Water and electrolyte disturbances

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Case Reports
Male 45 years, 10 years hypertension, treated with diuretics

History

- Male 45 years
- 10 years of hypertension treated with diuretics
- Occasional muscle weakness and limb paresthesia
- Without vomiting
- Without the history of lung disease

Physical examination

- **BP: 158/102**
- Heart rate: 70/min
- **Respiration rate: 6/min**
- Mild muscle weakness otherwise normal finding
- Edema is not present

Laboratory
(venous blood sample)

- **Sodium** **146 (135-145) mmol/L**
- Chlorides 98 (98-106) mmol/L
- **Potassium** **2 (3.5-5.0) mmol/L**
- **HCO3-** **35 (22-26) mmol/L**
- Creatinine 55 (53-133) μmol/L
- BUN 2.7 (2.9-8.9) mmol/L
- **Glucose** **6.5 (3.9-5.6) mmol/L**

Causes of hypokalemie

A. Inadequate dietary intake
B. Excessive loss
C. Shift from extracellular to intracellular space

Causes of hypokalemie

A. Inadequate dietary intake

- elderly patients and patients on complete parenteral nutrition

B. Excessive loss

1. GI losses:
   - diarrhea
   - chronic laxative abuse
   - vomiting (dehydration, alkalosis – the loss of K+ through kidney excretion)

Causes of hypokalemie

A. Inadequate dietary intake

B. Excessive loss

1. GI losses
2. Renal losses:
   - **Diuretics (most cases)**
   - Mineralocorticoid excess (volume depletion, hyperaldosteronism)
   - Hypercortisolism
   - RTA
   - Metabolic alkalosis (vomiting)
   - Starvation
   - Antibiotics
   - Diabetic ketoacidosis

Causes of hypokalemie

A. Inadequate dietary intake

B. Excessive loss

1. GI losses
2. Renal losses:
3. Inherited ion channel mutations (Bartter's syndrome, Liddle's syndrome, hypokalemic periodic paralysis)
4. Hypomagnesemia

C. Shift from extracellular to intracellular space

- transient self limited BUT often together with loss
- alkalosis, barium poisoning, insulin overdose, epinephrin,....

Potassium

- Gastrointestinal absorption result in daily excess intake of ~ 1 mmol/kg/d (60-100 mmol/d).
- Ninety percent of this excess is excreted through the kidneys and 10% is excreted through the gut
- Intracellular cation
  - Intracellular/extracellular ratio = 10 : 1

Potassium homeostasis

- Potassium sensing?
  - adrenal glomerulosa cells
  - pancreatic beta cells
- Maintained
  - through the regulation of renal excretion
  - Site of regulation is the collecting duct (aldosterone receptors)

Excretion of potassium is increased by

- high serum potassium level
- aldosterone
- high sodium delivery to the collecting duct (e.g. diuretics)
- high urine flow (e.g. osmotic diuresis)
- delivery of negatively charged ions to the collecting duct (e.g. bicarbonate)

Excretion of potassium is decreased by

- low serum potassium level
- deficiency of aldosterone
- low sodium delivery to the collecting duct
- decrease glomerular filtration rate (renal failure)
  - kidneys maintain potassium homeostasis until GFR < ~ 0.3 ml/s (normal > ~ 1.5ml/s)
    - stage 4 (GFR 15-30 %) and 5 (GFR<15%) of chronic kidney disease
      - potassium is then maintained by colon excretion relatively efficiently (cannot maintain acute load)

Potassium regulation between the intracellular and extracellular space

- Glycoregulatory hormones:
  - **Insulin** enhances potassium entry into cells
  - **Glucagon** impairs potassium entry into cells
- Adrenergic stimuli:
  - **Beta-adrenergic** stimuli enhance potassium entry into cells
  - **Alpha-adrenergic** stimuli impair potassium entry into cells
- pH:
  - **Alkalosis** enhances potassium entry into cells
  - **Acidosis** impairs potassium entry into cells
- Acute increase in osmolality
  - potassium exit from cells
- Acute cell/tissue breakdown
  - releases potassium into extracellular space

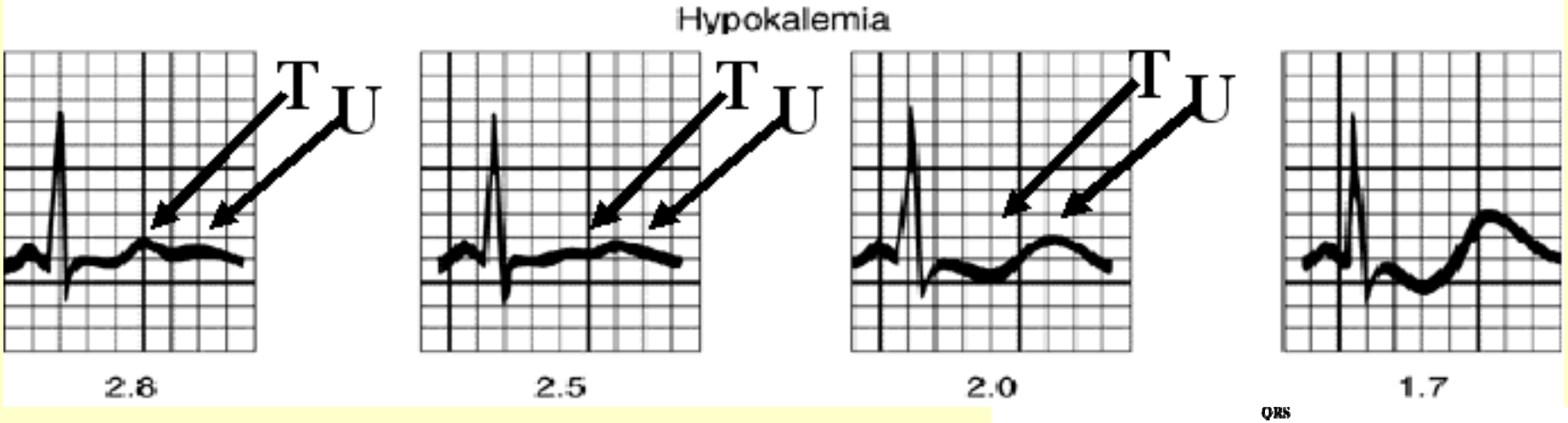
Serum potassium level

- Indicator of total K+ body stores **BUT** reflect movement of potassium between intracellular and extracellular fluid compartments
- Excreation through kidney
  - aldosterone-mediated enhancement of distal renal expression of secretory potassium channels (ROMK)
- Muscle can increase and decrease potassium intake to maintain blood K+ levels through sodium pump activity
  - insulin stimulated by K+ increase the sodium pump activity and uptake of K+

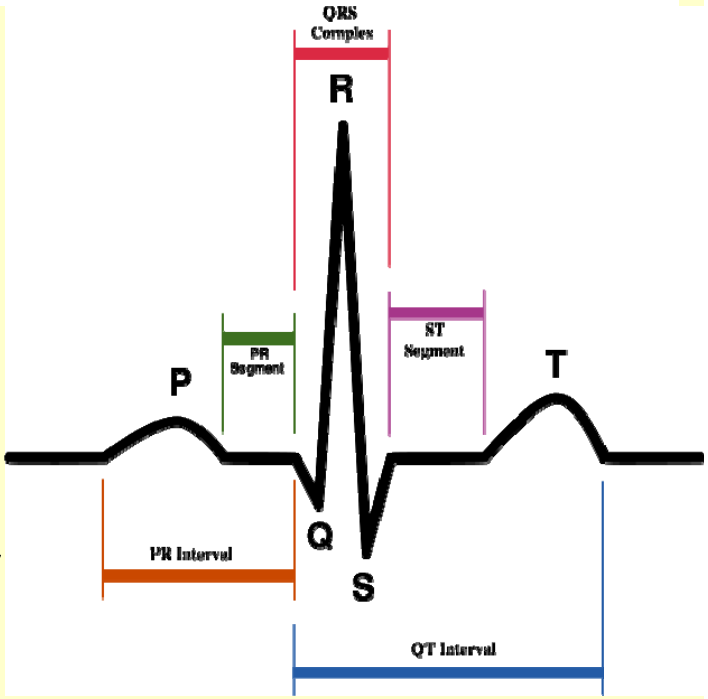
Clinical manifestation of hypokalemia

- Cardiac
  - ECG changes
  - risk of arrhythmia (esp. in patients on digoxin or after heart surgery)

Hypokalemia: Expected ECG changes



- T-wave flattening - inversion
- Appearance of U waves
- QT interval prolongation
- ST-segment depression
- Increased risk of atrial or ventr



Clinical manifestation of hypokalemia

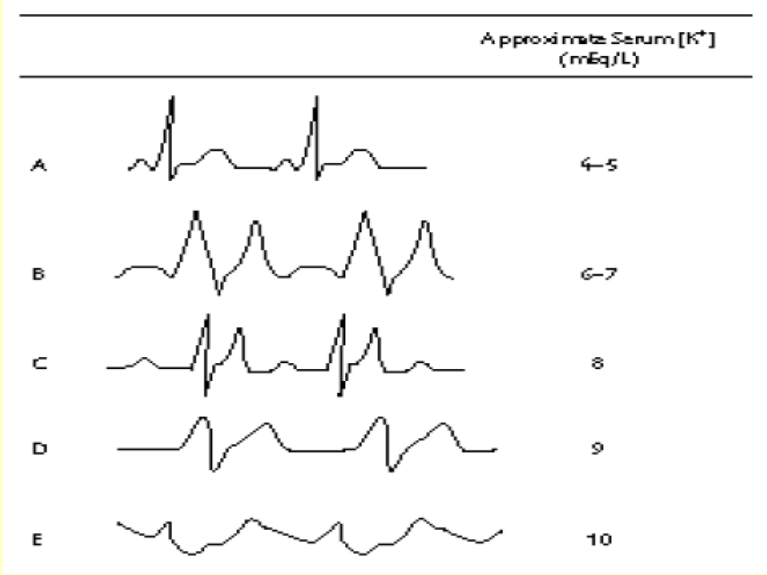
- Cardiac
  - ECG changes
  - risk of arrhythmia (esp. in patients on digoxin or after heart surgery)
- Muscle
  - weakness – paralysis - cramps and pain - rhabdomyolysis
- Gastrointestinal
  - hypomotility - constipation
- Metabolic
  - Hyperglycemia (e.g. worsening diabetes control)
  - ↑ NH3 production (renal amoniogenesis) and excretion
- Other
  - Polydipsia – Polyuria
  - decrease urinary concentration ability (nephrogenic diabetes insipidus)

Causes of hyperkalemia

- Excessive intake
  - with impaired mechanisms for the intracellular shift of potassium or for renal potassium excretion
- Decreased excretion
  - renal failure
  - ingestion of drugs that interfere with potassium (eg, potassium-sparing diuretics, ACE inhibitors, NSAID)
  - impaired responsiveness of the distal tubule to aldosterone (diabetes mellitus, sickle cell disease, chronic partial urinary tract obstruction)
- Shift from intracellular to extracellular space
  - hyperosmolality
  - rhabdomyolysis, tumor lysis
  - succinylcholine administration (depolarizes the cell membrane and permits potassium to leave the cells)
  - insulin deficiency, acute acidosis

Clinical manifestation of hyperkalemia

- Cardiac
  - Bradycardia due to heart block
  - on ECG
    - shortening of the QT interval
    - tall T waves
    - ventricular arrhythmias
    - widening of the QRS complex
    - PR interval prolongation
    - disappearance of the P wave
    - QRS complex degenerates
    - ventricular asystole or fibrillation



- Muscle weakness and flaccid paralysis
- Depressed or absent deep tendon reflexes

What is the most probable defect in acid-base balance of this patient?

- Summary of symptoms, signs laboratory findings
  - **Occasional muscle weakness and limb paresthesia**
  - **BP: 158/102**
  - **Respiration rate: 6/min**
  - **Sodium** **146 (135-145) mmol/L**
  - **Potassium** **2 (3.5-5.0) mmol/L**
  - Chlorides 98 (98-106) mmol/L
  - **HCO3-** **35 (22-26) mmol/L**
  - **Glucose** **6.5 (3.9-5.6) mmol/L**

What is the most probable defect in acid-base balance of this patient?

- Chronic metabolic alkalosis with respiratory compensation
  - high bicarbonate (**35 mmol/L**)
  - borderline low chlorides [98 (98-106) mmol/L]
  - low potassium [**2 (3.5-5.0) mmol/L]**
  - decreased respiration rate (compensation) **6/min**

What is the most probable cause of metabolic alkalosis of the patient?

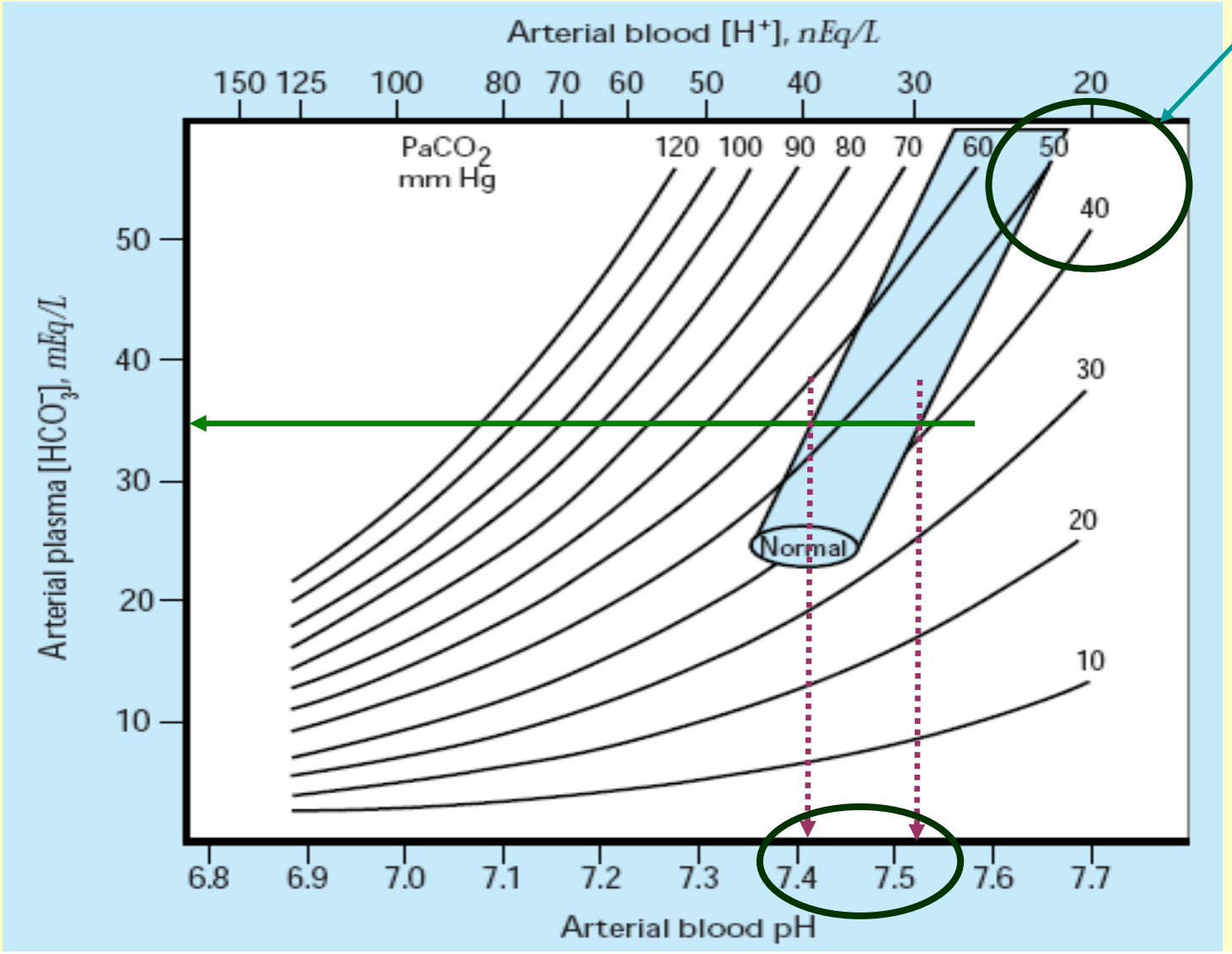
Based on the fact that the **patient is not vomiting**

- Administration of diuretics
  - lead to the kidney excretion of potassium ions together with hydrogen ions
- Excessive production of mineralocorticoids
  - may lead to the hypertension and persistent hypokalemia
- Combination of both

What changes in pH and pCO_2 do you expect?

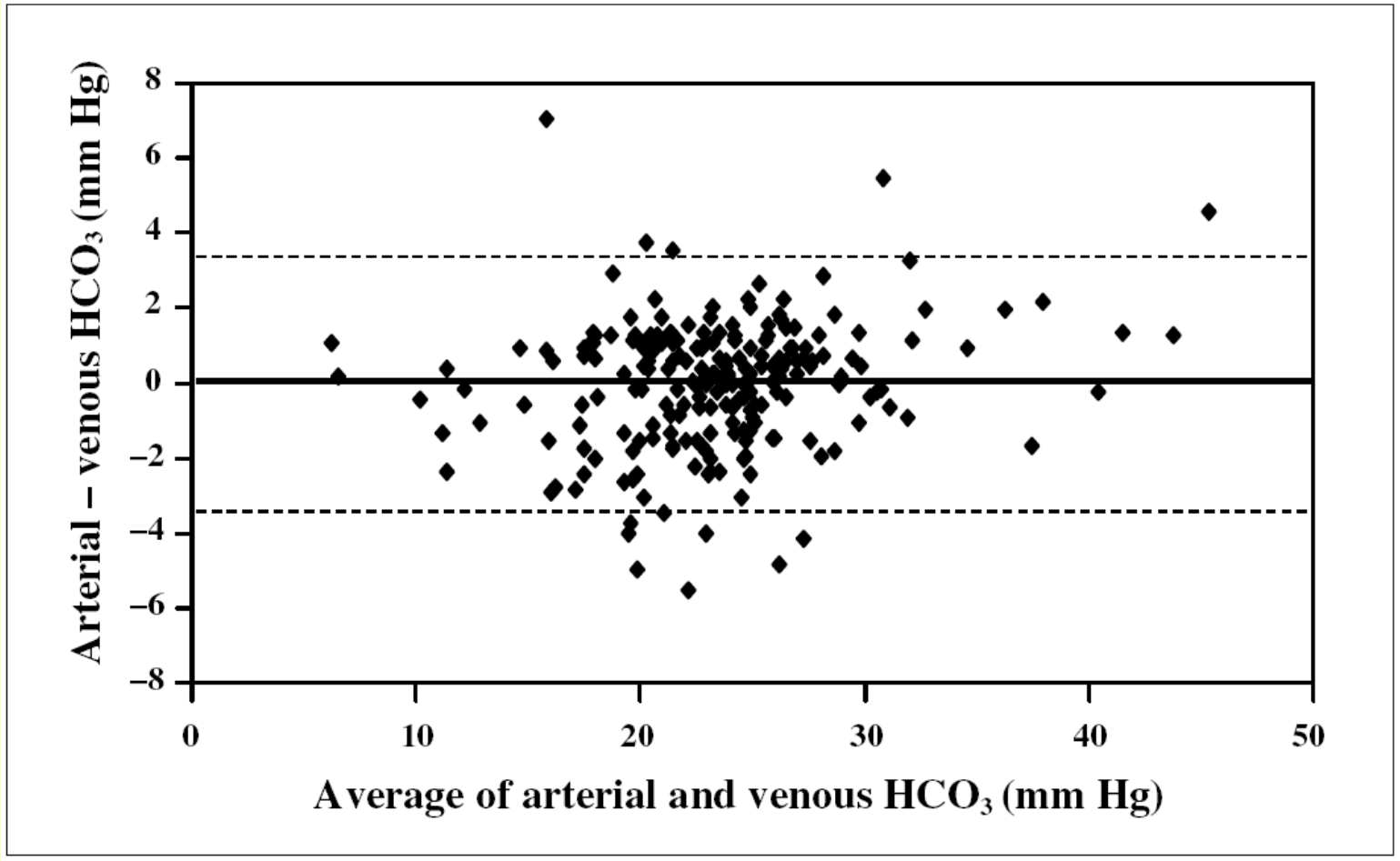
- pH of arterial blood is expected to be slightly higher than normal
- $PaCO_2$ will be slightly increased

Ninety-five percent confidence intervals for metabolic alkalosis.



Agreement between arterial and peripheral venous samples for bicarbonate

(calculated from pH and pCO2 using H-H equation)



Mean arterial HCO3, mmol/L 22.6 (21.8–23.3)
Mean venous HCO3, mmol/L 24.0 (23.3–24.7) Rang LCF et al, CJEM 2002; 4: 7–15.

What would be the next step?

Therapy change

angiotensin-converting enzyme inhibitors

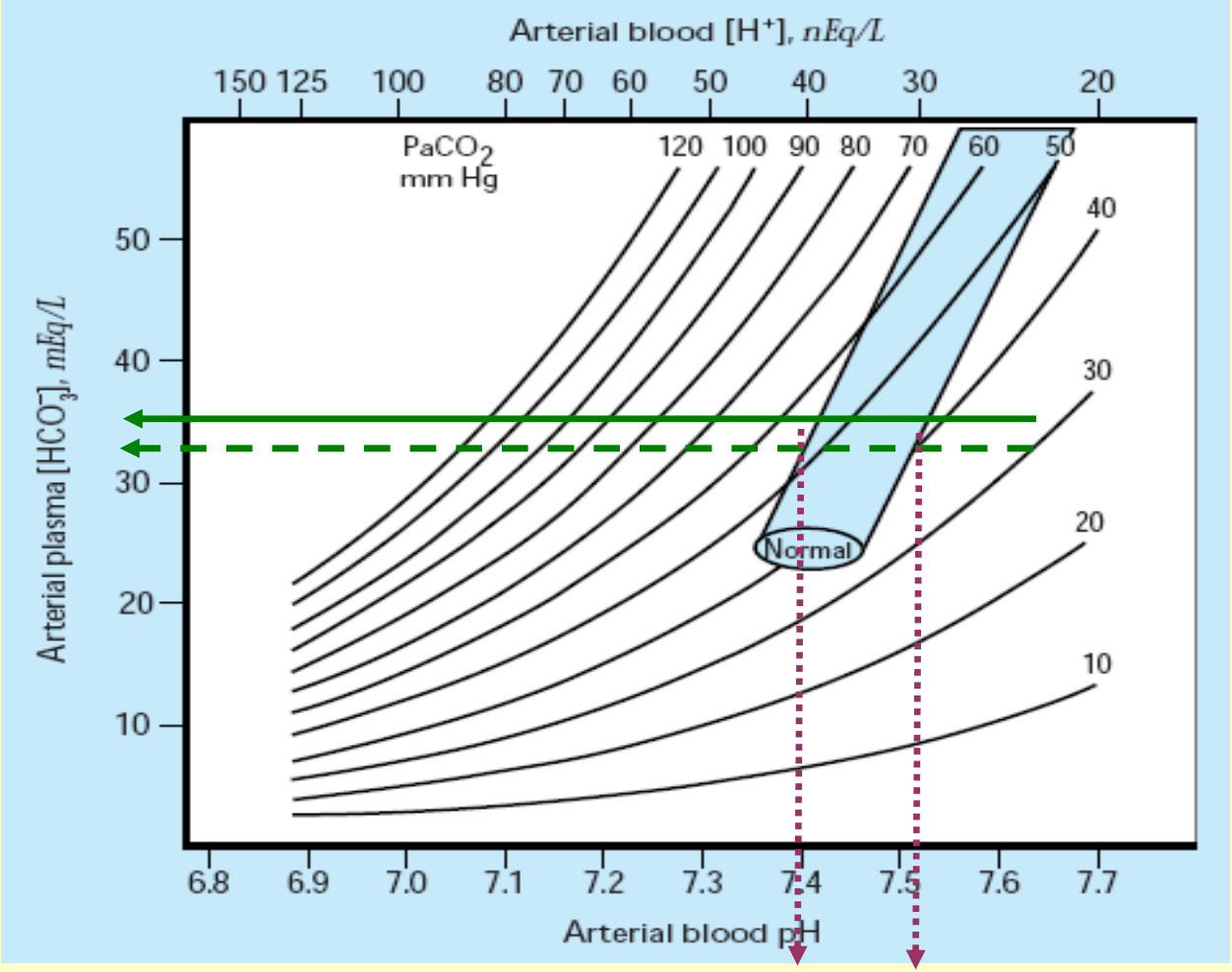
(ACE inhibitors)

Diuretics were switched for angiotensin converting enzyme (ACE) inhibitors and p.o. potassium was started to correct hypokelemia.

One week after the therapy change the following values were detected:

BP	**154 / 98 mm Hg** [from 158/102]
Sodium	145 mmol/l (135-145) [from 146]
Potassium	**2.6 mmol/l** (3.5-5.0) [from 2]
Chlorides	98 mmol/l (98-106) [from 98]
HCO3-	**33 mmol/l** (21-30) [from 35]

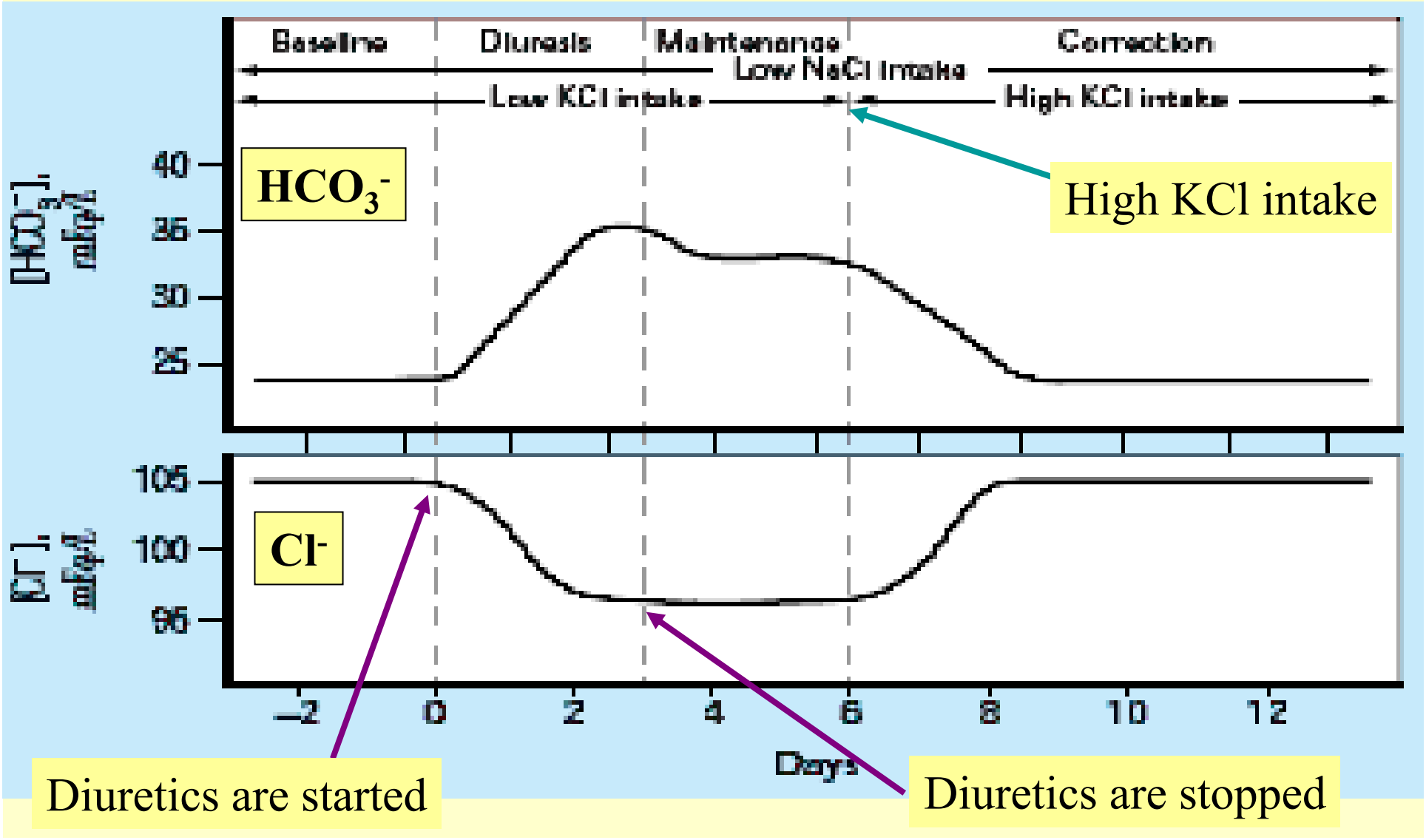
Ninety-five percent confidence intervals for metabolic alkalosis.



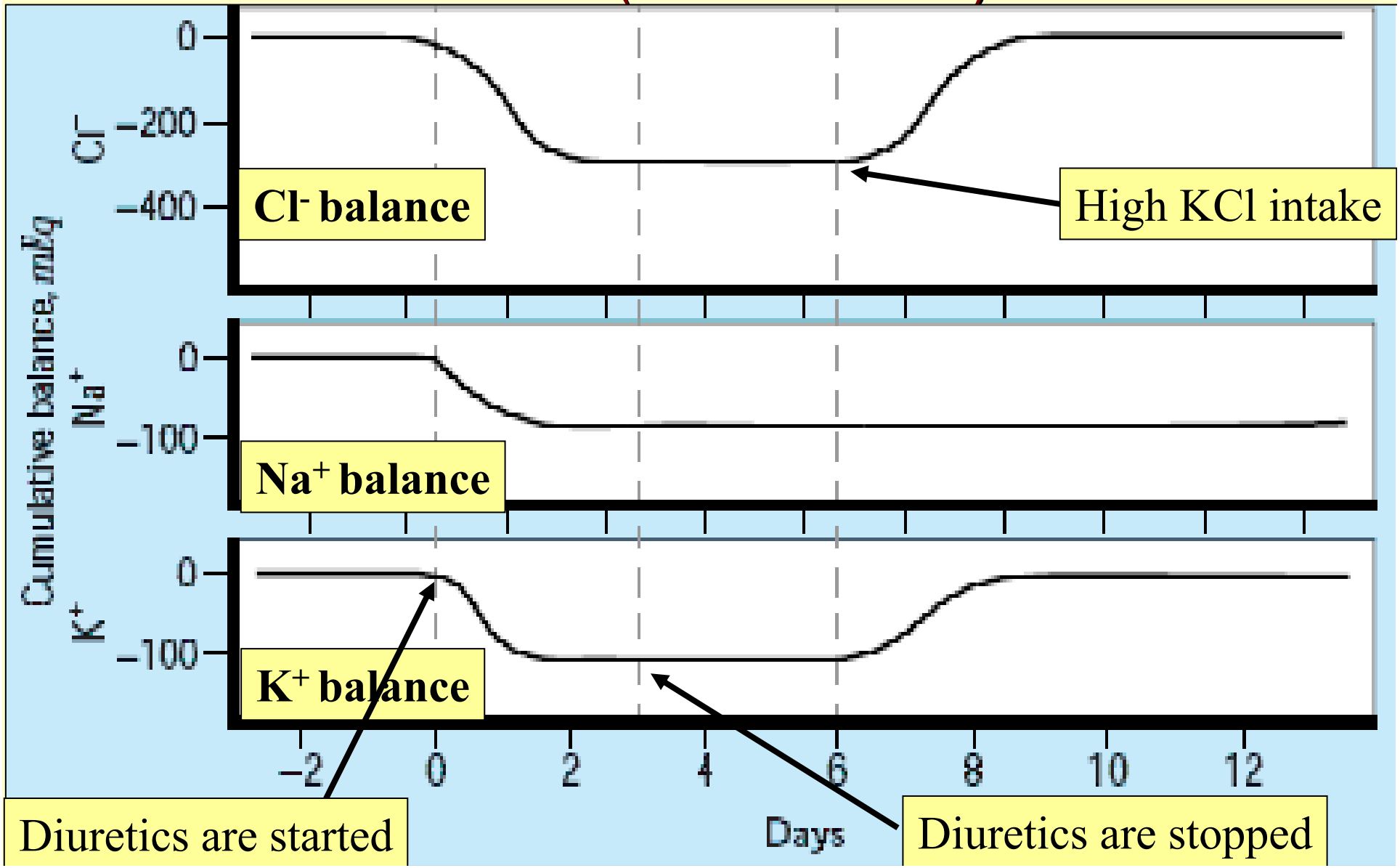
No significant improvement

Is one week enough to correct diuretic medication induced hypokalemia and metabolic alkalosis in patient on K+ supplementation?

Changes in **plasma** anionic pattern during development, maintenance, and correction of **diuretic-induced** metabolic alkalosis (Low NaCl intake)



Changes in **body** electrolyte balance during development, maintenance, and correction of **diuretic-induced** metabolic alkalosis (Low NaCl intake)



The high BP and laboratory values were repeatedly confirmed

- ACE inhibitors were replaced by another drug
- Potassium administration continued
- Blood pressure decreased to 130 / 82 mmHg and also electrolyte levels normalized and clinical signs diminished

- **What is the drug to replace ACE inhibitors?**

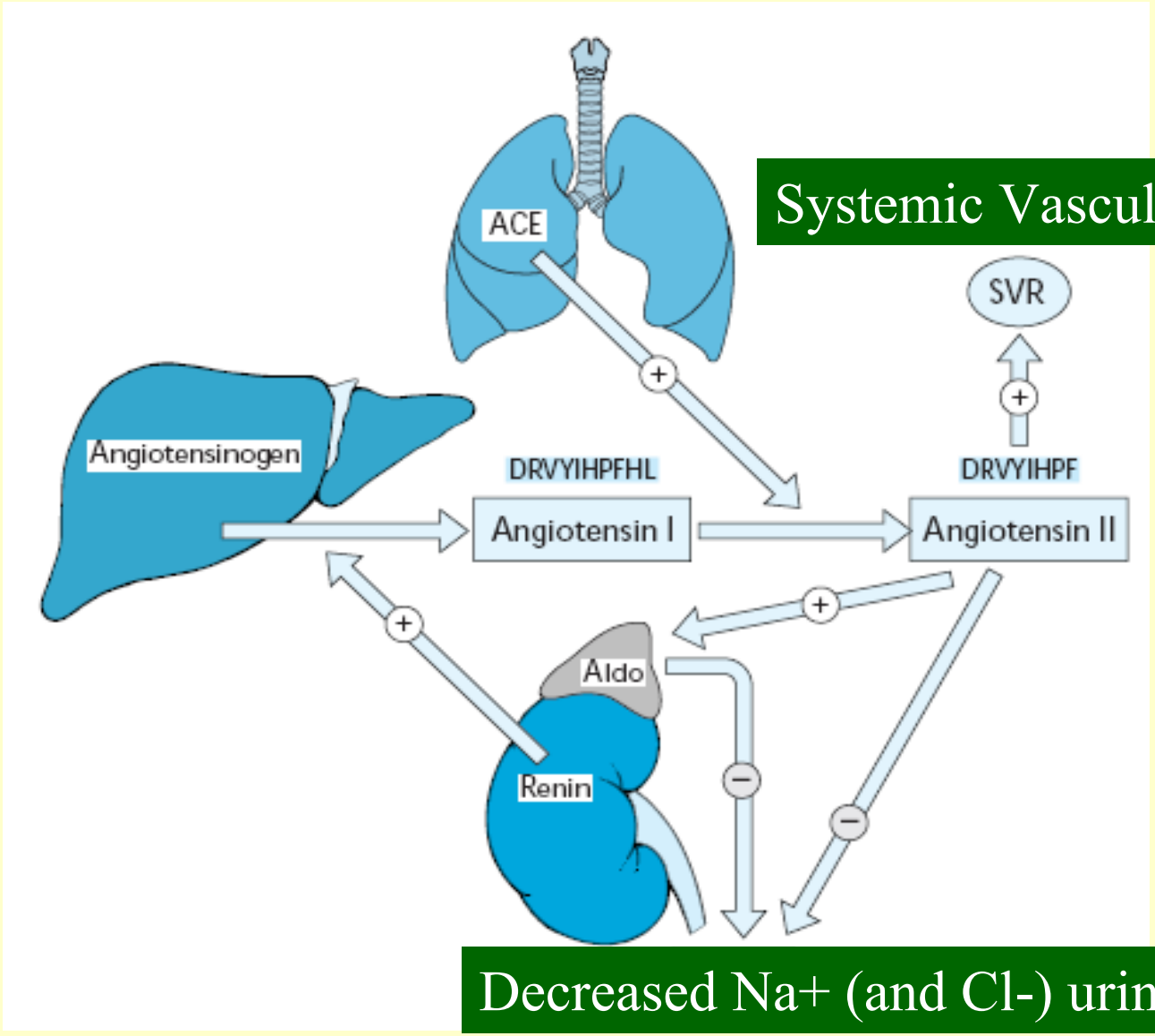
What is the drug to replace ACE inhibitors?

- **Potassium-sparing diuretics**
  - competitive antagonists
    - compete with aldosterone for intracellular cytoplasmic receptor sites
      - Spironolactone, Eplerenone
    - directly block sodium channels
      - Amiloride, Triamterene

What hormones will you measure to confirm diagnosis?

- Aldosterone
  - horizontal position and high sodium diet lower aldosterone secretion
  - if aldosteron is high the renine levels should be measured
- Plasma level of renin (PRA)
  - upright position and low sodium diet elevates renin level
  - if low PRA autonomous hypersecretion of aldosterone is suggested
- ARR = Aldosteron / plasma renin activity ratio
  - (ARR > primary hyperaldosteronismus)

Overview of the renin-angiotensin-aldosterone system



Systemic Vascular Resistance

Decreased Na+ (and Cl-) urinary excretion

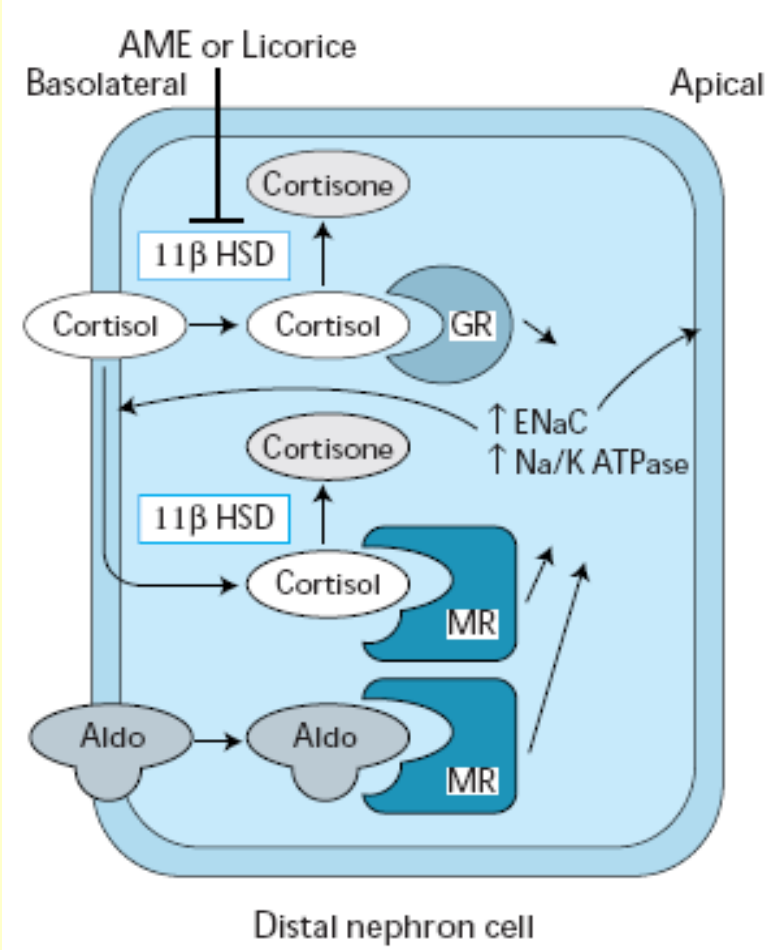
Cortisol vs. aldosterone

- Cortisol and aldosterone bind the mineralocorticoid receptor (MR) with equal affinity.
- Cortisol circulates in the bloodstream at about a thousand-fold higher concentration:
  - Cortisol: 138-670 nmol/L
  - Aldosterone: 0.03-0.5 nmol/L

- **How aldosteron execute its action in the tubular cells?**

Cortisol vs. aldosterone

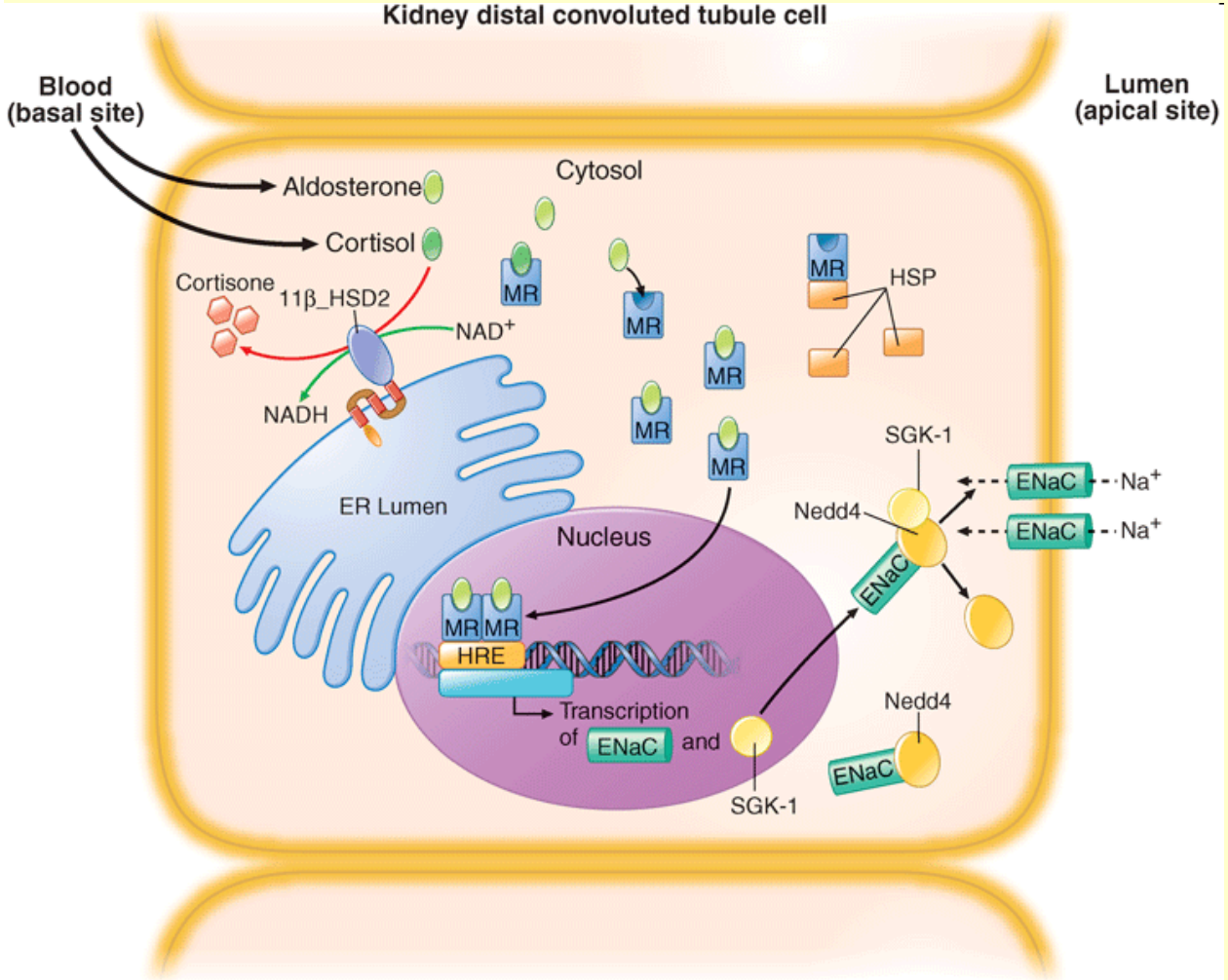
- Cortisol is inactivated to cortisone by the microsomal enzyme 11-hydroxysteroid dehydrogenase type 2 (11-HSD2).
- In the kidney and other target tissues for aldosterone (colon, salivary glands.....)



How aldosterone influence the potassium level?

- Aldosterone
  - Binds intracellular receptor to form complex which is transported to the nucleus and induce the expression of Na+,K+ - ATPase
  - Na+,K+ - ATPase is increased on basal membrane of distal convolute tubule cells within 10 - 30 min
  - Na+,K+- ATPase channel cause decreased excretion of sodium and increased excretion of potassium (transport of sodium ions from tubules to the ICF and plasma and transport of potassium ions to the tubular lumen)

Rapid inactivation of cortisol to cortisone by 11-HSD2 prevents MR activation by excess cortisol



- 11-HSD2 act as a tissue-specific modulator of the aldosterone pathway
- MR = mineralocorticoid receptor

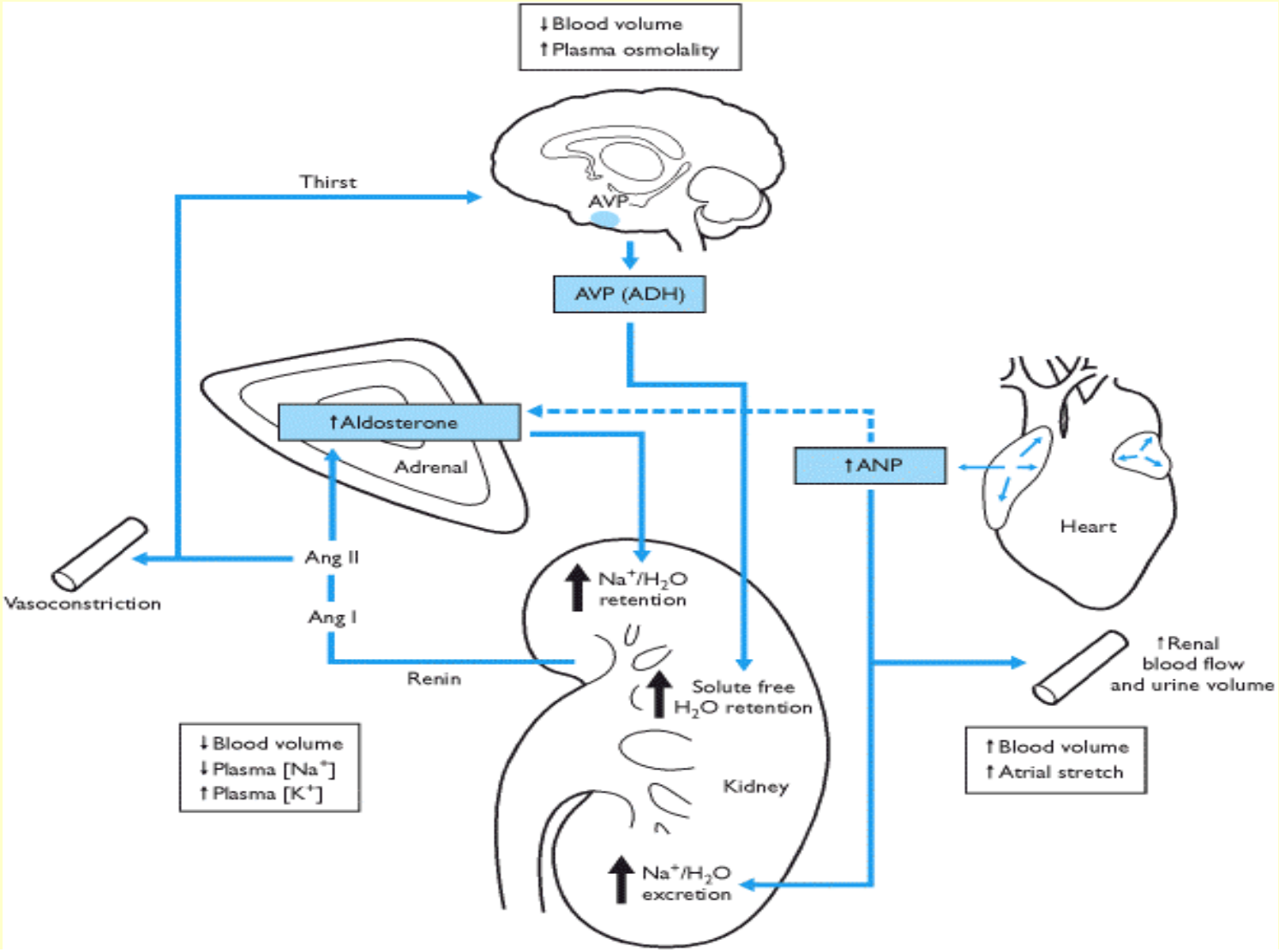
Explain the cause of patient muscle weakness and paresthesis?

- Hypokalemia
  - responsible for the defect in the generation of normal action potential (muscle cell hyperpolarization) and defects in musle perfusion.
- Alkalemia (severe)
  - increases protein binding of ionized Ca++, leading to hypocalcemia and subsequent headache, lethargy, and neuromuscular excitability (tetany and seizures)
- Metabolic alkalosis cause vasoconstriction → decreased cerebral blood flow
  - may lead to tetany, seizures, and decreased mental status

Why patient doesn't have edemas?

- Hyperaldosteronism does not lead to edema:
  1. Expansion of intravascular volume and pressure
     - GFR is increased
     - stimulate the production of atrial natriuretic peptide (ANP) which directly decrease the reabsorption of sodium and subsequently water retention

Integrated actions of aldosterone, ADH, and atrial natriuretic peptide (ANP) in the control of salt and water balance



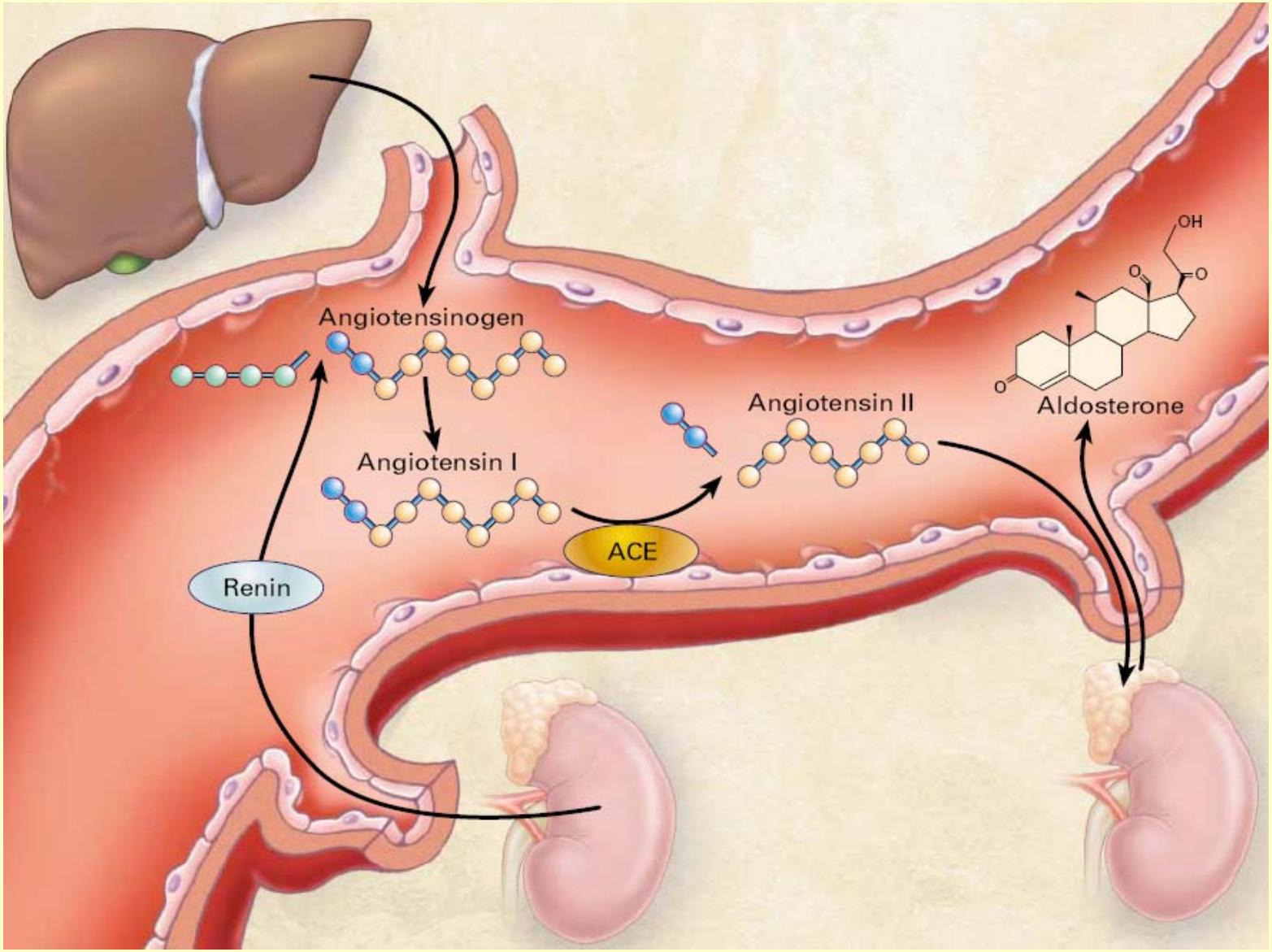
How do you explain increase glucose plasma levels?

- Hypokalemia
  - Decrease insulin release = increase in fasting glucose level
  - decreases peripheral insulin sensitivity
- Hyperaldosteronism
  - induce insulin resistance in vascular smooth muscle cells (Roberge, Am J Physiol Endocrinol Metab, 2007)
- Angiotensin II
  - angiotensin II decreased insulin-induced glucose uptake into the skeletal muscle (Ogihara, Hypertension 2002)

Why Angiotensin converting enzyme inhibitors didn't lead to the blood preasure decrease?

- Primary hyperaldosteronism
  - is probable cause of patients hypertension
  - e.g. caused by autonomous secretion of aldosterone by zona glomerulosa cells (e.g. adenoma, adrenal hyperplasia)
- The level of renin and angiotensin is probably low
- Pacient's hypertension was independent on the conversion of angiotensine I to angiotensine II

The Renin–Angiotensin–Aldosterone System



Summary

- Primary hyperaldosteronism
  - primary hyperaldosteronism affects 5–13% of patients with hypertension

- Conn's sy
  - Primary hyperaldosteronism caused by adrenal gland adenoma
  - hypokalemia
    - muscle weakness
    - metabolic alkalosis
  - hypertension
  - expansion of ECF
  - w/o hypernatremia and edema (increased production of ANF)

Testing for primary aldosteronism should be considered in any of the following circumstances:

- Hypertension and spontaneous hypokalemia
- Hypokalemia provoked by administration of a low-dose diuretic
- Hypertensive relatives of patients with primary aldosteronism
- Severe hypertension
  - i.e. ≥160 mmHg systolic and/or ≥100 mmHg diastolic
- In patient on three or more antihypertensive drugs
- Hypertension manifested at a young age (<20 years)

Dehydratation

Dehydration

- Body does not have as much water and fluids as it should
- Severe dehydration is a life-threatening emergency

At higher risk

- Infants, children
- Elderly
- Adults with illnesses

Causes, incidence, and risk factors

- Losing too much fluid
  - Vomiting
  - Diarrhea
  - Excessive urine output (uncontrolled DM, diuretic use, acute renal failure)
  - Excessive sweating
  - Fever
- Not drinking enough water or fluids
  - Nausea
  - Loss of appetite due to illness
  - Sore throat or mouth sores

Symptoms

- Dry or sticky mouth
- Low or no urine output; concentrated urine appears dark yellow (except for kidney disease)
- Not producing tears
- Sunken eyes
- Markedly sunken fontanelles in an infant
- Lethargic or comatose (with severe dehydration)

Signs

- Low blood pressure
- Blood pressure that drops when you go from lying down to standing
- Rapid heart rate
- Poor skin turgor
  - the skin may lack its normal elasticity and sag back into position slowly when pinched up into a fold
  - normally, skin springs right back into position
- Delayed capillary refill
- Shock

Skin turgor


Skin with decreased turgor
remains elevated after
being pulled up and
released

Laboratory Tests

- Blood chemistries
  - electrolytes (sodium, potassium, and bicarbonate)
- Urine specific gravity
  - a high specific gravity indicates significant dehydration
- BUN
  - blood urea nitrogen - may be elevated with dehydration
- Creatinine
  - may be elevated with dehydration
- Complete Blood Count (CBC)
  - to look for signs of concentrated blood

Measuring the Volumes of the Body's Compartments

- The volumes of some of the compartments can be measured by the dilution method
- One adds an extrinsic, measurable, compound that distributes fully within the compartment of interest. This method relies on the formula:

Concentration = Amount / Volume

or:

Volume = Amount Added-Amount Lost / Measured Concentration

Directly Measurable volumes

- **Total Body Water (TBW)**:
  - Use D_20 or radioactive water (tritiated). Distributes throughout all aqueous solutions.
- **ECF Volume**:
  - Use Inulin (a starch) or Sucrose. These distribute throughout body, but are excluded from cells.
- **Plasma Volume**:
  - Use radioactive albumin or dye (Evans Blue)

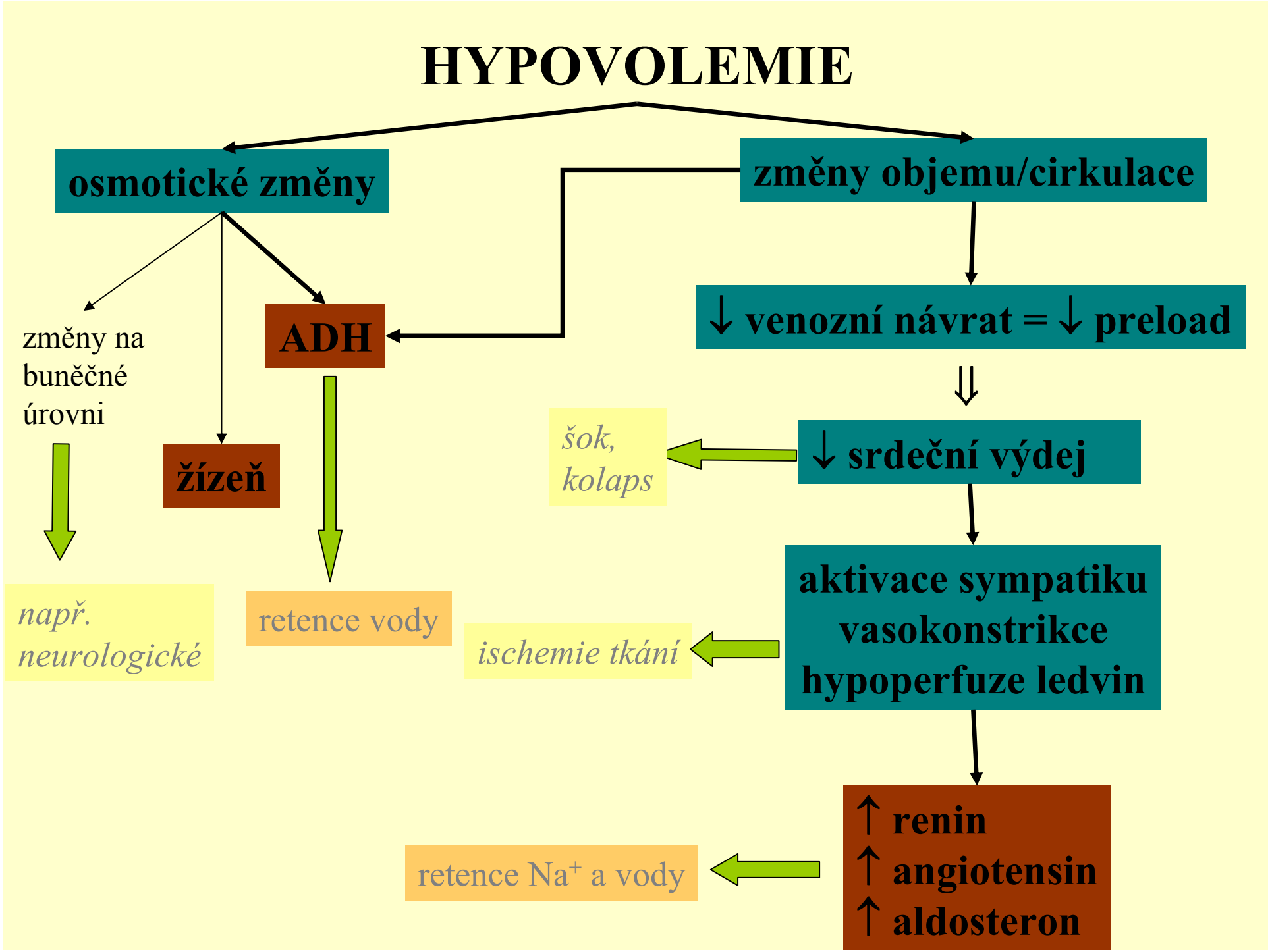
Indirectly Measurable Volumes

- Intracellular or the interstitial volumes are calculated by combining the measured volumes

- Interstitial Volume
  - Extracellular volume minus the plasma volume.
- Intracellular Volume:
  - Total Water minus the Extracellular Volume

Determination of ECF volume status in clinical practice

- Central venous pressure
  - CVP = 1 - 8 cm H_2O ~ 1 - 6 mm Hg
- Pulmonary capillary wedge pressure
  - PCW = 6 - 13 cm H_2O ~ 5 - 10 mm Hg
- Edema:
  - ECF volume excess (> 3 L in 70 kg adult)
  - pulmonary edema (cardiac status + distribution of ECF)


HYPOVOLEMIE
osmotické změny
změny objemu/cirkulace
změny na buněčné úrovni
ADH
žízeň
↓ venozní návrat = ↓ preload
⇓
šok, kolaps
↓ srdeční výdej
aktivace sympatiku
vasokonstrikce
hypoperfuze ledvin
např. neurologické
retence vody
ischemie tkání
↑ renin
↑ angiotensin
↑ aldosteron
retence Na+ a vody

END