7 CHAPTER Cardiovascular physiology

1. General description of the functions of the cardiovascular system

1.1. The morphological organization of the cardiovascular system.

The cardiovascular system from the morphological point of view is a series of connected vessels of different caliber, filled with blood, and connected to the central pump – the heart. This pump constantly generates a pressure gradient in this system that provides continuous circulation of blood. The blood picks up oxygen and gives off carbon dioxide in the alveoli of the lungs, absorbs nutrients from the digestive tract, delivers them to the tissues while simultaneously removing the end products of metabolism and the heat from them. Along with this, the cardiovascular system plays a key role in the intercellular communication, delivering regulatory substances (hormones, enzymes, antibodies etc.) from one cell to another, and protects the body from harmful antigens . All objects that are transported by the cardiovascular system are listed and classified in a table 7.1.

Thus, the main function of the cardiovascular system is to transport the various substances from and to all parts of our body. Oxygen enters the body through the inner surface of the alveoli. Nutrients and water are absorbed in the intestinal epithelium. Once these substances appear in the blood they are distributed to all tissues by circulatory system. Delivery of oxygen to the tissues is critically important because even short periods of oxygen deprivation cause irreversible destructive changes in many cells. For example, if the brain doesn't get blood supply for 5-10 seconds the loss of consciousness occurs and 5-10-minute period without blood flow in the brain causes death of the patient. Brain dependence from its blood supply is

Table 7.1

Transport in the cardiovascular system

Substance Moved	From	To
Materials entering the body		
Oxygen	Lungs	All cells
Nutrients and water	Intestinal tract	All cells
Materials moved from cell to cell		
Wastes	Some cells	Liver for processing
Immune cells, antibodies, clotting proteins	Present in blood continuously	Available to any cell that needs them
Hormones	Endocrine cells	Target cells
Stored nutrients	Liver and adipose tissue	All cells
Materials leaving the body		
Metabolic wastes	All cells	Kidneys
Heat	All cells	Skin
Carbon dioxide	All cells	Lungs

determined by the very high energy requirements of neurons due to the aerobic processes in their mitochondria, This distinguishes the brain from some other organs, which can obtain energy by anaerobic oxidation of substrates (e.g., skeletal and smooth muscles). Thus, the homeostatic mechanisms that control blood flow, in the first line, are set to ensure the cerebral blood circulation even if it limits the blood supply to other organs. Intercellular communication is another of the most important functions of the cardiovascular system. The hormones that are secreted by endocrine glands are transported via the blood to distant target cells. Glucose from the liver and fatty acids from adipose tissue are delivered to metabolically active cells. Finally, different types of white blood cells and antibodies in the blood protect the body from foreign antigens that can penetrate into the internal environment.

The cardiovascular system also removes the carbon dioxide and other toxic metabolic end products (urea, uric acid, creatinine, bilirubin) from the cells and transports them to the excretory organs. Some of them are transported to the liver where they are converted into less toxic compounds that are excreted with the urine and feces.

Blood circulation in the cardiovascular system is unidirectional due to the valves of the heart and the large veins (Fig. 7.1). The heart is divided by septa into right and left part (hemicardium), each of which consists of the atrium and the ventricle and functions independently of the other. The right hemicardium receives venous blood from the tissues and directs it to the lungs for oxygenation and release of carbon dioxide, forming a small (pulmonary) circle of blood circulation. The left hemicardium receives oxygenated blood from the lungs and ejects it to all organs and tissues of the body, forming a large (systemic) circle of blood circulation. The large circle of

blood circulation begins with the left ventricle, which ejects blood into the aorta. It is branching out on numerous arteries, which supply all body organs and tissues with blood. The arteries are divided dichotomically, so as their diameter decreases, the total number of them is increasing. As a result of branching of the smallest arteries, which are called arterioles, a capillary net is formed. Capillaries are a special type of vessel with very thin walls providing gas and substance exchange between the blood and tissues. The total inner surface area of the capillaries in the human body is about 1000 m^2. Capillaries merge and form venules that are collected into the veins. The number of veins gradually decreases, while their diameter increases. As a result, only the two big veins enter the right atrium, where the systemic circulation ends: the vena cava inferior and superior. This general scheme does not fit to the blood supply of some organs of the abdominal cavity (in particular, the liver and kidneys) as well as the hypothalamic-pituitary system. Thus, the portal vein, which carries the blood flowing out of the

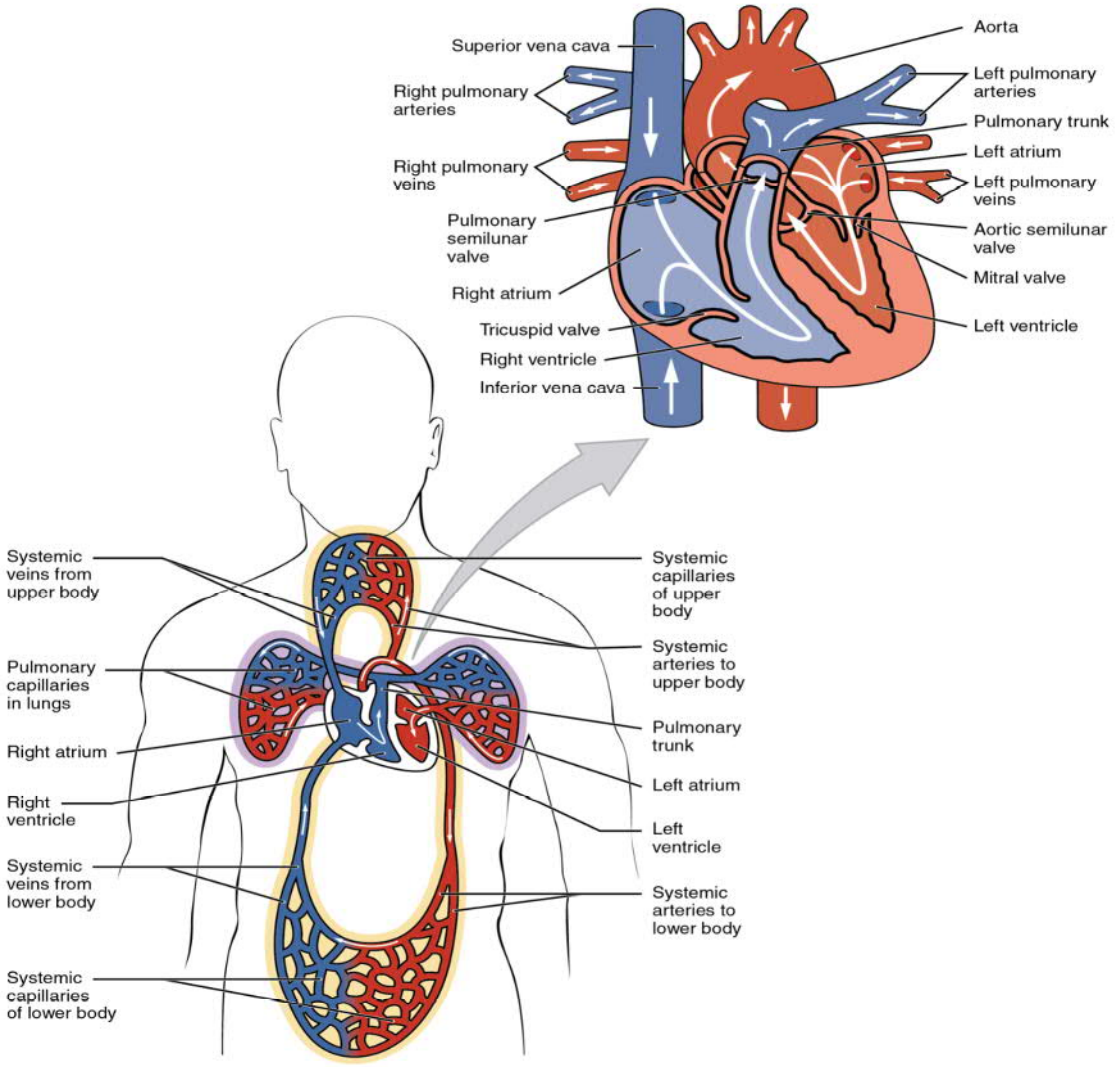

Fig.7.1. Morphological organization of the human cardiovascular system.
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capillary net of the intestine and spleen, branches again into the capillaries of the portal system in the liver. The blood returns from the portal system to the right atrium through the vena cava inferior. In the kidneys, the capillary bed of the glomeruli is re-branching into the peritubular capillary net, and finally the blood flows out from here into the venules. The upper pituitary artery, in the pituitary gland, (branching to the capillaries in the hypophysotropic region of the hypothalamus) forms another capillary net in the adenohypophysis after the fusion of capillaries in the portal pituitary vein. These exceptions will be considered in details during the explaining of the blood supply in different organs.

Pulmonary circulation starts from the right ventricle, which ejects blood into the pulmonary artery. After that, blood enters the vascular system of the lung, which has the same structure as that in a systemic circulation. The pulmonary circuit ends in the left atrium into which the four pulmonary veins fall. From the left atrium blood enters the left ventricle. Thus, both circles are connected in that way. Since both circuits are consecutively connected, the right and left ventricles should normally eject the same blood volume. The difference in systolic volume of the left and right ventricle can be only short-term and quickly disappears due to myogenic self-regulation of the heart and extracardial reflexes.

The first physiologist who proved the existence of two circles of circulation was the English scientist William Garvey. In 1628 he published his famous work " Anatomical Study on the Movement of the Heart and Blood in Animals ". Before Garvey's work publication, the views of Galen (120-201 BC) had been prevailed, who believed that blood flows to the tissues through the veins while the arteries transport the air.

1.2 The functions of the heart.

The heart as the central pump in the cardiovascular system performs 3 main functions:

1. *It generates the pressure gradient between the aorta and right atrium* in a systemic circuit (up to 130 mm Hg) and the pressure gradient between the pulmonary artery and the left atrium (up to 25 mm Hg) in a pulmonary circuit. The pulmonary circuit resistance of the vascular bed is 5 times smaller in comparison with the systemic one. It is explained by almost 5 times difference between the gradients in the systemic and pulmonary circuits. These gradients are the main driving force for blood moving (hemodynamics) in both circles.
2. *It directs the movement of blood in two sequentially connected hemodynamic circuits: systemic and pulmonary*. This movement occurs only in one direction - from the arteries to the veins - with the help of the heart valves, which prevent the retrograde flow of blood. Blood output from both ventricles occurs synchronously, with the volume of this blood

practically identical for the left and right ventricles. In the case of a pathological condition in one of the heart chambers (for example, myocardial infarction of the left ventricle) the volume of blood ejected by the left ventricle becomes smaller than the right for some time, what causes the stagnation of the blood in the pulmonary circuit, and sometimes pulmonary edema. However the compensation mechanisms restore the coordination of the right and left hemicardia function very soon.

3. *It regulates total blood supply to the body*. The heart provides coordination the overall blood flow with the metabolic needs of the body. This is achieved by changing the heart rate and force of heart contractions, which form an adequate cardiac output (CO) for this condition. For example, by maximal physical activity, the CO increases 5-6 times in comparison with the resting state. The reflectory, humoral and local (myogenic) regulation mechanisms that will be described in this section are capable to affect the heart rate and force of myocardial contractions.

2. Electrical activity of the heart and its physiologic meaning

The heart is one of the most powerful generators of biopotentials in the human body. The total electrical activity of the heart is conducting even to the surface of the body and may be registered in the form of the electrocardiograms (ECG). Deciphering of ECG records gives the doctor a lot of diagnostic information. However, for its correct interpretation, it is necessary to know the nature of electrophysiological events in the myocardium at the cellular and subcellular levels. This knowledge is also needed in order to understand the action mechanism and the proper assignment of modern pharmacological drugs used in cardiology. This chapter will focus attention on modern representations about specific mechanisms of resting potential and action potential producing in the myocardial cells, the relationship between the excitation and contraction of cardiac fibers, and the function of the heart conduction system, which provides the coordination and sequence of heart chambers contractions.

The heart contains two types of cardiac muscle cells: contractile (typical) cardiomyocytes that make up 99% of all the fibers of the myocardium, ejecting blood from ventricles, and autorhythmic (atypical) cardiomyocytes, which make up 1% of all cardiac fibers and specialize in generating rhythmic excitations, conducted to the contractile cardiomyocytes.

2.1 Pacemaker activity of the atypical cardiomyocytes.

The pacemaker cells don't have a phase of resting membrane potential, unlike neurons and fibers of the skeletal muscles. Instead, they form an initial depolarization (spontaneous diastolic depolarization) phase, during which the membrane potential slowly drifts to a critical level of depolarization close to -40 mV. This phase mainly is responsible for autorhythmic pacemaker activity of the atypical cardiomyocytes.

Ionic mechanisms of action potential (AP) in the autorhythmic cells are associated with the unique combination of ion channels in their cell membrane, which form the specific action potential curve (fig. 7.2.)

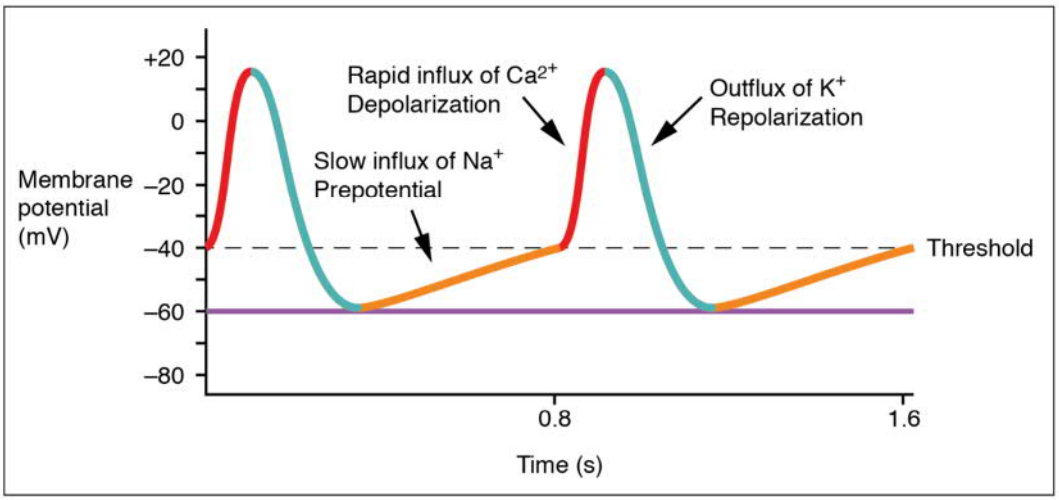

Fig.7.2. Action potential of the pacemaker cell in the sinoatrial node.
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In particular, three ionic mechanisms determine different phases of the AP in the pacemaker cells. The first of these phases is called ***a phase of spontaneous diastolic depolarization***. It begins with the opening of a special type of Na^+ channels, which are often referred to as "funny" channels (or F-type channels). These channels are opening during repolarization when the membrane potential reaches level -60 mV and allow Na^+ ions to enter the cell due to the concentration gradient (the concentration of the Na^+ ions in the extracellular environment is always higher than inside the cell). The behavior of the funny channels significantly differs from the behavior of typical Na^+ channels, which usually are opening during the depolarization of the cell membrane. In the second half of this phase Na^+ current joins with Ca^{+2} current caused by the short-term opening of a special type of Ca^{+2} channels (T-type Ca^{+2} channels). Both of these events occur in the background of the closure of voltage-gated K^+ channels. The result of the described events is slow influx of ions into the cardiomyocyte, which depolarizes the cell membrane to a critical level -40 mV and completes this phase.

The next ***phase of the depolarization*** is due to the opening of Ca^{+2} L-type channels that form the powerful flow of Ca^{+2} ions into the cell and depolarize the membrane to the level of around 0 mV. The achievement of this level causes opening of voltage-gated K^+ channels and gives the start of the last third ***phase of repolarization***, during which the K^+ ions leave the cell by a gradient of their concentration. It provides a return of the membrane potential to the level -60 mV, after that all processes are repeating. Relatively slow dynamics of the repolarization phase is explained by the gradual closure of the Ca^{+2} channels L-type and the continuing flow of Ca^{+2} ions into the cardiomyocyte.

Thus, the atypical cardiomyocytes are capable of spontaneous excitation and conduct action potentials along their membranes to other contacted cardiomyocytes. They are responsible for automaticity of the heart muscle. The duration of the action potential phases determines the frequency of the pacemaker cell excitation and therefore the heart rate. Pharmacological agents affecting the different types of ion channels are potentially capable to adjust finely the pacemaker activity. Currently, L-type Ca^{+2} channel blockers (verapamil, izoptin) are are widely used with the aim of normalizing heart rhythm disturbances.

2.2. Action potential of the contractile cardiomyocytes and it's ionic mechanisms.

Contractile cardiomyocytes do have a resting potential phase similar to nerve cells, skeletal and smooth muscle, unlike pacemaker cells. In this phase, the membrane is permeable mainly for K^+ ions and to a lesser extent for Na^+ ions, establishing resting potential at level about -90 mV (Fig.7.3.)

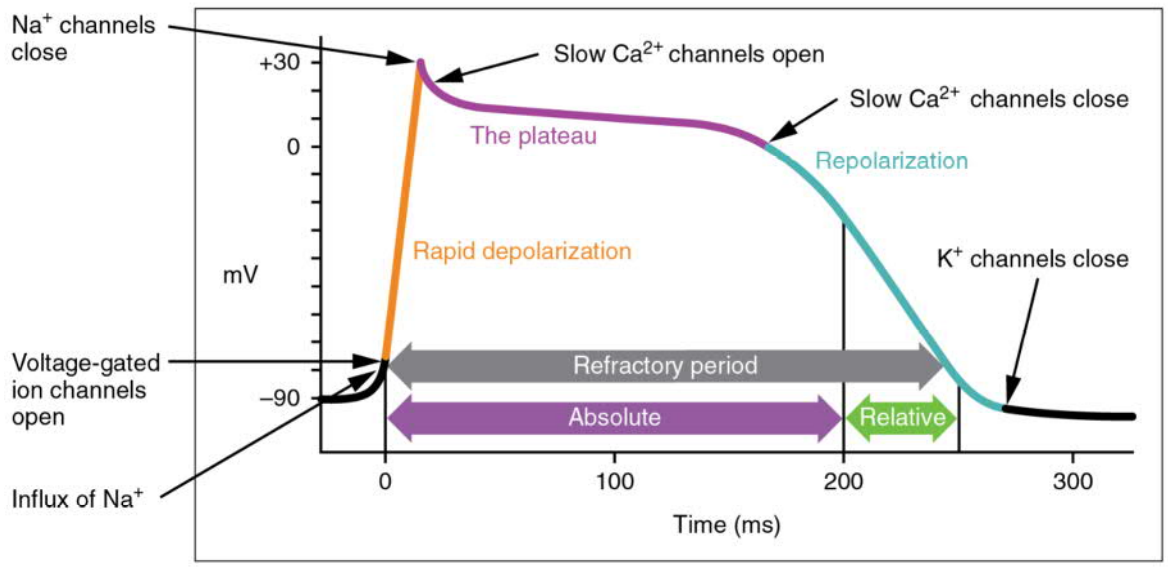

Fig.7.3. Action potential and refractory period of the contractile cardiomyocite.
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The generation of action potential begins with the membrane depolarization caused by the stimulation received from the fiber of the conducting system or adjacent muscle fiber through the nexus. The first phase of AP – ***depolarization phase*** – is created by Na^+ diffusion into cardiomyocytes through open fast Na^+ channels of the membrane. These channels remain open until the charge of the membrane reaches level close to +30 mV. Then they are inactivated but instead one of the subtypes of potassium channels is opening, giving start to fast second phase of AP - ***a phase of early rapid repolarization***. It continues until the level of the membrane potential reaches the level about +10 - +15 mV because of the diffusion of potassium ions into the extracellular space. At this point, slow calcium channels L-type are opening, what causes calcium ions to enter the cell.

Two competitive ionic currents - K^+ from the cells and Ca^{+2} into the cell produce the longest third phase of AP – ***the phase of slow repolarization (plateau)*** during which the charge of the membrane is close to 0 for about 150 ms and slowly drifts toward the resting potential value. The slow calcium channels of L-type are closing upon reaching the charge level of the membrane -5 - -10 mV and calcium ions flow into the cardiomyocytes gradually stops. At the same time another subtype of potassium channel is oppening, allowing an additional outflow of K+ ions from the cell. This outflow causes the membrane repolarization to the basal level and creates a fourth phase of AP - ***the final rapid repolarization phase***.

Thus, the main feature of AP in the contractile cardiomyocytes is the plateau phase. The crucial role in mechanism of this phase plays the L-type slow calcium channels (similar to calcium channels in atypical cardiomyocytes and smooth muscle). The plateau phase is important in several ways. First, it provides a long lasting period of absolute refractority of the myocardium, necessary for the fulfillment of the heart pumping function. Secondly, it supports the flow of calcium ions into the cardiomyocyte during systole of the ventricles and atria, what is important for the mechanisms of the heart muscle contraction.

2.3. The refractory period of the myocardium and it's physiological meaning.

The myocardium is not capable to twitch summation during repeated external stimulation like the skeletal muscles. Therefore, tetanus can't occur in the heart, when it is contracting. The reason for this is the relatively long-term ***absolute refractory period*** of contractile cardiomyocytes, which lasts an average for 250 ms (almost as long as action potential) (Fig.7.3.). Neither nervous nor humoral stimuli are able to trigger the next generation of AP during this period and somehow affect the process of myocardial contraction. This phenomenon is due to the inactivation of voltage gated sodium channels in the sarcolemma.

The relative refractory period of the myocardial cell lasts for next 20-30 ms. Only supraliminal stimuli can induce the re-excitation and followed premature myocardial contraction during this period. This explains the origin of ***extrasystole*** (premature contractions) under some conditions associated with hyperactivity of the sympathetic system or with local pathological pacemakers in the myocardium. Normally, the refractory state of the myocardium (sum of absolute and relative refractory period) ensures the ventricular ejection of blood in the vascular system during systole. This, in turn, creates the preconditions for subsequent myocardial relaxation and filling the heart with blood in diastole. Therefore, the long-term refractory period provides the optimal pumping function of the heart.

2.4. The excitation-contraction coupling in the myocardium.

The special feature of the myocardium in comparison to the skeletal muscle is that an excitation not only triggers the process of contraction but supports it throughout the duration of the whole action potential (Fig.7.4). This connection is called the excitation-contraction coupling. The leading role in its implementation play Ca^{+2} ions and their transport mechanisms.

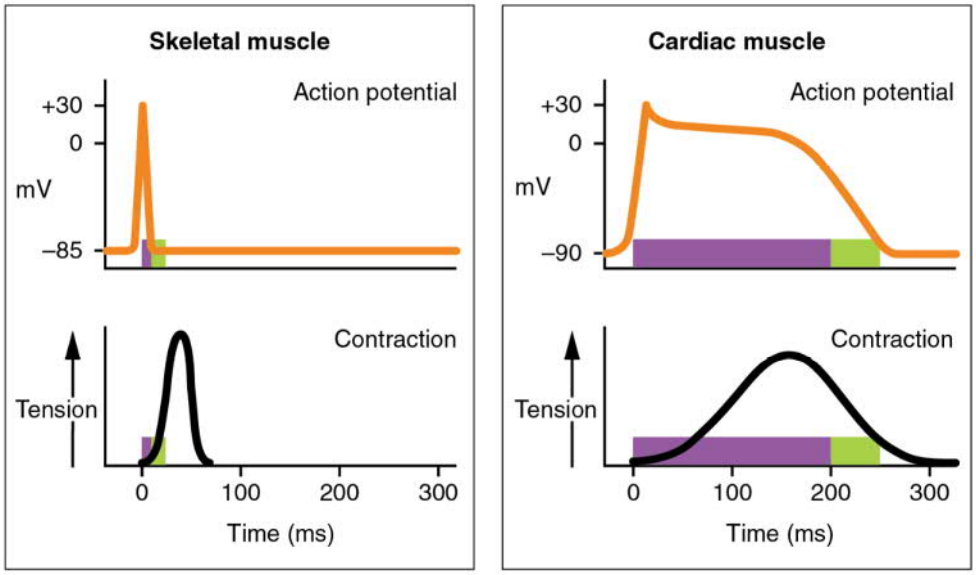

Fig.7.4. The relationship between the action potential and contraction in the skeletal and cardiac muscle.
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An action potential that reaches a contractile cell spreads across the sarcolemma and enters the t-tubules, where it opens voltage-gated L-type Ca^{+2} channels(Fig.7.5.). Ca^{+2} from extracellular space enters the cell and contacts with the ***ryanodine receptors*** ***(RyR)*** in the sarcoplasmic reticulum, causes opening of the ryanodine calcium channels. When the RyR channels

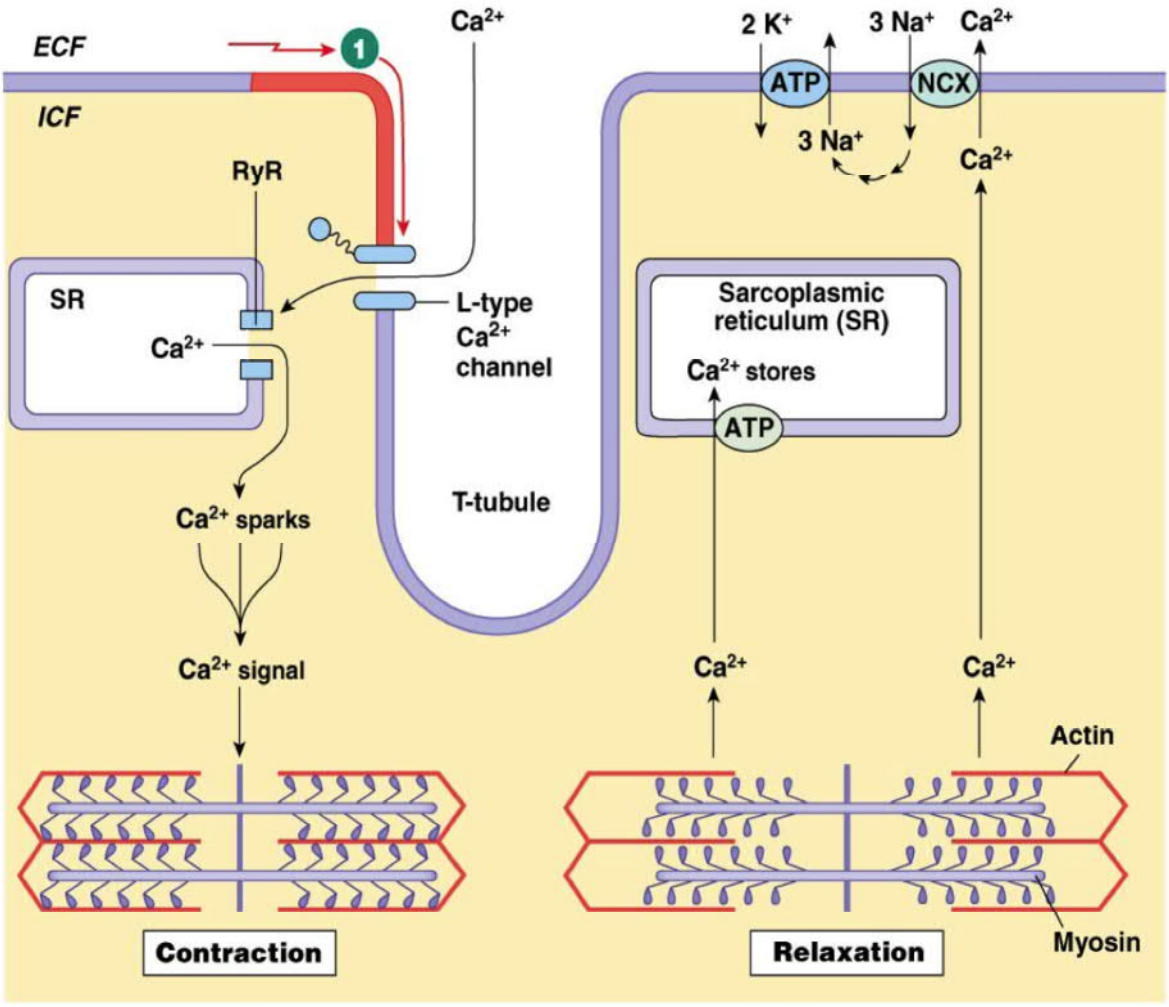

Fig.7.5. Cardiac excitation-contraction coupling.

are opened, stored in the sarcoplasmic reticulum Ca^{+2} ions diffuse into the cytosol because of the concentration gradient and are accumulating near the cross bridges in the area of actin and myosin interaction. This process is called ***Ca^{+2}-induced Ca^{+2} release.*** Calcium released from the sarcoplasmic reticulum provides about 90% of the Ca^{+2} needed for muscle contraction, while the remaining 10% enter the cell from the extracellular fluid. Calcium diffuses through the cytosol to the contractile elements, where the ions bind to troponin and initiate the cycle of crossbridge formation. Contraction in cardiac muscle is realizing by the same type of sliding filament movement that occurs in skeletal muscle.

Ca^{+2} unbinds from troponin, myosin releases actin, and the contractile filaments slide back to their relaxed position. As in skeletal muscle, Ca^{+2} is transported back into the sarcoplasmic reticulum with the help of a Ca^{+2} - ATPase. However, in cardiac muscle Ca^{+2} is also removed from the cell in exchange for Na^{+} via the Na-Ca^{+2} exchanger (NCX) . Each Ca^{+2} ion moves out of the cell against its electrochemical gradient in exchange for 3 Na^{+} ions

entering the cell down their electrochemical gradient. Sodium that enters the cell during this transfer is removed by the Na-K pump.

The peculiarities of the participation of calcium ions in excitation-contraction coupling in the myocardium cause another significant difference from skeletal muscle. Thus, it is known that the single contraction of the whole skeletal muscle and individual muscle fibers corresponds to the law "everything or nothing": that is, in response to threshold stimulation, these structures generate a contraction with the maximum possible force. At the same time, in the myocardium a different amount of calcium ions is releasing from the sarcoplasmic reticulum, depending on the stimulus strength and, accordingly, a different number of cross bridges are involved to the contraction. Therefore, the myocardium, stimulated by threshold and super threshold stimuli, contracts with force proportional to the magnitude of the stimulus.

The exclusive dependence of excitation-contraction coupling on the mechanisms of transport of calcium ions is a theoretical basis for the pharmacological regulation of the myocardial contractility, and hence it's needs for oxygen, by the drugs blocking different types of calcium channels (L-type and RyR-type). In particular, the previously mentioned drug verapamil (a blocker of calcium channels L-type) is successfully used not only to stabilize the heart rate, but also in the treatment of coronary heart disease to reduce myocardial oxygen demand.

2.5. The conduction system of the heart and its participation in the coordination of the heart pumping function.

Effective pumping of blood by the heart depends on coordinated contraction of it's chambers in a certain sequence and with a certain rhythm. This coordination is provided by a special conduction heart system, built from autorhytmic (atypical) cardiomyocytes. This system consists of sinoatrial node (SA) and atrioventricular node (AV), internodal bundles, an atrio-ventricular bundle of His, branching on the right and left legs, and Purkinje fibers, which are directly contacted with contractile cardiomyocytes (Fig.7.6). There is an automatism gradient between different structures of the conduction system, what means that the most frequent rhythm (about 70 beats per minute) is generated by the SA node, somewhat less (40-50 beats per minute) by the AV node and the most rare (20-30 beats per minute) by atypical cardiomyocytes of the His bundle. Purkinje fibers do not possess the ability to generate their own rhythm. The cause for the automatism gradient is the different Na^+ permeability of the cell membranes in the conducting system structures. It is the highest in cells of the SA node, which dominates over other pacemakers. Therefore, it is called ***the pacemaker of the 1st order***. Normally, all components of the conducting system are fired from the SA node and can't exhibit their own rhythm.

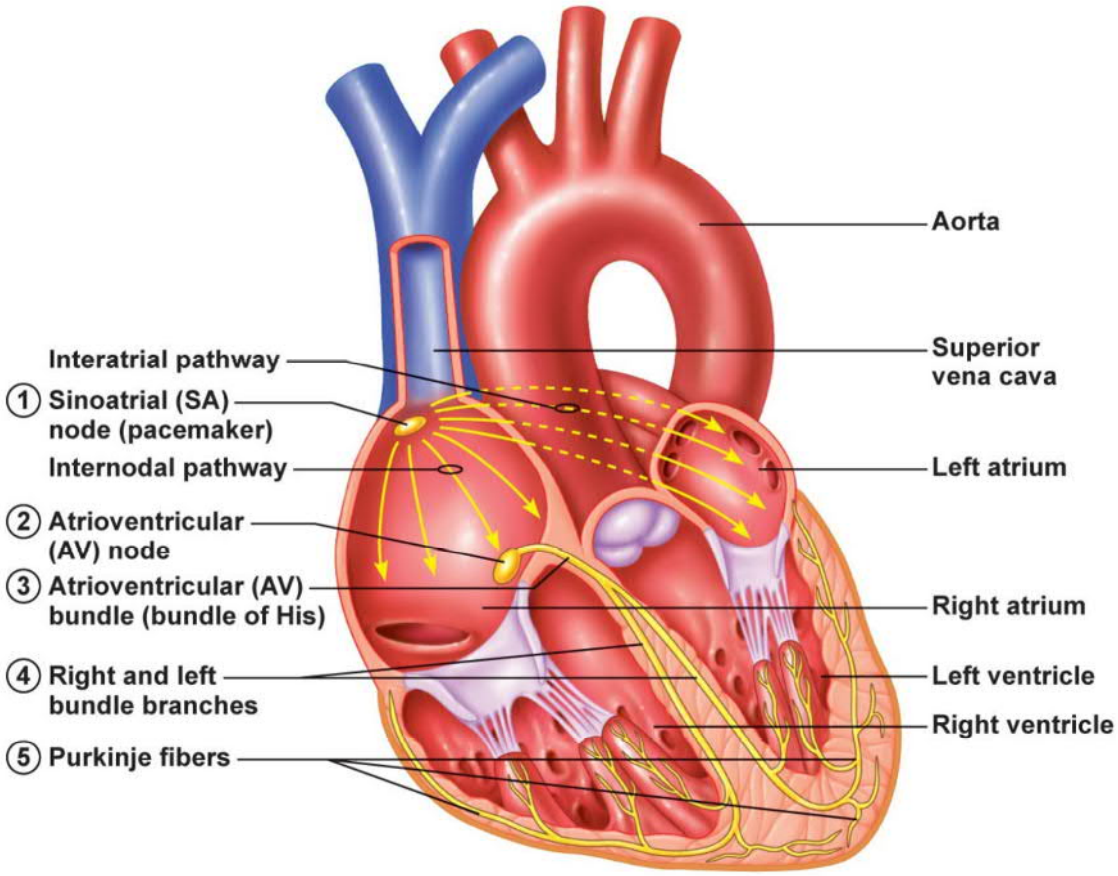

Fig.7.6. Heart conduction system.

However there are such situations when the action potentials from the sinus node does not reach the AV node (for example, because of a scar after a myocardial infarction), and this node starts to generate its own rhythm with a lower frequency. These conditions are called heart blockages. Normally, the excitation from the SA node rapidly spreads across the internodal bundles to the AV node and relatively slowly through the atria myocardium towards the heart apex. To adjust the excitement and contraction of the ventricles with atrial contraction, it is necessary that, the atria can complete their contraction before the start of the ventricles excitation. Such coordination is achieved by delaying the excitation in the AV node by about 0.11 seconds. Further, the action potentials come to the Hiss bundle, which passes through the fibrous membrane between the atria and the ventricles, and transmits the APs to the cardiomyocytes of the interventricular septum. Since the fibrous membrane is an electrical isolator, in a healthy heart, the His bundle is the only way to transfer the APs from the AV node to the ventricular myocardium, what prevents the excitation from being recirculated inside the atria. However, some people have got the variants of a conduction system with accessory atrio-ventricular bundles (Kent's, James' and Mahaim's), by which the excitation is conducting sometimes faster as usually without stopping in the AV node. In these cases, some part of the ventricle myocardium fibers is excited and contracted prematurely (WPW syndrome).

The His bundle, passing through the interventricular septum branches into the right and left legs, which diverge on the top of the heart and rise upwards along the walls of the right and left ventricles respectively. The final branches of the His bundle inside the ventricular myocardium are called *Purkinje fibers.* These fibers directly contact with contractile cardiomyocytes and initiate their excitation and contraction. A significant portion of the ventricular myocardiocytes receives electrical stimulation through the nexus from adjacent contractile fibers. The rapid conduction of APs by Purkinje fibers and their diffuse distribution through the myocardium provides practically simultaneous excitation of the right and left ventricles in the direction from the top to the heart base. Such a sequence of excitation and subsequent contraction of the different parts of the heart is optimal for pushing the blood towards the semilunar valves, similar to squeezing the toothpaste from the tube. The excitation arising in the sinus node spreads throughout the atrium myocardium with speed 0.8-1.0 m/s. Internodular bundles, a His bundle and Purkinje fibers conduct the excitation with a speed 1.5 - 4.0 m/s. The excitation is spreading throughout the myocardium of ventricles with a speed 0.3 - 0.6 m / c.

3. Physiological aspects of electrocardiography

3.1. Basic elements of ECG and their origin.

Electrocardiographic examination in our time is one of the most accessible and most informative diagnostic methods. At the same time, for the correct interpretation of the electrocardiogram (ECG) it is necessary to understand its physiological basis. The ECG tracing does not reflect the dynamics of the activity of individual cardiomyocytes and does not even resemble it, since it is the result of the total electrical activity of all myocardial fibers during the cardiac cycle. The simultaneous emergence of APs in many cardiomyocytes creates a potential difference between them and neighboring cells that have not been excited yet. This potential difference due to the electrical conductivity of the body tissues is carried out on the surface of the body and can be registered by the applying of at least two electrodes on it. The potential difference between 2 points on the surface of the heart is about 120 mV, while its magnitude reaches only 1.0-1.5 mV on the surface of the skin. It is reduced approximately 100 times because of high electrical resistance of the body tissues. This signal needs to be amplified and filtrated to record it in the form of a curve, like the modern electrocardiographs do. Fig. 7.7. shows the typical ECG curve, recorded when 2 electrodes are applied to the left and right arm, and its

correspondence with the wave of excitation spreading throughout the heart. A typical ECG tracing includes the following elements:

- The P wave, which reflects depolarization of the atria myocardium.
- The QRS complex, which is formed by a depolarization wave gradually covering the interventricular septum (Q), the heart tip and the lateral walls of the ventricles (R) as well as the base of ventricles bordering with atrioventricular septum (S). An isoline (absence of potential difference) with a duration of about 0.1 s (segment PQ) is recorded between the end of the P wave and the beginning of the Q wave, which corresponds to the time delay of

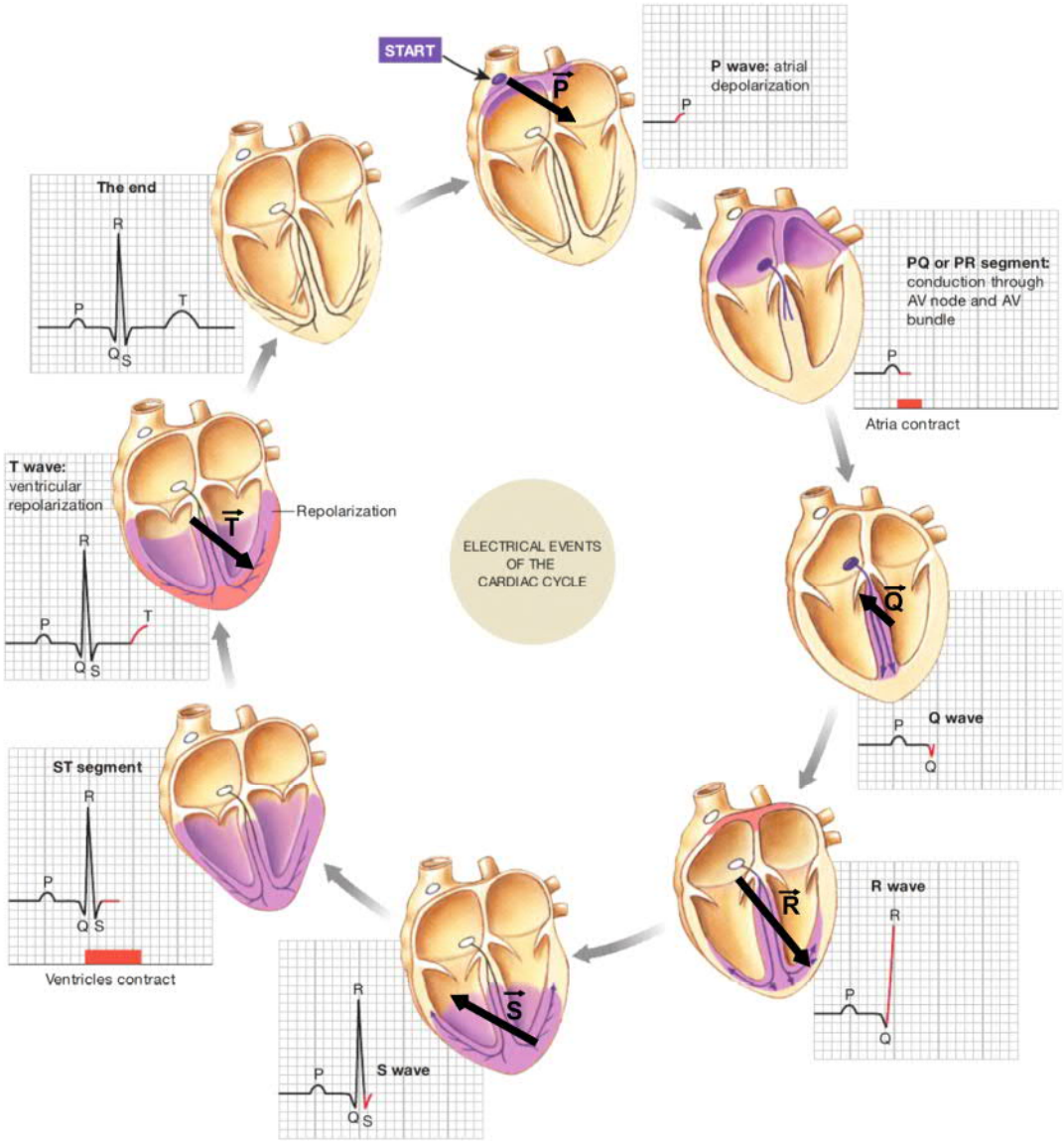

Fig.7.7. Typical ECG tracing and its correspondence to spreading of excitation wave through the heart forming main electrical vector during the cardiac cycle.

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excitation in the atrioventricular node and its conduction time through the Hiss bundle to the contractile myocardium.

- The T wave, which reflects the repolarization of ventricular myocardium. The isoline lasting up to 0.1 s (segment ST) is recorded again between the end of the wave S and the beginning of the T wave, because the most of myocardial fibers are in the plateau phase and no potential difference between them exists.

The configuration of the curve (waves and segments) depends on the method of applying electrodes (leads) when the ECG is recording. In clinical practice, the most common is the 12-axis system of leads, which allows to bind the pathological changes in the myocardium to their anatomical localization. We will consider this system later in detail, since the competent interpretation of the ECG is impossible without it. At the same time, it must be remembered that ECG reflects only electrical activity of the heart, but not its mechanical properties. Typically, pathological changes in the myocardium change this activity, and therefore they can be seen on the ECG trace. However myocardial abnormalities may not be present on the ECG if the pathology does not affect the generation and conduction of APs in the myocardium.

3.2. Electrocardiographic leads and their axes in the frontal and horizontal plane.

The electrical potentials of the heart can be registered using the leads from two electrodes, which are placed on certain areas of the body. One electrode is connected to the positive pole of the electrocardiograph, the other to the negative one. Leads can be bipolar and unipolar. *Bipolar leads* reflect the potential difference between the two points of the body, and the unipolar ones - between any point of the body and the constant potential conventionally taken as zero point. To create such a potential, the combined Wilson electrode is used. It is created by connection of the three lead electrodes - the right and left arms and the left leg. A 12 leads system is used in electrocardiography most often. It includes 3 standard leads, proposed by Einthoven in 1908, denoted by the Roman numerals I, II; III; 3 augmented unipolar leads from the extremities (aVR, aVL, aVF), and 6 unipolar thoracic leads (V_1-V_6) (Fig.7.8.).

The first standard lead (I) records the potential difference between right and left hands. In this case, the right electrode is connected to the negative pole, and the left to the positive.

The second standard lead (II) reflects the potential difference between the right hand connected to the negative pole and the left foot connected to the positive pole.

The third standard lead (III) records the potential difference between the left hand connected to the negative pole and the left foot connected to the positive pole.

The augmented leads from the limbs were proposed by Goldberger in 1942. These are so-called unipolar leads. One indifferent electrode, whose potential is close to zero, is connected to the negative pole, and the second electrode - active - is applied to one of the limbs and connected to the positive pole. An augmented lead from the right hand is called ***aVR***, from the left hand - ***aVL***, and from the left foot - ***aVF.*** In these abbreviations, the first letter "a" is the abbreviation of the English word ***augmented***, the letter V is the abbreviation of the English word ***voltage***, and the letters R, L, F denote right, left, foot.

The thoracic leads (precordial leads) proposed by Wilson are also unipolar. Wilson's indifferent combined electrode is connected to the negative pole, and the active electrode is connected to the positive pole and placed at different points on the chest wall. These leads are designated by the Latin letters ***V*** and Arabic numerals. The active electrode V_1 is placed at the 4th intercostal space on the right side of the sternum; V_2 at the fourth intercostal space on the left edge of the sternum; V_3 in the middle between V_2 and V_4; V_4 at the fifth intercostal space on the left medioclavucular line; V_5 at the fifth intercostal space on the left anterior axillary line; and V_6 at the fifth intercostal space on the left middle axillary line.

Lead axis is explained as a hypothetical line that connects the electrodes, used to record ECG in this lead, and passes through the hypothetical point of the zero potential. This point divides each axis into a positive and a negative part depending on the polarity of the limb to which

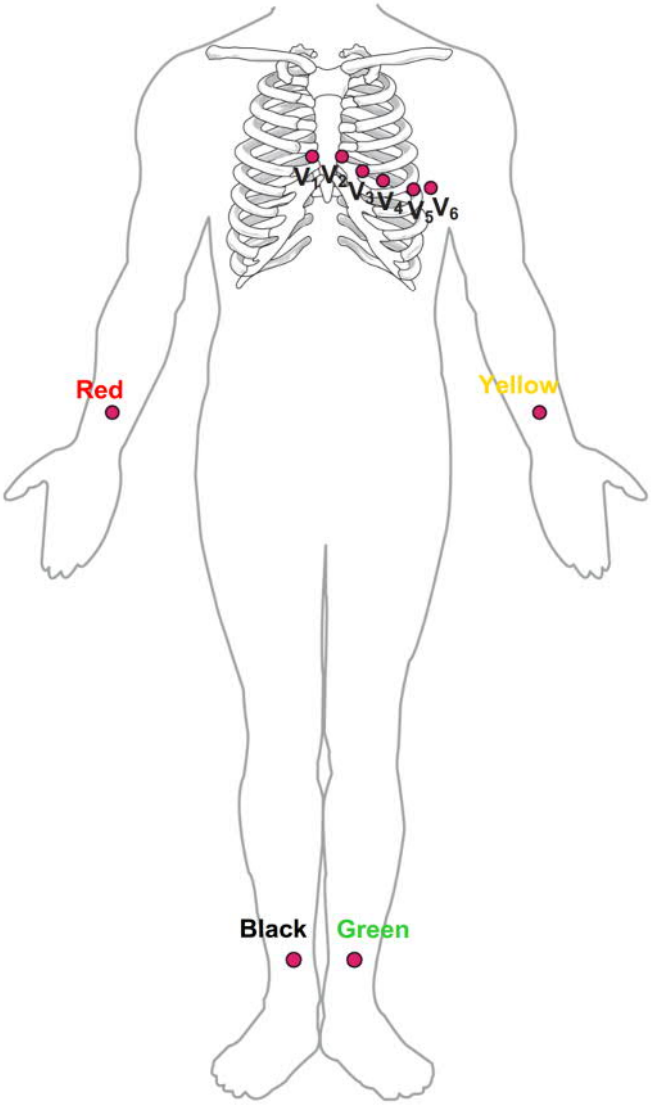

Fig.7.8. Placement of electrodes in the 12 leads ECG system.

the electrode is attached. The dynamics of the integral electric vector in the frontal plane is analyzing using a special axis system, build from axes of standard I, II, III leads and augmented unipolar leads aVL, aVR and aVF intersecting in the zero point potential. The angle between two adjacent axes in this scheme is 30 degrees.

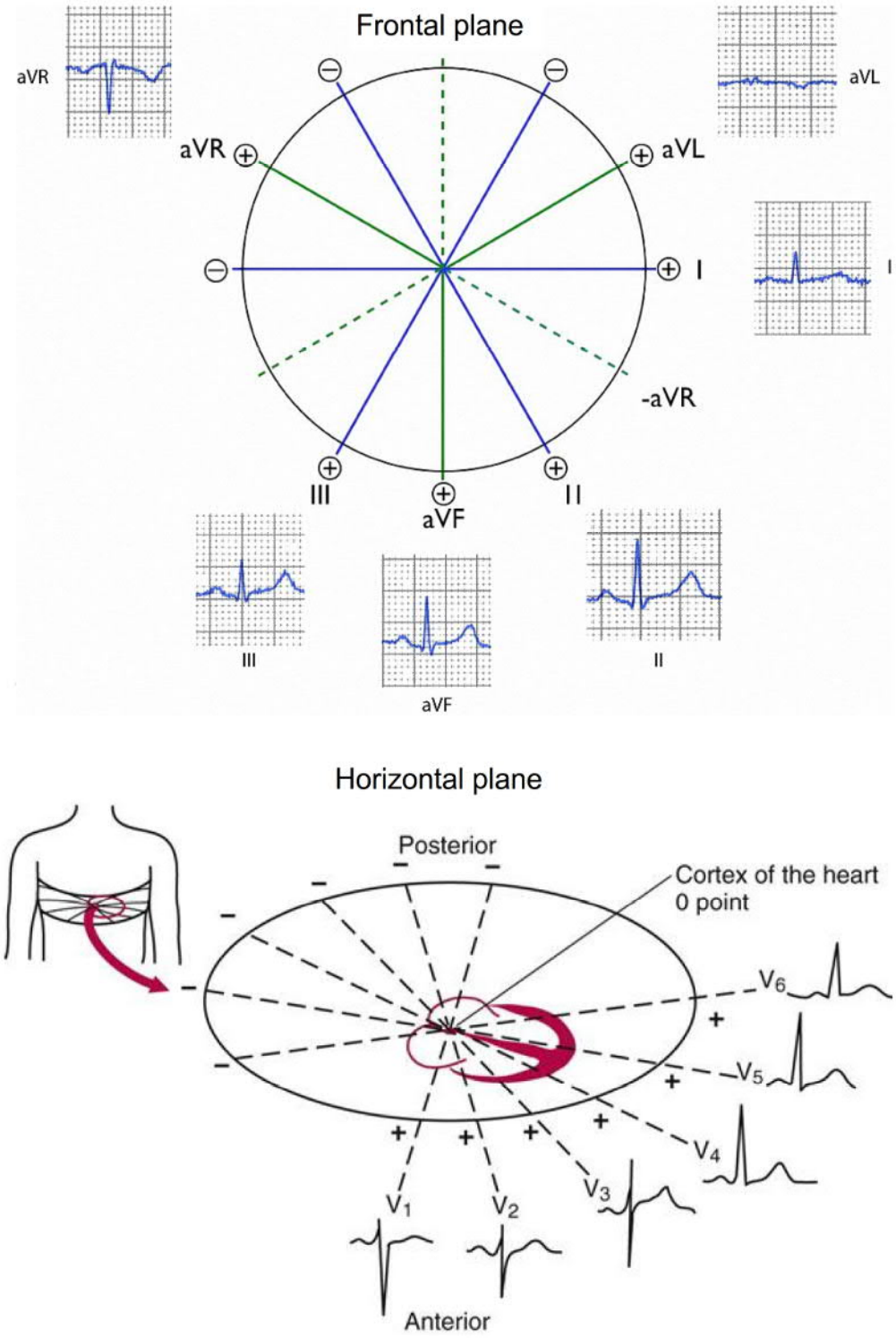

Fig.7.9. Axes of the ECG leads in frontal and horizontal plane.

Thoracic leads give information about the dynamics of the total electric heart vector in the horizontal plane. These leads are also analyzed using the 6-axis system, in which the axes pass through the center of the heart, and their positive ends are located on the surface of the chest (Figure 7.9).

3.3. The concept of an integral electric vector of the heart and its projection on the axis of electrocardiographic leads.

A theoretical model considering the heart as a conditional point of a zero electric potential, from which ***the main electric vector*** of the heart comes out, is used for the ECG analysis. This vector is the geometric sum of elementary dipole vectors that reflect the excitation of a separate myocardial fiber. At each time during the heart cycle, the main electric vector has a different direction and magnitude. However, it is possible to distinguish the periods when this vector represents averaged information on the excitation dynamics of different myocardial structures (Fig. 7.7.).

The dynamics of the integral electric heart vector during the cardiac cycle. Excitement arising in the SA node diffuses over the right and left atria for approximately 0.1 seconds. The main electric vector of the atria (P) is directed to the left, forward and down, forming the P wave on the ECG.

The following 0.08-0.1 seconds the excitation wave propagates through the fibers of the conduction system to the contractile myocardium, delaying at the AV node. At this time, the main vector has a very small value (due to the relatively small mass of the conducting system fibers) and the recorded ECG looks as isoline. The myocardium of both ventricles begins to excite simultaneously in the direction from subendocardial layer to the epicardium. It is accepted to distinguish the three vectors of the ventricles depolarization, which form a QRS complex. The initial (septal) vector Q arises during the first 0.03 sec of the ventricles excitation and reflects the interventricular septum depolarization. It is directed to the right, forward and upward. The main vector of the ventricle complex R forms during the next 0.03-0.05 seconds. It reflects the depolarization of the main part of the left and right ventricles and is oriented to the left, down and forward (since the mass of the left ventricle significantly exceeds the mass of the right one). The final vector of this complex S reflects the depolarization of the ventricles base during the following 0.03-0.04 seconds and is directed up, back and to the right or left. Next vector T which is oriented tj the left, down and forward arises during the period of ventricular repolarization (it lasts 0.16-0.22 seconds). At the same time, the wave of repolarization moves from the epicardial layer to the subendocardial one, what contrasts with the direction of depolarization wave.

The ECG trace will be recorded up from the isoline if the main vector is projected on the positive side of the axis. It will be recorded down from the isoline if this vector is projecting on the negative side of axis. The ECG curve in any lead is obtained by the time scanning of the main vector projection on

the axis of this lead (Fig.7.10). The vector principle of ECG analysis makes it possible to understand why the curve of an electrocardiogram in different leads has different configurations, as well as why the waves have the different voltage. For example, in aVR lead of healthy people, most of the waves are directed below the isoline, due to the negative projections of the forming this lead vectors on its axis.

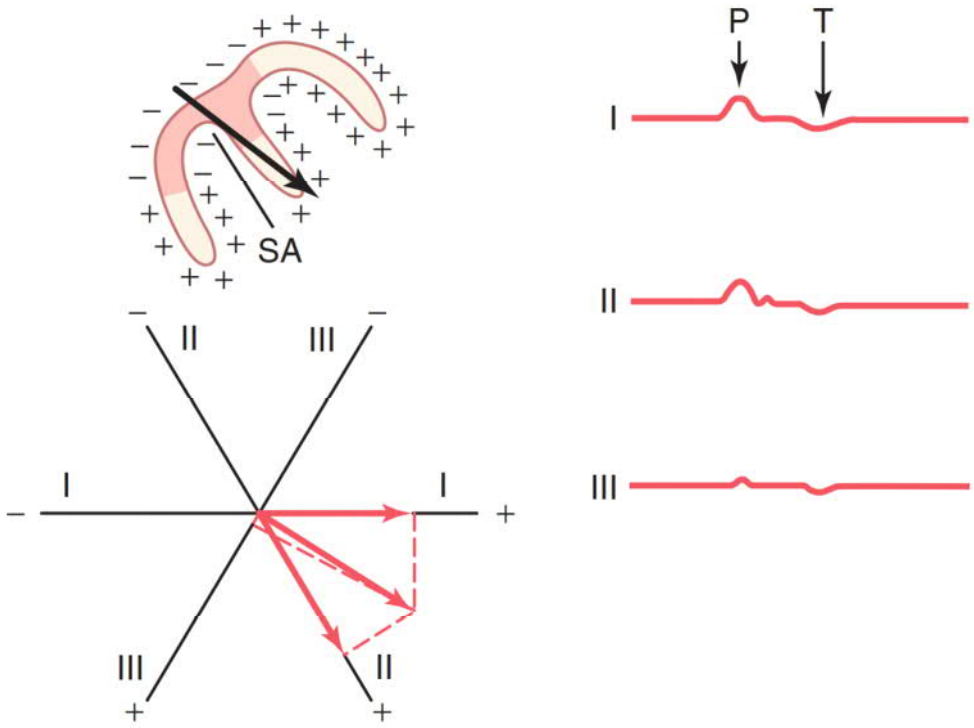

Fig.7.10. Vector principle of forming ECG waves and segments.

The same principle is used to analyze the abnormal waves detected in pathology. As a rule, they are caused either by the deviation of the main vector from its normal direction or by the appearance of the vector in those periods of the cardiac cycle, when it does not have to be in a healthy heart. The formation of *a monophasic ventricular complex* during acute myocardial infarction can be a good example (Fig.7.11). In this pathological condition, the damaged area of the myocardium creates an electronegative medium because of the release of negative ions through the damaged cell membranes. Neighboring undamaged areas have a normal distribution of ions (positively charged ions are outside the membrane and negative – inside the cell). Thus, a permanent potential difference is created between the destruction site and the intact parts of the myocardium, which forms an abnormal vector (injury vector) manifested itself even during the phase of the plateau when the isoelectric segment ST is recorded in healthy heart). This vector deforms the ECG curve in those leads that are closest to the damaged area and forms a special electrocardiographic phenomenon - the monophasic ventricle complex called *Pardee's wave* (by the name of the

American cardiologist who first described it). It should be noted that this diagnostic sign exists only in the first hours after the onset of myocardial infarction, and subsequently is transforming into a pathologic ventricular QRS complex with a "deep" Q wave (more than ¼ of the amplitude of the R wave).

Another example of the vector analysis can be the changes in amplitude of R wave in standard leads in patients with the right or left ventricular hypertrophy. A sharp deviation of the integral heart vector occurs, respectively, to the right, or to the left. It causes the abnormal relationship between the amplitude of the R waves in standard and precordial leads. The ECG signs of the left ventricular hypertrophy due

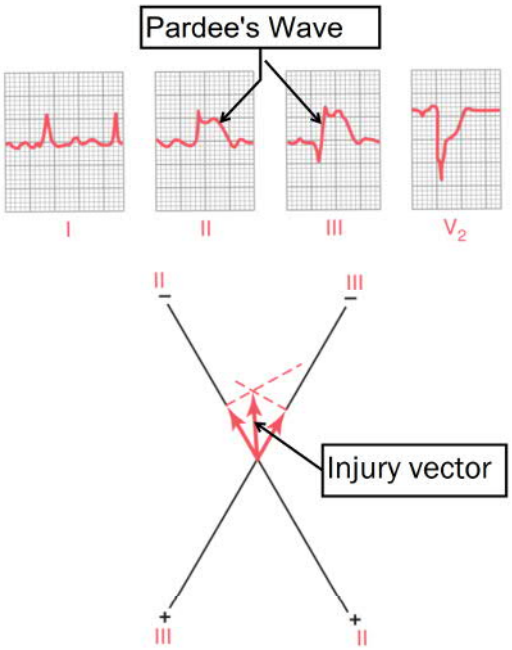

Fig.7.11. Monophasic ventricular complex (Pardee's wave) during acute transmural infarction of the left ventricle wall (1-st day).

to a sharp deviation of the integral heart vector to the left are shown on fig. 7.12. Analyzing the position of the integral heart vector and its projection on the lead axis, it can be seen that the largest projection is in the I lead, somewhat lower - in the II lead. And it is even negative in the III lead, because it falls into the negative half of the III lead axis,. Therefore, in this lead, the positive R wave was transformed into a high-amplitude negative S wave.

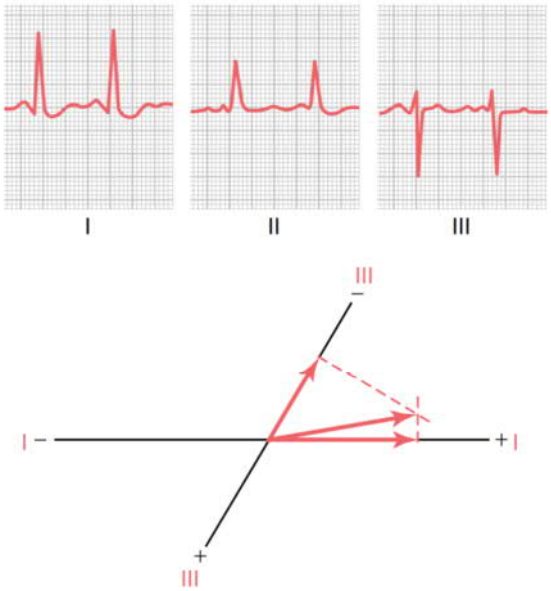

Fig.7.12. ECG signs of left ventricular hypertrophy caused by a sharp deviation of the main heart vector to the left.

3.4. Basic parameters of a normal electrocardiogram .

An ECG, regardless in what lead it is registered, consists of waves, segments and intervals. The waves are denoted by the Latin letters P, Q, R, S, T. The voltage and direction of the waves are determined in relation to the

level of the so-called ***isoelectric*** or zero line, which is recorded during the diastole period when the heart is not excited. The waves, directed upwards from the isoline, are considered positive, and downwards - negative. The voltages of the waves are expressed in millivolts, relating to the value of the calibration signal 1 mV, which is recorded before the registration of the ECG.

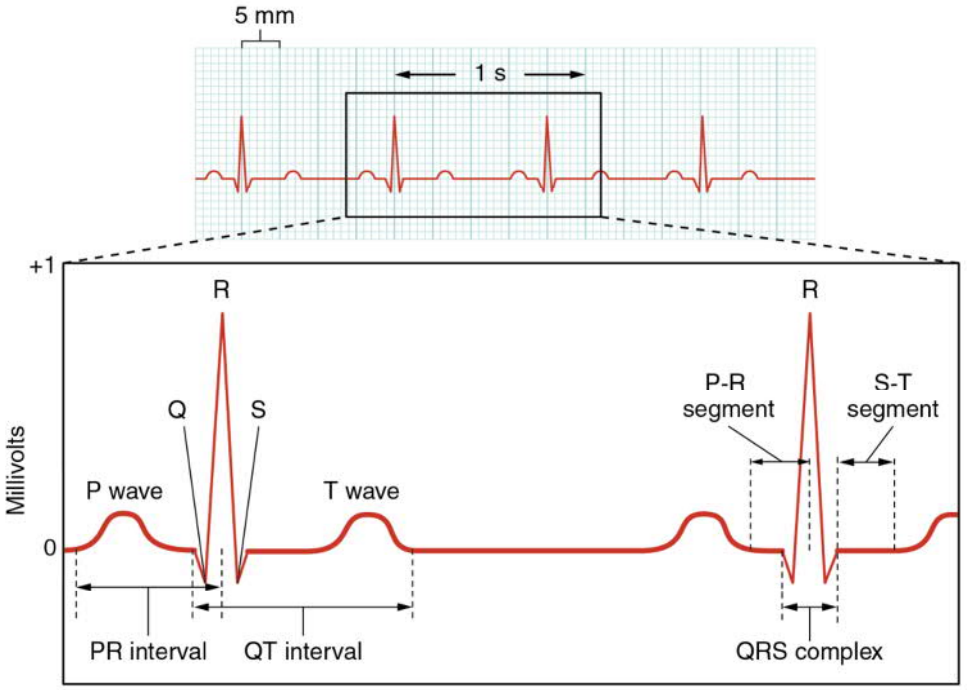

Fig.7.13. Main elements of typical ECG curve.
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The length of the waves, segments and intervals are measured in seconds, knowing the speed of the paper movement in the recording device (Fig.7.13).

The P wave reflects the excitation of the atria, its amplitude is <0.2 mV, and the duration is 0.06-0.11 s. Normally, this wave is always positive in leads I, II, aVF, V_2-V_6. In other leads, it can be both positive and negative.

The interval P-Q is measured from the beginning of the P wave to the beginning of the Q-wave and displays the time spending on conduction of the excitation from the SA node to the ventricular myocardium. This interval ranges from 0.12 to 0.20 seconds.

The P-Q segment reflects conduction of the excitations from the AV node to the ventricular myocardium through the conducting system. Normally, it is located on the isoline, because the involved part of the conducting system produces an integral vector of the heart close to zero.

Q, R, S, T waves form a ventricular complex. It is believed that the QRS complex reflects the depolarization processes in the ventricles. The first wave of this complex ***Q wave*** is negative; normally it is registered in all standard leads, augmented unipolar leads from the limbs and chest leads V_4-V_6. Its amplitude is <1/4 R, and the average duration is 0.03 - 0.04 sec.

The R wave is the largest and permanent positive wave of the ventricular complex. Its average amplitude in most leads (with the exception of aVL and aVR) is 0.8-1.2 mV, and the duration is 0.04-0.06 sec. In standard leads, the most frequently R (I) amplitude is slightly less than R (II), and R (III) usually is the smallest R wave in precordial leads increases from V_1 to V_4, and then decreases in amplitude. However, this depends on the electrical axis position of the heart.

The S wave is negative in all leads, with the exception of aVL, where it is usually absent. It can be equal to the amplitude of the R wave in the leads V_2 and V_3,. Its average duration is 0.04-0,05 sec.

The segment ST is registered from the end of the S wave to the beginning of the T wave, has a non-permanent duration and is ***always*** on the isoline. This is due to the lack of an integral vector during this period, since the charge of the membrane of all cardiomyocytes is practically the same in the phase of the plateau, which corresponds to the ST segment. It is considered normal for the chest leads, if the ST segment displaces from the isoline downwards or upwards by 0.1-0.2 mV.

The T wave is positive in the leads I, II, aVF, V_4-V_6, negative in aVR, may be negative, two-phase or positive in leads III, aVL, V_1-V_3. Its amplitude in standard leads is 0.5-0.6 mV, in precordial leads - up to 1.5 mV, its duration ranges from 0.16 to 0.24 sec.

The QRST complex is called electric systole and lasts for 0.35-0.40 sec at the heart rate equal to 75 beats / min.

3.5. Using of ECG in the diagnosis of heart disease.

The ECG is extremely important for clinical cardiology, because it allows you to recognize disturbances of the cardiac function resulting from heart lesions before they cause irreversible changes. ECG most often is used in order:

- *To determine the localization of the heart rhythm driver*. It can be determined where the rhythm driver is: in the SA node, the AV node, or in the His bundle analyzing the form of an ECG.
- *To detect heart rhythm disturbances (such as arrhythmias).* So, with ECG, you can diagnose sinus tachycardia, supraventricular and ventricular extrasystoles, fibrillation and tremor of the atria and ventricles.
- *For the diagnostics of myocardial conduction disorders.* The atrio-ventricular blockade of various degrees, intra-ventricular conduction disturbances, blockade of the Hiss bundle legs etc., can be detected with ECG.
- *To determine the direction of the heart electrical axis*, which depends on its normal anatomical placement in the chest. However this axis can be deviated from its normal position in case of hypertrophy of different heart chambers.

• *To diagnose myocardial infarction.* Myocardial ischemia in angina attacks have typical electrocardiographic signs: the displacement of the S-T segment down or up from the isoline, dome-shaped elevation, two-phase or inverted T wave in some leads. A myocardial infarction also has a characteristic electrocardiographic picture. Early, it is formed the already mentioned monophasic ventricular complex, and later, a deep and long Q wave appears in those leads that reflect the lesion location.

We can use ECG not only to diagnose myocardial disease, but also objectively control the process of treatment and the degree of heart function recovery. It should be remembered that, despite the great value, ECG is only an auxiliary diagnostic method and can only be used in combination with other diagnostic methods and has to be consistent with clinical data.

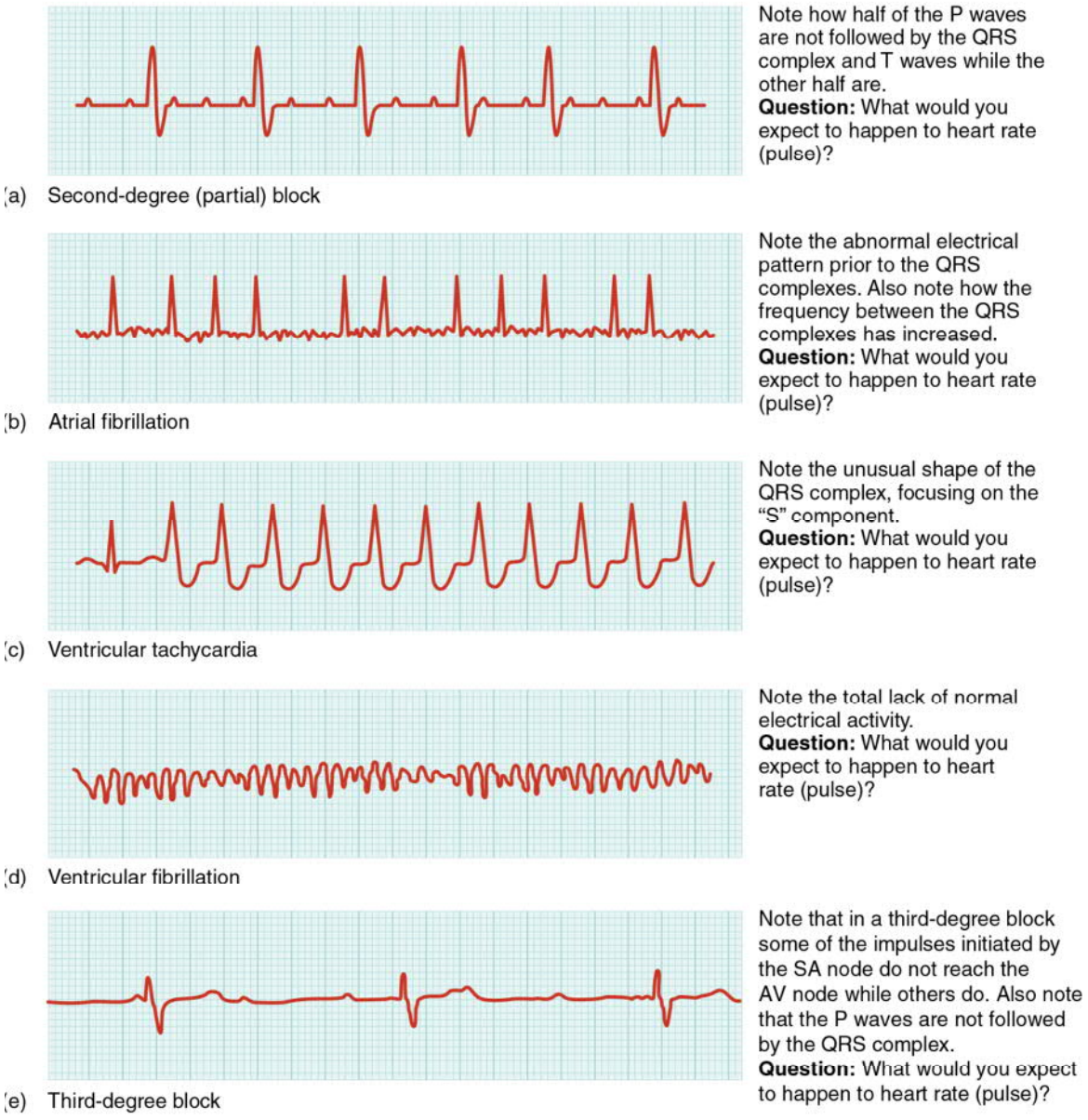

Fig.7.14. Some types of cardiac arrhythmias, that can be diagnosed using ECG.

4. The pumping function of the heart and its control

The electrical activity of the heart, discussed in the previous section, only serves the main function of the heart - the creation of a gradient of blood pressure in the vascular system, which ensures constant blood circulation. This gradient is created by periodically ejecting into the aorta and a pulmonary artery a small blood volume (about 60-80 ml), which is called ***stroke volume (SV).*** The contraction of the ventricles, due to which this ejection occurs, is called ***systole.*** After completion of the systole, the ventricles are again filled with blood from the atria due to their relaxation, which is called ***diastole***. The constant alternation of systole and diastole is called a ***heart cycle***. This concept can be applied not only to the ventricles, but also to the atria, which have their own cycle, finely coordinated with the cycle of the ventricles. The right and left half of the heart work synchronously, so the cycles of their chambers almost coincide in time. Well coordinated activity of the heart conduction system, contractile myocardium and valve apparatus is necessary for the effective heart pumping function. The blood pressure in the heart chambers, the state of the valves as well as the volume of the atria and the ventricles regularly change during the heart cycle. Based on these changes, the cardiac cycle is divided into phases and periods.

4.1 Phase structure of the heart cycle.

There are two large phases: ***systole*** and ***diastole*** in the cardiac cycle of both ventricles and atria (Table 7.2.). If the typical cardiac cycle lasts 0.8 seconds (at a heart rate of 75 beats / min.), the systole of the ventricles lasts approximately 0.33 seconds, ventricular diastole lasts 0.47 seconds, atrial systole - 0,1 s, and atrial diastole - 0,7 s. The systole and diastole of the ventricles are divided into periods depending on the condition of the

Table 7.2

Phase structure of the cardiac cycle

Atria	Phases	Diastole 0,7 sec			Systole 0,1 sec
Ventricles	Phases	Systole 0,33 sec		Diastole 0,47 sec	
	Periods	Isovolumetric contraction 0,08 sec	Ventricular ejection 0,25 sec	Isovolumetric relaxation 0,08 sex	Ventricular filling 0,39 sec

valve apparatus, their volume and changes in blood pressure. In the systole of the ventricles, a ***period of isovolumetric contraction*** lasts about 0.08 s and a ***period of ejection*** lasts for about 0.25 s. In diastole, a ***period of isovolumetric relaxation*** lasts for 0.08 s and a ***period of ventricular filling*** - for 0.39 s. The term isovolumetric means that the volume of the ventricles does not change, since the valves in these periods are closed. Duration of periods may change with the change in heart rate but the time relationship between them remains approximately the same (with the exception of tachycardia greater than 100 beats / min, when diastole is reduced to a greater degree). An integral picture of electrical and mechanical events during the cardiac cycle can be understood by analyzing the synchronous recording of physiological curves: an electrocardiogram, pressure values inside the aorta, left ventricle and left atrium, a phonocardiogram and volume dynamics of the left ventricles. (Wiggers diagram, fig. 7.15).

Let's start with the consideration the cardiac cycle in the left chambers of the heart from the atrial systole, which coincides with the end of the diastole of the ventricle. The contraction of the atrium is initiated by its excitation from the SA node and causes pushing a portion of blood into the

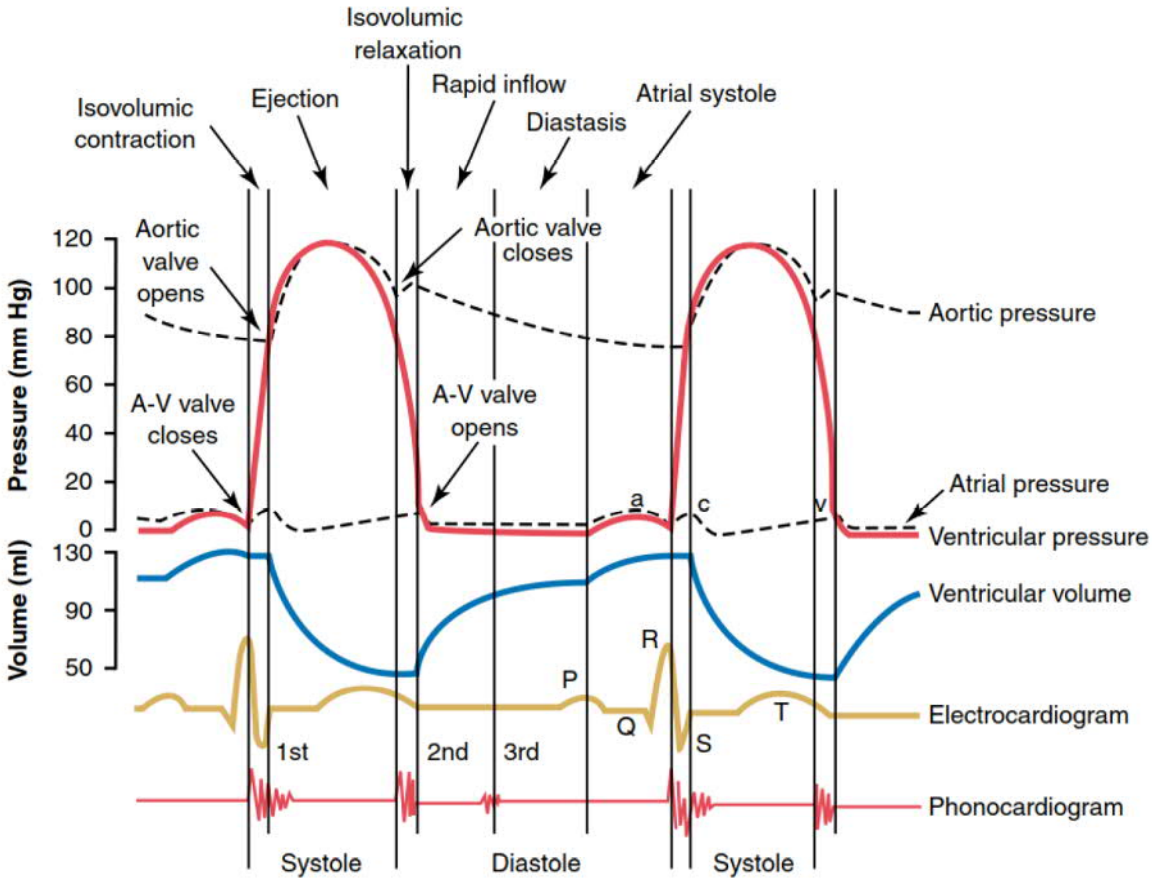

Fig.7.15. Summary of events in the left atrium, left ventricle, and aorta during the cardiac cycle (sometimes called the "Wiggers" diagram).
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ventricle through the open mitral valve in addition to that which has already filled the ventricle during the diastole. The volume of this blood makes up about 20% of the diastolic volume of the left ventricle. Since there are no valves between the atria and large pulmonary veins the retrograde flow of blood to the jugular veins appears as a result of the contraction of the atrium, what is manifested by the so-called "jugular" venous pulse.

After completion of the atrial systole, the wave of excitation enters the top of the heart through the conducting system and causes the myocardium to contract in the direction of the mitral valve, pushing the blood to the valve leaflets and closing them. Taking into account that the semilunar valve is closed at this moment, a period of isovolumetric contractions occurs in the ventricle, in which the volume of blood remains constant, but the internal ventricular pressure rapidly increases from 0 to about 80 mm Hg. As soon as the pressure inside the ventricle exceeds the

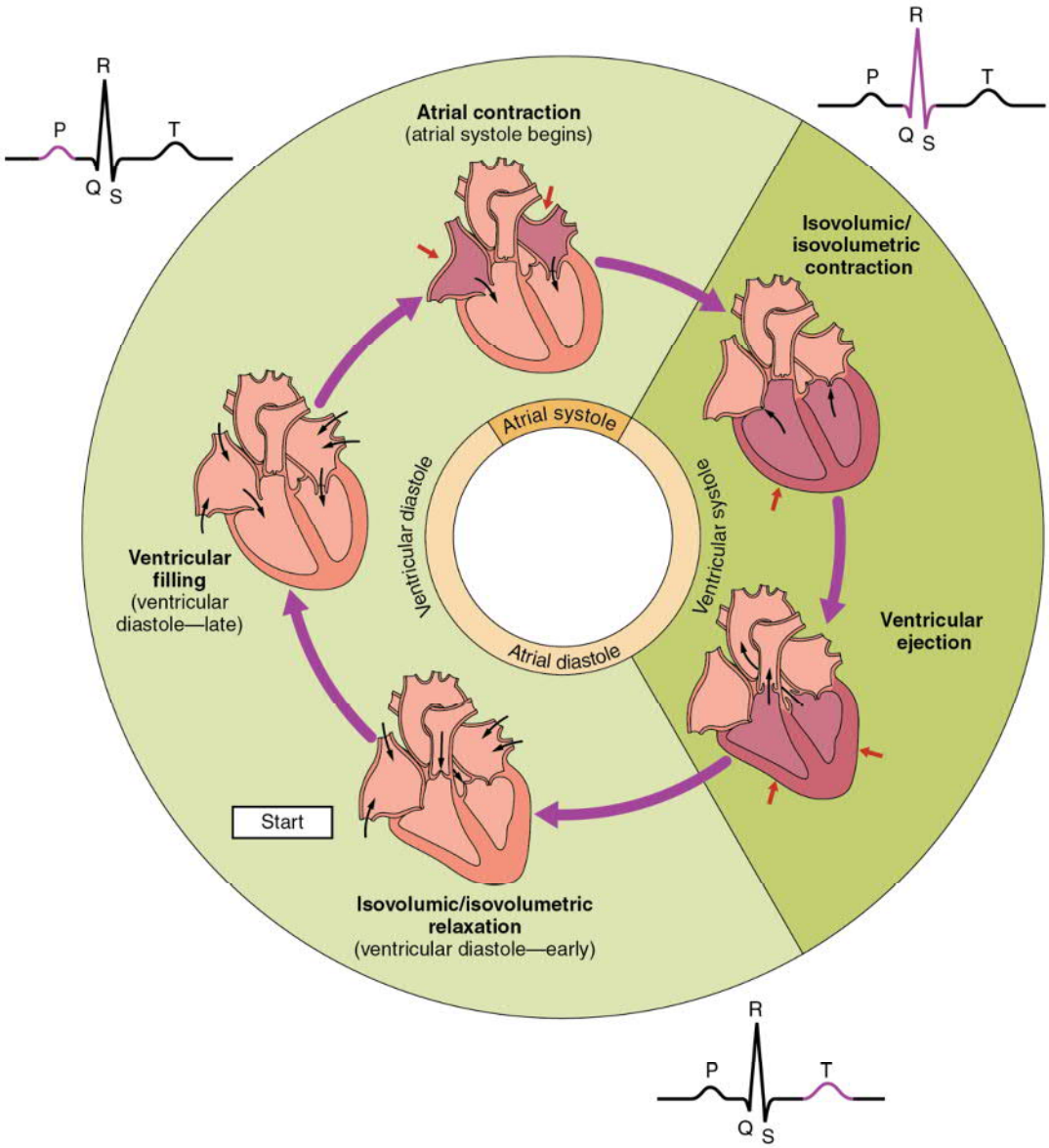

Fig.7.16. Phases and periods of the cardiac cycle.

pressure in the aorta, the aortic valve opens, the blood begins to come out into the aorta and the next period of the cardiac cycle begins: the period of ventricular ejection. In this period, the ventricle continues to contract until the maximal pressure in its cavity (125-130 mmHg) is reached, after which the relaxation of the myocardium begins. The blood ejection continues on the background of a gradual decrease in pressure to level of about 80 mm Hg. Followed dropping of intraventricular pressure results in a retrograde flow of blood from the aorta into the ventricle and filling the leaflets of the semilunar valve with blood, what causes it to close. From this moment, another isovolumetric period (the period of isovolumetric relaxation) starts, in which both the valves (at the entrance and at exit of the ventricle) are closed, the volume of blood inside the ventricle does not change, and the pressure continues to decrease from 80 mmHg to the level of 6-7 mm Hg. At this time, the atrium continues to be filling with blood from the pulmonary veins and the atrial pressure gradually increases to 6-7 mm Hg. As soon as pressure in the ventricle becomes less than the pressure in the atrium, the last period of the ventricular cycle occurs: the period of ventricular filling. The beginning of this period is associated with the opening of the mitral valve and the blood flow through it from the atrium into the ventricle. Fig.7.16. shows the position of the heart valves during the different periods of the cardiac cycle.

4.2. Pressure-Volume Curves.

Another way to describe the cardiac cycle is drawing a pressure-volume graph. This graph represents the changes in volume (x-axis) and pressure (y-axis) that occur during one cardiac cycle (Fig.7.17). Blood flow through the heart obeys the same physical laws that describe the movement of liquids and gases: the blood flows from areas of higher pressure to areas with lower pressure. When the heart contracts, the pressure increases, and blood flows out of the heart into areas with lower blood pressure.

The cycle begins at point A which corresponds to the moment of the mitral valve opening due to the pressure gradient between the atria and the ventricle. The ventricle has completed a contraction and contains the minimum volume of blood that it can hold during the cycle (***end-systolic volume*** or briefly ***EDV***). The ventricular myocardium has been relaxing, and its pressure reaches its minimal value. Atrial blood now flows into the ventricle, increasing its volume (point A to point B). Point B represents the end of diastole. A small increase in pressure is caused by the atrial systole, which pushes the last portion of the blood into the ventricle. The ventricle now contains the maximum volume of blood which he can accommodate during this cardiac cycle (point B). Because maximum filling occurs at the end of ventricular relaxation (diastole), this volume is called the ***end-diastolic***

volume (EDV). In most healthy people, the end-diastolic volume is about 130-140 mL, but this value varies depending on different conditions. It can be significantly lesser during ***tachycardia*** due to the reduction of the diastolic periods.

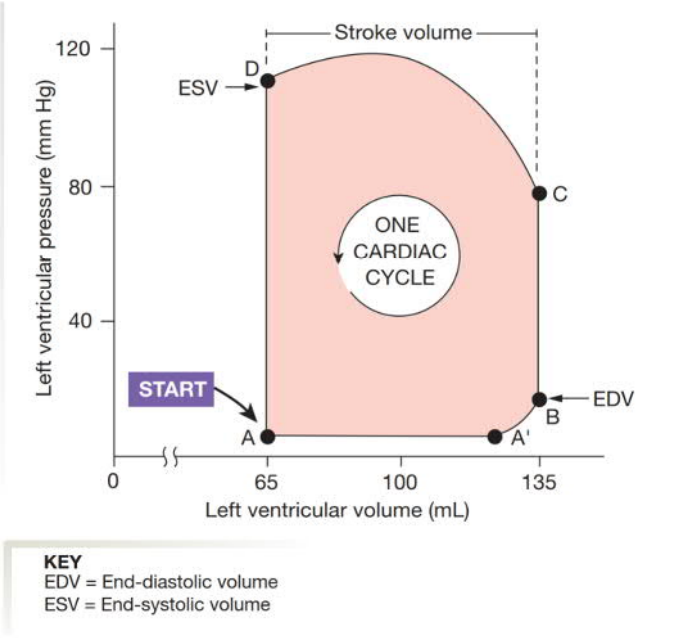

Fig.7.17. Left ventriclular pressure-volume changes during one cardiac cycle.
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In the interval between the points B and C, the pressure inside the left ventricle rapidly increases to the pressure in the aorta (point C) due to isometric contraction of the myocardium in the period of isovolumetric contraction. Once ventricular pressure exceeds the pressure in the aorta, the aortic valve opens (point C). Pressure continues to increase as the ventricle is contracting, but the ventricular volume is decreasing as blood is pushed out into the aorta (C-D). The volume of the ventricle in this phase decreases from the EDV to the ESV due to filling the aorta with blood, and the pressure in the ventricle increases to the maximum (120-130 mm Hg), and then gradually decreases to the level of pressure in the aorta. Once these pressures are equal (point D), the aortic valve closes and the period of isovolumetric relaxation begins, during which the pressure in the ventricle is decreasing to almost zero.

The volume-pressure curve can be used to quantify the energy consumption of the ventriclular myocardium during systole. Energy consumption consists of the work spent on ejecting blood from the ventricles, the kinetic energy of the ejected blood and energy costs spending on generating of the myocardium tension during isovolumetric contraction phase. The work of blood ejection can be estimated by the area of the figure, bordered by the pressure-volume curve. The kinetic energy of the ejected blood can be estimated by the mass of blood systolic volume (SV) and its linear acceleration ($mv^2/2$) where m is the mass of SV, and v is its linear speed). The sum of blood ejection work and blood kinetic energy is called ***the external work of the ventricles***. Since kinetic energy is only 1-2% of all external work, it can be ignored. From this it follows that almost total external work consists of energy consumed for blood ejection. Exact data of the actual blood pressure in the ventricles and their size can only be

obtained by invasive catheterization of the heart chambers and echocardiography or X-ray examination of the heart. However, for practical purposes, for the quantification of ventricular function, the simplified formula ***A = SV x MAP*** can be used, where ***A*** is an external work, ***SV*** is systolic volume, and ***MAP*** is mean arterial pressure. Calculations for the left ventricle show that its external work is about 1 J (Joule), and for the right one - about 0.2 J (due to approximately 5-6 times less MAP in the pulmonary circuit compared with the large one). However, the total energy consumption of the myocardium per systole is much larger, since most of the energy is spent on the generation of ventricular wall tension during the period of isovolumetric contraction. This part of the energy consumption is directly proportional to the tension in the ventricular wall ***(T)*** and the duration of the isovolumetric contraction ***(Δt)***. The total energy consumption of the myocardium during systole ***(W)*** is described by the equation:

$$\underbrace{W}_{\text{Total energy consumption of the myocardium}} = \underbrace{P \cdot V}_{\text{Work spent on blood ejection}} + \underbrace{\tfrac{1}{2} m v^2}_{\text{Kinetic energy}} + \underbrace{k \cdot T \cdot \Delta t}_{\text{Energy spent on the generation of myocardial tension}}$$

$$\underbrace{\qquad\qquad}_{\text{External work}}$$

The analysis of this equation shows that energy in the myocardium is spent most economically if the required systolic blood volume (V) is achieved at low values of intraventricular pressure (P), ventricular tension (T), and the high speed of the pressure increasing in the ventricle during the period of isovolumic contraction (it means that, Δt is as short as possible). In pathological conditions (heart valves defects, ventricular hypertrophy, cardiosclerosis, etc.), the energy expenditure increases several times, and coronary reserves do not provide an adequate increase in blood supply to the myocardium, which results in the myocardial ischemic states (angina pectoris, myocardial infarction). It occurs especially often by physical and psycho-emotional stress.

4.3. Basic physiological parameters of the heart pumping function.

The pump function of the heart can be quantified by the volume of blood that is pushed out by the right or left ventricle (normally, these volumes coincide) for one contraction. This volume is called ***systolic (stroke) volume (SV)***. SV value has sex differences. In men, this index in a rest state of t is 60-80 ml, in women, 50-70 ml. Invasive and non-invasive methods are used to measure SV. Invasive methods require intervention into the patient's internal environment (catheterization, blood test substances, etc.) and are sufficiently precise. The non-invasive methods are based on the recording of the physiological manifestations of cardiac activity from the surface of the

body and are less accurate. Among invasive methods, the direct Fick's method, the method of indicators dilution, the thermodilution method and electromagnetic flowmetry are used most often. The most common non-invasive methods include *thoracic tetrapolar rheography* and *echocardiography*. The advantage of the latter method is that it gives not only *SV*, but also such indexes as *EDV* (norm 130-140 ml), *ESV* (norm 60-70 ml) and allows to calculate the *ejection fraction (EF)* by formula: *EF = (EDV-ESV) * 100 / EDV* (norm 50-75%), which is considered as one of the indicators of myocardial contractility. A detailed description of these methods goes beyond the scope of this textbook and can be found in the special literature.

Taking into account that *the heart rate (HR)* in the rest state in healthy people is 60-80 beats / min, it is possible to calculate *the cardiac output (CO)* using the formula: *CO = HR × SV.* The norm for this parameter is 4.0-5.0 l / min for women and 4.5-5.5 l / min for men. However, for people with non-typical anthropometric parameters, these norms may be incorrect. For example, for a woman weighing 50 kg and a height of 155 cm, the normal value of CO is 3 l/min, and for a man weighing 120 kg and a height of 190 cm it will be 7 l/min. Therefore, the *cardiac index (CI)*, which is a hemodynamic parameter that relates the cardiac output (CO) *to the body surface area (BSA)* is more correct to use. It is calculated using the formula *CI = CO / BSA*, where BSA is the area of the body surface expressed in m^2, which is determined by special nomograms or formulas. The CI norm is 2.5-3.0 l/min/m^2.

The heart pumping function can be significantly increased if a person is in a state of physical or psycho-emotional stress. Thus, in the trained athletes, SV at maximum physical activity can reach 150 ml, and CO - 25-30 l/min. One of the endocrine glands can significantly change the pumping heart function by its pathology. This is the thyroid gland. By hyperfunction of this gland, cardiac pumping productivity is significantly elevated, and by hypofunction it is reduced.

4.4. Heart sounds and their diagnostic value.

Work of the heart is accompanied by sound phenomena, which are caused, first of all, by the functioning of the valve apparatus. These phenomena are called *heart sounds*. They can be heard from the surface of the chest using a special acoustic device - the stethoscope or graphically recorded by an electronic device - a phonocardiograph equipped with a piezoelectric microphone (special electrical microphone.) In the first case, the method of heart diagnostics is called *auscultation*, and in the second case it is called *phonocardiography.* Both methods require a stethoscope or a microphone to be placed on the chest in a fixed location for the best hearing of the heart sounds. These location do not coincide with the

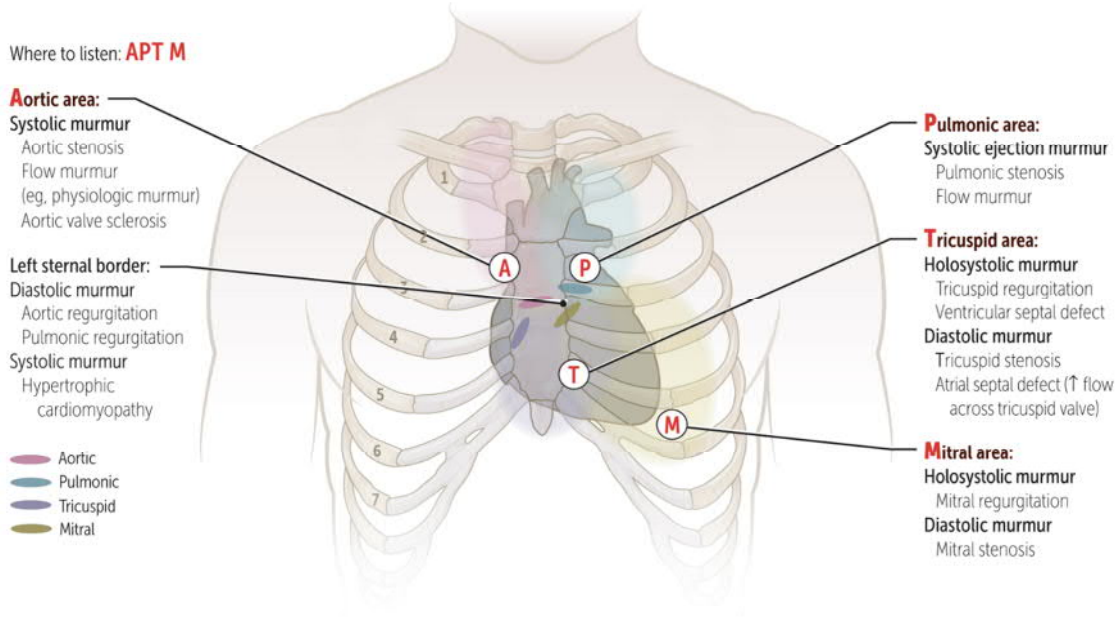

Fig.7.18. The typical places for auscultation and projections of the heart valves on the chest wall.

anatomical projection of the valves (Figure 7.18). The advantage of the phonocardiography is that it records even low-frequency sound phenomena (tones and murmurs) that the human ear does not perceive due to the lack of sensitivity of the auditory analyzer in the low-frequency range. In addition, these phenomena can be documented and used to assess the dynamics of cardiac function in the patient during treatment. Four basic heart sounds can be seen on the phonocardiogram of healthy people (Fig.7.19.):

The first heart sound (S_1) is producing at the beginning of the systole of the ventricles due to a hemodynamic stroke of the blood on closed leaflets of the atrioventricular valves. Its generation involves the valve structure, the walls of the ventricles and the walls of the aorta and pulmonary artery bases during the isovolumetric period and early ejection period of the ventricles.systole. The duration of this sound is about 0.1 seconds. Its absolute amplitude (expressed in mV) does not have a diagnostic value, since it depends in a great extent on the sound conducting features of the anterior chest wall. For example, in people with powerful thoracic muscles, the amplitude of heart tones is usually low compared with thin people, despite the powerful heart contraction. The diagnostic value has only the relative amplitude of the 1st sound in comparison with the 2nd sound. For example, at the top of the heart (the place of the best hearing of a mitral valve), the amplitude of the 1st sound should exceed the amplitude of the 2nd sound, and in the second intercostal space on the right edge of the sternum (the place of the best hearing of the aortic valve) the amplitude of the 2nd sound should be greater than amplitude of the 1st. In the case of

the opposite relationship between the amplitude of these tones, they are considered as weakened.

The second heart sound (S_2) starts at the beginning of diastole and is caused by the hemodynamic stroke of the blood returning from aorta and the pulmonary artery into the ventricles on the closed leaflets of semilunar valves. The walls of the aorta and pulmonary artery also participate in its generation in addition to the valves. Its duration in healthy people is about 0.08 sec.

The third heart sound (S_3) starts at the beginning of the period of ventricular filling and is caused by the opening of atrioventricular valves and the rapid filling of the ventricles with blood. At the same time, the walls of the ventricles create low-frequency vibrations, which are recorded as a heart sound. In most healthy people it can't be heard. However, in patients with myocardiosclerosis, the ventricular walls generate an enhanced 3rd sound that can be heard by the stethoscope or recorded by phonocardiograph. The produced sound in this case has a special pattern called the "rhythm of the gallop."

The 4th heart sound (S_4) is the smallest by an amplitude sound among all heart sounds. It is generated by the atrial myocardium during atrial systole. Registration of S_4 is a fairly rare phenomenon and has no diagnostic value.

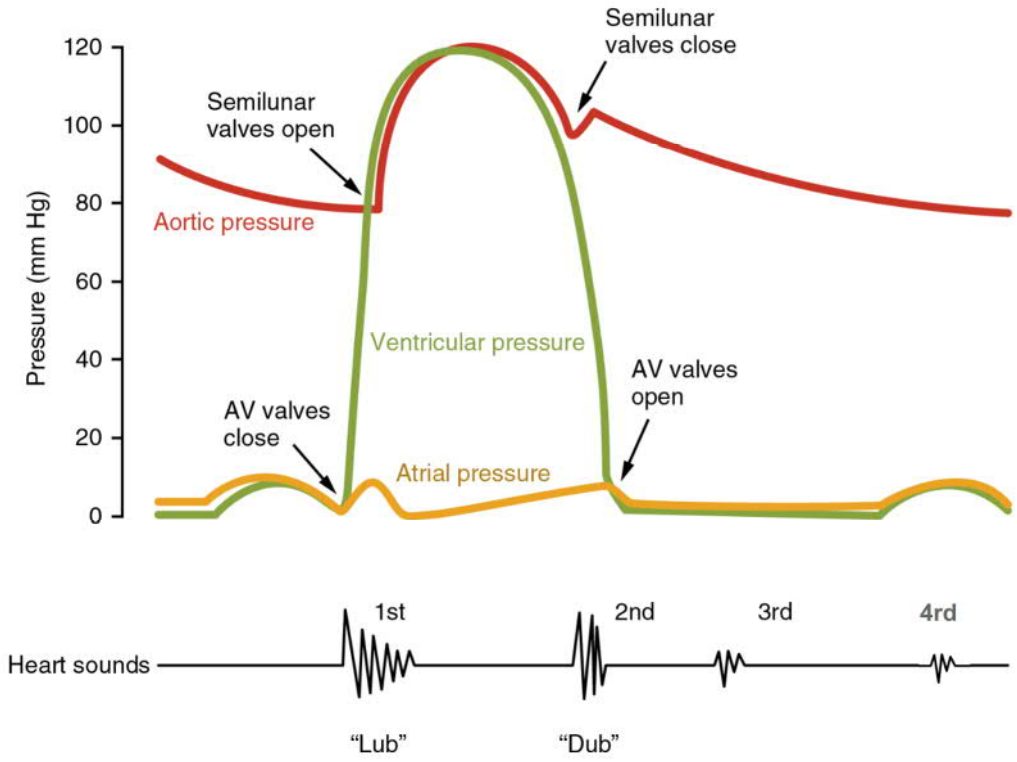

Fig.7.19. Mechanism of the heart sounds generation .
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In clinical practice, aus cultation and phonocardiography are used as objective methods for diagnostics of valve defects (heart defects). If a patient has such defect an additional noise can be recorded: low-frequency vibrations generated by turbulent blood flow through narrowed holes in the valves. There are 2 main types of valve defects: ***the valve insufficiency***, when a blood regurgitation occurs due to its incomplete closure (it is a flow in the opposite to the normal direction) and ***the valve stenosis*** when opening of the valve leaflets is incomplete, and the blood flow passes in the desired direction through a narrowed hole, creating the cardiac murmurs. Depending on time of the occurrence during the heart cycle, the murmurs are classified into ***systolic murmurs*** - they are producing during the systole or part of it, and the ***diastolic murmurs*** are produced during diastole or its part. Simple heart defects are usually manifested by one type of murmur, but complex defects (involving the pathological process in several valves) can produce both systolic and diastolic murmurs. The most common heart murmurs caused by heart defects are schematically illustrated in the Fig. 7.20.

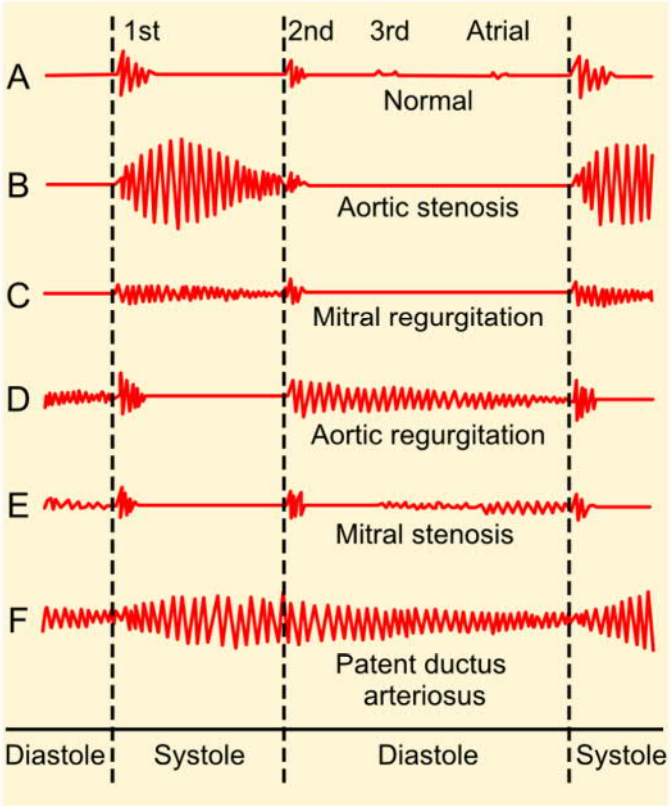

Fig.7.20. Phonocardiograms with normal and abnormal heart sounds.

4.5 Control of the heart pumping function.

Depending on the metabolic needs of the body, the heart pumping function provides a cardiac output varying in wide range. For example, the CO can be rising from 5 l/min (in rest) to 25-30 l/min during heavy physical activity. Such increase is achieved by changing the heart rate (HR) and the stroke volume (SV), which form the CO. Let's consider which control mechanisms can affect this parameters.

Heart rate control.

Sympathetic and parasympathetic part of the ANS are the main factors in the controlling of the heart rate. The heart receives sympathetic innervation from postganglionic neurons of the thoracic ganglia and parasympathetic one - from the branches of the vagus nerve. Sympathetic fibers create the synapses on atypical and contractile myocardial fibers, and the vagus nerve branches - m ainly on the cells of the heart conducting system in the SA and AV node. The sympathetic system realizes its influence through a neurotransmitter ***norepinephrine***, which binds to β_1 adrenergic receptors of the sarcolemma. The parasympathetic system works through a neurotransmitter ***acetylcholine*** that has affinity to M-cholinergic receptors. The effects of sympathetic and parasympathetic stimulation are opposite. If sympathetic stimulation increases the heart rate and the speed of the APs conduction, then parasympathetic system reduces heart rate and speed of the AP's propagation. These effects are realized by changing the duration of the phase of spontaneous diastolic depolarization in pacemakers (Fig.7.21). It is established that the permeability of funny channels for sodium ions increases due to excitation of β_1-adrenergic

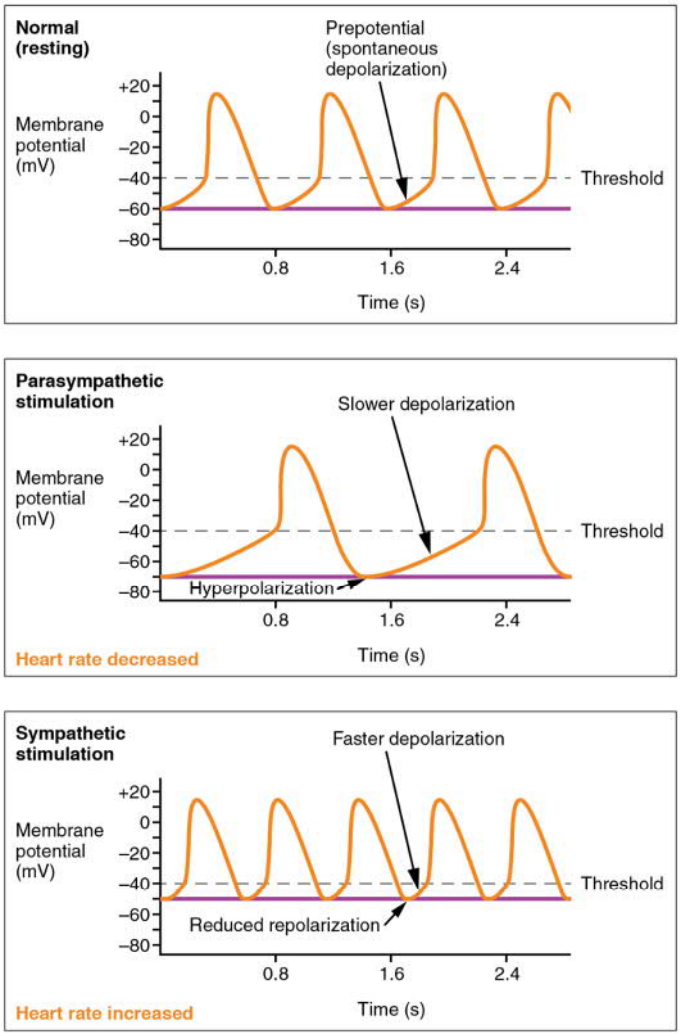

Fig.7.21. Mechanism of the autonomic nervous influences on heart rate.

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receptors, rising the steepness of the spontaneous diastolic depolarization phase, what makes the AP shorter. The opposite effects are observed when acetylcholine binds to the M-cholinoreceptors. In addition, parasympathetic stimulation enhances the hyperpolarization of the cell membrane of the pacemakers, and it takes more time to reach the critical level of depolarization. The influence of the sympathetic system on the cardiac rhythm is indicated by the terms ***positive chronotropic effect***(effect on heart rate), ***positive bathmotropic effect*** (effect on excitability) and ***positive dromotropic effect*** (influence on conductivity). Accordingly, the parasympathetic system produces the ***negative chronotropic, batmotropic and dromotropic effects***.

In the absence of any regulatory influences, the SA node generates rhythmic excitations with a frequency of about 100 AP/min. However, as you know, heart rate in a rest state is in the range of 60-80 beats/min. This means that the main pacemaker in the body is under the dominant control of the parasympathetic system. However, the sympathetic control is enhanced during stress. Activation of the sympathetic system involvs in the heart rate regulation also catecholamines secretion by adrenal medulla, which are a humoral part of a stress reaction. An increase in heart rate can be observed due to increased secretion of such hormones as thyroid hormones, glucocorticoids, and angiotensin-2, which have a reactogenic effect regarding to catecholamines.

Stroke volume control.

The SV is affected by three main factors: 1) changes in EDV, denoted by the term ***preload***; 2) the influence of ANS and hormones on ***myocardial contractility***; 3) changes in diastolic blood pressure against which ventricular ejection is occurred, which is commonly referred to as ***afterload.***

1). Dependence of SV on the EDV is known in physiology, as ***the law of Frank-Starling.*** According to this law, the more the ventricle is stretched with blood during diastole, the stronger will be the followed contraction in the systole, thus, the greater will be the SV. Graphically, this dependence is illustrated in Fig. 7.22. The degree of ventricle stretching in diastole is measured by EDV. As can be seen from the graph, the rising of SV is stopped if values of EDV are too high. Frank-Starling's law is executed even on an isolated heart (in an experiment), deprived of nervous and humoral regulatory

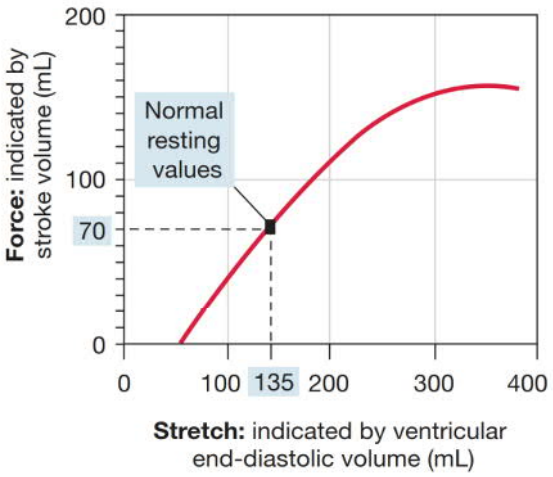

Fig.7.22. Length-force relationships in the intact heart: a Starling curve.
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influences. Therefore, it is believed that it is a manifestation of ***myogeneic auto-regulation*** of the heart. This autoregulation is called ***heterometric*** (associated with changes in the size of the heart).

The ultrastructural basis of the Frank-Starling mechanism is the mutual placement of actin and myosin fibers in the sarcomere before contraction. Thus, with the stretching of the sarcomere, the actin and myosin fibers are approaching, what increases the number of cross-bridges involved in the contraction, which, in turn, results in increasing the contraction force of the whole muscle. But excessive stretching of the myocardium may cause some part of the actin and myosin fibers not being overlapped and the force of contraction decreases. This situation is observed if EDV value is > 200 ml.

In the intact organism, the EDV depends mainly on the value of the venous blood return to the heart. In turn, the venous return depends on the activity of the skeletal muscles, the functioning of the Henderson respiratory pump, which will be analyzed in detail later, and the duration of the ventricular filling, which is inversely proportional to heart rate. For example, the venous blood return to the heart and SV in accordance with the Franck-Starling law are increased by rhythmic contraction of skeletal muscles, deep diaphragmic breathing and low heart rate.

Due to Frank-Starling's law, ventricles are able to adapt to sudden changes in hemodynamics in humans even after transplanting a heart when other regulatory mechanisms do not work.

2). Myocardial contractility is the sum of all forces generated by muscle fibers at a certain level of preload. Under normal conditions, ANS and some hormones can affect the contractility. Under special conditions (during a pathology, or pharmacological correction) contractility can be controlled by changes in the concentration of some ions in the intercellular fluid, or by the influence of drugs. All factors that increase myocardial contractility are considered as ***positive inotropic agents***, and those that suppress the contractility are considered as ***negative inotropic agents***. Positive inotropic effect is achieved, as a rule, by stimulating the entry of Ca^{+2} ions into the cardiomyocytes or by their accumulation within cells. Negative inotropic effect, on the contrary, is achieved by blocking the transport of Ca^{+2} ions into the cells or by inhibition of metabolism in them.

Positive inotropic agents include:

- sympathetic stimulation of the myocardium through β_1-adrenergic receptors;
- the effect of catecholamines (adrenaline and, to a lesser extent, norepinephrine) realized through these same receptors;
- the effect of iodinated thyroid hormones and glucocorticoids due to reactogenic action in relation to catecholamines;
- hormone glucagon, which directly activates the adenylate cyclase system (cAMP);

• synthetic agonists of catecholamines (isoproterenol, dobutamine):
• elevated concentrations of Ca^{+2} in the blood;
• digitalis drugs that inactivate Na^{+}-Ca^{+2} exchanger in the cardiomyocytes and delay these ions in the sarcoplasm.

The common feature of all positive inotropic agents is that they reduce ESV, thereby increasing SV.

Negative inotropic agents include:

• the effect of the vagus nerve realizing through the M-cholinoreceptors (more applies to the atrium than the ventricles);
• action of β-blockers - synthetic drugs that prevent the binding of norepinephrine and hormones to β_1-adrenoceptors (propranolol, metoprolol, atenolol);
• Ca-channel blockers (verapamil, bisoprolol);
• atrial natriuretic peptide (ANP) and bain natriuretic hormone (BNP).

All these factors increase ESV, while the EDV remains unchanged, what causes SV to decrease.

3). Afterload is the value of tension that ventricular myocardium should develop to provide the opening of the semilunar valve and begin to pull the blood into the aorta and pulmonary artery. Since the diastolic pressure creates the force counteracting the ventricular systolic pressure generated by ventricular contraction, its value can be considered as a quantitative characteristic of afterload. The greater the afterload, the longer is the isovolumetric contraction period, the shorter the period of ventricular ejection and the greater the ESV. As a result, SV decreases. The opposite statement is also true: with decreasing afterload (diastolic pressure) SV is increasing. Often, the cause of increased afterload is peripheral circulation

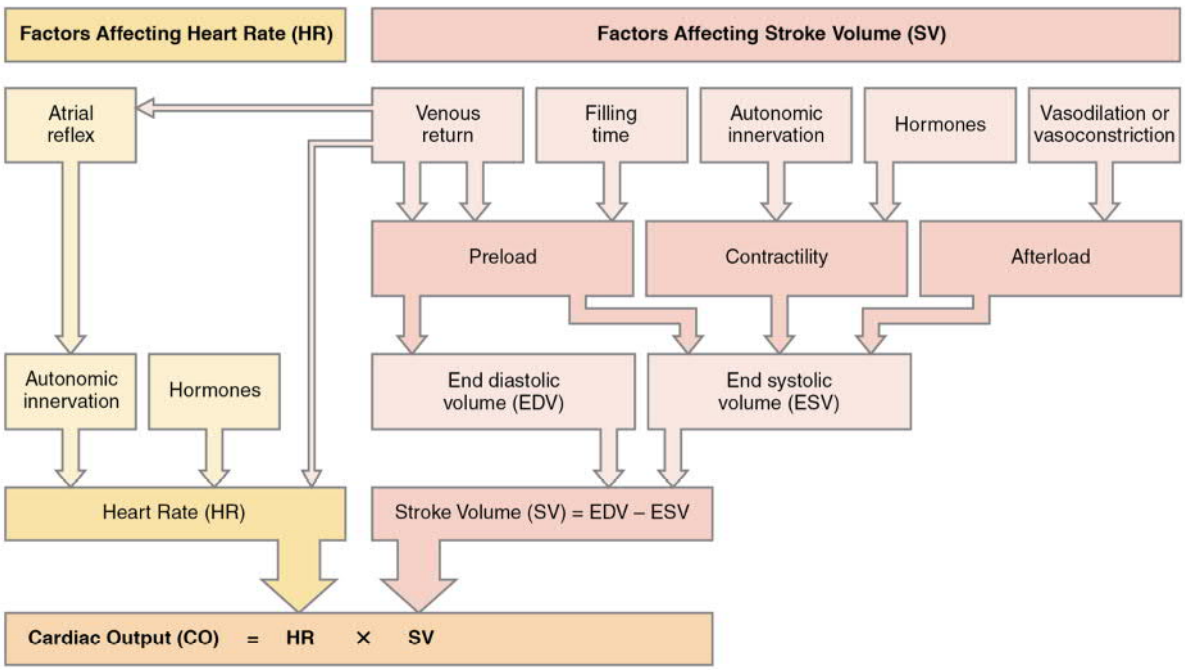

Fig.7.23. Summary of factors controlling cardiac output.

disorders (for example, vasoconstriction of the lower limb vessels, atherosclerosis of all vessels, increase of the tone of the sympathetic part of the ANS, etc.).

The diagram on Fig.7.23. summarizes all the mechanisms controlling CO in a healthy people. It is worthy to pay attention to the interdependence of all regulatory mechanisms. Thus, the sympathetic system stimulates not only the heart rate, but also increases the myocardium contractility and also contributes to an increase in venous blood return to the heart by stimulating the vasoconstriction of the veins. And this, in turn, activates the Frank-Starling mechanism, which enhances the ejection of blood during the ventricular systole.

4.6. Autonomic cardiac reflexes.

The influence of the ANS on the heart function is realized by autonomic cardiac reflexes. The heart receives both parasympathetic innervation (n.vagus) and sympathetic innervation from truncus sympaticus. The main centers responsible for the autonomic cardiac reflexes are the nuclei of the dorso-lateral and ventro-medial regions of the fourth ventricle and the posterior-lateral regio ns of the medulla oblongata. Some cardiac centers are contained also in the hypothalamus, the middle brain and the limbic system. However, it is not possible to clearly locate the heart centers in the central nervous system. Previously, it was believed that the influence of other nerve centers on the function of the heart is mediated by the medulla oblongata center, but nowadays the direct connections of the hypothalamus with the sympathetic neurons of the lateral horns of the spinal cord are described.

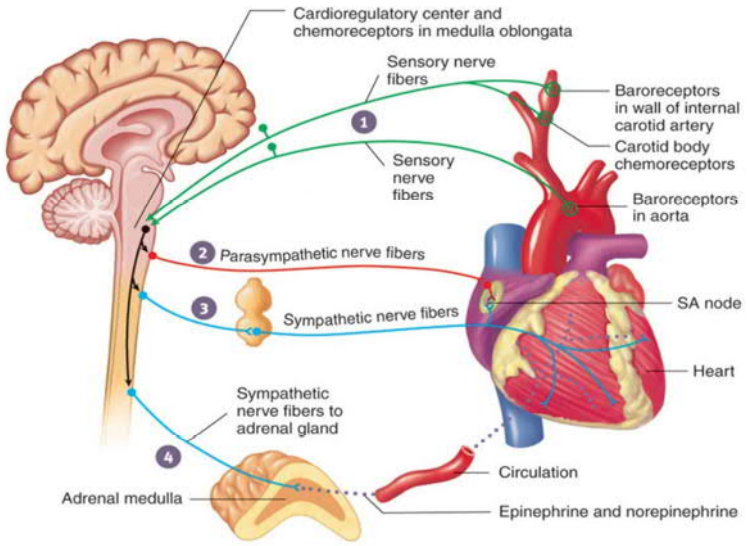

Fig.7.24. Autonomic control of the heart function.
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Reflexogenic zones, from which ***extracardiac reflexes*** originate, are baroreceptors of the coronary vessels, aortic arch, carotid arteries branching, vena cava, mechanoreceptors of the epicardium and chemoreceptors of the carotid sinus. The most important among them are

two populations of mechanoreceptors, which are located in the atria and left ventricle. These are: mechanoreceptors of type A reacting on changes in the tension of the cardiac wall and mechanoreceptors of type B, reacting on passive stretching of the myocardium.

An example of extracardiac reflexes is *Bainbridge's reflex*, manifesting itself by the increased ventricular contractions when the right atrium is stretching by large portions of blood entering from the vena cava inferior. In this case, mechanoreceptors of the walls of the cava activate the sympathetic nerve centers of the thoracic region of spinal cord and cause a positive chronotropic and inotropic effect.

Another example is *the Golz's reflex* - which manifests itself as a temporary stopping of cardiac activity when a patient was hit in the stomach near the solar plexus projection. This reflex is realized by the afferent part of the abdominal nerve, conducting this excitation to the nuclei of the vagus nerve, which inhibits cardiac activity. A similar mechanism has *the Danini-Ashner's reflex* reducing the heart rate when you press on the eyeballs.

The chemoreceptor reflexes from the carotid sinus and the aorta arch are a special group of extracardiac reflexes, which are caused by changes in the oxygen tension of the arterial blood. Hypoxemia causes a reflectory tachycardia, and hyperoxemia (when a person breathes with pure oxygen), results in bradycardia. These reactions have extremely high sensitivity. An increase in heart rate occurs even if the blood oxygen level is reduced by only 3%, when there are no signs of hypoxia in the tissues.

Reflectory inhibiting of the heart activity can occur during a rapid cooling of the abdominal skin. This is the reason for accidents due to rapid immersion in cold water. For example, frequent drowning during bathing in the Synevyr Lake (Ukraine).

Acquired conditioned reflexes involving the cerebral cortex may also affect cardiac activity. An example is prelaunch tachycardia in athletes or tachycardia in students during examination.

4.7. Features of the metabolism in the myocardium.

The heart receives energy, required to perform mechanical work, mainly from oxidative processes in mitochondria. From this point of view, the myocardium fundamentally differs from skeletal muscle, which can obtain the energy due to anaerobic processes during intense short-term contractions. In a rest state a heart weighing 300 g consumes 30-40 ml of oxygen per minute, which is approximately 10% of the total oxygen consumed by the body. At the same time, the weight of the heart is only 0.5% of the body weight. During intensive work, the oxygen consumption by myocardium can increase by 4 times. With the same mechanical work of the heart, its need for oxygen is greater if it ejects blood against greater pressure than when it ejects a large volume at low pressure. Thus, the cardiac energy

using efficiency (that is, the ratio of energy expended for performing mechanical work) is greater when it loaded by volume than by pressure. The efficiency varies from 15 to 40% depending from heart preload and afterload. The main energy substrate for the myocardium is free fatty acids, glucose and lactic acid. The heart is also able to include in its metabolism underoxified intermediate substances from other organs, including skeletal muscles. Therefore, the main danger to the heart in violation of its blood supply is not the lack of energy substrate, but the lack of oxygen. Unlike other organs, the heart extracts from the blood up to 70% of the total oxygen (other organs, up to 35%), and does not have a significant oxygen reserve without increasing coronary blood flow.

One more special feature of energy metabolism in the myocardium is the presence in it, along with ATP, the *creatinephosphate*, which participates in the resynthesis of ATP from ADP.

5. Vascular physiology

5.1. General description of the vascular system functions.

Both large and small circle of blood circulation are constructed from

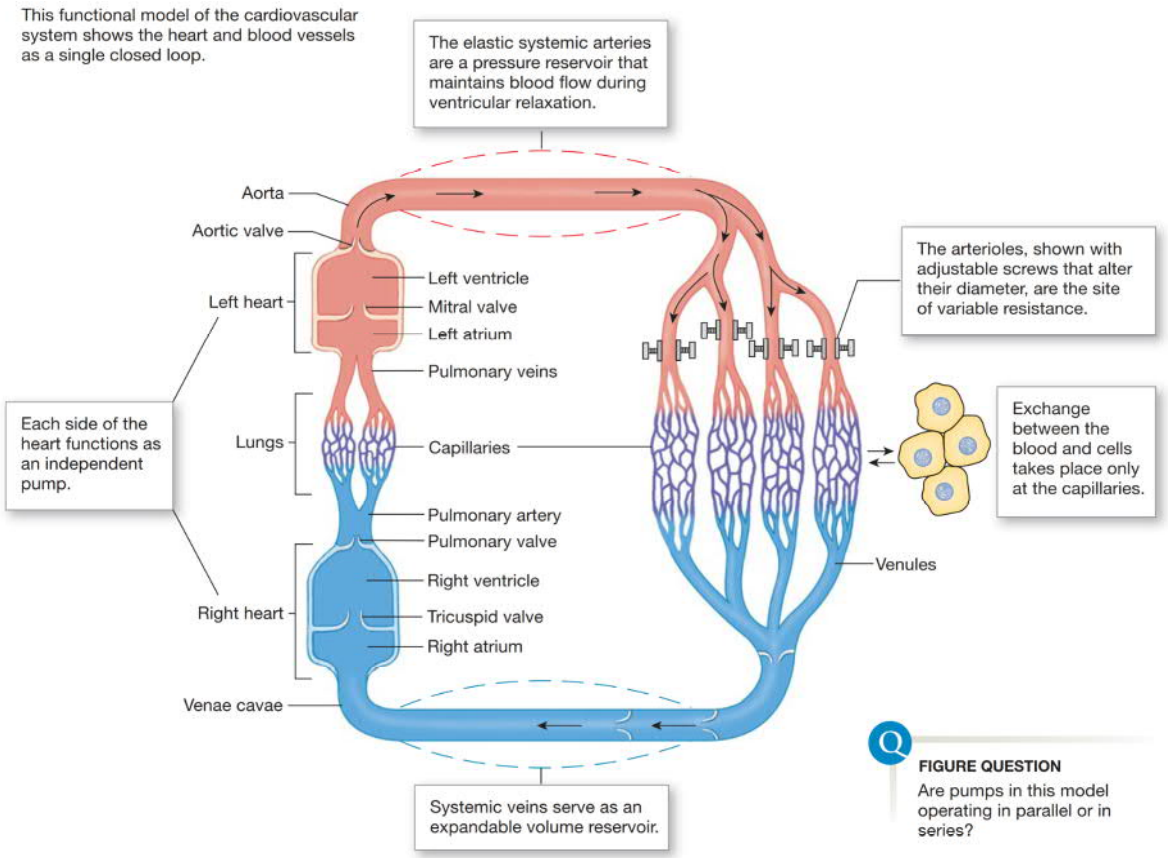

Fig.7.25. Functional model of the cardiovascular system.

sequentially connected blood vessels, which are divided into types depending on their morphological and functional features (Fig. 7.25):

Arteries are vessels that transport blood from the heart under high pressure. They have a powerful wall, which, unlike other vessels, includes elastic fibers, and the blood moves inside them with high speed.

Arterioles are the last part of the arterial system consisting of the smallest arterial branches. They have a powerful muscular wall and serve as a kind of "tap" for the microcirculatory bloodstream. Depending on the metabolic needs of the tissues, these taps can be opened (vasodilation), increasing the blood flow in the capillary networks several times, or closed (vasoconstriction), limiting local blood flow.

Capillaries are the smallest vessels that form the capillary network in the organs. The capillary walls contain “windows,” or pores, that penetrate the endothelial lining. Capillaries are permeable for water and low molecular weight dissolved substances due to these pores. Their main function is to provide gas and metabolite exchange between blood and tissues.

Venules are small caliber vessels that collect blood from a capillary network and transport it to the next chain of the vascular system.

Veins are the last part of the vascular system, represented by thin-walled vessels that transport blood to the heart. They serve as a blood reservoir that can accumulate blood (if necessary) and return it to the systemic circulation. This is possible due to a thin layer of smooth muscles,

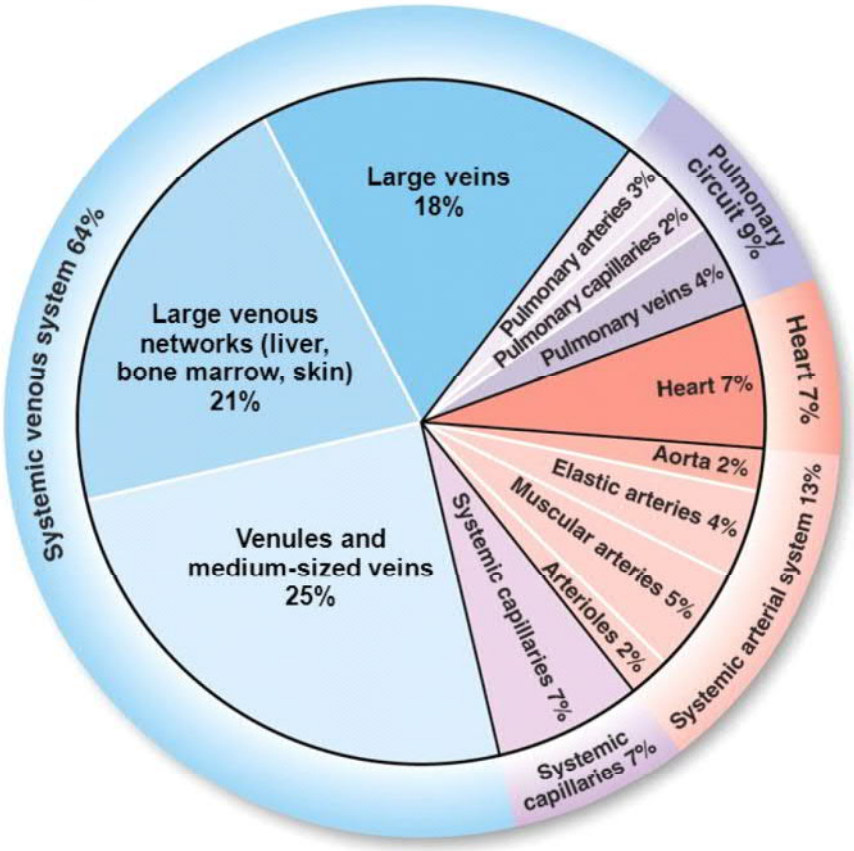

Fig.7.26. Distribution of circulating blood volume in the cardiovascular system.

controlled by the sympathetic part of the ANS.

Distribution of circulating blood volume (CBV).

Approximately 84% of CBV is in the systemic arterial system (without considering the heart): 64% of this value is in the veins and venules, 13% in the arteries, and 7% in the capillaries. 9% of the CBV is contained in the pulmonary circuit, and 7% of the CBV is inside the heart. These numbers relate to an average adult in a rest state. (Fig.7.26).

Hemodynamic parameters of blood flow in different parts of the vascular system.

As you can see on the Fig.7.27 the vessel diameter and the total cross-sectional area in the systemic circulation are in reverse relationship. It means that the smaller are vessels by diameter the greater is their total cross-sectional area. For example, the total cross-sectional area at the level of small veins is 4 times greater than the similar value for small arteries, and at the venules level it is 6.25 times higher than at the arterioles level. Taking into account that the same blood volume per time unit (cardiac output) flows at any level of the cross-section area of the vessels, it can be concluded that the linear velocity of blood in them is inversely proportional to the area of this section. Thus, in a rest state, the linear velocity of blood in the aorta is 0.3-0.5 m/s, and in capillaries it is 1000 times smaller (about 0.3-0.5

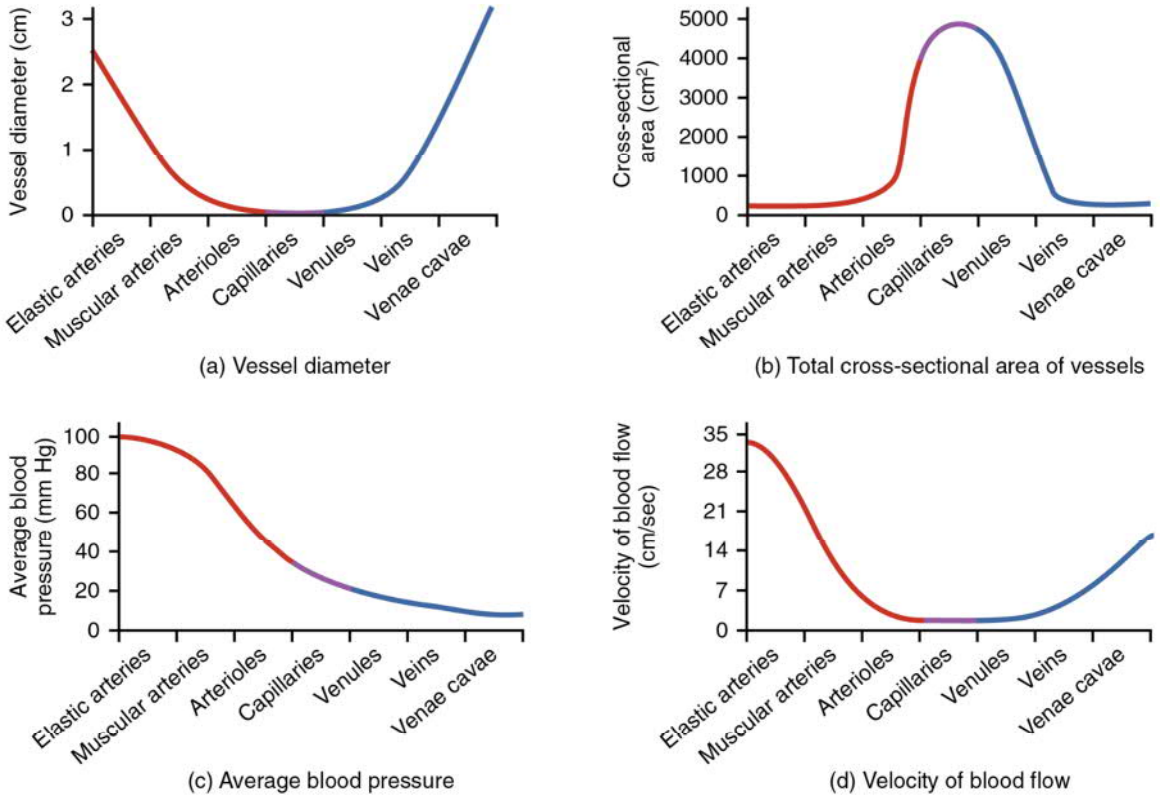

Fig.7.27. Hemodynamic parameters of the vessels in systemic circulation.
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mm/s). Since the average length of the capillary ranges from 0.3 to 1 mm, the blood flows through the capillary for 1-3 seconds. During this time, a complete diffusion of metabolites and gases between blood and extracellular space occur as well as transcapillary exchange of fluids.

In the systemic circulation, due to the alternation of contraction and relaxation of the left ventricle, the pressure in the aorta has a pulsating character, ranging from about 80 mmHg of the diastolic pressure (DP) to about 120 mmHg of the systolic pressure (SP). As the blood goes to the right atrium, the pressure in the vascular system decreases to almost zero level (in the vena cava). The pressure in the capillaries of a systemic circulation varies from 35 mmHg at the arterial end to 10 mmHg at the venous end, with the exception of the capillaries of the glomeruli in the kidneys. At the same time there are almost no pulse fluctuations of blood flow in the capillaries and they are minimally expressed in arterioles (Fig.7.28).

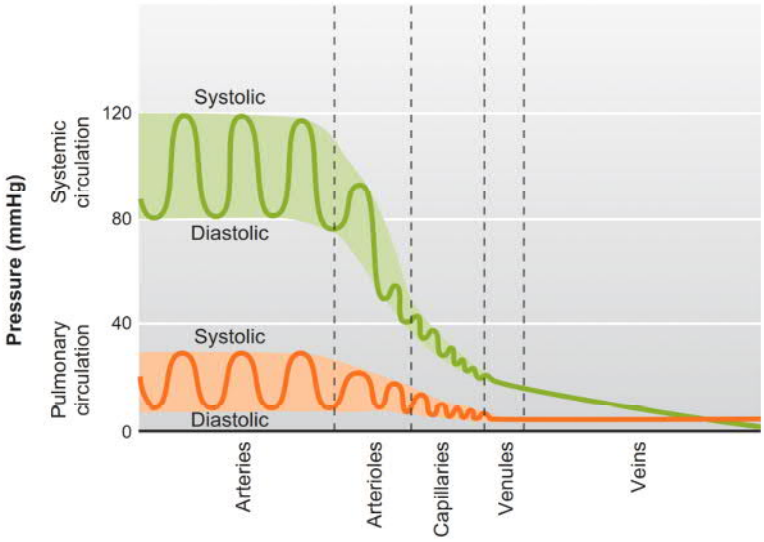

Fig.7.28. Pressures in the systemic and pulmonary vessels.

The highest values of the blood pressure in the pulmonary artery are 5-6 time lower than in aorta (SP = 25 mmHg, DP = 10 mmHg). The mean blood pressure in the pulmonary capillaries is only 7 mmHg, which almost eliminates the fluid filtration in the alveoli of lungs.

There are three main principles of blood circulation in the vascular system (A.Guyton, 2010):

1.The rate of blood flow to each body tissue is usually precisely controlled in relation to the tissue needs.

When tissues are active, they require a significantly increased supply of nutrients and therefore much more blood flow than when at rest, occasionally reaching as much as 20 to 30 times resting level. However the heart at maximum can increase its cardiac output only 5-6 times. Therefore, there are mechanisms that control local blood flow precisely to the level required for tissue activity. Obviously, the state of metabolism (the degree of hypoxia, hypercapnia, intermediate metabolites) affects the tone of the blood vessels dilating or constricting them. In addition, the

nervous and endocrine control of the circulation provide additional help in regulating the tissue's blood flow.

2. The cardiac output is controlled by the sum of all local tissue blood flows.

The blood that flows back to the heart from tissues forms venous return. The heart responds automatically by pumping blood immediately into the pulmonary circuit and returning it to the systemic circuit due to the Frank-Starling law. If the efficiency of this mechanism is insufficient, the central nervous system and the endocrine system help in the regulation of the cardiac output.

3. Arterial pressure is controlled independently of either local blood flow control or cardiac output control.

The cardiovascular system is provided with an extensive system for controlling arterial blood pressure. These include baroreceptors of the aorta arc, carotid sinus, vascular mechanoreceptors. Monitoring of systemic blood pressure immediately involves the mechanisms of its normalization if deviation from optimal values occurs, especially in the case of hypotension. For example, if at any time the pressure falls significantly below the normal level of about 60 mmHg, baroreceptor reflexes increase the pumping heart function, cause the generalized constriction of the most arterioles throughout the body and veins resulting in contraction of the large venous reservoirs to return more blood to the heart. Then the endocrine mechanism is activated (RAAS) and the excretion function of the kidneys is changed what results in fluid retention in the body.

In the following sections of the textbook, these principles will be used to explain the mechanisms of regulation of systemic and regional hemodynamics in different situations.

5.2 Basic laws of hemodynamics and their physiological interpretation.

Ohm's law. The principles of blood circulation in vessels called hemodynamics lows are based on the laws of hydrodynamics. According to these laws, the most significant factors determining fluid flow through the pipe are: the pressure gradient between the beginning and the end of the pipe and the hydrodynamic resistance of the pipe. The Ohm's law describes relationship between these parameters in such a way:

the volume of fluid flowing through a pipe per time unit is directly proportional to the pressure gradient and is inversely proportional to its hydrod ynamic resistance, what can be expressed by the formula:

$$F = \frac{P_1 - P_2}{R}$$

where F is volume of fluid per time unit; P_1 is pressure at the beginning of the pipe; P_2 is pressure at the end of the pipe; R is the hydrodynamic resistance.

The volume of blood flowing through each section of the vascular bed per time unit is the same due to the continuity of blood flow through the cardiovascular system,. This means that the same volume of blood, equal to the cardiac output (CO) flows, for example, through the aorta, through the pulmonary artery, or through the total cross-section of the capillaries for 1 min. If we replace the CO instead F, the mean arterial pressure in the aorta (MAP) instead P_1, the mean venous pressure in the vena cava (MVP) instead P_2 and the total peripheral resistance of the entire vascular bed (TPR) instead R, then we get a special version of the Ohm's law, relating to the systemic circulation (the big hemodynamics circle):

$$CO = \frac{MAP - MVP}{TPR}$$

Taking into account, that MVP value is close to 0, this equation can be represented in changed view:

$$CO = \frac{MAP}{TPR}$$

We can use the last equation in order to calculate TPR. In order to express the blood pressure value in dyn/cm^2 instead mm of Hg, it has to be multiplied by special coefficient equal 80: It must be done because mm Hg is a non-system unit of pressure measurement while all other indicators of this equation are measured in the CGS measurement system (centimeter-gram-second)

$$TRP = \frac{MAP \times 80}{CO}$$

MAP can be calculated using Hickam's formula:

$$MAP = DBP + \frac{SBP - DBP}{3}$$

where DBP is diastolic blood pressure, SBP is systolic blood pressure, expressed in mm of Hg.

Substituting in these equations the real values of SBP = 120 mm Hg, DBP=80 mm Hg and CO = 5 l/min, we obtain the value of TPR = 1488 dyn × sec × cm^{-5}. The average value of this index in systemic circulation is 700-1600 dyn×sec × cm^{-5}. In the pulmonary circulation, the TPR is approximately 100-300 dyn×sec×cm^{-5}. Different divisions of the vascular system make an

unequal contribution to the TPR. Thus, the aorta and large arterial trunks create for about 19% of the TPR, the terminal arteries and arterioles - 50%, the capillaries - about 25%, the venules - 4%, and the large veins - 3%. It means that the terminal arteries and arterioles are the main point for applying of the regulatory influences to significantly change the TPR.

Poiseuille's Law. Hydrodynamic resistance of single vessel (R) directly proportional depends on the length of the vessel (λ), blood viscosity (η) and inversely proportional from vessel radius (r) to the forth power. This dependence describes the Poiseuille's formula:

$$R = \frac{8\eta\lambda}{\pi r^4}$$

Analysis of this formula shows that vessel radius is the most important factor affecting the hydrodynamic resistance. For example, if it is decreasing by 3 times, then hydrodynamic resistance increases by 81 times (3^4=81).

If in formula describing Ohm's law we substitute R by its expression taken from the Poiseuille's formula, it can be modified as follows:

$$F = \frac{(P_1 - P_2) \times \pi r^4}{8\eta\lambda}$$

It means that volume of blood flowing through simple vessel per time unit (blood volume velocity) is directly proportional to the fourth power of the vessels radius. Therefore, both the volume of blood flowing through the vessel per time unit and the hydrodynamic resistance of this vessel depend mainly on changes in vascular lumen, and to a lesser extent, on changes in its length, gradient pressure or blood viscosity. For example, if the blood volume velocity in a vessel is equal to 1 ml /s, then with an increase of its radius twice, it will be incre ased by 16 times, and an increase of the radius 4 times results in growing the blood volume velocity by 256 times (Fig.7.29). At the same time the hydrodynamic resistance decreases accordingly by 16 and 256 times.

Since hydrodynamic resistance in the blood vessels of various organs are significantly different, each organ receives its share of CO depending on the total hydrodynamic resistance of its own vessels. Adaptive changes in the blood supply of organs in accordance with their needs are

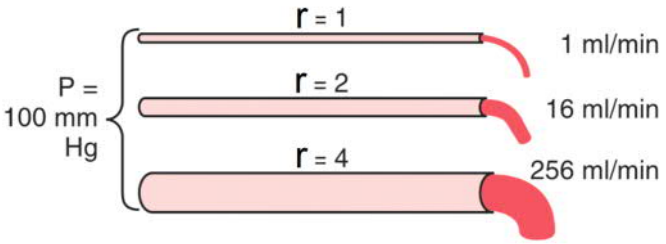

Fig.7.29. Dependance of the blood volume velocity on the vessel radius.

carried out both by changes in cardiac output and by changing the hydrodynamic resistance of various parallel vascular networks.

Types of blood flow in the vascular system. Reynolds number.

In physiological conditions, the *laminar* blood flow takes place in almost all parts of the vascular system. Blood flows by cylindrical coaxial layers, the axis of which coincides with the axis of the vessel. Blood particles in each layer are moved relative to other layers and their speed vector remain parallel to the vessel axis. The blood layer adjacent to the vessel wall hardly moves, the next layer slightly away from the wall moves a little faster, and the central layer is moving at the highest speed. As a result, a parabolic profile of the velocity distribution with a maximum in the center of the vessel is formed (Fig.7.30). The smaller the diameter of the vessel, the closer are the central layers to its wall and the more they are slowed down because of interaction with this wall. As a result, the average speed of blood flow in small vessels is lesser then it is predicted by Ohm's law. In large vessels, the central layers are located far from the walls and therefore as they approach the axis of the vessel, these layers slide one relative to other increasing overall blood speed. It causes the average speed of blood flow to increase significantly. The special feature of the laminar blood flow is that the larger the particles in the blood, the closer they are placed to the axis of the vessel. As a result, the axial flow is almost entirely composed of erythrocytes while its peripheral part is represented by plasma.

Under certain conditions, the laminar flow becomes *turbulent*. Turbulent flow is characterized by the presence of swirls, in which blood particles move not only parallel to the axis of the vessel but perpendicular to it. These swirls significantly increase the internal friction of the blood and the flow profile is considerably flattened. With this type of flow, the blood volume velocity is not anymore proportional to the pressure gradient, but it becomes proportional to the square root of it. To increase the blood volume velocity twice, for example, it is necessary to increase the pressure gradient by 4 times. This means that the load on the heart increases significantly due to transforming the laminar type of blood flow into the turbulent one.

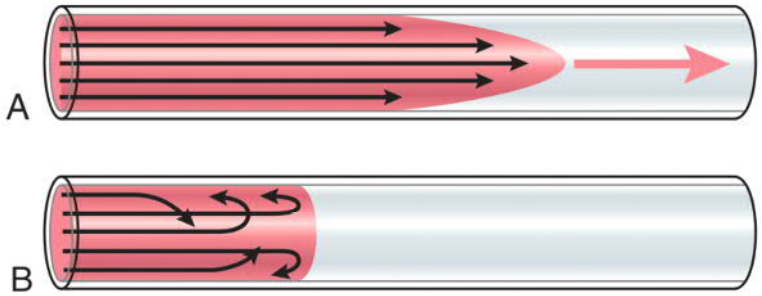

Fig.7.30. Two types of the blood flow in vessel: A - laminar; B - turbulent.

The flow type (laminar or turbulent) depends on many factors. There is a dimensionless value that reflects all of these factors together: the *Reynolds number*. This number is directly proportional to the radius of the vessel (r) in meters, the mean linear velocity of the blood flow (V) in m/sec, the blood density (ρ = 1060 kg / m^3) and inversely proportional to the blood viscosity (η) in Pa×sec:

$$Re = rV\rho/\eta.$$

Reynolds number (Re) lesser then 200 shows the laminar type of blood flow. If the Re exceeds 200, local swirls are formed in the blood flow. Such situation occurs in the places of branching and narrowing of the arteries, as well as in the region where the vessels are steep bended. If Re is within the range of 1000-1200, then the flow is quite turbulent. This type of flow takes place in the proximal parts of the aorta and pulmonary artery during the ventricular ejection phase. With an increase of blood flow velocity, or a decrease of blood viscosity (for example, by heavy anemia), the flow may become turbulent in all major arteries. In this case , the transmitted noises can be heard over the projection of these arteries on the body surface using stethoscope.

Blood viscosity and its effect on blood flow in vessels. The viscosity of blood is expressed in relative units, taking per unit water viscosity at 20 ° C. Thus, the viscosity of whole blood is 3-5 units, and the viscosity of the plasma – 1.9-2.3 units. The blood viscosity is not the same in all departments of the vascular system. It is significantly increased if linear blood flow velocity is low. Thus, the blood viscosity in small vessels (arterioles and venules) can reach 30-50 units. The increased blood viscosity can cause a complete cessation of blood flow in the vessels if they are significantly narrowed. At the same time, in the area which is located more distal than the place of narrowing, the blood flow slows down, increasing blood viscosity even greater and continues its slowing down. This slowdown is due to the temporary aggregation of erythrocytes. In vessels with a diameter less than 1mm *Fahraeus-Lindqvist effect* occurs, which causes the blood viscosity to decrease approximately 2-fold compared to vessels with diameter more then 1 mm.. This effect is due to the longitudinal orientation of erythrocytes along the axis of the vessel. Erythrocytes are arranged like a chain that moves in a peculiar shell from the plasma, similar to the snake's movements. The non-cellular boundary zone with low viscosity forms a layer along which red blood cells slip easily. The Phareus-Lindqvist effect at least partially counteracts the effect of increasing the viscosity of blood at low linear blood flow velocity.

Thus, it follows from the laws of hemodynamics, that changes of blood vessels radius, blood viscosity and blood flow type play a leading role in regulating the pressure and volume velocity of the blood flow in local or systemic adaptive reactions of the vascular bed. However, the application of

these laws is limited by the facts that they are valid for hard tubes, laminar flow, homogeneous fluids and wettable surfaces. The cardiovascular system consists of elastic tubes, in which, under certain conditions, a turbulent flow of a nonhomogeneous fluid can be observed. Moreover, in most parts of the vascular system, blood flow has a pulsating character associated with the rhythmic work of the heart. The difference between theoretical (predicted) and actual data under different conditions often is caused by ignoring these facts. For example, according to the Oma's law, an increase of the blood pressure in the vessel by 2 times, should result in increase of the blood flow also by 2 times. However, in reality, this increase is much larger, since high pressure stretches the vessel, increasing its radius and reducing its hydrodynamic resistance.

6. Features of blood flow in arteries and arterioles

6.1. Blood flow in the arteries. Blood pressure and its measurement.

Arteries are vessels responsible for transporting blood to arterioles and pushing blood from the heart in the diastole phase when the heart does not generate high blood pressure. This function is facilitated by the peculiarity of their walls structure, namely the presence of a strong elastic layer, which accumulates part of the kinetic energy of blood when stretching the wall in systole and gives this energy when pushing blood into diastole (Fig. 7.31). The described process is characterized by the maximal pressure in systole during the blood ejection from the ventricles with a gradual decrease the blood pressure to the minimal level (diastolic pressure) immediately before the next ventricular ejection. A typical blood pressure dynamics is shown in Fig. 7.32. A notch on the descending part of the curve displays the moment of the

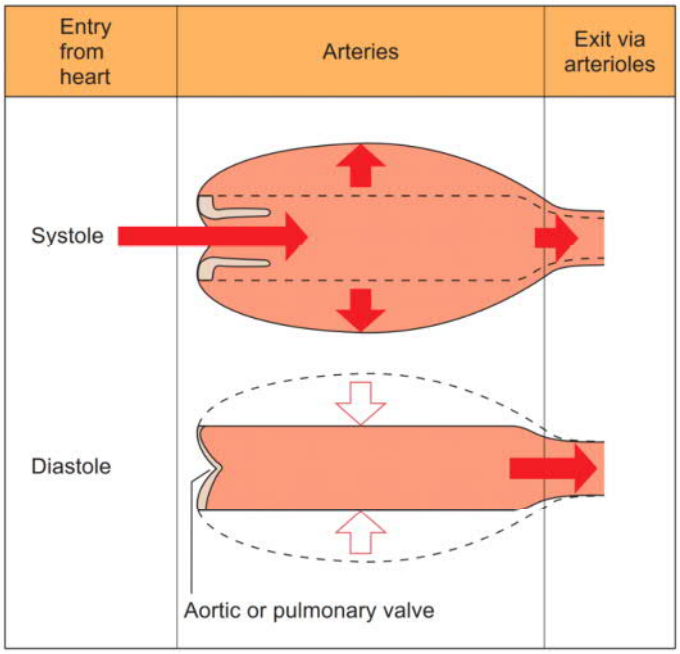

Fig.7.31. Movement of blood in the big arteries.
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aortic valve closing.

The systolic pressure in healthy people ranges from 100 to 140 mm Hg, and diastolic - from 60 to 90 mm Hg. Usually, in women, the pressure is by 5-10 mm Hg lower than that of men. The ***Korotkoff auscultation method*** is used most often to measure arterial pressure in clinical practice. This method is realized by using a special device called ***sphygmo-manometer*** (Fig. 7.33.) A cuff with a built-in pressure sensor is wrapped around the patient's upper arm. The cuff is then inflated with air to a pressure greater than systolic blood pressure (usually more than 180 mm Hg). After this, the air is slowly venting from the cuff, removing the obstacle to blood flow in the pressed shoulder artery. A specific sound phenomena known as Korotkoff's sounds can be listened by stethoscope, placed over the projection of radial artery in the elbow flexion during the decompression (cuff deflating). The appearance of Korotkoff's sounds corresponds to the moment of equalization of pressure in the cuff with systolic pressure, and their disappearance reflects the moment of equalizing

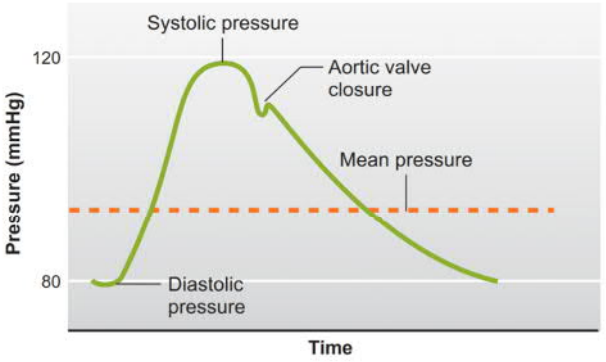

Fig.7.32. Typical fluctuation of the arterial pressure during the cardiac cycle.

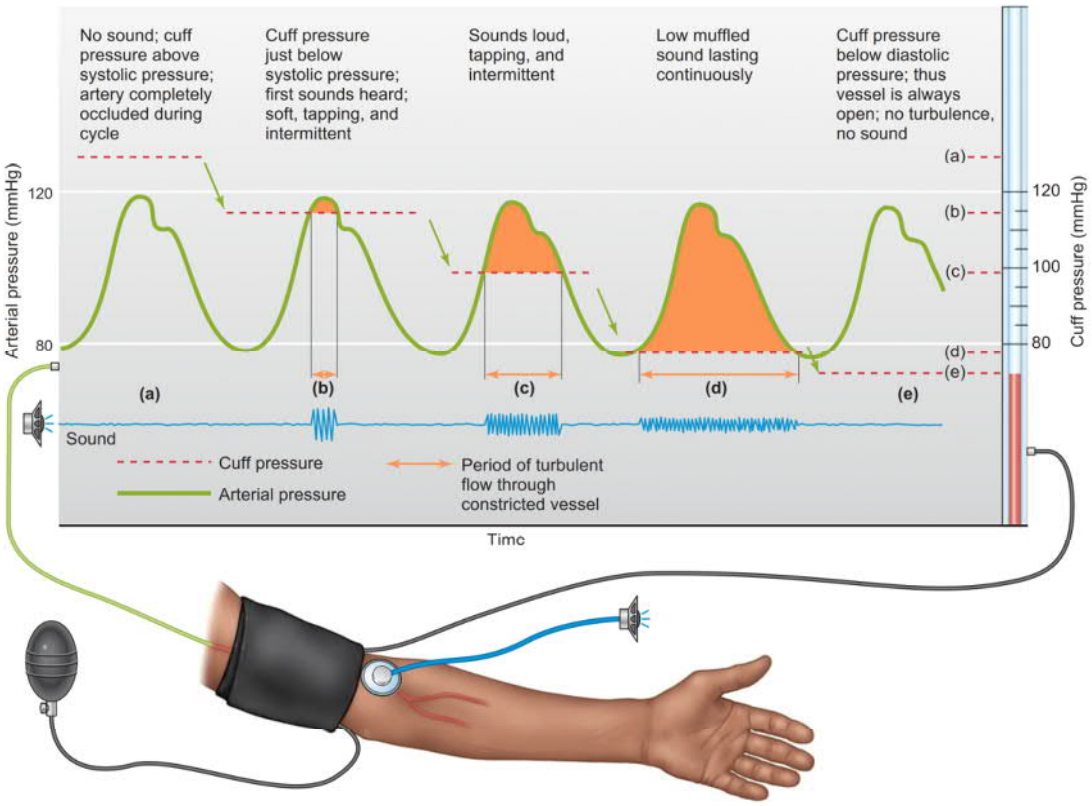

Fig.7.33. Measuring of arterial blood pressure by Korotkoff's method.

the pressure of cuff air with diastolic pressure when the cuff does not interfere with the free blood flow. The mechanism of occurrence of Korotkoff's sounds is explained by the formation of a turbulent blood flow in a narrowed (by cuff) section of the vessel.

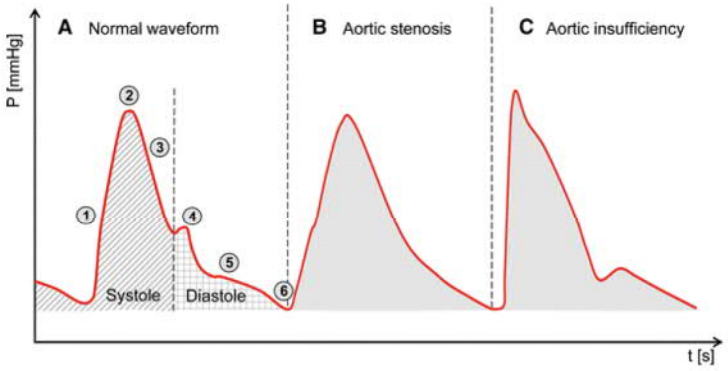

Fig.7.34. Diagnostic value of sphygmography.

The difference between systolic and diastolic pressure is called the ***pulse pressure***. Its average value in most healthy people is about 40 mm Hg. The pulse pressure is the reason for the formation of a pulse wave, which propagates along the artery wall with a speed of 5.5-8.0 m/sec. This wave can be palpated when you put two fingers over the projection of large arteries (shoulder, femoral, radial, cervical) or graphically registered by a device sphygmograph. ***Sphygmogram*** resembles by shape the blood pressure curve and provides information on the state of the vascular wall (Fig 7.34.). The stroke volume (SV), the speed of the stroke volume ejection and the rigidity of the vascular wall determine the size of the pulse pressure. The larger the SV, the shorter the period of ejection and the more stiffened the wall of the arteries, the greater is the pulse pressure. The rigidity of the vascular wall increases significantly in arteriosclerosis, as well as progress with age. Therefore, in older people, the higher pulse pressure is recorded.

6.2. Blood flow in arterioles and mechanisms of its regulation.

Arterioles perform 2 basic functions in the vascular system:

1. They are responsible for the regional redistribution of blood flow between the metabolically active and inactive tissues at a certain level of systemic arterial pressure;

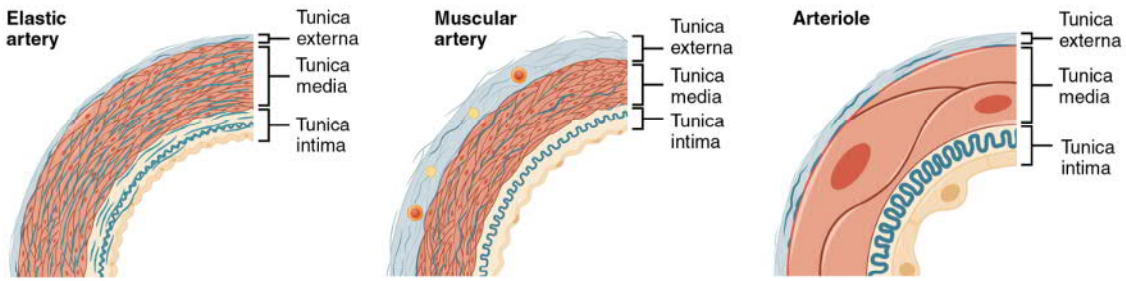

Fig.7.35. Morphological features of different artery types .
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2. They form an adequate level of systemic blood pressure due to the ability to change the total peripheral resistance.

The main morphological feature of arteriole wall is subordinated to the performing of these functions. They have relatively thick walls, and contain a high percentage of smooth muscle, comparing to big and midsized arteries (Fig.7.35). The contraction of powerful circular smooth-muscle layer can be changed due to the influence of various regulatory mechanisms. Even while being not affected by regulatory factors, the smooth muscles of the arterioles have a background level of constriction, which is called ***basal tone***. It is formed due to the spontaneous myogenic activity of smooth muscle cells and because of background sympathetic stimulation. Regulatory stimuli change this tone by controlling the concentration of calcium ions in the cytosol of muscle fibers. The result of this regulation is either ***vasoconstriction*** (with an increase in the concentration of Ca^{+2}), or ***vasodilation*** (with a $Ca+^{2}$ decrease). All mechanisms controlling vasoconstriction and vasodilation can be divided into 3 main groups:

1. Mechanisms of local control;
2. External neurogenic regulation of tone of arterioles;
3. Hormonal control of the arteriole tone.

The first group of mechanisms dominates in the rest state and during the moderate functional activity of tissues. However, the mechanisms of the 2nd and 3rd groups join them if the body is affected by the extreme factors (stress, injury, an abrupt change in temperature, etc.),.

1. Mechanisms of local control act independently from other regulatory mechanisms and coordinate local blood flow with the metabolic needs of the region. Active hyperemia, reactive hyperemia, myogenic autoregulatory reactions and local response to tissue damage are the main forms of these mechanisms.

Active hyperemia is the result of vasodilation caused by the accumulation of vasoactive agents in the extracellular space surrounding the vascular wall of arterioles during hypoxia. These factors include:

- Carbon dioxide released by cells as an end product of the oxidative metabolism;
- Hydrogen ions secreted by metabolic by-products (for example, lactic acid in skeletal muscle);
- Adenosine, a breakdown product of ATP, which is intensively used in a variety of cellular processes;
- Potassium ions accumulated during frequent repetition of AP repolarization in actively functioning cells;
- Osmotically active substances (ions, low molecular weight peptides, glucose, etc.) that are accumulating during the active metabolism;
- Eicosanoids (prostaglandins, prostacyclines): signaling molecules that are membrane phospholipid products of oxidation;

The listed above factors can directly relax smooth muscle of arterioles wall what results in vasodilation. In addition, they stimulate the secretion of paracrine vasoactive substances by the vascular wall endothelium, complementing their vasodilative effect. These substances include, first of all, *nitric oxide (NO)*, which is one of the most powerful vasodilators known today. The mechanism of its action is realized through the secondary messenger cGMP, which suppresses the phosphorylation of myosin protein in smooth muscle fibers, causing their relaxation. NO is secreted by the endothelial cells of arterioles in response to their direct stimulation by other mediators (in particular, bradykinin and histamine, which are formed during inflammatory processes). The physical factors inducing the active hyperemia include the local warming of the tissues. This method is often used in the clinical practice to stimulate blood circulation in pathologically altered parts of the body (for example, compresses). If there is a need to limit the blood flow in such areas, then, on the contrary, cold is applied to them (for example, ice bags).

Reactive hyperemia is a sharp increase in blood flow that occurs after the termination of prolonged vessel occlusions (for example, by thrombus). The mechanism of this phenomenon is similar to the above considered active hyperemia, but it is more pronounced due to the high degree of local hypoxia and a higher concentration of vasoactive agents. This kind of hyperemia can be observed on your own. Compress your finger around its base for 1-2 min. First, it will become pale, but after the stop of compression, it will be bright red within a few minutes.

Local reaction to damage is manifested by vasodilation in the damaged area and is an element of the inflammatory reaction. It is realized due to releasing of histamine, eicosanoids, kinin-kallikrein system and other mediators secreted by blood cells, endothelium, and tissues, or converted from their precursors in blood plasma. Mechanisms of inflammatory reactions are discussed in detail in pathophysiology course.

Local control of blood flow can result not only in its increase, but also in the restriction at a low level of metabolism. In this case, vasodilator substanses are not released in the extracellular space. The tone of smooth muscle rises and relative vasoconstriction occurs.

Vasoconstriction caused by the release of endothelial substances such as *endothelin-1* and *thromboxanes* is a special form of local blood flow limitation in arterioles. These substances are secreted in response to the action of damaging factors and are the elements of such protective reactions as primery and coagulation hemostasis.

Myogenic autoregulation of arteriol tone is a regulatory phenomenon that manifests itself when blood pressure changes in arterioles occur. Its purpose is to maintain a relatively constant blood flow through the region. Myogenic autoregulation causes vasoconstriction in response to increased

pressure and vasodilation in response to lowered blood pressure in arterioles. For example, if the pressure in the arterioles suddenly decreased due to partial blockage of the located above artery by thrombus, then their smooth muscles relax, vasodilation occurs and the blood flow is restored to the previous level. Opposite reactions are observed during sudden increases of blood pressure in the arterioles. This kind of local regulation is common for the brain and kidneys.

There are two theories regarding the mechanisms of myogenic autoregulation. The first is the ***metabolic theory***, which explains this effect by the accumulation or depletion of vasoactive substances in the extracellular space. The second is ***myogenic theory***, which explains this effect by increases in the concentration of Ca ions when the walls of arterioles are stretching by high blood pressure and a decrease in the concentration of these ions under conditions of low blood pressure with slight wall tension of arterioles.

2. External neurogenic regulation of arterioles tone is provided by sympathetic postganglionic neurons. These neurons innervate almost all arterioles in the body and carry out their effect through stimulation of α_1-adrenergic receptors by norepinephrine. The result of this stimulation is vasoconstriction of arterioles and limitation of blood flow through the region. However, in some cases the opposite reaction is possible. The vasodilation can occur due to suppressing the activity of the sympathetic system and removing the contribution of sympathetic impulses to the basal tone of smooth muscle of arterioles. Such a reaction, for example, is observed in the microcirculatory networks of the skin during rising of body temperature. When cooling the skin, on the contrary, vasoconstriction occurs and blood flow is limited. Under stress conditions, when the sympathetic part of the ANS is activated, the arterioles in most regions of the body are constricted (except heart, brain, skeletal muscle), what increases the level of TPR and maintains elevated systemic blood pressure. Some of the postganglionic neurons innervating the arterioles of the penis and the clitoris, as well as the gastrointestinal tract, cause pronounced vasodilation in these regions mediated by NO released during sympathetic stimulation.

3. Hormonal control of the arteriole tone is implemented by participation of such hormones as adrenaline, angiotensin-2, antidiuretic hormone (vasopressin) and atrial natriuretic peptide. The influence of these hormones supplements the local and nervous regulation of blood flow in arterioles in order to provide an optimal response to the stimulus that stimulated the hormonal secretion. For example the hormone ANP secreted in response to stretching of atria by blood, dilates arterioles in most regions of the body, reducing blood pressure. The influence of adrenaline on the tone of arterioles depends on the ratio of different types of adrenergic receptors in their wall. Thus, the arterioles of the myocardium and skeletal muscles contain mainly β_2-adrenoreceptors. Adrenaline has a higher affinity

to these receptor comparing to α_1-adrenergic receptors. Therefore, in these organs, the adrenaline will stimulate vasodilatation of arterioles and increase their blood supply. At the same time, in regions where $\alpha_1$adrenoreceptors dominate, vasoconstriction and decrease of blood supply will occur.

Such hormones as angiotensin-2 and vasopressin are components of the overall high blood pressure response, which is realized through RAAS activated by lowering systemic blood pressure. They will be considered later in context of the mechanisms of systemic blood pressure control. All of the described above regulation mechanisms are schematically represented in Fig. 7.36.

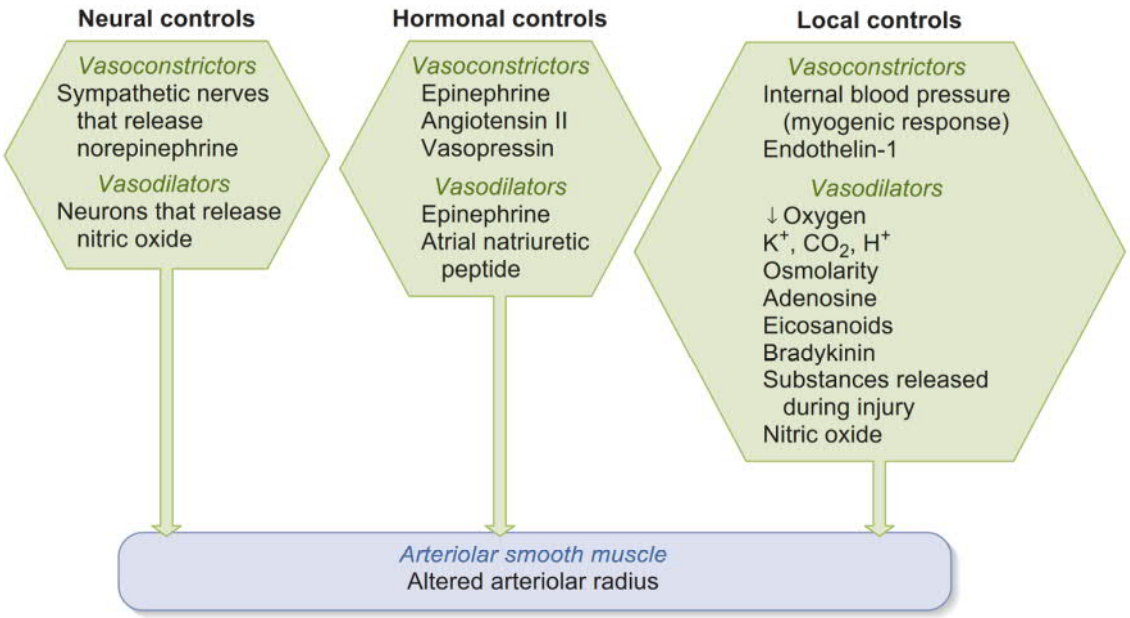

Fig.7.36. Major factors affecting arteriolar radius.

7. Physiology of microcirculation and lymph flow

7.1. Structure of the microcirculatory network.

Capillaries are vessels that are directly responsible for the exchange of respiratory gases and substances between blood and intercellular fluid. Capillaries contain only 5% of the total blood volume, but their total length is about 40 thousand kilometers, and the total area of their exchange surface is about 1000 m^2. Capillaries closely interact with the adjacent vessels and form a functional association with them, which is called the microcirculatory network (Fig. 7.37). The structure of the microcirculatory network includes

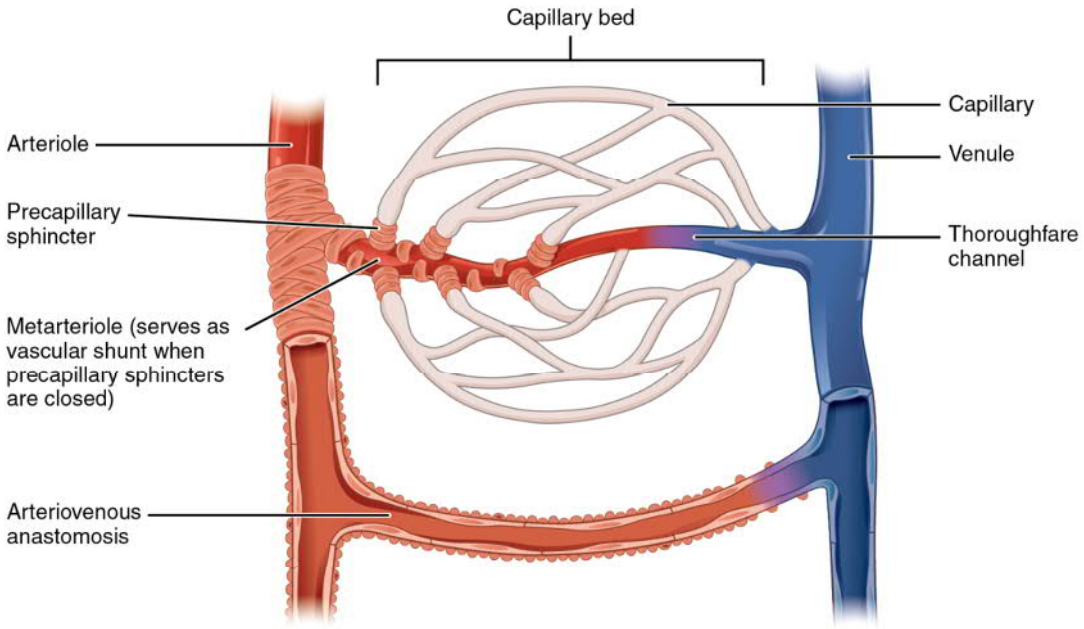

Fig.7.37. Typical microcirculatory network.
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terminal arterioles, metaraterioles, precapillary sphincters, capillaries, thoroughfare channels, postcapillary venules, and in some organs (for example, in the skin) arteriovenous anastomoses. The main part of the microcirculatory network are capillaries, where the most favorable conditions for the exchange of substances between blood and intracellular fluid exist. These conditions include: 1) high permeability of the wall of capillaries to water and substances dissolved; 2) different hydrostatic pressure at the arterial and venous end of the capillary, which provides the processes of filtration and reabsorption; 3) slow linear velocity of the blood flow (0,3-0,5 mm/sec).

In most cases, capillaries are branching at a right angle from metarterioles, which proceed to the thoroughfare channel. They intertwine, forming a capillary bed. Some capillaries converge to the thoroughfare channel or directly contact with wenules. There are smooth muscle elements in the walls of metarterioles, the number of which decreases from the proximal end to the distal. The thoroughfare channels fall into venules, which practically do not contain the smooth muscles. Circular smooth muscle sphincters (***precapillary sphincters***) are located in the place where capillaries leave metarterioles. In other parts of the capillaries, there are no contractile elements.

The blood volume passing through cappilaries depends on the degree of the precapillary sphincters contraction. The total volume of blood flow through the microcirculatory bed depends on the contraction of the smooth arteriole muscles. The arteriovenous anastomosis directly binds arterioles with venules and is presented only in some organs. The walls of the anastomoses are also rich on smooth muscle fibers. Most of arteriovenous anastomoses are found in the skin of the fingers, toes and the auricle, where

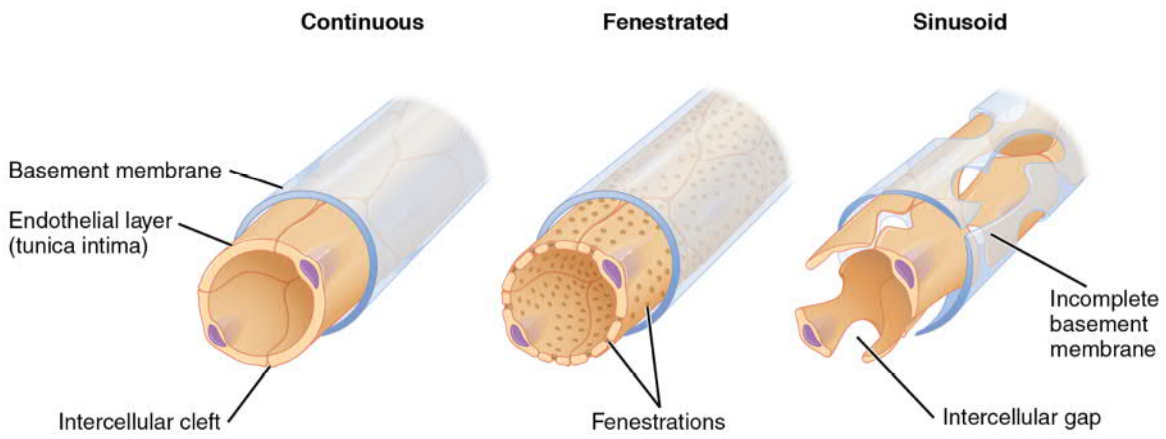

Fig.7.38. Three major capillary types.
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they play an important role in thermoregulation. Approximately only 10% - 30% of capillaries contain blood in a rest state depending on tissues function. Therefore, the microcirculatory network has a significant reserve for increasing the blood supply of tissues. The density of capillaries in various organs varies significantly. There are 2500 - 3000 capillaries in 1 mm^3 of myocardium, brain, liver, kidney. The slow skeletal muscles contain 300-400 capillaries in 1 mm^3 while fast skeletal muscles - 1000 capillaries in 1 mm^3. The density of capillaries is relatively low (200-300 / mm^3) in the bone, fat and connective tissue. Capillaries are divided into 3 types, depending on the ultrastructure of the walls (Fig.7.38):

1) Capillaries with a continuous wall are formed by a continuous layer of endothelial cells. There are very small (4-5 nm) intercellular clefts in their membrane. These capillaries are presented in skeletal and smooth muscles, fatty and connective tissue, and the microcirculatory beds of the lungs. The exception is the capillaries of the brain, which are deprived of clefts since their endothelial cells are very closely adjacent to each other. Such a feature of the brain microcirculatory network creates the hematoencephalic barrier. It protects the brain from potentially dangerous low molecular weight substances and macromolecules dissolved in the plasma.

2) Fenestrated capillaries have fenestrations (windows) in their wall by a diameter of about 0.1 microns. The glomeruli of the kidneys and the intestinal mucosa usually contain capillaries of this type. They are permeable not only for substances dissolved in the plasma, but even for low molecular weight proteins.

3) Sinusoid capillaries have large intercellular gaps in the wall comparable with the capillary diameter. Therefore, not only large molecules but also cellular elements of blood can easily pass through them. Such capillaries are found in the bone marrow, in the sinus of the liver and the spleen.

7.2. Capillary hemodynamics and mechanism of substances exchange across a capillary wall.

The average capillary has a radius of 3 to 6 microns, its length is 0.7-1.0 mm. and the cross-sectional area is about 30 μm^2. The linear velocity of blood in the capillary is 0.3-0.5 mm/sec, what allows the erythrocyte to pass the capillary for 2-3 seconds. Hydrodynamic pressure at the arterial end of the capillaries is approximately 35 mm Hg, and at the venous end it is 15 mm Hg. These values vary in different organs and tissues and depend on the ratio of pre- and post-capillary resistance.

Capillary blood flow has a complex nature. In a biomicroscopic study, the spontaneous periodic replacements of some capillaries by others can be seen, which are called ***vasomotions.*** The vasomotion are due to an intermittent asynchronous contraction of the precapillary sphincters. Blood cells often clog capillaries and stop blood flow in them. Blood volume flow through the capillary beds direct proportionally depends on the level of metabolism. Since the capillaries do not have their own smooth muscle fibers, their passive narrowing or expansion and the number of functioning capillaries depend on the tone of the smooth muscle structures of the terminal arterioles, metarterioles, and precapillary sphincters. Blood flow in the capillaries is facilitated by the ***Fahraeus-Lindqvist effect:*** the decrease in blood viscosity compared with the same blood flowing in the arteries.

The total amount of blood flowing through the capillary network is determined by the tone of the terminal arterioles, which is controlled by local metabolic factors, nervous and humoral influences (see previous section). The percentage of functioning capillaries depends on the tone of the precapillary sphincter, which is controlled only by local metabolic factors (the same as for arterioles).

There are three types of substances which are transporting through the capillary wall (Fig. 7.39). Lipid-Soluble Substances (including blood gases) can freely diffuse through lipid membranes of endothelial cells. Low molecular water-soluble substances are transported through the clefts in the capillary wall. Some low molecular proteins pass through the capillary wall by vesicular transport (exocytosis and endocytosis).

7.3. Substances and fluids exchange in capillaries.

The two-ways diffusion is the most important way for the exchange of dissolved substances between the capillary blood and the intercellular space. The diffusion is the transport of substances through biological membranes carried out due to the concentration or electrochemical gradient. The diffusion rate is so high that plasma can exchange its components with the liquid of the intercellular space 40 times when blood passes through the capillaries,. Thus, both of these fluids are constantly

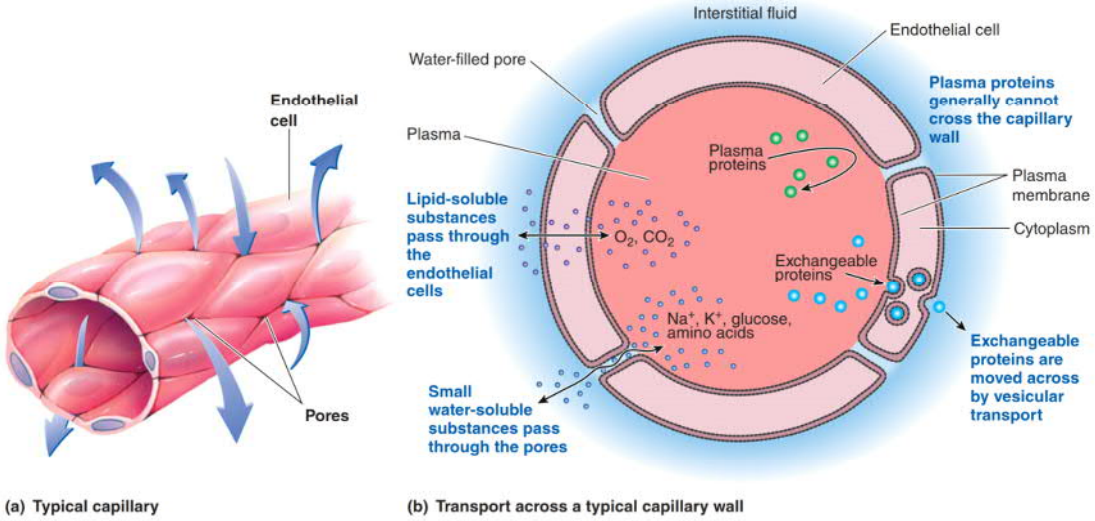

Fig.7.39. Transport of substances across a typical capillary wall.

stirring. The number of molecules that pass from the capillary to the intercellular space and in opposite direction, is approximately the same. Therefore, the plasma and intercellular fluid volume are practically unchanged.

The diffusion rate through the total exchange surface of the capillaries is approximately 60 liters per 1 minute or 85,000 liters per day. The capillary permeability for various substances depends on the size of the molecules comparing to the pores in the endothelial capillary wall. Thus, small molecules such as H_2O or NaCl diffuse more easily than larger molecules of glucose or albumin. If we take the permeability for water as 1, then the relative permeability for glucose will be 0,6, and for albumin - 0.0001. That's why the concentration of albumin in plasma is significantly higher than its concentration in the intercellular fluid. The diffusion rate of substances through the capillary membrane is directly proportional to the gradient of concentrations of these substances between the blood and the intercellular fluid. For example, increasing metabolism causes cells to consume more oxygen and nutrients, and release more carbon dioxide and terminal waste products, so the diffusion rate of these substances increases.

Another mechanism of metabolism between capillaries and intercellular space is a ***transcapillary fluid exchange*** (bulk flow) . Unlike two-way diffusion, this mechanism is almost not important for cellular metabolism. Its main role is to regulate the ratio of plasma volume and intercellular fluid volume. As you know, the total extracellular fluid (ECF) is the sum of these fluids. 70 kg adult has the average volume of ECF about 14 liters. It's divided into 3 liters of the plasma and 11 liters of the intercellular fluid. This ratio can (within a few minutes) vary according to systemic blood pressure what affects circulating blood volume (CBV). The mechanism of

transcapillary exchange of fluids is explained by *Starling theory*, according to which the process of ultrafiltration of a fluid occurs at the arterial end of the capillary and its reabsorption at the venous end. The term ultrafiltration emphasizes the fact that the plasma output from the capillary occurs due to very narrow spaces between the endothelial cells (4-5 nm) and only plasma passes through them, except of proteins. There is a dynamic equilibrium between these processes. This means that the volume of fluid that is filtered at the arterial end of the capillary is almost equal to the volume of fluid that is reabsorbed at its venous end. If this equilibrium is disturbed, a faster significant redistribution of intravascular and intercellular fluid volume occurs. The driving forces of ultrafiltration and reabsorption are determined by the following parameters (Fig. 7.40):

- Capillary hydrostatic pressure (P_c);
- Plasma-colloid osmotic pressure ($\boldsymbol{\pi}_c$);
- Interstitial fluid hydrostatic pressure (P_{IF});
- Interstitial fluid colloid pressure ($\boldsymbol{\pi}_{IF}$).

The effective net filtration pressure can be determined using the Starling's formula:

$$\textbf{Net filtration pressure} = P_C + \pi_{IF} - P_{IF} - \pi_C$$

The calculations have shown that the hydrostatic pressure at the arterial end of the capillary is about 35 mm Hg, in the intercellular fluid - 1

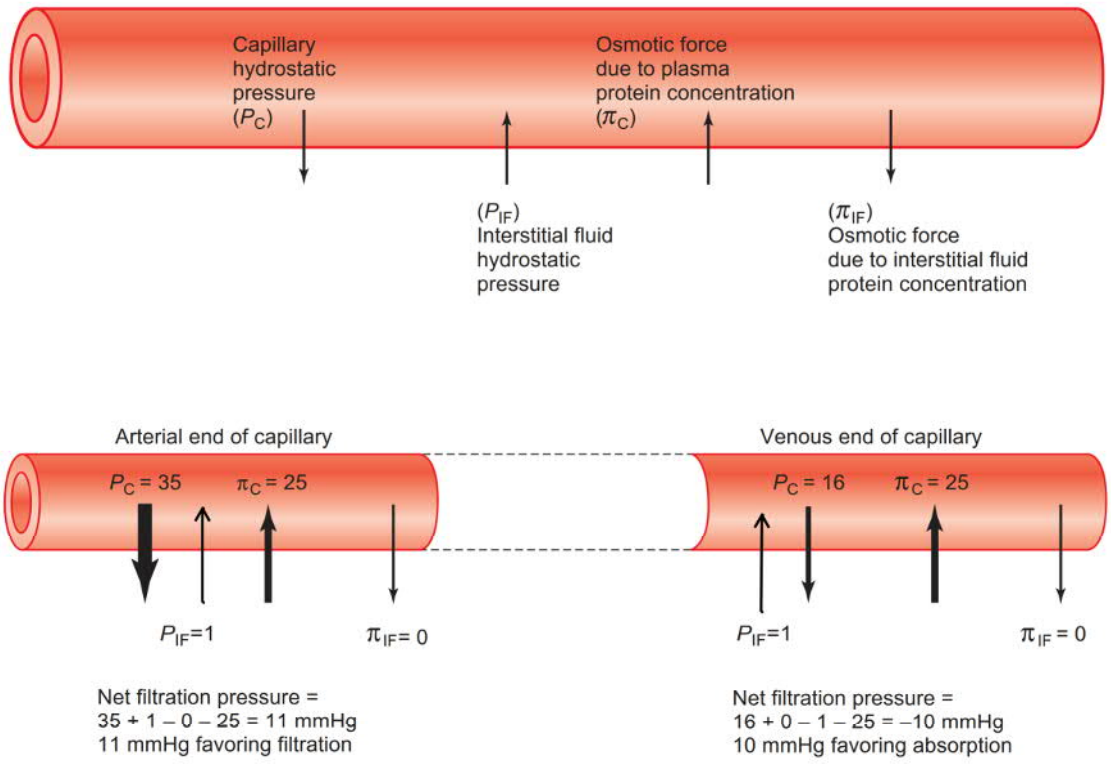

Fig.7.40. The four factors determining fluid movement across capillary wall.

mm Hg. The plasma colloid osmotic (oncotic) pressure is approximately 25 mm Hg, and the interstitial fluid colloid pressure is close to 0. Substituting these values into the formula, we obtain the value of net filtration pressure equal to 11 mm Hg. As a result, water, along with dissolved low molecular weight substances exit out at the arterial end of the capillary.

The mean hydrodynamic pressure at the venous end of the capillary is about 16 mm Hg. All other pressures are the same as at the arterial end. Therefore the net filtration pressure is - 10 mm Hg. This means that the water, along with the dissolved substances, will return to the vascular system at the venous end of the capillary. Since the net filtration pressure at the arterial end is slightly higher than the net reabsorption pressure at the venous end, only 80-90% of the fluid returns to the vascular bed. The 10-20% of remaining fluid returns to the blood through the lymphatic vessels. 20 liters of fluid is filtered, 16-18 liters of fluid is reabsorbed on average per day in adults, and 2-4 liters form the lymph.

The ratio of filtration and reabsorption may be violated when any of the parameters from the Starling formula is changing. One of the most important factors is hydrostatic pressure in the capillaries. Its increase leads to prevailing of filtration over reabsorption and results in the tissue edema. This pressure often is increased due to action of the inflammatory mediators on the microcirculatory blood flow which have a vasodilator effect (histamine, bradykinin, prostaglandin). As a result, the blood overflows the capillaries, the plasma is more intensively filtered into the intercellular space and forms local inflammatory edema. In addition, inflammatory mediators increase the permeability of the vascular wall to proteins, which, in turn, increase the oncotic pressure of the intercellular fluid and promotes additional plasma filtration. Systemic edema may occur during chronic hypertension or prolonged fasting, when oncotic blood pressure is reduced due to the consumption of plasma proteins. You can verify this by yourself, substituting modified hydrostatic pressure and oncotic pressure into the Starling formula.

The lymphatic system plays an important role in the outflow of fluid from the capillary bed. Sometimes edema is caused by stopping of this outflow. Edema may not appear even during changes in filtration and reabsorption if the lymphatic system is functioning normally. In this case, the lymph circulation compensates the violations of filtration-reabsorption equilibrium. The above described values of pressure in the capillaries of different organs may vary depending on the specific function of these organs. Thus, in the capillaries of the renal glomeruli, the hydrostatic pressure is 65-70 mmHg, and in the capillaries of the renal tubules, only 14-18 mmHg. Therefore, only filtration occurs in the glomeruli, and only reabsorption takes place in tubules. The hydrostatic pressure of blood in the capillaries of the pulmonary blood circuit is also relatively low (8-10 mm Hg), what makes the filtration impossible and prevents pulmonary edema.

7.4. Physiological role of lymph circulation.

The lymphatic system is a vascular network consisting of lymphatic vessels and lymph nodes and interacts with three other organism systems: cardiovascular, digestive and immune (Figure 7.41). The *main functions* of the lymphatic system include:

1. Return of fluid and proteins (which are filtered in the microcirculatory network) from the intercellular space to the cardiovascular system.

2. Transport of lipids absorbed in the villi of the small intestine into the venous department of the cardiovascular system.

3. Filtering of intercellular fluid in lymph nodes in order to delay and destroy the foreign antigens and pathogenic factors.

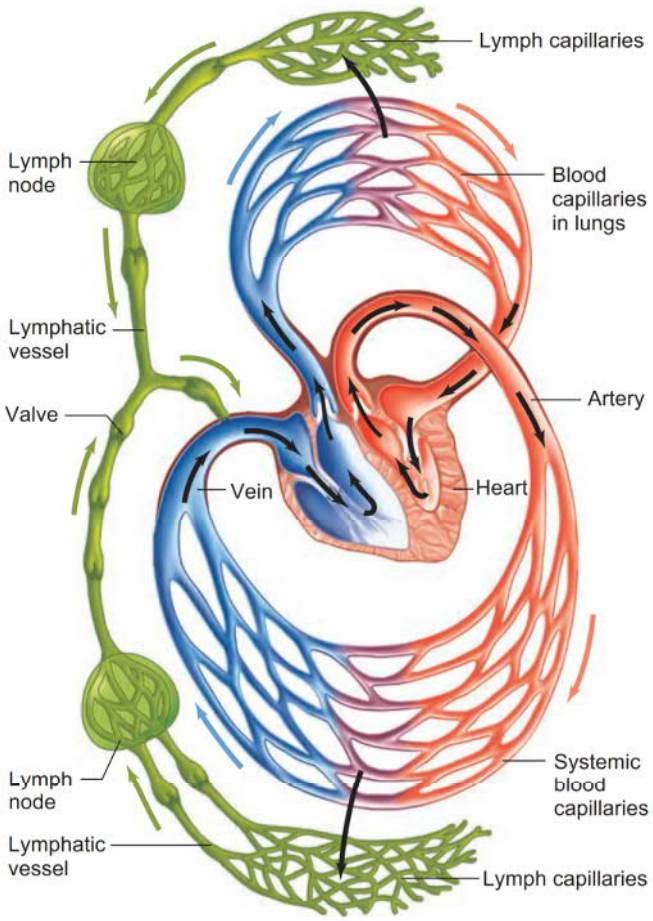

Fig.7.41. Relation of the lymphatic system to the cardiovascular system.

We will consider the first function of lymphatic system in this chapter. The key vessels of the lymphatic system are ***lymphatic capillaries***, which accompany the blood capillaries (with the exception of the kidneys and the central nervous system). Lymphatic capillaries differ from the blood vessels. They have bigger spaces between their endothelial cells, which allow entering not only water and low molecular weight substances, but also proteins, and even bacteria and viruses. The fluid in the interstitial space moves to the lymphatic capillaries by the so-called paralymphatic pathways. Lymphatic capillaries encircle the fragments of a blood capillary network and are topographically linked with postcapillary veins (Fig.7.42). The main ways for transporting the large particles into the lumen of the lymphatic capillaries are: 1) spaces between endothelial cells 2) pinocytic vesicles. When the hydrostatic pressure of the intercellular fluid exceeds the pressure in the lymphatic capillary, the fluid stretches the endothelial contacts and enters the capillary. Lymph moves from the lymphatic capillaries in the small

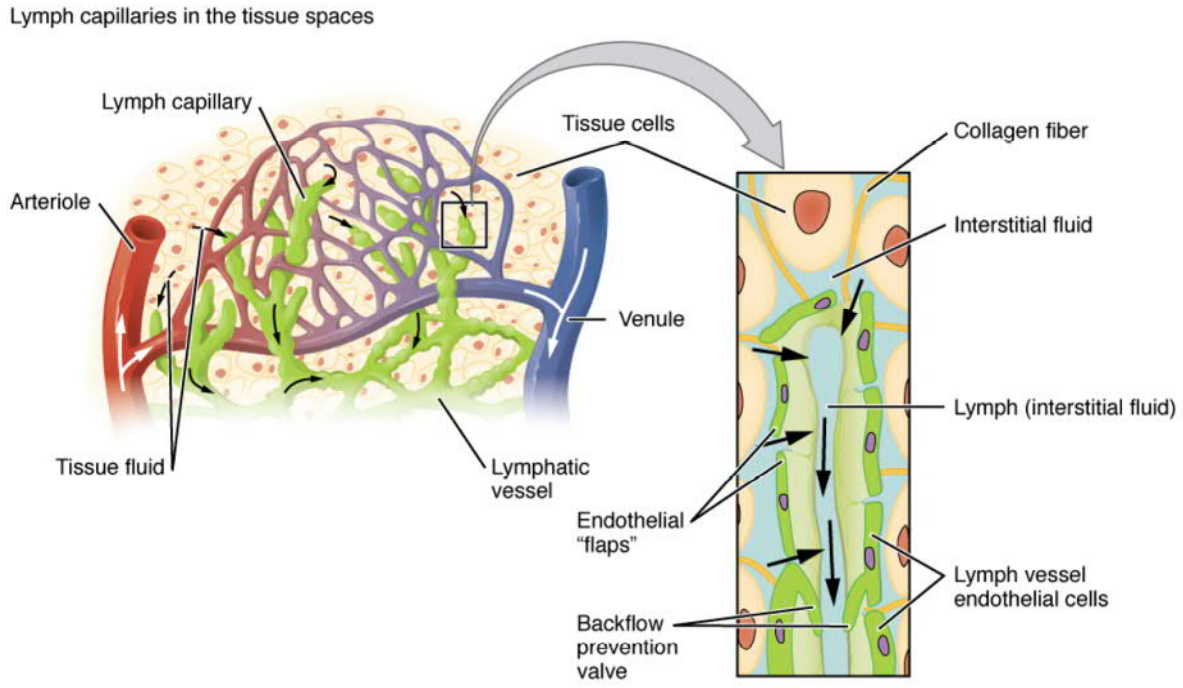

Fig.7.42. Topography of the blood and lymphatic capillaries.
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intraorganic lymphatic vessels and is transporting to the lymph nodes. Then it enters the large lymphatic ducts leading it to the venous system. The right and left thoracic duct flow into the right and left subclavicular veins, respectively, where they connect with the jugular veins.

The driving force of the lymphodynamics is the pumping function of small lymphatic vessels, which is provided by their myogenic activity and the semilunar valves similar to the valves in the veins of the lower limbs. The shape of the lymphatic vessels is generally cylindrical. It differs from the arteries and veins by the alternation of numerous narrowings and extensions that give them similarity to the string of prayer beads. These vessels contain the valves that prevent the reverse current of the lymph flow. The part of the lymphatic vessel located between the two valves is called ***lymphangion***. It has a muscle part and a valve part, where smooth muscle fibers are absent. Lymphatic vessels exhibit a spontaneous myogenic activity, which occurs in three forms: phase rhythmic contractions, slow waves and basal tone. Pumping function of lymphangion is caused mainly by the rhythmic contractions, producing a rapid narrowing of a separate area of a vessel, followed by rapid relaxation. The rhythmic contractions of the skeletal muscles promote the lymph flow, pushing the lymph toward the venous system. That is why, edema occurs due to the disturbance of the lymph flow from the limb when the limbs are immobilized and the skeletal muscles do not work for a long time.

Lymphatic nodes also affect both the volume and composition of lymph (Fig.7.43). There are about 460 lymph nodes in the human body. The functions of nodes are: hemopoetic, immunopoetic, protective, reservoir and

propulsive. Lymph nodes act not only as a mechanical but also as a biological barrier, delaying the foreign proteins, bacteria, cells of malignant tumors, toxins, etc. As a rule, up to 2-4 afferent vessels enter to the node, and only 1-2 go out, therefore the amount of lymph after the node is 2-3 times smaller than the before the node. This means that lymph deposition and fluid redistribution between the lymph and blood occurs in the nodes. Lymph nodes also contain smooth muscle cells and can contract when affected by the neurohumoral or local factors.

The lymphatic drainage may increase several times during the digestive process, after taking water, when a large amount of fats pass from the intestine into the blood. The lymph volume per day in health adult fluctuates in range 2-4 liters. The increase of the lymph formation and lymph drainage results in the decreased oncotic pressure of plasma proteins and increased venous pressure. For example, increasing venous pressure in the liver portal system leads to an increase in lymph drainage from the liver by 10-12 times.

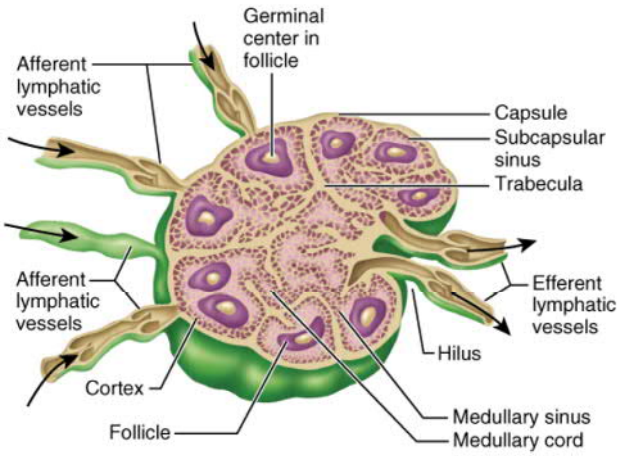

Fig.7.43. Structure of the typical lymphatic node.

Lymphatic vessels have sympathetic and parasympathetic innervation. Autonomic nerve fibers are coming to lymph vessels from arterial nerve plexuses. Stimulation of the s ympathetic nerves causes smooth muscle fibers in the lymphatic vessels to contract. Adrenaline, histamine, heparin, calcium and sodium ions produce the same effect. Parasympathetic nerves, as a rule, inhibit the pumping function of the lymphangions, but they can stimulate their myogenic activity on the low basal tone background.

8. Physiology of the venous system

8.1. The role of venules and veins in the cardiovascular system.

The venous system is the final component of blood circulation in both circles of hemodynamics. It provides blood outflow from the microcirculation bed and its return to the atria. ***Venules*** are the smallest vessels in this system. They are part of the microcirculatory network that does not only remove blood from the capillaries, but also takes part in metabolic exchange

between the blood and the intercellular fluid due to diffusion processes. After merging, the venules form the small veins, which gradually unite into larger veins. Upper and lower vena cava veins enter the right atrium ending the systemic circulation. Four pulmonary veins enter the left atrium in the pulmonary circuit.

The morphological features of veins are a much lesser circular smooth muscle layer and a small number of elastic fibers. That's why the veins are very easy to stretch and why they deposit blood without significant changes in blood pressure. Smooth muscular layer of veins has a slight basal tone but can significantly increase it during sympathetic stimulation. In this case, the vein radius decreases increasing the venous pressure, which contributes to the blood outflow to the heart. Another important feature of the limb large veins is the presence of valves in them, which make impossible the retrograde blood flow to the capillaries. The vein valves provide unidirectional blood flow in the cardiovascular system together with the valves of the heart. In addition, they play a key role in the mechanism of the venous muscle pump (Fig. 7.43). This pump is realized by rhythmic contractions of the skeletal muscle. It happens due to an exertion of blood in the direction of the heart and its suction during muscle relaxation.

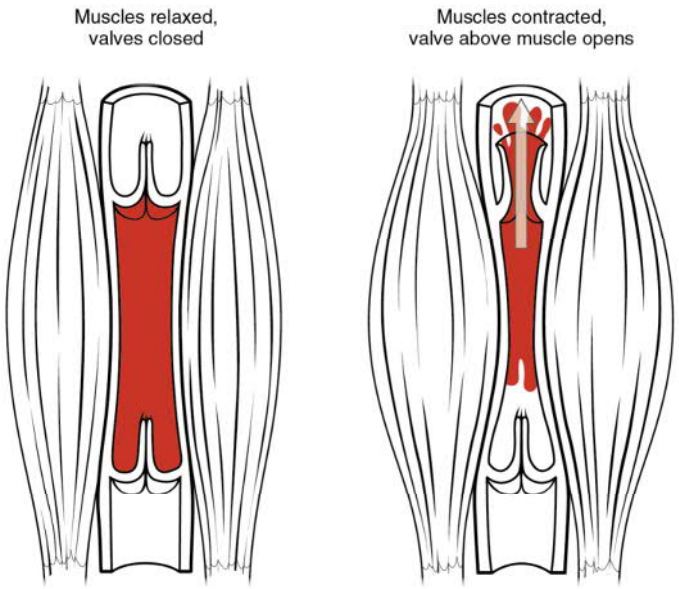

Fig.7.44. Mechanism of the venous vuscle pump.
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Normally, about 60% of the circulating blood volume (CBV) is contained in the venous system. Therefore, these vessels are called ***capacitive vessels*** which form ***a dynamic capacitive blood reservoir.*** This reservoir can, if necessary, quickly deposit 1-1.5 liters of blood due to relaxation of the vein wall. However, it can quickly provide other parts of the body with additional blood due to contraction of the circular muscles and returning the more blood into the arterial system.

Blood pressure in the venules varies within 12-18 mm Hg, in small veins it decreases to 8-10 mm Hg. Blood pressure in the large veins is on average 4-5 mm Hg, and is called the ***central venous pressure***. In the right and left atria, blood pressure is close to 0. Thus, the pressure gradient, which ensures the blood return from the microcirculatory bed to the heart,

ranges from 10 to 15 mm Hg. It should be noted that such values of venous pressure are only if a person is in a horizontal posture. In other cases, the blood flow parameters in the veins are affected by gravity (gravitation). The influence of gravity on hemodynamics will be considered later in detail.

8.2. Mechanisms of blood venous return to the heart.

The venous return is a term denoting the blood flow from the capillaries to the heart through the venous system. Since the pressure gradient in this department of the cardiovascular system is relatively low (10-15 mm Hg), there are additional factors that contribute to the movement of blood to the heart under different physiological conditions. They are called *extracardial factors* and include following physiological mechanisms:

1. *Sympathetic stimulation the smooth muscles of vein wall,* resulting in veins vasoconstriction. Blood pressure in the veins increases and accordingly, the pressure gradient between them and the heart increases too. As result, an acceleration of the blood flow to the atria and a decrease blood volume in the venous reservoir occurs.

2. *Venous muscle pump* that contributes blood return to the heart and is implemented with the participation of the vein valves. In adittion, there is a hypothesis about the existence of a *capillary muscle pump* operating in the microcirculatory networks of skeletal muscles (M. Arinchin, V. Feketa, 1993). According to this hypothesis, skeletal muscles can suck the arterial blood and pump it into the veins with strength greater than the arterio-venous pressure gradient in the cardiovascular system. This function of skeletal muscles is realized at the level of capillaries by the vibrational interaction of the skeletal muscle fibers with endothelium of capillaries. It is facilitated by the mutual longitudinal orientation of muscle fibers and capillaries. Muscle fibers vibrate at a frequency of 20-40 Hz and pump blood into the venules. Unlike a venous muscle pump, the capillary muscle pump *(micropumping function)* is manifested not only by rhythmic contractions, but also during isometric contractions and even by moderate stretching of skeletal muscles.

3. Henderson thoracic (respiratory) pump. It is realized due to the influence of respiratory excursions of the chest on venous blood flow. When you inhale, thoracic internal pressure and simultaneously the blood pressure in vena cava inferior drops. The downward movement of the diaphragm raises the pressure in your abdominal cavity, causing the blood pressure in the abdominal part of the same vein to increase. As a result, an additional pressure gradient is formed that promotes blood flow towards the heart. When you exhale, pressure changes in the thoracic and abdominal cavities occur in opposite directions. However the blood does not move in the direction of the lower limbs, because the venous valves there prevent the retrograde blood flow. Central venous pressure during breathing

fluctuates from 2 mm Hg at the maximum inhalation to 6 mm Hg at the maximum exhalation due to the respiratory pump. These oscillations can be recorded on the curve of the central venous pulse in the form of "respiratory waves".

4. *Cardiac suction of blood.* It occurs during the ventricular systole and relates to the blood entering the atria from big veins. The closed atrioventricular valve cusps move downward during blood ejection, increasing to some extent the volume of atria, what creates the effect of suction, like the drag of the syringe piston.

Extracardial factors of hemodynamics are especially important for the venous return if the body is in a upright posture, when hemodynamics in the veins is affected by the effects of gravity.

8.3. Effect of gravity on hemodynamics.

As you know, the vascular system is in the gravitational field of the Earth. Thus, the blood pressure in the vessels, which is created by the heart (hydrodynamic), adds with the hydrostatic pressure created by the gravity of the blood in the vessels. This explains the fact that the total blood pressure in blood vessels located below the heart level increases, and in vessels located above the heart level it decreases proportionally to the distance from

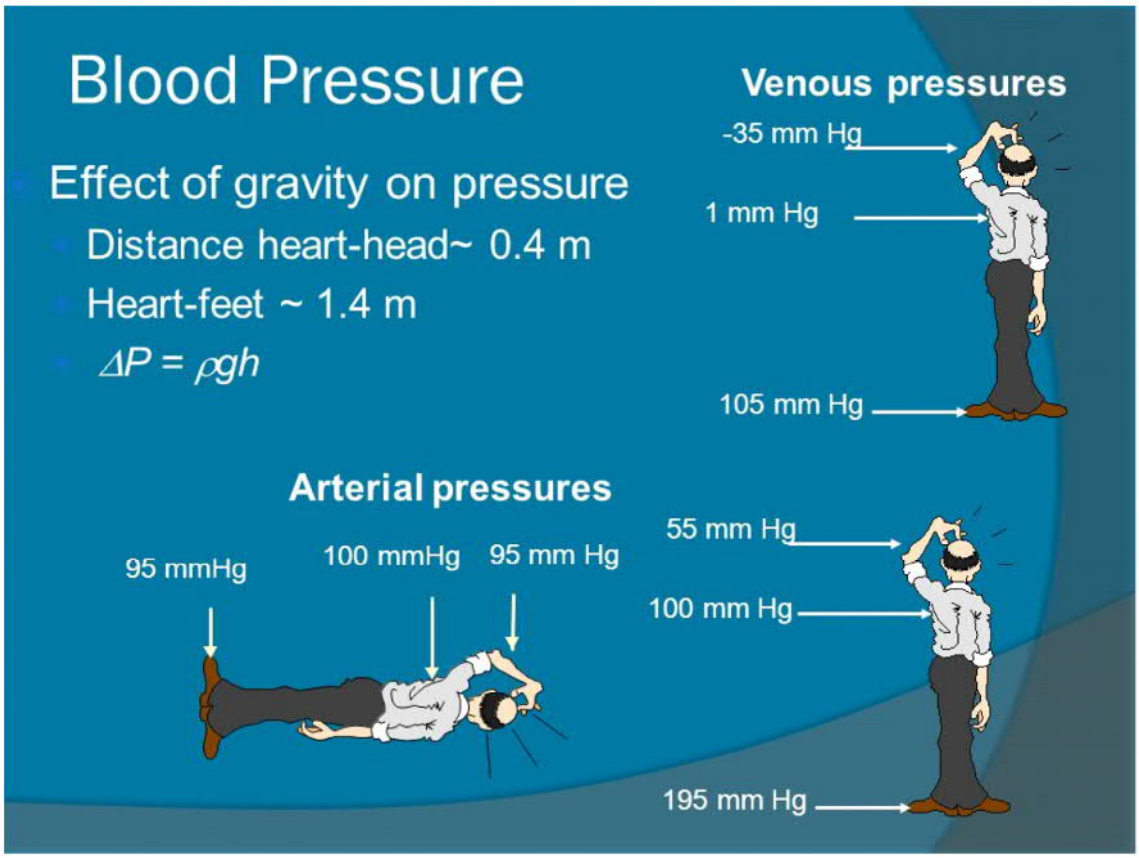

Fig.7.45. Effect of gravity on hemodynamics.

the heart.

In the horizontal posture of the body, the difference in the placement of different vessels in relation to the heart level is insignificant, so gravity almost does not affect hemodynamics (Fig.7.45). In the upright posture of the body, the hydrostatic pressure in the vessels of the foot (that is, 125 cm below the heart level) is about 95 mm Hg. Taking into account that the mean arterial pressure reaches a level of 100 mmHg, the total blood pressure in the arteries of the foot can be about 195 mmHg. In the arteries of the brain, located about 45 cm above the heart, the total pressure is only 55 mm Hg.

The blood pressure in the veins is affected by gravity in a similar way. Thus, in the veins of the foot, it is about 105 mm Hg, and in the veins of the head it is even lower than atmospheric (-35 mm Hg). In this case, the arterio-venous pressure gradient, which creates the driving force of the hemodynamics, does not change. But *the transmural (stretching) pressure* in the veins is much higher compared to the transmural pressure in the horizontal posture due to the hydrostatic pressure. Rising of transmural pressure in the veins results in their significant dilatation and, consequently, depositing of blood in them. That's why up to 1000 ml of blood can be temporary deposited in lower limbs veins, when a person moves from a horizontal position into a vertical posture. This in turn can cause a temporary decrease in blood pressure, which is called *orthostatic collapse*. A high transmural pressure in the lower limbs veins can cause insufficiency of the valves and lead to the development of varicose disesase in case of insufficient motor activity.

Effect the gravity creates the embolization risk for the head veins in case of venous wall damage because of injuries, or when squeezing furuncles in the skin of the face. Negative pressure in the veins has a suction effect on the air bubbles or particles of damaged tissues (pus) that can enter the brain tissue or cerebellum with blood flow and cause the onset of meningitis or encephalitis.

The increase of blood pressure in the vertical posture of the body does not significantly affect the arterial system This is due to the powerful wall of the arterial vessels that can compensate the stretching action of increased transmural pressure and the blood volume in the arteries is practically unchanged.

9. Regulation of systemic blood pressure

9.1. The main determinants and principles of systemic blood pressure control.

Systemic arterial pressure (SAP) is the mean arterial pressure in the large (systemic) circle of hemodynamics. This parameter is maintained in the

human body at a relatively constant level in the range of 80-100 mm Hg. The main determinants (factors that determine the magnitude) of the SAP and their interaction are shown in Fig. 7.40. First of all, SAP depends on the cardiac output (CO) and the total peripheral resistance (TPR). This dependence is describing by Ohm's law. The CO, in turn, depends on the heart rate (HR) and the stroke volume (SV) of the left ventricle. The heart rate basically depends on the balance between the activity of the parasympathetic part of the ANS, which reduces heart rate, and the activity of the sympathetic part, including the effect of the catecholamines, that increase HR. SV increases in response to sympathetic stimulation in accordance with the external reflex mechanisms of the pumping heart function control. SV may also increase with increasing venous blood flow in accordance with the Frank-Starling law. Venous return increases during sympathetic vein stimulation (as a result of vasoconstriction), activation of the venous muscle pump, respiratory pump and suction function of the heart.

According to the Poiseuille's law, TPR mainly depends on the radius of all arterioles and the blood viscosity. The radius of arterioles, in turn, depends on the local metabolic control that coordinates the local blood flow with current metabolic needs. For example, active muscular work leads to vasodilation in this region. The radius of arterioles is also affected by the sympathetic part of the ANS and by catecholamines, which cause vasoconstriction and increase the TPR. However, the component of RAAS angiotensin-2 and vasopressin (which are powerful vasoconstrictors) also affect the radius of arterioles and simultaneously regulate the water-salt balance. The main factor determining blood viscosity is hematocrit.

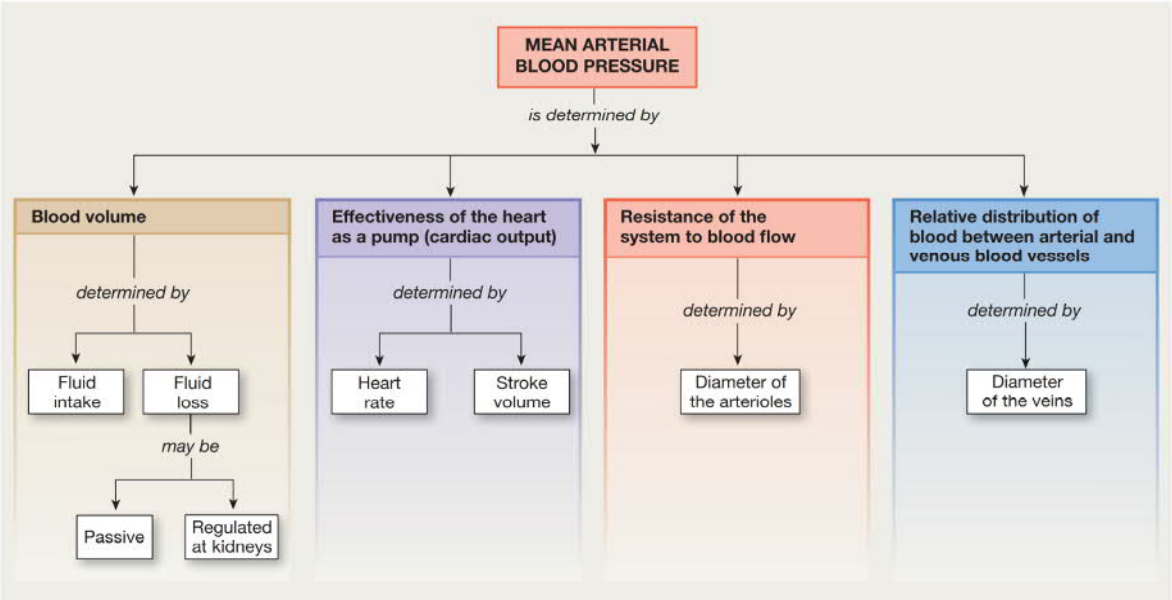

Fig.7.46. Factors affecting systemic arterial pressure .

The circulating blood volume (CBV) also affects the venous return, and depends on the shift of the filtration-reabsorption equilibrium in the microcirculatory system and the water-salt balance. This, in turn, is controlled by the renin-angiotensin-aldosterone system (RAAS) and vasopressin. The key organ in blood volume regulation is the kidneys, which adjust the consumed and removed fluid volume with blood volume in the vascular system.

Finally, the blood volume in the arterial system is affected by its additional depositing or removing from the venous system. The main factor affecting such blood redistribution is the tone of the sympathetic department of the ANS, which has a vasoconstrictor effect on the veins wall as well as stimulates the activity of "venous pump" during active muscular work of the lower limbs.

As we see, the regulatory factors affecting different levels of maintaining the optimal level of SAP are mutually interconnected. Changing any of the factors in this scheme shifts the SAP from its baseline to the point when other factors start to compensate these changes, or until it is established on a new optimal for metabolism level. ***Maintenance of the optimal SAP level is achieved by mutually compatible changes in the TPR, CO, CBV and blood redistribution between the arterial and venous parts of the vascular system***. Therefore, for example, if the total peripheral resistance decreases due to the dilatation of resistive vessels, then the compensatory reactions occur increasing the cardiac output and the CBV. And totally opposite changes arise if the vessels are constricting. However, these regulatory mechanisms are expanding with different speed. The changes in the vascular tone and cardiac output occur within a few seconds, and changes in the CBV are establishing for several hours or even days. Therefore, all mechanisms of SAP regulation are divided into 2 groups: short-term and long-term mechanisms depending on the development speed.

9.2. Short-term regulation of blood pressure.

Short-term regulation includes mainly reflectory mechanisms: baroreceptor reflexes; chemoreceptor reflexes; brain ischemic reflex and stimulation of catecholamines secretion by the adrenal medulla. Reflectory mechanisms are intense enough, but they are significantly weakened during the prolonged action of stimuli, due to the rapid adaptation of baroreceptors to a new level of blood pressure.

Baroreceptor reflexes. The reflexogenic zones for the baroreceptor reflexes are the aortic arch and the carotid sinus, where the baroreceptors are located. They react to the stretching of the vascular walls. Action potential frequency from these receptors almost linearly increases when mean blood pressure increases from 80 to 170 mm Hg. With an increase in SAP, afferent impulses from the baroreceptors enter the cardiovascular

centers of the medulla oblongata, where they stimulate cardiac inhibitor center, simultaneously inhibiting the cardiac accelerator and vasomotor centres. The result is a decrease in the frequency of efferent sympathetic impulses to the heart and arterioles, which causes a decrease in heart rate, SV, and vasodilation of arterioles. At the same time, the neurons of the cardiac inhibitor center cause negative chrono-, batmo-, dromo- and inotropic effects on the heart through the vagus nerve stimulation. Correspondingly, the main determinants of SAP (CO and TPR) decrease, what results in a decrease of SAP. All described regulatory reactions act in the opposite direction if SAP decreases (Fig.7.47).

Recall that the vascular system, with a few exceptions, has only sympathetic innervation (excepting the vessels of the external genital organs, which are innervated by special autonomous NO-producing fibers). Through these nerves, impulses with a frequency of 1-3 imp/s reach the vessels in a rest state. The maximal smooth muscle contraction occurs by the impulse frequency of 10 imp/s. Thus, an increase in the impulse rate of sympathetic vascular fibers within these limits leads to vasoconstriction, and a decrease leads to vasodilation. This vasodilation is limited by the basal tone of the vessels, that remains in the vessels even after their denervation.

The heart also adjust its function to a new total peripheral resistance

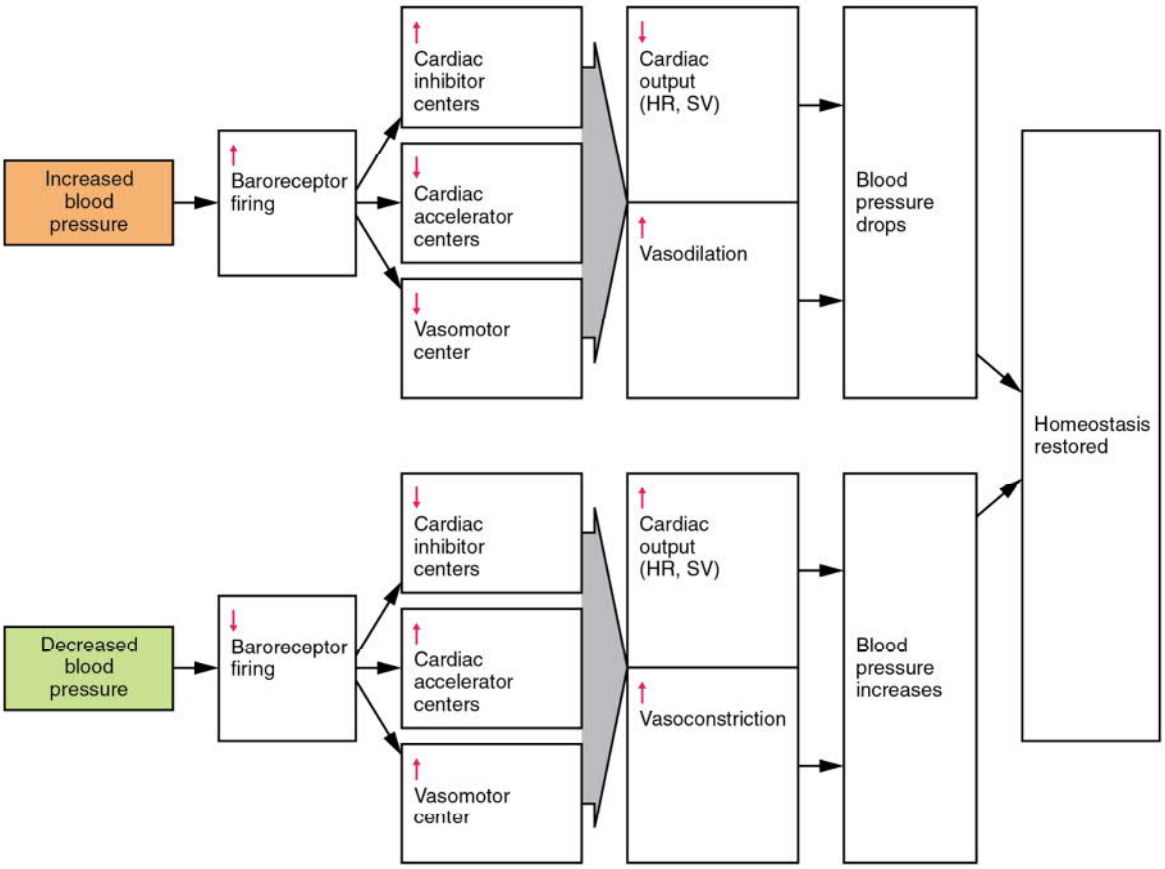

Fig.7.47. Baroreceptor reflex and its influence on the blood pressure.

due to intracardiac and extracardiac reflexes. It means that heart increases SV because of reducing afterload or decreases SV in case increasing the afterload. In addition, vasodilation of the venous vessels leads to the depositing of the blood, what also contributes to a decrease in blood pressure. The venous return of blood to the heart decreases and, according to Franck-Starling's law, SV decreases. At the state of low blood pressure, the vasoconstriction effect dominate over vasodilatation one. This effect plus stimulation of myocardium contractility leads to an increase in arterial pressure.

The effectiveness of baroreceptor reflexes can be illustrated by the reaction of hemodynamics to the transition of a person from a downright to the upright posture. In this case, the venous return is significantly reduced because of high hydrostatic pressure in lover limbs veins. In accordance with the Franck-Starling law, SV and also CO decrease, what in turn causes a decrease in systemic blood pressure (the so-called *orthostatic collapse* occurs). However, SAP rapidly returns to normal values during 15-30 sec due to baroreceptor reflexes. Another example illustrating the clinical use of baroreceptor reflexes is an implantation of electrodes in the area of the carotid sinus, which can stimulate baroreceptors at the right time and cause a depressor effect. It is known that a strong hit to the area of the carotid bifurcation may result in a cardiac arrest. Since the vasomotor center is linked with other parts of the central nervous system, the firing of baroreceptors may cause a decrease in respiration rate, muscle tone, and tendon reflexes.

Chemoreceptor reflexes. The chemoreceptors are represented by the aortic and carotid bodies located in aortic arch and carotid sinus. They are stimulated by decreasing of O_2 pressure (hypoxemia), increasing of CO_2 pressure (hypercapnia) or increasing of the H^+ ions concentration (acidosis) in the arterial blood. Action potentials conducted from these receptors stimulate not only the vasomotor center but also the respiratory center of medulla oblongata. Therefore, the hemodynamic reactions are combining with changes in breathing. Chemoreceptor reflexes also affect the tone of arterioles, causing vasoconstriction, which leads to an increase in TPR and blood pressure. The main role of such reflexes is to coordinate the respiratory and cardiovascular reactions on tissue hypoxia.

Brain ischemic reflex. The central nervous system react to ischemia because of.the direct excitement of the vascular and motor centers of the medulla oblongata by the lack of oxygen and excess of carbon dioxide and hydrogen ions in arterial blood. These reactions are vasoconstriction and an increase in TPR resulting in increasing of SAP. The intensity of the central nervous system reaction to ischemia depends on the degree of cerebrovascular damage.

Sympathetic stimulation of catecholamines secretion is an element of a general pressure-response on stress and is considered as one of the

short-term regulation mechanism of SAP. The adrenal medulla has a direct sympathetic innervation from the preganglionic sympathetic neurons of the spinal cord, and its endocrine cells may be considered as modified postganglionic neurons that secrete hormones adrenaline and noradrenaline in the proportion of 4:1 instead of the mediator. Adrenaline, having a greater affinity for β receptors, stimulates cardiac activity, and norepinephrine, due to a higher affinity for α_1 receptors, causes vasoconstriction in arterioles and veins.

9.3 Long-term regulation of arterial pressure.

Regulatory mechanisms of this group are aimed on controlling the circulating blood volume (CBV) .They include: shifts of the transcapillary fluids exchange, renin-angiotensin-aldosterone system (RAAS), secretion of antidiuretic hormone (ADH, or vasopressin), atrial natriuretic peptide (ANP) its an analogue brain natriuretic peptide (BNP).

Shifts of the transcapillary fluids exchange. Reflectory changes in the tone of the precapillary sphincters and postcapillary venules affect the net filtration pressure, displacing the filtration and reabsorption equilibrium. In particular., an increase in blood pressure due to impulses from baroreceptors leads to a decrease in the tone of the precapillary sphincter. This causes an increase of net filtration pressure resulting in the reinforced transport of the fluid into the interstitial space. This, in turn, causes a decrease in the CBV. On the other hand, by lowering the blood pressure, the precapillary sphincters are constricting, the net filtration pressure decreases and the fluid is more intensively reabsorbed into the bloodstream, what causes an increase in the CBV.

Renin-angiotensin-aldosterone system. Renin (an enzyme secreted by the juxtaglomerular apparatus of kidneys) converts the inactive plasma protein *angiotensinogen* (belonging to the fraction of alpha-2-globulins) to the *angiotensin-1*.. It is converted into angiotensin-2 due to the action of a converting enzyme of plasma. This reaction occurs mainly in the vessels of the lungs. However it has recently been found that these transformations can occur also in other tissues of the body (in particular, in adipose tissue and in the pancreas). This gave rise to the concept of the so-called *"tissue RAAS"*, the effects of which are similar to the renal RAAS.

Angiotensin-2 causes a very powerful vasoconstrictor effect, both on the arteries and on the veins. In addition, it stimulates the central sympathetic structure and stimulates the secretion of aldosterone by the glomerular layer of the adrenal glands. The result is an increase of the systemic arterial pressure (SAP). The action of the renin-angiotensin-aldosterone system reaches its maximum in about 20 minutes after the start of the secretion of renin and lasts for several days. The launch of all this reaction chain is closely related to the kidneys. Secretion of renin increases

by reduced blood supply to the kidneys of any origin: either as a result of the decrease of blood pressure, or during kidney disease, or by the narrowing of the renal arteries. A change in the electrolyte composition of the plasma, in particular, hyponatriemia, also stimulates the rennin secretion.

The antidiuretic hormone is secreted in response to a decrease in blood pressure. Changes in blood pressure stimulilate the baroreceptors and therefore increase the secretion of this hormone in the posterior pituitary gland. The physiological effects of ADH are to enhance the reabsorption of glomerular filtrat in the distal tubules and collecting tubules, what results in a decrease in the volume of the secondary urine and the increase of CBV. In the case of a high concentration of this hormone in the blood, it has a vasoconstrictor effect on the arterioles and veins. It received its second name, vasopressin because of this effect. However, this hormone can also be secreted in response to an increase in osmotic blood pressure (even in the absence of SAP changes). It promotes reabsorption of water in the renal tubules into the blood, as well as produces a feeling of thirst. This hormone supplements the effects of RAAS during compensation of hypotension.

The atrial natriuretic hormone (ANP) is secreted by the cells of the right atrium in response to stretching of it by increasing venous blood return to the heart. The physiological effects of this hormone are the opposite to the effects of aldosterone. It causes a decrease in reabsorption of sodium and water ions in the renal tubules and also causes moderate dilatation of

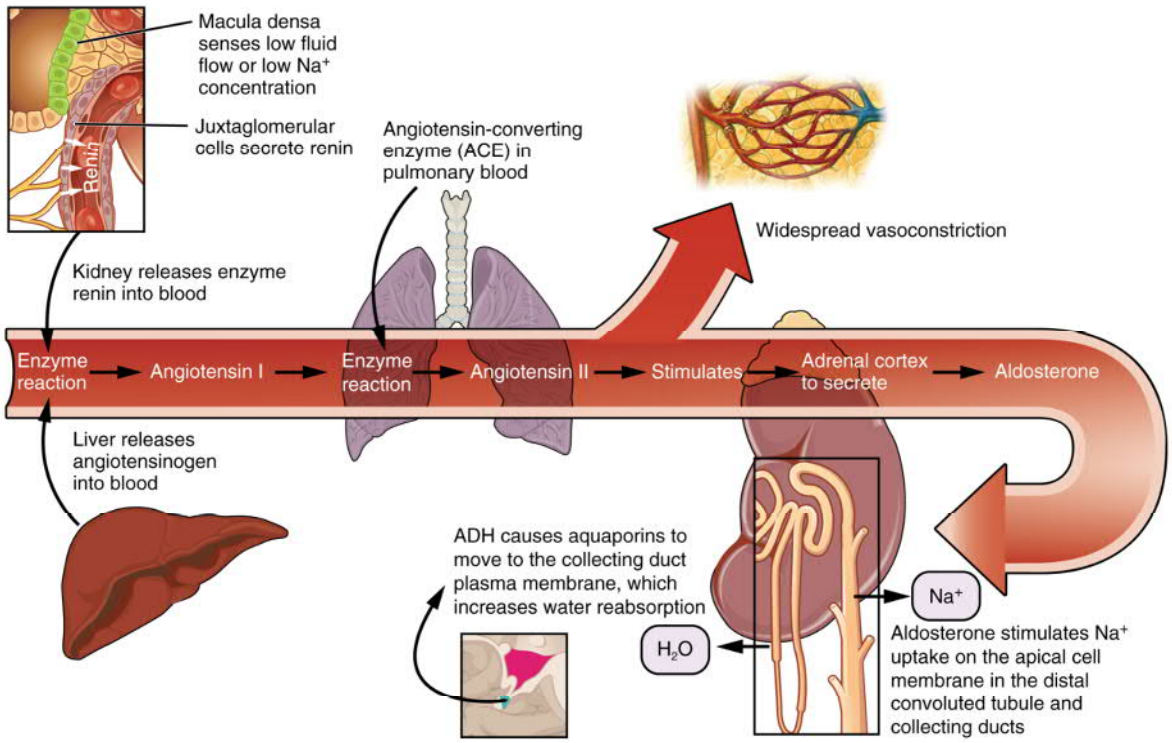

Fig.7.48. Renin-angiotensin-aldosteron system (RAAS) and its main effects.
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arterioles and veins. The result of these effects is an increase in urine excretion by the kidneys, a decrease in CBV and a decrease in SAP. It has been established that ventricles, in response to excessive stretching, secreted an ANP-like hormone called the ***Brain Natriuretic Peptide (BNP),*** since it was first detected in the neurosecretory cells of the brain.

10. Features of regional blood circulation in some organs and tissues

10.1. Features of blood supply of the brain.

The cerebral blood flow in the resting state is approximately 750 ml / min, which is about 15% of CO. Gray matter is supplied with 5-6 times more blood than white matter. The cerebral blood flow can be increased no more than 50% even during high functional activity. This is a small range of changes compared with other organs, but in the brain, there is a redistribution of blood between inactive and active areas in favor of the latter.

The main feature of the cerebral blood flow are the 1) ***myogenic autoregulation*** and 2) ***its dependence on local metabolic factors***: partial pressure of CO_2, O_2 and pH of the interstitial fluid. The most important factor of them is CO_2 partial pressure. Hypercapnia causes a pronounced relaxation of precapillary sphincters, resulting in increased blood supply of the brain. In contrast, the cerebral blood flow decreases during the hypocapnia (for example, in mountains or because of hyperventilation), what can lead to vertigo and even loss of consciousness.

Myogenic autoregulation provides relatively constant blood flow independent from fluctuations of systemic blood pressure in the range from 60 to 160 mm Hg. However, if SAP goes out this ranges it becomes dangerous. At SAP <60 mm Hg fainting occurs and at SAP> 160 mmHg the cerebral edema can occur due to increased capillary permeability. Autonomic nerves and hormones make insignificant influence on the cerebral hemodynamics.

10.2 Features of blood supply to the myocardium.

The cardiac blood flow is about 250 ml/min at rest, which is about 4% of the CO. At maximal heart work, coronary blood flow can increase in 4-5 times. The most important feature of blood supply to the myocardium is its ***dependence on the phases of cardiac cycle***. Blood flow is maximal in the diastole phase and slows down with systole. Another feature of blood supply to the myocardium is an ***extremely high oxygen extraction from arterial***

blood. Therefore, the deficiency of oxygen in the myocardium can be covered only by the proportional increasing of coronary blood flow. The intensity of myocardium vascularization increases from epicardium to endocardium. But there is the thin layer of the myocardium, bordering with the endocardium, which is supplied with blood only through the thebesian veins. That's why it is most often affected by coronary heart disease. In the left coronary artery at the beginning of the systole, the blood flow is almost stopped, but it is sharply increasing during diastole. In the right coronary artery , the pressure is less (compared with the left coronary artery) during the systole. Therefore, the blood flow during the systole is reduced there insignificantly (Fig.7.42). The outflow of venous blood from the coronary sinus, on the contrary, is greater during systole and decreases during diastole.

Coronary vessels have a large number of adrenoreceptors. In the proximal vessels mainly α-adrenergic receptors are found, and in the distal vessels mainly β-adrenergic receptors are located. The number of β-adrenergic receptors significantly exceeds the number of α-adrenergic receptors, and therefore catecholamines predominantly act as vasodilators in the coronary bed.

Metabolites that are formed during the myocardial contraction or are deposited in it with blood play an important role in the regulation of coronary blood flow. Adenosine, prostaglandins, potassium ions cause vasodilator effect due to direct action on smooth muscle of the coronary vessels. These vessels are also dilated under the influence of hypercapnia, hypoxia, and acidosis.

Myogenic autoregulation of coronary vessels predominates in the state of rest, what maintains a relatively constant level of blood supply to the myocardium in the range of changes in SAP from 50 to 140 mm Hg. However, during exercises, the local metabolic factors play leading role causing pronounced

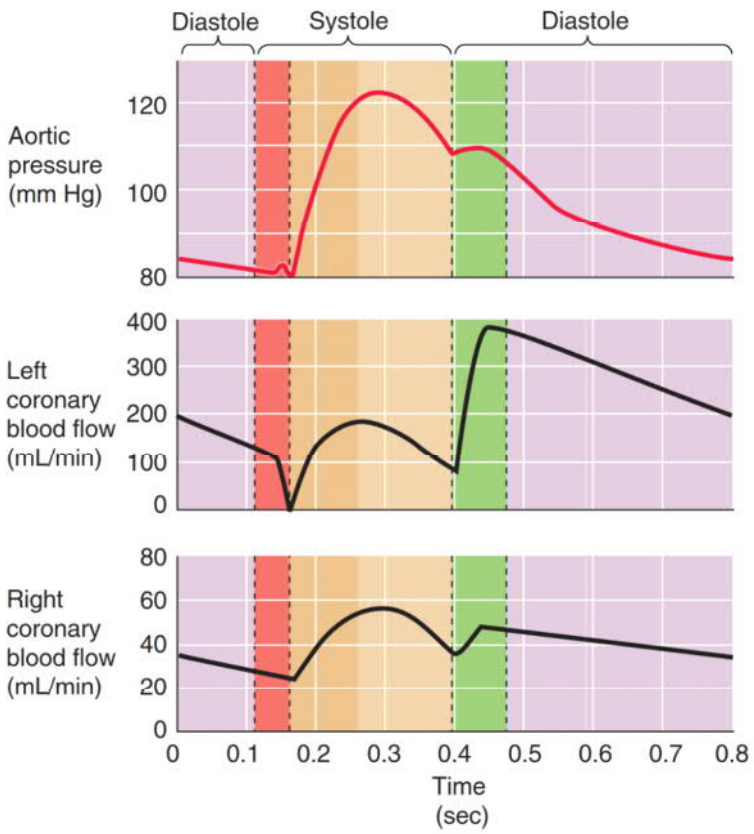

Fig.7.49. Coronary blood flow during cardiac cycle.

vasodilatation of arterioles (active hyperemia).

10.4 Features of blood circulation in the skin.

Blood flow in the skin is very dependent on the skin temperature. The total blood flow through the skin can vary in the range from 50 to 2500 ml/min. The skin gets about 5% of CO (250 ml/min.) at room temperature. Two different mechanisms are involved in the regulation of skin blood flow. The skin of acral areas (hands, feet, ears) is well innervated by sympathetic fibers, which provide high tone of the vessels in these areas, even at room temperature. Dilation of such vessels is achieved by central inhibition of the tone of sympathetic nerves. The vessels of the proximal areas of the extremities and trunk are dilated because of the tissue hormone bradykinin released during the stimulation of the sweat glands that are innervated by the sympathetic cholinergic nerves.

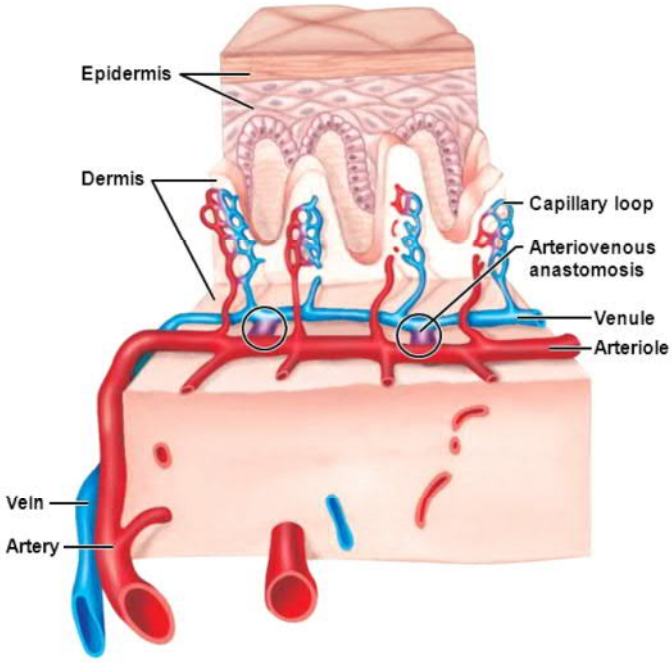

Fig.7.50. Circulation in the skin.

The subcutaneous venous plexus has a large capacity and can deposit a relatively large blood volume (up to 1500 ml) there. An important function of the skin blood flow is thermoregulation. Thus, at high temperatures, blood flow through the skin can reach 2500 ml/min. But this increase isn't the same in different parts of the skin. The greatest variations are observed in the distal limb parts. Reactions of the limb proximal areas and trunk are much weaker. Arterio-venous anastomoses are widely represented in the microcirculatory bed of the skin and play the most important role in the increase in blood flow during thermoregulatory reactions.

10.5 Features of blood supply of the lungs.

Since the intravascular pressure in the pulmonary circulation is relatively small (pulmonary artery pressure is 25/10 mm/Hg, and the average blood pressure in the capillaries 6-7 mm Hg), the blood flow in the lungs in upright body position depends on the hydrostatic pressure of the

blood column relating to the heart. The top of the lungs in adult staying in the upright position, are located 15 cm above the heart, so the hydrostatic pressure at this level is almost equal to the arterial pressure but directed against it. As a result, the tops of the lungs are perfused with blood very little. On the contrary, the hydrostatic pressure is added to the arterial pressure at the base of the lungs. That's why the vessels are stretched with blood in this region. The blood flow in the lungs is uneven due to these features and depends on the position of the body.

The heart pumps CO with a significantly lower gradient pressure in the vessels of the pulmonary circulation than in the systemic circle. The cause is that the TPR of a pulmonary circle is 6 to 7 times lower, then in systemic circulation. Pulmonary vessels have a high distensibility and can easily deposit a significant blood volume, what prevents pulmonary edema during the left ventricular heart failure.

Pulmonary vessels are innervated by sympathetic vasoconstrictive fibers, which can change the firing frequency, and accordingly, the lumen of the pulmonary vessels due to central inhibition. The vessels can constrict and limit the perfusion of alveoli due to the decrease in partial pressure of O_2 or an increase in partial pressure of CO_2 in the alveoli. As a result, a redistribution of blood flow in the alveoli occurs in accordance with their ventilation. Blood flow increases in those alveoli which are well ventilated compared to those which are ventilated poorly. In the systemic circulation, hypoxia, hypercapnia and acidosis cause vasodilation which is diametrically opposite to the analogous vessels in the pulmonary circle.

Adrenaline and norepinephrine constrict pulmonary vessels because they contain predominantly α_1-adrenergic receptors. There are numerous baroreceptors in the pulmonary arteries, which provide the reflectory coordination of pulmonary hemodynamics with systemic hemodynamics. Thus, pressure increase in the pulmonary arteries inhibits the inotropic function of the heart, and the pressure decrease in the pulmonary vessels, on the contrary, causes an increase in the blood pressure in the systemic circle.

11. Hemodynamics at different functional states of the body

11.1 Changing body position.

Changing the body position from the horizontal to the vertical (passive or active) is accompanied by redistribution of blood in the vascular system. The veins of the lower limbs stretch and deposit up to 500 ml of

blood, which is temporary excluded from systemic circulation due to the influence of gravity creating the increased hydrostatic pressure. This blood deposition reduces the venous return to the heart and leads to a decrease in SV and systemic blood pressure. Such changes trigger a number of regulatory mechanisms aimed to restore SAP. Thus, the baroreceptor reflexes from the aorta arc and the sinocarotid sinus cause vasoconstriction of the arteries and veins, especially expressed in the vessels of the skin, skeletal muscles, abdominal cavity. The same receptors trigger cardiac reflexes resulting in a positive chrono- and inotropic effect. This causes a rise in SV. Part of the deposited blood return to the vascular bed because of the veins constriction. Hormonal mechanisms also are involved in compensation, in particular, catecholamines, vasopressin secretion, and the renin-angiotensin-aldosterone system are activated. If these mechanisms are able to stabilize the systemic blood pressure, then hemodynamics is normalized. However, if these mechanisms are insufficient, loss of consciousness can occur which is associated with inadequate blood supply to the brain.

The clino-orthostatic test is used for testing blood circulation self-regulation systems. The criterion for evaluating this test is the dynamics of the heart rate (HR) when a person moves from a horizontal position to a standing, vertical one, and vice versa. The heart rate should decrease by 4-6 beats/min. in the clinostatic part of test (from vertical to horizontal position), and it should increase by 10-24 beats per minute in the orthostatic part of test (from horizontal to vertical position). Normalization of the HR should occur in 3-5 minutes.

11.2. Physical activity.

Physical activity increases the cardiac output (CO) due to increased heart rate and stroke volume (SV). The changes of these parameters depend on the level of exercise training. Thus, in trained people, CO increases mainly at the expense of SV and to a lesser extent due to heart rate; in untrained, the opposite is true. The first way is much more favorable in energy terms because the minute work of the heart is lower. If HR is reduced, blood supply to the myocardium is much better, because blood flow in the myocardium is most intense in the diastole phase.

There is a significant redistribution of CO during physical activity in favor of skeletal muscle at the expense of other organs. The increase in blood flow in working muscles is mainly due to local metabolic mechanisms and hemodynamic micropumping function of skeletal muscles. The total peripheral resistance of the vascular bed is significantly reduced by lowering the peripheral resistance in the intramuscular vessels. With an increase in the load from easy to intense physical activity, the skin blood flow initially decreases and then increases for the purpose of heat transfer. Coronary

blood flow increases in accordance with the work of the heart, and the brain blood flow remains relatively constant at any load due to mechanisms of myogenic autoregulation. As a result of the skin vessels vasoconstriction and release of blood from other depots (liver, spleen), the circulating blood volume increases.

Systolic blood pressure during exercise usually is increased, and diastolic either decreases or remains constant. As a result, the mean arterial pressure changes only slightly. Its high increase due to diastolic blood pressure indicates an unbalanced regulation of hemodynamics.

Fig. 7.43 illustrates changes in the distribution of CO between different organs and systems during medium exercise training in the mode of rhythmic contractions of skeletal muscles (eg, jogging) in comparison with rest. From the data presented, it is clear that the blood supply of skeletal muscles, which consumes 73% of CO (in a state of rest, only 20%), increases to a great extent. During the moderate exercise the blood supply of the heart is 3-4 times, of the skin 4-5 times and of the skeletal muscles 10-12 times bigger than in a rest state (in absolute values). Blood supply of the brain remains at practically the level of rest, blood flow in the kidneys and digestive organs is significantly reduced. Such changes are provided by the influence of ANS and a number of hormones on regional hemodynamics in these organs. Active hyperemia in skeletal muscles and myocardium is due to local metabolic factors and hemodynamic micropumping function.

In the case of a physical activity in the isometric contractions mode, this redistribution is different. The difference is that such muscle contractions compress the blood vessels in the muscles and the conditions for their blood supply become worse. The active hyperemia in skeletal muscles is much less pronounced, as a result, a TPR tends to increase, which creates more stress on the heart and

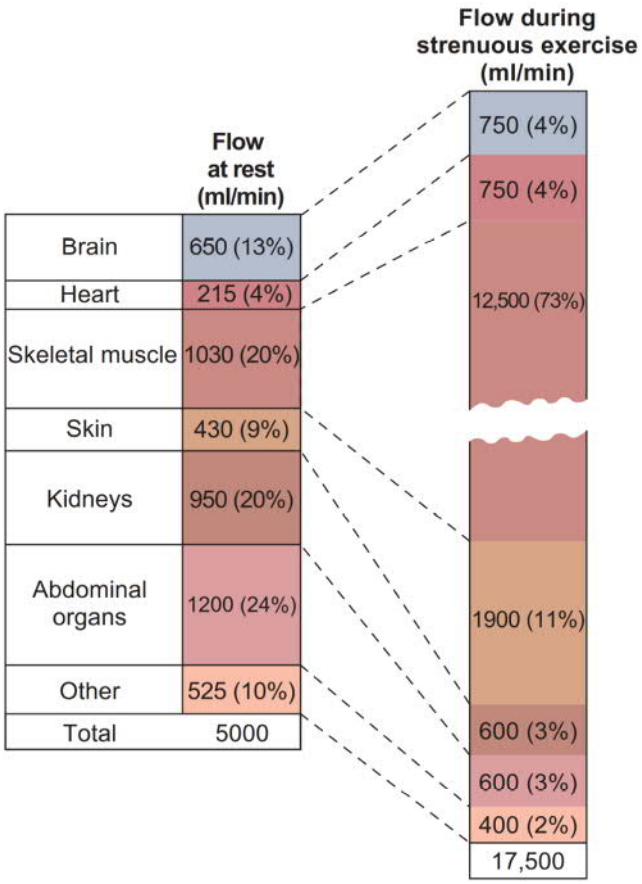

Fig.7.51. Distribution of the systemic cardiac output at rest and during strenuous exercise.

leads to a significant increase in systemic blood pressure. Long-term training in such mode causes the formation of left ventricular hypertrophy and may in the future become a cause of congestive heart failure.

11.3. Compensatory hemodynamic reactions in blood loss.

Hemodynamics disturbance due to a blood loss is associated with a change in the ratio of the vascular system capacity and volume of circulating blood. When the blood loss begins, the reflectory mechanisms that responsible for maintaining systemic arterial pressure and venous return are activating in the first line. Later, the reserves for increasing circulating blood volume are mobilized. An increase in the venous return of blood to the heart and the rising of SV is achieved by the same mechanisms as in the orthostasis. These mechanisms can effectively compensate the changes in hemodynamics if the blood loss does not exceed 25% of the CBV. With greater blood loss, reflex compensation is not sufficient and SAP decreases.

Arterial and venous baroreceptors detect the dropping of blood pressure, what results in activation of vasoconstrictor influences and acceleration of heart rate. First of all, vessels of the skin, muscles and internal organs (excepting the brain and myocardium) are constriciting. A state called *the centralization of blood flow* develops: a smaller volume of blood remaining in the systemic blood circulation is redistributed in favor of the most important organs. At the same, time hormonal mechanisms of increasing CBV are unfolded. To these mechanisms belong, first of all, a shift in the capillary filtration-reabsorption equilibrium in the direction of predominance of reabsorption, increased secretion of ADH and activation of the renin-angiotensin-aldosterone system. Only after the restoration of CBV activity of the mechanisms maintaining the blood pressure decreases. Later, the processes of hematopoiesis continues compensatory reactions, which replenish the plasma cellular elements. In the case of insufficient compensation of blood loss, hemodynamic shock occurs.