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THE CARDIOME PROJECT:

An Integrated View of Cardiac Metabolism and Regional Mechanical Function

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INTRODUCTION

In this presentation the first goal is to give an idea of the broader aspects of the Physiome Project, its origins and its current state. The second goal is to give an example of the kind of approaches that will support the Physiome Project by contributing a component that is in the process of being developed into a functioning model and a database entry point: a piece of the Cardiome Project.

THE PHYSIOME PROJECT

The PHYSIOME PROJECT is a loosely integrated multi-centric program to design, develop, implement, test and document, archive and disseminate qualitative and quantitative information, e.g., databases and models, of the functional behavior of organelles, cells, tissues, organs, and organisms. It is a successor to the Genome Project. The focus of the Human Physiome Project is on the human organism, its physiology and pathophysiology, to provide eventually full working models of physiological systems that integrate the observations from many laboratories into quantitative, self-consistent, comprehensive descriptions.

The goal is to provide functional descriptions of human biological systems in health and disease to the community of scientists, physicians, teachers, and manufacturers. A major feature of the project is the databasing of laboratory and clinical observations on all organisms for retrieval and evaluation. A network of Physiome Centers would comprise an adaptable international resource for integrated physiological systems, structured for accessibility via Internet, for the immense databases of information on methods, data, and models.

There is a growing effort to raise consciousness about integrative biology and to provide a setting for the scientific results from research laboratories concerned with genomics, molecular and cell biology, biology in general, and clinical medicine. For those with a primary interest in therapeutics, the Physiome Project can provide a framework for determining the effects of pharmaceutical or genetic interventions on target molecules and functional systems through an in depth, comprehensive understanding of biology at the level of the cell, the tissue, the organ and the organism. The Project will need to be supported by the development of databases that follow upon those developed from the Genome and the Proteome.

In addition to the structural and static information in the databases, a salient goal of the Physiome Project is to integrate dynamic information and modeling, which may be considered to include the protein folding, DNA/RNA conformational dynamics, protein-DNA and other protein-protein interactions, solute-ligand competition for binding sites on enzymes and receptors, and antigen-antibody reactions. Integrations only at static, structural levels (at the level of molecules, organelles, cells, and broader), may not always be sufficient as the bases for understanding human biology and physiology. Many important biological and physiological phenomena have to be explained by a non-dynamic perspective at the molecular as well as the systemic level.

The Physiome Project combines engineering applications with biology, informatics and databasing, and large scale systems analysis. It is potentially a vehicle for discovery and invention, and is a good subject for society-sponsored conferences which would provide an open forum for scientific presentations and advancement of plans, much as in the style of the Gordon Research Conferences in the US. The topics covered would be both on the logistics of specific aspects of the Physiome Project and on its strategies and scientific advances. Government agencies are demonstrating clear interest (particularly NIH, NSF, NASA, and DOE).

In parallel, we need meetings with officials from government agencies to discuss funding mechanisms. One that I feel is important is to obtain better national funding for those agencies which are appropriate to supporting a “set of networked research resource facilities” to take on specific aspects of the program in various countries.

Meetings in 1997 and 1998 that were pertinent to the Physiome Project are summarized or linked at the Physiome Website (www.physiome.org).

THE CARDIOME PROJECT

The Cardiome Project aims to develop a visualizable, interactive model of the physiologically normal working heart. It is a part of the Physiome Project. The Physiome Project is the all-encompassing project, endorsed at an international conference in St. Petersburg in July 1997, “On Designing the Physiome Project,” by the International Union of Physiological Sciences, and the project is targeted now by units within NSF, NIH, and DOE. *The Cardiome*, our specific target, is one of the eight fields selected at the St. Petersburg meeting to demonstrate the practicality and utility of the approach.

The Cardiome is the description, in quantitative, testable form, of the functioning of the normal heart and its responses to intervention. It will prove helpful in integrating results from many years’ efforts into a comprehensive understandable scheme. These efforts have spanned the fields of transport within blood vessels, the distributions of regional coronary blood flows, permeation processes through capillary and cell walls, mediated cell membrane transport, diffusion, electrophysiology, metabolism of the prime substrates (fatty acid and glucose), and studies of metabolism of the purine nucleosides and nucleotides (mainly adenosine and ATP).

The overall Cardiome Project is a large-scale multidisciplinary, multiuniversity effort. It involves physicians, computer scientists, pharmacologists, electrophysiologists, and biomedical engineers working together to develop a model of the human heart. A model heart put together through the collaborative efforts of Hunter, Smaill, Noble, Winslow, McCulloch and others provides fully quantitative descriptions of the electrical currents and ion pump, of the spread of electrical activity across a finite element representation of the fibre directions in the myocardium, and the cardiac contraction itself. We at the University of Washington are expanding this to account for the spatial distribution of the coronary arteries, the regional myocardial blood flows, the uptake and metabolism of glucose, fatty acids and oxygen used for the energy to form ATP, which is in turn used to fuel the work of contraction and ion pumping. In order to link the metabolism with the finite element representations of the mechanics of contraction we will collaborate with Peter Hunter at Auckland University, New Zealand, Andrew McCulloch at UC San Diego and Theo Arts, Maastricht University, Maastricht, The Netherlands. The ionic currents in the Hunter-McCulloch model use the equations either of Denis Noble (Oxford University, UK) or of Yoram Rudy (Case Western Reserve University). Rai Winslow (Johns Hopkins University) used these currents to drive the spread of excitation throughout the three-dimensional cardiac structure.

To model the chemical-mechanical conversion of high energy phosphate for contraction we have begun a collaboration with Amir Landesberg and Samuel Sideman, at Technion University, Haifa, and with Martin Kushmerick, Michael Regnier and Albert Gordon at the University of Washington. The fatty acid metabolism studies are a continuation of work in collaboration with Ger van der Vusse, Rob Reneman, and Jan Glatz at Maastricht University and James Caldwell at the University of Washington. The glucose studies are a continuation of a collaboration with Claudio Cobelli and Paolo Vicini at The University of Padua which, like most of the others above, is formalized through their participation in the activities of our Simulation Resource Facility at the University of Washington.

DESIGN PHASE

In order to provide a demonstration of the utility of modeling we would like to have a functional version of the Cardiome developed within three years to the level where it is useful for predicting responses to blockage of coronary arteries, to pharmaceutical agents used for blocking channels or pumps (e.g., digitalis in cardiac failure), and to metabolic stimuli or exercise. It will require many additional steps of subsequent development to account for intracellular regulatory processes, so our planned initial result can only be regarded as a primitive beginning.

The goal is to develop an integrated synthesis of cardiac metabolic, electrical, and mechanical events into a visualizable form that can be seen by the *public* to represent cardiac mechanics in health and disease and can be used by *investigators* as a stepping stone for developing insight into the complex metabolic and biophysical interrelationships that are the basis for cardiac function. Within this context we define four linked modules which, along with two modules already well developed by others for the electrophysiology and the mechanics, describe cardiac function. The six modules are as diagrammed in Figure 1.

1. **Coronary artery anatomic localization and regional myocardial flows**, providing substrate and oxygen delivery,
2. **Metabolism of the substrate for energy metabolism**, fatty acid and glucose, the tricarboxylic acid cycle, and **oxidative phosphorylation**,
3. **Purine nucleoside and purine nucleotide metabolism**, describing the formation of ATP and the regulation of its degradation to adenosine in endothelial cells and myocytes, and its effects on coronary vascular resistance,
4. **Excitation-contraction coupling (ECC)**, calcium release and reuptake, and the relationships between these and the strength and extent of sarcomere shortening.
5. **The electrical currents and their spread across the myocardium**: these are described by either the Luo-Rudy model (Luo and Rudy, 1994a, 1994b; Shaw and Rudy, 1995; Rudy and Shaw, 1997), or the Noble-DiFrancesco model (DiFrancesco and Noble, 1985; Ch'en et al., 1997).
6. **The three-dimensional finite element representation of the contracting heart** has been brought to an advanced stage by Peter Hunter and his group at University of Auckland, New Zealand (Hunter et al., 1988; Hunter and Arts, 1997) and Andrew McCulloch and his group at San Diego. (See McCulloch et al., 1998.) It is into their three-dimensional finite element reconstructions of the mechanically contracting heart that we will put our components of the physiological responses.

The major inputs to the model will be: aortic blood pressure, hematocrit, pO_2 , pCO_2 , heart rate, concentrations of palmitate, lactate, acetate, glucose, pyruvate, pH, Na^+ , Ca^{2+} , K^+ , Cl^- , PO_4 , HCO_3 , Mg^{2+} . To take this through the first stage, gross simplifications must be made, so we

will temporarily omit incorporating: (1) mechanico-electrical feedback, (2) systolic compression of intramyocardial coronary arteries and veins, (3) regulation of intracellular enzymes by secondary processes, (4) vascular and tissue remodeling, (5) protein metabolism, (6) systemic influences on total body vascular resistance, (7) changes in cardiac pool sizes of glycogen and di- and triphosphoglycerides, and many other features. Any list of omissions should be nearly infinite; these are merely the more obvious ones. These, and others found to be critical, will be the subject of later modifications.

The overall schema (Figure 1) is centered around the fluxes of ATP, ADP/Pi, and H⁺ in Module 3, linking the other modules in the regulation in the functioning heart. Module 4 for the excitation-contraction coupling now exists only as a purely empirical relationship without adaptability or regulatory control, or any link to ATP. The other modules, for coronary flow distribution and substrate and oxygen delivery to tissue, for substrate utilization and oxidative phosphorylation, and for purine metabolism are new undertakings. We will focus initially on the single sarcomere level modules and their interactions with one another. Periodically, we will incorporate each module into the integrated whole organ model for testing there. Each stage remains archived through our Source Code Control System to preserve all previous versions. As information from experiments is gathered, or inconsistencies recognized from the behavior of the whole organ model, improvements will be made in the sarcomere modules. To give users prompt responses we must code for computational efficiency. Periodic reviews to improve speed will be essential in a large long-range project like this.

MODULE 1. CORONARY SYSTEM AND REGIONAL FLOW DISTRIBUTIONS

Intramyocardial flow distributions are remarkably heterogeneous (Yipintsoi et al., 1973; Bassingthwaighe et al., 1990), showing a range of 6 to 10-fold in normal hearts in awake or anesthetized animals. This is explained by the fractal self-similar branching of the coronary arteries (Bassingthwaighe et al., 1989). Anatomic data from van Bavel et al. (1992) and Kassab et al. (1993) serve as a more realistic basis for network reconstructions than we achieved earlier (van Beek et al., 1989). Network reconstructions developed by Daniel Beard exhibit appropriate pressure distributions, regional flow heterogeneities and fractal spatial correlations in flows, and the same power law form ($\sim 1/t^3$) for the washout time course as is observed (Bassingthwaighe and Beard, 1995).

The next stages concern the delivery of substrates and oxygen. The mechanism for glucose delivery to myocytes is through the interendothelial clefts, and from the interstitium via a transporter across the cell membrane (Kuikka et al., 1986). Fatty acid transport is more complex because it binds tightly to albumin; it does not traverse the clefts, but must be stripped off the albumin before being translocated (reviewed by van der Vusse et al., 1999, submitted). The inhibition of tracer palmitate permeability by high albumin concentration was explained by Bassingthwaighe, Noodleman et al. (1989) in a model form for the fatty acid translocation. In a further refinement, Caldwell et al. (1994) found in exercising dogs that the regional density of fatty acid transporters in the heart is proportional to the regional flows.

The non-invasive measurement of regional myocardial blood flow (MBF) and oxygen consumption (MRO₂) using positron emission tomography (PET) that we have developed in the past two years contributes directly to the Cardiome project, and leads to an important simplification. The most direct measure of oxidative tissue metabolism is the conversion rate of oxygen to water via mitochondrial respiration. A sequence of cardiac images obtained at two-second intervals after single-breath inhalation of ¹⁵O-oxygen (Li et al., 1997) gives, in each region of interest, the time-activity curves of the sum of the ¹⁵O-oxygen and its product, ¹⁵O-water. Their relative amounts can be distinguished by kinetic modeling (Figure 2) because the mean transit time for water produced in the tissue is much longer than that for

untransformed oxygen, most of which is in the form of oxyhemoglobin within the red blood cells. Consequently, the extraction of ^{15}O -oxygen can be estimated and used to calculate the steady-state oxygen consumption within each ROI. The model (Figure 2) accounts for intravascular convection, penetration of capillary and parenchymal cell barriers, the metabolism to ^{15}O -water in parenchymal cells, and ^{15}O -water transport into the venous effluent. Nonlinear binding of oxygen to hemoglobin in erythrocytes and to myoglobin in myocytes is explicitly incorporated in the model. This model is more accurate and much easier to use than the linear model by Deussen and Bassingthwaighte (1996) because the local volumes of distribution for oxygen are calculated automatically from oxygen supply and demand at steady state.

With this PET method we were able to study the correlation between regional myocardial blood flow and oxygen consumption *in vivo*. Our results from a limited number of experiments showed that the regional oxygen consumptions were approximately proportional to the regional flows as measured by the microsphere technique (Yipintsoi et al., 1973; Bassingthwaighte, Malone et al., 1990) (Figure 3). These results support the generality that flows, transport conductance for substrate (Caldwell et al., 1994), and oxygen consumption are regionally matched. This strong evidence for proportional regional requirements will simplify the overall modeling project if we find that there is regional matching with ATP usage.

The methods for using models to determine the parameters of transport and metabolism are discussed by Bassingthwaighte and Goresky (1984), by Kuikka et al. (1986), and in a book slated for publication next month (Bassingthwaighte, Goresky and Linehan, 1998). Optimized parameter adjustment can be accomplished manually under XSIM, a graphical user-friendly interface developed by Richard King et al. in our group, or by using automated optimization, e.g., by a steepest descent technique modified from that of Bronikowski et al. (1980) with our sensitivity function based approach (Chan et al., 1993). As a standard technique for evaluating the error and bias in estimates, we use Monte Carlo assessment of the effects of adding noise to form “pseudo data” from model solutions.

A satisfactory first definition for regional substrate delivery therefore provides for the fluxes by flow and transmembrane transport of oxygen, the substrates, and the metabolites, including lactate and CO_2 . The oxygen model diagrammed in Figure 2 is of the same general form as for these other solutes, all of which can be metabolized, but the others are more complex because they need specialized transporters, e.g., for fatty acid and for adenosine.

MODULE 2. METABOLISM AND OXIDATIVE PHOSPHORYLATION IN MITOCHONDRIA

Module 2, “Metabolism & Oxidative Phosphorylation,” contains the detailed enzymatic reaction network for **Glycolysis, TCA cycle, oxidative phosphorylation, and acyl CoA mobilization** from fatty acids and pyruvate. General overviews of cardiac metabolism are given by Randle and Tubbs (1979) and Bassingthwaighte (1991). Mitochondria, which comprise one-third of myocyte volume, are well dispersed among and closely apposed to bundles of myofilaments.

The heart uses substrates principally for energy production. The main substrate is fatty acid, supporting about two-thirds of the caloric needs; the range of estimation is very wide, from 35% to 95%, which reflects the ability of the myocyte to shift fuels under different circumstances. The remainder of energy comes from glucose, lactate and amino acids. Glucose also provides pyruvate and lactate needed to maintain the constituents of the TCA cycle. Amino acids maintain intracellular proteins and enzymes and support transport reactions, exemplified by the role of carnitine in the transfer of fatty acids across the mitochondrial membrane. The

overall processes of substrate metabolism include: delivery by flow into capillaries; transport across the capillary walls and across the sarcolemma of myocyte; diffusion and reaction in the cytosol; transport across the mitochondrial inner membrane; intramitochondrial reactions; breakdown of 2-carbon fragments into CO₂ and water through the TCA cycle; the reactions of the electron transport chain; and the production of ATP from ADP, coupled to the electron transfer chain and to other reactions in the glycolytic series. For fatty acids, Chatham et al. (1995) provide data on TCA fluxes of 2-carbon fragments and the shifts between oxidative and anaerobic metabolism.

For fatty acid metabolism, the thiokinase reaction requires one ATP-to-AMP reaction per free fatty acid. β -oxidation produces one molecule of FADH₂ and one molecule of NADH per 2-carbon fragment (total eight 2-carbon fragments from palmitate), and yields 35 molecules of ATP (one NADH yields 3 ATP, one FADH₂ yields 2 ATP). Each acetate molecule gives a total of 12 molecules of ATP in TCA and respiratory chain. So the total ATP generation per palmitate is $8 \times 12 + 5 \times 7 - 2 = 129$ molecules of ATP.

In glucose metabolism, for every molecule of glucose, 4 molecules of ATP are produced in anaerobic (2 ATP) and aerobic (2 ATP) glycolysis, and 32 molecules of ATP are produced in TCA and respiratory chain by oxidation of NADH and FADH₂ (for every molecule of glucose, 6 molecules of NADH and 2 molecules of FADH₂ are formed in the TCA cycle; 2 molecules of NADH are formed during aerobic glycolysis and 2 molecules of NADH are formed during pyruvate oxidation). To relate ATP generation to oxygen utilization, for glucose, 6ATP per O₂; for palmitate, 5.6ATP per O₂. So the oxygen cost per ATP is similar with fatty acid versus glucose during aerobic metabolism. Module 2 can therefore in its most elementary form for the normal physiological state be represented by the stoichiometric conversion of substrate and oxygen to ATP, with proportional usage the same everywhere.

Through the supply/demand imbalance the cardiac contractile performance influences and indirectly governs the blood flow and oxygen delivery in normal physiological states. The rate of carbon flux through TCA cycle is reduced when the O₂ supply is low, inducing a switch from aerobic fatty acid and glucose metabolism to glycolysis and lactate production. This shift toward anaerobic metabolism means there is zero ATP from palmitate (actually a net loss due to diacylglycerophosphate production) and only 2 ATP per glucose, in glycolysis, and at the expense of H⁺ production and whose metabolism must be included (Achs and Garfinkel, 1977). The apportionment between glucose and fatty acid as substrate is governed by their availability and by pO₂, pH, and NADH levels.

To develop this part of the model we need values for the various biochemical constants for the enzymes; Evgeni Selkov has developed an enzyme database for the metabolic pathways (Selkov et al., 1996,1997). This module is complex, but simplified versions have been worked out, for example by Magnus and Keizer (1997). Theirs has the explicit advantage of incorporating the influences of Ca²⁺ on the transformations within the mitochondrion. Selkov has such a model himself.

MODULE 3. ATP AND ADENOSINE METABOLISM AND RELEASE

The “Purine Metabolism” module contains the kinetic reactions for myocardial phosphoenergetics (Figure 1). Purine, as both ATP and adenosine, is an important biochemical regulator for the cardiac muscle mechanics. This key to understanding the energetics was extensively studied experimentally and computationally by the late Professor Keith Kroll (Kroll and Stepp, 1996;Kroll et al., 1997;Kroll and Bassingthwaight, 1998). Based on experimental measurements on rabbit heart and subsequent comparison with the simulation from this kinetic model, he showed that an energy imbalance arises in the underperfused heart, and that the intracellular free energy loss is minimized by losing adenosine and AMP from the

cell. Further study (Gustafson and Kroll, 1998) suggests also that the enzyme 5'-nucleotidase is down-regulated when PCr and ATP decrease.

The descriptive element, the imbalance, Δr_{ATP} , must be replaced by the appropriate reactions for formation and degradation of ATP. The former are in the "Oxidative Phosphorylation" module and the latter in the modules for "Contraction" and for the ion pumps, included in "Ionic currents" and "ECC". All modules are tested for adherence to mass balance; for this module the test is to set the membrane permeabilities to zero for all forms of creatine, phosphate, and purine base while running model solution for conditions that degrade ATP and PCr and to see whether or not their totals remain constant; such constancy is a minimal requirement, without which the model is invalid. There is never a proof of validity, but when many tests against observed data are satisfied one gains confidence in such a model as a working hypothesis.

The computer simulation program we developed for this uses mouse clicks to bring out deeper features. A click on a bottom "Cr K'ase" pops up a new window to show the underlying mechanics for the enzyme.

MODULE 4. EXCITATION-CONTRACTION COUPLING

Our earliest model of excitation-contraction coupling (Bassingthwaighe and Reuter, 1972) included our kinetics of the slow inward calcium current reported formally in the Beeler-Reuter (1977) model of the action potential. It was timely as a step in integrated modeling and it incorporated the concepts of that time on how calcium cycling in the myocyte served as the key factor in the governance: trigger Ca^{2+} current, calcium release from the SR, calcium-troponin binding, contractile filament shortening and reuptake of calcium by the sarcoplasmic reticulum, SR. A more modern view is provided for example by Bers (1991) in an excellent monograph. Module 4 requires information from the Ionic Currents (Module 5). Initially we will not use the detailed time course of the currents, but to speed computation will use the total net quantities of each ion transferred during the action potential to determine the concentrations within the cytosol. These are the quantities that need to be removed by the pumps and exchanges during the remainder of the cardiac cycle during any steady state. These will determine the ATP usage for ionic balance.

The ATP used for cross-bridge shortening is influenced by the tension and the time course of the shortening velocity in the sarcomere (Landesberg et al., 1994a,b; 1996a,b; Regnier et al., 1995, 1997; Blei et al., 1993; McFarland et al., 1994; Wiseman et al., 1995; Chase et al., 1995). Because local Ca^{2+} and early systolic pre-ejection phase shortening cause a shift from the strongly to the weakly bound form of ATP-myosin, this reduces the amount of ATP required during a contraction. Consequently our modeling needs to take this level of detail into account when it comes to examining the relationship between local flows, local metabolism, and contractile function, especially in situations such as prolonged ventricular pacing where remodeling occurs (Arts et al., 1994, 1995), thinning the ventricular wall at sites of early activation and causing hypertrophy in late activated regions. Since there is potential benefit in using pacing as an inhibitor of outflow tract obstruction in hypertrophic subaortic stenosis, for example, testing this approach in a model of an intact heart may be one way to use the modeling in defining therapy. Since one can obtain individual cardiac structural descriptions from MR and regional physiological information from PET and ultrasound, this could evolve to a stage, as it has for repairing knees, where the modeling is key to the therapeutic intervention.

The myosin ATP form and Ca^{2+} influence the patterns of deformation through the ventricle; the ventricular structure has been precisely detailed in two dog hearts (LeGrice et al., 1995, 1997) with fiber directions over the whole ventricle, and fibre sheets and bundles between which the vessels are positioned. These have been integrated into whole heart mechanical

models (Module 6) by our collaborators (McCulloch et al., 1989, 1991, 1998; Hunter et al., 1988; Hunter and Arts, 1997) and it is with these model structures and the Ionic Current Module 5, that we will integrate our Modules 1 to 4.

SUMMARY

The goal, to develop a functioning three-dimensional computational model of the excitation, metabolism and contraction of the heart within three years, is one of the beginnings for the Cardiome Project. Our first stage will not be likely to provide highly accurate prediction of physiological behavior in general, but will be focussed so that it is adequate for at least three specific purposes: response to regional flow reduction, response to heart rate changes, and response to increased metabolic drive. We would like to make the model visualizable by three-dimensional viewing, with cross-sectional and transparency viewing approaches, illustrate the fiber directions, the arteries, the deformation with contraction and images of regional functions such as oxygen consumption, pre-ejection strain, or lactate concentration. The display techniques developed by Hunter et al. and by McCulloch et al. would be excellent for such demonstration and teaching purposes, and should be attractive enough for public display.

The Physiome Project is underway now, with growing government and private support. Now we are going from the era of molecular biology, led by the Genome Project, into a new era of integrative biology. The goal is to understand biology so deeply and so broadly that predictions about interventions can be made. Methods of experimentation and of diagnosis are critical to acquiring the data, and therefore in making the prediction, and so all aspects of our Society's efforts and interests are relevant to undertaking this grand challenge.

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Figure 1.
Overall diagram of the Cardiome Model components.

Figure 2.

Dual capillary-tissue model for ^{15}O -oxygen transport and metabolism into ^{15}O -water. The four concentric regions are red blood cells (rbc), plasma (p), interstitial fluid (isf) and parenchymal cells (pc). The symbols used are F for flow, $\text{ml min}^{-1}\text{g}^{-1}$; V for anatomical volumes and V' for volumes of distribution, ml g^{-1} ; PS for permeability-surface area product, $\text{ml min}^{-1}\text{g}^{-1}$; G for the first-order consumption rate, $\text{ml min}^{-1}\text{g}^{-1}$; and D for the axial dispersion coefficient, $\text{cm}^2 \text{s}^{-1}$. The superscripted "o" and "w" denote oxygen and water, respectively.

Figure 3.
Correlation between blood flow (rMBF) and oxygen consumption (rMRO₂) in regions of interest (0.9 ± 0.3 g) of the LV myocardium of a closed-chest dog.