hydrogen onto oxygen within the respiratory chain, thus forming H_2O. Simultaneously, phosphorylation is carried out, which means that energy produced by means of respiration and liberated in a cascade-like manner is being bound gradually by the conversion of ADP+Pi to ATP.

36 to 38 molecules of ATP are produced by processing of 1 molecule of glucose in the mentioned aerobic manner. Processing of 1 molecule of fatty acid results in a several-fold higher ATP production, the particular value of which depends on the chain length of the particular fatty acid.

3.2.2 Energy storing

The energy within heart muscle is stored in form of two basic macroergic compounds – adenosine triphosphate (ATP) and kreatin phosphate (KP). ATP serves as a prime energy donor for the process of contraction as well as for energetically dependent transportation membrane systems (ATP-ases). KP is a substance which stores energy. Under the condition of a fluent and sufficient supply with oxygen and substrates, the ADP and Pi formed by splitting are resynthetized to ATP and the energy necessary for this resynthesis is provided from kreatinphosphate. The ATP level is preserved while the cytoplasmic level of KP, representing a form of stored energy, decreases. When energetic situation improves, KP is replenished by energy from the respiratory chain.

The store of kreatinphosphate in the cardiac muscle is relatively small and can preserve the ATP level merely for a relatively short period of time. A severe ischemia finally implies a decrease of ATP and thus a decrease of cardiac muscle function.

Besides its store function, kreatinphosphate plays the role of a transporter of energy from mitochondria toward myofibrils. ATP, that is to say, originates in mitochondria, but is being utilized in other intracellular sites – predominantly in myofibrils.

3.2.3 Energy utilization

Energy is utilized in the process of contraction which is going to be explained in the following chapter.

3.3 Contraction-relaxation cycle

The most specific property of the cardiac muscle is the ability to contract.

Contraction is a complex process which is represented by a precisely balanced interaction between contractile proteins (actin, myosin and tropomyosin), calcium ions, cellular transportation systems of calcium (sarcolemma, sarcoplasmic reticulum, mitochondria) and high energy phosphates (ATP, KP). The initial step in this complex reaction is **the origin of action potential (excitation) and the resultant action is the shortening of muscular fibers (contraction)**.

The thick filaments of myosin and thin filaments of actin are the proper elements of contraction. Troponin is firmly bound with tropomyosin thus forming one functional unit, troponin-tropomyosin complex. The latter participates in contraction as a regulatory protein. During diastole, the troponin-tropomyosin complex is firmly bound on actin and thus inhibits chemical interaction between actin and myosin. The surface of troponin contains a receptor which is able to bind calcium. Providing this site is not occupied by calcium ion, the troponin-tropomyosin complex is in a position which inhibits the chemical interaction between actin and myosin. Such a situation supervenes during diastole. During excitation (during the plateau period of action potential) which closely precedes the systole, the cytoplasmic concentration of calcium elevates. Calcium is bound with troponin. Thus the troponin-myosin complex is released from the binding with actin. In this way the inhibitory effect of troponin-myosin complex on actin is removed, and chemical interaction between actin and myosin takes place. The clubbed molecules of myosin after being bound with actin are leant thus shifting actin and myosin filaments propel in mutually opposit directions. According to the sliding theory the actin filaments slide telescopically between the myosin filaments while the length of either of filaments is not changed. This process is manifested as contraction. Hence, in this difficult process, calcium plays an important role of being the contraction inducer.

Calcium which induces contraction may originate from several sources:

- from extracellular space, in which calcium is present in two sites. On the superficial film of sarcolemma – glycocalyx, and in sarcolemma per se.

- from sarcoplasmic reticulum which is formed by a system of vesicles and minute channels mutually transconnected and forming a sort of calcium depot.

The calcium ions are transferred from the extracellular space inside the heart muscle cell during depolarization of myocardial tissue (see fig. 3.8 on page 96). This transfer takes place via slow calcium channels which are open during the plateau period of action potential. Since, via these channels, a relatively small amount of calcium ions is transferred into the cell, this process is supported also by the so-called Na^+ –Ca^{2+} **exchange mechanism**. This system is capable of calcium and sodium transportation in both directions. When intracellular concentration of sodium ions is high and that of calcium outside the cell low, the mentioned mechanism secures the transfer of calcium inward and sodium outward the cell. At opposite concentrations the transportation takes place in opposite directions.

Extracellular calcium ions which enter the cell by means of the two mentioned mechanisms can be effective in myocytes in two different manners (see fig. 3.8 on page 96). They may function directly as **activating calcium**. It means that after entering the cell they bind directly to troponin triggering thus the contraction. However they may also be effective in the process of the so-called calcium induced **release of calcium from sarcoplasmic reticulum**. In the beginning of this process a small amount of calcium transported into the cell during action potential binds on the sarcoplasmic reticulum. In consequence, the SR becomes irritated and liberates its own calcium, the amount of which is sufficient to be able to activate the cellular contractile apparatus (see fig. 3.8 on page 96).

Besides these actions it is assumed that there is still another mechanism of calcium liberation into the cytoplasm. It is the so-called **release of calcium from SR induced by depolarization** (see fig. 3.8 on page 96). This mechanism is based on irritation of

vesicles located closely beneath the sarcolemma surface due to action potential of cellular membranes. In consequence, these vesicles depolarize thus becoming more permeable to calcium. Depolarization itself induces a release of calcium from the sarcoplasmic reticulum in an amount which is sufficient for the event of contraction.

The presented events result in an increase of calcium concentration level from 10^{-7} to 10^{-5} which is the value necessary for contraction.

Periodic repetition of systole and diastole does not require purely the increase of Ca^{2+} from level 10^{-7} to that of 10^{-5} mmol/l during contraction, but subsequently a reverse decrease to the former level 10^{-7} mmol/l must take place. The latter enables the relaxation of myocardium and the event of diastole. Several mechanisms participate in this process. The main role is assigned to sarcoplasmic reticulum which uptakes calcium into its depot vesicles. The decrease of Ca^{2+} concentration takes place also due to sarcolemma which rejects calcium ions by active mechanisms into extracellular space. Under normal circumstances the diastolic amount of rejected calcium ions into the extracellular space equals the amount of calcium ions which had entered the cell during systole. This process assures the cellular homeostasis.

The process of contraction does not represent **solely** a result of interaction of contractile proteins with calcium. **A very important role is played by ATP and the products of its splitting. High energy adenosine triphosphate is inevitable not only as a donor of chemical energy in the event of contraction (systole), but it is equally necessary for relaxation of contractile proteins – diastole.**

During diastole the ATP is bound in the myosin molecule. In a certain way ATP yields a similar function as the troponin-myosin complex. Hence, ATP, by its linkage to myosin, inhibits the actin-myosin interaction. This property of ATP is called the **ATP plasticizing effect**. Hence, the process of relaxation is secured by two distinct mechanisms.

The increase of the cytoplasmic level of Ca^{2+} ions at the beginning of systole affects the contractile proteins in two ways. Calcium combines with troponin, due to which the inhibitory effect of troponin-tropomyosin complex on actin increases. Aside from this, Ca^{2+} ions activate myosin ATP-ase which is present in the myosin molecule. The activated myosin ATP-ase splits ATP bound to the
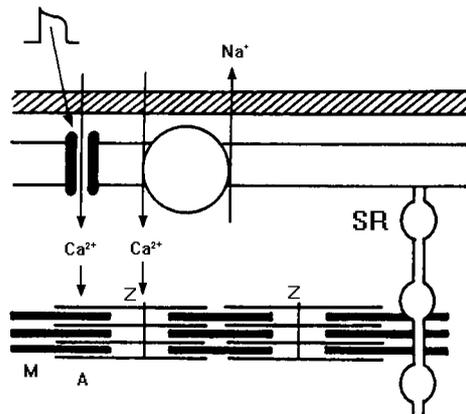
Influx Ca² ions during depolarisation occurs via slow calcium channels and using Na⁺ - Ca²⁺ exchange mechanism. Calcium may be used directly as " activating " calcium initiating contraction.
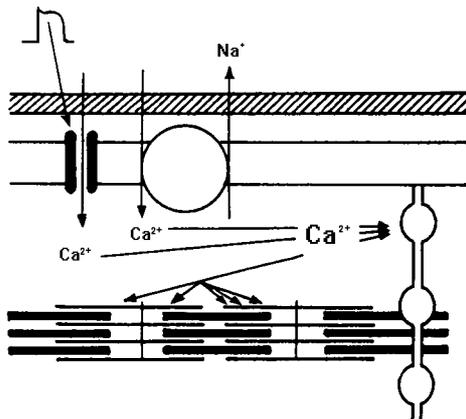
Contraction may by also induced by releasing of " secondary " calcium from sarkoplasmic retikulum.
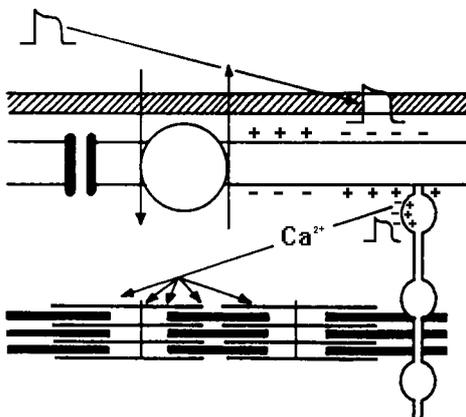
Contraction may be provoked by depolarisation of sarcoplasmic reticulum membrane, which leads to increased permeability to calcium.

Figure 3.8: Calcium as an inductor of contraction

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 supressed 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 telescopical 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 atrii

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.