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Heterogeneities in Myocardial Flow and Metabolism: Exacerbation with Abnormal Excitation

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Abstract

Because regional myocardial blood flows are remarkably heterogeneous—with a 6- to 10-fold range of flows in normal hearts—and because the spatial profiles of the flows are stable over long periods and over a range of conditions, the relation between flows and other physiologic functions has been explored. Local fatty acid uptake and oxygen consumption are almost linearly related to the flows. Coronary network structure and hydrodynamic resistances give suitable flow heterogeneity but are thought to be a response to local needs rather than being causative. Presumably the cause is the need for adenosine triphosphate (ATP) synthesis locally, and therefore flows, substrate delivery, and oxygen utilization are driven primarily by local rates of ATP hydrolysis, mainly by contractile proteins. This hypothesis is by no means fully tested. Data on pacing dog hearts from different sites, on patients with left bundle branch block, and on unloading transplanted rat hearts, all point in the same direction: unloading ventricular muscle leads to diminished flow and exaggeratedly diminished glucose uptake. The mechanism is likely to be that discovered by Taegtmeier and colleagues, namely, the expression of fetal genes in regions where the muscle is unloaded and particular metabolic enzymes and transporters are downregulated.

Regional blood flows in the left ventricle alone are remarkably heterogeneous.^{1,2} The range of regional flows, per gram of tissue, is 6- to 10-fold at a spatial resolution of 0.5% of the left ventricular mass, even in awake baboons.³ The standard deviation of the distribution is about 25% and is even broader if smaller tissue pieces are used for the measurement.⁴ Fluctuations in flows over time are small,⁵ so small that a high-flow region never diminishes its flow to the average, nor does a low-flow region ever raise its flow to the average for the heart.

The heterogeneity is not random: near-neighbor regions tend to be alike, and there is self-similarity in the decay of the spatial correlation with increasing distance, a fractal phenomenon. The fractal relation is that, for a chosen ratio of distances between regions, there was a constant proportional diminution in correlation. We found that such flow distributions would theoretically occur with fractal self-similar branching of the coronary arteries.^{6,7} Anatomic data, also fractal in nature, from van Bavel and Spaan⁸ and Kassab et al,⁹ serve as a more realistic basis for network reconstructions¹⁰ than we achieved earlier with artificial branching algorithms.⁷ These, Beard's new network reconstructions, exhibit appropriate pressure distributions, regional flow heterogeneities and fractal spatial correlations in flows, and the same power law form ($\sim 1/\ell^3$) for the washout time course as is observed.¹¹ But no matter how realistic the coronary network models may be, they are not the explanation for the regional flow heterogeneity; the vessels are mere conduits, constructed and remodeled under the influence of more fundamental processes. It is our thesis that the governing process is the requirement for local energy production and that

coronary vessel sizes, regional flows, and the local consumption of substrates and of oxygen are all in response to the demand for adenosine triphosphate (ATP). Coronary network structure is the slave, we believe, not the master.

Substrate Uptake

Because fatty acid is the prime substrate for myocardial energy generation, its regional utilization provides a further clue. Fatty acid transport capacity is higher in regions where the flow is higher,¹² which implies that there must be more fatty acid transporter proteins or albumin binding sites¹³ expressed in regions requiring more uptake. Fatty acid transport is complex because it binds tightly to albumin and thus does not traverse the interendothelial clefts to any extent, but must be stripped off the albumin before being translocated (reviewed by Van der Vusse et al¹⁴). The inhibition of tracer palmitate permeability by high albumin concentration was explained by Bassingthwaighe et al¹⁵ in a model for fatty acid translocation. In a further refinement, Caldwell et al¹⁶ found, in exercising dogs, that the regional uptake of fatty acid is closely proportional to the regional flows. Because regions with high flow and high consumption remain so over long periods of time, this demonstrates that the heart is metabolically stable, although heterogeneous.

Oxygen Consumption

In the past 2 years, we have developed, using positron emission tomography (PET), techniques for noninvasive measurement of regional myocardial blood flows and regional oxygen consumption.

Regional oxygen consumption in 1 heart at a particular moment increases more or less linearly with regional flow. Regional oxygen consumption provides a direct measure of oxidative tissue metabolism; it reflects the rate of conversion of oxygen to water via mitochondrial respiration. This is tightly coupled with aerobic ATP generation in any steady state.¹⁷

The method begins with taking a sequence of cardiac images obtained at 2-second intervals after single-breath inhalation of ¹⁵O-oxygen.¹⁸ In each region of interest, the time-activity curves are the sum of those of ¹⁵O-oxygen and its product, ¹⁵O-water. Their relative amounts can be distinguished by kinetic modeling⁸ because the capillary mean transit time for water produced in the tissue is much longer (almost 10 times longer) than that for untransformed oxygen, most of which is in the form of oxyhemoglobin within the red blood cells. The ¹⁵O-oxygen extraction is estimated and used to calculate the steady-state oxygen consumption within each region of interest. The model accounts for intravascular convection, penetration of capillary and parenchymal cell barriers, the metabolism to ¹⁵O-water in parenchymal cells, and ¹⁵O-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.

The methods for using models to determine the parameters of transport and metabolism are discussed by Bassingthwaighe and Goresky,¹⁹ Kuikka et al,²⁰ and Bassingthwaighe et al.²¹ Optimized parameter adjustment can be accomplished manually under XSIM, a graphic user-friendly interface developed by King and Butterworth,²² or by using automated optimization, for example, by a steepest descent technique modified from that of Bronikowski et al²³ with our sensitivity function-based approach.²⁴

The Matching of Regional Myocardial Blood Flows and Regional Oxygen Consumption

The regional oxygen consumptions were approximately proportional to the regional flows as measured by the microsphere technique. These results support the generality that flows, transport conductance for substrate,¹⁶ and oxygen consumption are regionally matched. These results also provoke us to try to determine what might be the cause of such correlations.

The standard thinking has been that the heart metabolizes uniformly, that is, all regions use the same amounts of oxygen and substrate. The same idea was applied to force generation: it is expected to be uniform, and mechanical models have been developed that support this concept.^{25,26} Microsphere flow studies by Hoffman et al^{27,28} and our own laboratory (Yipintsoi et al¹ and subsequent studies, including Bassingthwaighe et al²) demonstrated that the flow heterogeneity was consistently large, and comparisons with molecular microspheres removed all doubt that the magnitude of the variance of the flows might have been attributable to peculiarities of distribution of particulate spheres,² and led to the conclusion that the heart was regionally heterogeneous metabolically. A clear message came from the low-flow regions in the normal heart: these regions did not receive enough oxygen, even at 100% extraction, to metabolize at the average rate for the whole left ventricle. Having flows consistently from 25–40% of the mean left ventricular flows, these regions would have to extract >100% of the oxygen to do so.

What are Regional ATP Requirements?

It is important to determine whether or not there is matching among the local regional myocardial functions. We have focused on flows, transport capacity for essential barrier-limited substrates of energy metabolism, and oxygen consumption, and from the latter we infer that the rates of ATP turnover and the demands for ATP to support contractile work and ionic balance must be what is driving these proportionalities. The general concept is diagrammed in Figure 1. An explicit question is whether or not contractile work is really proportional to regional myocardial blood flows. Because it is certain that myocardial regions with flows of 20–30% of the mean flow cannot be using oxygen at the average rate for the heart, the implication is that these regions do less work (internal and external work) than the average for the heart. Although hearts may transiently show net lactate production, it seems unlikely that specific regions are consistently anaerobic, so we look for an explanation as to why regional work should be less in low-flow regions than in high-flow regions.

The Maastricht group of Prinzen et al²⁹ explored the relations among flow metabolism and epicardial strain patterns in open-chest dogs by pacing hearts from varied sites. On changing the site of activation (either right ventricular outflow tract or left ventricular apex), regional myocardial blood flows diminished at sites that were activated early after the electrical stimulation compared with when normal sinus node stimulation was used. Contrarily, flows became higher at sites activated later by the spreading excitation. This is shown in Figure 2, a composite figure we made from their illustrations. The middle column shows a 4 by 4 set of numbers giving the maximum strain during ejection. Note that the earliest activated sites (indicated by the timing for the spread of activation indicated in the left panels) tend to shorten quickly during the early isovolumetric phase of systole before ejection begins and before there is a significant increase in left ventricular pressure. Regions with increased early preejection shortening usually had less ejection phase strain, and there was always less blood flow (right panels) than in the control state. Regions activated late (right lower corner of B panels, and left upper corners of C panels) often exhibited stretching during the

preejection phase and showed greater shortening during the ejection phase; their flows increased compared with the control state.

These results have been confirmed in later studies by other investigators.^{30–32} They have found that the relation between activation time and ejection phase strain is consistent and independent of the site of activation: early activation → small strain during ejection, and late activation → larger strain during ejection. They also showed that there was a striking inverse relation between isovolumic phase strain and ejection phase strain.

These data may explain the observations by McGowan et al³³ that scintiscans of patients with left bundle branch block (LBBB) showed septal perfusion defects with normal coronary arteries. Early-activated regions (the septum in LBBB) require less blood flow. More recent studies summarized in an editorial by Altehoefer³⁴ have made the observation that F-deoxyglucose uptake in the septum is decreased out of proportion to flow in LBBB, leading to a summary description as “reversed mismatch” in F-deoxyglucose uptake and flow. We would guess this phenomenon is due primarily to early septal contraction against no load and resultant “shortening deactivation” decreasing ATP requirements there, but there is still the question of why F-deoxyglucose uptake might be decreased even more than flow. With some presumption, it might be explained on the basis that in regions where the metabolic demands are decreased below normal, the glucose uptake is further subnormal, whereas fatty acid metabolism is less affected. It is conceivable that the flows and choice of metabolic substrate are linked through diminished endothelial nitric oxide release, in accord with observations and concepts put forward by Hintze in the study by Xie et al.³⁵ Diminished flows, diminished endothelial shear stress, and diminished nitric oxide release may decrease the nitric oxide-induced drive toward glycolysis and leave fatty acid as the dominant substrate.

Direct evidence of the effects of unloading cardiac muscle is provided by Depre et al³⁶: they showed, in rat hearts unloaded on being transplanted into isogenic recipients, reactivation of fetal genes for growth factors (transforming growth factor- β 3) and proto-oncogenes (*c-fos*), strongly decreased expression of the glucose transporter GLUT4, and reduction of the muscle isoform of carnitine palmitoyltransferase I.

In LBBB, the interventricular septum is unloaded because the bulk of the left ventricle contracts so much later. This can explain the septal flow reduction. GLUT4 downregulation in the unloaded septum would explain the striking diminution in F-deoxyglucose uptake in these patients. This fits the observation by Deussan³⁷ that uptake of glucose, like that of fatty acids, is proportional to flow regionally, and fits the perspective that GLUT4 transporters and glucose uptake increase with exercise, as reviewed by Zierler.³⁸

ATP Hydrolysis by Myosin ATPase

The data make sense in terms of theories of cardiac muscle contraction. The early-activated site, compared with late-activated sites, has fast and almost isotonic initial shortening during the isovolumetric phase of systole but later has smaller isometric strain. The early isotonic shortening induces “shortening deactivation,” or what Brutsaert and Rademakers^{39,40} and Sys and Brutsaert⁴¹ thought of as “load-dependent relaxation.” This has been explored by Allen and Kurihara⁴² and by Allen and Kentish⁴³ and pulled together in a quantitative comprehensive theoretical study by Landesberg and Sideman.^{44,45} It causes reduction in the amount of calcium bound to the myosin ATPase in the “strong” form, implying that the rapid shortening against low resistance decreases ATP hydrolysis. This is termed “shortening deactivation.” The small ejection phase strains in these same regions would give a second reason for decreased ATP usage. The quantitative relation between the strain patterns, the intramyocardial stress, and ATP hydrolysis require elucidation at the level of

the cross-bridge. This is likely to be the underlying metabolic mechanism for the redistribution of the local flows, that is, metabolic demand is low in early-activated regions and high in prestretched late-activated regions. The observations of “mismatches” of flow and metabolism therefore may be “misexpectations” rather than mismatches.

Integrating Cardiac Behavior: The Cardiome Project

The Cardiome is defined as the description, in quantitative, testable form, of the functioning of the normal heart and its responses to intervention. It is intended to integrate results from many years' experimentation into a comprehensive understandable scheme. In our laboratory 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). It is important to link our work more closely to that of others working on the heart.

The Cardiome Project is a large-scale, multidisciplinary, multiuniversity effort,⁴⁶ a part of the Physiome Project (<http://www.physiome.org>). 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 fiber directions in the myocardium, and of the cardiac contraction itself. The beginnings of this were presented by Glass et al⁴⁷ and Noble.⁴⁸ A recent volume put together by McCulloch et al⁴⁹ summarizes the current state. Since the early 1970s, our group at the University of Washington has been putting together whole organ models describing transport and exchange of substrates and accounting 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 energy to form ATP, which is in turn used to fuel the work of contraction and ion pumping. These endeavors are summarized in the book by Bassingthwaighe et al.²¹

Conclusion

Asynchronous activation causes redistribution of regional myocardial blood flows. The expectation, based on current theory, is that regional oxygen consumption is changed in the same way that flow is changed, given that regional oxygen consumption is a good measure of ATP turnover rate locally in the steady state. However reasonable, these conjectures will remain unproved until studies on local oxygen metabolism, regional oxygen consumption, and local strain and stress can be made simultaneously. Such studies are needed to provide direct experimental links between local oxygen consumption, local flow, local activation, and local myocardial mechanics, and to provide a practical test of the energetic inferences of the cross-bridge theory of Landesberg and Sideman.^{44,45} Theory and experiment go hand in hand; the more complex the known system becomes, the more need there is for a comprehensive model of the system for use in experiment design and interpretation. The modeling and experimental studies discussed here form a small part of a grander effort—the Cardiome Project—just now in its nascent stage.

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FIGURE 1.

Diagram of oxygen consumption (rMRO₂) with respect to local needs for adenosine triphosphate (ATP). ATP required for ionic balance is probably almost independent of work load, except for Ca²⁺ cycling.

FIGURE 2.

Electrical activation, regional shortening patterns, and blood flows in a 5×4 cm patch of dog left ventricular free wall divided into 16 regions. *Left panels:* electrical activation times (milliseconds). *Middle panels:* Strains (fractional length changes) during systolic ejection phase are shown numerically, negative sign indicating shortening; to the sides are continuous recordings of the regional segment lengths between epicardial markers. Pre-ejection negative strain shortening deactivation. *Right panels:* regional myocardial blood flow values in underlying myocardium by the microsphere technique. Upper row, labeled *A*: Normal sinus node activation. Middle row, labeled *B*. Right ventricular outflow tract stimulation near the left upper corner of the observed epicardial 4 by 4 region. Lower row,

labeled C: left ventricular apical stimulation near the right lower corner of the observed region. (Adapted with permission from *Am J Physiol.*²⁹)