of fibers gradually increases, but they do not become shorter. The ventricular pressure rapidly elevates which consequently evokes enclosure of AV valves. In this phase the semilunar valves are still enclosed, since the ventricular pressure has not yet transgressed those in aorta and a.pulmonalis.

As soon as the ventricular pressure transgresses the diastolic pressure in aorta and a.pulmonalis, the semilunar valves open and the blood begins to be ejected into large vessels. This phase is referred to as **ejection phase**, in the course of which the volume of ventricles decreases by the ejected volume. The ventricular pressure augments as high as to the maximal systolic value (130 torr in the left ventricle and cca. 25 torr in that of the right) At the end of systole the intraventricular pressure decreases. Hence, the end-systolic pressure is lower than the maximal systolic pressure.

Half of the ejected blood volume is being ejected during the first fourth of the ejection phase. The second half is being ejected during the subsequent two fourths. During the last fourth no blood is ejected into large vessels in spite of the fact that the ventricles are subdued to contraction. This period is referred to as **protodiastole**. During the ejection phase under resting conditions cca 60-70 % of the end-diastolic volume of blood is ejected.

During the period of protodiastole the blood pressure decreases as no blood is ejected from the heart, on the contrary it flows toward the periphery. Rapid stoppage of blood ejection from ventricles causes that the arterial pressure transgresses the value of the ventricular pressure. In consequence of such pressure alterations the aortic and a.pulmonalis semilunar valves close. The ventricular musculature begins to slacken. This period is referred to as **izometric** or **izovolumetric relaxation**. During this phase the ventricular pressure achieves the lowest values. When the ventricular pressure drops below the level of atrial pressure, the AV valves open and the ventricles begin to be filled with blood from atrii. By the opening of AV valves the ventricular diastole is initiated. At the end of diastole the atrii and ventricles are activated from the sinus bundle. By means of atrioventricular valves enclosure the ventricular systole is reinitiated.

3.5 Pathomechanism of heart failure

Heart failure is a state when in spite of normal or increased filling pressure, the heart fails to secure an adequate perfusion of peripheral tissues. The term heart failure does not include the states when hypoperfusion of tissues supervenes in consequence of reduced filling pressure (e.g. shock), or when hypoperfusion is accompanied by increased filling pressure due to extracardiac reasons (e.g. inadequate extensive and rapid infusion therapy).

There is a certain difference between the clinical and pathophysiological comprehensions of the term heart failure. The clinical comprehension of the term includes foremostly the secondary consequences of heart failure per se (dyspnea, edemas), eventually the symptoms of compensatory mechanisms (hypertrophy). The term **congestive heart failure** used in literature explicitly comports the clinical conception of this syndrome in which heart failure is equalled with the conception of congestion. The left-sided heart failure results in congestion in the pulmonary circulation circuit which is accompanied by dyspnea. The right-sided heart failure results in congestion in the systemic circulation circuit which is often accompanied by peripheral edemas. In addition, as the definition implies, the primary consequence of heart failure is represented by insufficient perfusion of peripheral tissues. The fact that the clinicians notice especially the congestion as a secondary consequence of heart failure, results from the fact that these symptoms are much more conspicuous in comparison with the consequences of hypoperfusion of peripheral organs as e.g. oliguria, muscular weakness, fatigability, dyspepsia. The symptoms of peripheral hypoperfusion are not only less conspicuous, but also better tolerated by a patient. Usually it is the dyspnea, or edemas which force the patient to consult the physician.

Heart failure does not represent a clinical unit. It is a state which can supervene in consequence of various cardiac diseases.

1. Causes of heart failure:

   (a) Myocardial impairment due to ischemic heart disease
   (b) cardiomyopathies
   (c) toxic impairment of myocardium (diphteric, etanaltoxic, meadicamental – Adriamycine)
   (d) myocardial impairment due to endocrinopathies (diabetes mellitus, hyperthyreoidism and hypothyreoidism)

2. Chronic hemodynamic overload of the heart
   (a) pressure overload (hypertension disease, stenosis and coarctation of the aorta – left heart, pulmonary hypertension, a. pulmonalis stenosis – right heart)
   (b) volume overload (mitral, aortic insufficiency, arterio-venous shunts, all types of hyperkinetic circulation)

3. Disturbances of the heart rhythm
   (a) extreme tachyarrhythmia (supraventricular tachycardia, fibrillation and flutter)
   (b) extreme bradycardia (sinus or AV block of higher grades)

4. Restricted filling of ventricles (constrictive pericarditis, cardiac tamponade, endomyocardial fibrosis)

The most frequent causes of heart failure are the ischemic heart disease and hypertension disease. These together represent cca 70 % of reasons of heart failure.

The moment which triggers off a series of subsequent events leading to the development of heart failure is the **decrease of ejection volume of the heart**. In consequence heart failure manifests itself in two different ways: forward failure - in the direction of blood flow, and backward failure - against the direction of blood flow.

Forward failure - represents the consequence of a decreased stroke and minute cardiac volumes determined by the decrease of ejection fraction. Under normal circumstances the amount of ejected blood forms cca 70 % of the end-diastolic volume. Heart impairment leads to the reduction of this amount, which results in the deterioration of the blood supply in peripheral tissues and organs. It results in insufficient performance of various organs, e.g. digestive system, kidneys, liver, brain etc. (see fig. 3.11 on page pagerefo2-11).

Backward failure – is caused by the fact that by means of the decrease of ejection fraction greater amount of blood remains in the inflicted ventricle at the end of systole. Due to the reduction of ejection fraction, e.g. to 50 %, the 50 % of the end-diastolic volume persists in the inflicted ventricle in contrast to normal 30 %. In regard to the fact that during diastole normal amount of blood flows into the ventricles, the end-diastolic volume and pressure in the inflicted ventricle gradually increases. Inleft ventricular failure this pressure elevation is conveyed into the right atrium, pulmonary veins, and finally into pulmonary capillaries. This process manifests itself clinically by various levels of dyspnea. Failure of the right heart brings along augmentations in volume and pressure in the right ventricle. The increase in pressure is conveyed into the right atrium, capacity bed and finally into capillaries in peripheral organs. Augmentation of the hydrostatic pressure in capillaries finally leads to peripheral edemas (see fig. 3.11 on page o2-11).

A various period of time can elapse from the particular moment of heart impairment until the clinical symptoms of heart failure become evident. During this period the heart impairment manifestation is being eliminated by the so-called **compensatory mechanisms**, which may be acute (applied practically immediately after heart failure onset), or chronical which become evident as a result of a long-term hemodynamic overload. In the acute phase of heart insufficiency two compensatory mechanisms come into play: Frank-Starling mechanism and catecholamines which stimulate contractility and heart rate. In cases of chronic failure in consequence of long-term hemodynamic overload, still another compensatory mechanism develops, namely myocardial hypertrophy.

If compensatory mechanisms entirely prevent the onset of clinical manifestation of heart failure it is referred to as **compensated heart failure. Decompensated heart failure supervenes** when in spite of the fact that compensatory mechanisms are in action the clinical symptoms of heart failure become evident.

Catecholamines-derived stimulation and Frank-Starling mechanism begin to act immediately after

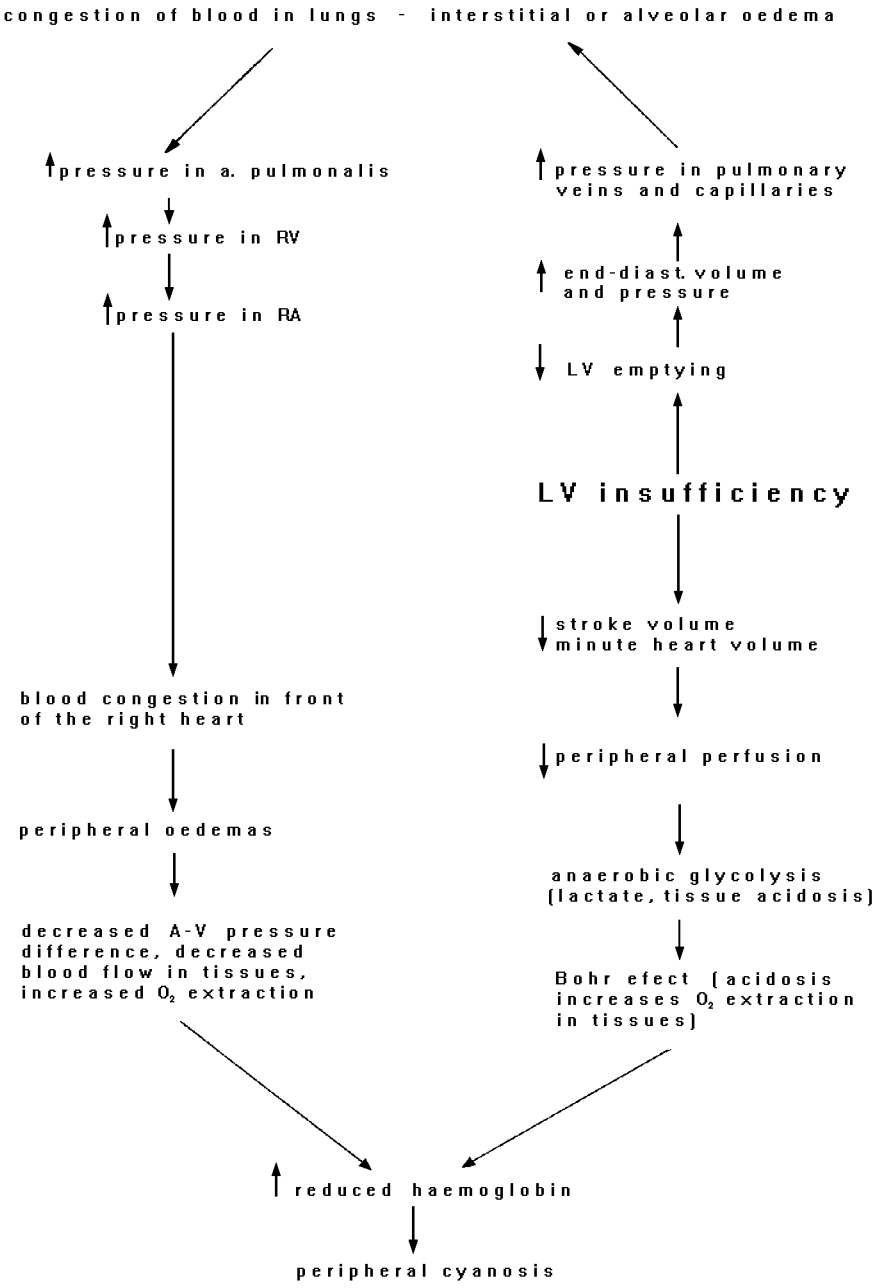

Figure 3.11: Hypertrophy and dilatation of the heart

the origin of heart impairment associated with a decreased minute ejection.

The reduction of aortic pressure, elevation of pressure in the left ventricle, and later in the left atrium and pulmonary bed stimulate the special receptors, namely pressoreceptors and chemoreceptors in aorta, cardiac ventricles and atrii as well as in pulmonary bed. These receptors provide information to vegetative centres in the fundus of the fourth brain chamber, by means of which the activity of nervus vagus is supressed. Consequently, the **sympathetic nervous system** becomes dominant. Noradrenaline released from the sympathetic nerve endings, and noradrenaline and adrenaline released from the medulla of suprarenal glands stimulate by means of the β_1 receptor the system of proteinkinase in cardiomyocytes. These via phosphorylation of subcellular structures accelerate the Ca^{2+} supply toward contractile elements and the muscular contractility increases. Catecholamines simulataneously stimulate the electric events in the heart and the frequency increases. Increased contractility and frequency result in augmentation of the minute heart volume, improving thus the perfusion of peripheral tissues.

In additon to catecholamines also the **Frank-Starling mechanism** comes into force since the very onset of heart impairment. The reason to it is that the reduced ejection fraction results in augmentation of the end-diastolic ventricular volume. Consequently, also the initial length of muscular fibers increases and saromeres are prolonged to the optimal value near 2,2 μm, which enables the heart to exert the maximal force of contraction. Both acute mechanisms participate in prevention of heart failure manifestation in spite of the fact that the heart which is responsible for the maintenance of blood flow toward the periphery is already impaired.

At long-term hemodynamic overload of the heart, the chronic **heart hypertrophy** representing a chronic compensatory mechanism comes into play.

It is a so important and complex process that it must be subdued to thorough analysis in the entire following chapter.

Herein it is necessary to emphasise at least the fact that hypertrophy does not mean merely the growth of cardiac tissue mass. It represents a complex reconstruction of architecture, ultrastructure and biochemism of the myocardium. These alterations, both quantitative and qualitative, are of adaptational character and enable the heart to deal with the hemodynamic overload for a long period.

Hence, while in acute myocardial impairment the heart failure is prevented by catecholamines and Frank-Starling mechanism, in chronic hemodynamic overload it is foremostly hypertrophy of the heart which to a significant extent normalizes the hemodynamic situation.

The presented compensatory mechanisms able to maintain the adequate minute volume of the failing heart are, however, limited by the extent of heart impairment and its duration. The pathological process in the heart can be so intensivesince the very beginning that the compensatory mechanisms in spite of their maximal activation are not able to compensate adequately (e.g. in the case of extensive myocardial infarction). In other cases the formerly adequate compensation may become insufficient during the course of pathological process. This second alternative develops either in consequence of heart impairment progression, or due to the exhaustion of the compensatory mechanisms. The Frank-Starling mechanism has a very restricted capacity which is limited by expansion of sarcomere to 2,2 μm. Also the sympathetic system fails after its prolonged activation A long-term hyperfunction of the sympathetic nervous system results in impaired catecholamines synthesis, reduction of catecholamines uptake and reduction of the number of β-receptors on the surface of myocytes. Hypertrophy of myocardium in the majority of cases fully compensates the increased hemodynamic overload for a long period. Nevertheless, it becomes insufficient after a particular time (often decades). A whole series of mechanisms participate in this process, part of which are elucidated and some still remain unexplained.

If even maximal exploitation of compensatory mechanisms is not able to maintain the adequate perfusion of peripheral tissues, the heart failure starts to be also clinically manifested. Heart failure represents a stress situation for the organism which has many characteristics in common with the general stress syndrome. Hence, all the following adaptational mechanisms bear the character of stress reaction with the typical neurohumoral reaction and subsequent rebuilding of circulation and metabolism. **In this stage the maintenance of adequate pumping performance of the heart ceases to be the actual aim. There is nothing more to be mobilized within**

the heart as the compensatory mechanisms are already maximally activated. The organism struggles to maintain an adequate perfusion of vital organs – heart, brain (and eventually kidneys) in spite of the reduced minute volume of the heart. This state of course can be achieved exclusively by redistribution of the blood flow, i.e. the increased perfusion of vital organs is achieved owing to vasoconstriction (and relative ischemia) of all other systems (skin, splanchnic region, striated muscles, etc.).

The main neurohumoral component of the ultimate adaptational reaction when an organism no longer struggles to maintain a harmonic performance of individual systems, but merely to survive, are catecholamines and renin – angiotensin II – aldosterone system. However, the position of catechlamines in this typical stress reaction substantially alters in comparison with the initial stage of heart failure. Their secretion remains to be administered by stimulation of baroreceptors and chemoreceptors by relative hypotension of central parts of arterial bed and by raised pressure in the pulmonary venous system, however neither their maximal stimulation is capable to increase the pumping activity of the heart. Intesified stimulation of the sympathetic nerve system manifests itself however by an excessive vasoconstriction of the peripheral organs which secures the elevation of the mean arterial pressure. Vasoconstriction in kidneys and subsequent hypoperfusion of vas afferens evokes activation of the system renin – angiotensin I – angiotensin II – aldosterone. Angiotensin II supports the pressoric effect of noradrenaline, and aldosterone helps to preserve the blood volume and thus to maintain the mean arterial pressure. Antidiuresis is intensified also by the antidiuretic hormone which is released either by direct stimulation of the posterior lobe of the pituitary gland by the activated sympathetic nerve, or on the basis of hyperosmolarity. The latter is caused by resorption of sodium with a relatively less intensive resorption of water under the influence of aldosterone.

Peripheral compensatory mechanisms which represent a component of the typical alarm reaction are effective merely for a short period. The general vasoconstriction in the peripheral tissues forces the left ventricle to work against great resistance. The afterload increase decreases the pumping ability of the heart, and the minute volume decreases. At this stage even the increase in venous return in consequence of vasoconstriction of the capacity bed does not improve the pumping ability of the heart. Frank-Starling mechanism is as a matter of fact already exploited to the maximal extent and an increase in the venous return does not increase the cardiac ejection, but deteriorates the pulmonary congestion. In addition elevation of both afterload and preload have a negative impact on ATP reserves in myocardium, which supports the deterioration of the cardiac function.

Conclusion: Heart failure represents a state when the heart is not able to secure an adequate perfusion of peripheral organs in spite of normal blood return. At its onset the impairment of cardiac function does not manifest itself clinically since the compensatory mechanisms stimulate the reserve forces of the heart and circulation in order to prevent the deterioration of the hemodynamic situation. When the pathological process becomes more prominent, the effectivity of compensatory mechanisms decreases. In spite of their maximal exploitation they are not able to maintain an adequate perfusion of the periphery any longer. At this stage, the stress reaction in response to the impaired performance of the heart comes into play. Preservation of the adequate peripheral perfusion ceases to be the aim of subsequent neurohumoral alterations. The only aim is to delay the death of the organism per se. The stress mechanisms maintain perfusion via vital organs, namely the brain and heart on the account of other tissues. The life quality of such an individual is considerably deteriorated. The stress reaction is an energetically demanding event even in a healthy cardiovascular system. In failing heart despite the positive adaptive character of stress reaction, the heart function worsens gradually and the heart definitively fails.

3.5.1 Symptoms of left ventricular heart failure

The symptoms of cardiac failure resulting from hypoperfusion of tissues (forward failure) most frequently occur at the beginning, but are less salient than the consequences of blood stagnation before the heart (backward failure). Hence, the clinical severeness of heart failure is judged mainly in dependence on the stage of dyspnea due to left ventricular failure and on the severity of peripheral edemas due to right ventricular failure.

3.5.1.1 Dyspnea

Dyspnea is a subjectively percieved sensation of breathlessness in a patient. This being so, the information of it can be gained only from the patient's reference. Hence it is incorrect to use this term in coincidence with an unconscious patient with breathing difficulties, or experimental heart failure induced in laboratory animals.

According to the severity of heart insufficiency several forms of dyspnea are distinguished:

- **exertional dyspnea** occurs in a person with impaired heart functions, though symptomless during rest, owing to exploitation of compensatory mechanisms. Increased physical strain accompanied by increased tonus of the sympathetic nervous system and vasoconstriction of the capacity bed results in elevated venous return. Nevertheless the impaired heart works on the borders of its possibilities already under rest conditions. Increased preload therefore does not evoke an increase in heart ejection, but elevates pressure in pulmonary capillaries. The stagnating fluid, though, does not transudate into interstice at the beginning, but reduces the pulmonary compliance. Hence, the ventilation ability deteriorates and the development of hypoxemia stimulates the activity of the respiratory muscles by means of stimulation of the respiratory centre.

- **dyspnea during rest** - its more moderate form is **orthopnea**, i.e. dyspnea which occurs in recumbent position. In horizontal position the blood is redistributed from the distal parts of the body toward the heart. This effect of increased venous return is the same as when evoked in consequence of physical exercise. When the patient acquires a sitting posture, the venous return decreases and the state recovers quickly. A more severe form of dyspnea is the **nocturnal paroxysmal dyspnea**. Besides the effect of horizontal position also the increase of the parasympathetic tonus during sleep participates in its onset. The latter decreases the contractile ability of the heart and reduces also the activity of the respiratory centre. Nocturnal paroxysmal dyspnea is accompanied not only by congestion but also by transudation into interstice which results in interstitial pulmonary edema. The reason is that the stimulation threshold of the respiratory centre during sleep is decreased and the information about hypoxemia development is delayed. A sleeping patient can thus tolerate relatively severe pulmonary swelling and may awaken after three or six hours, i.e. when hypoxemia reaches a severe stage. By this time the stagnating fluid transudates into the interstice. In such cases the recovery of dyspnea by means of changing position from recumbent to sitting posture is slow and some cases require pharmacological intervention. Bronchospasm participates in this form of dyspnea. It originates on a reflex basis when the congestion in the pulmonary bed and swelling of bronchial mucosa play the stimulatory role. This form of dyspnea is called **cardiac asthma**.

3.5.1.2 Pulmonary edema

Pulmonary edema means accumulation of excessive amount of fluid in pulmonary interstice or even in alveoli. There are at least three mechanisms which participate in formation of pulmonary edema.

- increased hydrostatic pressure in pulmonary capillaries
- increased permeability of the capillary wall
- decreased coloidosmotic pressure in blood

There are several protective factors which act against edema formation: Lymphatic drainage, the capacity of which increases five to sixfold already several hours following the onset of pulmonary congestion. In addition great difference between hydrostatic pressure in the capillaries (7 torr) and coloid osmotic pressure of blood proteins (28 torr) which has an opposite impact, also play a protective role. Pulmonary edema develops as late as when both the capacity of lymphatic drainage and pressure reserve are exceeded.

Pulmonary edema develops in coincidence with various diseases:

1. Diseases of the cardiovascular system:
   (a) Acute heart failure
   (b) Chronic heart failure
   (c) Excessive infusion therapy

   (d) Hyperdynamic circulation

2. Diseases of the respiratory system:

   (a) Pneumonia

   (b) Tumors causing lymphatic vessels obstruction

   (c) Inhalation of toxic and irritating gases

3. Diseases of the kidneys

   (a) Glomerulonephritis

4. Diseases of the central nervous system

   (a) Vascular incidents

   (b) Inflammatory diseases

   (c) Neoplastic diseases

5. Intoxications

   (a) Oxygen

   (b) CO

   (c) ether, hashish, etc.

Cardiac diseases bring about the development of pulmonary edema especially in cases of abrupt elevation of the capillary pressure. This process takes place in acute heart failure. The most frequent cardiac causes of pulmonary edemas are the following: extensive myocardial infarction, hypertension crisis, bacterial endocarditis with perforation of the mitral or aortic valves, pneumonia accompanying severe aortic or mitral stenoses which were until then compensated. Chronic heart failure and repeated formation of interstitial edema cause a thickening of alveocapillary membranes, thus forming a barrier for transudation of fluid into alveoli. Therefore, alveolar edema relatively seldom accompanies chronic heart failure.

The onset of pulmonary edema is associated with accumulation of fluid in interstice which is able to absorb a double amount of fluid in comparison with physiological circumstances. This state is referred to as **intraalveolar edema** (see fig. 3.11 on page 105). It manifests itself clinically as nocturnal paroxysmal dyspnea. In regard to the fact that then the only barrier for liquid transudation is the thin alveolar membrane, even moderate excercise with subseqent increase of capillary pressure are sufficient to enable the fluid to enter the alveoli. **Intraalveolar edema develops**.

The clinical picture of pulmonary edema is extraordinarily dramatic. A patient is significantly breathless, cyanotic, and expectorates pink foamy sputum. Similarly as in myocardial infarction, this state is associated with the sensation of anxiety of death – horror mortis.

The pathogenesis of pulmonary edema developed due to heart failure is of a complex character. Its origin is to the major extent the result of increased postcapillary pressure in the lungs and thereby the increase of capillary hydrostatic pressure. Besides the latter also some additional factors participate in this process. Hypoxemia of the liver with subsequently reduced albumin synthesis cause reduction of coloid osmotic pressure of proteins. If the right heart simultaneously fails, the long-term hepatic congestion participates in impairment of the proteosynthetic function of the liver. Hepatic congestion can lead to the origin of Pick's cirrhosis. Long-term reduction of renal perfusion sometimes results in renal impairment with subsequent proteinuria. Proteinuria continues in deteriorating the hypoproteinemia. Prolonged hypoperfusion of the kidneys at the same time stimulates the renin-angiotensin II-aldosterone. As a result the so-called secondary hyperaldosteronism develops which maintains the amount of circulating fluid and thereby also the blood flow toward the lungs via the right heart. This process supports transudation of fluid.

The oxygen level gradually decreases as a result of deteriorated exchange of gases in consequence of fluid being present in interstice or pulmonary alveoli. At the same time the ventilation deteriorates due to pulmonary congestion which is associated with decreased pulmonary elasticity. Finally hypoxemia completes the damage and thus increases permeability of the alveolocapillary membrane which facilitates the pulmonary edema development. Alveolocapillary membrane is often impaired iatrogenically due to prolonged therapeutic application of oxygen in high concentrations.

Especially in elder people the congestion contributes to the origin of inflammatory process in the lungs and hypostatic pneumonia may develop. Swollen hila of lymphatic nodes can deteriorate the lymphatic drainage and support the onset of pulmonary edema.

Summary: The pathogenesis of pulmonary edema due to the left heart failure includes several factors. The main role is ascribed to the elevation of the hydrostatic pressure in pulmonary capillaries in consequence of postcapillary hypertension. Hypoxemia, when at its onset, increases the capillary permeability. Hypoproteinemia with reduced coloid osmotic blood pressure develops due to hepatic impairment, namely by hypoperfusion and retrograde congestion. Under specific circumstances the deteriorated lymphatic drainage may also participate in pulmonary edema development.

Similarly also the subjective sensation of dyspnea is caused by several reasons. The main role is ascribed to stimulation of receptors in pulmonary vessels by means of their increased tension due to congestion. The sensation of dyspnea occurs obviously due to increased respiratory work and consequent muscular fatique along with decreased elasticity of the lungs. An important role is played also by direct stimulation of the respiratory centre due to hypoxemia and lactic acid which accumulates in respiratory muscles. The subjective picture of dyspnea is supported by bronchoconstriction evoked by edema of bronchial mucosa.

Increased muscular fatigue and decreased physical performance belong to less salient but often initial signs. In consequence of the decreased minute volume, and in advanced stages of heart failure also in consequence of concommitant sympathetic vasoconstriction, the oxygen supply of muscles decreases. Anaerobic glycolysis is not able to meet fully the energetic needs and thus the level of high energy phosphates in muscles decreases. In consequence of ATP deficiency the muscles slacken. In such muscles the proprioreceptors are being less stimulated. A smaller number of impulses passing via afferent pathways into CNS is conceived as a sensation of fatigue. Fatiguability of muscles is supported by accumulation of lactate and formation of muscular acidity which blocks the glycolytic enzymes prior to the exhaustion of glycogen reserves. ATP is inevitable not only for contraction but also for relaxation of muscles. ATP deficit may lead to muscular spasms.

Cerebral symptoms include somnolence, sleep disorders, headache, decreased psychical activity. They originate in consequence of cerebral hypoperfusion and decreased load of oxygen carried by blood.

Cough is of intermittent, weak, nonproductive character. It is probably evoked by stimulation of receptors in the distended pulmonary vessels and in edematous mucosa of spastic bronchi.

Nycturia – nocturnal micturition is a sign of severe heart failure. During the day the peripheral mechanisms of vasoconstriction are maximally exploited. This results in decreased production of urine and oliguria. During sleep the tonus of the sympathetic nerve decreases, kidneys are better perfused and production of urine increases.

Dyspeptic syndrome originates in consequence of insufficient perfusion of digestive organs. Impairment of digestion and absorption of nutriments develop. Detoxication functions of the liver are disturbed. Both exogeneous and endogenous functions of pancreas are decreased. Sugar, lipid and protein metabolisms are impaired. The sugar metablism is impaired in consequence of decreased insulin production due to vasoconstriction of pancreas. ľ- oxidation of lipids is disturbed in the impaired liver and in muscles. Proteosynthesis in the ischemic liver is decreased and catabolism of proteins is increased due to a high level of stressogenic glucocorticoids. This complex of alterations together with pronounced anorexia lead to generalized reduction of muscular mass and cardiac cachexia develops.

3.5.1.3 Cyanosis

Cyanosis refers to a bluish colour of the skin and mucous membranes. It develops in consequence of increased amount of reduced hemoglobin in the capillary blood. It is the absolute amount of reduced hemoglobin, rather than the ratio of the reduced and oxidized forms which is important in producing the cyanosis. The limitating amount of reduced hemoglobin which triggers the development cyanosis is considered to be 50 mg/l. It is app. one third of the total amount of hemoglobin at its normal level being 150 g/l. Since it is the absolute amount of reduced hemoglobin which is important in cyanosis development, there is no, not even theoretical possibility of cyanosis development in patients with severe anemia in which hemoglobin decreases below 50 g/l, and even patients with light anemias rarely display cyanosis.

On the contrary, in polyglobulia in which the level of absolute hemoglobin is high, the critical value of its reduced form is achieved relatively easy. Therefore cyanosis is a frequent symptom of polyglobulia.

Regarding the cyanosis development, the deter-

mining amount of reduced hemoglobin is that in the capillary blood, not in arterial or venous blood. Capillaries run closely below the surface and that is why they determine the colour of the skin and mucous membranes. The value of reduced hemoglobin in the capillary blood represents approximately the average value of its arterial and venous levels. Under the condition of normal oxygen saturation in blood, the capillary value of reduced hemoglobin is app. 25 g/l. This value assures the phenomenon that cyanosis does not develop under physiological conditions.

Cyanosis can be of central or peripheral character. In pathological processes in the heart both forms may occur.

Peripheral cyanosis (stagnating, *cold* cyanosis) develops at normal saturation of blood with oxygen. In consequence of blood stagnation the tissues extract a relatively larger amount of oxygen from the blood. This condition is typical in heart failure. In heart failure the blood flow via capillaries is slowed down and the contact of tissues with blood prolonged. The factors which trigger off the onset of peripheral cyanosis development due to heart failure include also reduction of the minute volume of the left heart. In consequence of peripheral vasoconstriction of arterioles the capillary region receives a reduced amount of blood. This fact alone, regardless of the congestion in the systemic circuit prolongs the contact of erythrocytes with tissue. Moreover, due to tissue acidosis and Bohr's effect increased dissociation of oxygen from oxyhemoglobin takes place. Naturally, peripheral cyanosis occurs in all states characterized by prolonged contact of blood with tissues (e.g. vasoconstriction due to exposure to cold, shock, or locally obstructed blood return) (see fig. 3.11 on page 105).

Because of the fact that this form of cyanosis is accompanied by vasoconstriction with a reduced blood flow, the tissues are cold. This form manifests itself especially in those regions where the capillary bed is situated closely below the surface (auricles, nose, cheeks, external lips, tips of fingers and toes).

Central cyanosis (arterial, *warm* cyanosis) originates in consequence of the fact that the arterial blood itself contains a smaller amount of oxidized hemoglobin than under physiological conditions. When the tissues extract the adequate amount of oxygen from blood, the level of reduced hemoglobin at the venous capillary ending can elevate above the critical value. This state accurs especially due to increased physical exersise, when the tissues extremely extract oxygen. The central cyanosis appears in inborn heart defects with right-left shunts and in some pulmonary diseases. It is, however often seen in the syndrome of heart failure. Naturally, in such a case the central cyanosis is not a sign of retarded blood flow in capillaries but represents a concomittant sign of the disease which has caused heart failure (right-left shunt, respiratory disease).

Since the cause of central cyanosis resides on the level of central organs (heart, lungs) the consequences inflict all tissues, which is especially visible on the skin and mucous membranes, and is not limited merely to acral localization. The signs include also the cyanotic tongue, palate, internal mucous membrane of the lips). While the peripheral cyanosis is associated with vasoconstriction, the central cyanosis manifests itself by symptoms of peripheral vasodilatation. It can be explained as a struggle of tissues to compensate their oxygen hyposaturation by enhancement of the blood flow. Vasodilatation manifests itself by warm skin, capillary pulsation, dilated veins of the forearms and hands. The next compensatory mechanism of central cyanosis is represented by polyglobulia. Clubbed fingers are a sign of chronic hypoxemia and they are the evidence of prolonged duration of the disease (years, or decades).

3.5.1.4 Disturbances of rhythm in heart failure

The term rhythm includes periodic electrical and subsequent hemodynamic changes, the aim of which is to pump blood from the venous into the arterial system. Smooth coordination of the presented electrical and mechanical events manifests itself acoustically by rhythmic changing of sounds of typical intensity and quality. When the events of depolarization and repolarization are disturbed, or when the characteristics of the myocardial tissues alter per se (contractility alteration, resp. myocardial stiffness), various changes in regularity and quality of the external signs of cardiac activity develop. Their hemodynamic and prognostic consequence may be insignificant, but on the other hand they may represent signals of severe impairment of cardiac functions.

One of the most typical manifestations of the alteration of normal rhythmicity in failing heart is the **gallop rhythm**. In gallop rhythm during one cardiac

revolution, three instead of two sounds can be heard. The mechanism of their origin is quite complex and its comprehension requires a concise conception of atrial hemodynamics.

Hemodynamic manifestation of atrial activity can be simply divided into three periods: Period of rapid ventricular filling which represents an early phase of diastole. The blood flows freely into ventricles on basis of pressure gradient. Hence the ventricle receives 80 % of the total amount of the end-diastolic blood volume. The subsequent diastasis, i.e. a pause in ventricular filling, is followed by a period of active contraction of atrii. By means of the latter the remnant 20 % of blood is distributed into ventricles.

Regarding the chronological localization of the third heart sound protodiastolic and presystolic gallops are distinguished. **Protodiastolic gallop** (diastolic gallop being a more correct term) produces the third heart sound at the end of rapid filling of ventricles. It occurs aside from the states of heart failure e.g due to mitral or aortic regurgitations, constrictive pericarditis and in infants and adolescents. The mechanism of the third heart sound origin is sometimes explained by an abrupt expansion of ventricles in the phase of their rapid filling. In fact the situation is much more complex. **The third heart sound is dependent not only upon the abrupt expansion of the ventricular wall, but also upon its rapid return to its original shape**. During this event the ventricular pressure elevates, the pressure gradient between the atrium and ventricle transiently swaps and at the end of the rapid ventricular filling **the atrioventricular valves enclose abruptly for a short while**. The latter is assumedly the most important component of the third heart sound in the diastolic gallop. The atrial pressure, however, continues to elevate due to the venous return, the atrioventricular valves subsequently reopen and owing to atrial contraction the remnant 20 % of the diastolic volume of blood flows in. This is the particular moment, which is followed by an enclosure of the atrioventricular valves for a longer period of systole.

The third heart sound can be **physiological** in children, since large elasticity enables the ventricle to expand and subsequently to take up the previous shape. This process results in an abrupt pressure elevation and the atrioventricular valves enclose temporarily. The pathological gallop occurs due to various reasons. In mitral and aortic insufficiencies, and in hyperkinetic states it is caused by a large volume of blood flowing into a ventricle. Presence of gallop in patients with constrictive pericarditis is dependent upon the restrictive effect of calcified pericardium which due to its minimal elasticity halts the diastolic filling abruptly, the expanded ventricles rapidly take up their initial shape. Consequently the atrioventricular valves are enclosed rapidly in the middle of diastole.

The situation in heart failure is different. The elasticity of a failing heart is significantly decreased and does not participate in the gallop origin. In consequence of congestion in the pulmonary circuit the pressure gradient between the left atrium and ventricle, achieves high values at the beginning of diastole. This situation causes rapid elevation of ventricular pressure during the passive blood filling of ventricles in the first phase of diastole and rapid temporary enclosure of atrioventricular valves in the early phase of diastole.

Presystolic gallop is dependent upon the origin of the third heart sound in late diastole, i.e. presystole. The mechanism of the third heart sound **coincides with a strong contraction of atrii in the last phase of diastole. Assumedly also the premature enclosure of either the mitral or tricuspidal valves at the end of diastole participate in its origin**. Premature enclosures of one or two atrioventricular valves take place owing to the rapid increase of ventricular pressure during strong contraction of atrii.

Under normal circumstances the enclosure of atrioventricular valves is a component of the first heart sound. It originates during ventricular systole. The third heart sound is physiological in young people and is caused by increased sympathetic tonus (rapid contraction of atrii) and increased elasticity of ventricles (premature enclosure of AV valves). However at an older age it indicates a pathological situation, namely hemodynamic overload, rather than heart failure per se. When the ventricle is hemodynamically overloaded, it holds up a larger amount of blood at the end of diastole. Therefore, in the final phase of diastole it is more difficult for atrii to press the last 20 % of blood into ventricles. A strengthened and accelerated contraction of atrii rapidly elevates the ventricular pressure and determines thus the enclosure of AV valves prior to the isometric contraction of the ventricle. If the hemodynamic overload is associated with chronic heart failure, the presystolic gallop

reflects besides the momentary hemodynamic overload, also the increased stiffness of ventricles. Both factors are responsible for the fact that the acoustic phenomenon accompanied by premature enclosure of AV valves ceases to represent a component of the first heart sound and manifests itself chronologically closely prior to the latter as being the third heart sound. It can occur in cases of failure either of the left or right side of the heart, respectively in cases of simultaneous failure of both sides of the heart. **Summation gallop**. If under pathological circumstances both protodiastolic and presystolic sounds occur simultaneously, they may merge into a single sound which is referred to as the summation gallop.

Tachycardia and extrasystoles are frequent findings in cases of heart failure. If tachycardia is of sinus character, it has a compensatory aim and originates in consequence of the sympathetic nerve activation and sinoatrial bundle stimulation. Extrasystoles can be atrial or ventricular. Their origin resides in both distension of the atrial or ventricular walls and enormous sympathetic stimulation. Consequently, depletion of ATP supervenes. According to Laplace's law the ventricular distension with increased tension in ventricular wall has a devastating effect on ATP reserves. It is supported also by the increased frequency of contractions and the so-called oxygen vasting effect of catecholamines. The oxygen vasting effect originates in consequence of the ability of catecholamines to uncouple oxidation from ATP production. Consequently energy formed in the respiratory chain leaks as heat, being inexploited. Energy depletion in a failing heart disturbs the Na^+-K^+-ATP-ase activity (and other ATP-ases), which impairs the normal ions-transport, and cardiomyocytes may become the source of pathological automation. This mechanism gives origin to extrasystoles, respectively tachycardia and atrial fibrillation, and in the terminal phase of heart failure also to ventricular fibrillation.

Pulsus alternans is characterized by regular alteration of pulses with both larger and smaller volumes. The mechanism of its origin has not been explicitly explained yet. A theory exists that on the basis of repolarization impairment, and thus partial refractoriness, less contractile fibers participate in the event of contraction during the weaker pulse. The impaired fibres recover during the weaker pulse and become active in the subsequent contraction. On the contrary, some fibres from the first beat are in a refractory state in the subsequent contraction. The presented facts, however, do not explain at all the alteration of pulse, since through the suggested mechanism all pulses would be attenuated.

An explanation that pulse alteration depends upon the reflex stimulation of atrii by means of sinus caroticus pressoreceptors is much more acceptable. This theory is supported by the fact that pulsus alternans is triggered by ectopic beat. When the pressure in arterial bed elevates due to the prolongation of diastolic pause after ectopic beat, and consequent larger end-diastolic volume, the activity of nervus vagus is stimulated on a reflex basis via sinus caroticus. Nervus vagus reduces the force of atrial systole diminishing thus the diastolic content of ventricles. At the following beat less blood is ejected. A relatively decreased pressure in sinus caroticus stimulates reflexively the sympathetic nerve system which supports the contraction of atrii. This mechanism elevates the end-diastolic ventricular volume and the following beat is more vigorous than normal. The more is the ventricular filling dependent upon the atrial contraction, the longer lasts the alternating pulse after the ectopic beat.

Alternating pulse is a frequent phenomenon in heart failure. It coincides with both frequent occurence of extrasystoles and simultaneous decrease in compliance of the failing heart's ventricle. In consequence of the decreased compliance of ventricles its diastolic content is significantly dependent upon the contractile function of atrii.

Cheyne–Stokes's respiration manifests itself by cyclically repeated, and gradually profound respiration until the maximal profound respiration is achieved. Consequently the respiration is debilitated to the extent of apnoe. After remaining in apnoe for several seconds the whole sequence is repeated. Such respiration occurs in all states where the respiratory centre is suppressed in consequence of deteriorated metabolism. They develop in cases of heart failure, but also in atherosclerosis of cerebral arteries due to skull injuries and in some intoxications.

In consequence of deteriorated perfusion and thus decreased formation of ATP, the respiratory centre becomes hyposensitive to normal levels of CO_2 and O_2. Therefore, the respiration gradually ceases. During the apnoic pause carbon dioxide accumulates in the blood and oxygen level decreases. When these

changes in blood gases are significantly marked, the respiratory centre starts to react again in spite of its hyposensitivity, and respiration is revived. During respiration normal levels of blood gases are soon set up and respiration ceases again. The respiratory centre is suppressed until a sufficiently high level of carbon dioxide and a sufficiently low oxygen tension are developed which are able to stimulate even the hyposensitive respiratory centre to its activity.

3.5.2 Right heart failure

The term heart failure designates prevalently failure of the left ventricle. It is natural however, that failure can inflict also the right compartment of the heart. Hypertrophy and dilatation of the right ventricle is often identified with the terms of chronic or acute cor pulmonale. In these cases the causes of right ventricular failure reside in hypertension in a.pulmonalis. This hypertension develops in consequence of pulmonary disease which evokes the so called pre-capillary pulmonary hypertension. However, right ventricular failure can develop in consequence of many more pathological states.

The right ventricle most frequently fails secondary to the left ventricular failure. The first step resides in elevation of pressure in pulmonary veins, and later in capillaries. The raised pressure can be gradually conveyed into a.pulmonalis and even into the right ventricle. Hence, the right ventricle is inflicted secondary to the left ventricular impairment. However, the right ventricle may fail without dependence on left ventricular impairment or on pulmonary disease. This type of heart failure can be caused by ischemic heart disease, valvular diseases of the right side of the heart, myocarditis, or hyperdynamic circulation.

It is necessary to realize that the compensatory capacity of the right side of the heart is much smaller than the compensatory capacity of the left heart side. Therefore a pathological process inflicting the right ventricle causes dilatation much sooner than it would have developed due to an analoguous infliction of the left ventricle.

Right-sided heart failure is subjectively less unpleasant for a patient and therefore better tolerated than breathlessness which represents the main symptom of left-sided ventricular heart failure.

Similarly as in left-sided heart failure also the symptoms of right-sided heart failure may be distinguished as forward and backward failure.

Forward failure develops in consequence of a decreased pumping capacity of the right ventricle. Due to this the lungs and the left side of the heart receive a smaller amount of blood. On the one hand this phenomenon has a negative impact in the deterioration of the peripheral blood supply. On the other hand the decreased pumping activity of the right ventricle developed due to primary left-sided heart failure, restricts the blood supply into the lungs. As a result the pulmonary congestion and thus also breathlessness may decrease. This paradoxical *mysterious improvement* occurs in severe forms of left-sided heart failure when as a consequence of increased pressure in a. pulmonalis the right ventricle dilates. The offer of blood to the lungs decreases and as a result the breathlessness withdraws. However, this takes place at the cost of a decreased blood flow into the left ventricle and thus decreased peripheral perfusion.

Backward failure – manifests itself as a stagnation of the blood in the venous system before the right atrium and has several symptoms: edemas of the lower limbs, ascites, hydrothorax, hepatomegaly, hepatojugular reflux, increased content of jugular veins, dyspepsia. All of these symptoms manifest congestion of the systemic circuit. Formation of edemas, similar to the pulmonary edema has a complex pathogenesis:

- increased hydrostatic pressure in capillaries
- hypoproteinemia in consequence of venostatic impairment of the proteosynthetic function of the liver
- increased permeability of capillaries in consequence of hypoxemia in regions of blood stagnation
- deteriorated outflow of lymph from edematous regions.