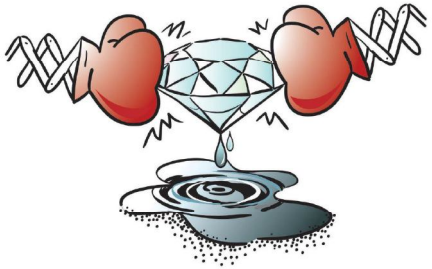
Systemic arterial hypertension (SAH)

Blood pressure (BP) regulation
The problem of defying „normal" BP
Pathogenesis of SAH (primary vs. secondary)
SAH as an example of „complex" disease

Pressure - hypertensions

- arterial
  - systemic
  - pulmonary
    - primary
    - secondary
      - pre-capillary
      - post-capillary
      - hyperkinetic
  - local
    - koarktace aorty
- venous
  - systemic
    - congestive heart failure
  - local
    - portal



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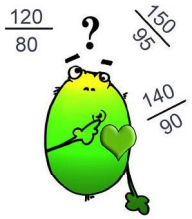
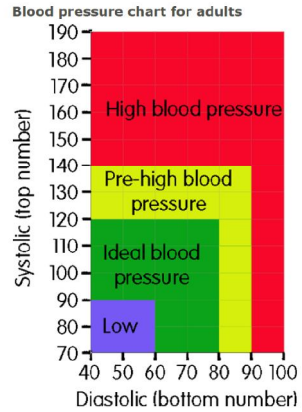


- Paul Dudley White (1931):
  - *"The treatment of the hypertension itself is a difficult and almost hopeless task in the present state of our knowledge and in fact, for ought we know the hypertension may be an important compensatory mechanism which should not be tampered with even if it were certain that we could control it."*
- original hypothesis
  - systemic arterial hypertension (SAH) is a compensatory mechanism of the arterial narrowing
- nowadays
  - SAH is the process leading to the arterial disease

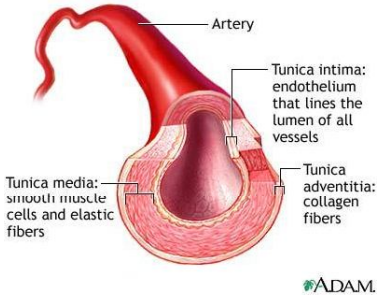
SAH = chronic elevation of BP

- **BP>140/90 mmHg** increases the incidence of cerebral, heart and renal events
  - initially
    - pressure overload of the left ventricle causing the LV hypertrophy,
    - mild cognitive dysfunction,
    - microalbuminuria
  - later
    - CHD (acceleration of atherogenesis),
    - myocardial infarction (plaque rupture),
    - (congestive) heart failure,
    - arrhythmia (atrial fibrillation due to dilation),
    - stroke,
    - renal failure (nephrosclerosis, proteinuria),
    - retinopathy,
    - vascular dementia
    - aortic dissection
    - …
- SAH is often associated with insulin resistance, overweight / obesity and dyslipidaemia
  - see further the pathogenic relationship



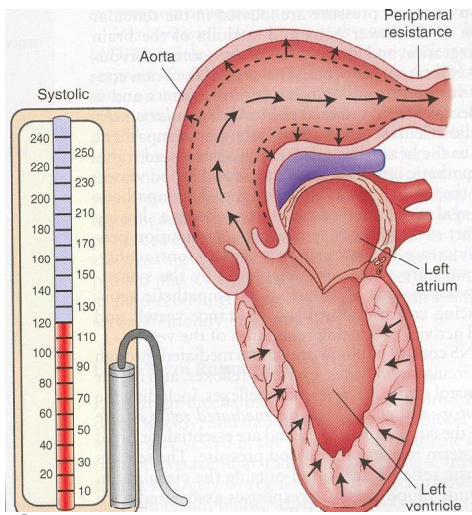
Vessels – morphology & function

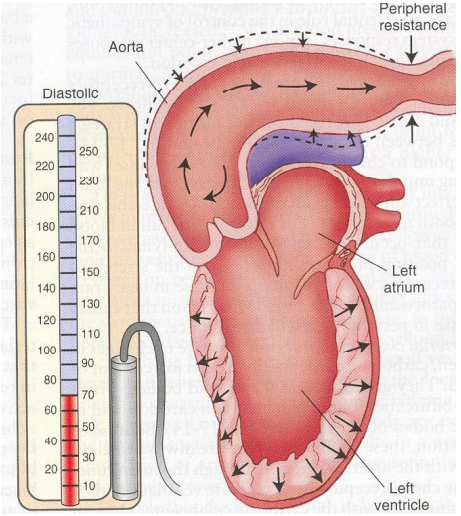
- prototypic structure
  - intima
    - endothelium + basal membrane
  - media
    - SMC, elastin
  - adventicia
    - collagen
- parameters of blood circulation influenced by blood vessels
  - velocity and resistance = SMC
  - pulse wave = elastin
  - limitation of the stretch = collagen
- types of vessels
  - capacitance (e.g. aorta, carotids, large limb vessels)
    - elastin (conservation of energy)
  - resistance
    - variable resistance
  - nutritional – terminal
    - regulation of perfusion by capillaries
  - capillaries
    - filtration, diffusion
  - capacitance venules and veins
  - shunts (AV anastomoses)
    - bypasses capillaries
  - lymphatic



	Aorta	Artery	Arteriole	Capillary	Venule	Vein	Vena Cava
Diameter	2 cm	4 mm	50 μm	8 μm	40 μm	1.5 mm	3 cm
Wall Thickness	2 mm	1 mm	20 μm	1 μm	2 μm	5 μm	1.5 mm
Wall Thickness / Lumen Radius	1/5	1/2	>1	1/4	1/10	1/5	1/10
Endothelium							
Elastin							
Smooth Muscle							
Collagen							

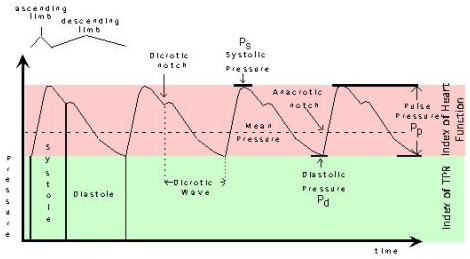
Factors ensuring blood flow continuity – vessel elasticity

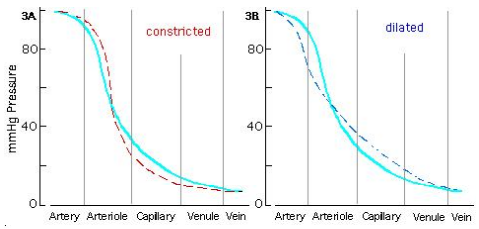




Blood flow

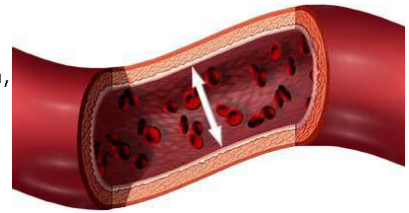
- arteries
  - pulsatile, discontinuous
- pressures
  - arterial
    - systolic
      - physiologically increases with age and with 'stiffening' of arteries
    - diastolic
      - marker of the total peripheral resistance (TPR)
  - pulse
    - difference between SBP and DBP
      - significant parameter of mortality
      - contributes to the 'shear stress'
  - mean arterial pressure (MAP)
    - integral of the curve of fluctuations





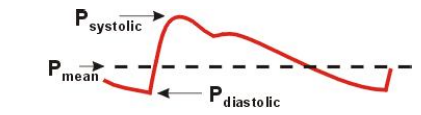
Blood pressure (BP)

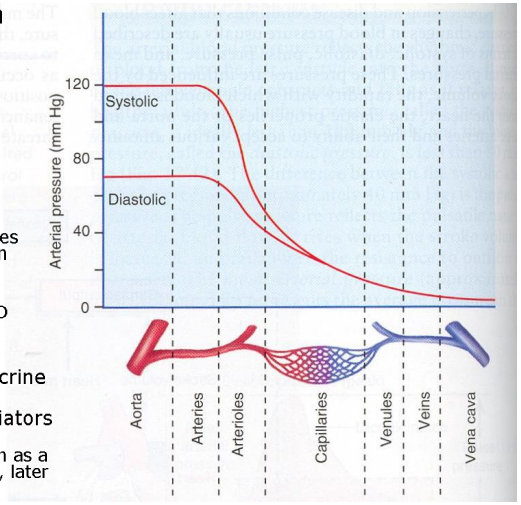
- BP = force moving fluid through circulation and, at the same time, force applied on the vessel wall
- BP is a result of physical properties of the circulation (= compliance) and its distension by circulating volume
  - **P = Q × R** (Ohm's law)
    - Q = **flow** ~ CO (cardiac output) = SV (stroke volume) × f (frequency)
      - SV = EDV – ESV (end-diastolic and end-systolic volumes)
        - EDV → preload → filling of the heart, i.e. venous return, i.e. effective circulating volume
        - ESV → afterload and contractility
    - R = **resistance** = $k \times \eta \times d / \pi \times r^4$
      - η = blood viscosity
        - CAVE: anemia (↓), polyglobulia, paraproteinemia (↑)
      - d = vessel length
      - r = vessel radius
        - CAVE: action of vasopressors (e.g. AT2, endothelin, vasopressin, catecholamines, …) and vasodialtors (e.g., PGI, NO, adenosin, …)



BP regulation

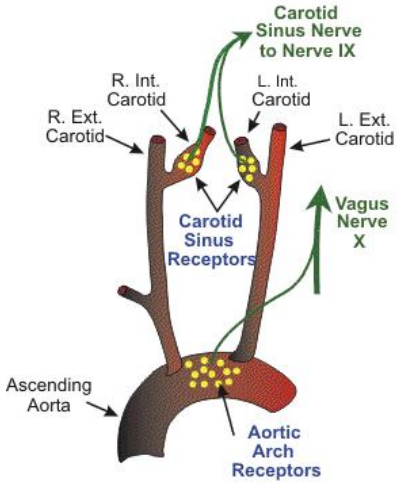
- BP changes periodically due to rhythmical ejection of blood from heart
  - SBP, DBP, MAP
    - MAP=DBP+1/3(SBP-DBP)
- **P = Q × R** → BP is regulated via changes of Q or R or both
  - regulatory systems
    - (1) neural
    - (2) humoral
  - regulation effectiveness
    - (1) short-term regulation
      - operates mainly with CO (**f** and **contractility**) and **r**
        - r – resistance vessels (= arterioles) which modulates influx into microcirculation
    - (2) long-term regulation
      - operates mainly via changes of circulating **volume** (Na and H_2O reabsorption)
  - extent of regulation
    - (1) systemic = baroreflex, endocrine hormones
    - (2) local = auto-/paracrine mediators
      - responsible for the **fixation of hypertension** (vasoconstriction as a defence against hyperperfusion, later hypertrophy of the vessel wall)



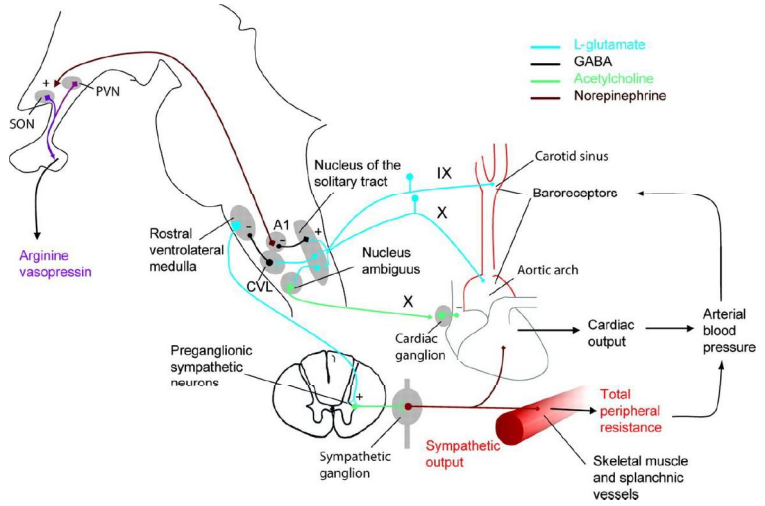


BP neuroregulation - baroreflex

- main **short-term** (but permanent) regulation of BP
  - afferent pathways
    - signalisation into prim. cardiovascular centre (n. tractus solitarii) from:
      - baroreceptors in the aortic arch
      - chemoreceptors in carotid bodies
  - efferent pathways
    - variations in activity of efferent sympathetic neurons (β-adrenergic stimulation)
    - (in)activation of efferent parasympathetic neurons (n. vagus)
    - stimulation of vasopressin release from hypothalamus
    - stimulation of rennin release form juxtaglom. apparatus of kidneys
- intermittent hypoxia (see further **obstructive sleep apnoea**)
  - since peripheral (and partly central) chemoreceptors have afferents also to the vasomotor centre → activation of SNS by hypoxia (during sleep)
  - gradual fixation of hypertension by increase of peripheral resistance



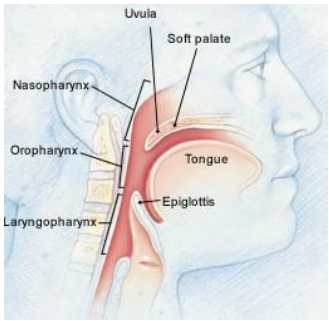
The arterial baroreflex circuit

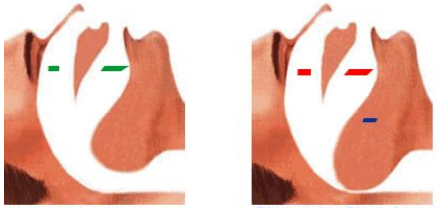


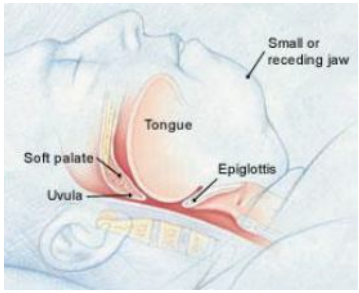
The arterial baroreceptors are mechanoreceptors located in the carotid sinuses (innervated by the glossopharyngeal nerve, IX) and aortic arch (innervated by the vagus nerve, X) that respond to stretch elicited by increase in arterial pressure. Primary baroreceptor afferents provide monosynaptic excitatory input to the nucleus of the solitary tract. Barosensitive NTS neurons initiate a sympathoinhibitory pathway that involves a projection from the NTS to interneurons in the caudal ventrolateral medulla (CVL) that send an inhibitory projection to sympathoexcitatory neurons located in the rostral ventrolateral medulla. The baroreflex-cardioinhibitory pathway involves a direct input from the NTS to a group of vagal preganglionic neurons located in the ventrolateral portion of the nucleus ambiguus (NA). These neurons project to the cardiac ganglion neurons that elicit bradycardia. The baroreflex, via the NTS, also inhibits secretion of arginine vasopressin by magnocellular neurons of the supraoptic (SON) and paraventricular

Obstructive sleep apnoea (OSA)

- periodical collapse and obstruction of airways during sleep
  - disposition: short thick neck, oral cavity anatomy, receding jaw, obesity!!
- 10-60s lasting apnoea with variable frequency (up to 1× in 30s)
- affects ~ 4% middle age people
- consequences: daily tiredness, morning headache, memory impairment, mood changes, hypertension

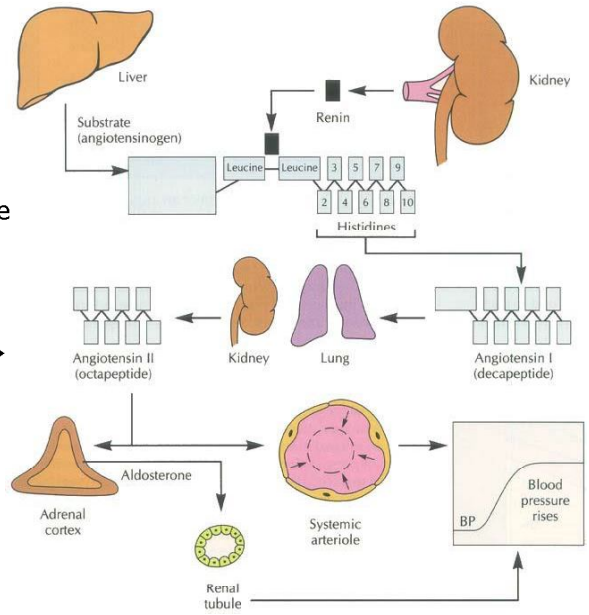




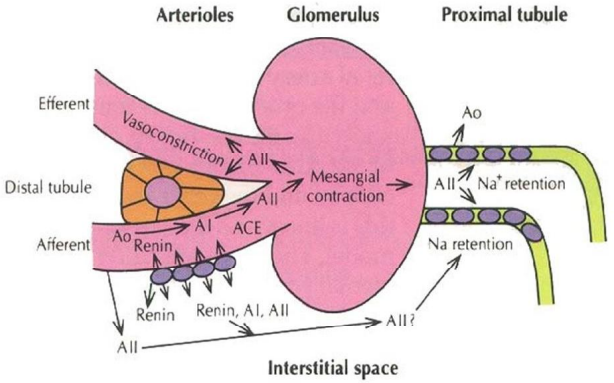


Humoral BP regulation

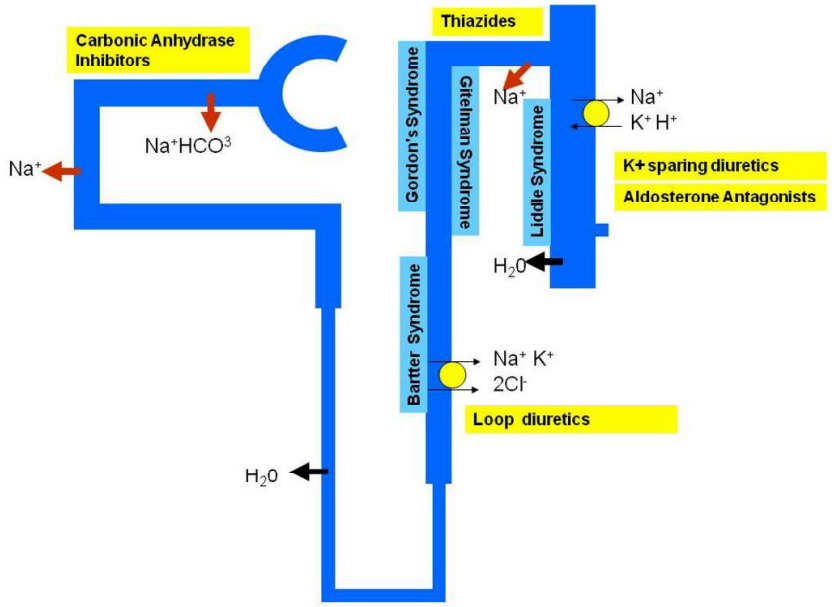
- (1) kidney / adrenal cortex → RAAS – main **long-term** regulation
- (2) hypothalamus / posterior pituitary → vasopressin (ADH)
  - via V_2 receptors
  - auxiliary role, main role is the regulation of osmolality
- (3) adrenal medulla → epinephrine
- (4) heart atria (right) → ANP
- (5) others
  - glucocorticoids
  - insulin
  - thyroid hormones
  - growth hormone



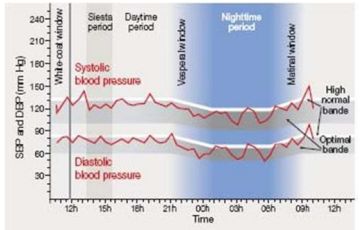
Effect of AT II in kidneys



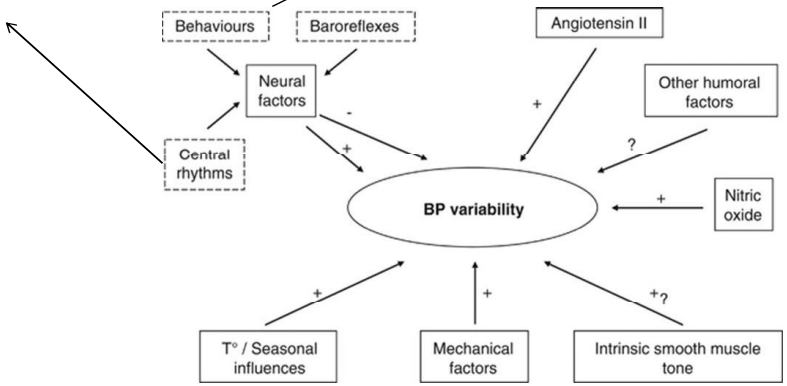
Kidneys - diuretics



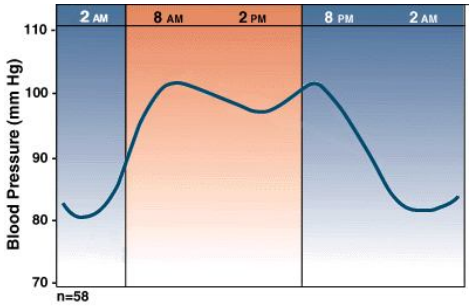
BP variability



↑ smoking
↑ alcohol
± caffeine
± sodium (genetics)

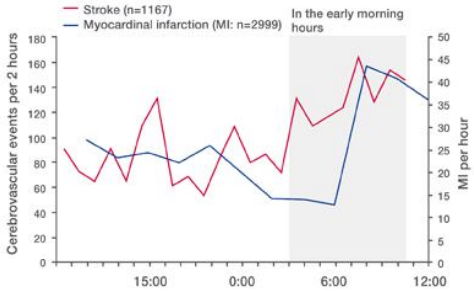


BP circadian rhythmicity

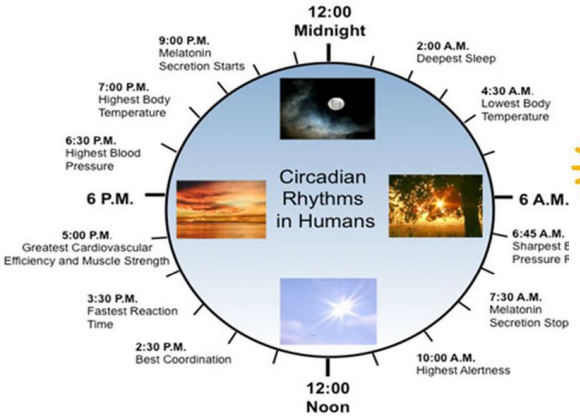


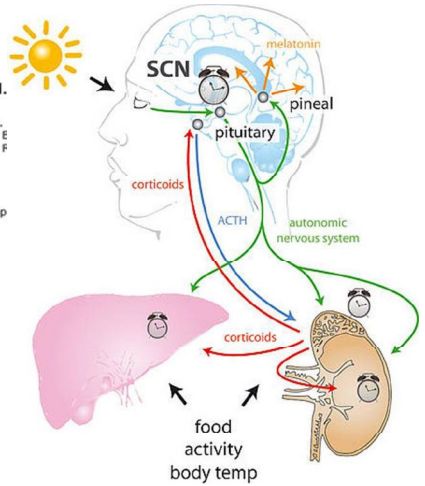
measured as an ambulatory blood pressure – continuous 24hrs monitoring

effect of catecholamines and cortisol cycling



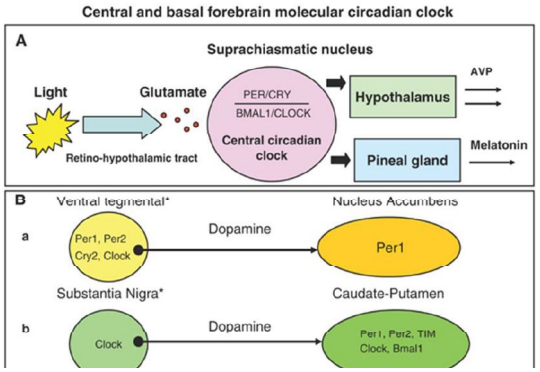
Principle of the circadian rhythm



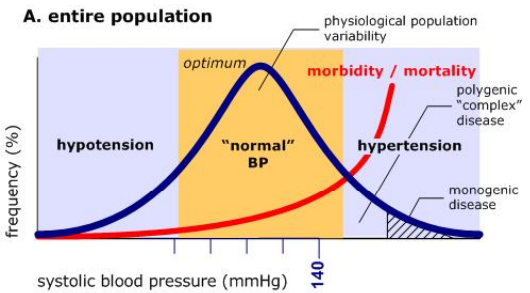


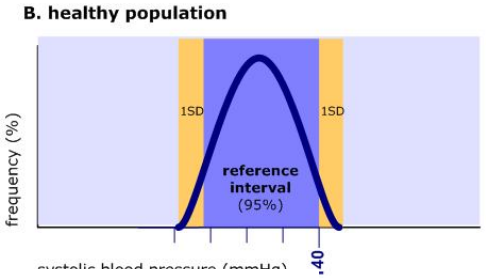
„Molecular clock"

- inner biological rhythmicity is caused by negative and positive feedbacks between transcription of clock genes (CGs), their translation, postransl. modification and degradation
- their products - proteins – then serve as transcription factors of other hundreds of genes (CCGs) in n. suprachiasmaticus and peripherally
  - they synchronize the body according to external environment
- hypothalamus
  - clock genes (CGs)
    - Clock
    - BMal1 (Mop3), BMal2
    - Per1, Per2 (Period)
    - Cry1, Cry2 (Cryptochrome)
    - Rev – Erb-α
    - CK1Є CK1δ (caseinkinase)
  - clock-controlled genes (CCGs)
    - Per 3
    - AVP (arginin vasopresin)
    - Dbp (D-element binding protein)
- peripheral organs



The problem of normal × high BP

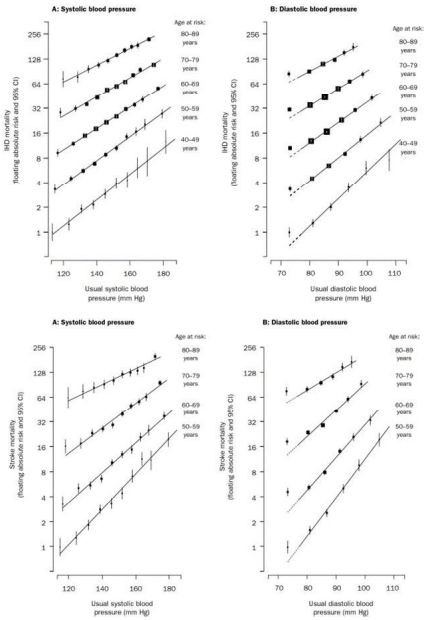




- BP is a **continuous trait** with characteristic **population distribution**
- decision about "normality" is always arbitrary → "**reference interval**" (incl. 95% of healthy population)
  - x ± 2SD for parameters with normal distribution
  - median [2.5% - 97.5% quintile] for others
- however, **common values in a given population needn't to be optimal**!
  - therefore morbidity and mortality associated with some values are taken into account
- BP in a given subjects is a product of:
  - genetic factors
  - environmental factors
  - activity of endogenous regulatory mechanisms

BP vs. cardiovascular

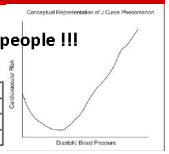
- BP is a major determinant of CV mortality
  - **hypertension is one of the most important risk factors of atherosclerosis**
    - **Framingham study** – identification of main CV risk factors – ↑ TK, ↑ cholesterol, ↑ triglycerides, ↓ HDL, smoking, obesity, diabetes, physical inactivity, ↑ age, gender (male) and psychosocial factors
      - original cohort (from 1948)
        - 5,209 subjects (aged 32 – 60 yrs) from Framingham, Massachusetts, USA
        - detail examination every 2 years
      - II. cohort (from 1971)
        - 5,124 adult offspring
      - III. cohort
        - 3,500 grandchildren of original participants
- every BP increase of 20mmHg SBP and 10mmHg DBP roughly doubles the risk of CVD
  - both chronic (atherogenesis – mechanical damage of endothelium) and acute MI(plaque rupture)
- late clinical manifestation of long-term untreated / decompensated hypertension were then taken into account for definition of cut-off values of BP
  - however in the presence of co-morbidities it is necessary to accommodate (personalise) these cut-offs
    - it is often recommended to maintain lower BP than 140/90



SAH definition and criteria

- criteria used depend on the environment and type of measurement
- SAH criteria
  - BP ≥ 140/90 mmHg in adult of any age in the rest (>10 min) repeatedly at least 2-times from 3 independent measurements on several occasions
    - diabetics and renal failure patients <130/80mmHg
    - ideally SBK<120 and DBP<80mmHg
- SAH grades
  - mild 140 – 179/90 – 104
  - moderate 180 – 199/105 - 114
  - severe ≥ 200/115
  - isolated systolic hypertension SBP >160 with DBP <90 mmHg
  - resistant BP ≥140/90 with combination of 3 antihypertensives
- SAH stages
  - I – simple increase of BP without organ changes
  - II – left ventricular hypertrophy and/or microalbuminuria/proteinuria and/or calcification of aorta
  - III – complications: heart failure and/or renal failure and/or heart attack and/or stroke

BUT careful in older people !!!



Měření tlaku	Systolický tlak (mm Hg)	Diastolický tlak (mm Hg)
Ve zdravotnickém zařízení	≥ 140	≥ 90
24hodinové monitorování	≥ 125	≥ 80
V domácích podmínkách	≥ 135	≥ 85

Tabulka 1. Hraniční hodnoty systémového arteriálního krevního tlaku (mm Hg) podle podmínek měření.

Klasifikace	Systolický tlak (mm Hg)	Diastolický tlak (mm Hg)
Optimální	< 120	< 80
Normální	120 – 129	80 – 84
Vysoký normální	130 – 139	85 – 89
Hypertenze 1. stupně („mírná")	140 – 159	90 – 99
Hypertenze 2. stupně („středně závažná")	160 – 179	100 – 109
Hypertenze 3. stupně („závažná")	≥ 180	≥ 110
Izolovaná systolická hypertenze	≥ 140	< 90

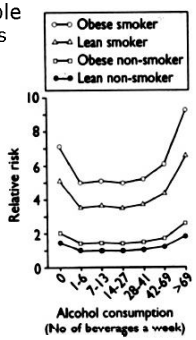
Tabulka 2. Kategorie hladin systémového arteriálního krevního tlaku.

SAH forms/classification

- **secondary (~5%)** = ↑ BP is a symptom of another primary disease
  - (A) renal
    - renovascular (due to renal artery stenosis or fibromuscular dysplasia of renal artery)
    - renoparenchymatous (due to glomerulonephritis nephropathy)
  - (B) endocrine
    - prim. hyperaldosteronism (due to adrenal adenoma)
    - pheochromocytoma
    - Cushing's syndrome (due to adrenal or pituitary adenoma)
    - acromegaly (due to pituitary adenoma)
  - (C) monogenic forms of hypertension
    - mutations in genes affecting renal handling of Na (see further genetics)
- **essential (primary, idiopathic, ~95%)** = many pathogenic mechanisms are known, but the very etiology is not
  - prime suspects are the kidneys:
    - abnormal renal handling of Na
  - ↑ endogenous sympathetic activity also plays a role
  - essential SAH is not just simple hemodynamic abnormality, in ~80% of cases in young and middle age SAH clusters with other metabolic disorders under the condition called **METABOLIC SYNDROME** (see further)
    - obesity
    - insulin resistance / impaired glucose tolerance / diabetes
    - dyslipidaemia

Pathogenic classification of SAH

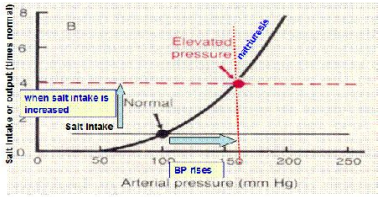
- SAH risk factors
  - modifiable
    - obesity
    - salt consumption (NaCl)
    - lack of physical exercise
    - chronic stress
    - high alcohol intake
      - „French paradox" (for CVD)
    - smoking
    - ~~caffeine~~
  - unmodifiable
    - genetics

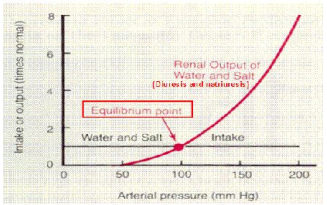


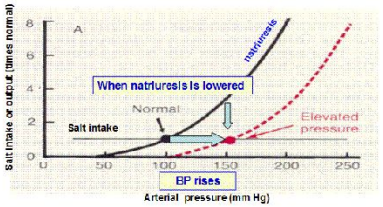
- **P=Q×R** → SAH can develop due to
  - (1) volume expansion
    - changes in natriuresis (i.e. any factors that lead to Na+ retention) will lead to pressure diuresis (i.e. increase in systemic BP)
      - initially: ↑ venous return, ↑ CO, ↑ BP
      - later: vessel and heart stretch lead to remodeling, ↑ periph. resistance (R), ↓ CO
        - vascular stiffening, glomerulosclerosis, microangiopathy, LV hypertrophy
    - etiology
      - primary hyperaldosteronism
      - SIADH
      - monogenic forms of SAH
        - but also common genetic variants!
      - m. Cushing
      - renoparenchymatous: loss of filtration capacity, tubulointersitial damage, Goldblatt 1K1C
  - (2) increase of peripheral resistance
    - the site od increased R can be anywhere above renal arterioles
    - etiology
      - renovascular: unilateral renal artery stenosis (Goldblatt 2K1C) or intra-renal stenosis
      - isolated systolic hypertension in older people
  - (3) mixed causes (constitution to both sodium retention and increased RAAS and sympathetic tone
    - etiology
      - obesity, stress

Salt sensitivity/intake (NaCl)

- for the 99.8% of their time (~3.5 mil yrs) humans consumed little Na^+ (30mmol = 1.8g) but more K^+
- today 170-260mmol (=10-15g of NaCl) that is 10-15× higher
- ethnicity matters!!!
  - increased salt-sensitivity (i.e. tendency to retain salt and, subsequently, responsibility to the salt restriction) is more apparent in some populations (e.g. blacks) while in others not
    - populations that lived in areas with limited access to the salt (i.e. inland sub-Saharan Africa) and thus low intake developed more efficient reabsorption of Na
    - the trait is still maintained in different (affluent) environment - "slave's gene"
- on the contrary, majority of European populations have generally high salt intake but not all are hypertonics
  - evidently different sensitivity (= salt wasting) and efficient excretion
- dietary salt reduction is the most commonly recommended intervention, however, sometimes with limited or no effect (not harmful though)
  - vessel remodeling „fixates" hypertension and high BP becomes less reversible

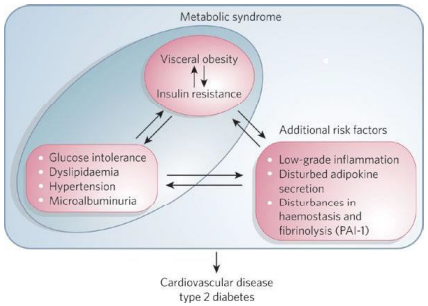






MS - why obesity increases BP

- relationship between BMI and SBP or DBP is nearly linear
  - approx. 78% of primary SAH in men and 65% in women can be ascribed to excess weight gain
  - even in obese normotensives BP rises to some extent
- distribution of fat is an important consideration – visceral rather than subcutaneous obesity!!!
- pathogenic mechanisms
  - (1) physical compression of the kidneys by fat in and around the kidneys
    - activation of RAAS
  - (2) increased sympathetic nervous system activity
    - renal afferent nerves
      - effect of renal denervation
    - RAAS dependent
    - RAAS-independent (leptin, MCR4 etc.)
      - obese leptin deficient individuals are not hypertensive
  - (3) abnormalities of ANF (deficiency)



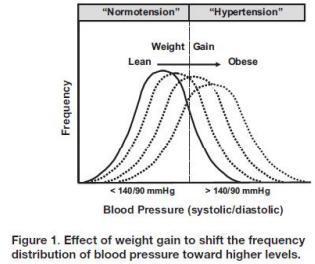
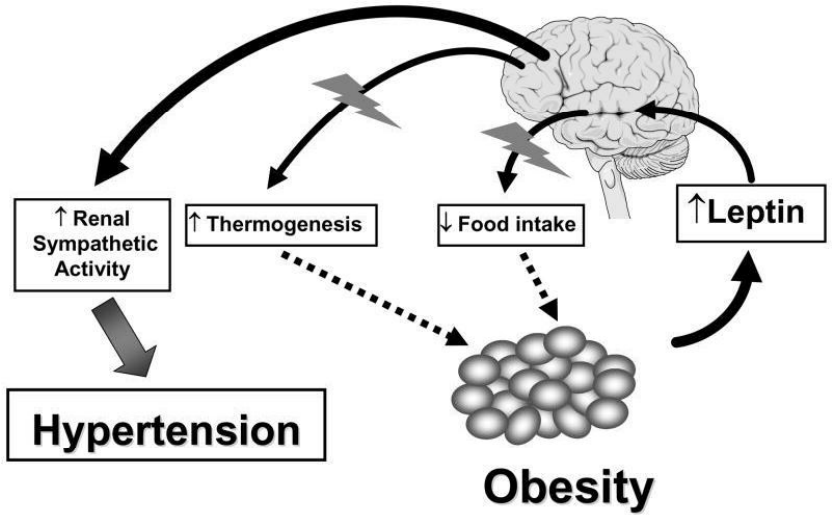


Figure 1. Effect of weight gain to shift the frequency distribution of blood pressure toward higher levels.

Cardiovascular sympatho-excitatory actions of leptin

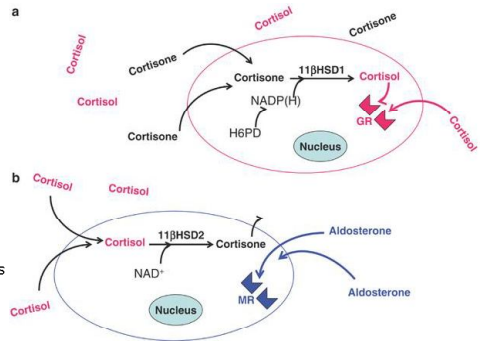


Chronic stress and BP

- predefined series of reactions aimed to fight or flight
  - lack of counterbalancing physical activity today
- chronic phase – dominance of **glucocorticoids**
- initially reactive ↑ of BP leads later to the active remodelation of vessel wall and thus "fixation" of hypertension
  - epidemiologically proven by the studies comparing groups of subjects of similar age, gender, education and social background but different profession (= level of stress) living in the same geographical area (nuns vs. primary school teachers, air traffic controllers vs. gardeners etc.)

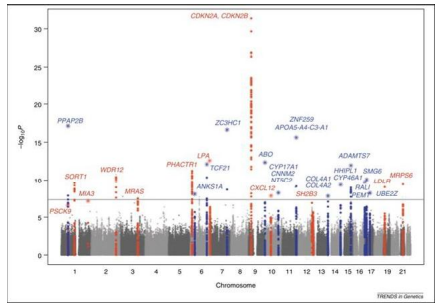
Peripheral modulation of GC availability

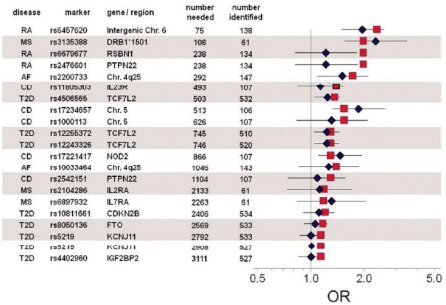
- peripheral tissue-specific modulation of cortisol availability by enzymes catalysing interconversions of active and inactive forms of GCs
- **(a) 11β hydroxysteroid dehydrogenase type 1 (11βHSD1)**
  - act as a reductase regenerating cortisol from cortisone → ↑ intracellular corticol concentration
    - mainly in liver and adipose tissue
      - expression of 11βHSD1 is higher in visceral than subcutaneous fat! → visceral fat is therefore more flexible pool of energy substrate
  - often co-localises with GR (e.g. in liver and adipose tissue) and thus locally amplifies the GC action
    - 11βHSD1 overexpressing mice develop obesity, while 11βHSD1 knock-out mice are protected from overeating-induced obesity
    - liver and fat-tissue specific inhibitors of 11βHSD1 could be used for treatment of metabolic syndrome and obesity
  - pathology associated with 11βHSD1
    - Cushing syndrome – higher expression of 11βHSD1 in visceral fat – normally first source of substrate, but higher suppression with GC, while enhanced GC action leads to lipolytsis in adipose tissue, the fat cumulates in visceral
    - congenital deficiency of 11βHSD1 (apparent cortison reductase deficiency) → compensatory over-activation of HPA axis → adrenal androgen excess, oligomenorhea, hirsutism in women
    - overexpression of 11βHSD1 in subcutaneous tissue (congenital or acquired) leads to lipodystrophy
    - 11βHSD1 plays a role in the pathogenesis of polycystic ovary syndrome
  - regulation: starvation, cortisol, other hormones
- **(b) 11β hydroxysteroid dehydrogenase type 2 (11βHSD2)**
  - act as a dehydrogenase degrading cortisol to cortisone → ↓ intracellular corticol concentration
    - mainly in kidney
  - by degrading cortisol 11βHSD2 enables tissue-specific preferential action of aldosterone on MR even though concentration of plasma cortisol >>> aldosterone
  - pathology associated with 11βHSD2
    - congenital deficiency of 11βHSD2 (apparent mineralocorticoid excess) → monogenic form hypertension
    - 11βHSDē is expressed in placenta (maintains lower cortisol in fetal circulation than in maternal) – deficient action contributes to pregnancy pathologies (preeclampsia, IUGR, ...) and possibly to fetal metabolic programming



Genetics of ESAH

- proved by studies (population, twins, adoption) – **heritability of BP ~30-60%** dependig on definition of phenotype
- "candidate genes" approach – pathogenesis-based approach
  - SNS, RAAS (rennin, AGT, ATR1, ACE, ...), endothelin, TXA, ANP, NO synthase, ...
    - so far only several unequivocal genetic factors identified and confirmed
  - genome-wide association studies (GWAS)
- monogenic forms of EH
  - (1) glucocorticoids-suppressed hyperaldosteronism
    - mutations in the promoter of the gene for aldosterone synthase → production of aldosterone is not regulated by ATII but ACTH (therapy by glucocorticoids to suppress ACTH)
  - (2) Liddle's syndrome
    - mutations in the genu for Na-channel subunit, → increased reabsorption of Na in the kidney proximal tubule
  - (3) apparent mineralocorticoid excess (AME)
    - mutations in the enzyme 11βHSD2 degrading cortisol in kidneys → locally increased activity of cortisol → mineralocorticoid effect in higher concentrations
  - (4) pseudohyperaldosteronism
    - mutations in the gene encoding mineralocorticoid receptor → aldosterone resistance
  - (5) adrenogenital syndrome/congenital adrenal hyperplasia (CAH)
    - defect of 11-β-hydroxylase or 17-α-hydroxylase → excess of mineralocorticoids



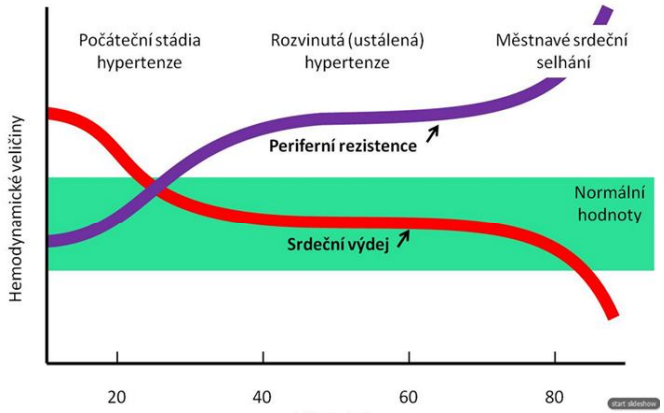


Ethiopatogenetic heterogeneity of SAH form clinical perspective

- Essential SAH is quite likely **HETROGENOUS DISEASE** developing due to various sets of abnormalities – multifactorial or complex disease – with contribution of both environmental and genetic factors
  - different patients will thus have been treated differently in the future - **PHARMACOGENETICS**
  - (1) factors influencing **cardiac output**
    - ↑ activity of SNS, ↓ insulin sensitivity, ↓ baroreflex sensitivity, activation of the hypothalamus (CRH) - pituitary (ACTH) - adrenal (GC and aldosteron) axis, ↑ left ventricle mass
  - (2) factors influencing **circulating volume**
    - ↑ plasma levels of RAAS components (i.e. rennin, ACE, AGT), variability in enzymes synthesizing steroids (aldosteron synthase), ↑ salt (Na) sensitivity (central osmoreceptors and tubuluglomerular feed-back), ↓ insulin sensitivity, atrial natriuretic peptide (ANP)
  - (3) factors influencing **peripheral resistance**
    - ↑ activity of SNS, ↑ plasma levels of RAAS components, ↑ activation of ATR1 (genet. variability), kalikrein-kinine system, balance between levels of para-/autocrine vasopressor (endothelin, TXA) and vasodilating mediators (NO, adenosine)
  - (4) factors influencing **compliance, hypertrophy and vascular remodelation**
    - growth factors and their receptors, oxidant stress, transport processes on plasma membranes (Na^+/H^+ transport)
  - (5) others
    - ↓ number of nephrons, foetal programming

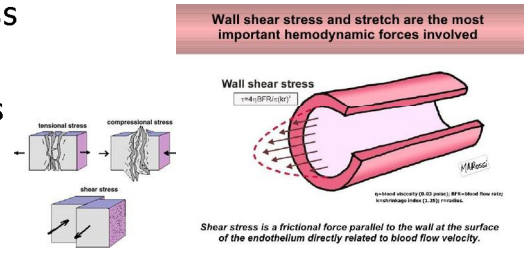
Time matters in SAH

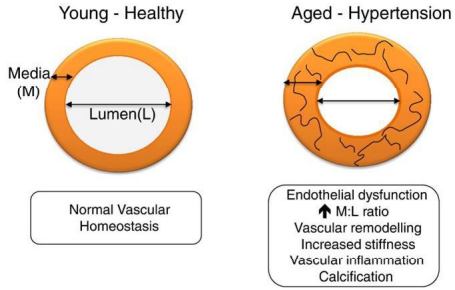
- initially transitional changes lead to
  - short-term responses such as myogenic reflex
  - long-term responses such as vascular remodeling



„Fixation“ of SAH

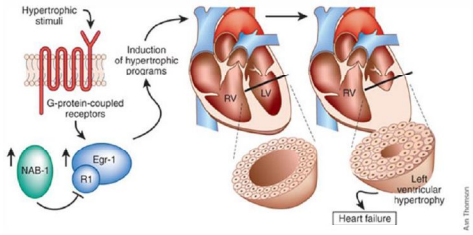
- SAH changes shear stress and circumferential wall stress (stretch)
- SAH accelerates changes otherwise seen during aging
  - endothelial cell damage
  - increased vascular smooth muscle cell growth and migration
  - inflammation
  - fibrosis (extracellular matrix deposition), contraction and calcification
- stiffness of arteries results in increased aortic pulse pressure and pulse wave velocity (PWV)

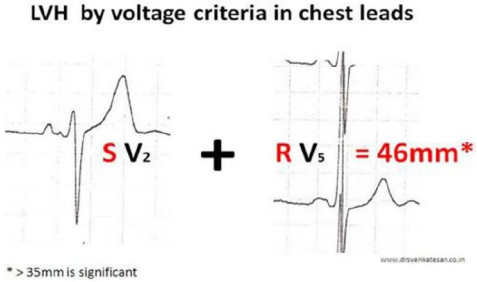




Consequences of SAH

- pressure overload hypertrophy – pathological LVH
  - hypertrophy of cardiomyocytes
  - myocardial fibrosis
    - not present in physiological heart hypertrophy in exercise training
  - media of coronary arteries
    - impaired coronary vasodilator reserve





Diagnostics of SAH

- (1) random BP
  - after at least 10min. rest, sitting, dominant arm, with supported forearm, tonometer in the height of hear, adequately wide and long cuff
    - for arm circumference <33cm = 12cm, for arm 33-41cm = 15cm, for art >41cm = 18cm
  - classic tonometer – auscultation
  - digital – oscilometric
  - dopplerometry
- (2) invasive BP measurement – catheter filled with fluid
- (3) ambulatory BO monitoring (AMBP)
  - 24-h BP record (or 48-h)
  - record every 15–30min during the day, every 30–60min during the night
  - indications
    - suspect „white coat syndrome“
    - resistant hypertension
    - episodic hypertension
    - autonomous neuropathy
    - therapy monitoring
    - unexpected collapses

“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”