

Secondary hypertension

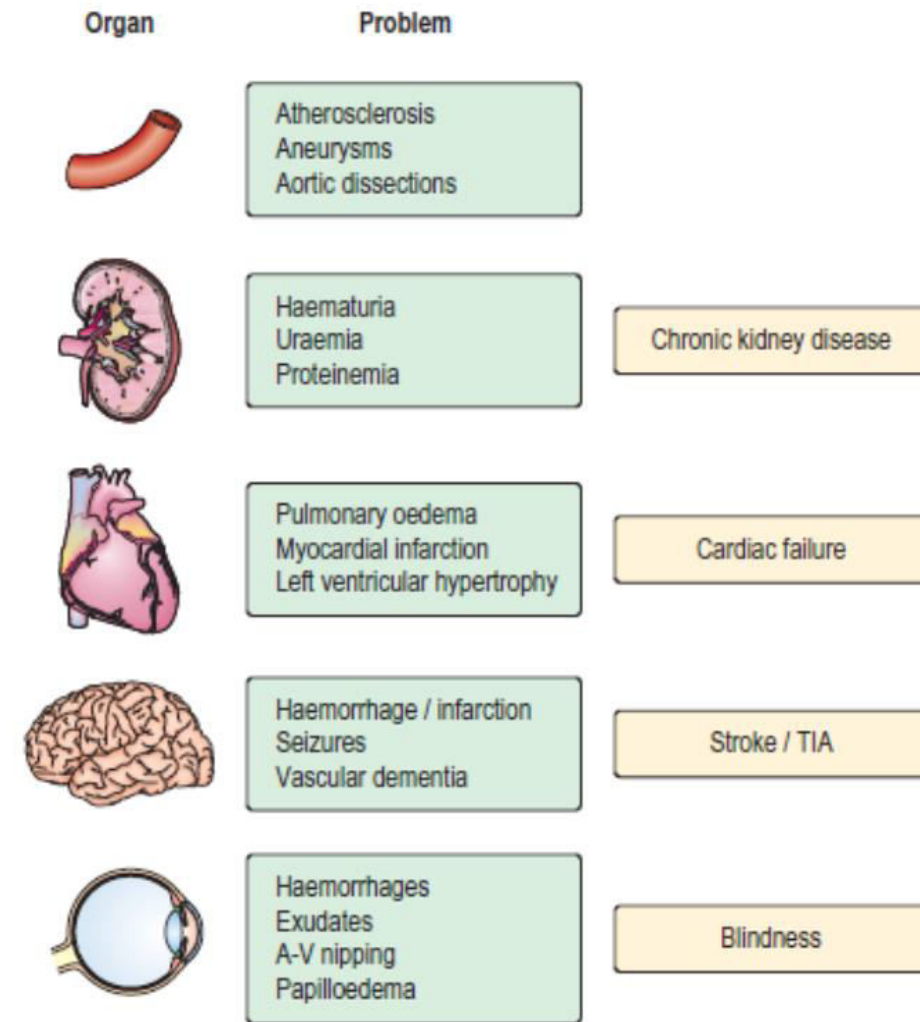
Renal ischemia part 2

Conceptual definition of hypertension

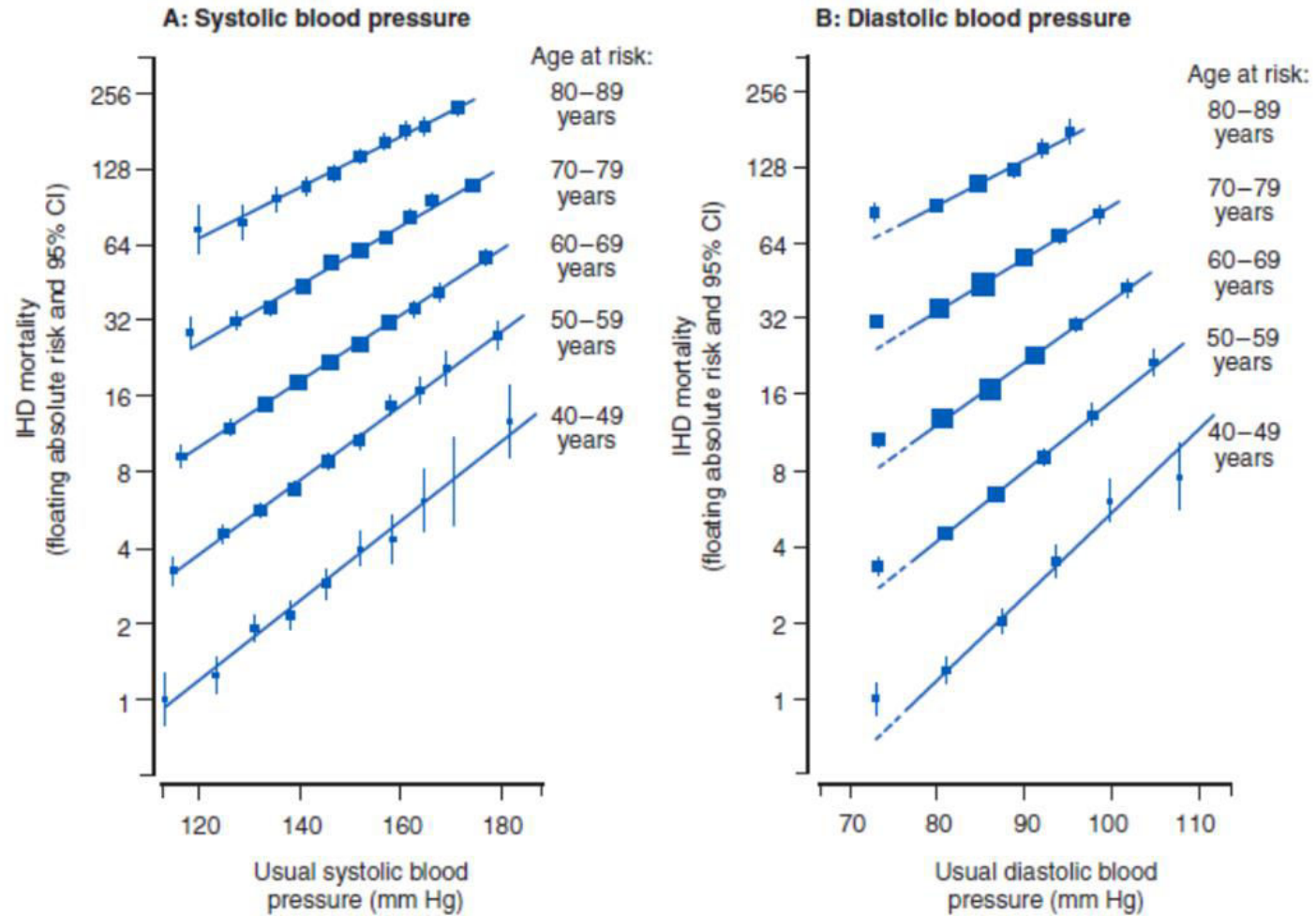
- blood pressure > **140/90** mm Hg
- artificial dichotomy between normo- and hypertension
- the level above which harm is accrued and treatment below that level mitigates the harm
- benefit of drug treatment have been definitely established in randomized placebo-controlled trials

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



BP and ischemic heart disease mortality



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



Major forms of secondary hypertension

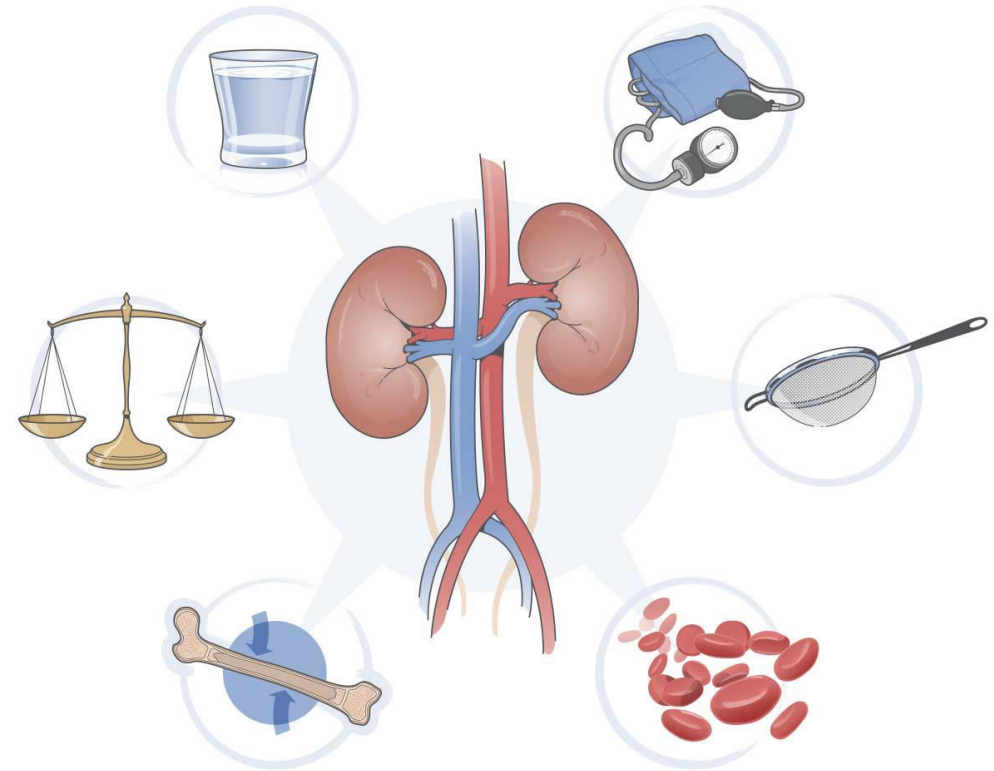
- renal disorders
 - parenchymal
 - renovascular
- endocrine disorders
 - Cushing syndrome
 - primary aldosteronism
- vascular disorders
 - coarctation of the aorta
- pregnancy
- exogenic cause
 - medication
 - contraception
 - drugs
 - cocaine, amphetamine
 - licorice

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...

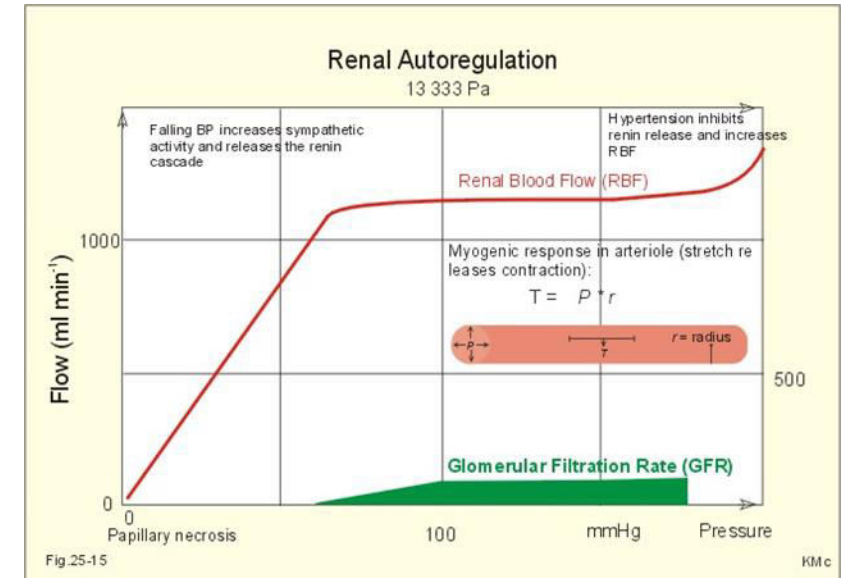
Kidney function

- regulation of
 - extracellular 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



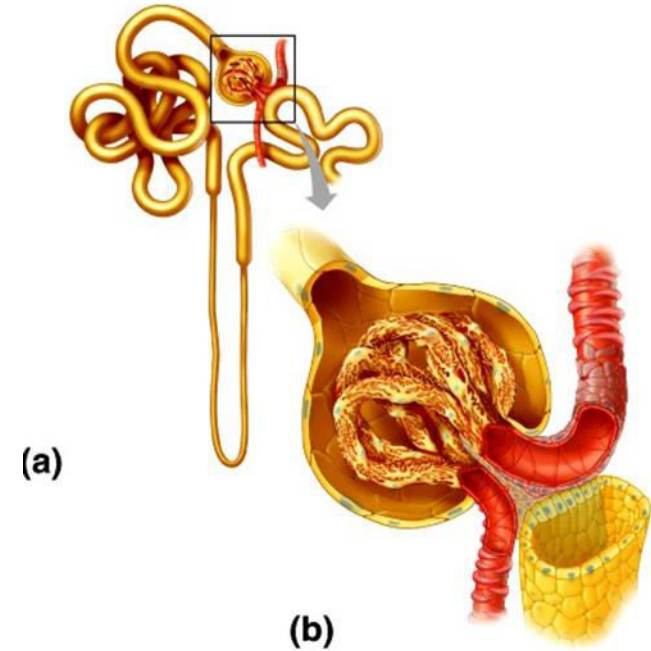
Regulation of kidney perfusion

- GFR is remarkably constant over a wide range of blood pressures
 - 80-180 mm Hg
- autoregulation
 - locally controlled process
 - relatively constant GFR in the face of normal fluctuations in blood pressure
 - protects filtration barrier from high blood pressure
 - myogenic feedback
 - intrinsic to the smooth muscle blood vessels
 - if the pressure within a vessel is suddenly increased, the vessel responds by constricting
 - vascular smooth muscle cells depolarize when stretched, leading to contraction
 - tubuloglomerular feedback
 - changes in the Na^+ , Cl^- , and K^+ concentrations in the tubular fluid are sensed by the macula densa via the $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ cotransporter

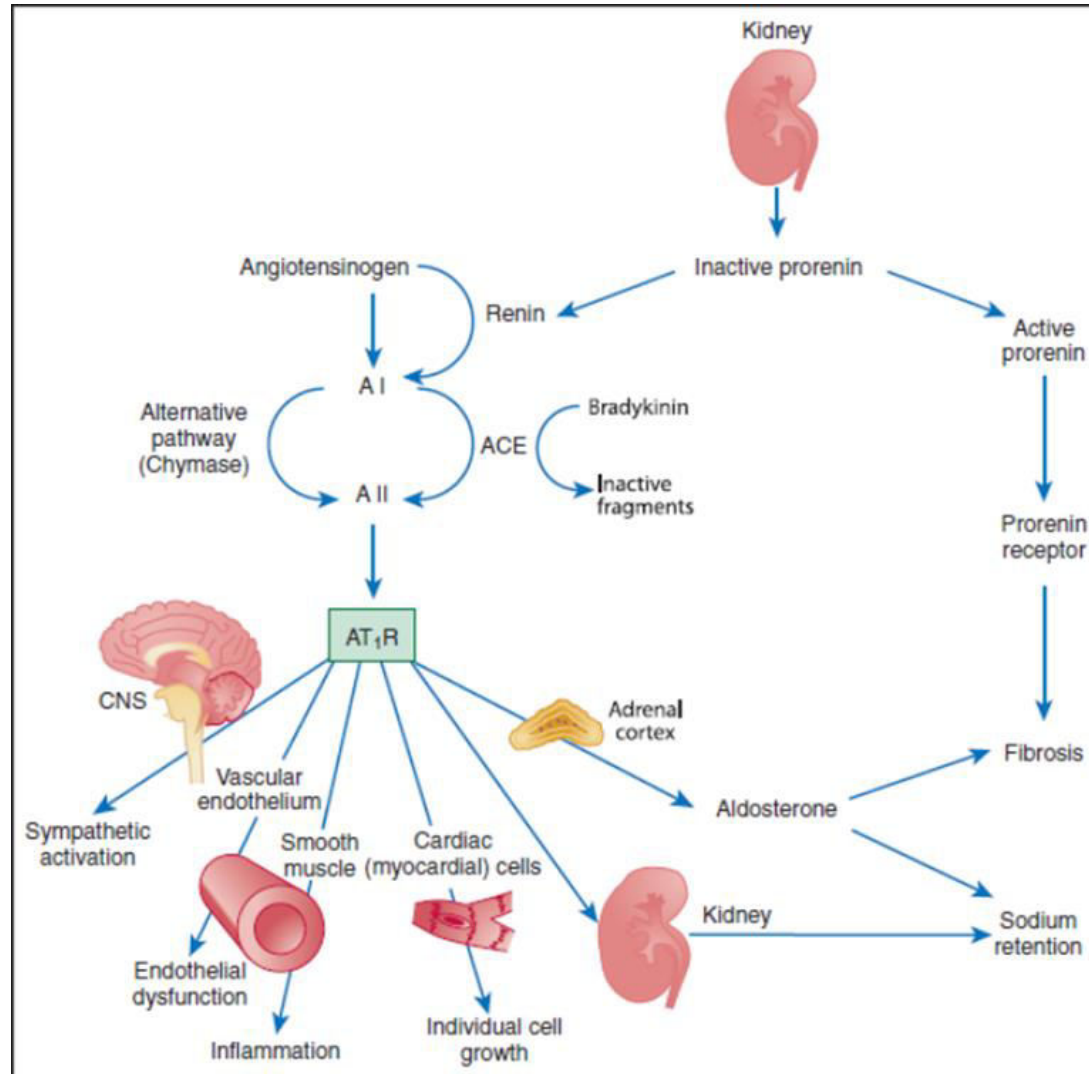


Juxtaglomerular apparatus

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



RAAS overview



THE LARAGH VASOCONSTRICTION-VOLUME SPECTRUM OF CLINICAL HYPERTENSION

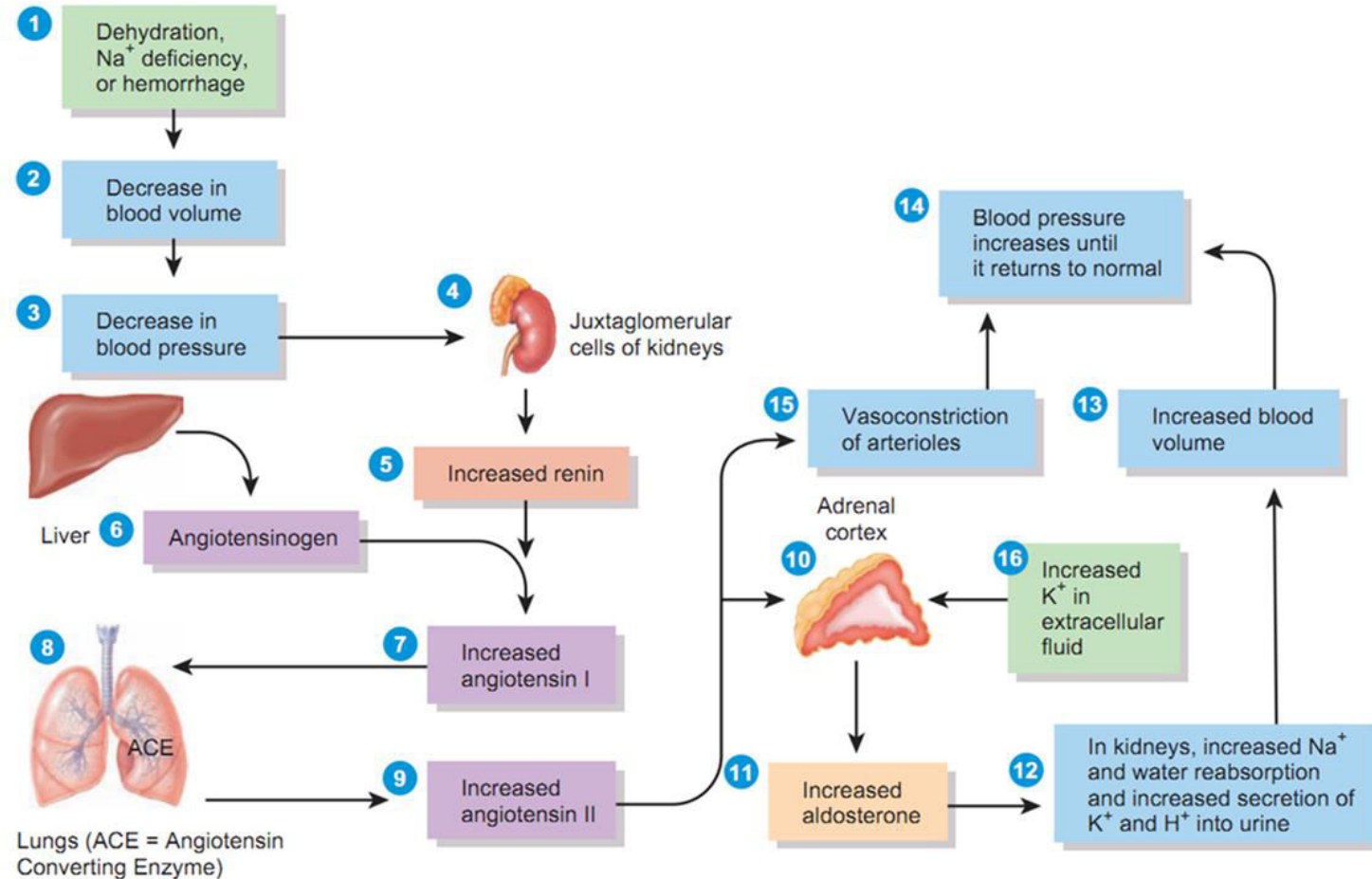
PRA		Body Na ⁺	
High	↑ Vasoconstriction	↓ Volume	Malignant Hypertension
			Unilateral Renovascular
			High-Renin Essential Hypertension
Medium			Pheochromocytoma
			Medium-Renin Essential Hypertension
			Bilateral Renovascular Hypertension
Low			Low-Renin Essential Hypertension
			Primary Hyperaldosteronism

$$\text{Normal BP} = (\text{PRA}) \times (\text{Na}^+ - \text{Volume})$$

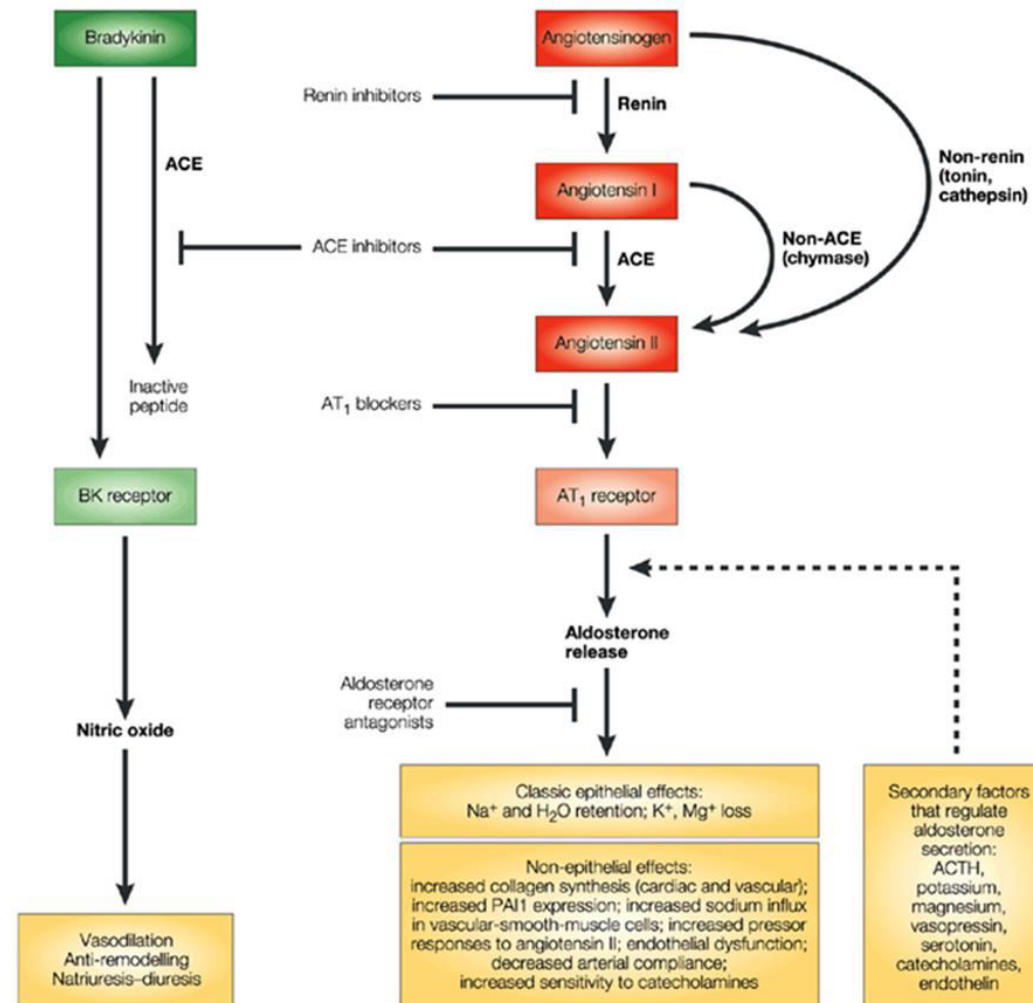
RAAS overview

Regulation of aldosterone secretion by the renin–angiotensin–aldosterone (RAA) pathway.

Aldosterone helps regulate blood volume, blood pressure, and levels of Na^+ , K^+ , and H^+ in the blood.



RAAS manipulation



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
 - \uparrow SBP, \downarrow DBP, \uparrow pulse pressure

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

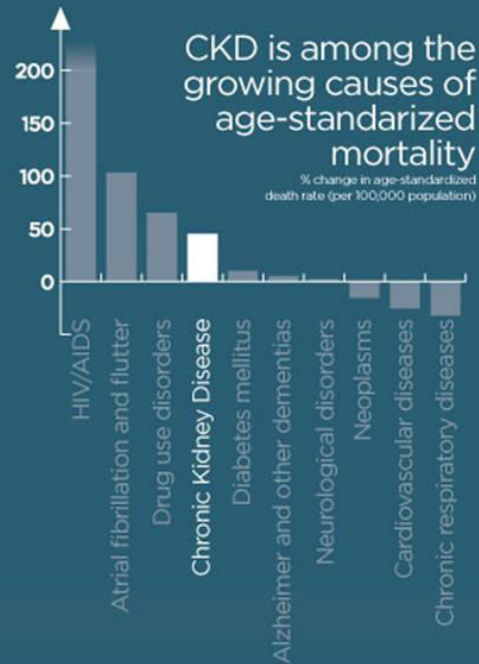
CHRONIC KIDNEY DISEASE (CKD)

Impact on global mortality*

956,246
deaths directly
related to CKD in 2013



1 in 57
deaths worldwide
due to CKD



7%

of all cardiovascular deaths
are attributable to CKD



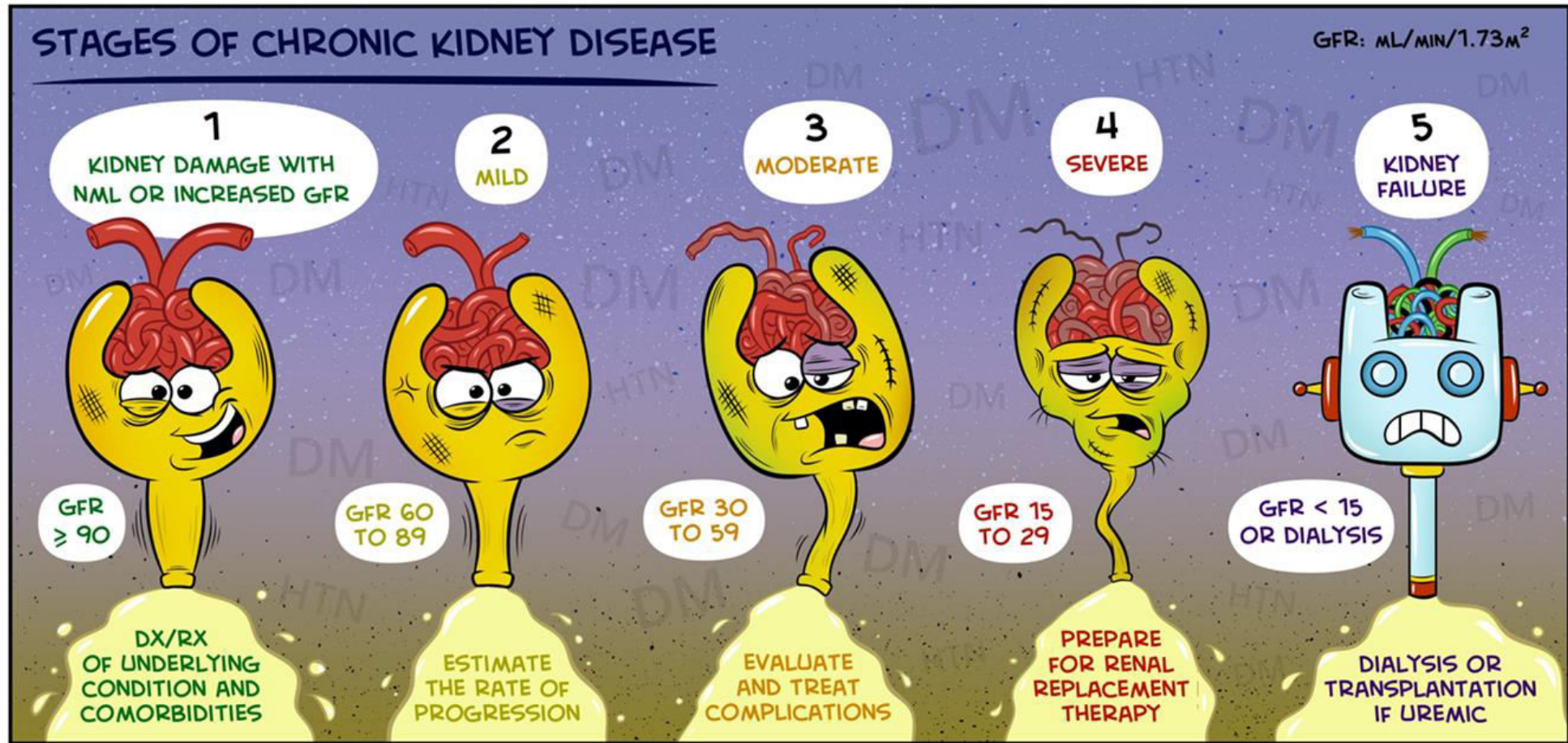
1,207,453

cardiovascular deaths were attributed
to one of the principal CKD markers,
low Glomerular Filtration Rate

134%

Increase in # of
deaths from CKD
1990 - 2013

CKD stages



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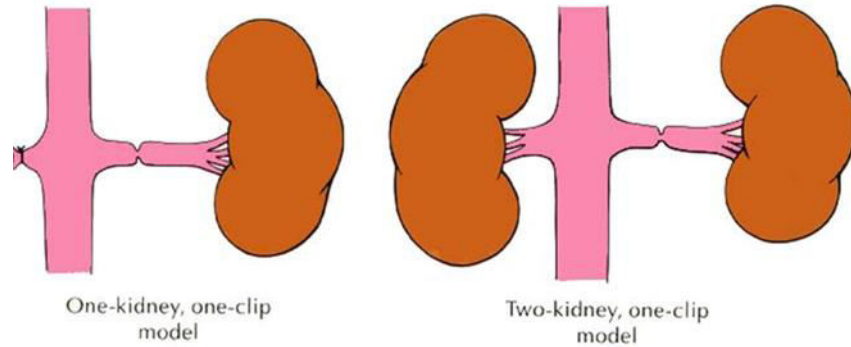
Renovascular hypertension

- 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
- suspicion 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

Renovascular hypertension

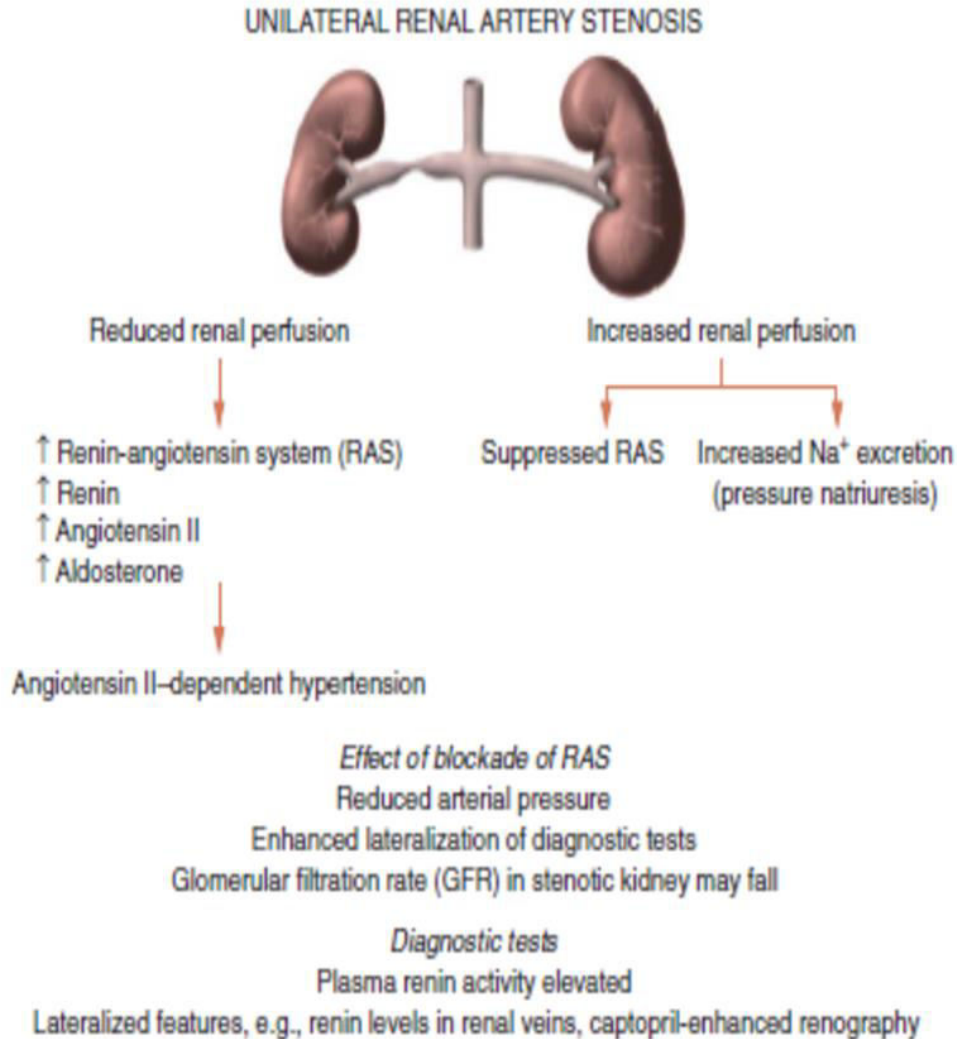
- atherosclerosis
 - 90 % of RVH
 - affects mainly proximal third of the main renal artery
 - seen mostly in older men
 - bilateral in 30 %
- fibromuscular dysplasia
 - 10 % of RVH
 - noninflammatory vascular disease
 - involving mainly distal 2/3 and branches of renal arteries
 - rarely bilateral
 -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

Goldblatt's experimental hypertension



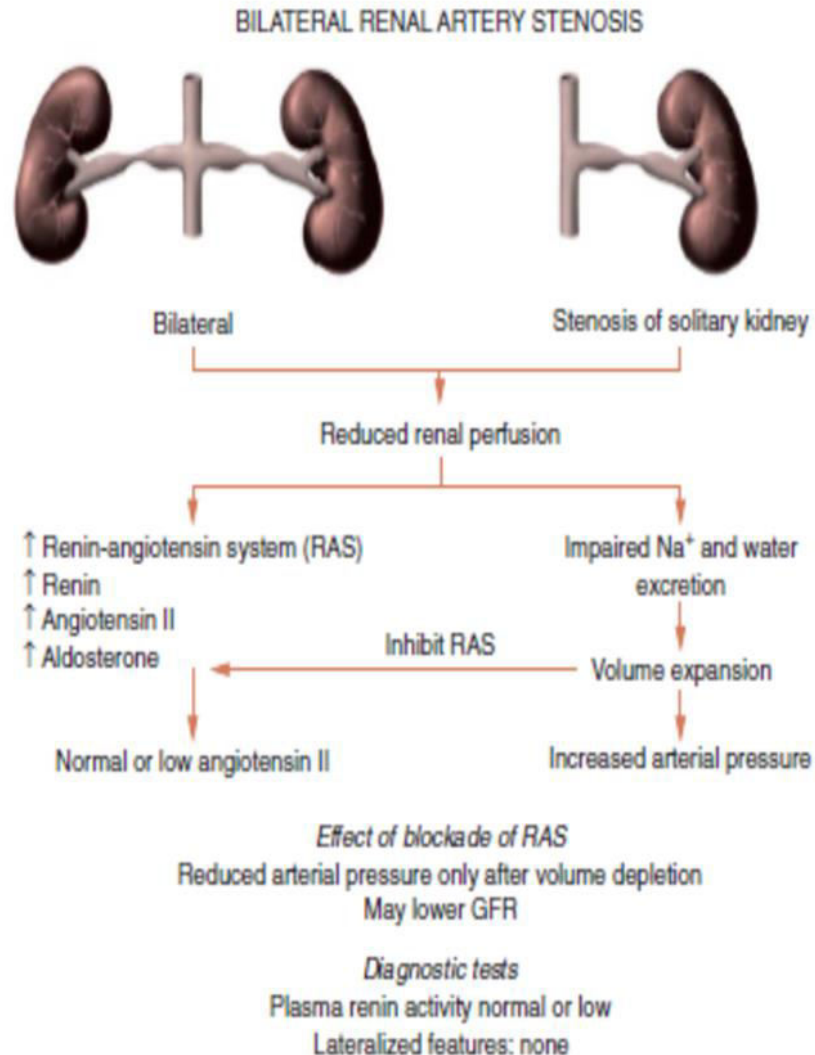
- 2 kidneys/1 clip (2K1C)
 - hypertension + preserved regulation of extracellular volume
- 1 kidney/1 clip (1K1C)
 - hypertension + disorder of extracellular volume regulation

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

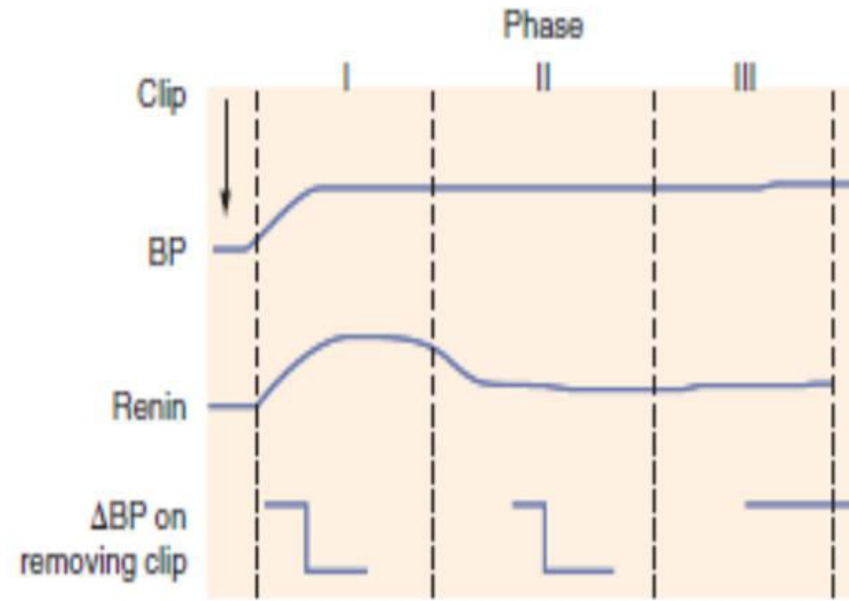
1K1C hypertension



- bilateral stenosis and 1K1C lead to more severe hypertension

Phases of experimental hypertension

- early phase
 - 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?



Mineralocorticoid-induced hypertension

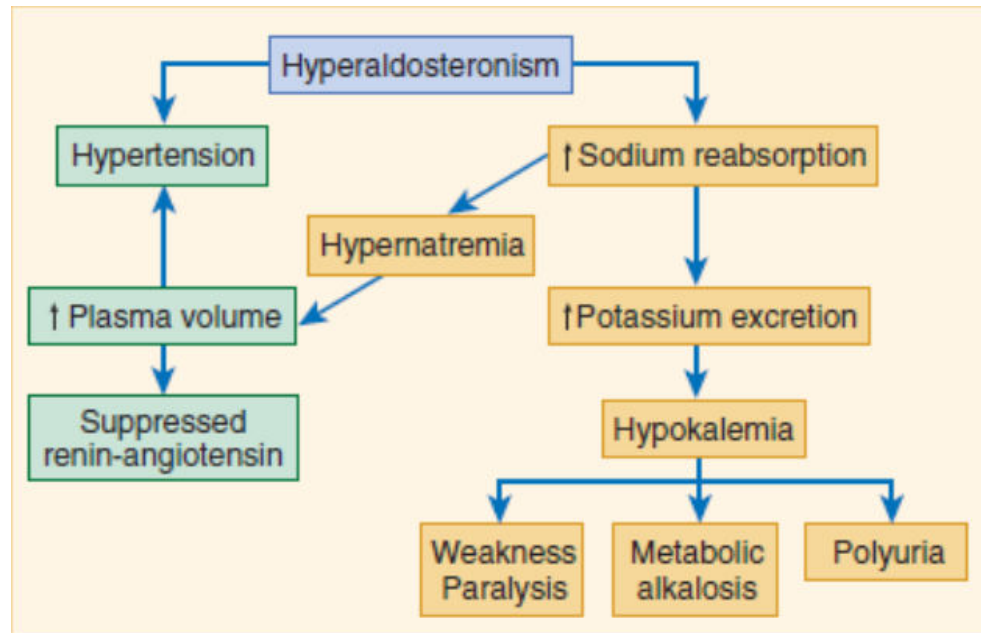


TABLE 45-5 Syndromes of Mineralocorticoid Excess

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
- 11 β -Hydroxylase deficiency
- 17 α -Hydroxylase deficiency

Cortisol excess

- Cushing syndrome from ACTH-producing tumor
- Glucocorticoid receptor resistance

Renal origin

- Activating mutation of mineralocorticoid receptor
- Pseudohypoaldosteronism, type II (Gordon)
- 11 β -Hydroxysteroid dehydrogenase deficiency
 - Congenital: apparent mineralocorticoid excess
 - Acquired: licorice, carbenoxolone

Primary aldosteronism

- the most common of syndromes with mineralocorticoid excess
- common in patients with resistant hypertension
- renin-independent overproduction of aldosterone
- several types
 - solitary aldosterone-producing adenoma
 - bilateral hyperplasia
- profibrotic effect of aldosterone
 - more CV events in patients with primary aldosteronism than in patients with primary hypertension

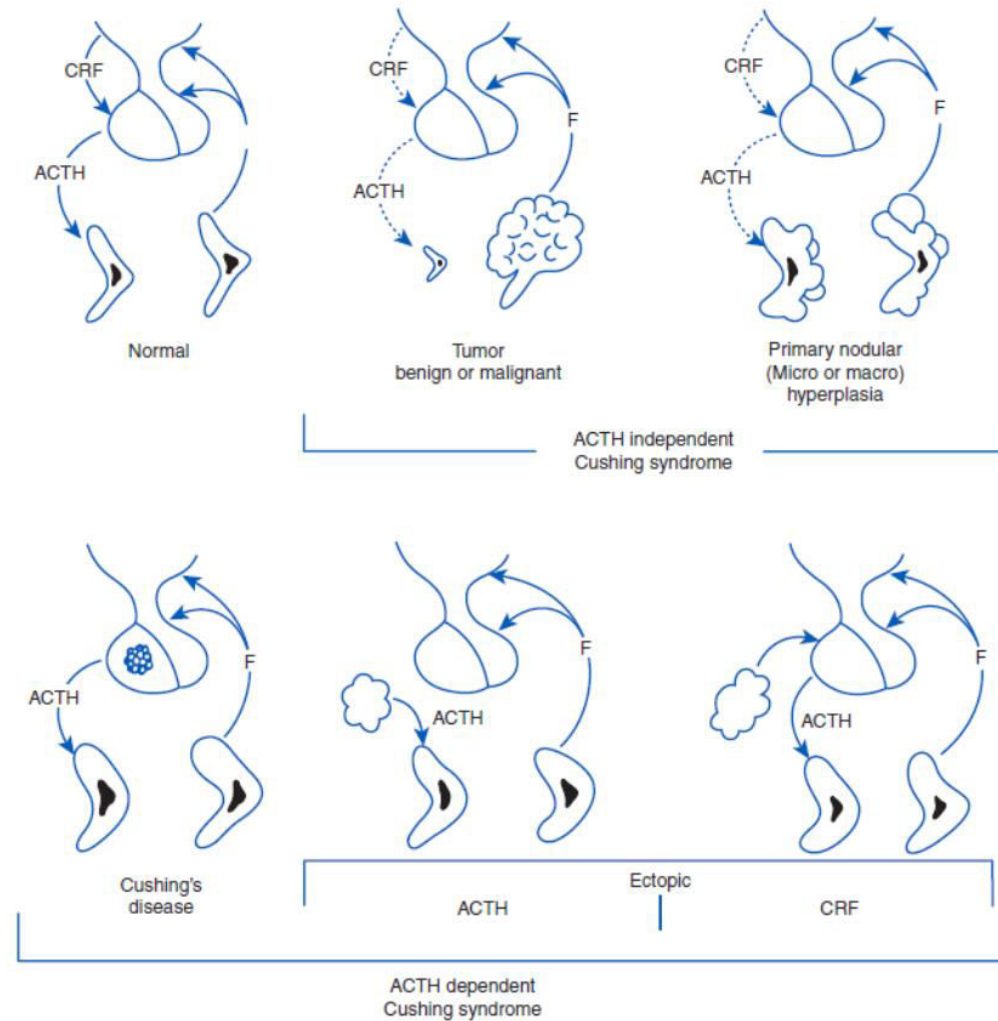
Hypertension induced by cortisol

- 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

Causes of endogenous Cushing syndrome



Classification and mechanisms of hypertension

ACTH dependent

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

ACTH independent

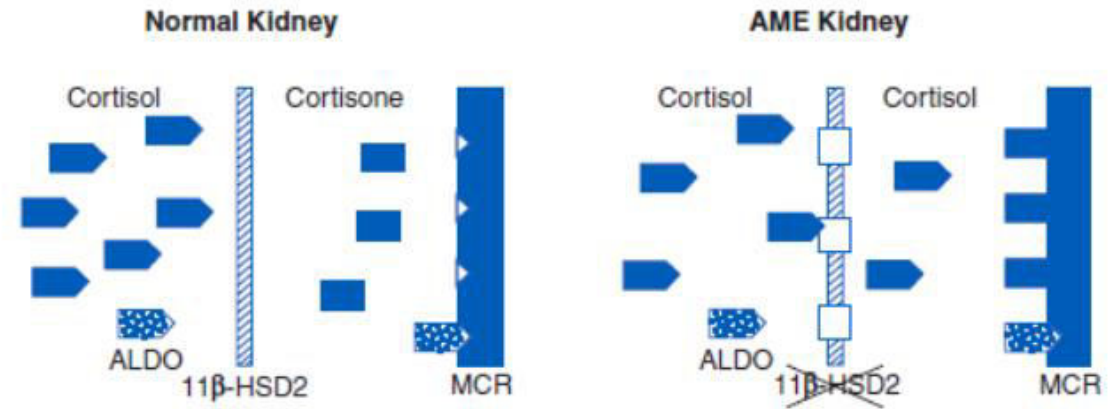
Adrenal adenoma
Adrenal carcinoma
Micronodular hyperplasia
Adrenal hyperplasia from other stimuli (e.g., GIP)
Exogenous glucocorticoid intake

• mechanisms of hypertension

- Na retaining action of cortisol
 - \uparrow cortisol overwhelms 11β -HSD2
 - cortisol acts on mineralocorticoid receptor (MR)
- direct action on smooth muscle cells
- \uparrow production of mineralocorticoids
- \downarrow activity of eNOS
- \uparrow angiotensinogen

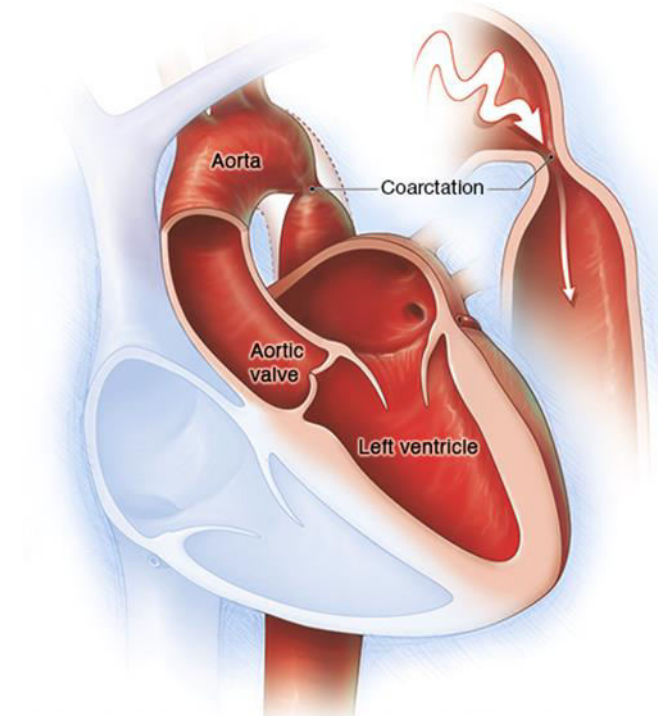
Increased access of cortisol to MR

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



Coarctation of aorta

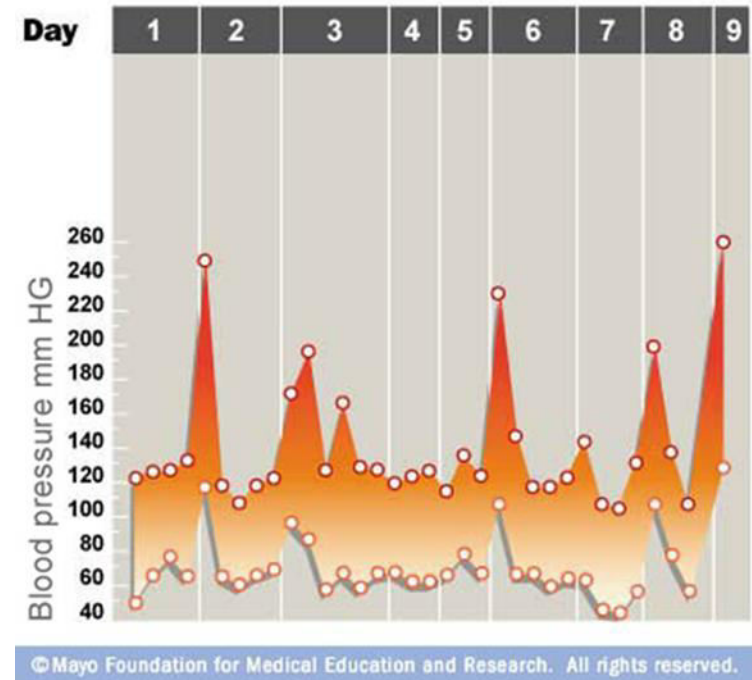
- distal to the origin of subclavian arteries
- signs
 - hypertension in the arms
 - weak or absent femoral pulses
 - BP on lower extremities is normal or low
- reduced blood flow to the lower part of the body
 - kidneys – RAAS activation
 - increased stroke volume
- probably also generalized vasoconstrictor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



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Pheochromocytoma

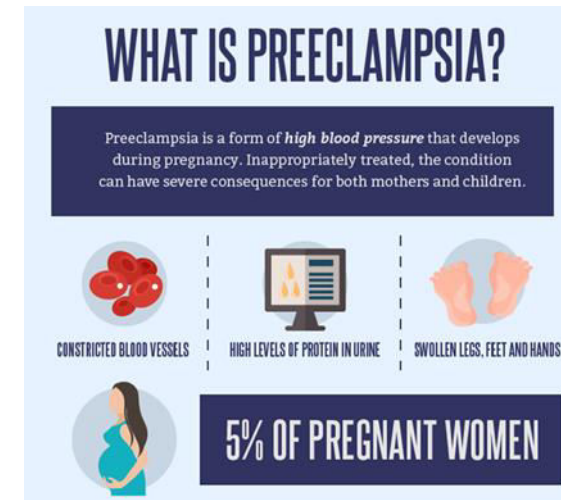
- tumor of chromaffin tissue
 - adrenal medulla
 - sympathetic ganglia
- 0.1 – 0.5 % of people with hypertension
- can cause serious hypertensive crisis
- production of epinephrine and norepinephrine
 - paroxysmal or continuous
 - episodes of headache, sweating, palpitations
 - weakness, fatigue, weight 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 sustained hypertension
some may be normotensive

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 resistance (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 resistance may predispose to hypertension

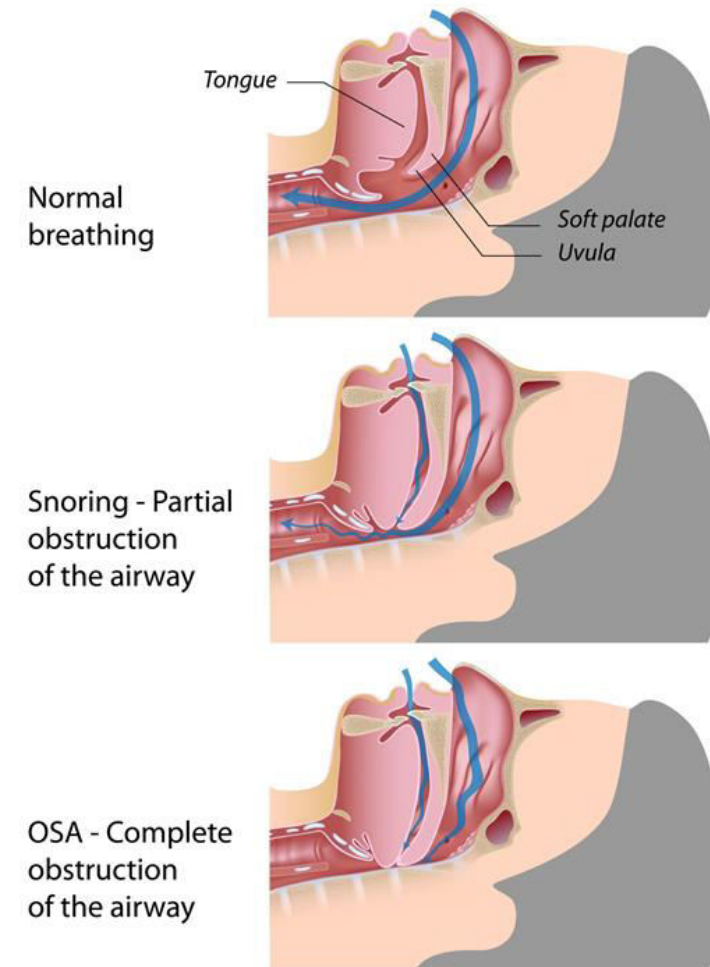


Oral contraceptive drugs and hypertension

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

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



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, hypocalcemia, proteinuria
- prolonged exposure to high BP
 - arterioles injury
 - intravascular coagulation and RBC fragmentation
 - renal damage
 - ↑ creatinine
 - proteinuria

Practical part

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

