ity and afterload, but by means of increased diuresis and decreased volume of circulating fluid they reduce also the preload. Obviously in the near future they are going to become the alternative approach to the generally used therapy by digitalis and diuretics and they might mean a significant prolongation and improvement of life quality in patients with heart failure.

## 3.7 Hypertrophy of the heart – nechanism of adaptation to chronic hemodynamic overload

The Frank-Starling's mechanism and increased sympathetic stimulation represent acute compensatory mechanisms. They manifest themselves immediately after the heart work demands have been increased thus preventing acute heart failure. However, when the heart has to perform increased volume or pressure work for a longer period (neither minutes, nor hours, but weeks or years) chronic compensatory mechanism come into force – hypertrophy of the heart muscle.

**Hypertrophy represents a structural adaptation of the heart to a long-term hemodynamic overload**.

Regarding energy metabolism, it is the effectivity of the work which is of importance beside the general amount of work being performed. The effectivity means the amount of performed work in dependence on the amount of supplied energy, in other words the performace. It is easy to achieve for the heart to perform a great amount of work providing it consumes a large amount of ATP. Such a state can last but several minutes, or at the longest several hours. However if it is necessary to perform intensive work for a long period the consumption of energy must be inevitably adequate to the amount of performed work.

The consumption of energy in the heart is determined by three basic factors: **wall stress, contractile state of myocardium and frequency**. The increases in contractile state and frequency increase the minute volume and improve peripheral perfusion. The increase in wall stress wastes a considerable amount of energy without any positive perfusion effect (the so-called internal work).

Hypertrophy is stimulated particularly by a non-adequate increase in ventricular wall stress. Hypertrophy may be then interpreted as an *protectory mechanism* helping the heart to recover wall stress to the original level.

Ventricular wall stress is from the physical point of view defined by means of Laplace's law:

$$T = \frac{P \cdot r}{2 \cdot h}$$

where $T \ldots$ *stress,* $P \ldots$ *intraventricular pressure,* $r \ldots$ *ventricular radius,* $h \ldots$ *ventricular wall width*

The fact that the denominator represents a doublefold value of the wall width, implies that even a relatively small thickening of the ventricular wall significantly decreases the value of wall stress. The formula implies that the larger the ventricular radius the larger ventricular stress (force) is needed in order to achieve the given pressure.

In order to make the relation between particular quantities more comprehensible it is recommended to imagin an insuflated balloon. Providing the balloon is inflated but moderately, it has a small radius, low intraventricular pressure and the wall is moderately tense. As soon as it is blown up with a large amount of air, its radius increases, its intraventricular pressure elevates, and simultaneously the wall becomes thinner and almost transparent. The wall of such a balloon is significantly tense and there is the threat of bursting.

From the biochemical point of view it is essential that the increased stress wastes ATP completely in vain. Macroergic phosphates are not utilized on the behalf of increased work, but their prevailing amount is spent on the behalf of the mere survival of cardiomyocytes in state of their prolongation. From the energetic point of view the high ventricular wall tension represents a disadvatageous state which the heart struggles to eliminate by means of hypertrophy.

### 3.7.1 Pressure and volume overload of the heart

Two types of hemodynamic overloads of the heart are distinguished – pressure and volume overload.

**Pressure overload** is referred to in cases where the primary cause is the increase in afterload. Afterload is the stress in ventricular wall during systole. It is determined in a decisive measure by resistance juxtaposed to blood flow by aorta and peripheral vessels. In a case of left ventricle this type of overload is represented by stenosis and aortic coarctation, arterial hypertension and obstructive hypertrophic cyrdiomyopathy. Increased pressure overload of the right ventricle is entailed by stenosis of a.pulmonalis and pulmonary hypertension of variable etiology.

Since during systole the blood flow is hindered by an obstacle, the intravenricular systolic pressure elevates. Increased systolic intraventricular pressure causes systolic tension in the ventricular wall which stimulates the growth of the width of myocytes. This process results in the thickening of the ventricular wall. At the same time the end-diastolic volume does not change substantially. Hypertrophy at pressure overload, i.e. concentric hypertrophy, is therefore characterized by the fact that the **proportion between the wall width and end-diastolic volume changes remarkably in favour of the wall width**.

In a case of concentric hypertrophy the transiently increased ventricular wall stress evoked by increased intraventricular pressure is according to Laplace's law eliminated by the thickening of the ventricular wall at a constant ventricular radius.

**Volume overload** is referred to when the primary cause is represented by increased preload. The particular value of preload depends predominanntly on the blood volume which is present in the ventricle at the end of diastole. Increased preload of the left ventricle is usually present under the circumstances of insufficiency of aortic or mitral valves, open ductus Botalli and aortopulmonary bypass Increased volume overload of the right ventricle is observed under the circumstances of insufficiency of pulmonal or tricuspidal valves and defect of the atrial septum. Volume overload in some cases inflicts both the left and the right sides of the heart – increased physical excercise, bradycardia, so-called hyperdynamic circulation, ventricular septum defect.

Increased ventricular volume and thus the tension at the end of diastole automatically increase the tension in the ventricular wall also at the beginning of systole – afterload. The latter determines the growth of myocytes width which is however smaller at the volume overload than at pressure overload. The volume overload thus results in a significant volume increase of the ventricle and simultaneously less prominent thickening of its wall. It is specific of the excentric hypertrophy that **the proportion between the wall width and its volume is shifted in favour of the ventricular volume**.

In a case of volume hypertrophy the increased tension in the ventricular wall evoked by increased enddiastolic volume is according to Laplace's law compensated by a subsequent prolongation of muscular cells, thus accompanied by the growth of ventricular cavity resulting in a decrease in intraventricular pressure. The thickening of the ventricular wall also participates in the decrease of tension. These two factors overbalance the third factor of the Laplace's law, namely the radius which is increased in the case of excentric hypertrophy.

### 3.7.2 Direct stimulus of hypertrophic growth

In spite of the fact that non-muscular elements form as much as 75 % of the total number of cells in the heart, the main mass is formed by cardiomyocytes since they are much larger than the remnant cellular elements. In comparison with other cells in the myocardium the cardiomyocytes are capable of reproduction merely during prenatal life. After birth the muscle cells do not divide, their number remains unchanged throughout the postnatal life. The growth of contractile mass within hypertrophy is determined exclusively by the growth of muscular cells.

Increased proteosynthesis of cardiomyocyte structures is a response to increased ventricular wall stress. This response can take place **providing that the information about the increased ventricular wall stress is transfered into the cellular nucleus**. The nucleus is a place where the genetic information for cellular proteosynthesis is stored. The question as to which factor represents the direct stimule triggering the proteosynthesis is not explicitly settled. The situation is complicated by the fact that in various types, due to intensity and duration of overload different stimulators may come into play:

1. In consequence of increased tension in the ven-

tricular wall, respectively in consequence of the fact that each unit mass of the contractile tissue must perform more work, a marked increase in energy consumption takes place. This results in **a decrease in concentration of macroergic phosphates in myocardium** – ATP which is the direct donor of chemical energy and KP which represents a chemical compound in which a form of energy is stored. Simultaneously, the intracellular concentration of the products of their breakdown – ADP, creatindiphosphate and creatinin increases. The manner of stimulation of proteosynthesis inside the nucleus is probably identical with the Jacobs-Monod's opinion concerned with derepression of genetic information. The products of the splitting of high energy phosphates bind to the repressor, in consequence of which the latter loses its inhibitory effect to the operator gene. Deblockated operator gene stimulates the activity of structural genes and transcription of information carried by DNA to a molecule of RNA messenger can take place. Subsequently, mRNA binds on ribosomes. Molecules of transfer RNA carrying individual aminoacids are arranged in order according to the compatibility of their triplets with mRNA (translation). The order of aminoacids determines the particular type of protein which is to be synthetized.

2. The state of increased ventricular wall stress entails an increase in the turnover of subcellular structures. This results in **accumulation ... of the products of the splitting** of structural proteins (especially the constituents of myofibrils) which can play the role of further stimulators of nuclear DNA.

3. It is agreed upon the assumption that **the tension of sarcolemma per se** can influence the genetic expression. It takes place either by changes in transport properties of sarcolemma to various ions, but obviously also by the increase in transport af aminoacids. The change in ion concentration, respectively the increase in intracellular concentration of aminoacids can stimulate the nucleus to the increase in protheosynthesis.

4. **Substances of hormonal character**. It is experimentally proved that catecholamines, glucocorticoids, thyroxine, somatotropic hormone, insulin, and other hormones are able to stimulate the growth of cardiac tissue. However it is not known which of the hormones particularly plays the role of the stimulator under in vivo conditions. Investigators discuss catecholamines as being likely involved as stimulators. The levels of catecholamines in the blood and in the heart per se significantly change during individual stages of hypertrophy. The catecholamines intermediate the activation of sarcolemma and sarcoplasmic reticulum by activating the mebrane receptor-adenylcyclase-proteinkinase system. Due to this the intracellular concentration of calcium which is supposed to be the possible direct inducer of genetic derepression increases. The activated proteinkinase could though stimulate the genetic expression also by means of direct phosphorylation of the repressor. Marked stimulatory effects supporting the growth of cardiac cells were discovered in thyroxine and glucocorticoids. The mechanism of the thyroxine effect resembles that of catecholamines (by means of the second messenger – cAMP). Glucocorticoids do not bind with the membrane receptor of sarcolemma but pass through the membrane. They bind with the intracellular cytoplasmatic porter which transports them into the area of the nucleus. Here, owing to the interaction with the repressor gene they have an impact as being inducers of expression of a particular part of genome.

5. In the recent period a considerable attention has been paid, namely in coincidence with hypertrophy, to the struggle of isolating the **cardiac growth factor**. The consideration of the existence of a particular substance responsible for hypertrophic growth of the heart was enhanced by clinical and experimental observations that the overload of one of the ventricles enlarges the mass of the other ventricle. It is considered that the hemodynamic overload is the triggering factor of a specific substance production which stimulates hypertrophy of the heart. In spite of several positive experimental results the existence of such a hypertrophy stimulator is until now hypothetic. Since until now it has not been isolated, nor has its structure been assessed. It is assumed that it is produced in the pituitary gland or in the cortex of suprarenal glands. It is

supposed to be of steroid structure and its effect takes place by means of the $Na^+$–$K^+$ ATP-ase inhibition. Assumedly a whole group of substances is involved. Since both the mechanism of their effect, and structure resemble those of digoxin, these presumedly hypertrophy stimulating factors are called **digoxin like substances**. In regard to their resemblance to digoxin also the resultant effect of these two factors could theoretically reside in the increase of contractility. Simultaneously, by means of the $Na^+$–$K^+$ ATP-ase blockade in the tubules of the kidneys they could inhibit resorption of sodium and subequently resorption of water and thus increase diuresis. This mechanism would serve as means of the delaying of the acute heart failure. Their prolonged discharge within the frame of chronic hemodynamic overload could possibly stimulate the growth of myocardium. The idea that this substance could be produced by cardiomyocytes themselves is not entirely excluded. Either all cardiomyocytes with increased tension, or only a specific group of cardiomyocytes might be involved. Confirmation of these theoretical considerations requires inevitably chemical isolation of the subjective substance.

### 3.7.3 Hypertrophy stages and their characteristics

In spite of considerable differences in the nature of hypertrophic growth in individual types of overload, the adaptation of the heart at increased hemodynamic overload can be (on the basis of experimental results) divided into several characteristic periods:

1. period of hypertrophy development
2. period of developed hypertrophy
3. period of hypertrophy regression
4. period of heart failure

**1. Period of hypertrophy development** – begins subsequently after the exposition to increased overload – e.g. valve rupture, experimental stenosis of aorta, etc.. The stress in the wall of ventricle rapidly increases, which in turn increases the consumption of energy by unit mass, and the content of macroergic phosphates in the heart decreases. The struggle to compensate this energetic deficit leads the myocytes to synthetize an increased amount of mitochondrial proteins and in the first days of hypertrophy development the ratio mitochondria: myofibrils significantly increases in myocytes. After several days also the synthesis of contractile proteins increases. As a result the ratio mitochondria: myofibrils is brought to normal and later it may even turn out in favour of myofibrils.

At the beginning the hemodynamic overload entails ventricular dilatation, but the effects of Frank-Starling mechanism and catecholamine stimulation help to maintain the ejection fraction at normal values. Later, increased overload of the heart as a whole is gradually compensated by enlargement of the mass of contractile elements. This helps to decrease the overload accounted to a unit mass of contractile tissue. The contractility is at the beginning markedly decreased, later in the period of developed hypertrophy it achieves an approximately normal value. The ejection fraction does not change connsiderably, neither in the later period of overload.

**2.** The situation in a growing heart becomes gradually stabilized, and ultrastructure, biochemism and function yield the character similar to that prior to overload exposition. It is the period of **stabilized - developed hypertrophy**.

**3.** In spite of the fact that the hemodynamic overload which had represented the stimule to trigerring the growth and leading to the formation of stabilized, fully compensated state, persists in an unchanged form, after a various period disadvantageous changes develop in the heart. This period is referred to as **hypertrophy regression**. It is accompanied by a decrease in mass weight of the left ventricle, decreased synthesis of proteins of mitochondria and myofibrils, and their increased proteolysis. The contractile function of the heart is simultaneously decreased and in consequence of increased content of fibrous tissue in the myocardium the left ventricle becomes stiffer. It results in deterioration of relaxation and restricts the filling of ventricle during diastole. It is to say that this period of spontaneous regression was proved in rabbits with aortal insufficiency.

**4.** The stage of regression transits ultimately into the **stage of heart failure**. This is characterized by continued increase in proteocatabolism in a cell, insufficient utilization of energy and progressive de-

terioration of systolic and diastolic functions of myocardium.

### 3.7.4 The problem of hypertrophy regression

The experimental investigations leave the problem of hypertrophy regression unsettled. The point at issue is why in severe experimentally evoked valvular defect (aortic insufficiency) the achieved stage of hypertrophy is not maintained, namely in spite of the permanent presence of the etiologic factor. A plausible explanation is offered that in spite of that the hypertrophic left ventricle as a whole performs a greater amount of work than normal, the contractile overload accounted to a mass unit of myocardial substance is however significantly reduced. Hence, one mass unit of myocardial substance performs a smaller amount of work than prior to the origin of overload. It is probable that the adaptation process to chronic hemodynamic overload is overpiled. Hypertrophy achieves a measure greater than is inevitable for compensation of the hemodynamic overload per se. The contractile mass is therefore never fully exploited under the conditions of rest. It is not out of the question that this reserve ability is to serve as a contractile potential enabling a hemodynamically adequate performance of myocardium not only under rest conditions, but also due to hemodynamic stress – e.g. at physical exercise. If this reserve ability is not being functionally exploited, its gradual breakdown takes its course.

Another explanation of hypertrophy regression and heart failure is feasible, namely *exhaustion of genetic information*. It is assumed that the genetic apparatus is set up to a particular number of syntheses of each protein molecule. In a case of hemodynamic overload the individual structural and enzymatic proteins wear out faster. Their halftime is therefore shortened. Resyntheses of individual types of protein molecules take place in shorter intervals. The total posssible number of syntheses of individual protein molecules of a cardiomyocyte is exhausted sooner than under physiological circumstances. As a result the functional life span of the heart as an organ is shortened.

The above mentioned experimental results differ considerably from the clinical situation. The nature of hypertrophic growth to a considerable extent depends upon the type of overload, its duration and intensity, as well as upon the state of myocardium and age of organism. For example many hypertonic patients yield a morphological and functional recovery of the concentrically hypertrophic heart after elimination of hypertension. In a number of patients, however, in spite of successful therapy of hypertension, hypertrophy of the heart persists and gradually leads to deterioration of the cardiac function. The situation is similar in patients operated due to valvular defects with a pronounced hypertrophy of the left ventricle (e.g. aortic insufficiency). Elimination of the cause of hypertrophy entails its withdrawal obviously in cases where severe ultrastructural and molecular defects had not developed. When serious alterations of myocardium develop, hypertrophy will not withdraw in most cases. Regarding the prognose of hemodynamic overload it might be convenient to distinguish not only the physiological, but also pathological regression of hypertrophy. **The pathological regression** is characterized not only by reduction of the mass weight of the heart but simultaneously by deterioration of biochemical and functional parameters. **Physiological regression** develops due to the elimination of the cause of hemodynamic overload in cases where the hemodynamic overload had not evoked irreversible changes in the cardiac muscle. In such a case the reduction of mass weight is accompanied by improvement of biochemical and functional parameters.

### 3.7.5 Physiological hypertrophy

Hypertrophy does not occur only as a chronic compensatory mechanism of the heart hemodynamically overloaded in consequence of a pathological process which ultimately leads to heart failure. Controversely to this pathological hypertrophy there exists **physiological hypertrophy** which develops as a response to physiological overload. **It does not lead, neither in cases of its prolongated duration to heart failure, and elimination of the etiologic factor makes it completely reversible**.

Physiological hypertrophy is conceived, regarding the etiologic factor, to include 2 forms of overload. Firstly, it is the growth of the heart during the period from birth to adult age (ontogenetic development) and secondly an adaptation of the heart to increased physical activity. Postnatal development of the heart represents in principle groundwork a hyper-

trophic growth which takes place due to an increased volume load. Volume overload is determined by increasing blood volume in the growing organism and thus increased minute volume which represents a response to the increase in metabolism of the enlarged mass of tissues and organs.

Increased physical activity can be either of volume character when dynamic overload prevails (e.g. speed excercise – running) or of pressure character when the pressure overload is dominant (strength excercise – body-building). The factors determining whether the physiological or pathological hypertrophy is going to develop are the following:

- the degree of hemodynamic overload (quantity of overload)
- duration of hemodynamic overload (quantity of overload)
- the character of hemodynamic overload (quality of overload)

Physiological hypertrophy is apt to develop when the intensity and duration of overload do not exceed particular measure, when the overload develops gradually, and when it is interrupted.

Similarly as in pathological hypertrophy also the physiologically hypertrophic heart is able to perform increased work as a whole. However, controversely to the pathologically hypertrophic heart, the function of each mass unit is normal, or even increased. **Hence, improved contractile ability of a physiologically hypertrophic heart is not determined merely by enlargement of the muscle mass, but also by simultaneous improvement of contractility of each mass unit**. The biochemical fundament resides assumedly in the increase in myosin ATP-ase activity (in the way of which energy utilization improves) and obviously also in improvement of the transport ability of sarcoplasmic reticulum. The presented biochemical changes determine especially the improvement of systolic heart functions. In a physiologically hypertrophic heart, moreover conntroversely to the pathological hypertrophy the content of connective tissue does not increase. This contributes to the maintenance of elasticity and thus to sufficient relaxation during diastole which determines preservation of diastolic function.

Hence, physiological hypertrophy represents a fully adequate growth of myocardial tissue. Increased physical exercise represents from the genetic point of view such a type of stimulation which evokes on the nuclear level the expression of those genes which are responsible for the growth of nuclear structures with a short half-life (sarcolemma, mitochondria, sarcoplasmic reticulum). Since these structures are responsible for energy production and transport of ions as well as electrical activities of a muscular cell, enhancement of their working capacity accelerates the formation of actin-myosin connections. This increases the contractility of cardiac tissue.

### 3.7.6 Hypertrophy and dilatation of the heart

In clinical practice it is quite obvious that the terms hypertrophy and dilatation are confused and inconsistently used. It implies from the incompletely settled interpretation of concentric and excentric hypertrophies.

The terms concentric and excentric hypertrophy have their origin in the endeavour to interprete x-ray findings of an enlarged shadow of the heart. When the x-ray shadow of the heart is symetrically enlarged while its position in the thorax does not change substantially, it is referred to as **concentric hypertrophy**. The concentric hypertrophy is a synonym to hypertrophy due to pressure overload (viz. fig. 3.12 on page 125).

When the x-ray shadow of the heart enlarges asymetrically (predominantly leftward), it is referred to as **excentric hypertrophy**. Excentric hypertrophy is a synonym to hypertrophy due to volume overload.

Uncertainty resides in the fact that an x-ray picture of an excentrically enlarged heart occurs not only in hypertrophy due to volume overload but also in the case of heart dilatation. This is the reason why the terms excentric hypertrophy and heart dilatation are often inconsistently used and mutually interchanged. difference is in the fact that in hypertrophy of the volume type beside the enlargement of the left ventricular volume the ventricular wall becomes thicker. **Dilatation includes enlargement of the heart in which the ventricular wall becomes absolutely or relatively thinner**.

With respect to the fact as to whether the attenuation of ventricular wall is absolute or relative the dilatation is distinguished as being primary or secondary.

- Primary dilatation develops when the ventricle

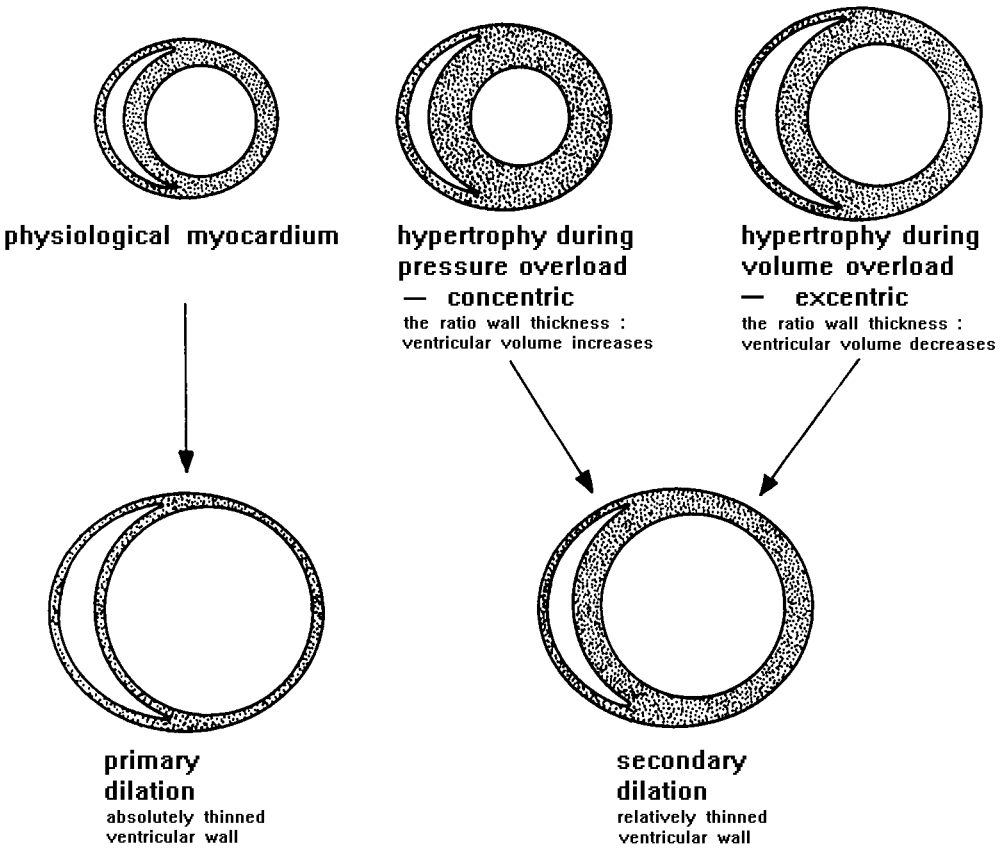


Figure 3.12: Hypertrophy and dilatation of the heart

distends in consequence of acute overload. As a result the ventricular wall becomes thinner than in physiological state (viz. fig. 3.12 on page 125).

- secondary dilatation (viz. fig. 3.12 on page 125) develops when the heart which is already hypertrophic due to chronical hemodynamic overload begins to fail. The ventricular volume enlarges and the already hypertrophic wall becomes thinner ( in comparison to its hypertrophic width).

Primary dilatation can end up in compensatory hypertrophy (when the developed overload is of long-term character providing it is not inadequately large), it stimulates by means of increased ventricular wall stress its hypertrophic growth). Secondary dilatation develops after the compensatory mechanisms become exhausted and represents the cardiac failure.

Fundamentally both forms of dilatation, however, can be considered (to a particular extent) as compensatory mechanisms. It resides in the fact that the absolute size of the ejection volume at the enlarged radius of the ventricle (because Frank-Starling's mechanism comes into play) increases in spite of a significant decrease in contractility. Dilatation is though at the same time disadvantageous as there is an enor-

mous tension in the ventricular wall, namely not only during diastole, but also in consequence of decreased contractility during systole. As a result this type of maintenace of the minute volume is very uneconomical. The excessive tension in the ventricular wall replenishes energy of the heart, and its pumping function in spite of maximal utilization of Frank-Starling's mechanism definitely fails.

## 3.8 Valvular defects of the heart

The role of both atrioventricular and semilunar valves is to assure an interrupted movement of the blood in the direction from atrii toward the aorta or a. pulmonalis. In dependence on the degree and speed of the development the valvular disorder has a distinct impact on organism. A moderate degree of a valvular lesion does not entail any hymodynamic changes. The only symptom may be an auscultation finding, sometimes it is even entirely symtomless. On the other hand a severe anatomical valvular change can lead to a significant deterioration of hemodynamics and to alteration of the health state of a patient. An especially dramatic clinical picture develops when the severe valvular lesion supervenes rapidly. The resultant clinical picture is moreover determined also by the functional reserve of the cardiac muscle.

Two types of valvular lesions are distinguished:

- valvular stenosis – manifests itself in that phase of the cardiac cycle, when the valve is closed and the blood is thus propelled via a narrowed orifice.
- valvular insufficiency – manifests itself in the phase of the cardiac cycle when the valve is to be closed; in consequence of imperfect packing of the valvular orifice a part of the blood regurgitates into the precedent compartment of the heart.

Pure valvular stenosis or insufficiency are rare. The majority of cases yields a simultaneous development of both types of valvular lesions.

Valvular lesions can be inborn or acquired. Acquired valvular lesions develop most frequently due to rheumatic fever. Less frequently they can develop in consequence of bacterial endocarditis, syphilis and at an older age degenerative changes as valvular fibrotization and calcification.

### 3.8.1 Mitral stenosis

Stenosis of the mitral valve develops predominantly in consequence of rheumatic endocarditis. It develops in the course of several years following the attack of the rheumatic fever. In consequence of immunoalterative inflammatory process the free margins of the mitral valve stick together. The mitral orifice which is in an adult person 4–6 $cm^2$ in surface diminishes. The clinical picture depends upon the degree of narrowing of this orifice.

The hemodynamic disturbance manifests itself during ventricular diastole when the blood flows from the left atrium into the left ventricle. Moderate stenosis of the left AV orifice does not manifest itself hemodynamically. It is the stenosis below 2,0 2 when the blood flow from the left atrium into the left ventricle deteriorates. The subsequent consequence is represented by accumulation of the blood in the left atrium with a subsequent elevation of atrial pressure. The character of the diastolic filling of the left ventricle substantially alters. A normal diastole has three phases:

1. The phase of rapid filling of ventricles when after the opening of AV valves the ventricles are dumped with 80 % of the total amount of inflowed blood.
2. The first phase is followed by the phase of diastasis. The elevated pressure in the left ventricle encloses the AV valve nearly completely, and the blood flow into the ventricle soon ceases.
3. The third phase is the period of atrial systole; during this time the remnant 20 % of the filling volume of blood is forced into the ventricle

The stenosis of the mitral valve disturbs the three - phase character of the diastolic filling. The blood during diastole flows but gradually via the narowed orifice into the left ventricle. In consequence of high