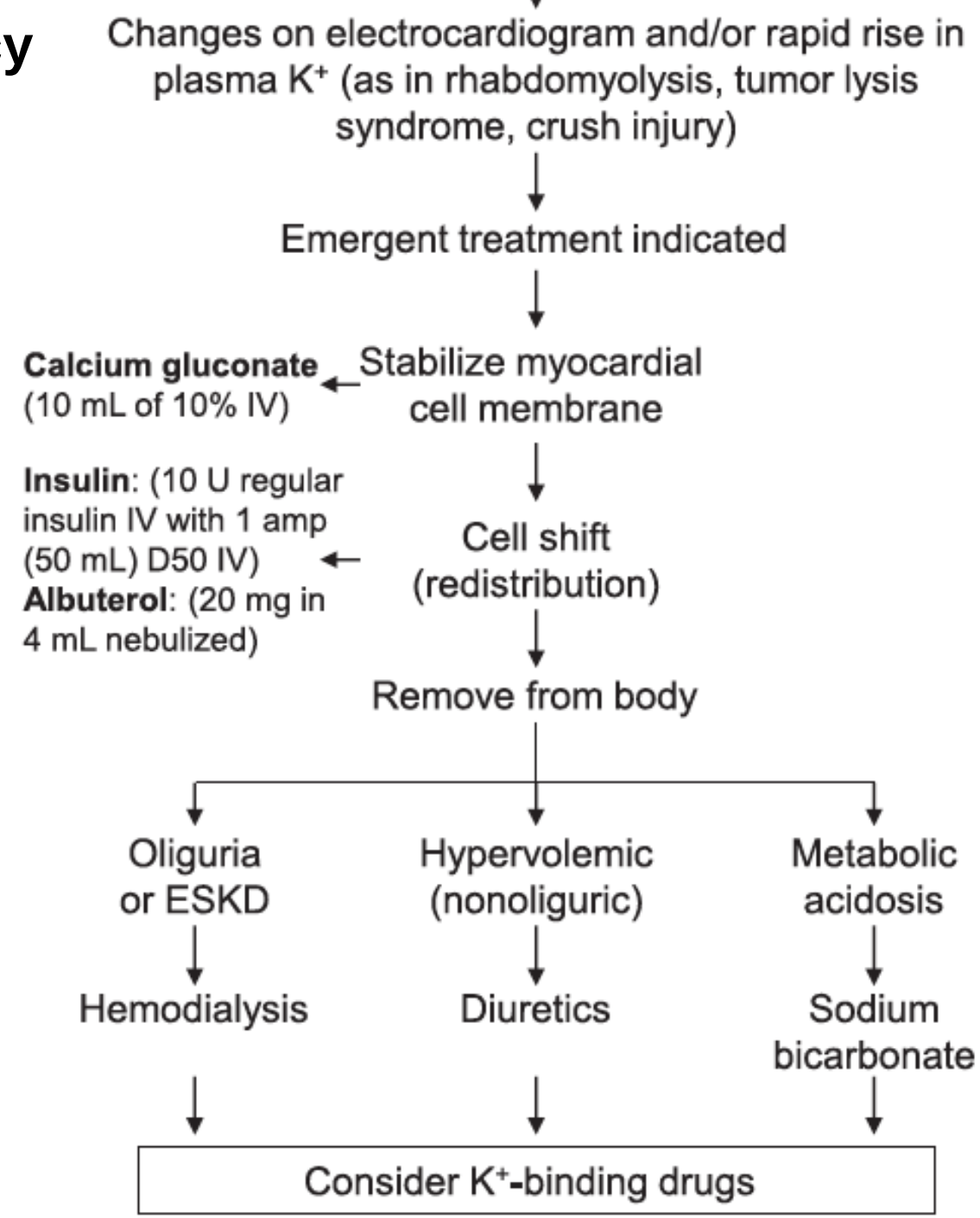
She becomes hypotensive and receives a phenylephrine infusion

In the recovery room, she is too weak to be extubated and her potassium is 7.0 mmol/L

Which of the following explain the acute hyperkalemia?

1. Hypoaldosteronism
2. Metabolic acidosis
3. Beta adrenergic stimulation
4. Alpha adrenergic stimulation
5. Pseudohyperkalemia

Emergency


Changes on electrocardiogram and/or rapid rise in plasma K+ (as in rhabdomyolysis, tumor lysis syndrome, crush injury)
Emergent treatment indicated
Stabilize myocardial cell membrane
Calcium gluconate (10 mL of 10% IV)
Cell shift (redistribution)
Insulin: (10 U regular insulin IV with 1 amp (50 mL) D50 IV)
Albuterol: (20 mg in 4 mL nebulized)
Remove from body
Oliguria or ESKD
Hypervolemic (nonoliguric)
Metabolic acidosis
Hemodialysis
Diuretics
Sodium bicarbonate
Consider K+-binding drugs

Patient #6

55 year-old patient with stage 3 CKD has knee osteoarthritis. He is prescribed ibuprofen. Meds are hydrochlorothiazide, Losartan, metformin, and pravastatin

Vital signs are normal

Exam unchanged

Na, 142, K 5.7, Cl 108, HCO3 18 (mmol/L)
Glucose 230 and creatinine 2.8 (mmol/L)

What should be done about this hyperkalemia?

1. Nothing
2. Switch to furosemide
3. Begin spironolactone
4. Stop ibuprofen
5. Start patiromer

Non-emergency

Dietary K^+ counseling, avoid salt substitutes

↓

Discontinue drugs (if possible) that interfere in kidney K^+ secretion, inquire about use of over-the-counter NSAIDs and herbal preparations

↓

Ensure effective diuretic therapy (loop diuretics with eGFR < 30 mL/min)

↓

Oral $NaHCO_3$ to treat metabolic acidosis

↓

Consider K^+-binding drugs (can facilitate recommended doses of RAASi)*

	Sodium polystyrene sulfonate	Patiromer	Sodium zirconium cyclosilicate
Mechanism of action	Na^+-K^+ exchange resin often given with sorbitol, nonselectively binds K^+, Ca^{2+}, Mg^{2+}	Exchanges Ca^{2+} for K^+, also binds Mg^{2+}	Binds K^+ in exchange for H^+ and Na^+
Time of onset	Variable (hours to days)	7 h	1 h
Binding site	Colon	Colon	Entire intestinal tract
Commonly reported adverse reactions and precautions	Diarrhea, metabolic alkalosis, hypernatremia, volume overload, rarely colonic necrosis, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, flatulence, hypomagnesemia, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, edema, can increase gastric pH potentially interfering with drugs having pH dependent solubility

Worthless, hideously expensive, not yet available

Take home?

1. We can only see 2% (Plasma K)
2. Understanding physiology is the key
3. The kidney‘s regulatory capacity is profound
4. Unless we compromise it with drugs
5. With very few exceptions, disturbed K means:
6. Acid-base disturbances; therefore always measure!