

**REGULATION/DYSREGULATION
in BLOOD PRESSURE**

Blood pressure – the most important parameter in cardiovascular system – „high-profile“ parameter



- **Blood pressure (BP) – pressure of the blood to the wall of the vessels**
- **Systolic BP, diastolic BP, pulse pressure, mean arterial pressure (MAP)**

$BP = CO \times R$ CO – cardiac output, R – resistance

$CO = SV \times HR$ SV – stroke volume, HR – heart rate

ESH AND ESC GUIDELINES

**2013 ESH/ESC Guidelines for the management of
arterial
hypertension**

**The Task Force for the management of arterial hypertension of
the European
Society of Hypertension (ESH) and of the European Society of
Cardiology (ESC)**

Authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy) * , Robert Fagard (Chairperson)

Classification BP values

category	Systolic BP (mmHg)	Diastolic BP (mmHg)
optimal	< 120	< 80
normal	120 – 129	80 – 84
high normal pressure	130 – 139	85 – 89
Hypertension - mild	140 – 159	90 – 99
Hypertension - moderate	160 – 179	100 – 109
Hypertension - severe	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90

According the Guidelines of European Society of Cardiology 2013

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

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European Heart Journal (2018) 39, 3021–3104

Classification of BP

- **It is recommended that BP be classified as optimal, normal, high-normal, or grades 1–3 hypertension, according to office BP.**

Classification of office blood pressure and definitions of hypertension grade_b

Category	Systolic (mmHg)		Diastolic (mmHg)
• Optimal	<120	and	<80
• Normal	120–129	and/or	80–84
• High normal	130–139	and/or	85–89
• Grade 1 hypertension	140–159	and/or	90–99
• Grade 2 hypertension	160–179	and/or	100–109
✓ Grade 3 hypertension	≥180	and/or	≥ 110
• Isolated systolic hypertension _b	≥ 140	and	<90

- BP = blood pressure; SBP = systolic blood pressure.
- A) BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
- B) Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
- The same classification is used for all ages from 16 years.

- **Changes in recommendations**

- 2013

- Diagnosis: **Office BP** is recommended for screening and diagnosis of hypertension.

- 2018

- Diagnosis: It is recommended to base the diagnosis of hypertension on:

Repeated office BP measurements; or **Out-of-office BP** measurement **with ABPM and/or HBPM** if logistically and economically feasible.

Treatment thresholds

2013

- Highnormal BP (130–139/85–89 mmHg): Unless the necessary evidence is obtained, **it is not recommended to initiate antihypertensive drug therapy at high–normal BP.**

2018

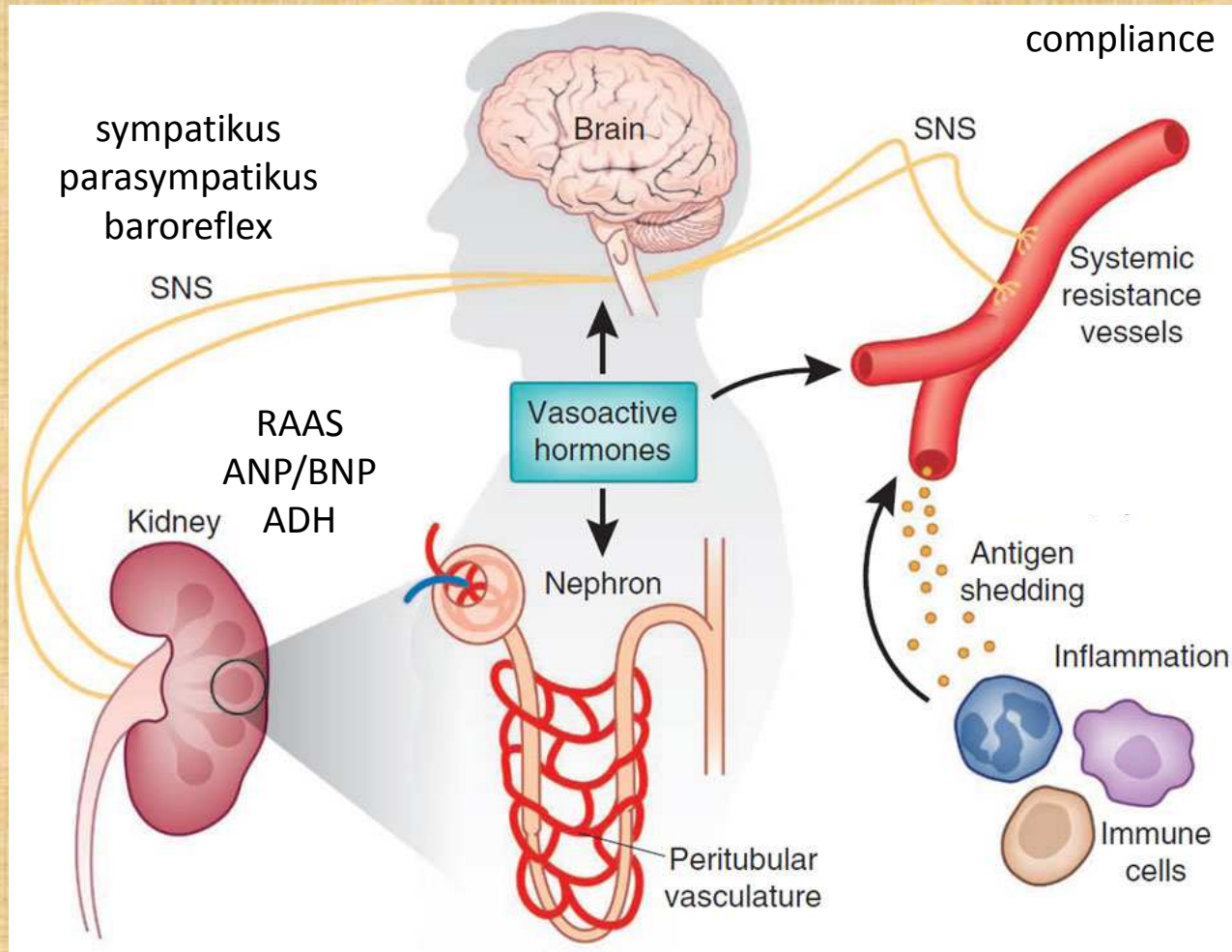
- Highnormal BP (130–139/85–89 mmHg): **Drug treatment may be considered** when CV risk is very high due to established CVD, especially CAD.

- Definitions of hypertension according to office, ambulatory, and home blood pressure levels

Category	SBP(mmHg)		DBP(mmHg)
• Office BP	≥ 140	and/or	≥ 90
• Ambulatory BP			
Daytime (or awake)	mean ≥ 135	and/or	≥ 85
Night-time (or asleep)	mean ≥ 120	and/or	≥ 70
24 h	mean ≥ 130	and/or	≥ 80
• Home BP	mean ≥ 135	and/or	≥ 85

- BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Regulation of blood pressure – complex process



Vasoconstriction:
 angiotensin II, vasopresin, epineprin (α_1), serotonin, PGF/TXA₂, endothelin, cofein, NPY

Vasodilatation:
 NO, adrenalin (β_2), adenosin, acidosis, histamin, PGD₂/PGE₂/PGI₂, prostacyclins, VIP, bradykinin

EXERCITATIO,
ANATOMICA DE
MOTV CORDIS ET SAN-
GVINIS IN ANIMALL
BVS,
GVILIELMI HARVEI ANGLI,
*Medici Regii, & Professoris Anatomia in Col-
legio Medicorum Londinensi.*



FRANCOFRTI,
Sumpibus **GVILIELMI FITZERI.**
ANNO M. DC. XXVIII

Obr. 4.28. Titulná strana prvého vydania Harveyovho diela z roku 1628

let me remark that 400 years ago

REGULATION IN CARDIOVASCULAR SYSTEM

Main function:

- keep relatively constant arterial blood pressure
- keep perfusion of tissues

Regulation of vessels tone

- Tone of the vessels = basic tension of the smooth muscle inside of the wall
(vasoconstriction x vasodilatation)
- Regulation - local autoregulation
- system regulation

Autoregulation

Autoregulation – the capacity of tissues to regulate their own blood flow

Myogenic theory – Bayliss phenomenon (as the pressure rises, the blood vessels are distended and the vascular smooth muscle fibres that surround the vessels contract; the wall tension is proportional to the distending pressure times the radius of the vessels – law of Laplace)

Autoregulation

- **Metabolic theory** – vasodilator substances tend to accumulate in active tissue, and these metabolites also contribute to autoregulation
 - ending products of energetic metabolism – CO_2 , lactate acid, K^+
 - effect of hypoxia (circulation: vasodilatation x pulmonary circulation: vasoconstriction)
 - Adenosin – coronary circulation: vasodilatation

Autoregulation

- **by substances which releasing from:**
 - endothelium
 - tissues

Substances secreted by the ENDOTHELIUM

Vasodilatation:

Nitric oxide (NO) from endothelial cells

(originally called: EDRF)

Prostacyclin is produced by endothelial cells

Vazoconstriction:

Endothelins (polypeptids – 21peptides)

three isopeptides: ET 1, ET 2 , ET 3

Substances secreted by the tissues:

Histamine – primarily tissue hormones.

General affect: vasodilatation - decrease periphery resistance, blood pressure

KININS: 2 related vasodilated peptides

Bradykinin + lysylbradykinin (kallidin).

Sweat glands, salivary glands

10x stronger than histamine

Relaxation of smooth muscle, decrease blood pressure

Systemic regulation

By hormones

Catecholamines – epinephrine, norepinephrine - effect as activation of sympathetic system

RAAS - stress situation

ADH - general vasoconstriction

Natriuretic hormones - vasodilatation

Neural regulatory mechanism

Autonomic nervous system

Sympathetic: vasoconstriction

All blood vessels except capillaries and venules contain smooth muscle and receive motor nerve fibers from sympathetic division of ANS (noradrenergic fibers)

- Regulation of tissue blood flow
- Regulation of blood pressure

Parasympathetic part: vasodilatation

Only sacral parasympathetic cholinergic fibres (Ach) innervated arteriols from external sex organs

Sympathetic nervous system

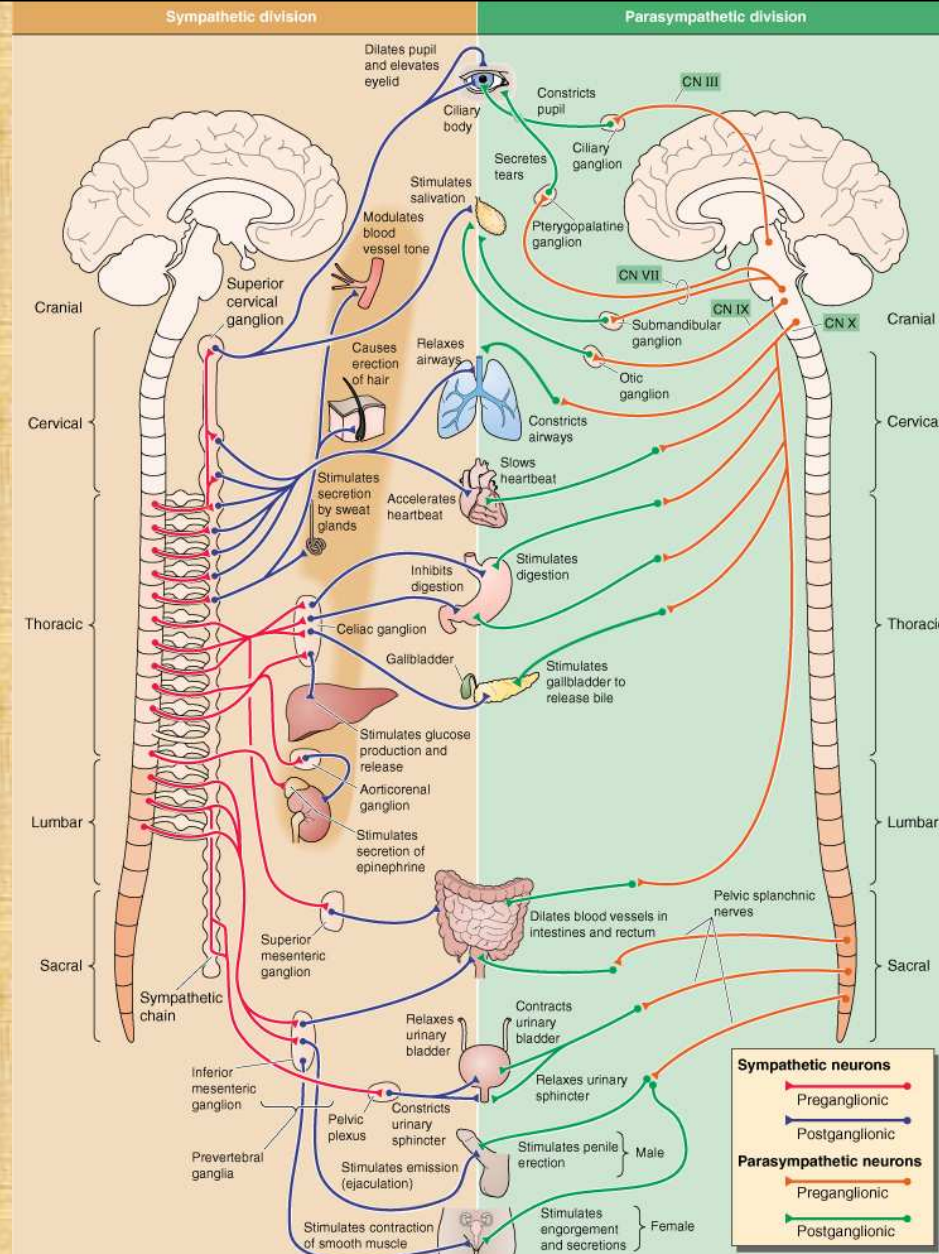
Fight or flight response

Energy/store consumption

Preganglionic neuron
 - Spinal cord
 - Thoraco-lumbar system

Ganglia
Paravertebral
 - Truncus sympathicus
 - Majority
Prevertebral
 - Plexus aorticus

Mostly diffuse effect



Parasympathetic nervous system

Rest and digest response

Energy conservation/en. store production

Preganglionic neuron
 - Brain stem and spinal cord
 - cranio-sacral system

Ganglia
Close to target organs or intramurally

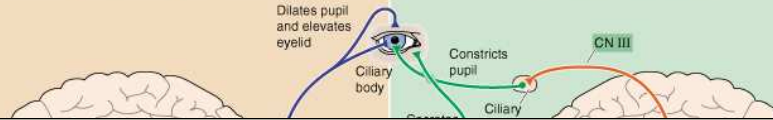
Mostly local effect

Sympathetic nervous system

Sympathetic division

Parasympathetic division

Parasympathetic nervous system

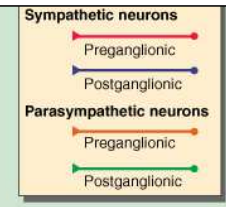
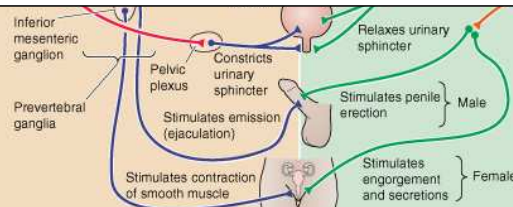


Fight or flight
 resp
 Energy consumption
 Preganglionic neurons
 - Spinal
 - Thoracic system
 Ganglionic
 Paravertebral
 - Truncus system
 - Major
 Prevertebral
 - Plexus aortic

System/function	Parasympathetic	Sympathetic
Cardiovascular	Decreased cardiac output and heart rate	Increased contraction and heart rate; increased cardiac output
Pulmonary	Bronchial constriction	Bronchial dilatation
Musculoskeletal	Muscular relaxation	Muscular contraction
Pupillary	Constriction	Dilatation
Urinary	Increased urinary output; sphincter relaxation	Decreased urinary output; sphincter contraction
Gastrointestinal	Increased motility of stomach and gastrointestinal tract; increased secretions	Decreased motility of stomach and gastrointestinal tract; decreased secretions
Glycogen to glucose conversion	No involvement	Increased
Adrenal gland	No involvement	Release epinephrine and norepinephrine

digestive
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 or
 rally

Mostly diffuse effect



Mostly local effect

INTEGRATION of regulation in cardiovascular system

The regulation of the heart:

- Rami cardiaci n. vagi

Cardiac decelerator center - medula oblongata (ncl.dorsalis, ncl. ambiguus) – parasympathetic fibres of nervus vagus

: vagal tone (tonic vagal discharge)

Negative chronotropic effect (on heart rate)

Negative inotropic effect (on contractility)

Negative dromotropic effect (on conductive tissue)

INTEGRATION of regulation in cardiovascular system

The regulation of the heart:

- nn. cardiaci

Cardiac accelerator center – spinal cord, sympathetic ganglia – sympathetic NS

Positive chronotropic effect (on heart rate)

Positive inotropic effect (on contractility)

Positive dromotropic effect (on conductive tissue)

INTEGRATION of regulation in cardiovascular system

Vasomotor centre (regulation for function of vessels)

Medula oblongata

- ✓ *presoric area* (rostral and lateral part – vasoconstriction – increase blood pressure)

- ✓ *depresoric area* (medio-caudalis part – vasodilatation, decrease of blood pressure)

INTEGRATION of regulation in cardiovascular system

- Influence by central nervous system
 - cerebral cortex
 - limbic cortex
 - hypothalamus

Regulation of blood pressure

Short - term regulation

- baroreflex

Middle - term regulation

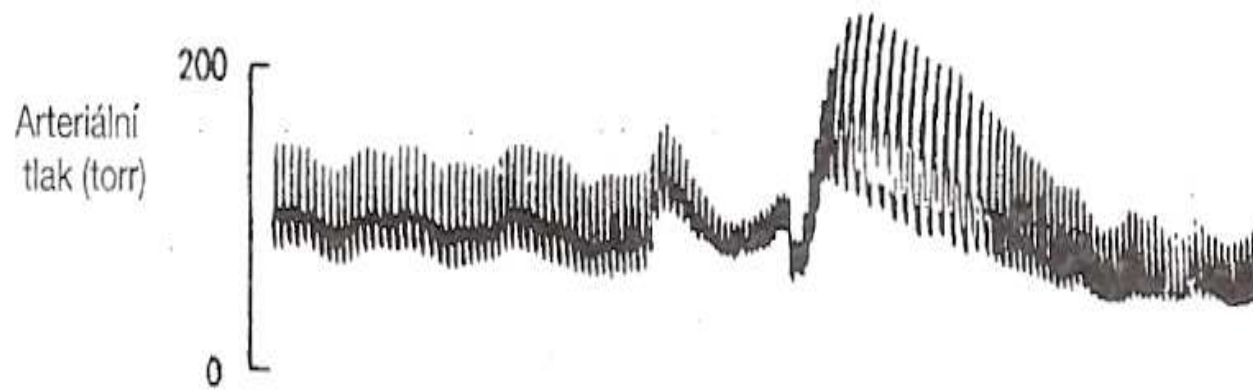
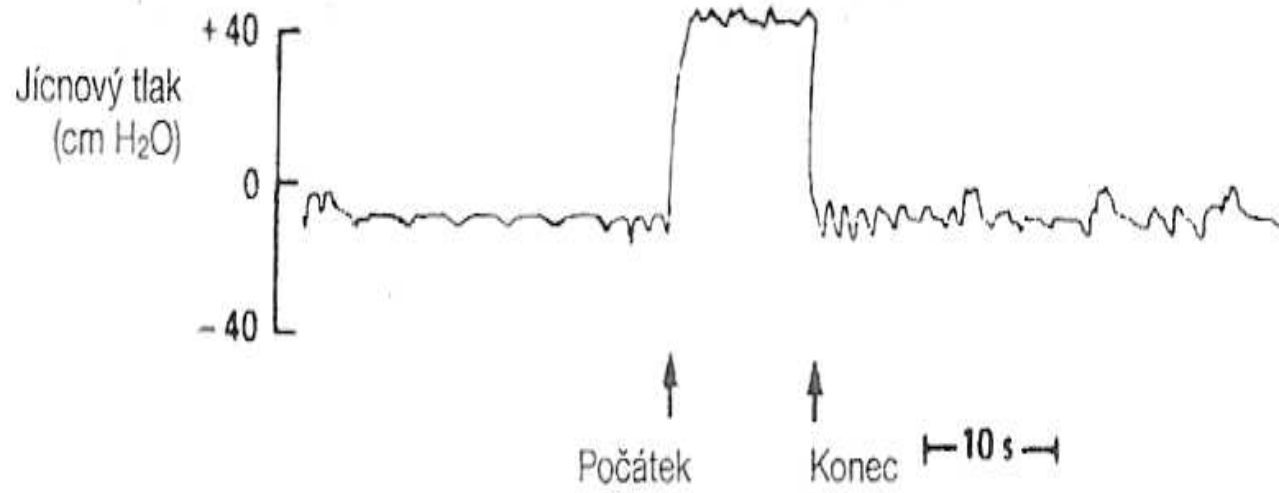
- humorals regulation

- sympathetic - catecholamines
- RAAS (decrease perfusion pressure in kidney – secretion of renin)
- ADH

Long – term regulation

- kidney regulation

- Baroreflex – in every day life
- Orthostatic – clinostatic reaction
- Valsalva manœuvre



Resetting of baroreflex

- During repeated raising of blood pressure - **e.g. in chronic hypertension** - the force of baroreflex reaction on systemic blood pressure is lower
- ??? Why???mechanical changes in baroreceptors – decrease sensitivity due to structure changes on the vessels wall OR dysfunction of endothelium OR down-regulation in the brain center due to their increasing frequency of stimulation
- Resetting of baroreflex can regulate the changes in blood pressures, but the resetting is unable to go back on „normal“ level
- Resetting is a partially reversible – during a short-term influence of raising blood pressure
- *Notice: in clinical practice:*
!start treatment of hypertension in time!

BAROREFLEX SENSITIVITY

A change of duration of pulse interval (in ms) due to a change of blood pressure by 1 mmHg

Laboratory methods:

- Phenylephrin application
 - neck suction
- Valsalva manoever

Spontaneous methods:

- **in time-domain**
 - Sequence analysis
- **in frequency-domeain**
 - cross-spectral analysis
 - α -index

BAROREFLEX SENSITIVITY

- Phenylephrin application

Bolus injections of vasoactive drugs

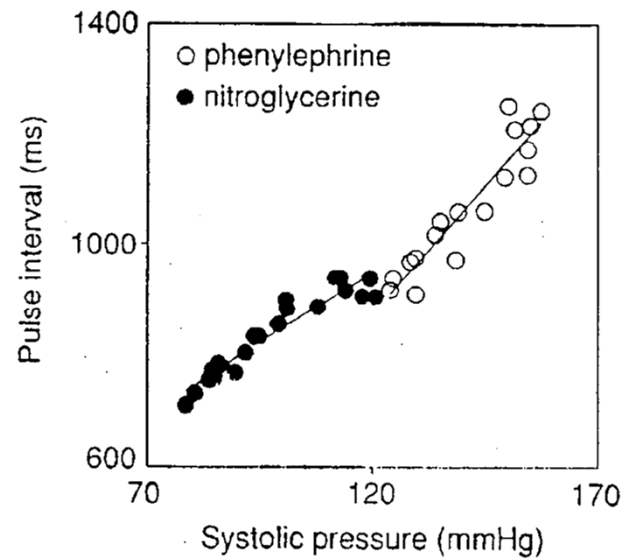
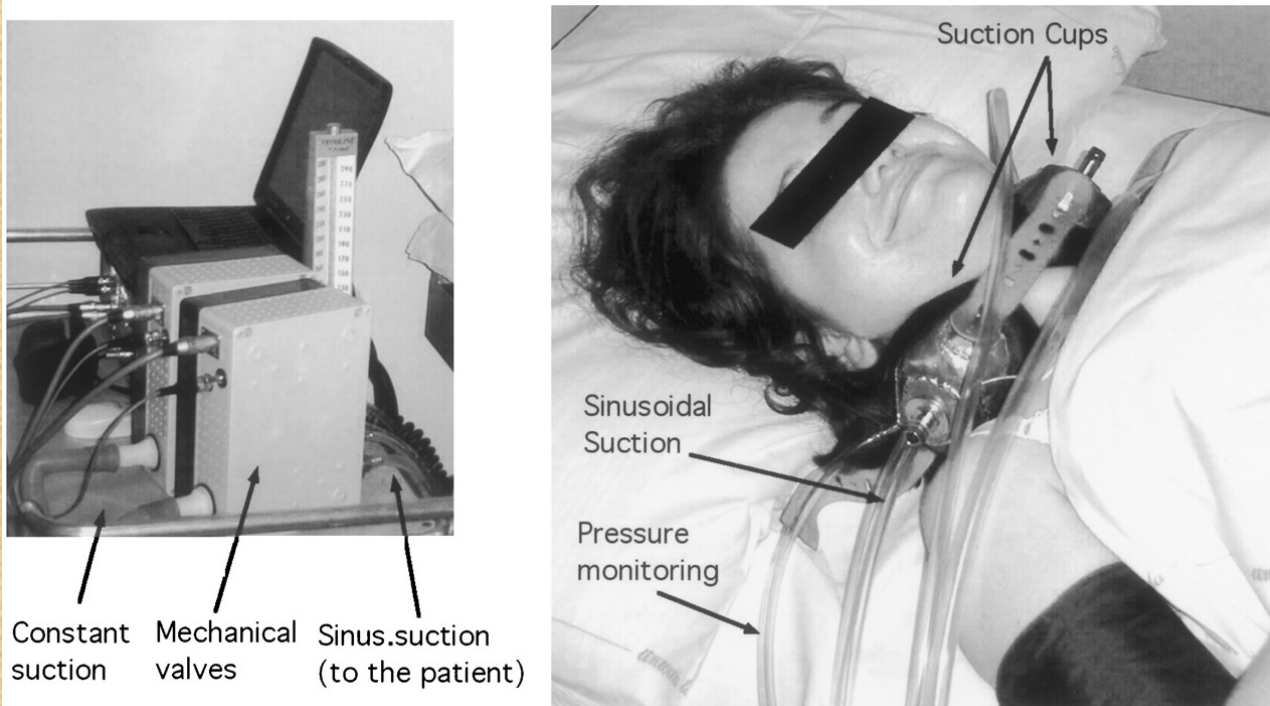


FIG. 5.4. Comparison of R-R interval responses of one subject to intrabolus injections of phenylephrine and nitroglycerine. Adapted with permission (Pickering *et al.* 1972c).

BAROREFLEX SENSITIVITY

- Neck suction



Furlan R et al. *Circulation* 2003;108:717-723

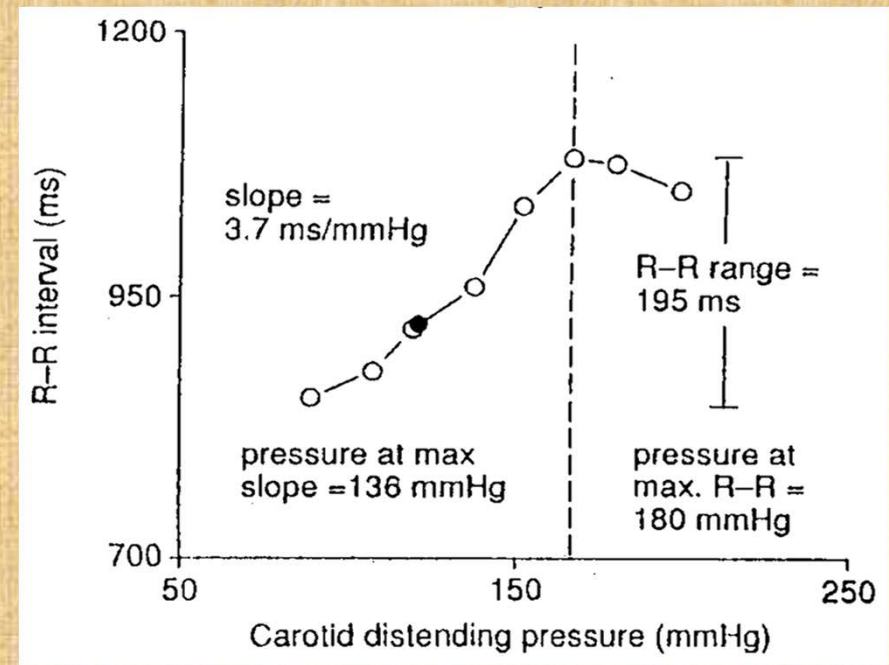
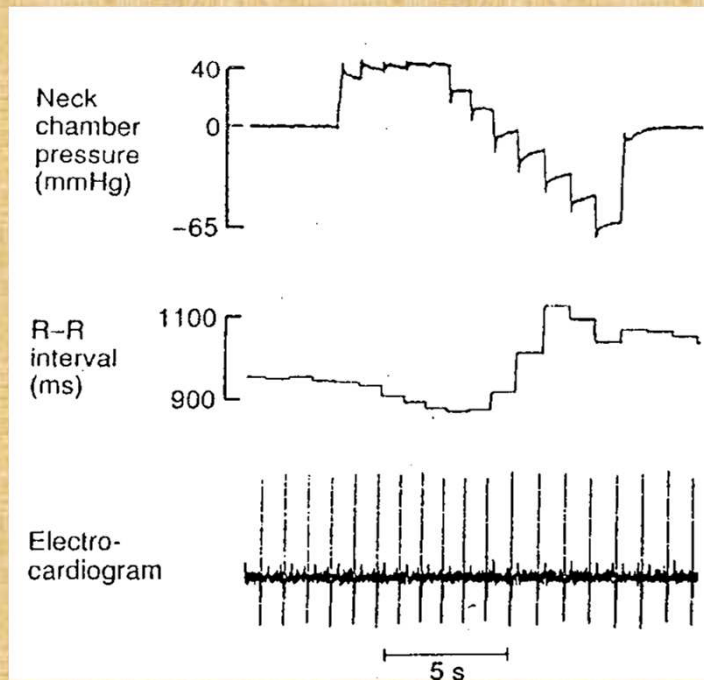


FIG. 5.13. Stimulus-response relation provoked with neck chamber shown in Fig. 5.12. Adapted with permission (Fritsch *et al.* 1989).

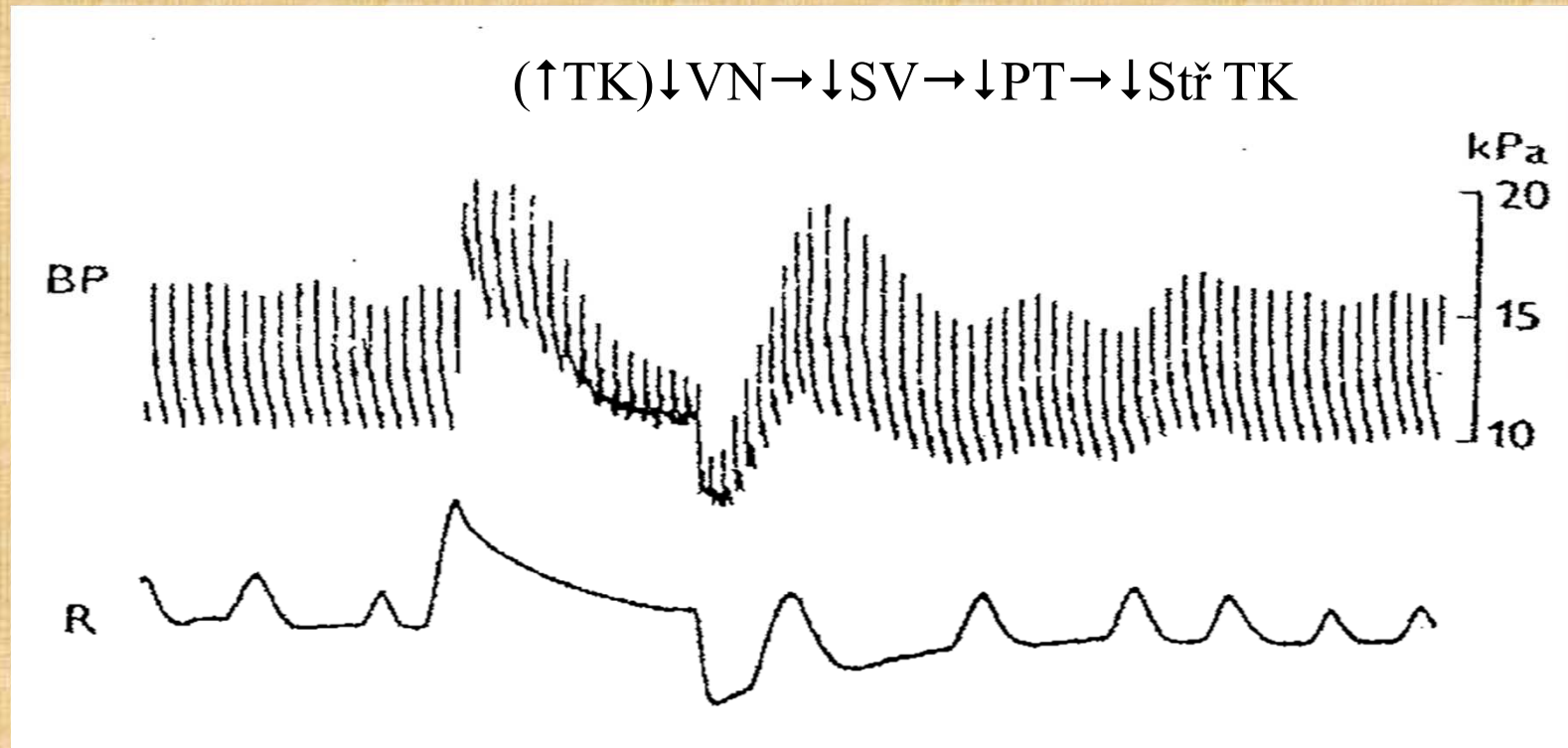
BAROREFLEX SENSITIVITY

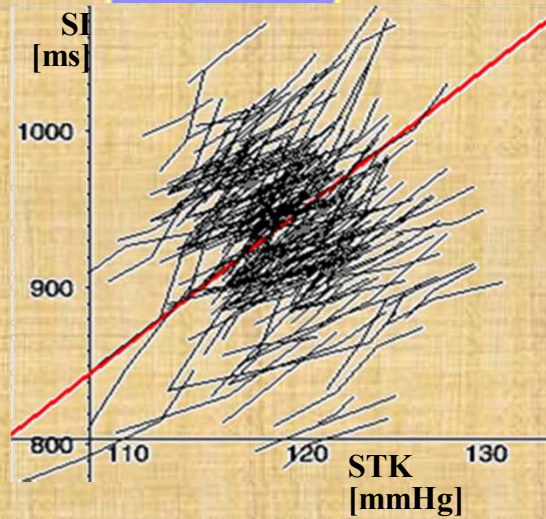
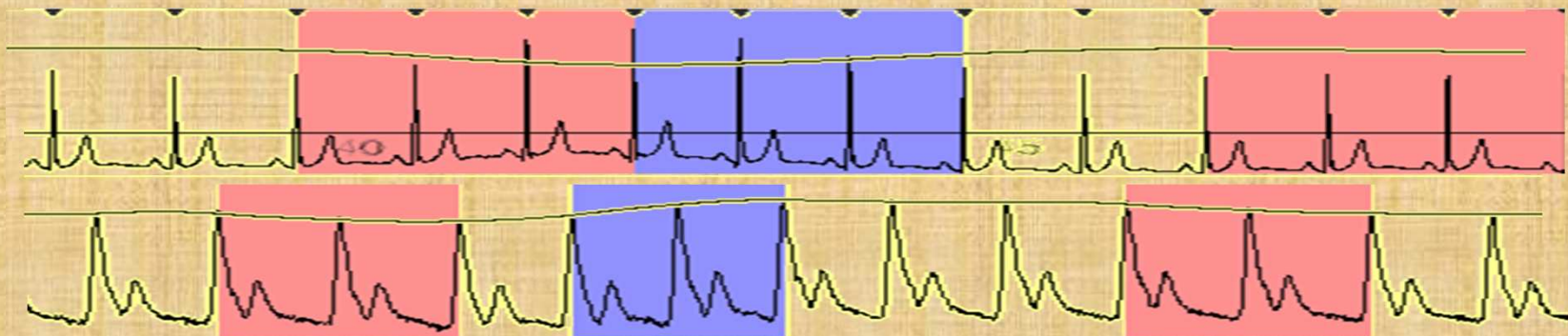
- Neck suction

BAROREFLEX SENSITIVITY

- Valsalva manoeuver

(↑TK) ↓VN → ↓SV → ↓PT → ↓Stř TK



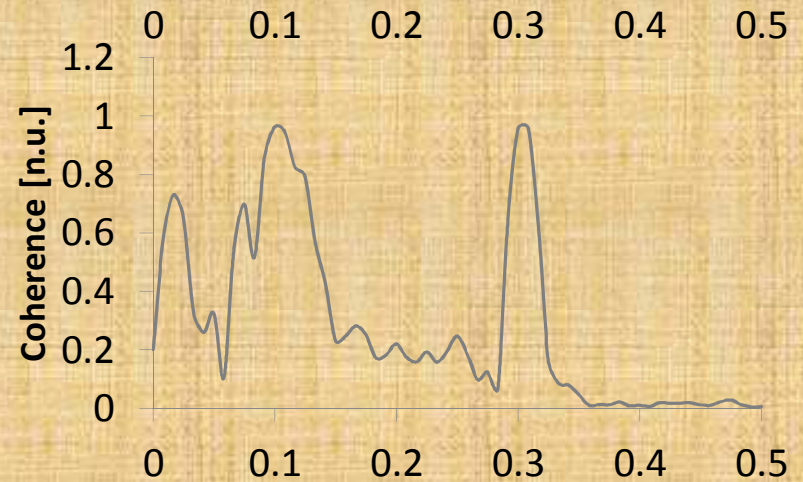
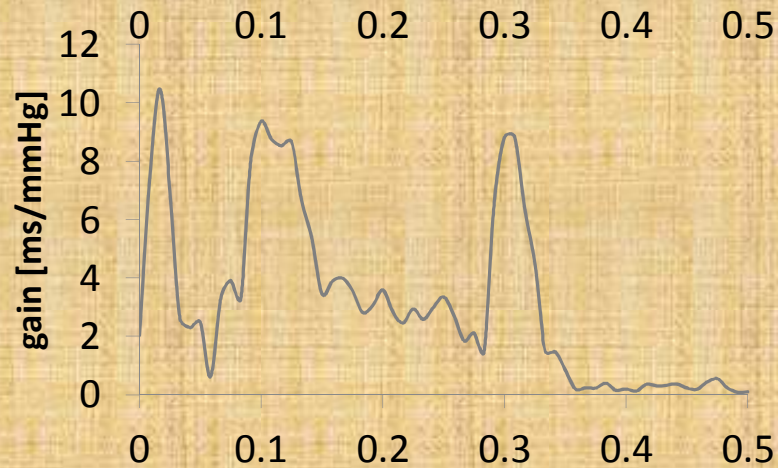
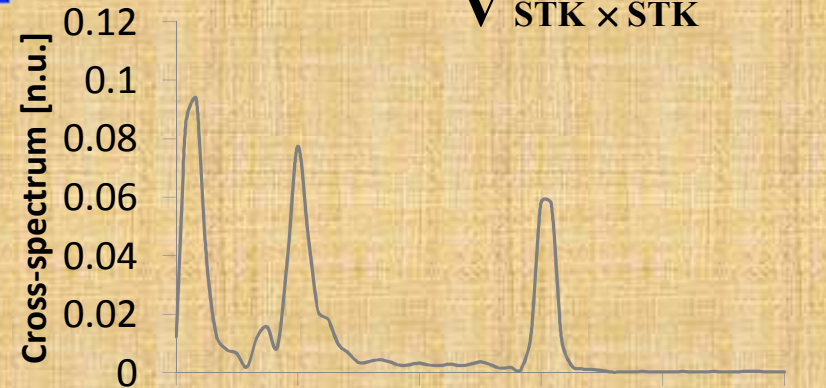
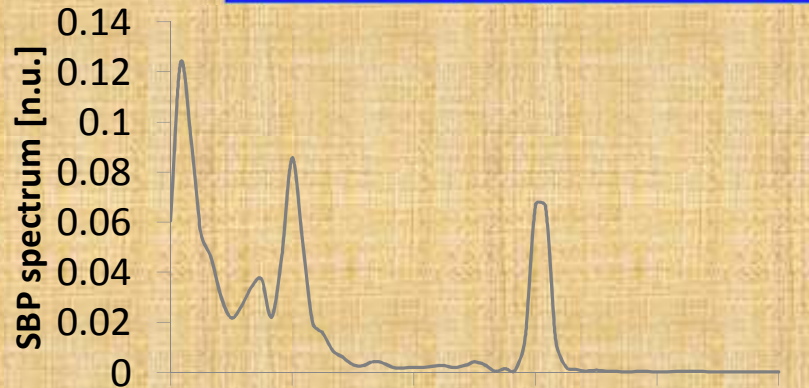


BAROREFLEX SENSITIVITY
- Sequence analysis

BAROREFLEX SENSITIVITY

- cross-spectral analysis

$$\text{BRS} = \frac{V_{\text{STK} \times \text{SI}}}{V_{\text{STK} \times \text{STK}}}$$

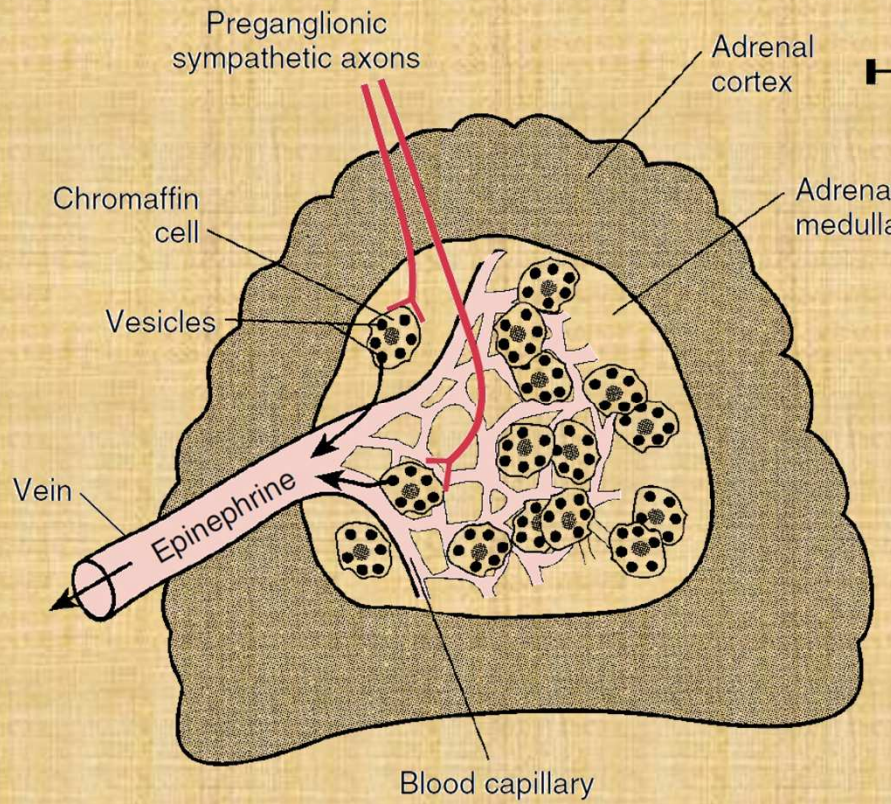


Middle – term regulation 1

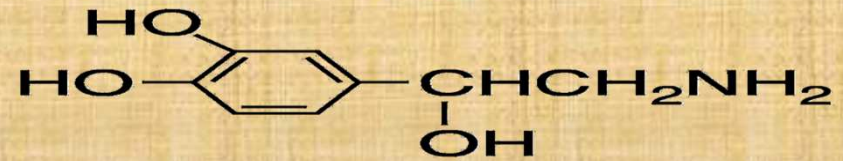
catecholamines

- Mediators of sympathetic nerves for baroreceptors and chemoreceptors
- Sympathetic nervous system stimulates releasing of epinephrine and norepinephrine from adrenal medulla – main function: vasoconstriction – chronotropic effect – inotropic effect
- Its function start during minutes or hours

ANS



NE



Adrenal medulla

- modified sympathetic ganglion
- release stress hormone to blood stream

Middle – term regulation 2

Renin - angiotensin - aldosteron

- System in kidney
- +
extrarenal system (in other tissues – brain, adrenal medulla, gonades, eyes)
- +
Intermediate system – heart, smooth muscles

- Renin – in juxtaglomerular cells in kidney
- In liver – glycoprotein angiotensinogen – release angiotensin I (decapeptid) – due to angiotensin converting enzyme to angiotensin II(oktapeptid) or angiotensin III (aminopeptidase)

- Angiotensin II – other way – chymase – in th heart and arterioles
- (it is reason why during treatment by ACE blocatores – the angiotensin level is not reduce)

Secretion of renin is modulated by

- Sympathetic nervous system – beta 1 receptors activation – main mechanism of secretion of renin
- Second way – by special mechanism due to sensitivity on sodium
 - exists a special intrarenal mechanism – negative sodium balance increase the renin secretion
 - ??? hypothesis – macula densa register of sodium concentration in renal tubular system – this information transports to juxtaglomerular cells where activated renin-angiotensin system (has an influence on secretion of renin – release angiotensin II);
 - Increase level of sodium – decrease releasing of renin (mediator – Nitric Oxide)
- ??? Arterial pressure – stretch receptors (baroreceptor) in vas afferens (juxtaglomerular cells) – influence on blood pressure in kidney or also in systemic circulation???

Angiotensin II - Effects (Overview)

- Vasoconstriction
- Change in renal hemodynamics – decrease of blood flow in kidney and glomerular filtration
- Influence on reabsorption of sodium in renal tubules
- It invokes or enhances the presynaptic release of noradrenaline
- Stimulates the release of ADH

Effect of ANGIOTENSIN III

- Stimulation of aldosterone secretion from the adrenal cortex

Middle – term regulation 3

ADH - vasopressin

- During a strong decline of blood pressure
from posterior pituitary – vasoconstriction

May be: slowly effect – retention of water in distal tubule and proximal part of collecting ducts

Long – term regulation

- Little is known about how this occurs
- **Pressure diuresis** regulates the volume in circulation and keep „pressure homeostasis“
- Blood pressure increases longer than 2 hours (persistent increase)– started pressure diuresis, its time duration a lot of days (increase blood pressure – increase excretion of sodium - osmotic activity – increase excretion of water ---decrease extravascular volume and decrease blood pressure)
- **a single control system which is not subject to adaptation** – the action takes as long as the pressure is returned to the original values (or if its action is not reversed by other mechanisms)
- With persistent decrease of BP - the opposite effect

Long – term system of pressure natriuresis

- It is a **cascade of regulatory processes**:
- the mechanical effect of increased blood flow through the kidney ... increased blood flow in the kidney papilla - increased renal interstitial hydrostatic pressure - increased tight junction of epithelial cells of the renal tubules for sodium - increased sodium excretion - increased excretion water - decrease in volume of circulatory fluids - pressure drop in the systemic circulation
- System of internal renal baroreceptors ... pressure increase in vas afferens ... restriction of renin production - attenuation of renal sympathetic stimulation - decrease in sodium reabsorption, reduction of fluid volume - pressure drop
- Na⁺- K⁺ - ATPase inhibitory factor – released from adrenal medulla (steroid-like digitalis - possibly ouabain)
- Increased AT₂ receptor expression for angiotensin II (may antagonize the effects of inadequate AT₁ receptor stimulation, in rat experiments demonstrated - increased sodium and water excretion)
- Others: bradykinin, urodilatin, renal natriuretic peptides