

myosin molecule into ADP+Pi. By this, on the one hand, the inhibitory effect of ATP on the formation of the actin-myosin connection is suppressed and on the other hand the chemical energy from the ATP molecule is acquired, which is converted to mechanical work of contraction. This process results, as it is previously stated, in telescopic sliding of thin filaments of actin in between the thick filaments of myosin. In this mutually inserted position (the so-called rigorous state) the actin and myosin fibres remain until a new molecule of ATP is bound on that of myosin. It is then, when the filaments return into the previous relaxed position and diastole takes place.

Let us briefly summarize the process of contraction as follows: Solely the filaments of actin and myosin are exclusively responsible for the process of contraction. During diastole two inhibitory systems come into play, which inhibit the interaction between actin and myosin. On the one hand it is the troponin-tropomyosin complex which binds with actin and on the other hand it is the ATP molecule which binds with myosin. Calcium concentration in the cell increases during depolarization. Calcium binds with troponin, and simultaneously it activates the myosin ATP-ase which splits ATP. This results in elimination of the inhibitory effect of the troponin-tropomyosin complex on actin and of ATP molecules on myosin and thus interaction between actin and myosin takes place.

3.4 Contractile function of myocardium and pumping function of the heart

In order to produce enough energy for their entity and function, it is necessary for organs and tissues to be sufficiently perfused with blood.

A sufficient blood flow depends on the heart function, blood distribution and on the entire volume of the circulating fluid.

The heart function should be considered from two distinct points of views: from the point of contractile

abilities of the myocardium and from the standpoint of the pumping function of the heart.

The contractile ability of myocardium is determined by two factors: by preload and contractility.

On the other hand **the pumping function of the heart** is a much more wider term. It depends on three basic factors:

- preload
- contractility
- afterload

Besides these three basic factors the pumping function is influenced by:

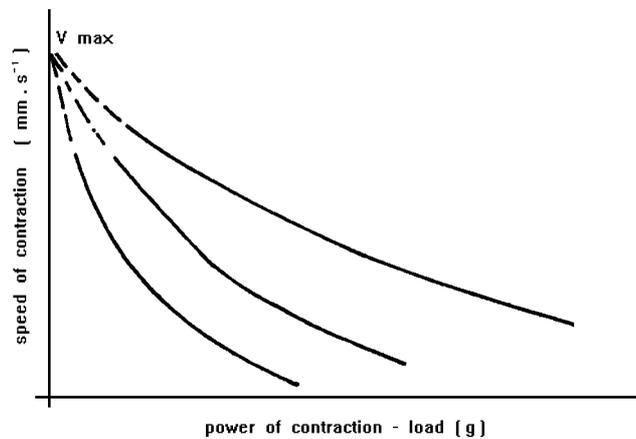
- frequency of contractions
- synergic activity of ventricles and contractile ability of atria

3.4.1 Preload

A general principle regarding the contraction of myocardium is that the velocity of contraction is inversely related to contractile force of contraction. This dependence has a hyperbolic, not a linear character.

It is very difficult to define preload, or afterload. Simply, preload can be imagined as a "load" which is put into the ventricle prior to the onset of systolic contraction. It means that this is a term tightly bound with the late diastole. Since increase of the end-diastolic volume brings along end-diastolic prolongation of muscular fibers, often the term preload is equalled with late diastolic length of muscular fibers. The end-diastolic length of muscular fibers influences the force of systolic contraction, and thus the heart stroke in a manner which is known as **Frank-Starling mechanism**. Essentially **the greater is the end-diastolic length of muscular fibers, the greater is the force of contraction during systole**. The curve of the relation between force and velocity of contraction is shifted rightward due to the increase of the initial length of muscular fibers. See fig. 3.9 on page 98 (Up: alterations of relation between force and velocity of contraction caused by alteration of the initial length of muscular fiber. Prolongation of the muscular fiber shifts the relation between force and velocity of contraction rightward whereas the maximal velocity of contraction – V max is not changed.

Frank - Starling mechanism



Contractility

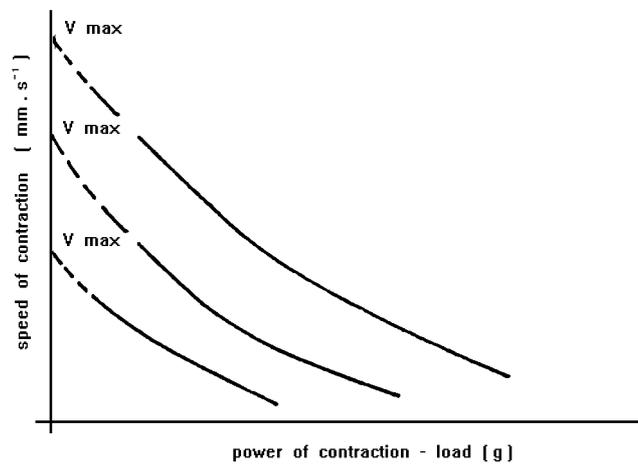


Figure 3.9: Relationship between the power and speed of contraction

1,2,3 – different length of muscular fibers: in the case of the longest muscular fiber length represented by curve 3, the curve of relation between force and velocity is shifted rightward to the greatest extent. Down: Alterations of relation between force and velocity of contraction caused by changes in contractility. Positively inotropic substances which increase contrac-

tility, shift the relation between force and velocity rightward while the maximal contraction velocity – V_{max} increases. 1 – contraction without the effect of positively inotropic substance, curves 2 and 3 – influence of the increasing concentration of inotropic substance).

From the subcellular point of view, the Frank-

Sterling mechanism is determined purely by mechanical principles. When the length of sarcomere is between $1,5-2,0\mu\text{m}$, the actin filaments are partially overlapped. Regarding the contraction mechanism the overlapping is not advantageous as the overlapped parts of actin cannot get into contact with myosin. The sarcomere is prolonged when the end-diastolic length of muscular fiber increases and mutual overlapping of actin filaments decreases. When the length of sarcomere is $2,0-2,2\mu\text{m}$, the actin filaments cease to overlap mutually. The reactive sites on actin filaments and clubbed molecules of myosin filaments get thereby into position which is optimal for interaction. Thus the greatest possible number of actin-myosin bridges is formed and the force of contraction is maximal. Prolongation of sarcomere above $2,2\mu\text{m}$ is inhibited by the natural rigidity of myocardium.

The increase in contraction force is in this case determined by purely quantitative principle – increased number of actin-myosin interactions.

3.4.2 Contractility

Contractility represents a factor which affects the contractile ability of the heart independently on the end-diastolic length of muscular fibers. The contractility increases under the influence of the so-called positively inotropic substances (adrenaline, noradrenaline, glucagon, digoxin). These substances increase the amount of calcium which comes into contact with contractile elements per time unit. Thereby they simultaneously increase the force and velocity of contraction. The action does not involve augmentation of the total number of actinomyosin bridges which does not increase, but remains unchanged. Principally, the contractility increases by means of increasing the number of actinomyosin connections formed per time unit, in other words, by acceleration of their formation.

E.g. catecholamines by means of stimulating the β_1 receptor system, adenylcyclase, cAMP and protein kinase phosphorylate and thereby activate the sarcolemma, sarcoplasmic reticulum and troponin. By activation of the sarcolemma and sarcoplasmic reticulum the offer of calcium ions toward troponin increases. Troponin is also phosphorylated and thus activated by catecholamines and promptly binds the offered of calcium. Thereby the number of ac-

tin-myosin connections formed per time unit is increased.

Hence, on the level of actin-myosin connections, the contractility affects the activity of the heart on the basis of both quantitative and qualitative changes.

Similarly as in the augmentation of preload also the increase in contractility shifts the curve of the relation force-velocity rightward. The difference is, however, that while the change in the initial length of muscular fibre does not affect the maximal velocity of contraction (V_{max}), the change in contractility brings about also the change in V_{ma} . It is, however, merely a theoretic value which under in vivo conditions can be achieved by extrapolation of measured values (see fig. 3.9 on page 98).

This dissimilar behaviour of maximal velocity of contraction in regard to the changes of preload and on the other hand in regard to contractility changes, bears a certain analogy with people who pull a burden on a rope. The more people pull, the faster they move and the heavier burden they manage to draw. The number of load pullers is analogous to the number of sites on the myofilaments which have the occasion of interaction. If the pulled rope is burdenless, the maximal velocity of movement does not depend on the number of pullers. The positive inotropic substances increase both the velocity and force of contraction by accelerating the reaction in active sites. Using our comparison, the velocity of pullers is being changed without the necessity of increasing the number of pullers, but by greater activity of each of the participants.

3.4.3 Afterload

In general, we can state that afterload regulates the pumping activity of the heart in an opposite way than preload and contractility. Both increase in preload and increase in contractility positively affect the pumping activity of the heart, on the other hand increase in preload decreases the stroke volume. In practice, afterload is represented by the aortic impedance which is determined by three factors:

- arterial compliance, i.e. elasticity of large arteries
- total peripheral resistance of arterioles
- blood volume in arterial bed

From the hemodynamic point of view, the afterload is comprehended as stress in the ventricular wall during systole. According to the **Laplace law** this stress is directly proportional to intraventricular pressure, the radius of the ventricular cavity, and inversely related to the doublefold of the thickness of the ventricular wall.

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

where: T...tension; P...intraventricular pressure; r...ventricular radius; w...thickness of the ventricular wall

It is obvious that augmentation of the total peripheral resistance results in elevation of intraventricular pressure and thus the afterload increases. Afterload is, however, simultaneously increased also due to the enlargement of the ventricular cavity radius and by thinning of its wall. These two alterations may, however, occur also by means of increase of the end-diastolic volume, i.e. by increase in preload. Thus, the term afterload includes not only the stress which is formed as late as during systole when arterial impedance comes into force (afterload in narrow sense of the term), but also the wall stress formed already in the phase of late diastole. In other words augmentation in preload leads automatically to an increase in afterload.

3.4.4 Frequency of contractions

Frequency represents a hemodynamic parameter which enables to increase the minute ejection volume by means of increased number of ventricular evacuations per minute. In addition, frequency augmentation stimulates the contractility of the myocardium. The explanation of this so-called **frequency effect** is complex. Basically it resides in a more optimal utilization of electro-mechanical association, i.e. association of depolarization and subsequent contractility. The positive inotropic effect of increased frequency enables a better evacuation of ventricles in states of tachycardia.

In the case of venous blood return being sufficient, the minute volume increases in direct proportional relation to the increase of frequency. In regard to the fact that when the heart rate is normal the diastole duration is substantially longer than systole, the

increased frequency actually results in the shortening of diastole. At a particular frequency the diastole duration equals that of systole. When the so-called critical value of the contraction frequency (cca. 170/min) is achieved, the duration of diastole is so short that the ventricle cannot be filled sufficiently. Hence, the stroke volume is reduced to such an extent that in spite of the high frequency vigour, the total minute volume declines.

3.4.5 Synergic activity of ventricles and the contractile ability of atrii

Maintenance of optimal complex activity of the heart requires coordination of its individual parts namely of those of the left ventricle (septum and free wall, basis, the central part and apex), synchronized activity of the left and right ventricles, and harmonization of the atrial activity with that of ventricles. The most important factor in this matter is the correct coordination of the left and right ventricles. The arterial volumes of the right and left ventricles are not exactly identical and their mutual size fluctuates reciprocally in relation to the course of the respiratory cycle. During inspiration the right ventricular volume increases in consequence of the increased filling and restricted evacuation. The left ventricular volume on the contrary decreases in consequence of the diminished inflow and easier evacuation. Expiration has the opposite consequences. This phenomenon can become more expressed under certain physiological conditions, namely respiratory dysrhythmia, profound respiration, Valsalve's manœuvre. These differences between the stroke volume of the left and right hearts mutually counterbalance, hence the minute volumes of the right and left ventricles are identical. Under pathological conditions the impairment of the coordination of the ventricles becomes evident as e.g. by impairment of the sequence of depolarization processes (bundle-branch-block), movement disturbances of a certain part of the left ventricle (myocardial infarction).

An important factor in this matter is the maintenance of the atrial contractile ability which takes place at the end of diastole. During this period of atrial contraction the ultimate 20% of the total venous blood return is pressed into the ventricle. Reduction of atrial contractile ability occurs primar-

ily due to intensive atrial dilatation, and the total loss of contractile ability occurs within atrial fibrillation. The loss of the final 20% of venous blood return which is transported to the ventricle by atrii under physiological conditions can be hemodynamically significant especially in states with reduced ventricular compliance. In such cases the deficiency in contractile ability of atrii can cause deterioration of the clinical state.

3.4.6 Pumping activity of the heart

The heart functions as a valve pump. It ejects blood toward the periphery, however not continuously, but in particular amounts – ejection volumes. The cardiac cycle takes place in two basic periods. The period of filling, when the heart fibers are in relaxed position – **diastole**, and the period of contraction, when the blood is ejected toward the periphery – **systole**.

During systole the blood is ejected into the aorta and pulmonary artery. At the end of the ventricular systole the atrii are already filled with the inflowed blood. The enlargement of atrial content results in increase in atrial pressure. Following the ventricular systole termination the intraventricular pressure decreases below the value of atrial pressure in consequence of the relaxations the muscular fibers. These events result in the opening of atrioventricular valves and the ventricles begin to be filled with atrial blood. In the beginning the blood flow into the ventricles is rapid – referred to as the phase of rapid ventricular filling. It lasts cca. one third of diastole and the ventricles receive 70% of the total amount of blood which had flown in during diastole. During the second third of diastole the blood flow from the atrii almost ceases. This period is referred to as **diastasis**. The last third of diastole represents a **period of active contraction of atrii**. This is the period during which the remnant cca. 20% of the total amount of blood which flows into ventricles during diastole, is forced into ventricles, already against considerable intraventricular pressure.

3.4.6.1 Atrial and ventricular pressure curves

Individual phases of the cardiac activity entail alteration of pressure parameters in both atrii and ventricles. These pressure values can be detected by means

of catheterization. Since in many pathological states the values of pressure in individual cardiac cavities undergo typical alterations, it is inevitable to apprehend the physiological course of pressure changes which impendently coincide with the pumping activity of the heart.

The record representing atrial pressure parameters displays three positive and two negative waves (see fig. 3.10 on page 102). The **first positive wave** is formed at the end of ventricular diastole. It is caused by active atrial contraction. The **second wave** is formed at the beginning of ventricular systole. This is the period of ventricular pressure elevation and this increase in pressure is conveyed via AV valves into the atrii. During the systolic blood ejection the basal part of the ventricle together with the AV annulus get nearer to the cardiac apex, in response to which the atrial cavity is temporarily enlarged and the pressure decreased. These events become evident as the **first moderately negative wave**. Thereafter the atrial pressure increases in direct proportion to the amount of blood flowed into the atrii which is recorded as the **third positive wave**. At the onset of diastole the AV valves open and the blood is propelled from atrii into ventricles. The decrease of atrial pressure is recorded as the **second – more expressed negative wave**.

Pressure curves of both atrii are almost identical, although the intracavity pressure in the left ventricle differs from that of the right. This difference concerns mostly the altitude of pressure as the value of the right ventricular pressure represents merely one fifth of the left ventricular pressure value. The character of the pressure curve is, however, in spite of the presented quantitative differences, almost identical in both ventricles.

The ventricular pressure curves yield several phases which are precisely demarcated. See fig. 3.10 on page 102 (The cardiac cycle can be divided into 8 phases. Three upper curves represent the pressure alterations in aorta, left atrium and left ventricle. The curve representing the left ventricular volume alterations represents to a certain degree a mirror reflection of pressure alterations. I, II, III represent the cardiac sounds. P sound – contraction of atrii. According to Katz 1992).

The first phase of the ventricular systole represents a period of the so called **isometric**, i.e. **isovolumetric contraction**. In this phase the tension

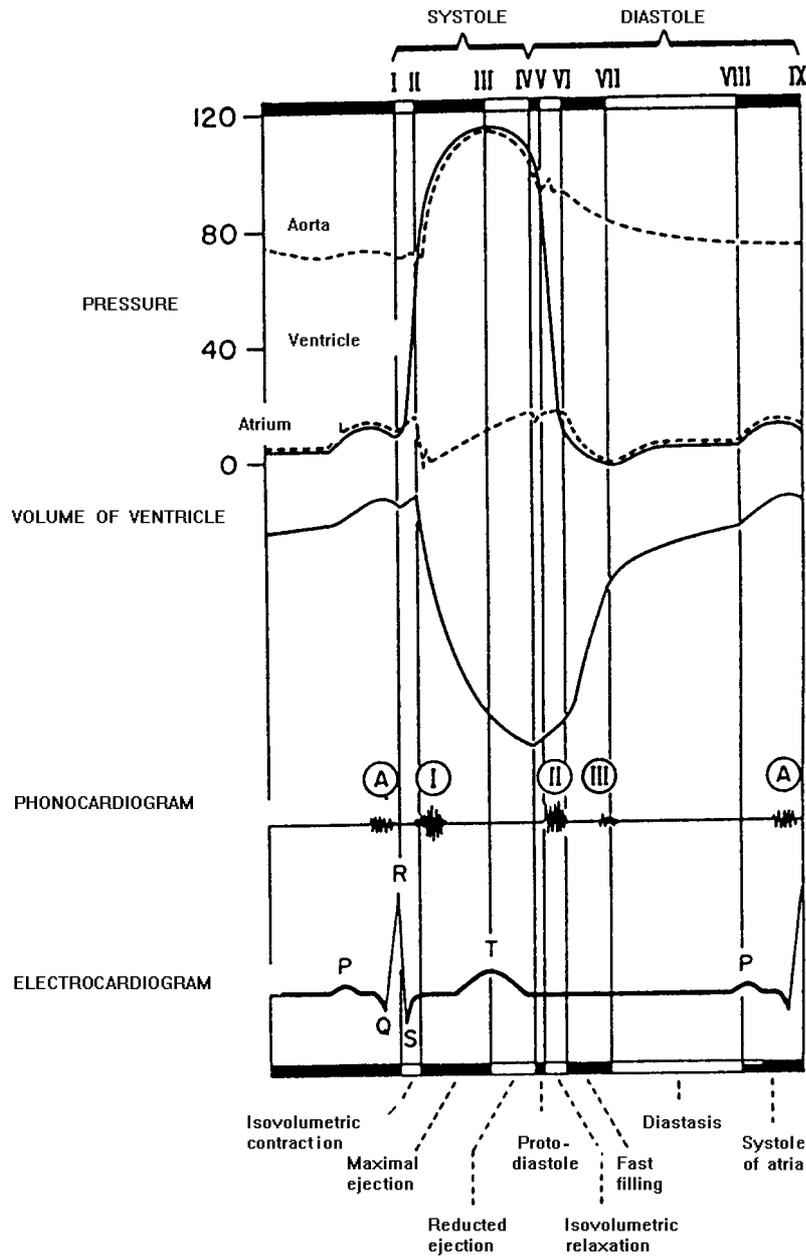


Figure 3.10: Pressure curves of left atrium and left ventricle

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 atri. By the opening of AV valves the ventricular diastole is initiated. At the end of diastole the atri 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: