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Department of Propaedeutics of Internal Medicine and Physical Rehabilitation

Student's scientific community
18 november 2021

Scientific discussion

Conn's syndrome (primary aldosteronism)

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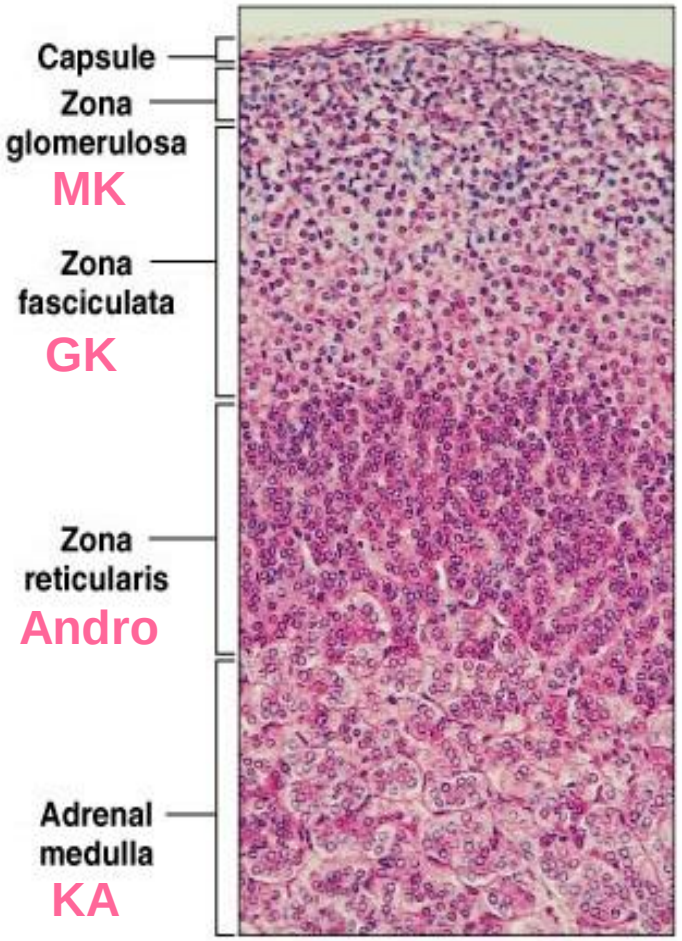
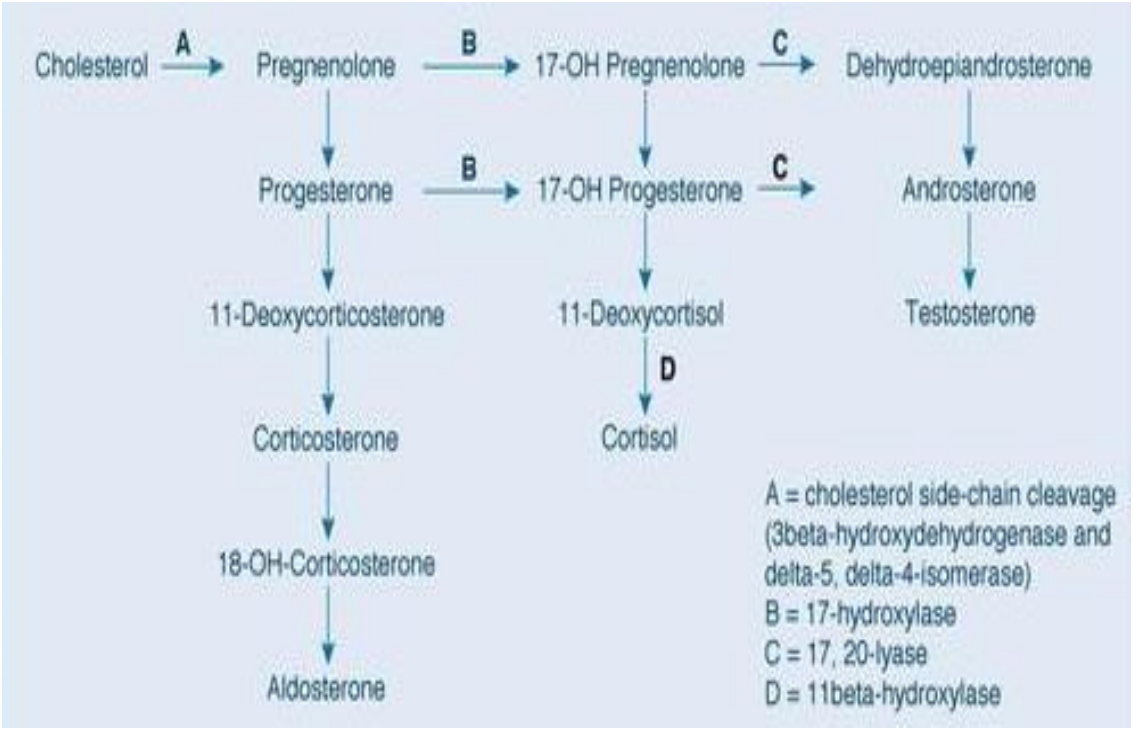
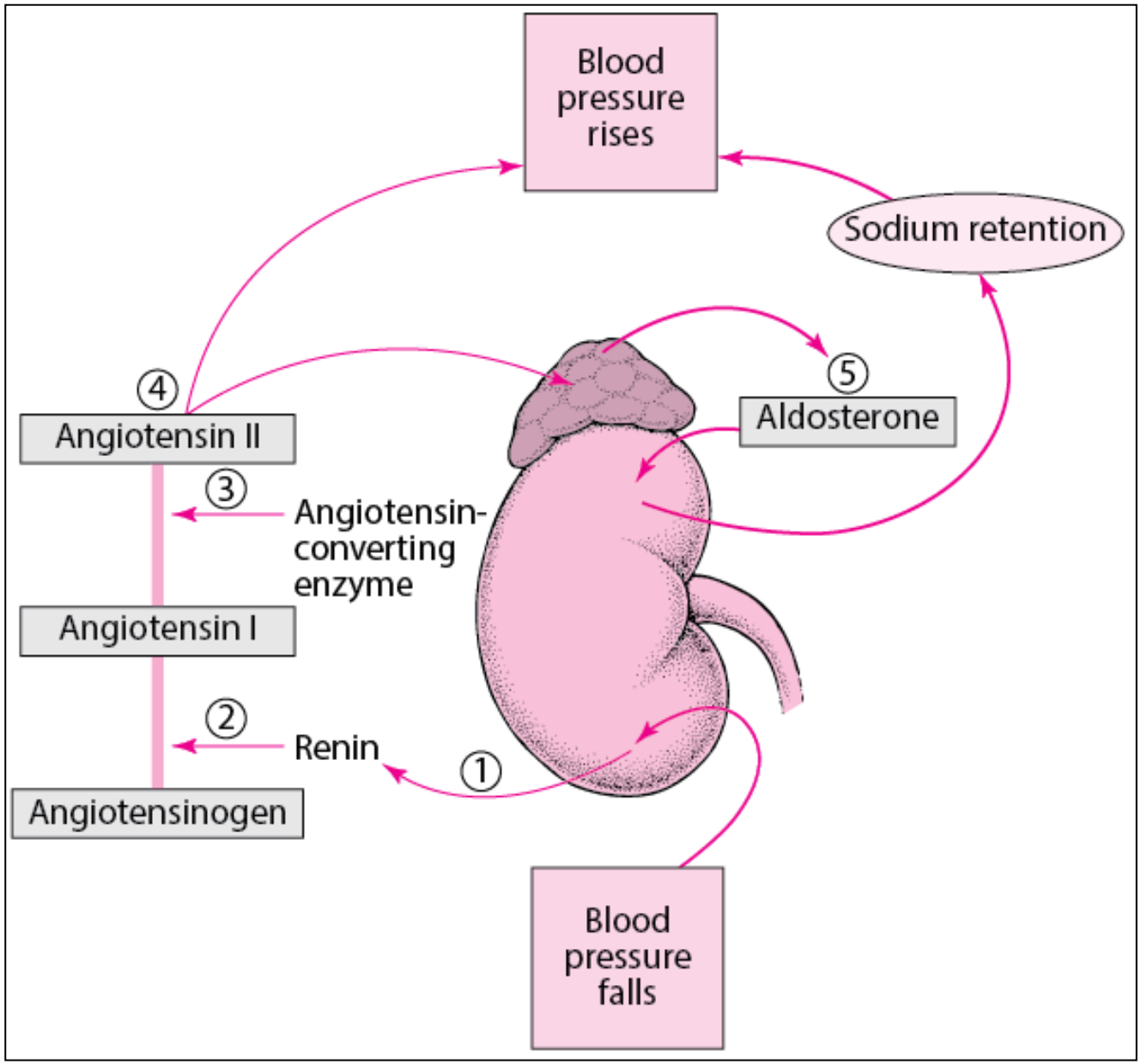
Aldosterone

Aldosterone is a hormone that controls sodium and potassium levels in the blood. Its overproduction leads to retention of salt and loss of potassium, which then leads to hypertension (high blood pressure).

Adrenal Steroids



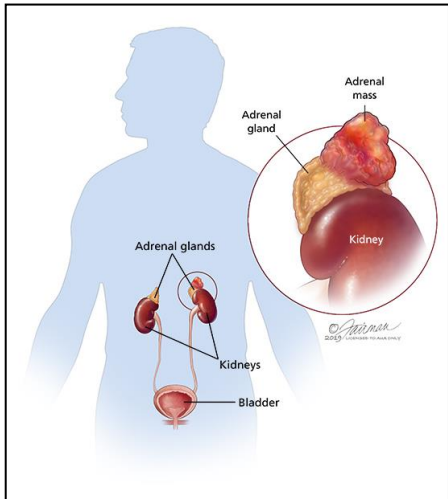



Blood pressure rises
Sodium retention
5
Aldosterone
4
Angiotensin II
3
Angiotensin-converting enzyme
Angiotensin I
2
Renin
1
Angiotensinogen
Blood pressure falls

What is PA?

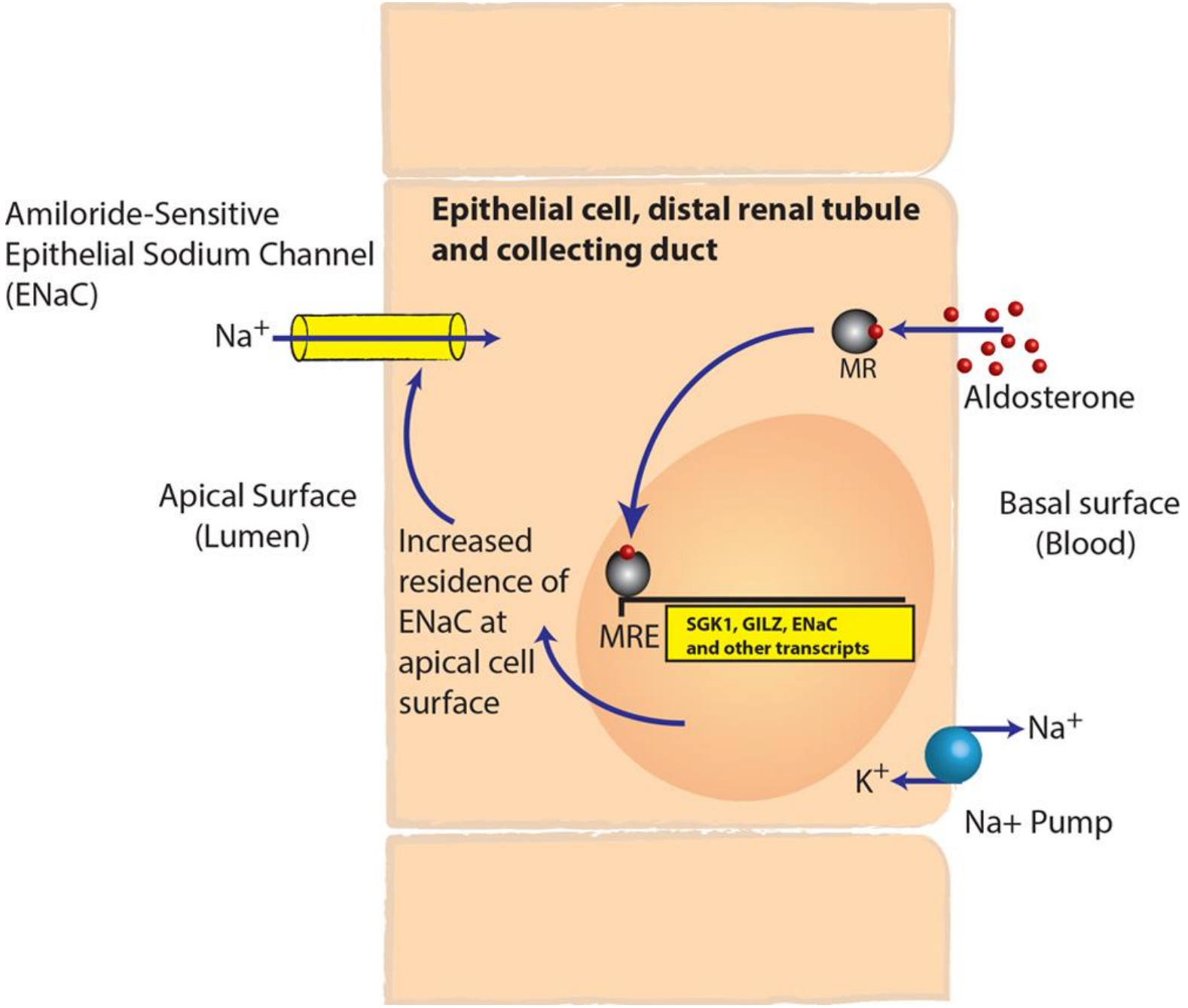
The primary aldosteronism is the syndrome of autonomouse hypersecretion of aldosterone by the cortex of adrenal glands

Primary hyperaldosteronism (PA) is one of the most common forms of secondary hypertension.



Jerome W.Conn
09 /24/1907 –06/ 11 1981

- **Conn's syndrome**
  was based on a thirty-four-year-old patient who entered the university hospital in **1954** complaining of seven years of episodic muscle weakness that often resulted in virtual paralysis of her lower legs. At Central Society for Clinical Research on **October 29, 1954**, he present for the first time his extensive clinical investigations of this new syndrome, which he called **primary aldosteronism.**


Amiloride-Sensitive
Epithelial Sodium Channel
(ENaC)
Epithelial cell, distal renal tubule
and collecting duct
Na+
MR
Aldosterone
Apical Surface
(Lumen)
Basal surface
(Blood)
Increased
residence of
ENaC at
apical cell
surface
MRE
SGK1, GILZ, ENaC
and other transcripts
Na+
K+
Na+ Pump

- Currently, primary aldosteronism is the leading cause of secondary hypertension, accounting for **up to 10%** of all hypertensive cases
- Primary aldosteronism can be divided into:

- idiopathic adrenal hyperplasia
- aldosterone-producing adenoma (rarely carcinoma)
- rare familial forms.

Subtypes of primary aldosteronism

Subtypes	Frequency
Idiopathic hyperplasia, bilateral (IHA)	60% – 65%
Aldosterone-producing adenoma (APA)	30% – 35%
Primary adrenal hyperplasia, unilateral	2% – 3%
Aldosterone-producing adrenocortical carcinoma	1%
Glucocorticoid-remediable aldosteronism (GRA) (familial hyperaldosteronism (FH) type I)	1%
Familial hyperaldosteronism (FH type II, APA, or IHA)	1%
Familial hyperaldosteronism (FH type III)	1%
Ectopic aldosterone-producing adenoma or carcinoma	1%

Who is affected by Hyperaldosteronism?

- People in their 30's-50's (adulthood), with prevalence increasing with age
- Females are more likely to be affected than males
- African Americans have a significantly greater risk of fatality from the disease than other races
- Rare in children (It is more likely to have been inherited if diagnosed in a child)

Detrimental effects from aldosterone excess

- Detrimental effects from aldosterone excess are mediated through the activation of mineralocorticoid receptor (MR), which is widely expressed in:

  - epithelial cells (including renal, colonic, and salivary gland),
  - smooth muscle cells,
  - myocardiocytes,
  - endothelial progenitor cells
  - neutrophils.

Detrimental effects from aldosterone excess

- Aldosterone exerts its actions on sodium and potassium handling through up-regulation of the activity of the distal tubule sodium epithelial channel.
- Aldosterone also increases oxidative stress

and collagen remodeling,

- triggering endothelial dysfunction,
- delayed endothelial recovery,
- subsequent ventricular hypertrophy and myocardial fibrosis.

Total loss of potassium, depletion of its intracellular reserves (reduced by 70%) leads to universal **hypokalemia**.

- **Hypocaligistia** - a decrease in the content of potassium in tissues (especially in erythrocytes, muscle cells).
- **The excretion of potassium in the urine increases.** Patients are unable to retain potassium in the body, and potassium supplementation is ineffective. A diet rich in sodium makes symptoms worse. A sodium-depleted diet increases potassium levels and improves the patient's condition.

With a deficiency of potassium, its ions are replaced by hydrogen ions - intracellular acidosis develops

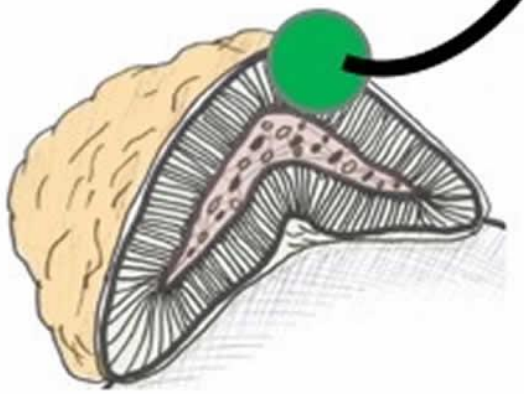
- **The intracellularly displaced hydrogen ions in the extracellular fluid are replaced by bicarbonates - extracellular alcolosis occurs.**

- **The increase in the biosynthesis of aldosterone in the adenoma is increased by 40-100 times**

- **Increased synthesis of aldosterone is not regulated and leads to suppression of the glomerular apparatus of the kidneys, resulting in a marked decrease in the amount of renin produced and its activity**

↑Renal sodium reabsorption
↑Intravascular volume expansion
↑Renal Hyperfiltration/perfusion
(suppression of renin secretion by JG cells)

↑Aldosterone



AGT

↓↓↓RENIN

AT-I

AT-II

ACE

Retention of sodium causes:

1. **Hypervolemia**
2. **Suppresses the production of renin and angiotensin II**
3. **Increases the sensitivity of the vascular wall to various endogenous pressor factors, promotes the development of arterial hypertension.**

There are three main groups of symptoms:

neuromuscular

cardiovascular

renal

Cardiovascular syndrom

Arterial hypertension is the most important symptom, often the only one.

- Due to an increase in vascular tone and peripheral resistance, persistent hypertension develops, which cannot be treated with conventional antihypertensive drugs, while systolic blood pressure (SBP) is more than 160 mm Hg, and diastolic blood pressure (DBP) is within 120 mm Hg. (pulse pressure is reduced).

- Hypertension does not respond to orthostatic load (renin-dependent reaction), is resistant to Valsalva's test (during the test, blood pressure does not increase, unlike other hypertension).

- Valsalva's test - the Valsalva maneuver is forced expiration against a closed glottis. Performing the Valsalva maneuver causes an increase in intrathoracic pressure, leading to a reduction in preload to the heart. Cardiovascular changes occur during and after this maneuver due to baroreflex and other compensatory reflex mechanisms that are initiated by decreased preload.

How to do the Valsalva maneuver

- To do the Valsalva maneuver, follow these steps:
- Inhale deeply and then hold your breath.
- Imagine that the chest and stomach muscles are very tight and bear down as though straining to initiate a bowel movement.
- Hold this position for a short time, usually about 10 seconds.
- Breathe out forcibly to release the breath rapidly.
- Resume normal breathing.

- Hypertension does not respond to treatment with conventional antihypertensive drugs. Blood pressure and hypokalemia can be corrected with spironolactone (400 mg / day for 10-15 days)

- When studying the features of the daily blood pressure profile, it was found that in most patients with Conn's syndrome, blood pressure rises more often at night, which may be the result of a violation of the circadian rhythm of aldosterone secretion

- Potassium deficiency can contribute to arrhythmias, often bradycardia.
- With a long course of the disease, hypertrophy and dilatation of the left ventricle, changes in the fundus (angiospasm, retinopathy), visual field defects develop

Cardiovascular and metabolic complications in primary aldosteronism (PA) compared to essential hypertension (EH). Meta analysis

	PA (%)	EH (%)	p
Cardiovascular events			
Atrial fibrilation	3.9	1.1	0.001
Coronary artery disease	5.7	2.8	0.03
Heart failure	4.1	1.2	0.003
Nonfatal myocardial infarction	4.4	1.7	0.01
Stroke	4.4	3.5	0.006
Metabolic alterations			
Metabolic syndrome	41.1	29.6	0.05
Abnormal glucose metabolism	22.4	16.8	0.04

Savard S, Amar L, Plouin PF, Steichen O. Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. Hypertension. 2013;62(2):331-6.

Syndrome of potassium penic nephropathy

- The epithelium of the distal renal tubules is affected, and they become refractory to antidiuretic hormone (vasopressin).
- As a consequence – **polyuria**

(*Polyuria* increases uresis to more than 2000 mL/24 h, which results in an increase in the glomerular filtration or decrease in the tubular reabsorption of water).

- Hypokalemic damage to the epithelium of the renal tubules against the background of general hypokalemic alkalosis disrupts a number of renal functions - the mechanisms of urine oxidation and concentration. This leads to a violation of the water-electrolyte balance.

Symptoms:

- **1. Polyuria**, mainly nocturnal (nocturia). As a reaction to polyuria, thirst occurs - **compensatory polydipsia**.
- **2. Hypoisostenuria** -1008-1012
- **3.** Possible transient, unexpressed **proteinuria**
- **4**. The reaction of urine is often alkaline, which increases the frequency of concomitant **pyelitis and pyelonephritis**.

The development of edema is not typical

- polyuria and sodium accumulation in cells do not contribute to fluid retention in the interstitial space. Edema can develop as a consequence of serious damage of the cardiovascular system or kidneys.

Neuromuscular syndrome

- Muscle weakness (myasthenia gravis) can be paroxysmal in nature, the duration of the attack ranges from several minutes to several hours.
- There may be transient paresis (Paresis refers to a condition in which muscle movement has become weakened or impaired) up to complete immobility of the lower limbs lasting up to several hours (pseudoparalysis).
- Also, patients have paresthesias (Paresthesia refers to a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body)

- Changes in potassium and magnesium levels increase neuromuscular excitability, which leads to periodic convulsions of varying intensity. Twitching of facial muscles is possible.

Changes in the central nervous system

- General weakness in 20% of patients. Headaches are observed in 50% of patients, are intense and are caused by an increase in blood pressure and hyperhydration of the brain.

Violation of carbohydrate metabolism

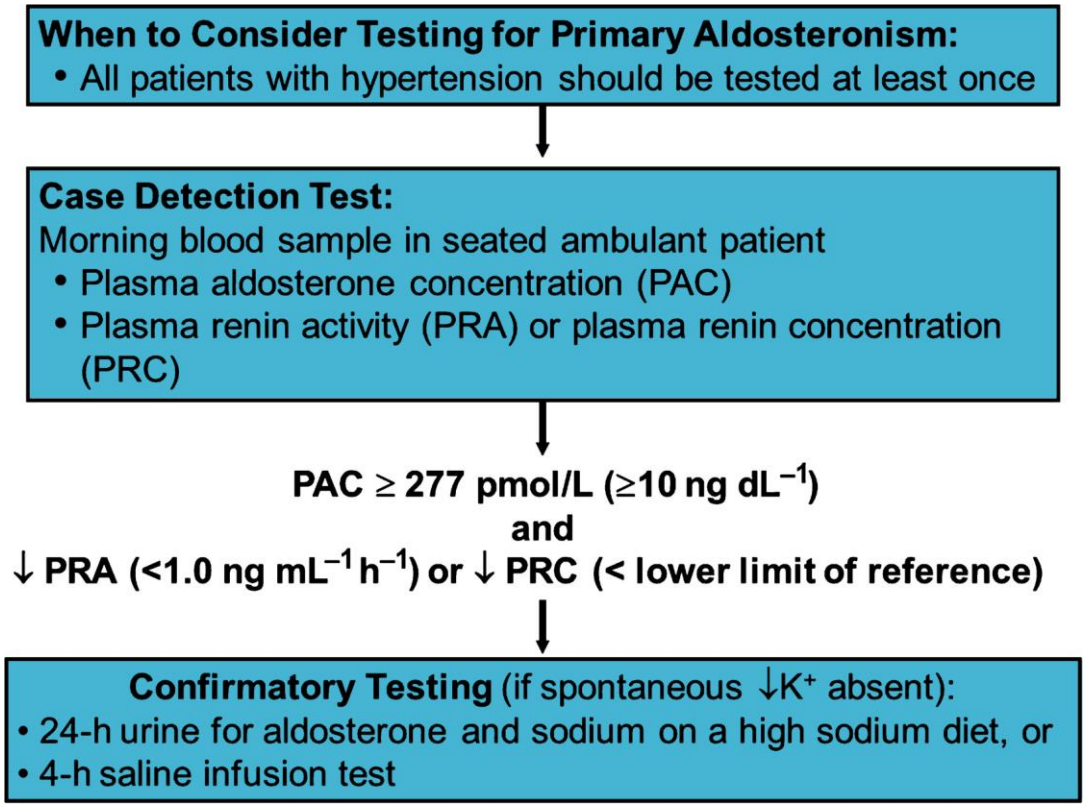
- Hypokalemia suppresses insulin secretion, promotes the development of reduced glucose tolerance.

Screening for primary aldosteronism

Risk groups recommended to be screened for primary aldosteronism according to ES guideline
Patients with sustained blood pressure above 150/100 mmHg, grade 2 and grade 3 hypertension
Patients with resistant hypertension (blood pressure not controlled by three conventional drugs including a diuretic) or controlled BP (<140/90 mmHg) on four or more antihypertensive drugs
Patients with hypertension and spontaneous or diuretic induced hypokalemia
Patients with hypertension and sleep apnea
Patients with hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
All first-degree relatives of patients with PA

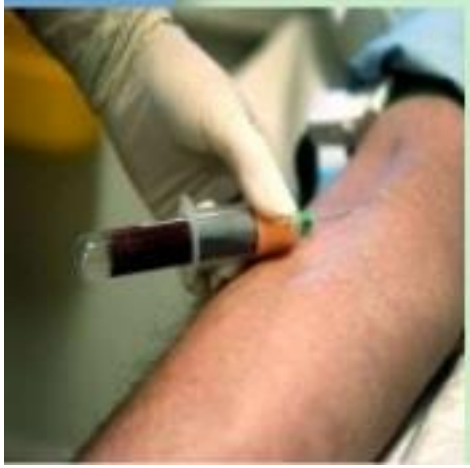
Diagnosis of Hyperaldosteronism

- Elevated aldosterone levels can be measured in the blood or urine.
  - In a blood test, PRA (Plasma renin activity), is used to distinguish between primary (low PRA) and secondary Hyperaldosteronism (high PRA).
- Abdominal CT scans can show adrenal masses
- Electrocardiograms (ECGs) can show abnormalities in heart rhythm that are often associated with low potassium level.
- It is likely that many cases of secondary Hyperaldosteronism are never detected.



Journal of Internal Medicine, Volume: 285, Issue: 2, Pages: 126-148, First published: 25 September 2018, DOI: (10.1111/joim.12831)

SCREENING TESTS



- *PAC:PRA ratio*

The first test used in patients suspected to have primary hyperaldosteronism measures the **Plasma Aldosterone Concentration (PAC)** to **Plasma Renin Activity (PRA) Ratio.**

A high ratio of PAC to PRA suggests primary hyperaldosteronism.

CONFIRMATION TESTS

Captopril Suppression Test

Captopril is a medication for high blood pressure. A patient is given a single dose of captopril, after which the levels of aldosterone and renin in the blood are measured.

In patients with primary hyperaldosteronism, the level of aldosterone in the blood is still high and the level of renin is low even after captopril administration.

Saline infusion test

- Patients stay in the recumbent position for at least 1 hour before and during the infusion of 2 liters of 0.9% saline intravenously (IV) over 4 hours, starting at 8:00–9.30 AM. Blood samples for renin, aldosterone, cortisol, and plasma potassium are measured at time 0 and after 4 hours, with BP and heart rate monitored throughout the test.

- Postinfusion plasma aldosterone levels less than 5 ng/dL make the diagnosis of PA unlikely.
- In individuals without primary hyperaldosteronism, plasma aldosterone levels should fall to less than 10 ng/dL.
- Plasma aldosterone values higher than 10 ng/dL confirm primary hyperaldosteronism, and levels 5-10 ng/dL may be considered borderline.

Table V. Available confirmatory tests for diagnosis of primary aldosteronism.

Confirmatory test	Procedure	Interpretation[a]
Oral salt loading test (OST)	Preceding 3 days of high salt intake (6 g NaCl/day), as verified by 24-hour urine Na content (should >200 mmol); check 24-hour urine aldosterone, Na, and creatinine level at day 4	Urine aldosterone >12 µg/day (33.3 nmol/day) is consistent with autonomous aldosterone secretion; <10 µg/day (27.7 nmol/day) is unlikely for PA presence
Saline infusion test (SIT)	Preceding overnight fast; in the next morning, recumbent for 1 hour, then start 2 liters of 0.9% saline infusion over 4 hours, in recumbent position; check peripheral blood PRA, PAC, cortisol, and K after the test	PAC >10 ng/dL (277 pmol/L) confirms patients with PA; PAC <5 ng/dL (138 pmol/L) excludes the diagnosis; values of 5–10 ng/dL (138–277 pmol/L) are indeterminate
Fludrocortisone suppression test (FST)	Administration of fludrocortisone (0.1 mg four times a day) and NaCl tablets (2 g three times a day) for 4 days; check peripheral blood cortisol at 7 a.m., and cortisol, PAC, and PRA at 10 a.m. on day 4 when patient is seated	Upright PAC >6 ng/dL (166 pmol/L) confirms the diagnosis of PA, if concomitant PRA <1 ng/mL/h (<12.8 pmol/L/min) and plasma cortisol (7 a.m.) less than cortisol (10 a.m.) value
Captopril suppression test (CST)	Administration of 25–50 mg captopril orally after sitting or standing for at least 1 hour; check peripheral blood PRA, PAC, and cortisol before and 1–2 hours after the test, with patient remaining seated	PAC remained elevated/PRA suppressed after captopril challenge confirms the diagnosis; normal individuals have a >30% suppression of PAC
Losartan suppression test (LST)	Similar to CST, with losartan 50 mg given instead.	Interpretation similar to CST

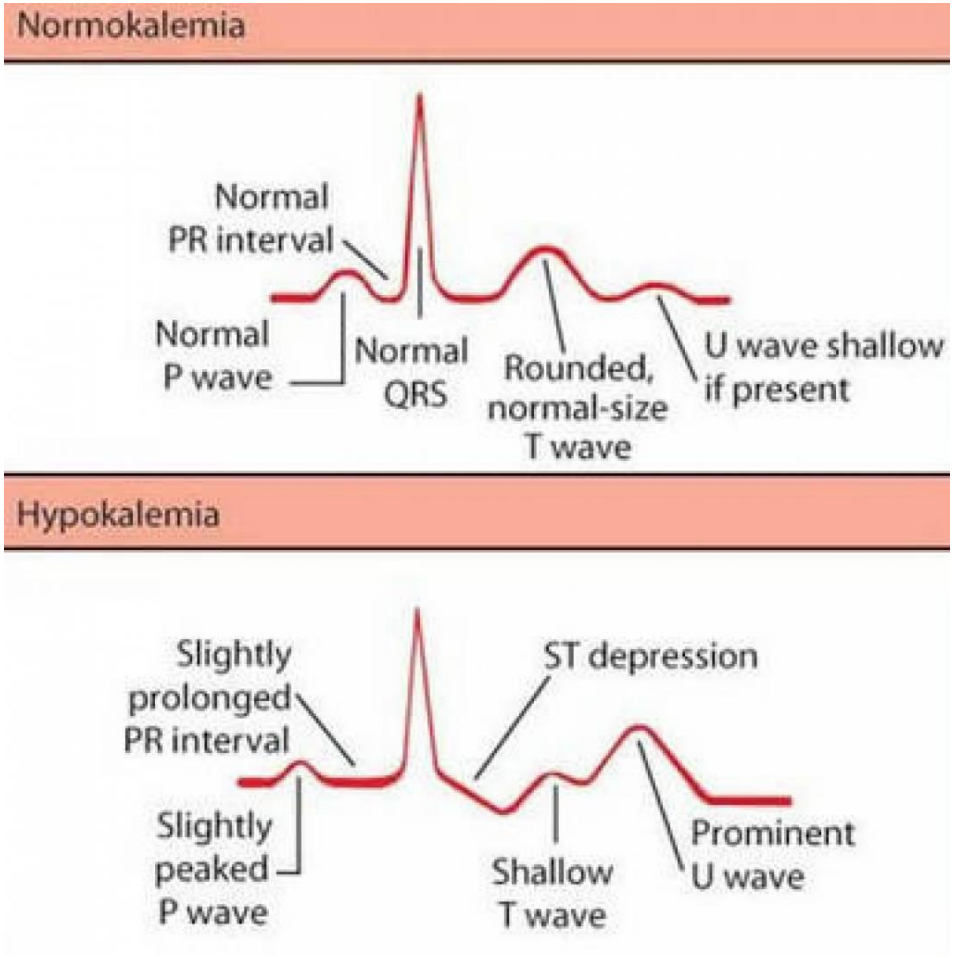
PAC = plasma aldosterone concentration; PRA = plasma renin activity.

[a]Medications potentially suppressing aldosterone levels should be avoided during confirmatory tests (angiotensin-converting enzyme (ACE) inhibitor, angiotensin-receptor blocker (ARB), beta-blockers, etc.).

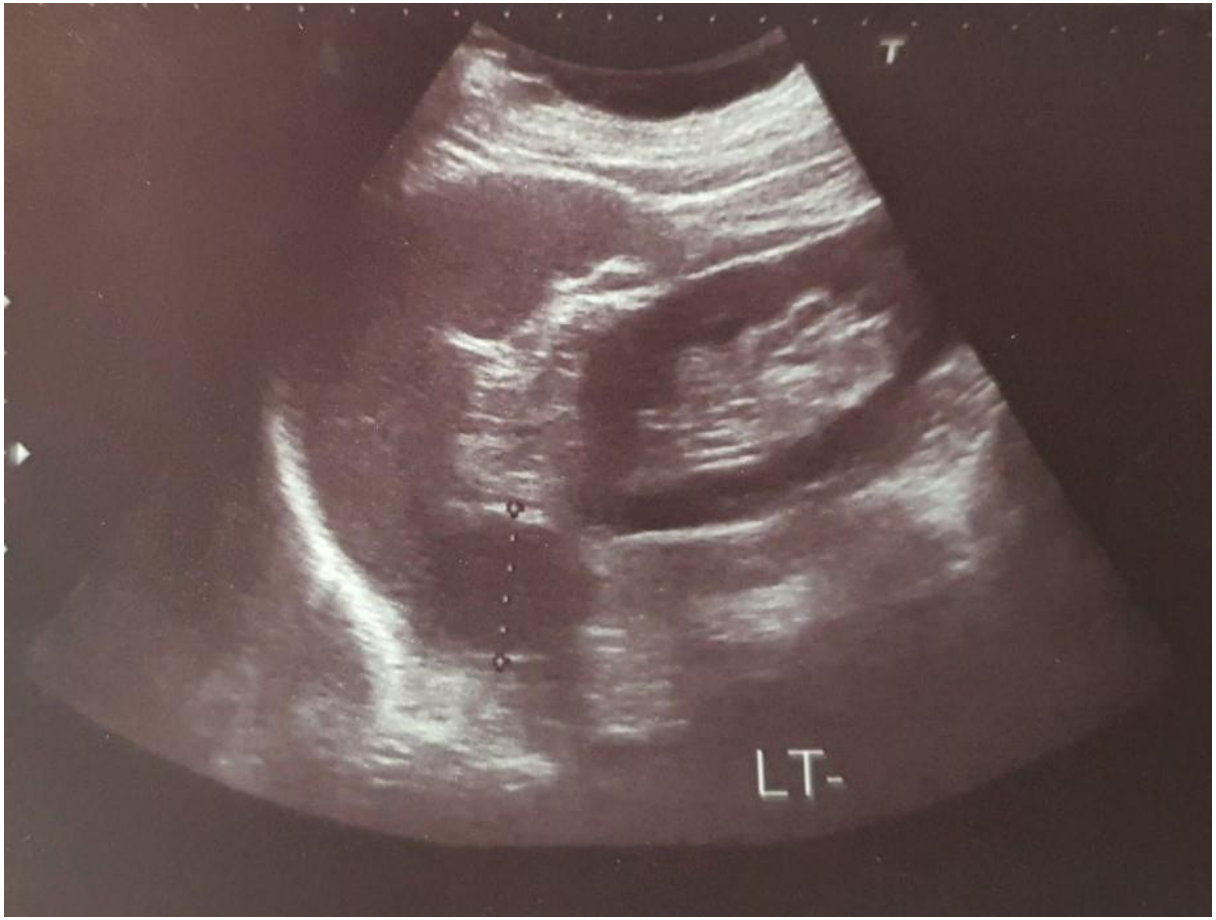
ECG examination

- Hypokalemia produces distinctive changes in the ST-T complex. The most common pattern seen is ST depressions with prominent U waves and prolonged repolarization. With hypokalemia the U waves typically become enlarged and may even exceed the height of the T waves.

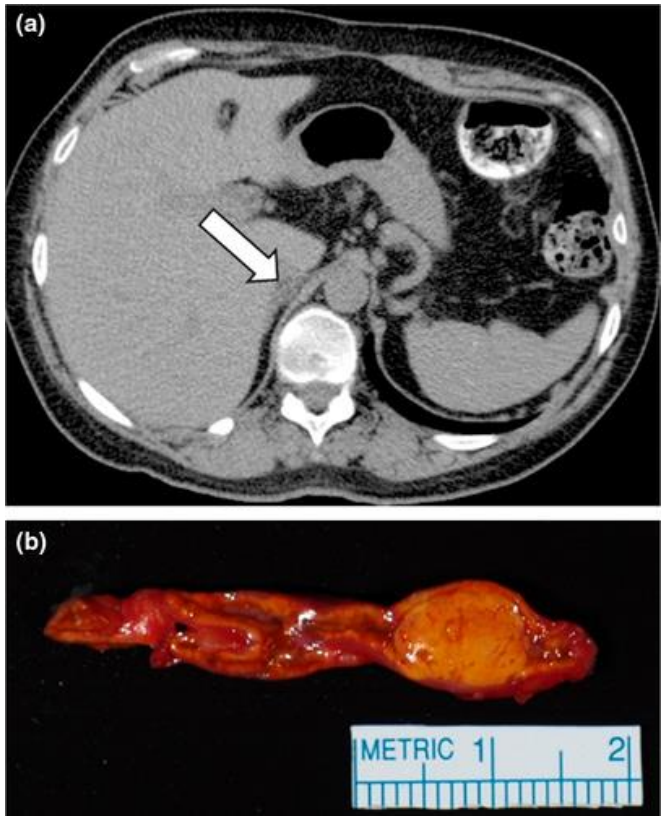
- Technically the QT interval with hypokalemia may remain normal whereas repolarization is prolonged (as shown by the prominent U waves). Because the T waves and U waves often merge, the QT intervals cannot always be accurately measured.



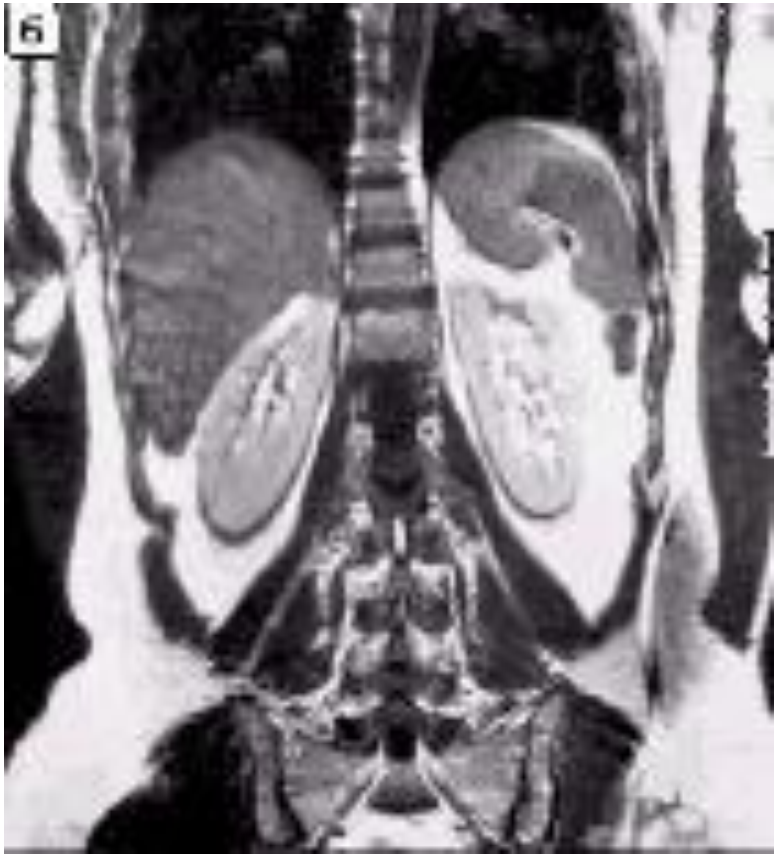
Ultrasound investigation - the sensitivity of the method for neoplasms more than 1 cm reaches 82-87%

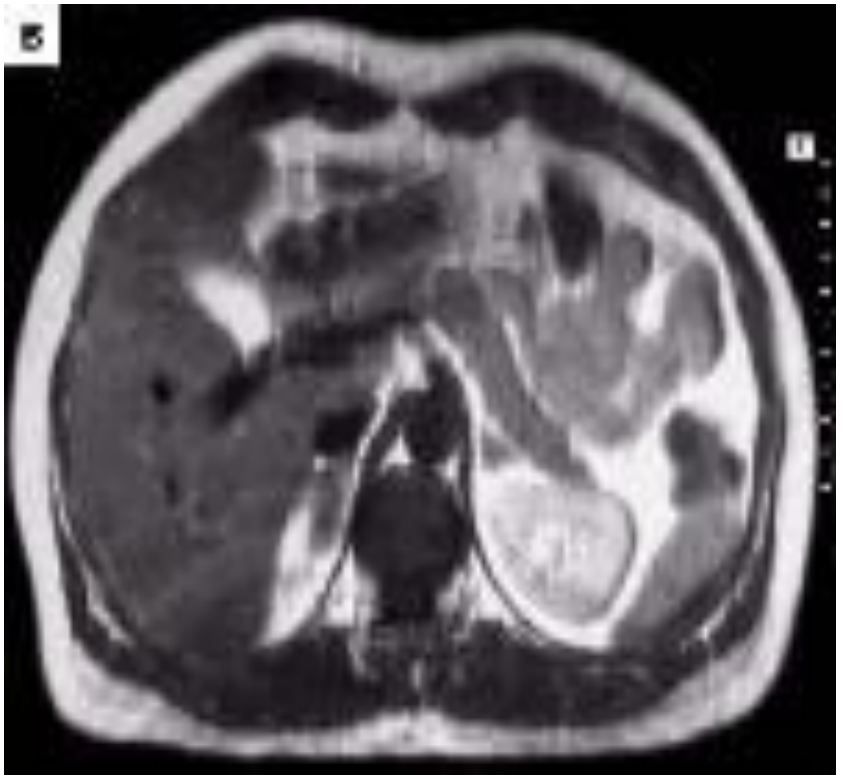


- Adrenal-directed CT scan should be the first test in the subtype evaluation of PA



Magnetic resonance imaging





Treatment

Unilateral adrenalectomy for APA and unilateral hyperplasia

Mineralocorticoid receptor (MR) antagonists

Spironolactone

Eplerenone Eplerenone is a more selective MR antagonist

Amiloride and triamterene – are distal sodium epithelial channel antagonists