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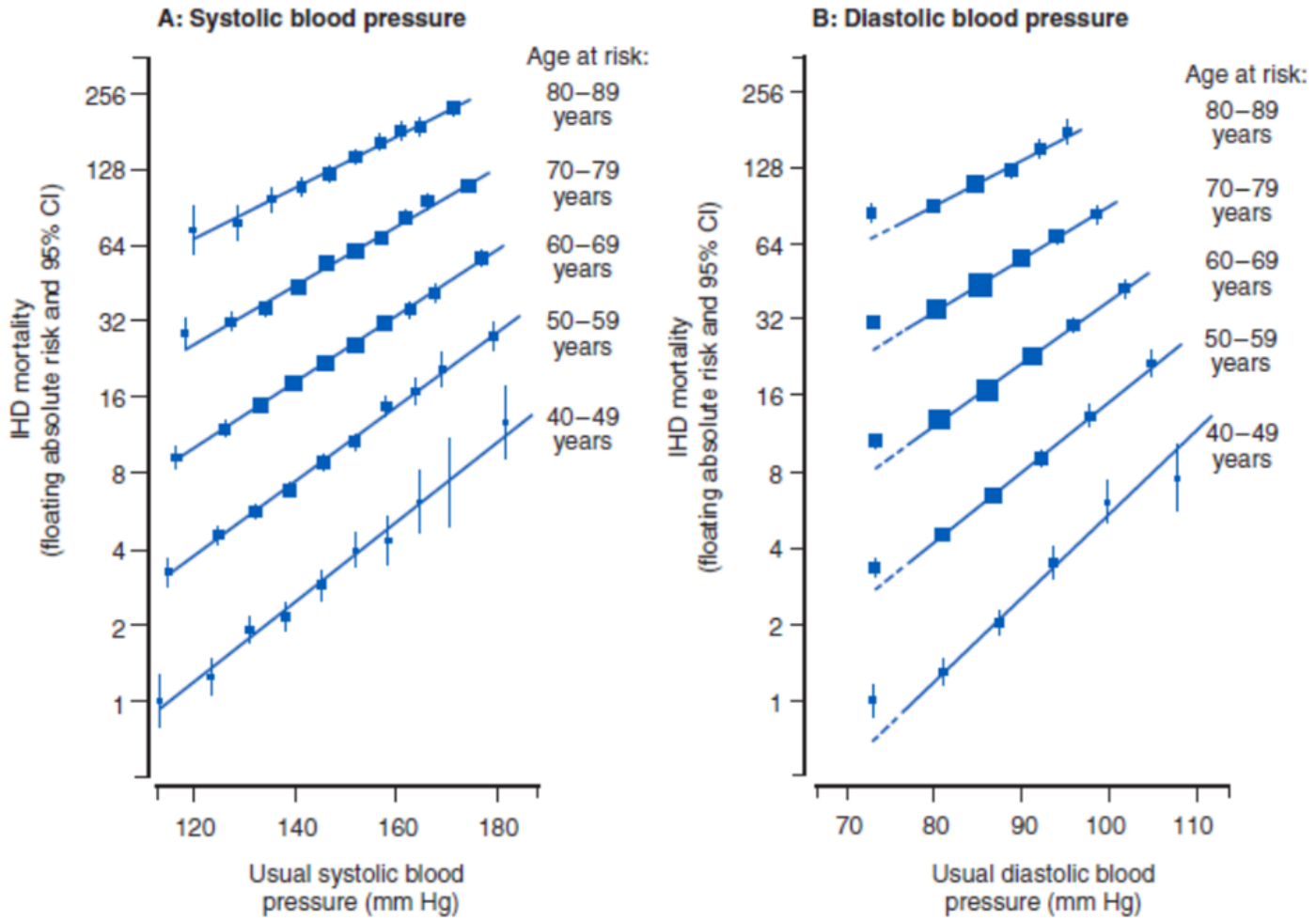
Secondary hypertension

Experimentally induced renal ischemia

Ústav patologické fyziologie LF MU

Blood pressure and ischemic heart disease mortality



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Conceptual definition of hypertension

- blood pressure > **140/90** mm Hg
- arbitrary definition reflecting CV-related morbidity and mortality
  - quantitative relationship between blood pressure and mortality
  - artificial dichotomy between normo- and hypertension
- the level at which the benefits of action exceed those of inaction
  - benefit of action – decreased risk of CV disease
  - risk of action – side effect of therapy
    - hypokalemia in diuretics-treated patients
    - elevation of triglycerides and glucose in β-blockers users
  - risk of inaction - increased risk of CV disease
- benefit of drug treatment have been definitely established in randomized placebo-controlled trials

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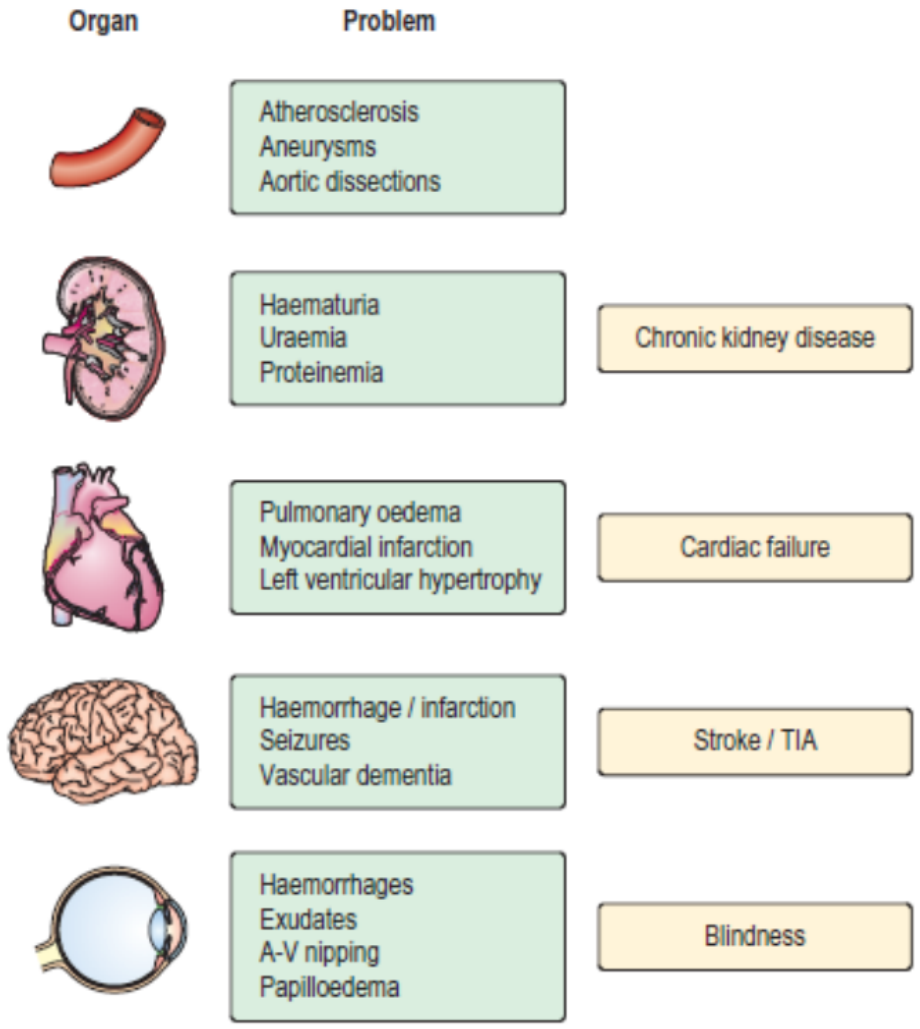
Hypertension and target organ damage

- types
  - primary and secondary
- hypertension
  - major risk factor for premature cardiovascular disease
  - leading cause of death worldwide
  - incidence continues to grow
- asymptomatic nature
- treatment remains most commonly empiric
  - often 3 or more pharmacologic agents with complementary mechanisms
- hypertension causes
  - 54 % of stroke
  - 47 % of ischemic heart disease
    - of all modifiable risk factors, hypertension is exceeded only by smoking



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Framingham study

- since 29.9.1948, Framingham, Boston, MA
- identification of major cardiovascular risk factors
  - blood pressure, cholesterol, triglycerides, HDL, smoking, obesity, diabetes, physical inactivity, age, gender (male) a psychosocial factors
- Initial cohort
  - 5209 people, 30-62 years, detailed examination every 2 years
- II. cohort (since 1971)
  - 5,124 adult offspring
- III. cohort
  - 3,500 children (grandchildren of original participants)
- late clinical manifestations of long-term uncontrolled hypertension
  - myocardial infarction, stroke
  - heart failure
  - kidney failure
  - retinopathy

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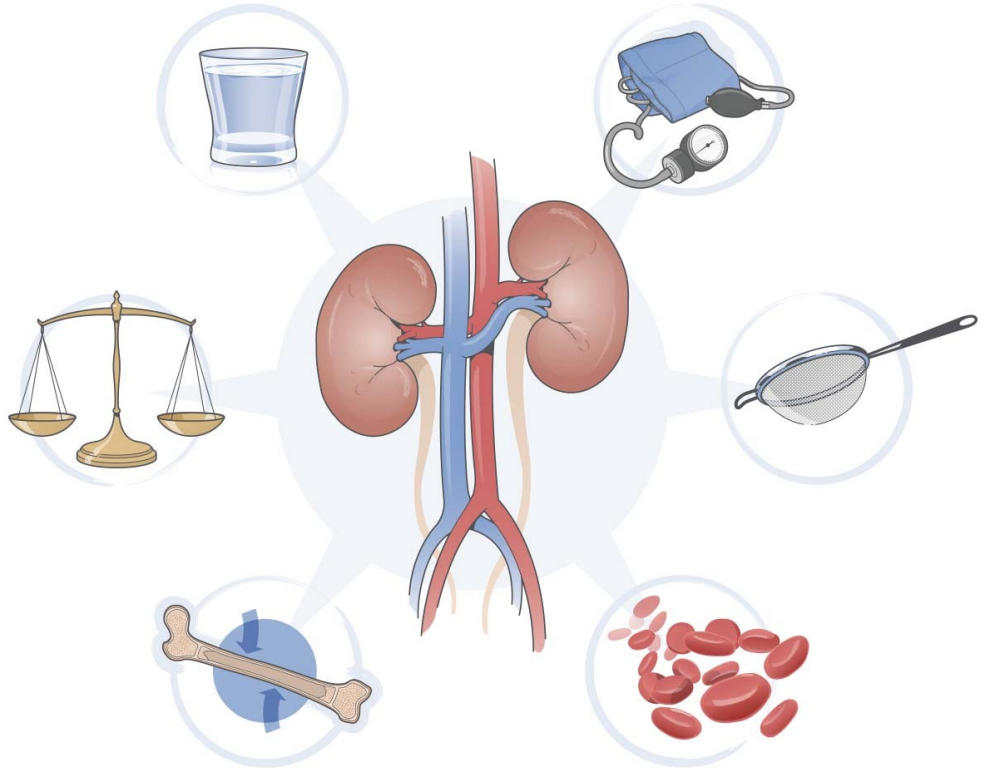
Kidney function

- regulation of
  - extracelllular fluid volume and blood pressure
  - osmolarity
  - acid-base balance
  - ion balance
  - excretion of wastes
  - production of hormones
- kidney perfusion
  - 20 – 25 % of minute heart volume
    - 1200 ml/min, 90 % goes to cortex
    - markedly more than would correspond to kidney weight
  - reasons for high perfusion
    - high energy need of tubular cells
    - production of primary filtrate in glomeruli
      - 20 % of perfusion
      - 150-180 l/day – 90 % reabsorption
      - glomerular filtration rate (GFR)
        - 100-120 ml/min



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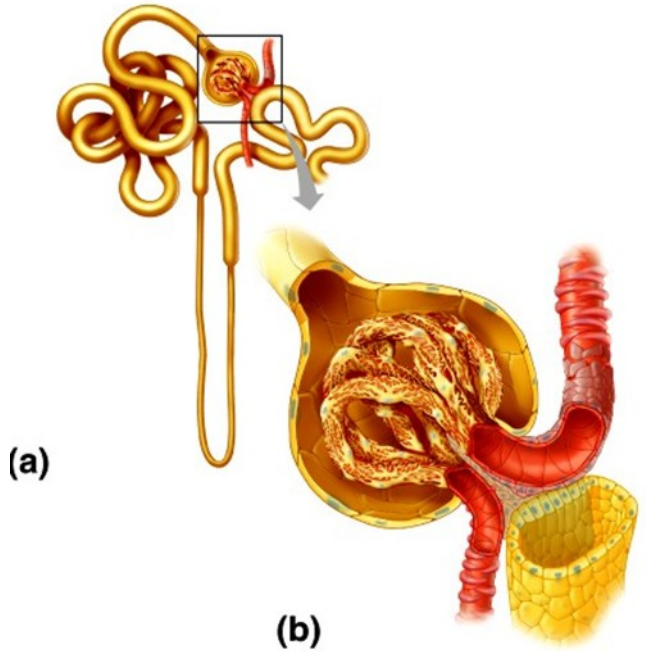
Juxtaglomerular apparatus

- juxtaglomerular (JG) cells
  - specialised muscle cells
  - advanced endoplasmic reticulum and Golgi apparatus
  - production of renin
  - blood pressure receptor
- macula densa
  - close to JG cells
  - senzitive to NaCl
- mesangial cells
  - specialized pericytes
  - contraction
- juxtaglomerular apparatus
  - sympathetic innervation



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Renin-angiotensin-aldosterone system

- plasma/systemic RAS
- tissue RAS
  - kidneys, adrenal gland
- intermediate
  - lungs, heart, vessels, liver
- renin – protease released by JG cells
- factors controlling renin release
  - drop in blood pressure
  - decrease in the amount of NaCl delivered to the kidney
  - β-adrenergic stimuli
  - angiotensin II
  - low potassium

- aldosterone
  - binding to cytosolic mineralocorticoid receptors (MR) in the renal collecting duct cells
  - sodium channels in the membrane and subsequent reabsorption of Na
    - volume re-expanding
  - MR expressed also outside the kidney
    - impairment of vascular health by multiple extrarenal mechanisms

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Effects of angiotensin II

- cardiovascular tissues
- brain
  - stimulation of thirst
  - release of ADH

- angiotensin II receptors
  - AT_1
    - responsible for the majority of Ang II action
    - smooth muscle, endothelial cells, adrenal cortex
  - AT_2
    - opposes the effect of AT1 (at least in rodent models), the role in humans is not explained
    - widely distributed in the fetus
    - in adults expressed in
      - adrenal medulla, endothelium, brain regions

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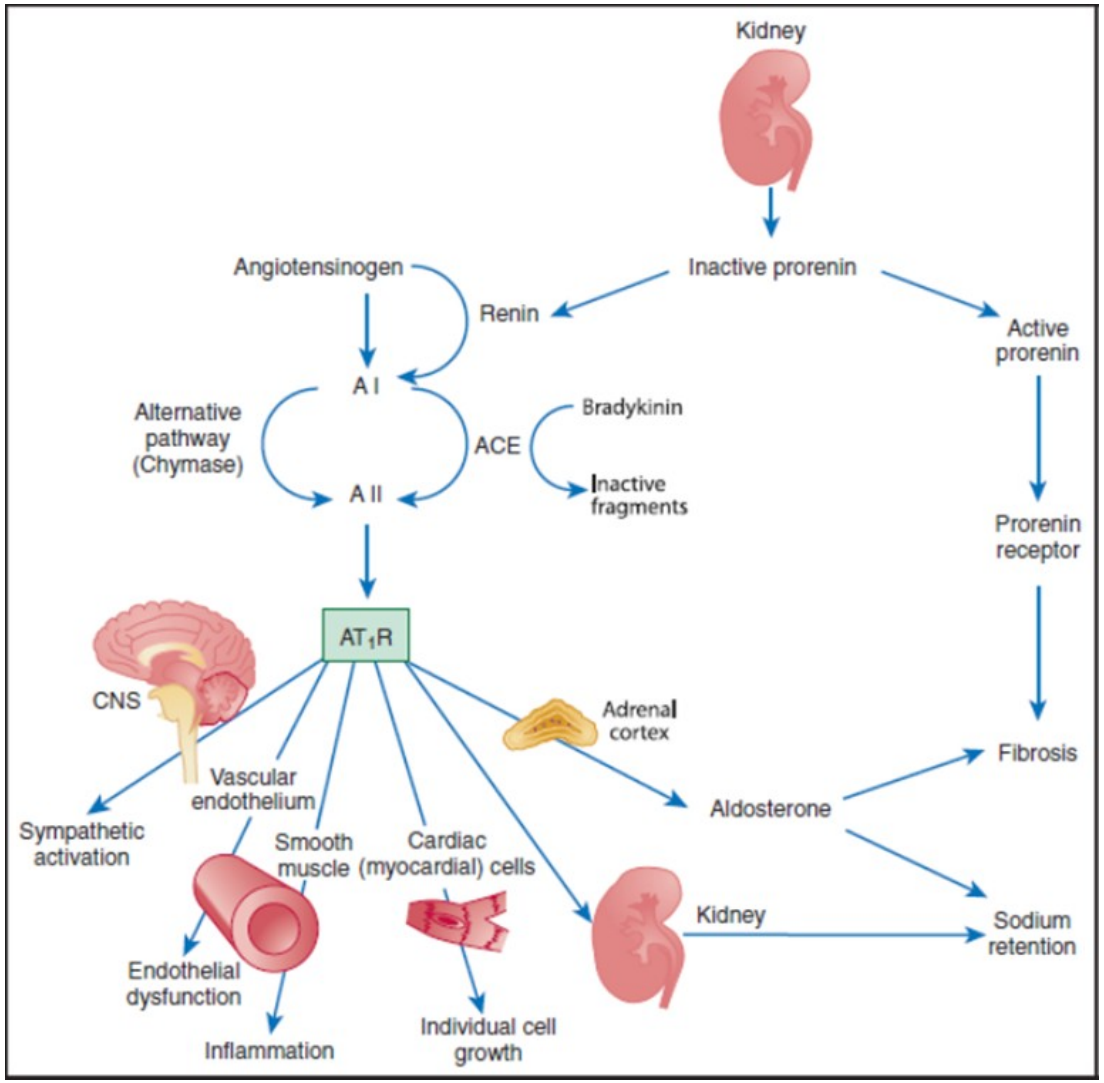
RAAS overview



THE LARAGH VASOCONSTRICTION-VOLUME SPECTRUM OF CLINICAL HYPERTENSION

PRA	Vasoconstriction		Volume	Body Na^+
High	↑	Malignant Hypertension		Low
		Unilateral Renovascular		
		High-Renin Essential Hypertension		
		Pheochromocytoma		
Medium		Medium-Renin Essential Hypertension		Normal
		Bilateral Renovascular Hypertension		
Low		Low-Renin Essential Hypertension	↓	High
		Primary Hyperaldosteronism		

Normal BP = (PRA) × (Na^+ – Volume)

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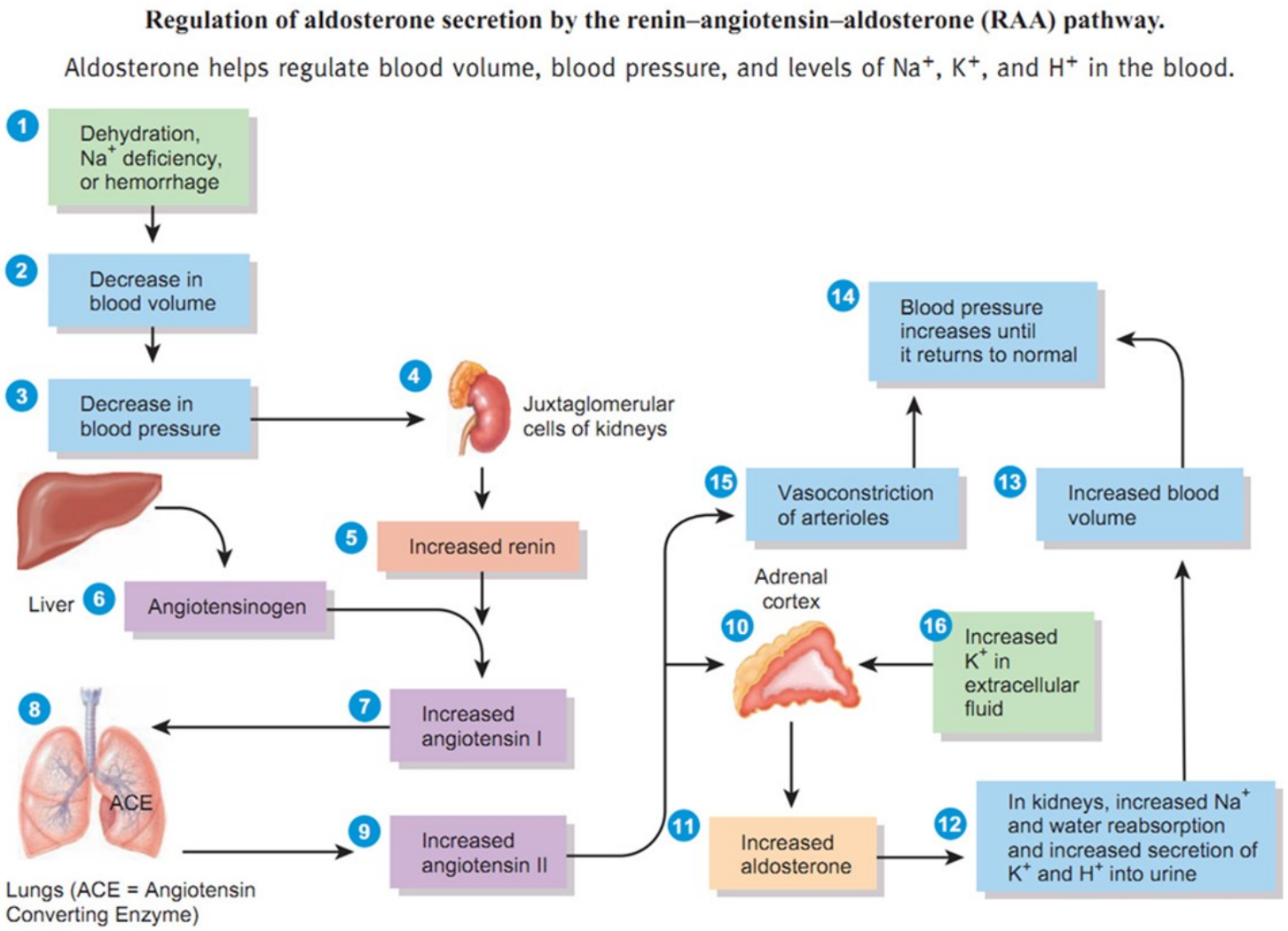
RAAS overview



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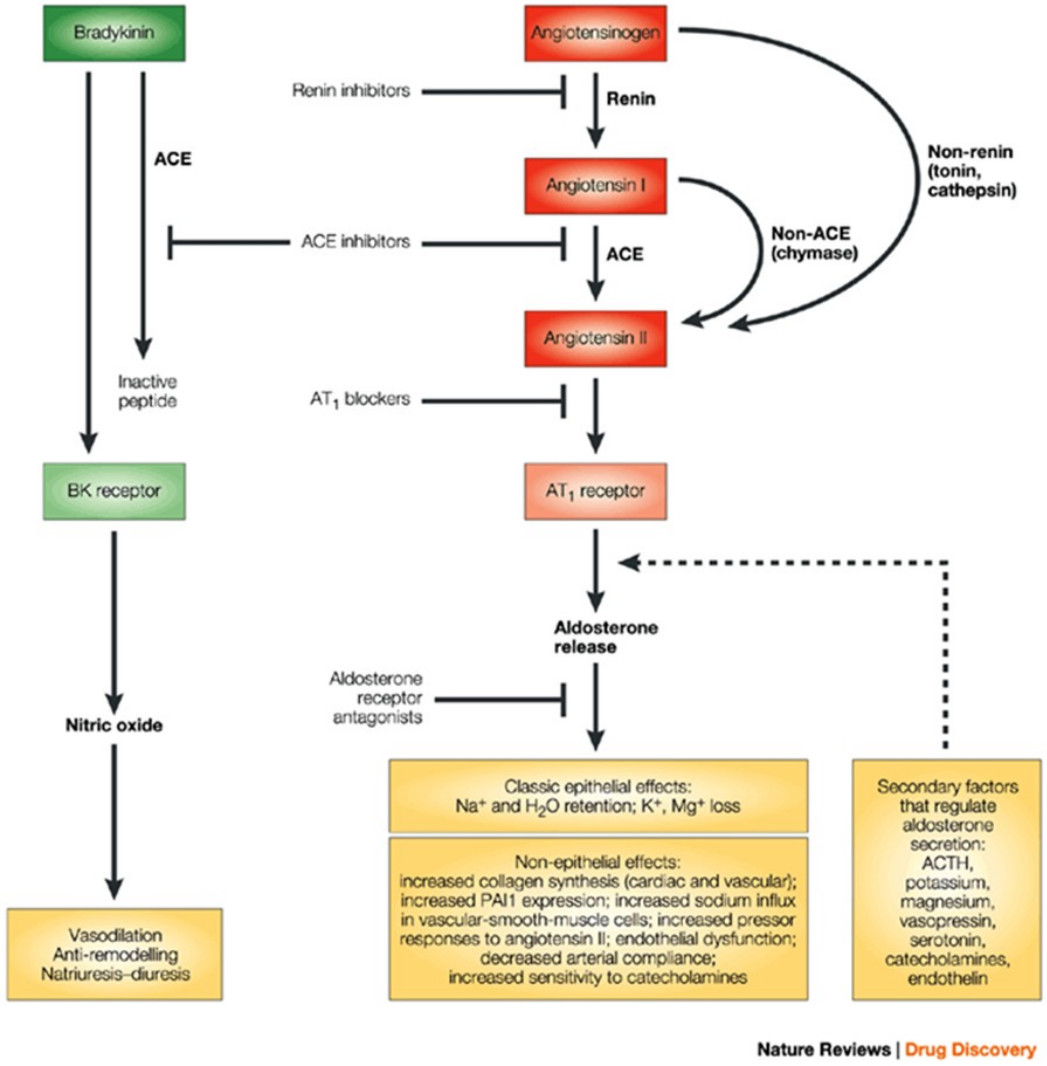
RAAS manipulation



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Major forms of secondary hypertension

- renal disorders
  - parenchymal
  - renovascular
- endocrine disorders
  - Cushing syndrome
  - primary aldosteronism
- vascular disorders
  - coarctation of the aorta
- pregnancy
- exogenic cause
  - medication
  - contraception
  - drugs
    - cocaine, amphetamine
  - licorice

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Screening for secondary hypertension

- secondary forms are rare and screening for them expensive and laborious
  - it is not cost effective to search for secondary causes of hypertension in every patient
- testing requires clinical suspicion and knowledge of limitations of different tests

- general principles
  - new onset hypertension if <30 or >50 years of age
  - hypertension refractory to treatment (>3-4 medications)
  - specific clinical/lab features typical for secondary HT
    - hypokalemia, differential BP in arms, episodic hypertension…

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Renal parenchymal disease

- 2 – 5 % cases of hypertension
- mechanisms
  - common pathway
    - impaired renal autoregulation
    - high perfusion pressure
    - damage of the glomerular cells
  - stiffness of the arteries
    - ↑ SBP, ↓ DBP, ↑ pulse pressure
  - retention of water and electrolytes due to significant decrease of glomerular fitration

TABLE 9-3

Features Associated with High BP in Chronic Kidney Disease

Preexisting primary (essential) hypertension
Extracellular fluid volume expansion
Arterial stiffness
Renin–angiotensin–aldosterone system stimulation
Increased sympathetic activity
Endothelin
Low birth weight with reduced nephron number
Decrease in vasodilatory prostaglandins
Obesity and insulin resistance
Sleep apnea
Smoking
Hyperuricemia
Erythropoietin administration
Parathyroid hormone secretion/increased intracellular calcium/hypercalcemia
Renal vascular disease and renal arterial stenosis
Aldosterone-induced fibrosis and sodium retention
Asymmetric dimethylarginine
Advanced glycation end products
Chronic allograft dysfunction
Cadaver allografts, especially from a donor with a family history of hypertension
Immunosuppressive and corticosteroid therapy
Heritable factors

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Renovascular hypertension

- 1-2 % cases of hypertension
  - atherosclerosis
    - 70 – 90 % of cases
      - in older adults
  - fibromuscular dysplasia
    - more common in women
    - non-inflammatory vascular disease
    - affects more commonly young women
      - often in the 3rd decade
- mostly partial obstruction of one main renal artery
  - decreased RBF, activation of RAAS
- suspiction of renal artery stenosis
  - hypertension in previously normotensive person
    - < 30 or > 50 years
  - severe or resistant hypertension
  - smoking
  - accelerated hypertension in previously controlled person
  - worsening renal function after RAS inhibition
- reduction in renal perfusion by 50 %
  - immediate and persistent increase of renin secretion from ischemic kidney
- renovascular vs. primary hypertension
  - hypokalemia
  - no family history of hypertension
  - duration < 1 year
- administration of ACE inhibitors may cause a decline in renal function
- diagnostic tests
  - assessment of renal function, RAAS
  - imaging studies
- treatment
  - blood pressure control
  - renal function stabilization
  - angioplasty

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Renovascular hypertension

- atherosclerosis
  - 90 % of RVH
  - affects mainly proximal third of the main renal artery
  - seen mostly in older men
  - bilateral in 30 %
- fibromuscular dysplasia
  - 10 % of RVH
  - noninflammatory vascular disease
  - involving mainly distal 2/3 and branches of renal arteries
  - rarely bilateral
    - predilection in the right renal artery
  - appears most commonly in younger women

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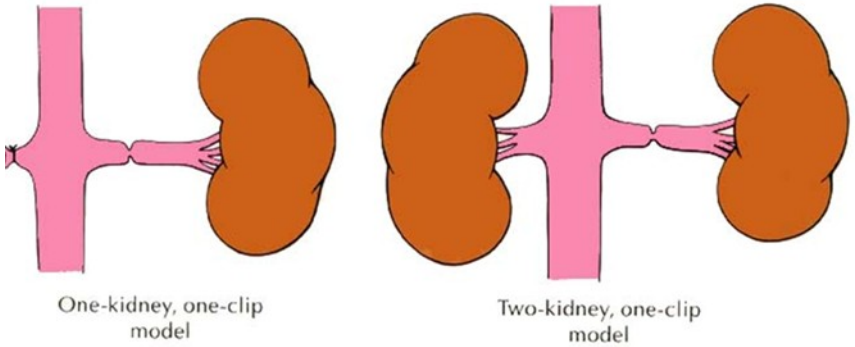
Goldblatt‘s experimental hypertension



- 2 kidneys/1 clip (2K1C)
  - hypertension + preserved regulation of extracellular volume
- 1 kidney/1 clip (1K1C)
  - hypertension + disorder of extracelllular volume regulation

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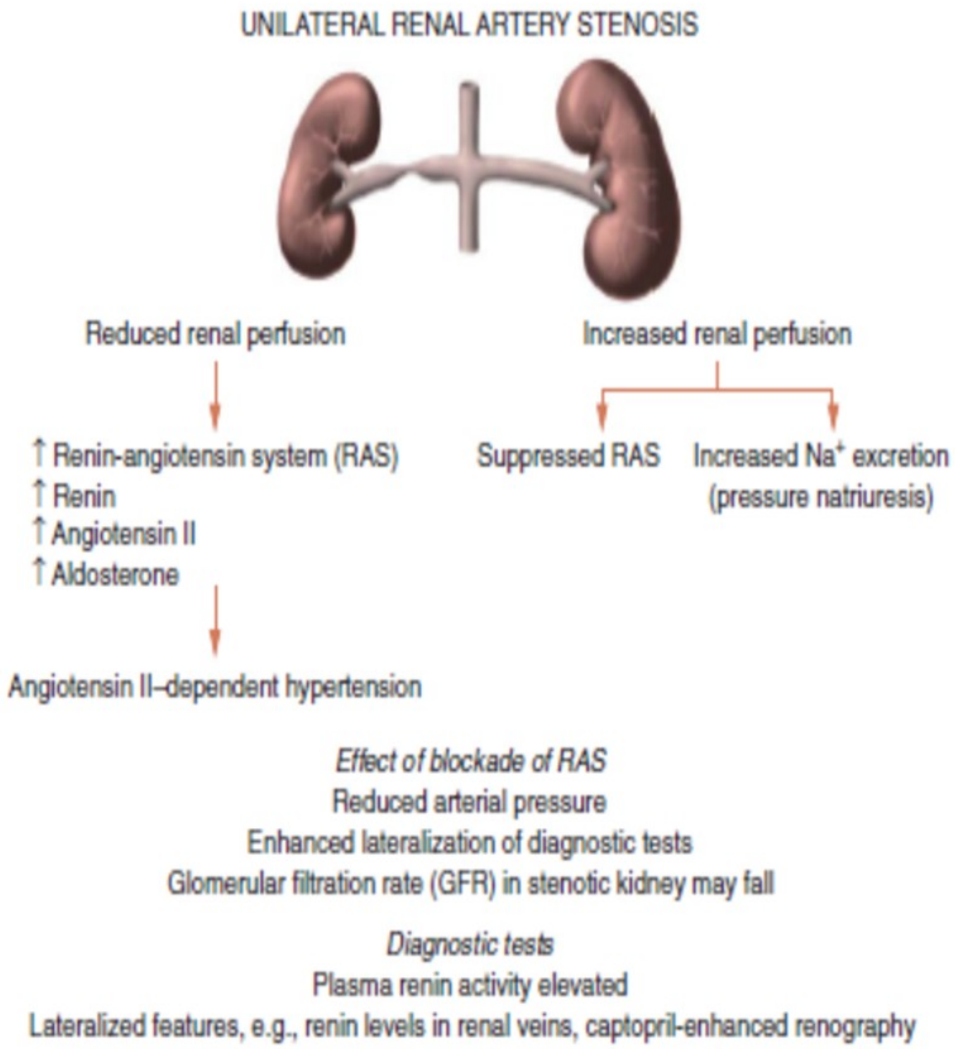
2K1C hypertension



- unilateral stenosis may be present with an intact contralateral renal artery
- counterregulatory processes in the contralateral kidney
  - sodium excretion in response to increased blood pressure

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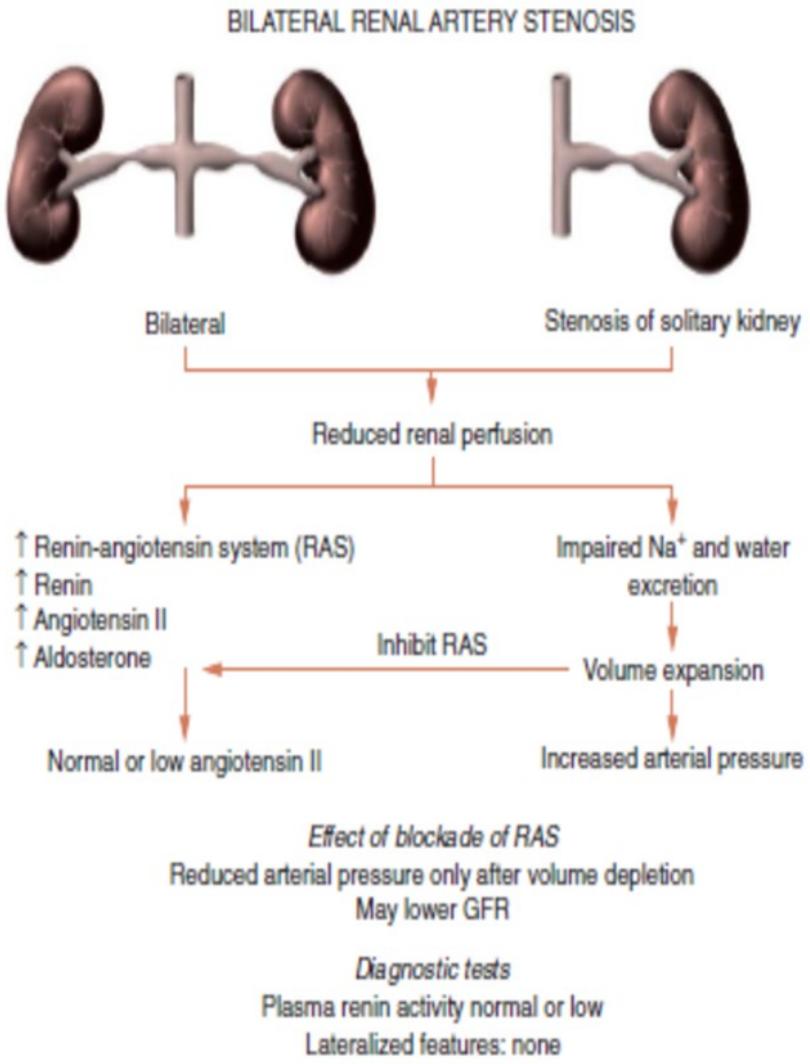
1K1C hypertension



- bilateral stenosis and 1K1C lead to more severe hypertension

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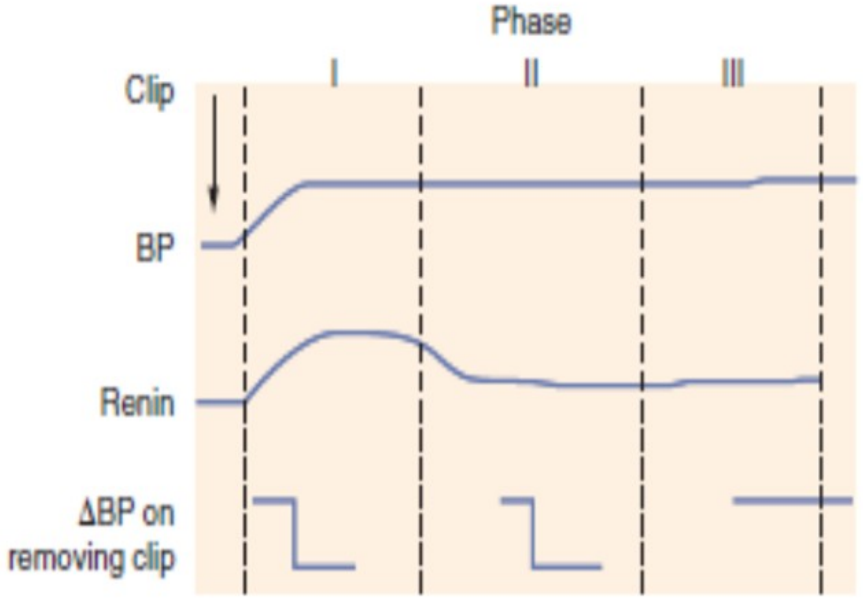
Phases of experimental hypertension

- early phase
  - renal ischemia, activation of RAAS
  - elevated renin, hypertension
- second phase
  - blood pressure responds to clip removal
- third phase
  - no reduction of blood pressure after clip removal
  - microvascular injury of contralateral kidney
  - oxidative stress?



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Mineralocorticoid-induced hypertension

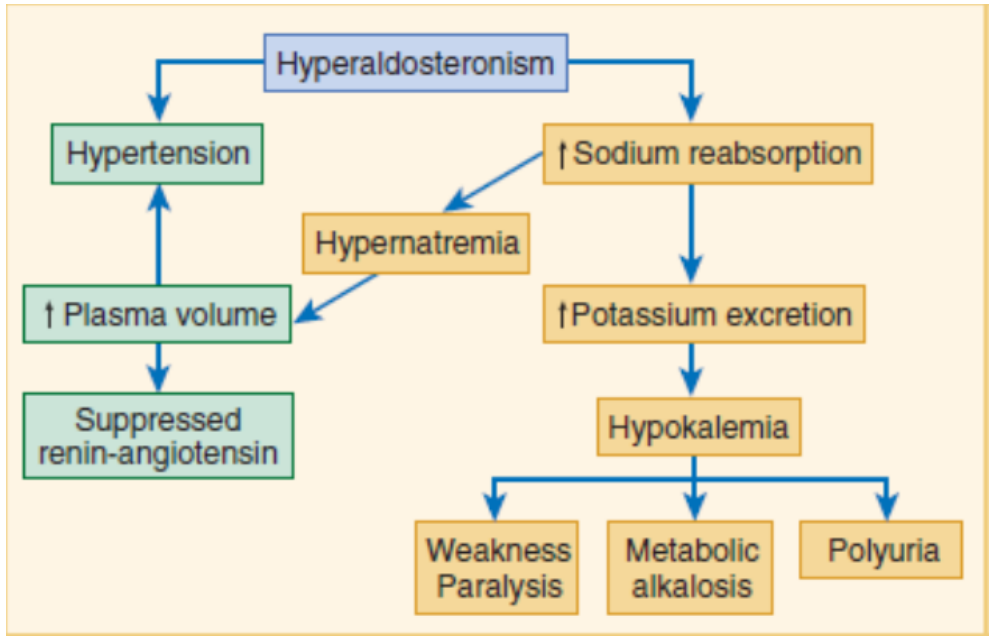

TABLE 45-5 Syndromes of Mineralocorticoid Excess

- Adrenal origin
  - Aldosterone excess (primary)
    - Aldosterone-producing adenoma
    - Bilateral hyperplasia
    - Primary unilateral adrenal hyperplasia
    - Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism, type I)
    - Adrenal carcinoma
    - Extra-adrenal tumors
  - Deoxycorticosterone excess
    - Deoxycorticosterone-secreting tumors
    - Congenital adrenal hyperplasia
    - 11β-Hydroxylase deficiency
    - 17α-Hydroxylase deficiency
  - Cortisol excess
    - Cushing syndrome from ACTH-producing tumor
    - Glucocorticoid receptor resistance
- Renal origin
  - Activating mutation of mineralocorticoid receptor
  - Pseudohypoaldosteronism, type II (Gordon)
  - 11β-Hydroxysteroid dehydrogenase deficiency
    - Congenital: apparent mineralocorticoid excess
    - Acquired: licorice, carbenoxolone

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Hyperaldosteronism

- group of conditions characterized by chronic excess aldosterone secretion
- primary
  - autonomous overproduction of aldosterone
  - supression of RAAS, decreased plasma renin
  - 3 types
    - bilateral idiopathic hyperaldosteronism
      - the most common cause of primary hyperaldosteronism (60 % of cases)
    - adrenocortical neoplasm
      - Conn syndrome – solitary aldosterone-secreting adenoma
    - glucocorticoid-remediable hyperaldosteronim
      - uncommon, familial
      - ectopic aldosterone synthase activity in the cortisol producting zona fasciculata of adrenal cortex
      - under the regulation of ACTH
        - glucocorticoid supression
- secondary hyperaldosteronism
  - aldosterone release occurs in response to activation of RAAS
    - increased plasma renin
  - conditions
    - decreased renal perfusion
    - hypovolemia
    - pregnancy
      - estrogen-induced increases in plasma renin substrate

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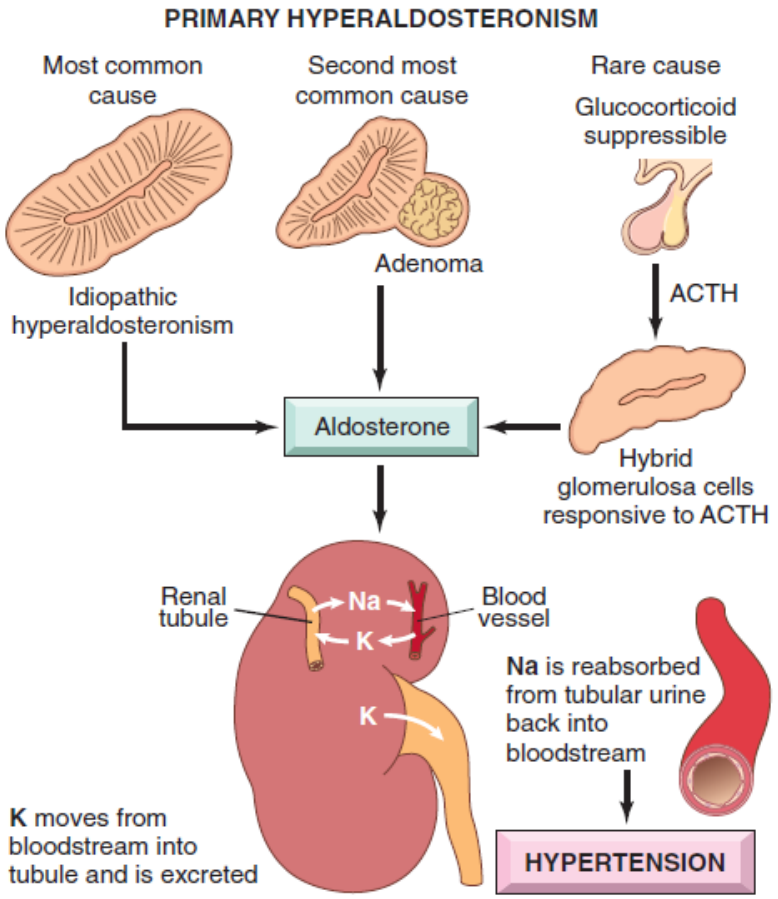
Hyperaldosteronism

- clinical consequences
  - hypertension
    - one of the most comman causes of secondary hypertension
      - in 20 % of patients with treatment-resistant hypertension
  - hypokalemia
  - profibrotic effect of aldosterone
    - more CV events in patients with primary aldosteronism than in patients with primary hypertension
- diagnosis
  - hypokalemia, low plasma renin
  - high plasma aldosterone/renin
  - decreased excretion of potassium



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Hypercortisolism (Cushing syndrome)

- conditions that produce elevated glucocorticoids levels
  - exogenous
    - administration of steroids is the most common cause of hypercorticolism
  - endogenous
    - ACTH dependent and independent
      - most often secondary to an ACTH-producing pituitary microadenoma (=Cushing disease)
- Cushing syndrome
  - serious disease
  - hypertension in ~ 75 %
  - often difficult to treat
    - incompletely controlled
  - 4-fold excess of mortality

Clinical Features of Cushing Syndrome

Clinical Features	Approximate Incidence (%)
General	
Obesity	80–95
Truncal	45–95[a]
Hypertension	70–90
Headache	10–50
Skin	
Facial plethora	70–90
Hirsutism	70–80
Purple striae	50–70[a]
Bruising	30–70[a]
Neuropsychiatric	60–95
Gonadal dysfunction	
Menstrual disorders	75–95
Impotence or decreased libido	65–95
Musculoskeletal	
Osteopenia	75–85
Weakness from myopathy	30–90[a]
Metabolic	
Glucose intolerance/ diabetes	40–90
Kidney stones	15–20

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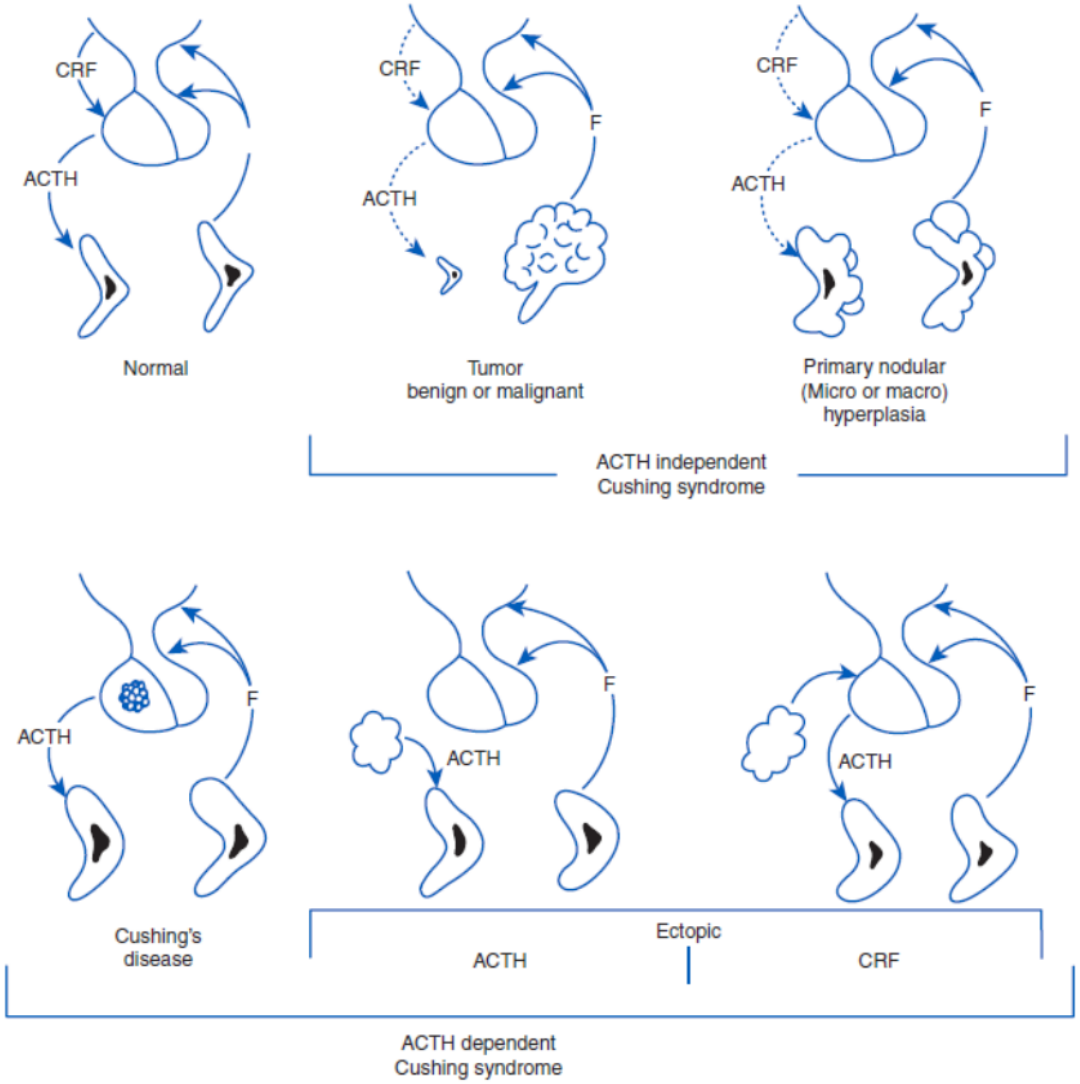
Causes of endogenous Cushing syndrome



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Classification and mechanisms of hypertension

ACTH dependent

Pituitary ACTH (Cushing disease)
Ectopic ACTH syndrome
Ectopic CRH syndrome
Macronodular adrenal hyperplasia

ACTH independent

Adrenal adenoma
Adrenal carcinoma
Micronodular hyperplasia
Adrenal hyperplasia from other stimuli (e.g., GIP)
Exogenous glucocorticoid intake

- mechanisms of hypertension
  - Na retaining action of cortisol
    - ↑ cortisol overwhelms 11β-HSD2
    - cortisol acts on mineralocorticoid receptor (MR)
  - direct action on smooth muscle cells
  - ↑ production of mineralocorticoids
  - ↓ activity of eNOS
  - ↑ angiotensinogen

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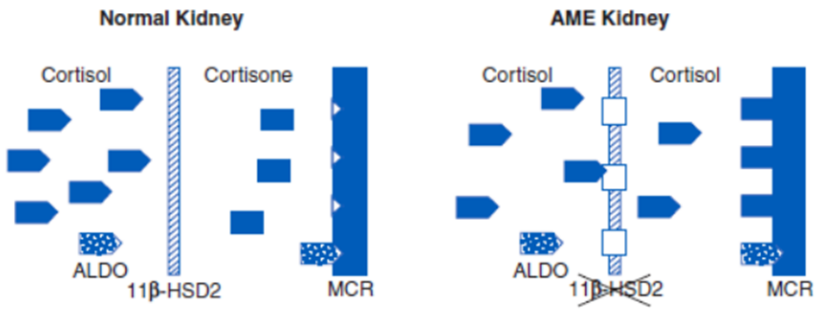
Increased access of cortisol to MR

- 11β-Hydroxysteroid Dehydrogenase
  - 11β-HSD1
    - regeneration of active glucocorticoids, amplification of their action
    - widely expressed in liver, adipose tissue, muscle, pancreas
  - 11β-HSD2
    - inactivates cortisol and corticosterone to the inert cortisone
      - protect mineralocorticoid receptor from occupation by cortisol
    - highly expressed in the distal neuron

- deficiencies of 11β-HSD2
  - enzyme deficiency
    - autosomal recessive
    - apparent mineralocorticid excess (AME)
  - enzyme inhibition
    - glycerrhizic acid
    - confectionery licorice
      - 50 g/daily for 2 weeks - ↑BP
    - treatment
      - competitive blockade of MR with spironolactone



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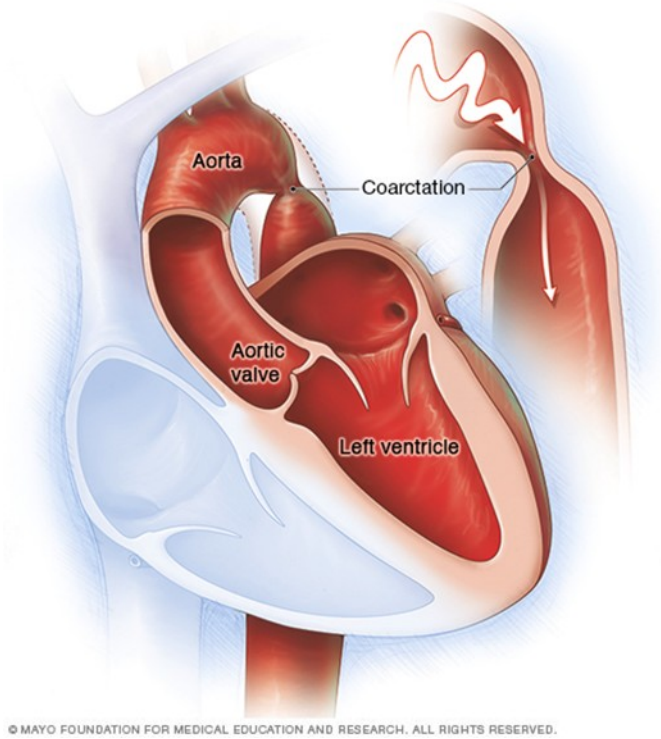
Coarctation of aorta

- distal to the origin of subclavial arteries
- signs
  - hypertension in the arms
  - weak or absent femoral pulses
  - BP on lower extremities is normal or low
- reduced blood flow to the lower part of the body
  - kidneys – RAAS activation
  - increased stroke volume
- probably also generalized vasoconstrictor mechanism
- diagnosis
  - pressure diference > 20 mm Hg
- treatment
  - surgical
  - angioplasty



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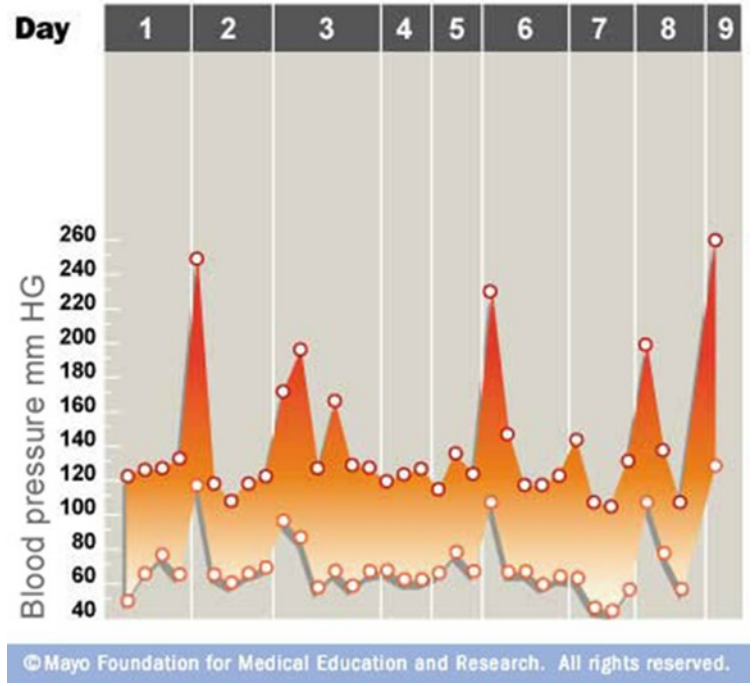
Pheochromocytoma

- tumor of chromaffin tissue
  - adrenal medulla
  - sympathetic ganglia
- 0.1 – 0.5 % of people with hypertension
- can cause serious hypertensive crisis
- production of epinephrine and norepinephrine
  - paroxysmal or continuous
  - episodes of headache, sweating, palpitations
  - weakness, fatigue, weight loss
  - marked BP variability
- diagnostic test
  - urinary catecholamines
  - localization of tumor
- treatment
  - surgery
  - blockade of catecholamines action or synthesis



50 % have paroxysmal episodes of hypertension
other 50 % have sustaines hypertension
some may be normotensive

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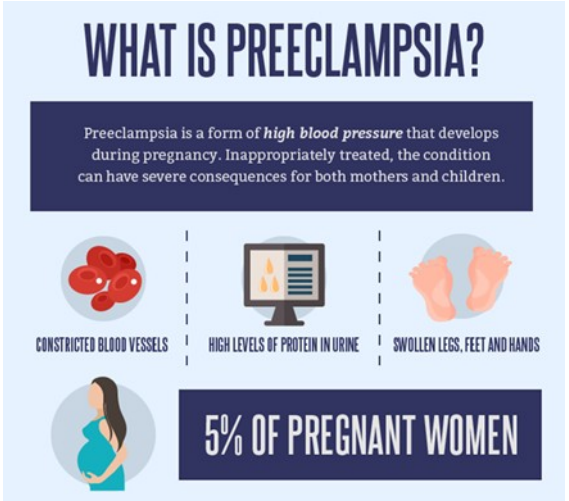
Hypertension in pregnancy

- 5-10 % of all pregnancies
- blood pressure changes during pregnancy
  - decrease during the first semester
  - lowest in the second trimester
  - rise during the third trimester
- changes of cardiac output (CO) and peripheral vascular resistence (PR)
  - large increase of CO in early pregnancy
    - high throughout pregnancy
  - decreased PR
- pregnancy is normally accompanied by
  - increased renin, ang I and II, estrogen, progesterone and aldosterone

- women with preeclampsia
  - new-onset hypertension with proteinuria
    - develops after 20 weeks of pregnancy
  - sensitive to the RAAS
  - also responsive to other vasoconstrictors
  - insulin resistence may predispose to hypertension



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Oral contraceptive drugs and hypertension

- the most common cause of secondary hypertension in young women
- mechanism
  - volume expansion
    - estrogens and progesterons cause sodium retention

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Malignant hypertension

- acute and life-threatening condition associated with a sudden increase in BP
  - usually in younger people
    - black men, kidney damage
  - diastolic > 120 mm Hg
- organ dysfunction
  - hypertensive encephalopathy
    - cerebral vasoconstriction
      - homeostatic response
    - brain edema
  - damage of kidney vessels
    - ↑ creatinine, urea
    - metabolic acidosis, hypocalcemie, proteinuria
- prolonged exposure to high BP
  - arterioles injury
  - intravascular coagulation and RBC fragmentation
  - renal damage
    - ↑ creatinine
    - proteinuria

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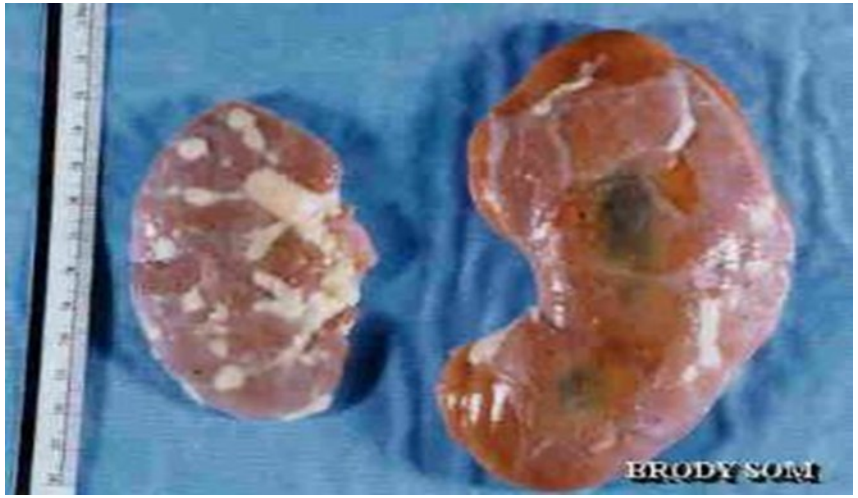
Practical part

- weight of
  - animal
  - kidneys
  - heart
- suture
- microscopic detection of renin



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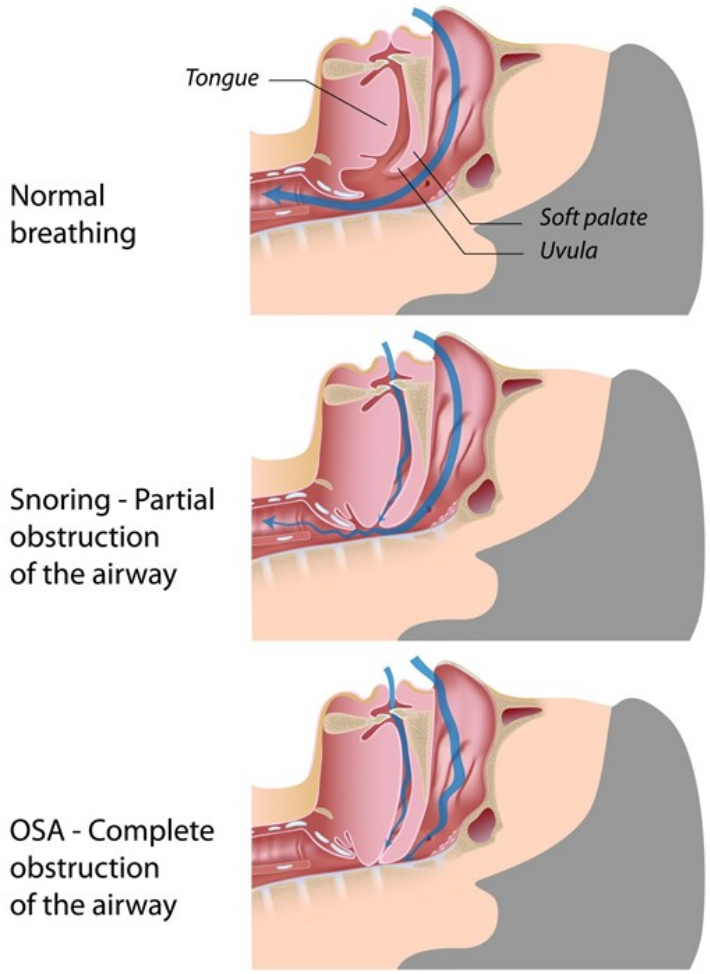
Sleep apnea syndrome

- prevalent in middle-aged and older adults
- mechanisms
  - obesity
  - craniofacial changes
  - alteration in upper airway muscle function
- consequences
  - intermittent hypoxia and hypercapnia
  - recurrent arousals and increase in respiratory efforts
  - secondary sympathetic activation, oxidative stress and systemic inflammation
  - daytime sleepiness



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