INVITED NEL REVIEW

Based on the Doctoral Thesis by Marko Vendelin

Cardiac Mechanoenergetics In Silico

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Abstract

The aim of this thesis is to investigate the link between biochemical intracellular processes and mechanical contraction of the cardiac muscle. First, the regulation of intracellular energy fluxes between mitochondria and myofibrils is studied. It is shown, that the experimentally observed metabolic stability of the cardiac muscle is reproducible by a simple feedback regulation mechanism, i.e., ATP consumption in myofibrils and ATP production in mitochondria are balanced by the changes of the high energy phosphate concentrations. Second, an important property of energy transformation from biochemical form to mechanical work in the cardiac muscle, the linear relationship between the oxygen consumption and the stress-strain area, is replicated by a cross-bridge model. Third, by using the developed cross-bridge model, the correlation between ejection fraction of the left ventricle and heterogeneity of sarcomere strain, developed stress and ATP consumption in the left ventricular wall is established. Fourth, an experimentally observed linear relationship between oxygen consumption and the pressure-volume area can be predicted theoretically from a linear relationship between the oxygen consumption and the stress-strain area. Summing up, it is shown how the macrovariables of a cardiac muscle are interwoven with intracellular physiological processes into a whole.
Introduction

The normal functioning of the heart requires a precise interplay of several types of physiological processes: electrical activation, energy transformation from biochemical forms to mechanical form, blood supply through the coronary blood vessel network, and regulation by hormones just to name a few. It is a common practice to focus research on one aspect of the heart functioning such as electrical activation, or mechanical contraction, or biochemical energy transformation, and ignore the interaction between the processes. Such partitioning has been very successful in understanding many aspects of heart physiology. However, the research in such areas as cardiac adaptation, for example, requires understanding of the complex interaction of the different types of processes in the heart. That is why an integrative approach in the studies of the heart function is becoming increasingly popular (see Hunter et al. [2001] for overview). One of the examples of this approach is electromechanics – studies of interactions between electrical activation and contraction of the muscle [Lab, 1996, Nickerson et al., 2001, Kohl and Sachs, 2001]. In this thesis, the aspect of interaction between the biochemical intracellular processes and mechanical contraction is investigated.

Biochemical energy is transferred to mechanical energy of contraction through hydrolysis of adenosine triphosphate (ATP). The binding of ATP molecule and its hydrolysis induces conformational changes of certain enzymes leading to mechanical contraction of the muscle. According to thermodynamic laws, the amount of energy discharged during hydrolysis depends on the levels of ATP and the products of the hydrolysis reaction – adenosine diphosphate (ADP) and inorganic phosphate (P). Since the concentrations of ATP, ADP and P are different in the different compartments of the cell, the local concentrations of the metabolites close to the enzymes determine the amount of energy available for the mechanical contraction. For normal cellular functioning, the local levels of ATP, ADP and P need to be controlled. In other words, a balance between ATP consumption and production in a cell has to be maintained. This is accomplished through several mechanisms. In the cardiac muscle cell, the processes regulating ATP, ADP and P concentrations are mitochondrial oxidative phosphorylation and the creatine kinase (CK) reaction. During the oxidative phosphorylation process in the mitochondrion, an ATP molecule is synthesized from the hydrolysis reaction products ADP and P. ATP and ADP concentrations are also maintained through the CK reaction which rephosphorylates ADP to ATP at the expense of phosphocreatine (PCr). The CK reaction is reversible and may rephosphorylate creatine (Cr) to PCr using ATP if needed. This rephosphorylation occurs in the functional complex of CK and adenosine nucleotide translocase on the inner membrane of mitochondrion [Wallimann et al., 1992, Saks et al., 1994]. In the cardiac muscle cell, the main ATP consuming (mechanical contraction) and ATP producing (oxidative phosphorylation) processes are spatially separated. Mechanical contraction occurs in myofibrils and oxidative phosphorylation in mitochondria. It is known that there exists a flux of ATP and PCr to ATP consuming from ATP producing enzymes (see Saks and Ventura-Clapier [1994] and Saks et al. [1998] for overview). Such flux is sometimes called “energy” flux indicating importance of both the metabolites for a cell. Regardless of the large amount of research in this area of intracellular energetics, the regulatory mechanism which balances ATP consumption and ATP production and maintains the energy fluxes in the muscle cell is still unknown. Below, the research in this area is overviewed.

Transformation of biochemical energy of ATP hydrolysis to mechanical energy of contraction occurs in myofilaments. According to the sliding filament theory, actin and myosin filaments (main filaments in myofibrils) slide along each other leading to contraction of the muscle. The filaments interact with each other through cross-bridges, small myosin molecule heads that link myosin and actin filaments. The cross-bridges are supposed to change configuration during ATP hydrolysis in such a way that the relative position of actin and myosin filaments is changed (see Pollack [1995] for alternative theories of contraction).

Several models of muscle contraction exist, from phenomenological models that describe certain properties of the muscle contraction [Arts et al., 1982, Hunter et al., 1998] to cross-bridge models which are often used to gain insight into the mechanisms of the muscle contraction. Actually, cross-bridge models include also phenomenological description but at a finer level. The cross-bridge models have been used in the cardiac muscle research for more than three decades [Wong, 1971] and have been used to relate the development of the mechanical stress to ATP consumption by the muscle [Panerai, 1980]. Several important mechnoenergetic properties of the cardiac muscle were not reproduced by the cross-bridge models [Taylor et al., 1993, Taylor et al., 1993] leaving a gap between the experimental knowledge and our theoretical understanding of the muscle contraction processes [Gibbs and Chapman, 1985, Gibbs and Barclay, 1995].

There is a special class of cross-bridge models which are based on the thermodynamic theory of the muscle contraction developed by T.L. Hill and Eisenberg [Hill, 1974, Hill, 1975, Eisenberg et al., 1980, Eisenberg and Hill, 1985]. The models, developed on the basis of this theory, take into account the free energy
available from the hydrolysis of ATP, the amount of mechanical work performed by cross-bridges and the free energy of the different cross-bridge configurations. The studies performed with this type of models successfully reproduced several important aspects of skeletal muscle contraction including the influence of metabolite levels on the contraction [Cooke and Pate, 1985, Pate and Cooke, 1989] and ATP consumption of rapidly contracting muscles [Cooke et al., 1994]. In this overview, a cross-bridge model that is able to reproduce several important mechanoeenergetic properties of cardiac muscle is described. The transformation of biochemical energy to energy of mechanical contraction of the left ventricle is not only dependent on the properties of the myofibrils (material properties) but on the alignment of the fibrils (geometrical properties or structure) in the heart as well. The importance of this structural component to the properties of the left ventricle is also overviewed.

The objective of this thesis is to investigate the link between energetics and mechanical contraction of the cardiac muscle at intracellular, muscle tissue and left ventricle levels. For that, mathematical modeling is used with careful testing the properties of models against the biochemical and physiological experiments. Provided the models describe satisfactorily the test problems, they can be further used for prediction and explanation of the phenomena listed above.

The thesis consists of publications [Vendelin et al., 2000, Saks et al., 2000, Saks et al., 2000, Vendelin et al., 2000, Engelbrecht et al., 2000, Vendelin et al., submitted] and this overview. The text in the overview is organized into four sections. This introduction should provide the reader with background information necessary for reading any of the following two sections in any order. Each of these two sections gives a short overview of a particular research field and outlines the main results obtained in this thesis. In the second section, specific properties of intracellular energy fluxes regulation are outlined [Vendelin et al., 2000, Saks et al., 2000]. In the third section, the studies of connection between mechanical stress developed by actomyosin complex and ATPase activity of this complex at tissue [Vendelin et al., 2000, Engelbrecht et al., 2000] and left ventricle [Vendelin et al., submitted] levels are overviewed. In addition, the influence of the alignment of the muscle fibers on the overall performance of the left ventricle is described [Vendelin et al., submitted]. The conclusions are drawn in the last section.

**Intracellular energy fluxes**

In the cardiac muscle cell, the rate of mitochondrial oxidative respiration depends on the substrate and oxygen supply, and on some intracellular factors that balance the energy consumption by myofibrils, ionic pumps and other processes consuming energy with ATP production by mitochondrial respiration and glycolysis. The mitochondrial respiration may vary 20 fold, from 8–10 µmol min⁻¹ g⁻¹ dry weight in resting (KCl-arrested) aerobic hearts [Saks et al., 1994] to at least 160 µmol min⁻¹ g⁻¹ dry weight in rat hearts [Williamson et al., 1976]. As it has been shown by Neely et al. [1967] and Williamson et al. [1976], the oxygen consumption of the heart muscle is linearly dependent on the heart workload in this range of the workloads. The changes in the workload of the heart muscle are often observed at constant levels of PCr, ATP and Cr, i.e. the heart is metabolically stable [Balaban et al., 1986] (for review see Saks et al. [1994]). Taking into account high activity of creatine kinase (CK) in the heart muscle and assuming that the CK reaction is in equilibrium, such remarkable metabolic stability of the heart muscle leaves no room to explanation of respiration regulation in conditions of sufficient oxygen and substrate supply by simple feedback mechanism through the changes in concentrations of participating high energy phosphates. On the basis of quantitative analysis, Korzeniewski [1998] proposed that energy-producing and -consuming processes are activated in parallel leaving only the fine-tuning to the feedback mechanism. Again, equilibrium state of the CK reaction was assumed. As it will be shown later, this is an important assumption and not always a correct one.

The second important assumption often used in the analysis of intracellular energy transfer between mitochondria and ATPases is as follows. The gradients of the metabolites in the intracellular space are supposed to be small due to relatively large diffusion coefficient of the metabolites measured in the tissue and small diffusion distances within the cell.

Recently, Aliev and Saks [1997] developed a mathematical model to analyze the fluxes of the metabolites between mitochondria and ATPases. The model took into account actual CK activity in the heart cell, functional coupling between CK and adenine nucleotide translocase (ANT) [Wallimann et al., 1992, Saks et al., 1994], and simulated diffusion between the mitochondrion and myofibril as one-dimensional process. According to the analysis of the model solution, myofibrillar CK reaction is in the equilibrium only during the diastole and is far from equilibrium during the systole. Thus, at least at higher workloads as used by Aliev and Saks [1997], it is wrong to assume that the CK reaction is in equilibrium.

In the studies of intracellular energy transfer conducted as a part of this thesis, we checked whether it is possible to explain the metabolic stability of the
heart muscle by feedback regulation mechanism taking into account measured activities of the enzymes.

**Model design**

In short, the model was composed on the basis of two earlier simpler models: (1) model of energy transfer [Aliev and Saks, 1997] and (2) model of oxidative phosphorylation [Korzeniewski, 1998, Korzeniewski and Fröncl, 1991]. In addition, we took into account the spatial distribution of CK and ATPases in myofibrils in transverse and longitudinal directions [Wegmann et al., 1992]. The maximal oxygen consumption by the muscle was assumed to be 160 µmol min⁻¹ g⁻¹ dry weight as it has been measured by Williamson et al. [1976]. The part of the model [Aliev and Saks, 1997] describing the functional coupling between CK and ANT was replaced by a coupling, where ANT is able to translocate adenine nucleotides from mitochondrial matrix to both micro-compartment and the mitochondrial intermembrane space. The new phenomenological equations describing CK-ANT coupling were derived and tested against measurements of Saks et al. [1975]. The constants in the mitochondrial inner membrane proton leak function were modified to account for the experimentally established relation between the membrane leak and protermotiv force at different workloads [Saks et al., 1994, Hafner et al., 1990, Duszynski et al., 1984]. The model equations were numerically solved by a finite-element method in conjunction with Galerkin’s method. The complete description of the model is published in Vendelin et al. [2000].

**Comparison with experiments**

In the simulations, the linear relationship between workload and oxygen consumption was reproduced [Vendelin et al., 2000]. The slight nonlinearity of workload-oxygen consumption relationship was caused by changes in the leak of protons through the inner mitochondrial membrane. The model describes quite satisfactorily the stable levels of PCr, ATP, and Cr at oxygen consumption rates up to 100 µmol min⁻¹ g⁻¹ dry weight, in accordance with the experimental data [Vendelin et al., 2000]. At higher workloads the drop of PCr-to-Cr and PCr-to-ATP ratios was caused by the limitation of maximal respiration rate of 160 µmol min⁻¹ g⁻¹ dry weight incorporated into the model. The metabolic stability is reduced together with maximal achievable VO₂ if the level of total creatine content is reduced [Saks et al., 2000]. If the CK reaction is inhibited then the maximum possible VO₂ is only 41 µmol min⁻¹ g⁻¹ dry weight in agreement with the measured maximum VO₂ = 35–50 µmol min⁻¹ g⁻¹ dry weight in similar conditions [Saks et al., 1998, Hamman et al., 1995, Zweier et al., 1991, Saute et al., 1998]. We reproduced ADP oscillations during the cardiac cycle predicted by the simulations of Aliev and Saks [1997]. The amplitude of ADP oscillations was increasing with an increase of the workload [Vendelin et al., 2000]. The average level of computed inorganic phosphate P_i was low at low to moderate workloads [Vendelin et al., 2000] in accordance with NMR measurements performed on pyruvate perfused hearts [Santos et al., 2000]. Thus, it is possible to reproduce the measurements of PCr, ATP, and Cr levels at different workloads by simple feedback regulation mechanism. It is important to note that this finding does not rule out the parallel regulation mechanism proposed by Korzeniewski [1998], it just shows that the parallel regulation is not required to explain the metabolic stability of the heart muscle.

Our model predicts an interesting feature of the regulation mechanism: the mitochondrial respiration is regulated by different cytoplasmic metabolites depending on the workload and CK activity. At low and moderate workloads, the oxidative phosphorylation is regulated by cytoplasmic P_i providing the required feedback signal and possibility for constant PCr-to-ATP ratio [Saks et al., 2000]. This result is in concord with the following experimental observation: if the P_i is increased as in glucose perfused hearts the metabolic stability is lost [Santos et al., 2000]. In other words, with non-limiting P_i, concentration oxidative phosphorylation is regulated by other means, such as PCr, ATP and Cr levels. At higher workloads the regulation is shared among the participating metabolites. If CK is inhibited, the oxidative phosphorylation is mainly regulated by cytoplasmic ADP level [Saks et al., 2000].

The intracellular gradients computed by the model were very small if diffusion coefficient measured in the cell was used [Vendelin et al., 2000]. When diffusion coefficient was reduced ten-fold, the difference of ADP concentration between myofibrillar core and myoplastic side of mitochondrial outer membrane was 0.2 mM. Taking into account that ADP concentration in the myofibrils in the resting state is about 50 µM, the computed gradient is relatively large. However, such gradient in ADP concentration should not influence ATPase activity of actomyosin complex in the healthy heart muscle if ATP concentration (about 9–10 mM) is taken into account.

We checked the influence of small gradients to the model solution by eliminating the metabolite concentration gradients through the increase of the diffusion coefficient by 10^6 times. According to our simulations, there was no difference between the original solution and the solution obtained with the very fast diffusion [Vendelin et al., 2000]. On the basis of these results, it is reasonable to use simpler ordinary differential equations based (ODE) models to study intracellular fluxes in the cardiac cell. These simpler models can be
included into the finite element models of the heart to study distribution of the metabolites in the heart wall. ODE based version of our model is published in [Vendelin et al., 2000].

**Cardiac mechanoenergetics**

In the heart, the energy of ATP hydrolysis is transformed into mechanical work of the cardiac muscle. This transformation occurs in the actomyosin complex, aligned into the filaments in the heart, as a result of cyclic interaction of myosin heads with actin filaments [Huxley, 1990, Irving, 1985]. The transformation of the actomyosin complex is driven by the free energy of ATP hydrolysis to ADP and P\(i\) [Goldman, 1987, Saeki, 1995, Taylor, 1992]. The mechanical performance of the ventricle depends on both the properties of the actomyosin complex and fiber orientation within the left ventricular wall. Here, the properties of the actomyosin complex and influence of fiber orientation on the left ventricular performance were studied. More specific overviews of those problems are given below.

**Mechanoenergetics of actomyosin interaction**

One important property of the cardiac muscle which links the energy consumption of the muscle with mechanical output is as follows. The oxygen consumption of the ventricle is linearly related to the pressure-volume area (PVA), the specific area in pressure-volume (PV) diagram surrounded by the end-systolic PV line, the end-diastolic PV line, and the systolic segment of the PV trajectory for a contraction [Suga et al., 1981, Suga, 1990]. A similar relationship was identified at the tissue level – the oxygen consumption of the cardiac muscle is linearly related to the stress-strain area, an analog of PVA [Hisano and Cooper, 1987]. In spite of the large amount of experimental evidence supporting the linear dependency between oxygen consumption and SSA, computations performed using Huxley-type models have always predicted a nonlinear relationship between these two variables [Taylor et al., 1993]. The importance of resolving this discrepancy between the current theoretical understanding of muscle contraction and fundamental property of cardiac muscle has been outlined in several reviews [1].

As a part of our research, we composed a cross-bridge model using the formalism developed by T.L. Hill and Eisenberg [Hill, 1974, Eisenberg et al., 1980, Eisenberg and Hill, 1985]. The main difference between our model and the cardiac muscle cross-bridge models that were used to compute ATP consumption dependency on SSA before [Taylor et al., 1993, Taylor et al., 1993], was the approach we used to obtain the model parameters. Namely, one of the requirements used in the model parameters estimation was the linear dependency between ATP consumption and SSA in isometric and shortening contractions. Thus, we treated the relationship between ATP consumption and SSA as a fundamental property of the muscle and found the cross-bridge cycling rate constants and the activation parameters using this macroscopical property of the muscle. When this approach was applied the following properties of the cardiac muscle were reproduced [Vendelin et al., 2000]: (a) the relationship between ATP consumption and SSA is linear, with contractile efficiency close to the measured one; (b) the computed isometric active stress during a beat replicates well the measured stress in the isosarcometric contraction at different sarcomere length values [Janssen and Hunter, 1995]; (c) the contraction duration is smaller in the isotonic case if compared with the isometric case, which reproduces the typical isotonic contraction experiment results [Brutsaert et al., 1978]; (d) the end-systolic point in the stress-strain diagram in isotonic contraction lies close to the end-systolic line computed for the isometric case [Hisano and Cooper, 1987]. The model was able to predict the following properties of the muscle: (a) shortening velocity-afterload relationship at afterloads higher than 2.5 kPa [van Heuningen et al., 1982]; (b) drop of ATP consumption by the cross-bridges during a cycle by about 40% if the muscle is released at the time of peak force [Hisano and Cooper, 1987].

It is possible to use the developed cardiac muscle cross-bridge model as a part of left ventricle or complete heart models using the formalism of internal state variables [Engelbrecht et al., 2000]. On the example of the cardiac muscle, we have shown that the internal variables reflecting microstructural properties of soft biological tissues may be organized into a hierarchy. This hierarchical structure incorporates the cross-bridge state distribution functions and the variables describing the activation of the actomyosin complex by calcium ions as used in [Vendelin et al., 2000].

**Fiber orientation in the ventricle**

It has been shown theoretically [Bovendeerd et al., 1994], that the distribution of stress and strain in the left ventricular wall is highly sensitive to the changes in the fiber orientation within the wall. Taking into account such sensitivity, the fiber orientation has to be regulated carefully in the ventricles by adaptation processes. Indeed, depending on the adaptation case, the fibers may be reoriented [Ursell et al., 1985] or remain similar to the orientation in the normal heart [Carew and Covell, 1979, Omens and Covell, 1991]. Here, we investigated the influence of fiber orientation on the ejection fraction and the heterogeneity of
the distributions of fiber stress, fiber strain and ATP consumption [Vendelin et al., submitted].

A finite element model similar to [Bovendeerd et al., 1994] was used with active properties described by the Huxley-type cross-bridge model [Vendelin et al., 2000]. The model computes the deformation of the ventricle, local strains, passive and active stress, and ATP consumption in the ventricular wall. The governing equations were discretized using the finite element method in conjunction with Galerkin’s method. The fiber orientation was quantified by two angles: the helix fiber angle, describing the crossover of fibers between base and apex of the heart, and the transverse angle, describing the crossover of fibers between inner and outer layers of the cardiac wall. According to our simulations [Vendelin et al., submitted], the variances of the sarcomere length, developed stress and ATP consumption during a beat have very similar dependencies on transmural course of the helix fiber angle. The optimal transverse angle value is also similar if the variance of the sarcomere length or developed stress is minimized. The dependence of sarcomere length, developed stress and ATP consumption variances on the helix fiber angle distribution is not simple: the variances have several minima at different helix fiber angle distributions. However, we identified only one region in the studied design space with high ejection fraction of the left ventricle and relatively homogeneous distributions of sarcomere strain, developed stress and ATP consumption within the ventricular wall. This region corresponds to the physiological distribution of the helix fiber angle in the LV wall [Streeter, 1979, Nielsen et al., 1991, Rijcken, 1997]. From our analysis we concluded that if the fiber orientation is regulated by strain or stress distribution the adaptation process should be stable and lead to the ventricles with high ejection fraction provided the difference between actual and optimal fiber orientation is relatively small.

In [Vendelin et al., submitted], a linear PVA-ATP consumption relationship was obtained. Since we used the cross-bridge model [Vendelin et al., 2000] which reproduced linear SSA-ATP consumption relationship, the measured PVA-ATP relationship can be predicted theoretically from the SSA-ATP relationship. The computed ATP consumption distribution was similar to the distribution of oxygen consumption estimated from PCr-to-ATP ratio measurements by NMR. According to the measurements, PCr-to-ATP ratio is slightly higher in the epicardial layer than in the endocardial layer and, with a midwall layer value between these two [Gong et al., 1999, Zhang and McDonald, 1995]. From the available PCr-to-ATP ratio measurements, one can conclude that oxygen consumption in epicardial layers is lower than in endocardial layers. According to our simulations, the highest ATP consumption rate is between the midwall and endocardial layers and the smallest ATP consumption in sub-epicardial layer.

Conclusions

The studies in this thesis are focused on the mechanoenergetics of the cardiac muscle, starting from the regulation of intracellular energy fluxes up to the behavior of the left ventricle as a whole. Below, the main conclusions, grouped according to physiological processes are reported.

From the analysis of intracellular energy fluxes in the cardiac cell, the following conclusion was made:

- It is possible to reproduce the metabolic stability of the cardiac muscle cell using simple feedback regulation mechanism at low and moderate workloads.

The regulatory mechanism used in the cardiac muscle cells has to be identified from combined experimental and theoretical studies. However, the relatively simple feedback mechanism based on the changes of the high energy phosphates can not be ruled out on the basis of available experimental data yet. From the computer simulations on the regulatory role of participating metabolites, the following was concluded:

- The regulator metabolite of the oxidative respiration is not fixed, but depends on the workload and enzyme availability.

Thus, there is most probably no universal regulator of the oxidative phosphorylation of the cardiac muscle mitochondria, but the regulatory role is shared among the participating metabolites.

In the muscle, the energy of biochemical reactions is transformed to the mechanical energy of muscle contraction. The following results were obtained in the theoretical studies of cardiac muscle contraction mechanism:

- It is possible to reproduce the experimentally observed linear relation between ATP consumption and stress-strain area with a model, composed of a 3-state Huxley-type model for cross-bridge interaction and a phenomenological model of Ca\(^{2+}\)-induced activation.
- The linear relationship between the stress-strain area and ATP consumption does not imply a high amount of the “passenger” cross-bridges, i.e. cross-bridges that detach without hydrolyzing ATP molecule.

The developed cross-bridge model of cardiac muscle contraction was used in the studies of the left ventricle mechanoenergetics.
The properties of the left ventricle do not depend only on the properties of the muscle cells, but on the alignment of the cells in the wall as well. The following conclusion has been reached from the analysis of the model solution:

- The variances of sarcomere strain and developed stress are minimized by almost the same fiber orientation, which is close to the measured one. There exists a local minimum of the sarcomere strain and stress variances in the region that corresponds to a high ejection fraction of the left ventricle. At this minimum, the distribution of ATP consumption in the left ventricular wall is relatively homogeneous.

From this result it can be concluded that, if the orientation of the muscle fibers in the left ventricle is regulated by the adaptation process to minimize the heterogeneity of the strain or stress distribution in the left ventricular wall, the resulting design of the left ventricle will lead to a good left ventricle performance as a pump.

Finally, by using the cross-bridge model composed in this thesis as a part of the left ventricle finite element model, the following was demonstrated:

- A linear relationship between ATP consumption and the pressure-volume area can be predicted theoretically from a linear relationship between ATP consumption and the stress-strain area.

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