Prof. Štefan Kujaník, MD, PhD: History of Physiology

Physiology (P) = the science studying the life reactions (i.e. function)

Recent concept – the science studying the function (action) of cells, tissues, organs, and the whole organism

Physiology is a branch of the biological sciences. Formerly the biological sciences have not been branched and later biology had grown in several disciplines which currently form two basic groups, named morphological and physiological.

Physiology – general, comparative, special (plant, animal and human P, normal and pathological)

IMPORTANT PHYSICIANS (not yet physiologists): Hippocrates, Abu Ali Ibn Sina (Avicenna), Ibn Roshd (Averroes), Galenos, Vesalius, Yan Jessenius (Slovak, dissection)

The first who has used **the term PHYSIOLOGY** is the French physician **Jean FERNEL** (1497-1558) in the 16th century. That are the living reactions.

The founder of P is an English physician **William HARVEY**, who described the **blood circulation** in 1628. He was the first who carried out the **animal experiment**.

The book "Elementa physiologiae corporis humani" written in 8 volumes by **Albrecht von HALLER** in Switzerland in 1757 to 1766 – P as an independent branch of medicine

Up to the 18th century P had been one independent branch of medicine not yet.

Jiří (Yiree) PROCHÁSKA (1749-1820) – professor of Anatomy, Physiology, and Ophthalmology in Prague – **the textbook** "Institutiones physiologiae humanae" (1797). In 1784 he was the first all over the world who formulated the concept of reflex as the element of the nervous function.

Luigi GALVANI (1737-1798) – studied existence of the animal electricity

Jan Evangelista PURKYNE (PURKINJE, 1787-1869) – professor of Anatomy and Physiology in Wroclaw (Poland) and Prague – one of the most famous physiologists all over the world in the 19th century. He has several priorities: (in what he was the first)

- systematic investigation by the microscope
- he named the living materia in cells "protoplasm"
- founder of dactyloscopy (science regarding to the finger prints)
- discoverer of the nucleus of the ovular cell in the ovary
- author of the cell theory in biology (1837)

Some anatomic terms carry his name:

- Purkyne fibers in the heart
- Purkyne cells in the cerebellum
- Purkyne figures showing the refractive areas in the eyes
- phenomenon of Purkyne in ophthalmology

Claude BERNARD (1813-1878) – the founder of **experimental investigation** in physiology and medicine

W. B. CANNON – the author of conception **homeostasis**, introduced the term „stress“

Ivan P. PAVLOV (1849-1936) – control of the heart, circulation, and digestion, author of the conception "**conditioned reflex**". Nobel prizer for investigations in digestion.

Vilém LAUFBERGER (1890-1986) – the discoverer of the molecule of ferritin, founder of the Czechoslovak Physiological Society (1952).

SLOVAK PHYSIOLOGY AND MEDICINE

There were 3 universities in Slovakia earlier (Academia Istropolitana in Bratislava, University in Trnava, and University in Košice in the 18th century) but no had the faculty of medicine.

The first Slovak University with the Faculty of medicine is the Commenius University in Bratislava, founded in 1919.

School of Medicine in Košice was founded in 1948

The University of P. J. Šafárik in 1959 (first it consisted of three faculties, later of 7, now after division into 2 universities (Košice and Prešov) it consists of 4 faculties – Medicine, Natural Sciences, Law, Civil Service)

The Medical faculty of Commenius University in Martin – 1962

Academician **Juraj ANTAL** in Bratislava is the first academician among the Slovak physiologists (worked in the cardiovascular system)

Academician **Branislav LICHARDUS** in Bratislava working in endocrinology.

Academician **Ladislav MACHO** – endocrinology

The physiological research is realized at Universities and in the Slovak Academy of Sciences (in Slovak it is named SAV, consisting of approximately 40 institutes).

There are several physiologic working places in Slovakia and in Košice

<u>In Košice</u>:

- **Department of Human Physiology, School of Medicine, P.J.Šafárik University**
- **Department of Pathological Physiology, School of Medicine, P.J.Šafárik University**
- **Department of Animal and Human Physiology, Faculty of Science, UPJŠ**
- **Two departments (Physiology + Pathophysiology) in University of Veterinary Medicine**
- **Institute of Neurobiology of the Slovak Academy of Sciences (SAS) in Košice**

Prof. Štefan Kujaník, MD, PhD: HELSINKI CONVENTION

The Conference on Security and Co-operation in Europe, which opened at Helsinki (Finland) on July 1973 and continued at Geneve (Switzerland) from 1973 to 1975, was concluded at Helsinki on 1st August 1975.

The High Representatives of the participating States have solemnly adopted the following principles valid for biology and medicine:

1. Many medical disciplines use the work with **living creatures** (healthy humans = usually you yourselves or patients in clinical disciplines or experimental animals in praeclinical disciplines)

2. The work on living creatures should be approved by **the Committee of Ethical Control** of all included institutions (faculty or hospital)

3. The work on living creatures is performed according to the special legislative and ethical rules approved by the European Union and named **The Helsinki convention (1975)**. Handling with animals is described in detailed in the Handbook for practicals, it is not an entertainment.

4. For demonstration the healthy humans are used in our department – **selfexamination** (blood groups, blood count) or examination of your colleagues (blood pressure, spirometry, ECG, basal metabolism, auscultation or percussion of the heart and lungs, reflexes)

5. The experiments are conducted on small (the mouse, rat, guiney pig, ferret) or large **laboratory animals** (rabbit, cat, dog, lamb, etc). In details it is described in the Handbook for practicals. The painful or invasive procedures are conducted on an anesthetized animal. Animals are different from the humans in some parametres and they are not allways used in experiments (e.g. the rat does not have the gallbladder, has a different cardiac action potential, the horse has a spontaneous emphysema, the rabbit is a sympathomimetic animal, etc).

6. Breeding, surgical procedures, and other works should be made under clean, natural, careful, and humane conditions. The incurably operated animals are killed after the experiment by several ways (e.g. overdosed anaesthetics or other drugs, decapitation, exposure to carbon dioxide).

The laboratory experiments, observation on the living animals, experiments on the living laboratory or domestic animals and class seminars are common fonns of performance of practical exercises. All of these fonns can be carried out on "live animals" or using multimedia simmulation or reproduction of "live" procedures as alternative or semialternative learning forms, respectively. All of these fonns are valuable but the minimal amount of experiments using living animals in the practical class should be required.

Basic questions before embarking on the experiment:

- Why am I doing this experiment? Can I responsibly justify that the expected potential benefit derived from the results overweigh the cost of the animal ?
- Does my propose do raise ethical issues? Will the planned experiment cause the animal any pain or any other form of suffering ?
- Is replacement of the animals possible ? Is it possible to achieve the same benefit by carrying out the experiment in vitro or using animals decided for slaughter in slaughter houses ?
- Is it possible to reduce the number of animals designed to be used for the experiment ?
- Is refinement of using animals possible ?

CLINICAL RESEARCH:

a) Clinical trials are used if the animal experiments do not solve the research topic sufficiently or the results in humans are needed. E.g., action of medicaments in humans during diseases.

b) At first the Ethical Commission of the faculty should approve research on humans or animals and its detailes (number, gender, procedure, methods used, etc)

c) Humans (healthy persons or patients) should be informed beforehand on the aims, the correct procedure and importance of that research, obtained results

d) Investigated persons should give Informed consent to participate in the trial

Prof. Štefan Kujaník, MD, PhD: The heart

MORPHOLOGY – cellular structure (Kölliker, 1850), syncytial function (all cells together)

Intercalated disks: nexuses (gap junctions) have low electrical resistance (1/400 of other membranes) – impulse conduction through their pores is much faster

FUNCTIONAL PROPERTIES OF MYOCARDIUM:

(1) AUTOMATICITY – spontaneous formation of the impulse (without external influences)

(2) RHYTHMICITY – repeated impulse formation (rate 60-80 per min)

(3) EXCITABILITY – acceptation of produced stimuli and reaction to them

(4) CONDUCTIVITY – conduction of stimuli through the myocardium from the first to last cell

(5) CONTRACTILITY – haemodynamic function (to pump the blood with oxygen for tissues)

THE LAW „EVERYTHING OR NOTHING" – after stimulation by the suprathreshold stimulus the heart reacts by contraction of all cells or does not react when the stimulus was subthreshold. However, the contraction force can be changed.

FUNCTION OF THE CONDUCTIVE SYSTEM:

- **connection between atria and ventricles**
- **formation of the cardiac impulse**
- **synchronized contraction of the whole heart**

GRADIENT OF THE CARDIAC AUTOMATICITY – the active centre is producing impulses with the highest rate (SA node > AV node > ventricular centres), other centres are inactive

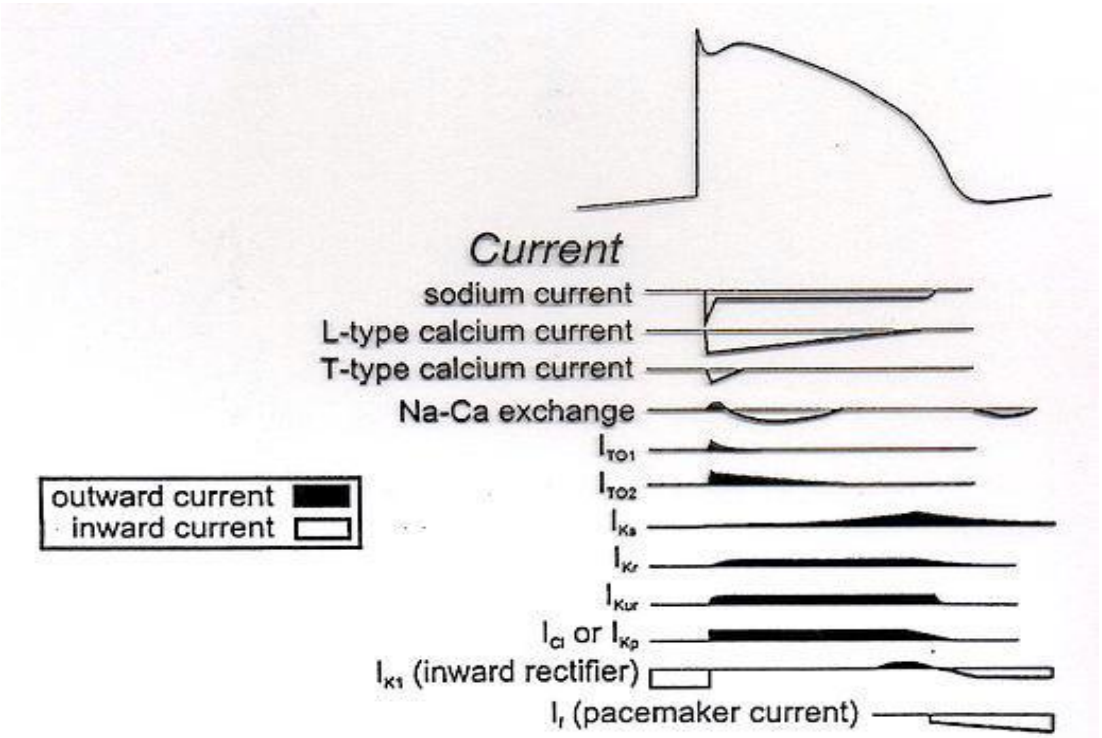
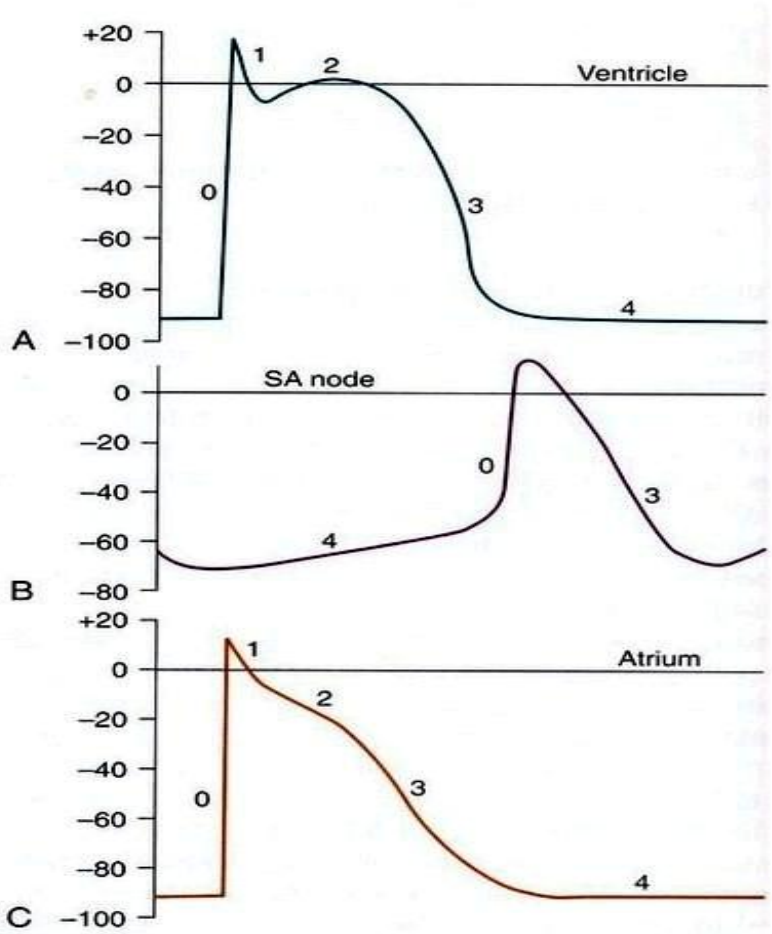


Figure 1 The action potential and currents that underlie it. The current amplitudes are not drawn to scale; the peak sodium current is much larger than any of the other currents shown here. Sodium currents, calcium currents, and transient outward currents display inactivating behavior, that is, during maintained depolarization they "turn off." In contrast, delayed rectifiers (I_{Ks}, I_{Kr}, and I_{Kur}) activate and remain activated as long as the membrane potential is depolarized. [Adapted by permission from the Task Force of the Working Group on Arrhythmias (23).]

Cardiac ionic currents



Phases of the action potentials in various parts of the heart

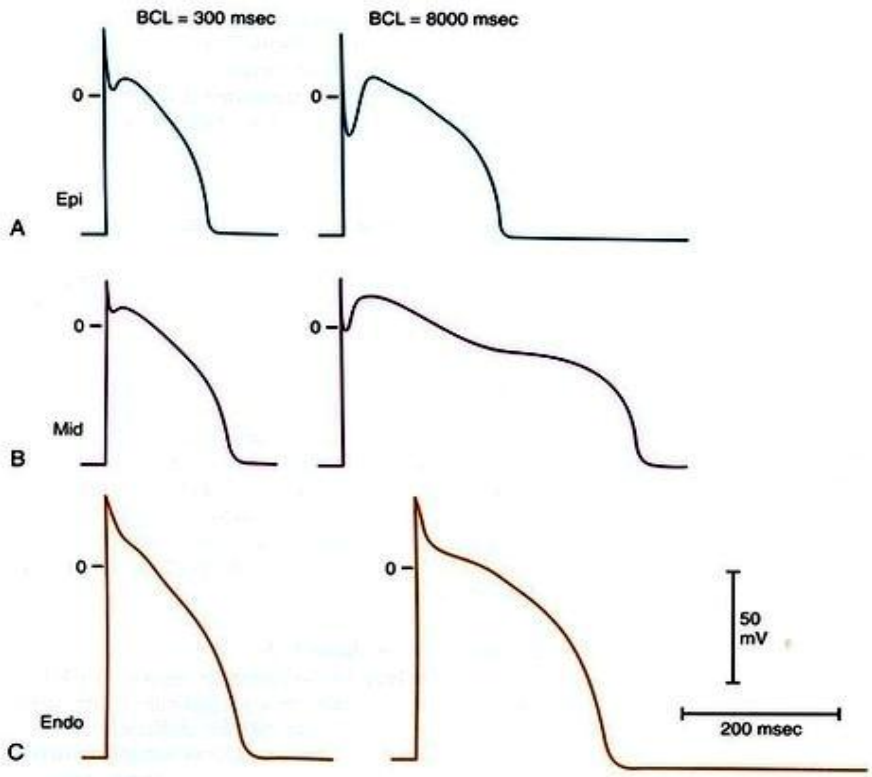
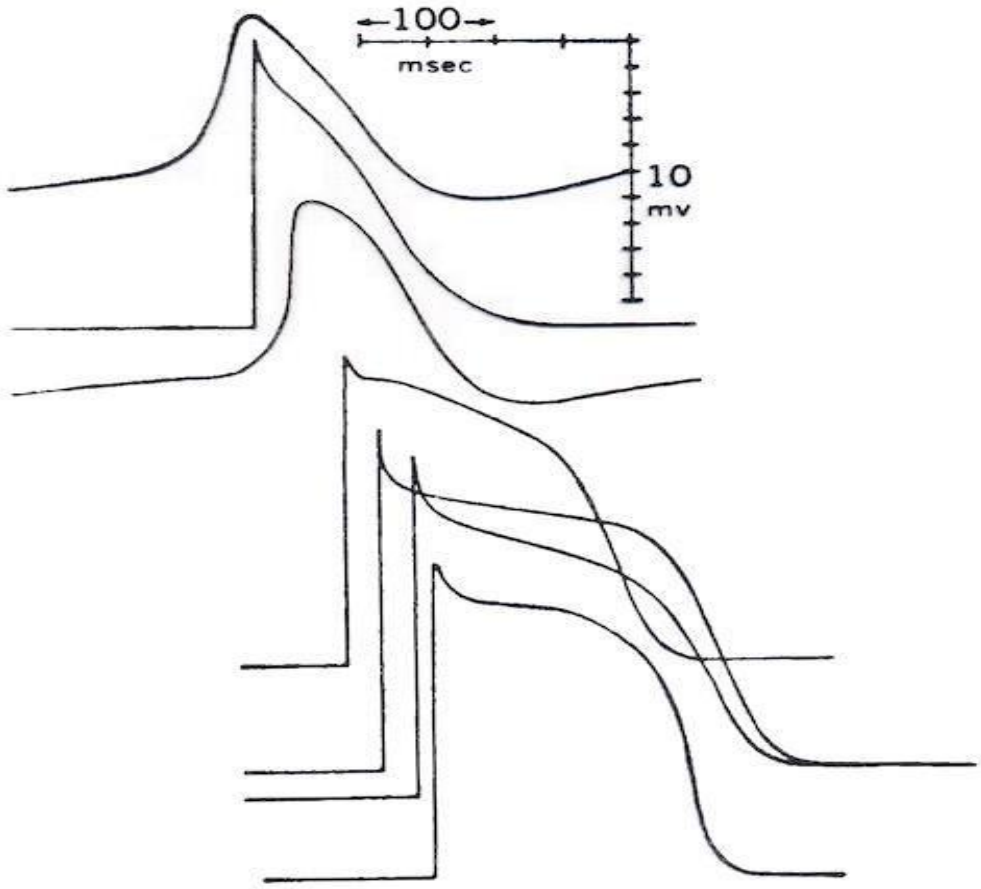


FIGURE 16–12. Action potentials recorded from the epicardial (A), midmyocardial (B), and endocardial (C) regions of the free wall of the canine left ventricle. The preparations were driven at basic cycle lengths (BCL) of 300 and 8000 msec. (From Liu D-W, Gintant GA, Antzelevitch C: *Circ Res* 72:671, 1993, with permission of the American Heart Association.)

Forms of cardiac action potentials 1



Forms of cardiac action potentials 2

LIGATURES OF STANNIUS IN A FROG (Handbook for PE)

IMPORTANCE: Demonstration of cardiac pacemakers & conduction system in a frog heart which has well expressed automaticity (in mammals it is less expressed)

<u>THE 1ST LIGATURE</u>: between the venous sinus and the right atrium

After tying up of the venous sinus the transmission of impulses to the atria and ventricles is blocked and therefore only sinus beats. The atria and ventricles are in diastole. After some time the A-V node can become the pacemaker (the secondary cardiac pacemaker) spontaneously. However, its rate of action is much lower than in the sinus node.

<u>THE 2ND LIGATURE</u>: between the atria and ventricles

After light tying up of the 2nd ligature (activation of the a-v node which is situated not far from the ligature) contraction of the asystolic ventricles is stimulated. Its HR is lower than the HR of the sinus node (sino-ventricular dissociation).

<u>THE 3RD LIGATURE</u>: between the apex and other parts of the ventricles

After tying up of the apex no its contraction can be seen. That is the prove that no pacemaker is situated in it. Its contraction can be elicited by external mechanical or electrical stimuli only or after release of the third ligature.

CHANGES of the membrane potential (MP):

DEPOLARIZATION – phase 0, from the RMP to overshoot (spike = +20-40 mV)

REPOLARIZATION – phases 1, 2, 3 (from the spike back to the RMP = -70 mV)

TRANSPOLARIZATION – during the positive MP (above 0) – a part of de- and repolarization

HYPERPOLARIZATION – more negative potential than the normal RMP

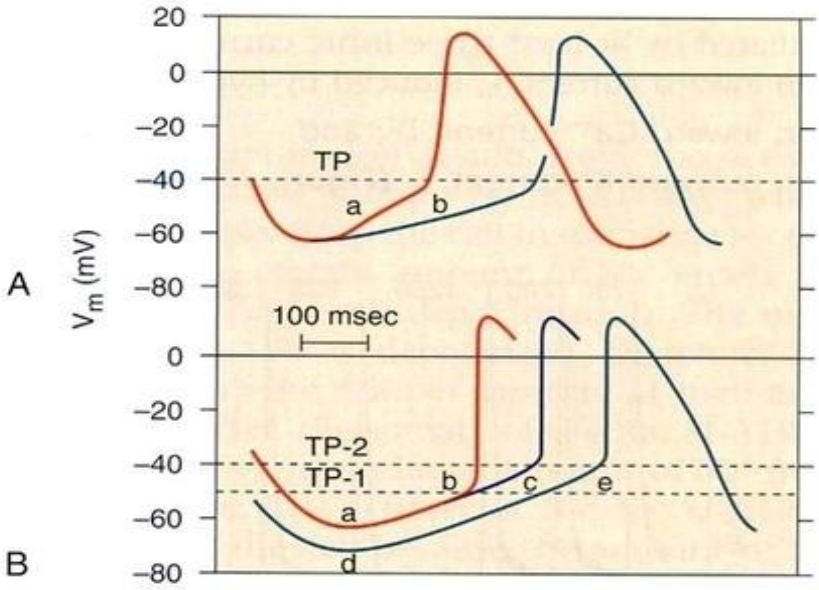


FIGURE 17–5. Mechanisms involved in the changes in frequency of pacemaker firing. In A, a reduction in the slope (from *a* to *b*) of slow diastolic depolarization diminishes the firing frequency. In B, an increase in the threshold potential (from TP-1 to TP-2) or an increase in the magnitude of the resting potential (from *a* to *d*) also diminishes the firing frequency. (Redrawn from Hoffman BF, Cranefield PF: *Electrophysiology of the heart,* New York, 1960, McGraw-Hill.)

SLOW DIASTOLIC DEPOLARIZATION AND ITS IMPORTANCE

MEASURING the absolute refractory period (ARP): 2 methods

- **extrastimulation (2 stimuli S1 + S2) (ARP = period S1-S2)**
- **increasing rate of pulses (ARP = period between 2 impulses)**

MEASURING the vulnerable period (VP) – by one single overthreshold pulse (situated around the top of T wave)

- **inner border (beginning of VP) – shifting the pulse from QRS complex to the right**
- **outer border (end of VP) – shifting from the diastole to the left**

EXTRASYSTOLES (ES = premature beats) – supraventricular (sinus, atrial, nodal, junctional) or ventricular (RV, LV)

- **compensated – the compensatory pause after ES, the primary rhythm remains**
- **uncompensated – no compensatory pause after ES and the new rhythm is produced**
- **interposed (intercalated) – during bradycardia, the ES is between 2 normal beats**

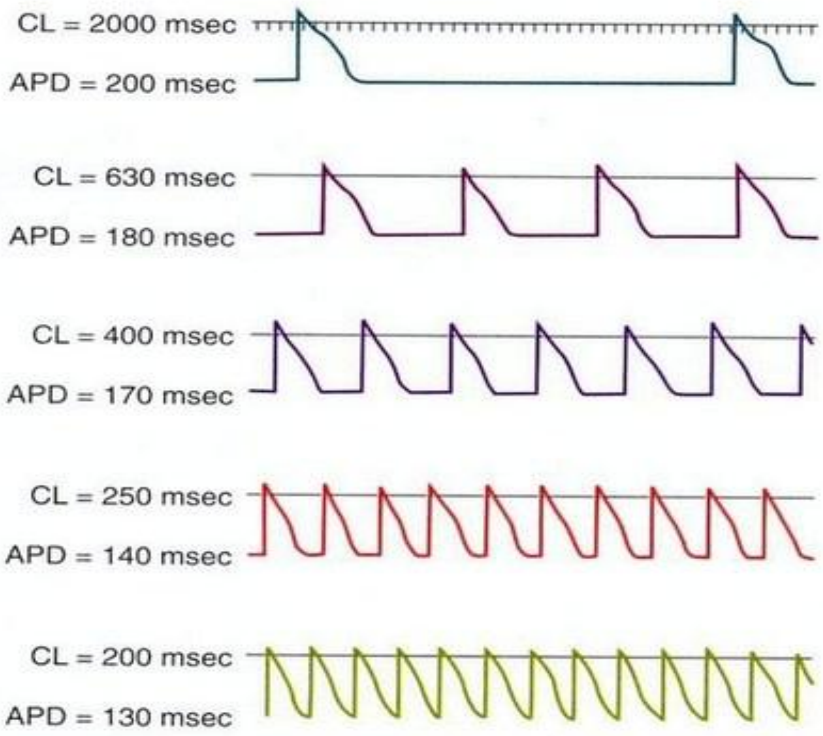
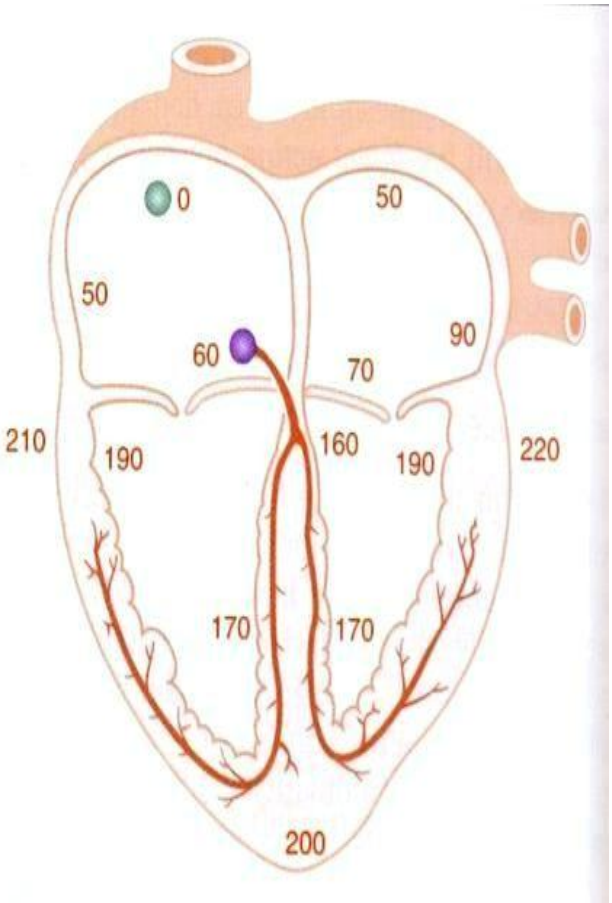
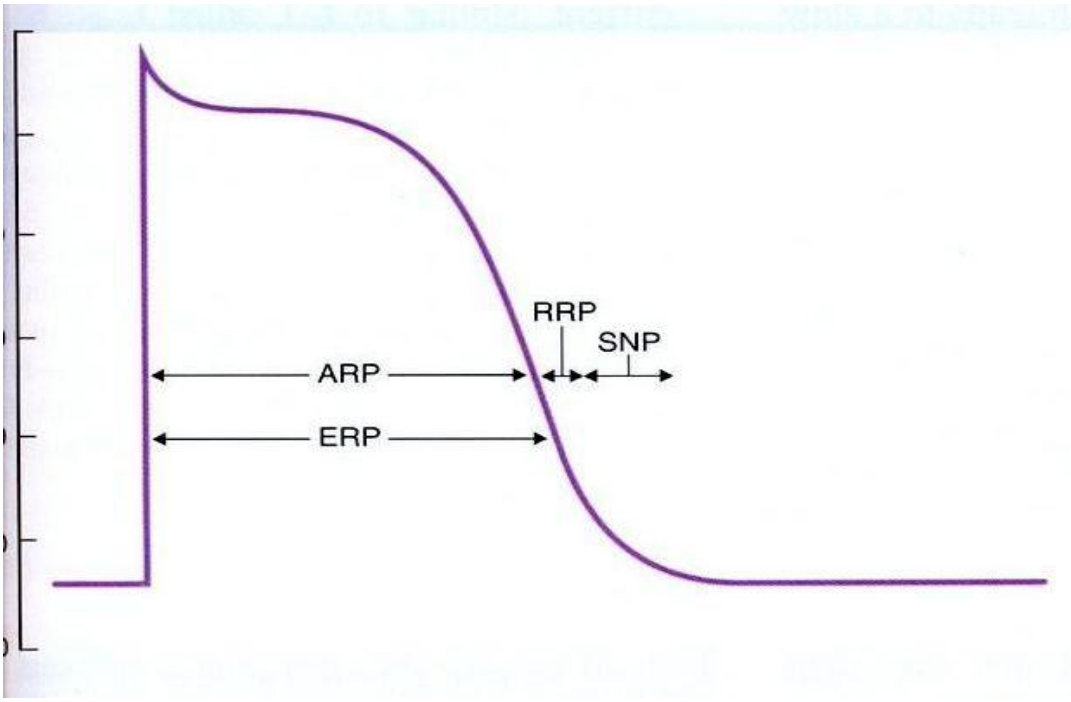


FIGURE 16–18. Effect of changes in cycle length (CL) on the action potential duration (APD) of canine Purkinje fibers. (Modified from Singer D, Ten Eick RE: *Am J Cardiol* 28:381, 1971.)

Conduction Velocity	
Atria	1 m/sec
AV node	0.01–0.05 m/sec
His-Purkinje	2–4 m/sec
Ventricle	1 m/sec





Refractory periods (RP) of the heart

ARP – the absolute RP, ERP – the effective RP, RRP – the relative RP, SNP – the supranormal phase

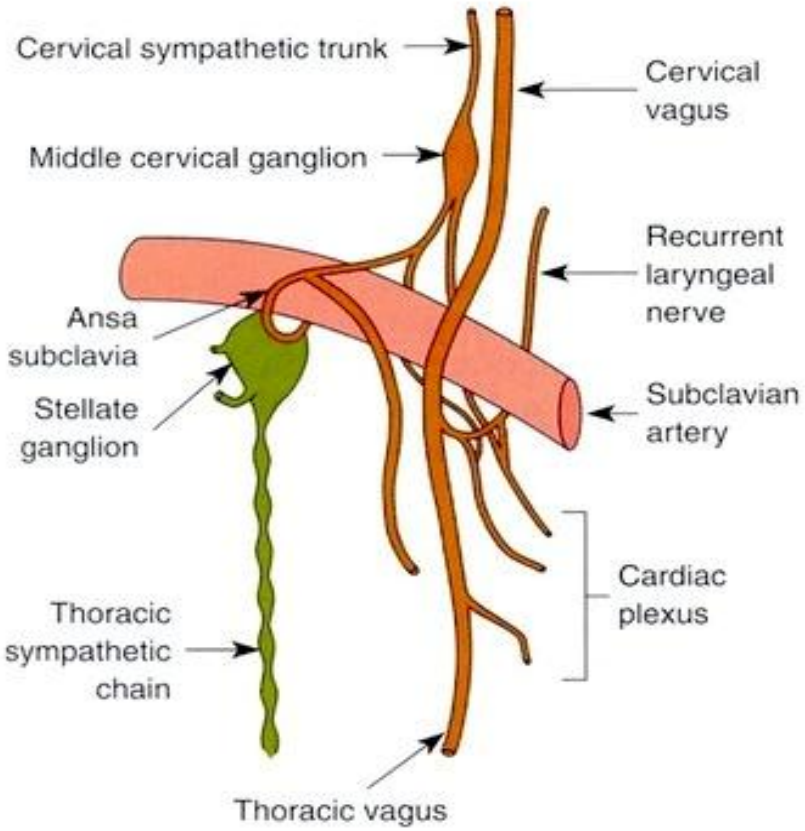


FIGURE 19–1. Sympathetic and parasympathetic (vagal) innervation of the heart on the right side of the body in humans.

ELECTRICAL MANIFESTATIONS of the CARDIAC ACTIVITY

1. ELECTROCARDIOGRAM (ECG) – Registration of the summary action potential of cardiac cells from the body surface. 12 STANDARD LEADS – bipolar limb I, II, III, unipolar limb aVR, aVL, aVF, unipolar chest V1 – V6. SPECIAL LEADS – Fr ank X, Y, Z, Nehb D, A, J, right-chest leads V1R -V3R, V7-V9, oesophageal, intracardiac ones

IMORTANT RULES IN the ECG curve:

a) spread of cardiac impulse – from upper right back position to lower left anterior parts

b) the impulse moves to the electrode – positive deflection, from the electrode – negative one

c) depolarization of the ventricular wall moves from endocardium to epicardium, repolarization from epicardium to endocardium

d) the cellular AP has amplitude about 100 mV, the ECG curve about 1 mV only

ECG EVALUATION: WHAT IS in this recording, NOT WHAT SHOULD BE there!!

(that means where concretely are the dicussed things visible)

- **rhythm – a) where is the main pacemaker (sinus rhythm or not present)**
  b) is the activity regular or irregular (sinus respiratory arrhythmia is physiologic)
- **heart rate – 3 ways (per min, formula during regular activity or irregular activity)**
- **time intervals – RR, PQ, QRS, QT (according to the paper speed)**
- **electric axis of the heart – from the Einthoven triangle**
- **changes of the amplitude (according to calibration)**
- **shape (form) of waves (comparison with description of normal ECG)**
- **conclusion (short summary of all 6 points by a doctor, by students a half of A4 page)**

MECHANICAL ACTIVITY OF THE HEART - CARDIAC CYCLE (CARDIAC REVOLUTION)

Cardiac cycle (1 unit of the cardiac activity) consists of systole + diastole

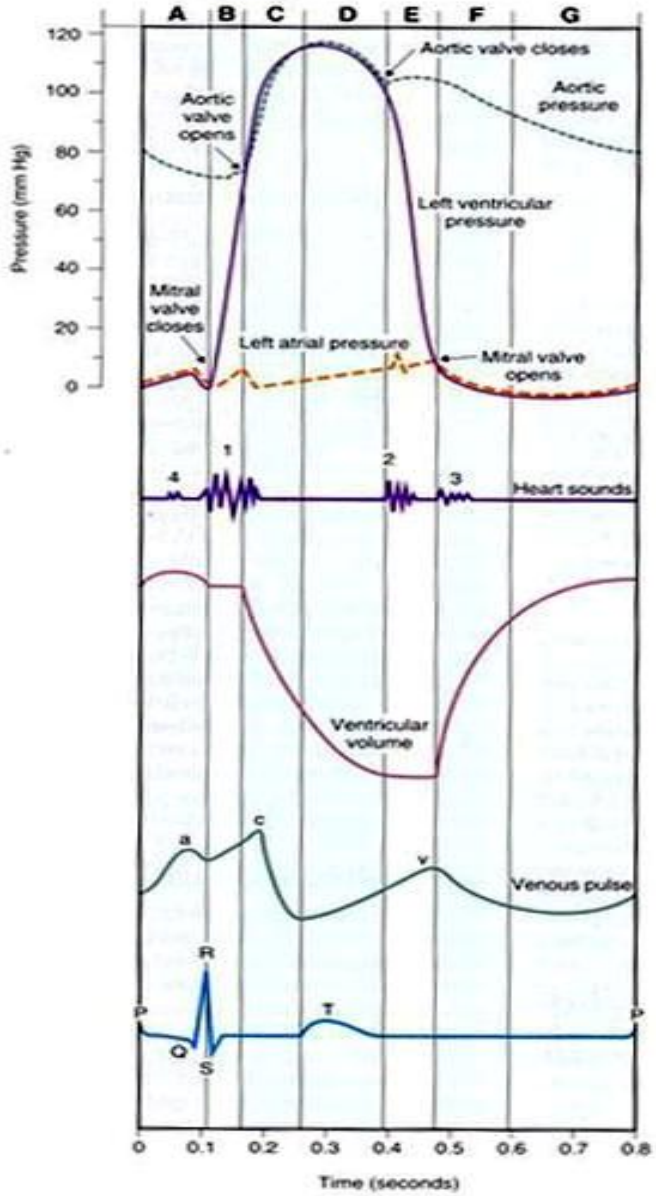
1. STRAIN (isovolumic, not "isometric") PHASE – first part of contraction, cardiac fibres are partly contracted but not yet shortened, all valves closed, BP stepwisely increases

2. EJECTION PHASE – at the highest BP the semilunar valves open and the blood is ejected (70 ml at rest) into the large vessels (aorta + pulmonary artery)

3. ISOVOLUMIC RELAXATION (PROTODIASTOLE) – the first part of relaxation, all valves are closed, intraventricular BP = 0 mmHg

4. FILLING PHASE – first fast filling phase + later slow filling phase

5. ATRIAL SYSTOLE – at the end of ventricular diastole, its haemodynamic importance durates in standing up position only and at increased heart rate



Changes within the cardiac cycle

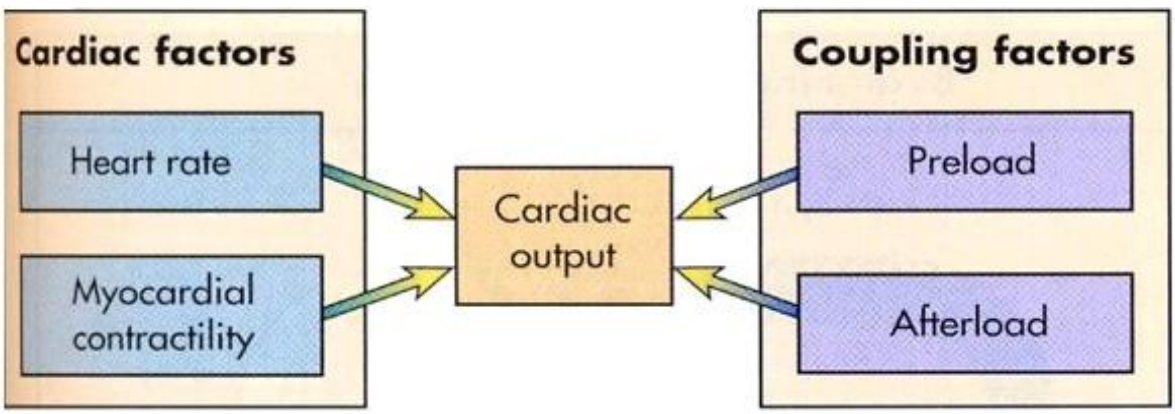


FIGURE 24–1. Determinants of cardiac output (Q_h).

CARDIAC WORK: is permanent, i.e. the whole life, without oxygen debt !!

Important: Volume work increases the oxygen consumption not very much!!

INFLUENCE OF HORMONES & ELECTROLYTES ON THE HEART

Experiments on the animal (frog or rat) heart (computer program or video)

POTASSIUM – abundance of K ≡ cardiac arrest in diastole = potassium inhibition

CALCIUM – abundance ≡ cardiac arrest in systole = calcium rigor

ACETYLCHOLINE produces decrease in HR = bradycardia or asystolia

ADRENALINE produces increase in HR = tachycardia

CONTROL OF THE CARDIAC ACTIVITY

It is control of contractility or cardiac output = SV x HR (regulated parametres) ⟹ changed blood supply ⟹ oxygen supply.

I. INTRACARDIAC MECHANISMS (M)

1. HETEROMETRIC M OF FRANK-STARLING (Starling's law of the heart)
2. HOMEOMETRIC M OF ANREP
3. RHYTHMO-INOTROPIC EFFECT – Bowditch steps (positive staircase), Woodworst steps (negative staircase)

MYOGENIC AUTOREGULATION – 1, 2, 3

4. INTRACARDIAC NERVOUS SYSTEM

II. EXTRACARDIAC MECHANISMS

A. NEURAL – Sympathetic nerves, Parasymp nerves

CARDIOMOTOR CENTRE

RESPIRATORY CENTRE

CEREBELLUM

LABYRINTH (semicircular canals of the inner ear)

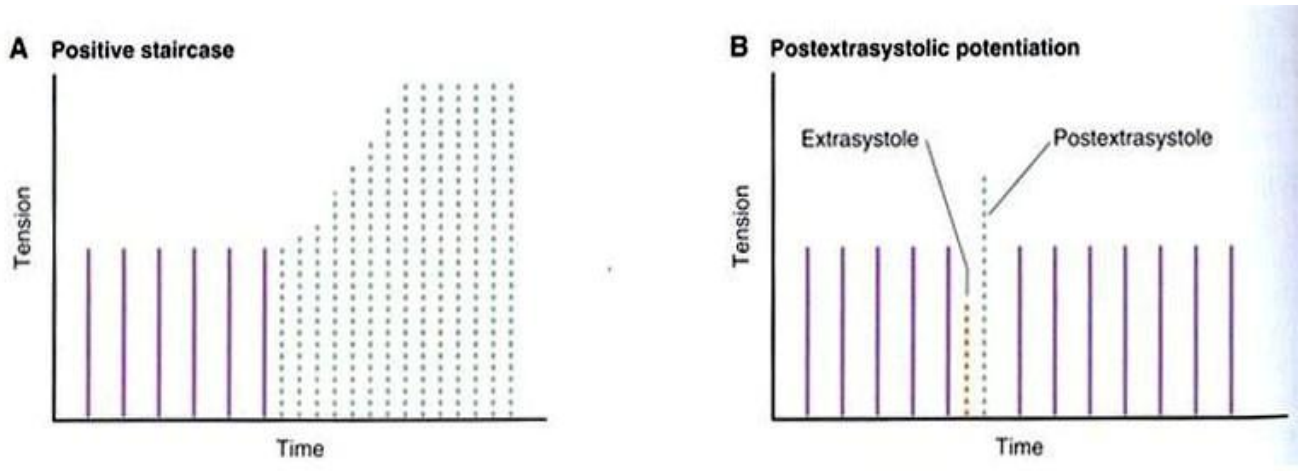
HYPOTHALAMUS

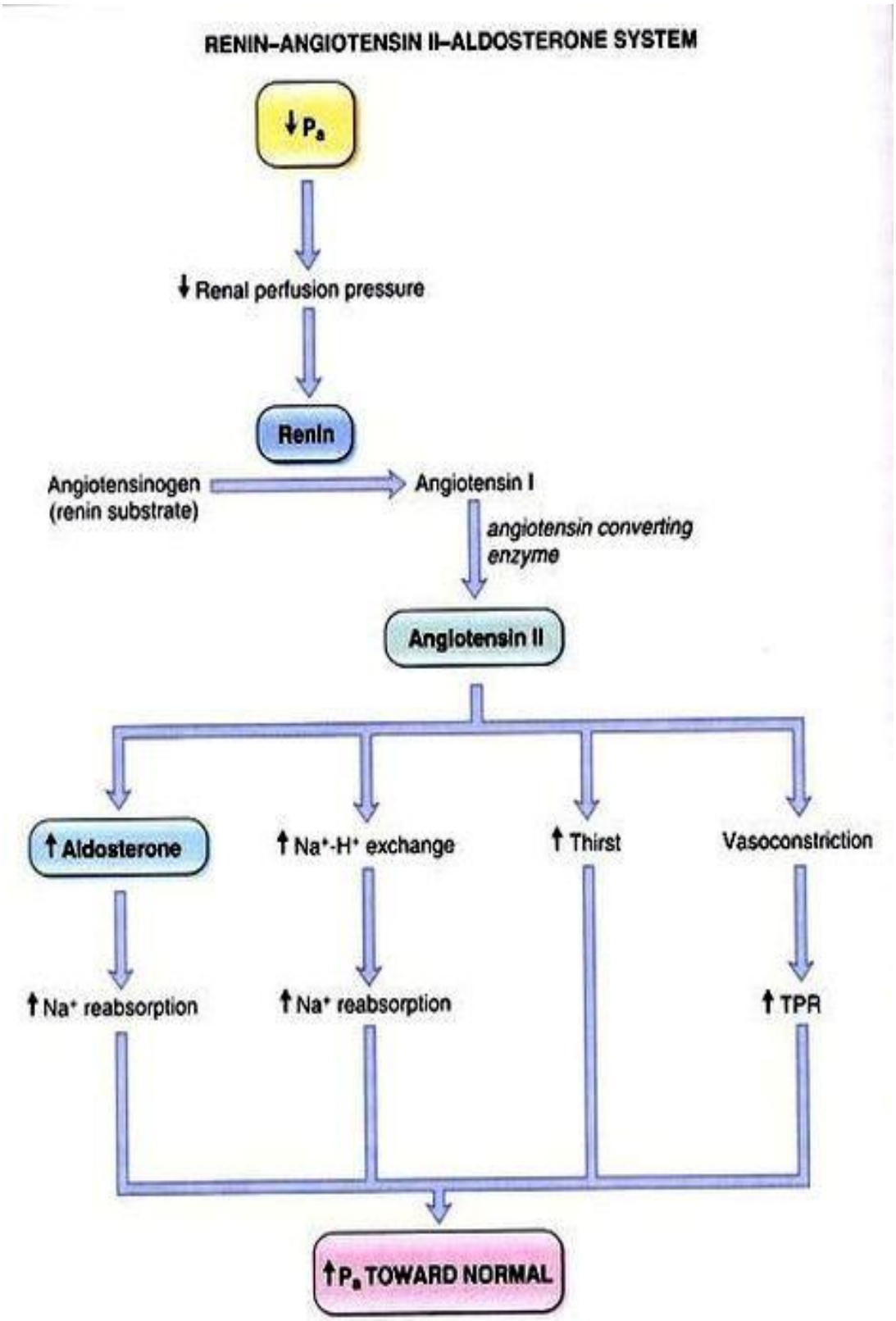
LIMBIC SYSTEM

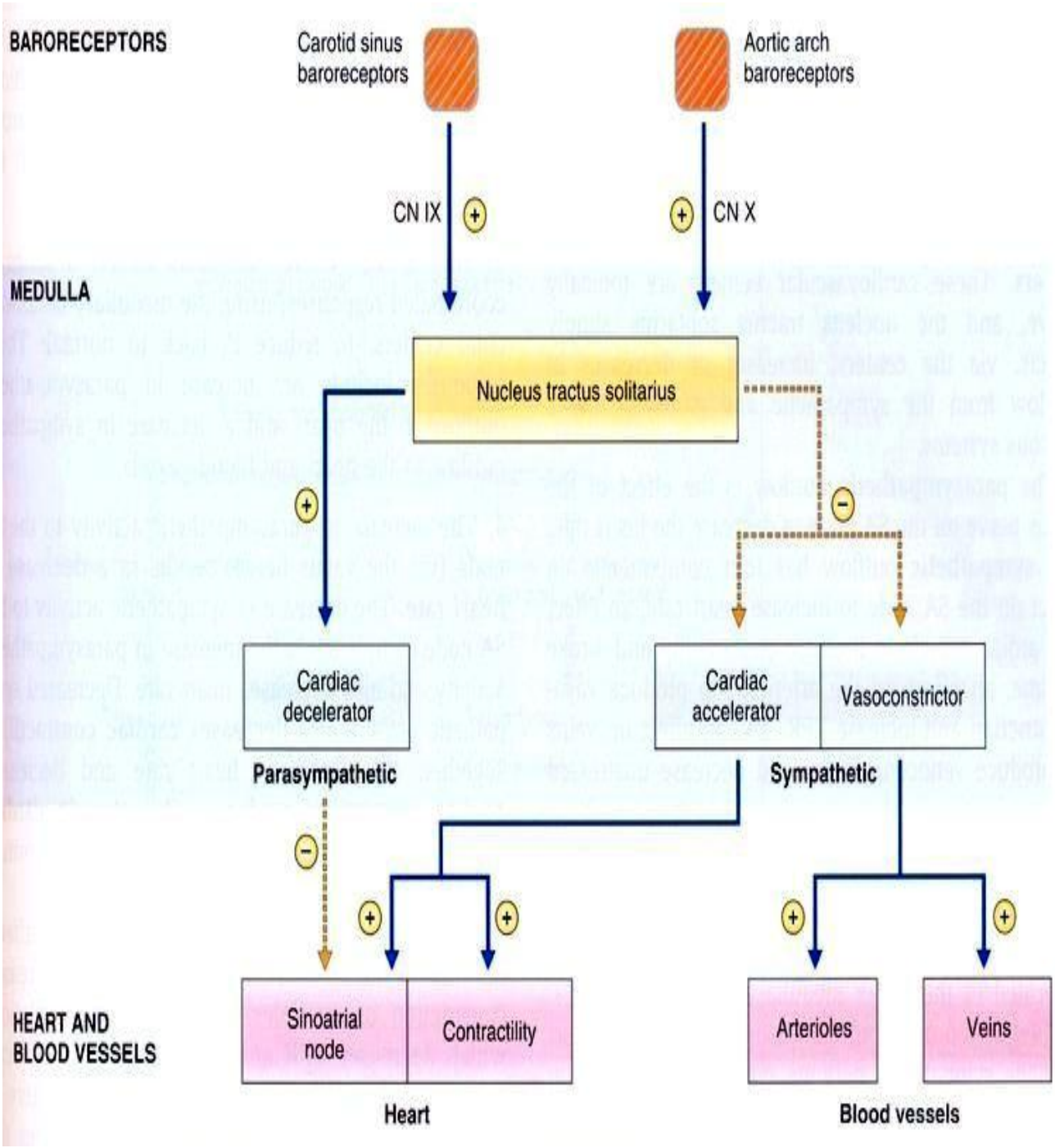
BRAIN CORTEX

CONTROL BY PERIPHERAL RECEPTORS

B. HUMORAL MECHANISMS OF CARDIAC CONTROL




RENIN–ANGIOTENSIN II–ALDOSTERONE SYSTEM
↓ P_a
↓ Renal perfusion pressure
Renin
Angiotensinogen (renin substrate)
Angiotensin I
angiotensin converting enzyme
Angiotensin II
↑ Aldosterone
↑ Na^+-H^+ exchange
↑ Thirst
Vasoconstriction
↑ Na^+ reabsorption
↑ Na^+ reabsorption
↑ TPR
↑ P_a TOWARD NORMAL


BARORECEPTORS
Carotid sinus baroreceptors
Aortic arch baroreceptors
CN IX
+
+
CN X
MEDULLA
Nucleus tractus solitarius
+
−
Cardiac decelerator
Cardiac accelerator
Vasoconstrictor
Parasympathetic
Sympathetic
−
+
+
+
+
HEART AND BLOOD VESSELS
Sinoatrial node
Contractility
Arterioles
Veins
Heart
Blood vessels

Prof. Štefan Kujaník, MD, PhD: Circulation (Vessels)

- the large (major) and small (lesser) circuits
- high-pressure (resistance) and low-pressure (capacitance) systems
- exchange (capillaries), distributive or damping (arteries), collecting (veins) parts

CENTRAL BLOOD VOLUME – from semilunar valves of the pulmonary artery to semilunar valves of the Ao (circa 700 ml) – small circuit + heart.
PERIPHERAL BLOOD VOLUME – the other parts of the vascular network

HAEMODYNAMICS IN ARTERIES

1. Law of POISSEUILLE – HAGEN

2. Law of LAPLACE

3. Number of REYNOLD

4. SKIMMING EFFECT (plasma skimming from erythrocytes)

5. BERNOULLI principle

6. ELASTICITY (Windkessel model, arterial compliance – the influence of an elastic reservoir)

Haemodynamics (blood flow) realizes according to gradient of the blood pressure (from the LV to the RA in the large circuit and from RV to LA in the small circuit)

BLOOD PRESSURE (BP): unit - 1 mmHg = 0.13332 kPa
Types of BP: systolic (maximal), diastolic (minimal), mean BP (BPm)
BPm = 1/3 BPs + 2/3 BPd or BPd + 1/3 PA (pressure amplitude PA = BPs - BPd)

Normal values of BP: 90-120 / 60-80 mmHg = 12-16 / 8-10.6 kPa
upper normal limit: 145/85 mmHg = 19.3/11.3 kPa (more is hypertension)

METHODS of BP measurement:

(1) direct (bloody – intravascular BP is measured) more correct

(2) indirect (bloodless – lateral compressing BP is measured) comfortable

(1) direct = cannulation of the blood vessel – BP in the vessel measured

(2) a) auscultatory method routinely used – by Riva-Rocci cuff, sphygmomanometer, stethoscope, sounds of Korotkow are heard

b) palpation method – arterial pulsations are palpated, less correct

Manometres – mercurial (removed now, but correct), ultrasound, metallic, oscillometric

Influences on the BP – age, gender (in men a little higher), body position (influence of the hydrostatic pressure), physical activity (higher, at rest lower), food intake

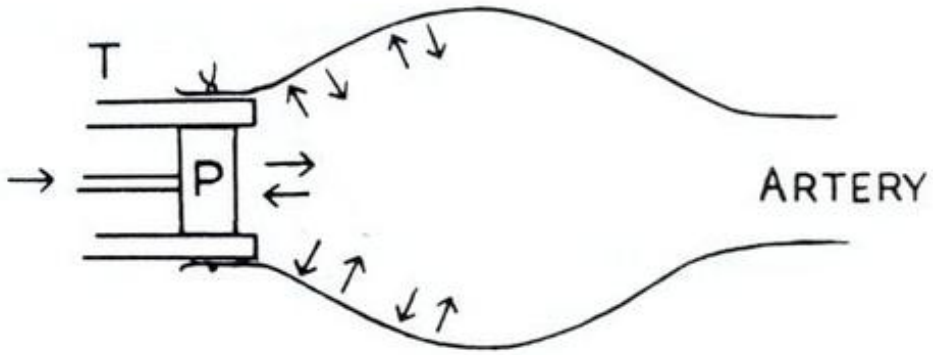


Fig. 8.2 Diagram to illustrate the initiation of a pulse wave in the aorta.

HAEMODYNAMICS IN CAPILLARIES

MICROCIRCULATION = haemodynamics in arteriols, capillaries, venules
CAPILLARY WALL – endothelium, basal membrane, pericytes, pores
Length – 1-2 mm, diameter – 3-6 μm => deformability of the Ery membrane
3 types of capillary walls: tight junctions, fenestrated, large pores (according to metabolism)

FUNCTION in capillaries: filtration, resorption, diffusion

1. genuine (normal, a-v) and arterial or venous capillaries

2. slow blood flow is present there - <1 mm/sec => therefore transit time in capillaries 1-2 sec

3. large total surface and lumen in the whole body – that has metabolic importance

4. distensibility of the capillary walls – dependent on the intravascular or extravascular pressures

5. low BP (ranges 40-15 mmHg) in the capillary, in tissues that is -2 to +6 mmHg

6. skimming effect => different hematocrit in different capillaries, important in the kidneys

7. importance of the oncotic pressure (OP = osmotic pressure of blood proteins) - osmotic pressure gradient holds some volume and produces reabsorbtion of fluids in capillaries

EFFECTIVE FILTRATION PRESSURE = blood pressure BP - (oncotic pressure OP + tissue pressure TP) = 35 - (25 + 2) = 8 mmHg (1 kPa) – at the beginning of capillaries, it successively decreases, at the end the EFP is 15 – (25 + 2) = -12 mmHg (-1 kPa **=>** therefore reabsorbtion of water is present there)

8. increased pO2 closes the precapillary sphincter and blocks the blood flow, decreased pO2 opens the blood flow. Approximately 25-30 % of capillaries are closed at rest.

VENOUS HAEMODYNAMICS

1. pressure gradient (produced by the left ventricle) decreases from the LV to RA – alone is not sufficient for blood flow in some regions => it needs several supporting mechanisms

2. negative intrathoracic pressure

3. alterations of the intrathoracic pressure – inspirium ↓, expirium ↑

4. action of muscles of the lower extremities

5. venous valves in the lower extremities

6. gravitation – hydrostatic pressure in feet is the highest, in the head even negative => transmission of blood down, autotransfusion – the lower extremities up and blood goes down to the thorax => better blood flow in central organs (important in the first aid)

7. great distensibility of vascular walls => small increase in BP, but large increase in blood volume

8. influence of arterial pulsations

9. activity of the venous smooth muscles in some regions

CORONARY HAEMODYNAMICS

2 coronary arteries – left - (85 % of blood flow in average), right - (15 %, but variable)
There are a lot of capillaries, a few collaterals (exercise ↑ them), all capillaries open at rest.

1. no oxygen debt in myocardium (even during hard work) **=>** no hypoxia in healthy persons
2. most of BF (3/4) is in the diastole
3. very high tachycardia decreases blood flow
4. stop of blood flow in the strain (isovolumic) phase (systole) in the LV, decrease in the RV
5. the most important controlling factor is pO_2
6. high a-v difference of O_2 (9 ml/min/100g) at rest, increase in BF is possible by vasodilation and velocity of blood flow only
7. SYMP vasoconstriction (alpha-receptors), SYMP dilation (beta-receptors), alpha receptors are more frequent in the large branches, beta ones more in smaller branches, PASYMP nerves has a very small importance in coronary arteries
8. metabolic vasodilation (by hypoxia, temperature, K, lactate, histamine)

PULMONARY HAEMODYNAMICS

1. importance – functional, blood reservoir, metabolic function, not nutritional (= bronchial arteries), numerous a-v shunts, short+distensible vessels
2. input of bronchial veins into pulmonary veins => the cause of 97-98 % saturation
3. small pressure gradient (RV → LA) because of small BP in the RV (30 mmHg)
4. not continuous flow – stop at the end of diastole
5. pulsatile flow, present also in pulmonary capillaries and veins
6. influence of alterations of the intrathoracic pressure during breathing
7. small influence of the hydrostatic pressure – that is not far from the heart
8. relation ventilation - perfusion (imperfused alveols are not ventilated)
9. low intravascular (8 mmHg), higher oncotic pressure (20 mmHg), the fluid remains in the vessels and is not present in alveoli, also active fluid reabsorption
10. a special intrauterine blood flow - around the lungs, foramen ovale, ductus Botalli
11. an important receptor region - volumoreceptors

CEREBRAL HEMODYNAMICS

20 % of cardiac output (CO): 2 carotid aa.+ 2 vertebral aa. → circle of Willis → cerebral arteries → short arteriols → venous sinuses → jugular vv.

1. Monroe-Kellie doctrine: Q + B + L = C (Q - blood volume, B - brain volume, L - liquor volume, C – constant in the non distensible skull) **=>** increase in the blood flow in a short time is possible by acceleration of BF only
2. important factor controlling BF is perfusion pressure **<=** mean BP influences it
3. important regulator is PCO_2 – produces local vasodilation
4. Cushing rfl – brain ischemia produces increase in systemic BP
5. innervation – PASY nerves – a few fibres, unclear function
   - SY nerves – a few alpha-receptors - weak vasoconstriction, for local BF
   - sensory nerves – vascular pain of the head (migraine)
6. nervous control hinders sudden alterations of the BP and blood flow
7. brain autoregulation – constant BF within wide range of BP - 65-140 mmHg (6.5-23 kPa)
8. influence of gravitation – in upright position mostly (possible orthostatic hypotension)
9. blood-brain barrier – only small molecules are transported to the brain, it fails in some places (median eminence, hypothalamus, neurohypophysis, etc.)

RENAL HAEMODYNAMICS

25 % of cardiac output at rest: renal a. – vas afferens – glomerular (arterial) capillaries – vas efferens – peritubular (a-v) capillaries – renal vein – skimming effect present

1. two capillary networks – arterial and a-v, special vessels – long vasa recta in the medulla
2. high glomerular BP (60 mmHg) => plasma filtration, no reabsorption
3. low peritubular BP (intravascular BP < oncotic pressure) => water reabsorbtion
4. BP control – renin-angiotensin system (RAS) – juxtaglomerular apparatus produces renin
5. blood volume control – ADH, ANF, RAS – angiotensin II (aldosteron + vasoconstrict)
6. nervous control of the BF – SY vasoconstriction via α-receptors in vessels

- humoral agents – control of the BP and blood volume
- autoregulation – constant blood flow and filtration within a large fluctuations of the BP (10.5-26 kPa)

HAEMODYNAMICS IN THE SKIN

1. thermoregulation - a-v shunts – blood goes round the skin capillaries if it is cold
2. influence of temperature on BF – at maximum blood flow is 30-times higher than at minimum
3. bilateral reflex – cooling one hand produces vasoconstriction in the second one, too
4. mechanical & chemical factors are independent on the nervous control,
   vasodilation – by histamin or bradykinin; vasoconstriction – by serotonin
5. peripheral axon reflexes – produce local vasoconstriction in the small parts of skin
6. main regulator – neurohumoral (not metabolic) influences, not much oxygen
7. white reaction – pale skin after weak drawing over it
8. triple response after stronger irritation – red reaction (capillary dilation), wheal (local edema because of fluid output), flare (arteriolar dilation)

SPLANCHNIC HAEMODYNAMICS

That is haemodynamics in the GIT, liver, spleen, and pancreas. Arterial blood comes from the coeliac, sup. & inf. mesenteric aa. → intestinal (a-v) capillaries → portal vein → hepatic (venous = sinusoids) capillaries → hepatic veins → inferior v. cava

1. two capillary networks present (normal a-v and venular hepatic sinusoids), many anastomoses
2. intestinal capillaries (for nutrition) in the intestinal wall situated
3. hepatic capillaries – with fenestrations (high permeability) – good for metabolism
4. extensive autoregulation – the blood flow markedly increases after a meal
5. reservoir function – 500 ml of blood in the liver situated, further volume also in the spleen, gut, etc.

HAEMODYNAMICS IN THE SKELETAL MUSCLES

Peculiarity: The skeletal muscles disturb homeostasis during a muscular work (pH).

18 % of the cardiac output flows through the muscles at rest, 90 % during maximum exercise

Red muscles (tonic, slow, postural) – higher BF and amount of capillaries

White muscles (phasic, fast) – for movements, lower BF + amount of capillaries

1. only a few capillaries open at rest, during maximum exercise all opened
2. an intermittent blood flow – present between contractions (during muscle relaxation), during tetanic contraction without BF

3. anaerobic metabolism (with oxygen debt) during exercise – up to the lactic acid only
4. the nervous control is prevailing at rest, during exercise the metabolic one

   NERVOUS CONTROL:

   - alpha rec. – vasoconstriction at rest (by NA)
   - beta rec. – vasodilation during exercise (by A)
   - sympathetic cholinergic fibres in muscles were not prooved in humans !!

5. muscular contractions are one of supporting factors for the BF in deep veins of lower extremities (muscular pump)
6. one of the receptoric zones for stimulation of SY nerves – hand-grip test
7. production of lactic acid during severe exercise in higher amounts causes acidosis, vasodilation and stimulation of nervous endings which stimulates the heart (SY reflexes)
8. exercise produces changes in homeostasis - ↓ pH, ↑ body temperature, hyperventilation, tachycardia, increased BF

DIVING REFLEX (Cold pressor or Immersion test):

It is developed in water birds and human newborns. In children and adults this test consists of immersion of the face (not of the other body) into cold water – apnoea, bradycardia, peripheral vasoconstriction are produced. This reflex is clinically important: it is able to block e.g. supraventricular tachycardias (suitable for first aid somewhere far from a physician or hospital). It becomes to reactions integrating the cardiovascular and respiratory activities.

FOETAL HAEMODYNAMICS

1. oxygenated blood comes from mother, placenta works like the fetal lung
2. one umbilical vein, two arteries in the umbilical cord
3. oxygenated blood is in the umbilical vein, partially deoxygenated in the umbilical arteries (branches of the foetal aorta)
4. mix of oxygenated and deoxygenated blood is present in foetusses
5. the most oxygenated blood (80 % saturation) is in the umbilical vein, least oxygenated venous blood is in the systemic veins (i.e. remains in foetus)
6. partially oxygenated blood is in the umbilical aa. (58-60 %) – they are branches of the aorta (normal foetal arterial blood for most of organs), adaptation for lower pO_2
   - the LV pumps a larger volume than the right ventricle
   - the foetal haemoglobin HbF, increased number of erythrocytes are present
7. parallel course of the blood flow in the right and left halves of the heart, opposite pressure gradient (in the pulmonary artery > aorta)

Shunts - mixing the blood:

- The VENOUS DUCT: from the umbilical vein most of well oxygenated blood goes round the liver into the inferior v.cava and later to the heart
- The OVAL FORAMEN in the interatrial septum (from the right atrium → left atrium)
- The ARTERIAL BOTALLI DUCT from the pulmonary trunc → aorta

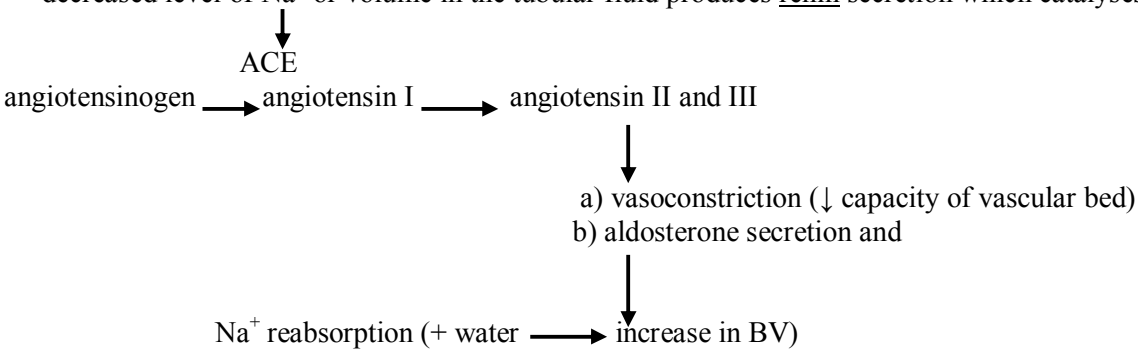
After birth:

- the umbilical cord is removed
- closing the umbilical aa. and the umbilical vein
- breathing and oxygenation of blood in the lungs
- increase in the left ventricular pressure, peripheral resistance and systemic (arterial) blood pressure (BP)
- decreasing resistance in the small circuit to 1/10, BP to ½-1/3 of the previous value
- changed pressure gradient closes the oval foramen & arterial duct
- obliteration of the venous duct (venous ligament is produced), Botalli duct and the beginning of the umbilical aa. (arterious ligament)
- the parallel circulation through the heart & lungs is no longer present
- the approximately same systolic volumes of the right and left ventricles
- changes in haemathological parametres (haemoglobin, erythrocytes, leucocyte types)

CONTROL OF THE BLOOD VOLUME (BV)

Blood volume is percepted as relation between the blood volume and capacity of the blood vessels. Therefore unchanged BV with changes in the vascular capacity or unchanged capacity with changes of the BV can be percepted like change of BV.

1. VOLUMORECEPTORS situated in the heart & pulmonary vascular bed, after ↑ in BV above normal one they stimulate 2 reactions:
   (a) atrial natriuretic factor secretion in the cardiac atria – produces natriuresis, vasodilation and decrease in blood volume
   (b) GAUER-HENRY diuretic reflex - (atrial B-receptors → vagus n. → brain stem → hypothalamus) – inhibition of ADH secretion by increase in blood volume, excretion of more water in the kidneys
2. OSMORECEPTORS in the HT – supraoptic & paraventricular nuclei, hyperosmia stimulates ADH secretion and more water is reabsorbed to normalize the osmotic pressure
3. JUXTAGLOMERULAR APPARATUS – activation of renin-angiotensin system by renal ischemia or decreased level of Na^+ or volume in the tubular fluid produces renin secretion which catalyses the reaction



4. BAINBRIDGE reflex – fast i.v. injection of a fluid produces tachycardia, afferent pathway – the atrial A receptorsare stimulated and vagus nerve afferent pathways, direct stimulation of SA node produces tachycardia as well!!

5. DIGOXIN LIKE COMPOUND produced in the CNS at hypervolaemia (inhibition of the Na-K pump) → vasoconstriction → decreased capacity of the vascular bed, decreased HR (negative chronotropy), and increased contractility (positive inotropy) of the heart

6. BARORECEPTORS – increased blood pressure stimulates vasodilation via baroreceptors (indirect influence on sensation of blood volume via capacity of the blood vessels) and decrease in blood volume

CONTROL OF THE BLOOD PRESSURE

Blood pressure ⟶ blood flow ⟶ oxygen supply for tissues (importance)

Blood pressure = CO.PR. (V.VW)

CO - cardiac output, PR - peripheral resistance, V - blood viscosity, VW - vascular wall quality

PERIPHERAL RESISTANCE CONTROL

I. NERVOUS CONTROL:

A - CENTRAL NERVOUS CONTROL – realized by the CNS

1. VASOMOTOR CENTER in the medulla oblongata – spontaneous production of vasoconstrictory impulses maintaining the smooth muscle tone of the vascular wall
 - vasopressoric part (increase in SY discharge and vasoconstriction) – increase in the BP
 - vasodepressoric part (decrease in SY discharge and vasodilation) – decrease in the BP

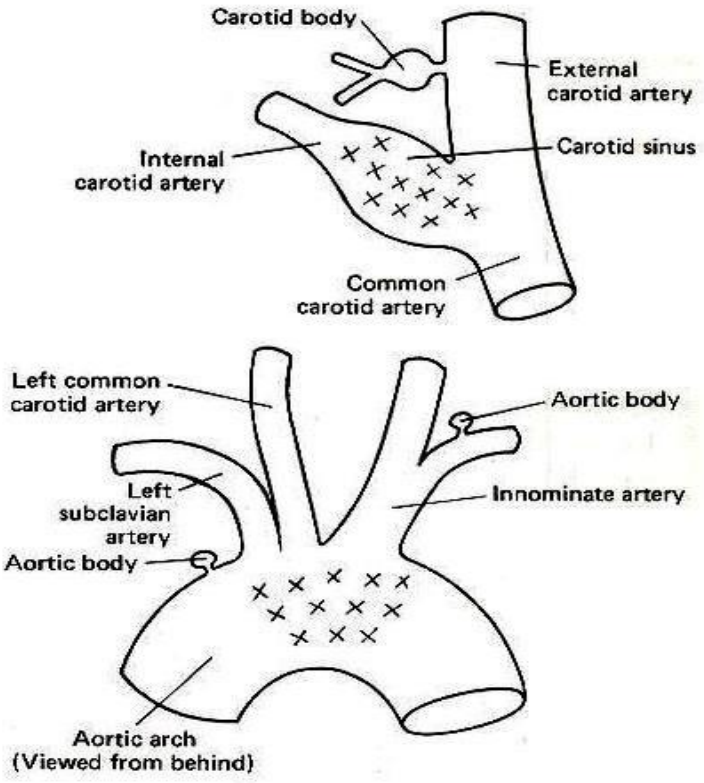
Most of vessels has no parasympathetic innervation !!!

a) basal vasoconstrictor tone at rest – its cause is the spontaneous formation of impulses in the neurons of the vasomotor centre, modulated by inputs from many structures
b) central inputs – from higher parts of the CNS
c) peripheral inputs – from the peripheral receptors in many organs
d) coordination with breathing – central and peripheral inputs are coordinated
2. VESTIBULAR NUCLEI – activation of vagal effects and bradycardia (decrease in BP)
3. CEREBELLUM – adaptation of the CVS to muscle activity (increased or decreased BP)
4. RETICULAR FORMATION of the midbrain – strong vasoconstriction
5. HYPOTHALAMUS – vasoconstriction, -dilation (during autonomic reactions)
6. LIMBIC SYSTEM – vasoconstriction, -dilation (during emotions)
7. AREA POSTREMA – vasoconstriction or -dilation
8. CEREBRAL CORTEX – vasoconstriction, -dilation (psychic influences)

The main controlling factor in the systemic haemodynamics are the SYMP nerves and the endothelial factors in the regional haemodynamics!!!

c) AFFERENT INFORMATIONS FROM RECEPTORS to the vasomotor centre:

- PRESSORECEPTORS – in the CAROTIC SINUS (innervated by the n. IX.)
  - in the AORTIC ARCH (innervated by the n. X.)



Mechanisms of baroreflectory decrease in the blood pressure:

- decrease in the SYMP discharge to vessels – vasodilation
- decrease in the SYMP discharge to the heart – bradycardia
- increase in the PARASYMP discharge to the heart – bradycardia

- CHEMORECEPTORS:

(a) Peripheral – CAROTIC BODY – stimulated by decrease in pO_2, less by increase in pCO_2 or decrease in pH – hyperventilation + tachycardia + weak vasoconstriction are produced

(b) Central in MEDULLA OBLONGATA – stimulated by increase in pCO_2

(c) Cardiac CHEMORECEPTORS – Bezold-Jarisch-Hirt reflex (bradycardia, hypotension, apnoea) – stimulated by ischemia or artificially by alcaloid veratrin

Summary * Effects of separate parts of the CNS can be different

* Higher parts of the CNS can modify effects of lower parts of CNS

*feed-back (centres are informed on situation in a periphery)

B - PERIPHERAL NERVOUS CONTROL

It is sometimes independent on the central control !!

1. GANGLIONIC REFLEXES – regional (local) changes of the blood flow (vasomotorics)

2. AXONAL REFLEXES – the reflectory arch is within one branched of the axon (they influence e.g. blood flow in the skin)

NERVOUS VASOMOTOR MECHANISMS:

(a) vasoconstriction – via SYMP adrenergic alpha-receptors (generalized in the whole body)

(b) vasodilation – several mechanisms of decreasing BP

- passive – by decrease in SYMP tone (inhibition of adrenergic alpha-receptors)
- active – via SYMP cholinergic fibres (in the sweat glands only)
  - via PASYMP cholinergic fibres (in the salivary glands and sexual organs only)
  - via beta-adrenergic receptors in vessels (diffuse in many organs but weak)

II. HUMORAL CONTROL

A - TOTAL HUMORAL ACTION in the whole body

1. Hormones of the suprarenal medulla (adrenaline, noradrenaline)

- vasoconstriction via alpha-receptors (more noradrenaline)
- vasodilation via beta-receptors (more adrenaline)

2. Hormones of the thyroid gland – a catecholamine effect (block of degradation of catecholamines → predominantly vasoconstriction and tachycardia)

3. Angiotensin II – renin-angiotensin system (RAS): renin → angiotensinogen → angiotensin I (+ACE) → angiotensin II (vasoconstriction + secretion of aldosterone → increase in the blood volume → increase in BP

4. Atrial natriuretic peptide (ANP) – vasodilation, natriuresis (decrease in BP)

5. Vasopressin (ADH) – vasoconstriction, physiological importance not known

6. Adenosin – vasodilation during hypoxia (decrease in BP)

B - LOCAL HUMORAL ACTION (regional haemodynamics)

1. CO_2 – vasodilation in many vascular regions (e.g. the heart, brain)

2. Lactic acid – vasodilation (e.g. in working muscles)

3. Histamin – vasodilation (in arteriols), secretion of the gastric juice

4. Kinins (callikrein, bradykinin) – vasodilation (in sweat)

5. Serotonin – vasoconstriction (hemostasis)

6. Prostaglandins – derivatives of the arachidonic acid and endoperoxides in many tissues (at first in the prostata discovered)

- mostly vasodilation – by PGI_2, PGE_1, PGD
- only THROMBOXAN produces vasoconstriction (+ platelet aggregation)

7. Neuropeptide Y (NPY) – vasoconstriction (in some regions)

ENDOTHELIAL FACTORS:

They are the most important control factors in the regional haemodynamics:

8. Endothelium derived hyperpolarizing factor EDHF (via receptors M_1) – activates K-channels, K^+ produces hyperpolarization in vascular smooth muscle and vasodilation

9. Endothelium derived relaxing factor EDRF (via receptors M_2) = nitrogen oxide (NO) – cGMP is produced and → vasodilation

10. Endothelium derived constricting factor EDCF – vasoconstriction

11. Endothelin-1 and endothelin-2 – vasoconstriction