3.6 Pathomechanism of cardiomyocyte damage in heart failure

Failure of the pumping function of the heart develops in consequence of pathological changes in the smallest contractile elements. The impaired function of the heart has its correlation on the cardiomyocyte level.

Impairments on subcellular level can be of various character in dependence on etiology of the underlying cardiac disease. Most thoroughly analyzed are the subcellular changes in coincidence with long-term hemodynamic overload. Heart failure per se is almost in all cases of chronic overload associated with impairment of contractile properties of the cardiac muscle. There is experimental evidence that primary impairment can develop practically in any of the cellular organelles participating in the contractile process.

Impairment of contractility of the myocardium can develop in consequence of **alteration in proteosynthesis of contractile proteins per se**, namely in sense of decreased proteosynthesis, or owing to alteration in quality of synthetized proteins. Also their inadequate degradation can represent one of the causes. Impairment of contractile proteins results in the decrease in the number and velocity of actin-myosin bridges formation and so the contractility of the heart decreases.

Also the function of sarcoplasmic reticulum may be decreased in the myocardium of a failing heart. There is evidence that the velocity of both the release and uptake of calcium, and binding capacity for calcium ions are decreased. Association between excitation and contraction may be thus impaired. Depolarization of sarcolemma and tubuli do not evoke an adequate increase of calcium level in cytoplasm. Hence, the offer of this ion for contractile functions is decreased and consequently the contraction properties of the heart deteriorate. The activity of central enzymes responsible for ATP splitting (myosin ATP-ase) and transport of ions (sarcolemmal and sarcoreticular ATP-ases) as well as the activity of enzymes designed for glycolysis in the cytoplasm and KrebÝs cycle and respiration chain in mitochondria may be also decreased through enhanced Ca^{2+}cytoplasmic level.

Also the metabolism of catecholamines is impaired. The number and function of beta-receptors is decreased and the content of catecholamines in the cardiac tissue is reduced. Since the catecholamines stimulate the contractility of the heart under physiological circumstances, their insuffient amount can lead to contractility impairment of the heart.

Intracellular ion metabolism is significantly altered in a failing heart. These alterations can be caused by some of the above mentioned changes. On the other hand however, they themselves can evoke the impairments of organelles. Sodium, potassium, magnesium and calcium ions and their mutual proportion can be inflicted. The calcium ions represent the direct factor determining the connection between excitation and contraction processes, whereas the rest of ions influence this process indirectly, namely by catalytic intervention into a whole series of metabolic reactions (glycolysis, oxidative phosphorylation, beta-oxidation of fatty acids). These ions participate also on electrical changes on the level of cellular membrane. Insufficiency in potassium manifests itself by undesired hyperpermeability of sarcolemma, sarcoplasmic reticulum and mitochondria. Excess in intracellular sodium osmotically attracts water and leads to intracellular hyperhydration. Simultaneously, however, sodium-calcium exchange mechanisms entail the increasing of intracellular calcium concentration. Inadequately high concentration of calcium can have a toxic impact on cells and even cause chemical death of cells. Magnesium is designed to catalyze a whole series of biochemical reactions, to participate in the normal response of cardiomyocytes to stimulation, and is important for normal activation of myosin ATP-ase.

Let the primary impairment be located in whichever organelle or enzyme, in ultimate consequence **two basic types of changes take place in a cardiomyocyte: overloading of a cell with calcium, and ATP depletion**. In dependence on subsequent order in which the two changes develop the cellular impairments are referred to as being calcium induced or ATP depletion-induced.

In a case of calcium induced impairment of myocytes the order of processes is as follows: The level of cytoplasmic calcium which under physiological cir-

cumstances fluctuates between 10^{-7} and 10^{-5} during systole and diastole gradually begins to increase. The reason of this inadequate increase is the impairment of transport capacity of sarcoplasmic reticulum for calcium as well as increased calcium influx via hyperpermeabile sarcolemma. Homeostatic mechanisms of cardiomyocytes are under physiological circumstances set up to maintain precisely the cytoplasmic calcium level. Its decrease leads to a reduction of actinomyosin bridges, owing to which the contractile ability of the heart decreases. On the other hand the inadequate increase of the calcium level in a cardiomyocyte can have a catastrophic impact. In order to prevent it a cell begins to use the calcium transport capacity of mitochondria. In a case when the stress factor is of temporary character (e.g. temporary hemodynamic overload) and thereby also alterations in sarcoplasmic reticulum and sarcolemma are transient, the calcium transport ability of mitochondria is able to maintain the adequate cytosolic concentration of calcium. A prolonged hemodynamic overload and irreversible impairment of transport structures cause permanent accumulation of calcium in mitochondria. This leads to the impairment of the process of oxidative phosphorylation and ATP synthesis. ATP depletion is supported also by its leak via hyperpermeabile sarcolemma.

In spite of mitochondrial calcium buffer activity, the level of plasma calcium may become inappropriately high. Calcium ions during systole saturates practically all binding sites on contractile proteins, but during the diastole calcium is not completely removed due to its high level in plasma. Actin-myosin interactions persist in many sites also during diastole and the so-called irreversible contractures representing permanent shortening of contractile elements develop. It leads to structural and functional extinguishment of contractile proteins. The impairment of relaxation of these structures is supported also by ATP deficit, the molecules of which function not only as donors of energy in favour of contraction, but their plasticizing effect is inevitable also for the process of relaxation. The development of contractures is supported also by impairment of ATP utilization in consequence of decreased myosin ATP-ase activity. ATP depletion, as well as the origin of contractures significantly decrease the function of cardiomyocytes and gradually lead to morphologic and functional extinguishment of cardiomyocytes.

The primary **ATP-dependent impairment of cardiomyocytes** is not evoked by calcium ions at the beginning, but the ATP depletion is entailed by other factors (hypoxia, deficit of substrates, glycolysis inhibition). Such a state is present in ischemic heart disease and in some cardiomyopathies, resp. myocarditis. In consequence of energy insufficiency the membrane ATP-ases responsible for transmembrane active transport cease to work. Failure of sarcolemmal Na^+ – K^+ATP-ase leads to accumulation of sodium in a cell. Intracellular sodium ions osmotically attract water and cellular edema originates. Owing to Na^+ – Ca^{2+}ions exchange mechanisms, the increased intracellular load of sodium may finally lead to the increase of cellular calcium. The level of calcium increases also due to the decreased activity of sarcolemmal ATP-ase and calcium sarcoretiular ATP-ase. ATP depletion and subsequent excess in calcium ions lead to necrosis of myocytes by means of the mechanism described above.

Summary. Failure of the heart per se has always its correlate on the cardiomyocyte level. Various etiologic factors leading to heart failure can cause cardiomyocyte impairment on various levels. In spite of a great variability of primary impulses leading to cardiomyocyte impairment, the order of subsequent actions is very similar. Either the cell is overloaded by calcium ions, or ATP depletion develops. In consequence of one of these two alterations a vitious circle of negative and mutually supporting processes develops leading ultimately to both ATP depletion and toxic impairment of cells owing to an excessive calcium load. These impairments finally lead to functional and morphologic extinguishment of cardiomyocytes.

3.6.1 Pathophysiological principles of therapy in heart failure

The basic requirement in therapy in each of pathological states is represented by elimination of its cause. This is valid also in therapy of acute and chronic heart failure. Mainly in acute heart failure the replacement of the trigerring cause has a prompt therapeutic effect. E.g. elimination of extreme tachycardia immediately improves, respectively completely normalizes the heart function, and dilatation of the heart and the concomittant breathlessness is removed. A similar effect is achieved by elimination of

other acute causes of heart failure (e.g. abolishment of hypertension crisis, reduction of excessive volume of circulating fluid, restoration of adequate oxygen and substrate supply in the case of acute ischemia etc.).

In cases of chronic heart failure it would be optimal to remove the pathological agens and at the same time to begin the therapy in the initial phase of heart failure. At this time the function of cardiomyocytes is impaired only in a specific manner which can be influenced therapeutically. In addition, in the initial phases of the impairment of function of myocytes the cardiac muscle cells have reserves which can be therapeutically stimulated.

The situation in clinical practice is entirely different. The diagnosis of heart failure is stated when a patient is afflicted by considerable subjective difficulties. In this phase the reserve capacity of cardiac muscle cells is usually exhausted in consequence of long-term ecploitation of compensatory mechanisms. In addition the neurohumoral compensation reaction is escaladed to such an extent that it is able to assure only the perfusion of vitally important organs, on the behalf of perfusion of peripheral tissues. In the developed phase of cardiac insufficiency the etiological agens can be influenced only with difficulties, or it cannot be influenced at all. This is so either because in many diseases the etiologic factor is not sufficiently ascertained (various forms of cardiopathies, myocarditis) or in the late phase of failure the original cause cannot be explicitly ascertained. However, even if the primary factor of the heart impairment would be successfully detected in the phase of developed heart failure, neither the entire elimination of the etiologic factor would not have to necessarily lead to improved cardiac function as alterations on the subcellular level are irreversible. In such a situation the therapy of cardiac insufficiency is only of symptomatic character. It does not eliminate the cause of failure, but improves the hemodynamic situation in the heart and peripheral tissues, it eliminates the negative consequences of excessive compensatory mechanisms and mitigates the subjective unpleasant sensations of a patient.

The pathomechanism of therapy resides in the reduction of requirements on the work of the heart, in improvement of the output of the heart per se and in improvement of the function of peripheral organs (especially kidneys). This can be accomplished by influencing the three basic regulatory mechanisms of the heart - contractility, preload and afterload.

3.6.1.1 Stimulation of contractility

Frequently (in the past almost in general) the main part of therapy is considered to be represented by the application of positive inotropic substances which stimulate contractility. Stimulation of contractility of cardiomyocytes is accomplished by means of the increasing of the level of activating calcium in cardiomyocytes which can be achieved by means of various mechanisms:

1. Inhibition of Na^+–K^+ ATP-ase entails accumulation of Na^+ ion which entered the cell during depolarization. Its high intracellular concentration stimulates the Na^+–Ca^{2+} exchange mechanism while the cells dispose sodium and increase the level of calcium (cardiac glycosids – digoxine).

2. Stimulation of the beta 1 receptor of cardiomyocytes - adenylcyclase - proteinkinase - the phosphorylation of subcellular structures which transport and bind calcium increases the supply with calcium and enhances its effectivity (catecholamines).

3. Inhibition of cardiac phosphodiesterase which acts as a degradating enzyme of cAMP results in increased level of cAMP. This stimulates the proteinkinases and phosphorylation processes and in the ultimate consequence evokes the same effect as in case 2 (methylxantines, amrinon, milrinon).

Positive inotropic substances are effective exclusively under under the pressumption that a cell still has functional reserves which can be stimulated. The offer of intracellular calcium in favour of contractile proteins in severe forms of heart failure is however sufficient in consequence of the stimulation of the sympathetic nerve with a subsequent abundant release of endogenous catecholamines. Further intracellular increase in calcium concentration owing to positively inotropic substances does not evoke any further increase in contractility, but has an explicit toxic impact on cells.

3.6.1.2 Stimulation of preload

Failing heart is overfilled with blood and the ventricular cavities are of large diameters at the end of diastole. The capacity of Frank-Starling's mechanism is maximally exploitated as the length of sarcomeres is closely near to 2,2 μm. Further elevation of the filling pressure does not increase the length of muscular fibres, but deteriorates the stagnation of fluid above the left side of the heart – in pulmonary veins and capillaries provoking thus dyspnea. Moreover, as a consequence of further increase in the filling pressure the heart can even more expand in spite of the fact that sarcomeres are not being prolonged. This is performed by means of the shift of muscular layers in the ventricular wall. The increase of the ventricular diameter and the thinning of ventricular wall evokes enhancement of ventricular wall stress which is energetically infavourable from the point of Laplace's law. Therefore the therapy struggles to achieve such a ventricular filling where the length of sarcomeres at the end of diastole would be optimal for utilization of Frank-Starling's law, but under such a filling pressure which does not evoke stagnation of blood in the lungs. In other words it is desirable to decrease the venous return to the optimal level. This effect can be achieved by the restriction of physical exercise, bz a decreased intake of salt in food (sodium osmotically retains water, increases the circulating volume and venous return) and by substances having a dilating impact on the venous system (the blood persists in the capacity bed and returns to the heart in a reduced amount). Such a therapeutical procedure naturally does not improve the perfusion of peripheral tissues, but eliminates the subjective sensation of breathlessness. At the same time by means of decreased stress in the ventricular wall the economy of contraction improves.

3.6.1.3 Stimulation of afterload

Afterload means the stress in the ventricular wall during systole. This stress depends on several factors according to the Laplace's law (intraventricular pressure, ventricular radius and thickness of the ventricular wall). In the narrower sense of the term, however, afterload is understood as the resistance against the heart work and this resistance is determined by arterial resistance. In the developed phase of heart failure, in consequence of maximal stimulation of the sympathetic nerve, **vasoconstriction of all peripheral organs including the kidneys** develops by means of stimulation of alpha receptors in vessels. Therefore the positive efect may be achieved by such medicaments which dilate the arterial bed (hydralasine preparates, alphasympatholytics) decreasing thus the peripheral resistance.

The heart works agains decreasing resistance and consequently the stroke volume increase improving thus the peripheral perfusion. As during each systole the heart ejects a larger amount of blood a relatively smaller amount of blood remains in ventricles and the end-diastolic pressure and volume are decrease. Decreased ventricular radius and intraventricular pressure in accordance with Laplace's law result in a decrease in ventricular wall stress and the energetic needs of the myocardium decrease. **The heart thus performs a greater work under lower energy consumption, in other words the effectivity of the heart increases**. Dilatation of peripheral arterial system improves also the perfusion of the kidneys, owing to which urine production increases and the volume of circulating fluid decreases. This results in a reduced venous return and optimalization of preload.

3.6.1.4 Inodilators

Substances which yield simultaneously both inotropic and arteriodilatory effects become very popular. For their simulataeous inotropic and vasodilatory effects they are sometimes referred to as inodilators. The mechanism of their effect resides in having a flexible molecule which is able to influence several types of receptors. Inodilators stimulate contractility in the heart by means of β_1 receptors, they cause vasidilatation by stimulating β_2 receptors in the arterial system, and on the level of the kidneys they dilate arterioles via histamine DA_1 receptors. Moreover, by stimulating also the DA_2 receptors at the sympathetic nerve hindering thus the nerve's endings they inhibit the release of noradrenaline and noradrenaline-induced alpha-receptor effect of vasoconstriction.

As a result the contractility increases, the arterial bed dilates and the volume of circulating fluid decreases. In this way not only the ejection fraction, but also the economy of the heart work increase. This is why dopamine and some of its derivates have a triple effect. They influence not only the contractil-

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 nonadequate 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.