

PHYSIOLOGY OF CARDIOVASCULAR SYSTEM

Physiology of the Heart

Heart rate = 70/min, 100 000/day, 5 l/min, 4 500 l/day

Morphology of the heart:

2 separate pumps – right/left

Each – from 2 pumps – atria/ventricle

Endocardium

Myocardium – heart muscle

Pericardium

Histology:

Arrangement of the cardiac muscle fibers (lattice-work)

Cardiac muscle – sui generis –

- striated as skeletal muscle

- syncytium – as smooth muscle

Cells – cylindric, length 50-100 μm , thickness 10-20 microns, intercalated discs (mechanical + electrical connection = functional syncytium).

Physiological Properties of the Heart

- 1) Automatic (autonomic) function
- 2) Conductivity
- 3) Excitability
- 4) Contractility
- 5) Rhythmicity

1) Automatic Function

= ability to work also after an isolation

Principle - existence of primary centre of automatic function – the sino-atrial node – special excitatory system of the heart

Necessity to fulfil some condition (temperature, humidity, supply – O_2 , energ. substances, transport away- metabolites...)

2) Conductivity

The special conductive system of the heart:

SA node – Keith-Flack's node (1907) – pacemaker

3 mm wide, 1 cm long – in the posterior wall of the right atrium (at the junction of v. cava sup. with RA). The fibers are only 3-5 microns in diameter.

In **atria** – conductive tissue – atrial muscle cells. Velocity – 1 m/s
+ 3 bundles of atrial fibers conducting SA-AV node imp.

Internodal tracts of: 1. Bachman
2. Wenckebach
3. Thorel

AV node – the atrioventricular node. Conduction in AV node (secondary centre of automatic function) is slow – delay of 0.1 s, velocity of conduction 20 mm/s.

Principle: Existence of junctional fibers and transitional fibers. Principle of a convergence and divergence. Reverberation circuits.

Physiological role: It allows time for the atria to empty their contents into the ventricles before ventricle contraction begins.

His bundle (v- 4-5 m/s), **right/left bundle branches, Purkinje system**

Very large fibers. This allows quick - immediate transmission of the cardiac impulse throughout the entire ventricular system.

Excitation of the myocardium from endocardium to epicardium.

3) The excitability

= ability to react to a stimulus

Phases:

1. Normal
2. Absolute refractory period
3. Relative refractory period
4. Supranormal excitability

Refractory phases – condition for alternation systole – diastole – against tetanization

Extrasystoles - interpolated
- compensated

Vulnerable period – just at the end of the action potential, because stimulation at this time will sometimes initiate flutter or fibrillation.

Flutter/fibrillation - atrial
- ventricular – fatal

Defibrillation – defibrillator – 5-7 kV

4) The contractility

= ability of the myocardial fibres to contract

Myosin – actin filaments

Tropomyosin, troponin

Excitation – Contraction Coupling:

Depolarization - electrical charges, T-tubules, release of calcium ions from the longitudinal sarcoplasmic reticulum – to promote sliding of the actin and myosin filaments along each other – muscle contraction

All or Nothing Principle of the Heart

= stimulation of any single atrial muscle fiber causes the action potential in entire atrial muscle mass. The same in ventricles.

Syncytial nature of cardiac muscle.

5) The Rhythmicity

= regular alternation of contraction and relaxation

HR – reflects metabolic rate/weight

birds 800/min

mice 500

men 70

elephant 25-30

whale 10/min

Required conditions for the heart activity

1) **Temperature** - optimal for humans 37°

- lower: decreasing of activity

- higher: increasing of activity + metabolic needs

2) **Metabolism** of the heart:

Aerobic – without possibility to cover energy demands of anaerobic pathway (only 1% of the total energy is provided by anaerobic metabolism). Lack of the O₂ debt.

Sources of energy for heart: Lactate, pyruvate, fat, FFA, AA, ketones.

3) **Oxygen consumption**: 10 ml/100 g/min, 35 ml/350 g/min = 10% of total O₂ consumption (250 ml/min). During physical work, 5x more

4) **Isoionia**:

Isoionic – environment (including perfusion fluid)

Balance between: Calcium and potassium

During Ca abundance – **rigor**

During K abundance - **inhibition**

5) **pH**: **acidosis** inhibition of the heart activity – heart

stops in diastole

alkalosis – heart stops in systole – rigor

The Cardiac Cycle

- the period from the end of one cardiac systole to the end of the next heart contraction.

1) Electrical cycle – depolarisation/repolarisation

2) Mechanical cycle – contraction/relaxation of cardiac muscle

Periods of the cardiac cycle

1) **Filling of the atria – during diastole = venous return**

Mechanisms of the filling:

- a) „Vis a tergo“ – residual energy from the left ventricle
- b) „Negative“ intrathoracic (interpleural) pressure:

Quiet breathing:

- expiration: $P_{pl} = -2.5$ mm Hg (relative to atmospheric)
- inspiration: -6 mm Hg during = thoracic pump.

Pressure is transmitted to the great veins and atria – aids venous return.

The movement of diaphragm – rise of P_{abd} .

- c) Shifting down of the A-V ring by contraction of ventricles „vis a fronte“.
- d) Gravity – from head and vessels above cardiac level
- e) Muscular pump

Filling of the ventricles

Accumulation of blood in the atria – elevated atrial pressure - decrease of ventricular pressure to diastolic value (near \emptyset) → pressure in the atria push open the A-V valves – blood flows into the ventricles

- 1) Period of rapid filling (first 1/3 of the diastolic time)
- 2) Period of slow filling – diastasis (next 1/3)
- 3) Atrial systole (last 1/3) + 20-30 % of the filling of the ventricles

Ventricular systole

1) Period of isovolumic .- isometric contraction

At the start of ventricular contraction, the ventricular pressure rises – causing the A-V valves to close. Also semilunar valves are closed – during first about 0.05 s – until the pressures in LV and RV exceed the pressures in the aorta and pulmonary artery – opening of the semilunar valves →

2) Period of ventricular ejection

- a) Phase of the rapid ejection (1/2 of V is ejected in the first 1/4 of the ventricular systole)
- b) Phase of the slow ejection (remaining 1/2 of V-during next 2/4 of the ventricular systole)
- 3) Protodiastole (last 1/4 of the ventricular systole)

The ventricular pressure falls to a value below that in aorta, closing of the semilunar valves – early diastole.

Ventricular diastole

- 1) Period of isovolumic (isometric) relaxation – the valves are closed, V pressures continues to drop
- 2) Filling of the ventricles:
Period of the rapid ventricular filling – when the ventricular pressure falls below atrial pressure and the AV valves opena new cycle.

HR = 72/min – 1 cycle lasts 0.83 s.

Length of Systole/Diastole

HR – 65/min:	S - 0.3 s	
	D - 0.6 s	1 : 2
HR – 200/min:	S - 0.16 s	
	D - 0.14 s	1 : 1

The duration of systole is more fixed.
 Tachycardia is accompanied mainly by shortening of the diastole – if more than 180/min – insufficient filling – critical frequency (HR) for adults.

Functions of the valves

The AV – valves prevent backflow of blood from V to A during systole

The semilunar valves prevent backflow from the aorta and pulmonary artery to V during diastole.

All valves close and open passively – by pressure gradient.

The Electrical Activity of the Heart

Resting membrane potential (RMP): myocardial fibers

approximately – 90 mV

SA node: -55 to –60 mV

Conductive tissue: - 90 to –100 mV

```

+++++++
-----
-----
-----
-----
+++++++
  
```

RMP depends on differences in concentration of K^+

K_i^+ 150 mmol/l; K_e^+ - 5 mmol/l = 30 x

RMP don't allow to K^+ to equalize concentrations.

Na_i^+ = 5-10 mmol/l; Na_e^+ = 140 mmol/l

Depolarization: Firing level –65 mV

Initial – is due to an increase in Na^+ permeability
 (through fast Na^+ channels)

Following – a slower increase in Ca^{2+} permeability
 (through slow Ca^{2+} channels) – plateau (!)

Repolarization is due to a delayed increase in K^+ permeability.

The excitation in the conductive system cells

Lower RMP (-60 mV) firing level – 35 mV

Fast Na^+ channel is not activated.

Unstable RMP – open slow (nonspecific channel) – pacemaker potential = prepotential – due to a steady decrease in K^+ permeability

Effect of heart nerves on prepotential:

- vagus – acetylcholine – increase in K^+ permeability – the slope of prepotentials is decreased
- sympathetic nerves – opposite effect - decrease in K^+ permeability ...

Prepotential in **SA node** has the slope increased in comparison to one in AV node –
 - **primary center**. Gradient of automaticity. The slope of the prepotential determines HR.

Electrocardiography (ECG)

Registration of electrical potentials from the heart also from body surface (the tissues of the body contain electrolytes – are conductive).

W. Einthoven (1903) – string galvanometer

A three – lead system: Leads I. II. III. – standard - frontal plane ECG – equilateral triangle

Unipolar leads – V – Wilson – potential of one site is 0.

Transverse plane, precordial leads V₁₋₆ (12)

Augmented unipolar limb leads – aVR, aVL, aVF.

Form of the ECG

Isoelectric line

Waves:

P – atrial depolarization (0.1 – 0.3 mV, 0.1 s)

QRS – ventricular depolarization (atrial repolarization)

Q – initial depolarization (His bundle, branches)

R – activation of major portion of ventricular myocardium

S - late activation of posterobasal portion of the LV mass and the pulmonary conus

T – ventricular repolarization

U – repolarization of the papillary muscles

The duration of the waves, intervals and segments

P – wave 0.1 s

PQ – interval 0.16 s

PQ – segment 0.06 – 0.1 s

QRS complex 0.05 – 0.1 s

QT interval 0.2 – 0.4

QT segment 0.12

T wave 0.16

The voltage of ECG curve

P - 0.1 – 0.3 mV

R - 0.7 - 1.5 mV

T - 0.3 – 0.5 mV

Q, S - -0.3 - -0.5 mV

Intracellular potential 100 mV

Explanation:

- 1) ECG potential represents an algebraic sum of the action potentials of myocardial fibres
- 2) loss of voltage during spreading of potential

Special use of ECG

Esophageal leads (e.g. E-30)

Intracardial leads – RA, RV – His bundle electrogram

Monitoring:

– permanent in UIC

- Holter's monitoring (tape recorder) diagnosis of arrhythmias

Cardiac Output

- of the LV = the quantity of blood pumped by the LV/min
- of the RV = the quantity of blood pumped by the RV/min

$$CO_{LV} = CO_{RV} !!!$$

$$CO = SV \times f = 70 \text{ ml} \times 72 = 5000 \text{ ml/min}$$

Normal values – 5-6 l/min

$$\text{Cardiac Index (CI)} = CO/m^2 = 3 - 3.2 \text{ l/min/m}^2$$

Stroke volume = volume of blood ejected per systole

Changes in CO

by changes in SV, or f, or both

Change in SV

End diastolic volume (EDV) – approx. 150 ml

End systolic volume (ESV) - 70 ml

More effective contractions – positive inotropic effect – ESV – functional reserve for the SV and CO increase

Change in f – heart rate

up to a critical level (180/min – in adults)

Cardiac Output Changes

Effect of age – CI in 10 years – 4 l/min/m²
80 - 2 l/min/m²

Effect of exercise – CO can rise to 30-35 l/min

Effects of metabolism – CO proportional to M

Effect of gravity - +40 - +80 %

Effect of posture – Co falls about 20 %

Measurement of Cardiac Output

- 1) Direct method: electromagnetic flowmeter
- 2) Indirect methods:
 - a) Fick's method
 - b) Indicator dilution methods
 - using dyes
 - thermal dilution - intermittent
 - continuous infusion
 - c) Doppler's method
 - d) echocardiography
 - e) bioimpedance method

Methods for heart examination

- 1) Invasive – cardiac catheterization (Forssmann 1929):
 - Measurement of pressure in atria, ventricles, aorta, pulmonary artery
 - application of dyes ...

- angiocardiography, coronarography - application of X-ray contrast material

2) Noninvasive methods:

- Electrocardiography
- Heart rate variability evaluation
- Auscultation of heart sounds
- Phonocardiography
- Echocardiography
- Polycardiography

Auscultation/registration of heart sounds

1st heart sound – associated with:

- 1) closure of the AV valves at the beginning of systole
- 2) vibration of the walls of the heart and ejected blood

2nd heart sound – result from closure of the semilunar valves and from reverberation of blood back

3rd heart sound – occasionally – at the beginning of the middle third of diastole – period of the rapid filling of ventricles

4th heart sound – during atrial systole

The Phonocardiography

Recording of the heart sounds simultaneously with ECG

Advantages:

- 1) More exact analysis of the heart sounds and murmurs
 - 2) A writing evidence
- The time relationships between ECG and PhCG

Echocardiography

Pulses of ultrasonic waves are emitted and received by transducer.

Reflected ultrasound from the structures with different densities = **echo**

f of ultrasound > 20 kHz – in EchCG

- 2.25 MHz - in adults
- 4.4 MHz - in children
- 7 MHz - in newborns

Evaluation of the thickness and motions of the heart walls, septum and function of the valves (mainly mitral) during the cardiac cycle. Valvular lesions.

Polycardiography

Simultaneous registration of: 1) ECG

- 2) PhCG
- 3) Arterial pulse
- 4) Venous pulse
- 5) Pressure curves (ao, LV, RV, PA ...)

Hemodynamics – Dynamics of Blood Circulation

- A) General Hemodynamics
- B) Special Hemodynamics

A) General – biophysical considerations:

Parameters:

- 1) Flow
- 2) Velocity
- 3) Pressure
- 4) Resistance

1) Blood Flow

$$F = \frac{V}{t} \quad (\text{m}^3/\text{s}; \text{l/s}; \text{ml}/\text{min} \dots)$$

Flow: – laminar (streamline)
 – turbulent

$$\text{Reynolds number} = \frac{\text{dens.} \times \text{diam.} \times \text{velocity}}{\text{Viscosity}}$$

Critical velocity – in ascending aorta
 – in anemia

Systolic murmurs

$$F = \frac{\text{Dif.}P}{R}$$

Critical closing pressure = P at which flow ceases.

Velocity of Blood

$$v = \frac{l}{t} \quad (\text{m/s}; \text{cm/s} \dots)$$

$$v = \frac{F}{A} \quad \begin{array}{l} = \text{flow} \\ = \text{cross-sectional area} \end{array} \quad \begin{array}{l} \text{cm}^3 \times \text{s}^{-1} \\ \text{cm}^2 \end{array} \quad = \text{-----} = \text{cm/s}$$

	d	v
Aorta	4.5 cm ²	30-40 cm/s (120)
A.a.	20	20-30 cm/s
Arterioles	400	3 mm/s
Capillaries	4500	0.5-1 mm/s
Venules	4000	0.5-1 cm/s
Veins	40	1-5 cm/s
v.cava	5	8 cm/s

Methods for Measuring Blood Velocity and Flow

- 1) Electromagnetic flowmeter
- 2) Plethysmography
- 3) Venous occlusion plethysmography
- 3) Rheoplethysmography
- 4) Radioactive methods
- 5) Measurement of circulatory time
- 6) Ultrasonic flowmeter (Doppler)

Blood Pressure

- Frontal
- Lateral

- Systolic
- Diastolic
- Mean
- Pulse amplitude

<u>Normal values</u>	<u>mm Hg</u>	<u>kPa</u>
LV	125/0	12-20/0
A.a.	120	12-20/8-13
Arterioles	40-50	4-6
Capillaries	30-15	4-2
Veins	4-7	0.5-1
CVP (RA)	-5+5	-0.4+0.4
RV	30/0	3.5/0
PA	27/10	3.5/1.2
Pcap.	10	1.3
LA	-5+5	0.4 + 0.4

Measurement of BP

Methods: - direct
- indirect

Direct methods: Hales 1773

Catheterization – electronic manometers with transducers

Indirect methods:

- Palpation (Riva – Rocci)
- Auscultatory (Korotkoff)
- Oscillometric (Pachon, electronic-digital)

Principles for accurate measurement of BP

Patient: should rest undisturbed in a quiet, comfortable setting at room temperature for at least 5-15 minutes. To avoid physical activity, food consumption, smoking, caffeine ingestion and emotional stress for at least half an hour before measurement. Full bladder or bowel can cause an increase in BP. Nonconstricting clothing – with no sleeves. Children – should be given sufficient time to recover from crying.

„White – coat hypertension“ – physicians cause + 27/15. Measurement at home.

Recommendations for observer measuring BP

- Have normal hearing and vision, be trained in the technique for measurement BP
- Support the patient's arm – the antecubital fossa at heart level
- Chair with back and arm support when the patient is sitting
- Use an appropriately sized cuff
- Check the BP by palpation before auscultation
- Deflate the cuff 2-3 mmHg/s
- Use the 1st and 5th Korotkoff sounds to determine BP syst. and BP diast.
- Allow 1-2 min. between readings
- Take readings with the patient in the lying or sitting position and in the standing position
- Assess the BP at least 3x over 3-6 months among patients with mildly elevated BP

BP depends on:

- 1) Heart activity
- 2) Vascular resistance
- 3) Volume and viscosity of blood
- 4) Compression vessels by different organs and pressures (e.g. intraabdominal)
- 5) Hydrostatic pressure – effect of gravity

1) Heart activity

$$CO = SV \times f$$

Increase in SV → increase mainly BP syst.
Increase in f (HR) → increase mainly BP diast.

2) Vascular resistance

increase → rise mainly BP diast.

3) Volume and viscosity of blood

a) Volume – hypovolemia/hypervolemia: hypotension/hypertension

b) Viscosity – the greater the viscosity, the less the flow in a vessel.

The viscosity of blood at normal hematocrit is about 3 (R for blood is 3x the R for water flow), at Ht 60-70 is viscosity about 10x that – of water – slow and difficult flow perfusion.

4) Compression of vessels by different organs and pressures

Compression by skeletal muscles, intraabdominal pressure ...

Coughing, defecation, delivery ... Transmission of the pressure to vessels.

5) Effect of gravity – hydrostatic pressure

In standing person the magnitude of the gravitational effect is 0.77 mmHg of height.

BP is increased by 0.77 mmHg for each cm below the RA and decreased by 0.77 mmHg for each cm above the RA.

Arterial BP in the foot = $100 + (0.77 \times 105 \text{ cm}) = 180 \text{ mmHg}$

Venous BP - “ - = 7 + - “ - = 87 mmHg

Physiological Changes in BP

1) Effect of age and sexual differences

Newborns, children, sexual differentiation in the pubertal age, BP in old subjects.

2) Postural effects

Orthostasis, klinostasis

3) Effects of organ activities

a) breathing – fluctuation of BP

b) GIT – food consumption, increase in BP syst., BP diast. unchanged, or decreased

c) CNS – sleep (REM/non REM)

d) skeletal muscles – exercise, physical work

Vascular Resistance

- the impediment to blood flow in a vessel

$$R = \frac{P}{F} = \frac{BP}{F}$$

$$\text{Total SVR} = \frac{BP_{\text{ao.mean}} - BP_{\text{RA}}}{F_{\text{ao}}} = \frac{100 - 0 \text{ mmHg}}{5 \text{ l/min}} =$$

$$= 20 \text{ mmHg/l/min}$$

$$\text{Pulmonary VR} = \frac{BP_{PA \text{ mean}} - BP_{LA}}{F_{PA}} = \frac{20 - 0}{5} = 4 \text{ mmHg/l/min}$$

Poiseuille – Hagen Formula

$$R = \frac{8 \times \eta \times l}{\pi \times r^4} \rightarrow$$

BF and R are markedly affected by changes in r (caliber of the vessels).

Two components of R:

- 1) Characteristics of wall vessel – reciprocal to elasticity
- 2) Caliber of vessels – mainly arterioles

Elasticity – arterial compliance

Importance in maintaining of: - BP diast.

- F diast.

„Secondary hearts“

Deterioration of the arterial elasticity → increased BP syst. and the pulse pressure (arteriosclerosis – systolic hypertension).

Changes of elasticity – changes in quality and velocity of the arterial pulse velocity.

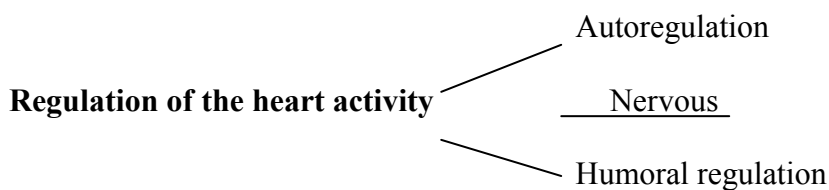
REGULATION OF THE CIRCULATION

regulation of action of the heart

Regulation of circulation /

\ regulation of diameter of the vessels

REGULATION OF THE CARDIAC ACTIVITY



1) **Intracardiac regulation - AUTOREGULATION:**

- a) Heterometric autoregulation – FRANK-STARLING LAW: „the energy of contraction is proportional to the initial length of the cardiac muscle fiber – to the end diastolic volume“

Relation between muscle fiber length and tension.

Diastolic filling = end diastolic volume

As the diastolic filling increases, the forces of contraction of the ventricles is increased.
Principle of this law is in ultrastructure of the cardiac muscle.

Physiological roles of the FS law:

1/ maintaining the equal CO_s of RV and LV
2/ compensation of the law of Laplace „pressure evoked by wall of a cavity is reciprocal to its diameter“

or: the distending pressure in a distensible hollow object is equal to the tension in the wall (T) divided by the radius

3/ regulation of the CO_s during venous return changes

b) Homeometric regulation – „Bowditch’s stairs“

– effect of heart rate on the force of contraction

Regulation due to changes in contractility independent on length – „force – frequency relation“

Principle - increased availability of intracellular Ca⁺².

Physiological role: better emptying of the ventricles during tachycardia

Optimal and critical frequency.

NEURAL CONTROL:

The autonomic nervous system:

1) Parasympathetic nervous system (craniosacral division) = cranial nerves: III, VII, IX, X, sacral. S₂ - S₄

Cholinergic system, receptors of muscarin type (M-receptors), blockade by the atropine.

Tonic discharge in vagus = vagal tone

After blockade (cutting X./atropine) – tachycardia (of 70 to 150/min)

Development of the vagal tone in ontogeny:

Newborns – weak tone – HR = 120/min.

During infancy – the tone rises – mainly in pubertal age

Sportsmen - stronger vagal tone

2) Sympathetic nervous system (thoracico – lumbar) = Th₁ – L₃₋₄

Noradrenergic system, receptors NA(A)

Receptors – alpha – mainly in vessels – vasoconstriction

- beta (heart-beta₁) – positive tropic effects

Tonic discharge in the cardiac sympathetic nerves = sympathetic tone

After blockade – beta₁ sympatholytics – bradycardia (of 70 to 55-60/min).

Vagal tone in humans – dominant.

Cardiomotoric center

Located bilaterally in the reticular substance of the medulla and in the lower third of the pons.

The *lateral portions* transmit excitatory impulses through the sympathetic nerve fibers to the heart with positive tropic effects = **cardioexcitatory part.**

The *medial portion*, which has in immediate apposition to the dorsal motor nucleus of the vagus nerve, transmits impulses through the vagus nerve to the heart – with negative tropic effects = **cardioinhibitory center**.

HUMORAL REGULATION

Catecholamines (E, NE) – *adrenal medulla*

T₃, T₄ - *thyroid gland*

Glucagon – *pancreas*

all = positive tropic effects

REGULATION OF DIAMETER OF THE VESSELS

- autoregulation
- nervous
- humoral

1)Autoregulation

Myogenic:

Compensation of pressure changes by changes in diameter (vascular resistance) for remaining constant blood flow:

The vascular smooth muscle in the vessels contract – in response to the tension of the vessel wall. *Stimuli from inside*.

Autoregulation of renal and cerebral BF.

Stimuli outside – mechanical – massage - vasodilatation

Humoral:

Vasodilator agents:

Metabolites – lactate, PCO₂, increase in temperature (working skeletal muscle), adenosine (from ATP) – in cardiac muscle

Bradykinin, lysylbradykinin (kaldin) in sweat and salivary glands

Histamine – in skin circulation

NO

Vasoconstrictors:

Serotonin, endothelins (ET1), PO₂ – different reactions in regional circulations (hypoxic pulmonary vasoconstriction, cerebral vasodilatation)

2/Neural regulation

Parasympathetic division – cholinergic **vasodilatory** fibres – only in some regions of circulation (genital)

Sympathetic division – adrenergic postggl. fibers, alpha_{1,2} receptors, **vasoconstriction**

Exception – *cholinergic sympathetic system in vessels in skeletal muscles*.

Permanent vasoconstrictory tone.

Vasomotor Centre

in medulla oblongata

Pressoric area – tonic activity – in rostral ventrolateral reticular area in medulla

Depressoric area – in the medial and caudal area

Afferents to the vasomotor centre:

- Direct stimulation by \uparrow CO₂, \downarrow O₂
- Excitatory impulses:
 - cortex – hypothalamus
 - pain pathways
 - peripheral chemoreceptors
- Inhibitory impulses:
 - cortex – hypothalamus
 - lung receptors
 - baroreceptors

Hormonal control of vessels

Vasodilatory hormones:

VIP - in splanchnic circulation

ANP – secreted by heart – in renal ...

Vasoconstrictory hormones:

norepinephrine, angiotensin II, vasopressin (ADH)

Short review of the Autonomic Nervous System Pharmacology

Sympathomimetic drugs:

alpha: Norepinephrine

beta: Isoproterenol (Isuprel)

Epinephrine (adrenaline)

Miscellaneous: the precursors of E, NE:

Dopamine (Intropin)

Dobutamine (Dobutrex)

Amphetamine (by releasing endogenous catecholamines)

Blocking agents:

Anti alpha – phenoxybenzamine (Dibenzylamine)

- tolazoline, phentolamine (Regitine)

- anti beta₁ – propranolol (Inderal)

- metipranolol (Trimepranol)

- pindolol (Visken).....

Parasympathomimetic drugs:

Acetylcholine

Pilocarpine

Methacholine

Muscarine (in Amanita muscaria)

Anticholinesterases:

Physostigmine

Neostigmine

Blocking agents:

- Anticholinergic - atropine
- scopolamine

CARDIOVASCULAR REFLEXES (CVR)

Reflex = regular response of the organism to stimulation mediated through central nervous system

Reflex arc:

- 1) receptor (sense organ);
- 2) afferent neuron;
- 3) center;
- 4) efferent neuron;
- 5) effector (in CVR – heart and vessels)

Receptors (for CVR):

- 1) **Interoceptors** – for perception of the internal environment:
 - a) Baroreceptors
 - b) Chemoreceptors

Baroreceptors – low – pressure receptors
- high pressure receptors

a) **Low – pressure receptors** – atrial stretch receptors:

- 2 types - „A“ – they discharge primarily during atrial systole
- „B“ - “ - atrial filling, peak – at the end of atrial diastole.

The discharge is increased when venous return is increased = volumoreceptors for monitoring venous return.

Effects of the increased stimulation of the atrial baroreceptors:

Vasodilatation – an accumulation of the blood in the periphery – a fall in BP.

Bainbridge Reflex – rapid infusion to the right atrium – changes in HR.

Initial basal increased HR – effect: bradycardia

- “ - decreased HR – effect: tachycardia

Two components:- reflex – through atrial baroreceptors

- mechanical – local stretch – effect on the SA node

b) **High – pressure receptors**

- carotid sinus
- aortic arch
- LV

Carotid sinus receptors: spray type nerve endings – in the adventitia of the carotid bifurcation and the internal carotid artery.

Afferent neurons: Innervation – through the branch of n. IX. – Hering's nerve.

Center of the carotid sinus reflex – tractus solitarius in the medulla,

Efferent neurons: n.X and parasympathetic + sympathetic nerves to vessels.

Effectors: Heart, smooth muscles in the vessels wall.

Stimulation: The baroreceptors are stimulated by distension of the vessels wall – stretch receptors.

Aortic arch receptors: in the wall of the aorta.

Afferent pathway: Innervation – through the vagus)

Center, efferent pathway, effectors and effects – the same as in CSR

Left ventricular receptors:

Afferent and efferent pathways: n. vagus.

Activity and effects of the HP baroreceptors

Normal BP – r. discharge at a slow rate

Increased BP – the discharge rate increases

Decreased BP - - “ - declines

Effects:

BP increase (hypertension): The increased discharge rate evokes rising activity in cardioinhibitory center and depressoric area of the vasomotor center – bradycardia, vasodilatation – a fall in BP to the normal level

BP decrease (hypotension): The decreased discharge ... vice versa. Normalization of the BP in different situations.

Baroreceptor Testing

- Pressure on the SC region – unconstant stimulus
Syndrome of the hypersensitive SC (sy HSC)
- Carotid Clamping – proximal or distal to the CS - on experimental animals
- Cutting the CS nerves - on experiments/ treatment sy HSC
- Application of the drugs eliciting an increase in BP (NE, dopamine)
- Different maneuvers (orthostasis, klinostasis, Valsalva ...)

Orthostatic Reflex

When a person stands – venous return decreases due to hydrostatic pressure of the blood.

A decrease in CO and systemic BP occurs.

Falling BP at the baroreceptors elicits an immediate reflex, with strong sympathetic activity – vasoconstriction, increase in BP diast., tachycardia.

The aim – to maintain an adequate perfusion of organs.

Valsalva maneuver

Forced expiratory effort against a closed glottis – $P_{pl} + 30-50$ mmHg.

5 phases:

1st. – at the onset of straining, the BP rises

2nd – a decrease of venous return, CO, BP; HR increases

3rd – reflex vasoconstriction – stop of the fall of BP, HR increases

4th – after the first inspirium, start of the breathing – decrease in BP –
- filling of the pulmonary circulation with blood

5th - an increase in BP – vasoconstriction persists, an excessive venous return – stimulation of baroreceptors, causing bradycardia and a drop in BP to normal values.

Chemoreceptors - peripheral
- central

Peripheral chemoreceptors:

Carotid and aortic bodies – near the carotid bifurcation, and the arch of the aorta.

The highest BF/g.

Stimulation – low PaO_2 (high $PaCO_2$, acidosis)

Effects – an increasing of pressoric area of vasomotor centre, vasoconstriction (splanchnic), redistribution of the blood, an increase in BP.

HR – primarily tachycardia, secondary bradycardia through baroreceptors

Central chemoreceptors: in the brain stem, on the ventral surface, H^+ zone.

Stimulation: a decrease in pH - acidosis.

Effects – changes in respiration, without any direct effect on cardiovascular system.

2) Nonspecific receptors

A) Trigeminal endings:

1) Oculocardiac reflex:

Stimulation: pressure on the mechanoreceptors of eye and orbit –

Effects: Depressoric effects on vessels and breathing - a decrease in
HR by 5-14 / min.

2) Kratschmer apnoeic reflex:

Stimulation: Intranasal insufflation of various irritant gases (smoke, ammonia ..)

Effects: reflex respiratory arrest + laryngoconstriction + bradycardia
+ redistribution of the blood to the vital most important organs
(from the splanchnic circulation).

3) The diving reflex:

Stimulation of the trigeminal region with cold (water).

Effects: the same as in Kratschmer.

Oxygen conserving reflex – the changes primarily safeguard the blood and oxygen supply of the heart, the brain.

B) Vagal receptors

Stretch receptors – localized in the smooth muscles of the airways –
- *the Hering-Breuer inflation reflex.*

Stimulation: lung inflation

Effects: termination of inspiration, systemic hypotension
(mechanical limitation of the venous return + reflex vasodilatation),
tachycardia.

Juxtapulmonary capillary receptors – *the pulmonary chemoreflex.*

Stimulation by interstitial pressure (pulmonary edema), chemical substances (PDG, NaS, hypertonic solution)...

Effects: biphasic – inhibition/stimulation reaction: apnoe/hyperpnoe;
hypotension/hypertension + bradycardia (through baroreceptors).

C-fiber endings in the coronary circulation – *the coronary chemoreflex*

Stimulation: by chemical substances (veratridine, serotonin, capsaicin, metabolites ...)

Effects: rapid shallow breathing, hypotension, bradycardia = depressor reflex (during myocardial infarct?)

The Coronary Circulation

Anatomy:

The right and the left coronary *artery*

- the anterior descending
- the circumflex branch

Smaller branches (epicardial arteries) give off tiny arteries that course at right angles through the myocardium = intramural vessels

Capillary number: 1 capillary/1 myofiber ($3000/\text{mm}^3$)

Venules converge to the coronary sinus – into the RA

The veins from the right side of the heart drain directly at multiple site within the RA and RV.

Blood Flow

BF = 250 ml/min; (60 ml/min/100 g heart w.) = 5% of CO

Pressure – Flow Paradox:

BF falls during systolic BP and it rises with the onset of diastole when BP is low – mainly in LV coronary intramural vessels

Explanation: Contraction of the LV squeezes the intramural vessels.

The flow dependence on the cardiac cycle phases – on differential pressure between $BP_{ao} - P_{in}$ myocardial ventricular wal (intraventricular P).

	Pressure			Gradient (dif. P)	
	Aorta	LV	RV	Ao – LV	Ao – RV
Systole	120	121	25	-1	95
Diastole	80	Ø	Ø	80	80

Regulation of the Coronary Blood Flow

1) Autoregulation:

When BP is elevated, BF initially rises – then returns toward the control level and vice versa. Functioning mechanism in the range 70-170 mmHg.

Explanation:

Myogenic hypothesis: the response is due to altered stretch of the smooth muscle in the wall of CA.

2) Neural: ANS

- a) The sympathetic nerve fibres – NE – alpha adrenergic receptors – vasoconstriction.
- b) The parasympathetic n. vagus – Ach – mild vasodilatation.

3) Humoral:

- a) Oxygen – extraction of O₂ in coronary bed is nearly complete.
Dif. a-vO₂ = 12 Vol. % - the highest in the body.
A decrease in PaO₂ – vasodilation (adenosine)

- b) An increase in PaCO₂ and decrease in pH – vasodilatation

Vasodilators:

- Adrenaline (epinephrine) – (beta 2 receptors)
- Adenosine – a metabolic product of ATP breakdown
- Prostaglandins: Prostacyclin (PGI₂) and PGE₂
- Calcium antagonists (e.g. Verapamil)
- **NO** -EDRF – endothelial derived relaxing factor – a substance released by endothelial cells – in response to increasing BF
Nitroglycerine

Vasoconstrictors

- Noradrenaline (norepinephrine)
- Vasopressin
- Angiotensin II.
- Ergonovine – used for provocation of coronary spasm in dg. of insufficiency coronary bed.

Inadequate coronary BF and coronary heart diseases

1-st situation: coronary arteries are narrowed but not completely occluded. Coronary BF is adequate to supply the resting metabolic needs of the myocardium but when O₂ demands are increased (exercise) – the blood supply becomes insufficient = ischemia – with a clinical syndrome – angina pectoris.

2-nd situation: Abrupt obstruction of a coronary artery produces within 1-2 min loss of contraction in the involved region. If sustained beyond 40 min – it produces necrosis = acute myocardial infarction.

Cerebral Circulation

Anatomy:

Arterial inflow through 2 internal carotids + 2 vertebrals. Circle of Willis.

Venous drainage by way of the deep veins and dural sinuses – into internal jugular veins.

Capillaries:

Number of capillaries of the brain gray matter is about 4x as great as that of white matter. Capillaries are supported on alar sides by „glial feet“ – providing physical support to prevent overstretching of the capillaries in case of high pressure and to prevent transudation of fluid into the brain – against brain edema.

Difficult penetration – the blood – brain barrier (except of some areas of the hypothalamus, the pineal gland and the area postrema).

Function of the B-B barrier

Barrier is highly permeable to H₂O, CO₂, O₂ and lipid soluble substances (alcohol, anesthetics).

Slightly permeable to the electrolytes (Na⁺, Cl⁻, K⁺)

Totally impermeable to plasma proteins and large organic molecules.

Importance: The BB barrier – maintains the constancy of the environment of the neurons in CNS.

- protects of the brain from toxins in the blood
- prevents neurotransmitters against the escape into the circulation

Ontogeny: BB barrier develops postnatal (jaundiced newborns – penetration of the bile pigments into CNS – kernicterus).

Clinical implication: Application of the drugs (ATB) penetrating in the BB barrier for treatment of cerebral diseases.

Cerebral Blood Flow

CBF = Adults: 750 ml/min = 54 ml/min/100 g of brain w. = approx. 15% of CO

Children: 105 ml/min/100 g

A decrease of CBF to „adult value“ in puabertal age (sex hormones)

BF in various parts of the brain:

BF in gray matter is about 6 times that in white matter.

A marked fluctuation in regional BF with changes in activity (the movements – motor area, the speech – sensory + motor area).

Regulation of CBF

Monro-Kellie doctrine: The sum of the volume of blood (75 ml), cerebrospinal fluid (75 ml) and brain (1400 g) in the cranium must be relatively constant.

1) Autoregulation:

The intracranial pressure (ICP – CSF pressure) = 10 mm Hg. When ICP > 33 mm Hg – CBF is reduced – ischemia – stimulation of the vasomotor and cardioinhibitory centers – hypertension, bradycardia = Cushing reflex – helps to maintain CBF and to preserve O₂ for brain and coronary circulation.

The myogenic autoregulation – in the range 65 – 140 mm Hg.

2) Humoral regulation:

Increase in PaCO₂ decreases in PaO₂, pH – vasodilatation

Cerebral tissue PO₂ – normal 35-40 mm Hg at PO₂ below 20 mm Hg – coma in 5 – 10 s.

Inhalation of CO₂ – increase in CBF by 75%

Inhalation of O₂ – decrease in CBF by 15 %

3) Nervous regulation:

Sympathetic innervation from the superior cervical sympathetic ganglia.

Vasoconstriction. During strenuous exercise – prevention against high pressure and cerebral stroke (a vascular hemorrhage into the brain).

Parasympathetic innervation: n. facialis. Vasodilatation. Mild importance.

Circulation in Skeletal Muscles

Flow – during rest 3-4 ml/min/100g

- during exercise – the increase more than 20-fold

Regulation

1) Local:

Mechanical: Muscle contractions → the decrease in BF (the importance rhythmic contractions). Between contractions – BF is increased.

Temperature: the increase - vasodilation

2) Humoral:

Vasodilators: Hypoxia, hypercapnia, lactic acid, K⁺, acetylcholine, epinephrine

Vasoconstrictor: Norepinephrine

3) Nervous control of muscle blood flow

- Sympathetic NA system – vasoconstriction

- Special – Sympathetic cholinergic system – vasodilation (activation before the start of muscular exercise)

The Skin Circulation

Anatomy: Blood vessels in the fatty subcutaneous tissue.-

Important for the thermoregulation:

- venous plexus supplied by inflow of blood from the skin capillaries

- arteriovenous anastomoses (in hands, feet, ears)

The Skin Blood Flow

F = 250 ml/min = 1-3 ml/min/100 g = 5% of CO – at rest

F = 150 ml/min/100 g – in response to thermal stimuli

Blood is shunted through the anastomoses.

Higher skin BF causes the conduction of the heat from the core to the skin – higher radiation of the heat.

Flow of blood to the skin is a most effective heat transfer from the body core to the skin.

Regulation of the skin BF

Autoregulation

Nervous: Sympathetic nerves: The increase of the sympathetic nerve traffic –
- vasoconstriction and vice versa. Vasoconstrictory tone.

Local axon reflexes:

Impulses initiated in sensory nerves (by injury) are relayed antidromically down by other branches of the sensory nerve fiber. The only one situation – antidromic conduction.

Humoral: - Histamine and H-like substances – H_1 – receptors – vasodilatation

- Bradykinin – sweat glands – kalikrein – effects on plasma proteins – bradykinin –
vasodilatation

- Serotonin, NE – vasoconstriction

Tests of the skin vascular reactivity

A) White reaction: the mechanical stimulation (pointed object is drawn lightly over the skin) – a pale line – due to contractions of the precapillary sphincters (in 10-15 s).

B) Trippl response: the skin attacked more strongly

1) Red reaction (in 10 s) – capillary dilatation

2) Swelling (local edema) increased permeability of the capillaries – histamine, H-
substances

3) Difuse reddening around the injury – arterial dilatation – axon reflexes.

Pulmonary Circulation

Morphology:

Circulation in series to the systemic circulation. The pulmonary vessels are short and have large diameter. The walls are thin and distensible.

Physiology

Flow: CO RV – 5.5 l/min; Velocity – 40 cm/s;

BF – is much more pulsatile than is systemic circulation (low arteriolar resistance)

Ventilation/Perfusion Ratio

Differences in various parts of the lungs.

Pressure: PA = 25/10 mm Hg. Mean = 15 mm Hg.

Pulmonary capillary pressure = 7-10 mm Hg.

Resistance: low – 2-3 mm/l/min

Volume of blood: 1 l of the blood in pulmonary bed – only about 75-100 ml is in the pulmonary capillaries. SV = 70 ml – all the capillary blood is replaced at each heart beat.

The increase of the volume after deep inspiration, in horizontal position. Reservoir function.

Distribution of blood flow in pulmonary circulation

The hydrostatic pressure of the blood within the pulmonary capillaries influences BF in different regions of the lungs. At the top of the lungs is little flow – in the lowest point in the lungs is max.