Response of Myocardial Metabolites to Graded Regional Ischemia: $^{31}$P NMR Spectroscopy of Porcine Myocardium In Vivo


The changes in myocardial high energy phosphates and pH during regional ischemia, and their potential role in mediating functional abnormalities, is unclear. To determine the degree of regional blood flow reduction required to induce changes in high energy phosphates and pH, and to correlate these metabolic changes with alterations in blood flow, $^{31}$P nuclear magnetic resonance spectroscopy was employed in an in vivo porcine model of graded coronary stenosis. Simultaneous measurements of regional blood flow and phosphate compounds were made during various steady-state degrees of regional ischemia in which subendocardial blood flow was reduced by as much as 80%. ATP did not fall over the total range of graded ischemia, while phosphocreatine (PCr), inorganic phosphate (P$_i$), and pH all changed progressively after blood flow was reduced below 50% of normal. The ratio of PCr/P$_i$ (a measure of the energy reserve of the myocardium) was strongly correlated to subendocardial blood flow ($r=0.94$) and declined by 25% when blood flow was reduced by only 21% below normal. These findings indicate that PCr/P$_i$ is a sensitive marker of ischemia and support the hypothesis that the in vivo energy status of the myocardium is closely coupled to myocardial blood flow. (Circulation Research 1989;64:968-976)

The changes in myocardial high energy phosphate concentrations in response to ischemia, and their role in mediating the accompanying functional abnormalities, have been the subject of several investigations. Some of these studies have examined the metabolic and functional responses of myocardium to acute total coronary artery occlusion and have suggested that changes in high energy phosphates occurred later than, and were not as severe as, changes in blood flow and function. Similarly, measurements of the metabolic and functional responses of myocardium to partial coronary stenosis have also suggested a dissociation between reductions in blood flow and changes in high energy phosphates. These studies have generally been performed in isolated heart preparations and have demonstrated a close relation between blood flow and cardiac function but a less significant relation between blood flow and high energy phosphates. Thus, the importance of high energy phosphates in mediating the functional consequences of ischemia is uncertain. However, problems with perfused hearts include the use of nonphysiological substrates, the absence of adrenergic and hormonal regulation, and the use of global, rather than regional, ischemia. Previous in vivo canine metabolic studies of partial regional ischemia have necessarily been limited to a few measurements of tissue biopsy samples at fixed time periods. Therefore, the response of high energy phosphates to regional ischemia in vivo is incompletely characterized and may be different from that of the globally ischemic perfused heart. Accordingly, to examine the role that high energy phosphates may play in modulating the effects of ischemia, we sought to define their response to graded regional ischemia using an in vivo porcine model of partial coronary stenosis.

Phosphorus-31 nuclear magnetic resonance spectroscopy ($^{31}$P NMR) can nondestructively and serially measure the concentrations of high energy phosphates in tissues. Hence, $^{31}$P NMR provides a unique opportunity to investigate the meta-
bolic effects of alterations in myocardial blood flow without the tissue sampling required for biochemical assays. Using \(^{31}\)P NMR, our goals were to 1) determine the degree of regional blood flow reduction required to induce changes in high energy phosphates and pH, and 2) correlate changes in myocardial blood flow with metabolic changes.

**Materials and Methods**

**Preparation**

Ten female Yorkshire-Landrace pigs weighing 35–40 kg were used. After pretreatment with ketamine HCl (10 mg/kg i.m.) and halothane (5%) by facial mask, they were intubated via a tracheostomy and ventilated with an Oneida anesthesia machine using 100% \(O_2\). Tidal volume was 10 ml/kg. The ventilatory rate was adjusted to maintain arterial pH between 7.35 and 7.45 and \(P_O_2\) greater than 100 mm Hg. Anesthesia was maintained during the entire experiment with 0.5–1% halothane and intermittent intravenous sodium pentobarbital (1 mg/kg every 15–30 minutes). A 7F catheter was placed in a carotid artery for blood pressure monitoring and arterial blood sampling. Lidocaine (1 mg/kg) was administered intravenously, and an infusion of 2 mg/min was maintained throughout the experiment. The heart was exposed via a median sternotomy and suspended in a pericardial cradle (Figure 1). A 1-cm length of the left anterior descending coronary artery (LAD) was dissected free just distal to the first diagonal branch and encircled by a hydraulic balloon occluder (In-Vivo Metrics, Inc, Healdsburg, California). A catheter was placed in the left atrium for radioactive microsphere injection and pacing wires were sutured into the left atrial appendage. To monitor coronary pressure distal to the stenosis, a 24-gauge plastic catheter was inserted into the terminal portion of the LAD and sutured to the myocardium. The occluder was temporarily inflated, and a two-turn, 2.5 centimeter phosphorus spectroscopy surface coil was glued over the center of the ischemic region using cyanoacrylate. The pig was transferred into a plastic cradle lined with a circulating water blanket to maintain body temperature.

The animal was then placed in a 1-m bore Philips Gyroscan 2.0 Tesla imaging and spectroscopy unit so that the surface coil was in the magnet isocenter. The ventilator and monitoring equipment (Gould Inc, Cupertino, California) were placed outside the magnetic shield, allowing continuous monitoring of arterial and distal LAD pressures. The pacing wires were attached to a pacing box (Medtronic, Inc, Minneapolis, Minnesota), and the animal was atrially paced at 100 beats/min.

After tuning the surface coil, shimming was manually adjusted on protons using a Gordin-Timms arrangement yielding typical linewidths under 35 Hz. A hexamethyl phosphorous triamide external standard was placed in the center of the surface coil, and the 90° flip angle pulse length for this standard was determined. The standard was then removed, and spectroscopy was performed using one-pulse experiments with flip angles of 180°. This pulse length was chosen from pilot experiments and computer modeling of the surface coil radiofrequency field to maximize the signal obtained from the subendocardium and yielded approximately 40% of the myocardial signal from the subendocardium. Since greater reductions in blood flow occur in the subendocardium for a given degree of coronary stenosis, weighting of the signal in this manner was selected to enhance the sensitivity of our metabolic measurements. Spectroscopy was electrocardiographically gated to the onset of diastole of every fifth beat, yielding a repetition time of 3 seconds. Forty free induction decays were summed for each measurement, resulting in a total acquisition time of 2 minutes for each spectrum.

**Protocol**

Three spectra were obtained under control conditions to establish the baseline measurement of high energy phosphates. The LAD occluder was then slowly inflated using a microsyringe (VWR Scientific, San Francisco, California) to achieve a fall in distal LAD pressure. After a stabilization period of 5 minutes, spectra were acquired for 2 minutes. In five of the 10 animals, this measurement was followed by left atrial injection of 2–3 million 15–20 μm diameter radioactive microspheres. Spectra were again acquired at this level of stenosis, and the occluder was released following the end of data acquisition. Spectra were then continuously acquired in 2-minute blocks until the levels of phosphocreatine (PCr) and ATP returned to control or stabilized over two data acquisitions. Another partial stenosis was then achieved by inflating the LAD cuff to obtain a different distal LAD pressure. As before, measurement of high energy phosphates was begun after a 5-minute waiting period, followed by microsphere injection, repeat spectral acquisi-
tion, and return to control conditions. This process was repeated in each animal from three to six times at different degrees of LAD stenosis. When possible, microspheres were injected during at least two control periods. At the end of the experiment, the animal was killed with an overdose of sodium pentobarbital, the location of coil marked with epicardial sutures, and the heart excised and placed in formalin. Seven animals died of ventricular fibrillation during the most severe stenosis, and only data preceding this level of stenosis are included.

Analysis of Spectra

Spectra were analyzed with Philips Gyroscan software using a convolution difference of 200 Hz, followed by an exponential multiplication of 15 Hz and phasing with a zero and first-order phase correction. Peak heights were measured for the observed peaks of phosphomonoesters (PME), inorganic phosphate (Pi), phosphodiesters (PDE), PCr, and the ß, α, and γ peaks of ATP. For each spectrum, the following quantities were calculated: Pi, PCr, and ATP as a fraction of control; the ratios of PCr/Pi and PCr/ATP; and the chemical shift of Pi (in ppm). Calculation of the ratios of high energy phosphates (PCr/Pi and PCr/ATP) was performed to minimize the variations in data acquisition between different animal preparations. In addition, these ratios may be more sensitive to reductions in myocardial blood flow since PCr and Pi concentrations change in opposite directions with ischemia. The chemical shift of Pi was measured to calculate the change in pH with ischemia. The resonance of 2,3-diphosphoglycerate (2,3-DPG) of the chamber blood was close to that of Pi, thus precluding exact measurement of Pi and ATP under control conditions. Therefore, under control conditions, Pi was assumed to be the most upfield peak in that region, consistent with its expected chemical shift. With ischemia, the Pi peak was easily resolved from the PEMP peak. In addition, the degree of line broadening was determined by measuring the half-height line width for PCr and ATP under control and ischemic conditions. This analysis demonstrated a standard deviation of less than 10% of the mean width for these resonances during each experiment.

Analysis of Blood Flow

After formalin fixation, approximately 2-g sections of myocardium were cut from the region below the center of the surface coil and from two regions of myocardium distant from the ischemic region. Each section was then divided into subendocardial, midmyocardial, and subepicardial thirds. After blotting dry and weighing, segments were counted for 10 minutes in a gamma counter. These counts were corrected for the known radioactivities and decay rates of the isotopes, as well as for the weight of each sample. The counts in the three segments below the center of the coil were referenced to the mean counts in the segments in the two normal regions. Thus, blood flow measurements were expressed as the ratio of blood flow in the ischemic zone below the center of the coil to the blood flow in normal myocardium. These data were analyzed for subendocardial and subepicardial segments as well as for total transmural blood flow.

Hemodynamic Analysis

Arterial blood pressure and distal LAD pressure were continuously measured during the experiment. After appropriate calibration, mean pressures were obtained from recorder tracings at each control level and for each period of partial stenosis. Pressure tracings were also examined to insure that the heart rate was 100 beats/min throughout the experiment. For each experimental period, pressures were expressed as mean LAD pressure as well as a pressure gradient index (PGI), defined as the ratio of the pressure gradient across the stenosis (aortic pressure–distal LAD pressure) to the aortic pressure. The PGI has been shown in previous canine experimental preparations to be linearly related to coronary blood flow over a wide range of pressures.19

Data Analysis

Results of the spectral analysis were related to relative blood flow in the subendocardial, subepicardial, and transmural segments in the five animals receiving radioactive microparticles. For all animals, the measured high energy phosphate values were related to the pressure gradient index. The relations between high energy phosphates and blood flow and pressure measurements were modeled using linear, polynomial, and exponential fits. Pearson's r was calculated for each regression fit. The metabolic data as a function of relative endocardial blood flow are shown with their linear regression fits. For the PCr/ATP data, the polynomial fit is also shown since the data appeared to have a plateau near control blood flows. Differences between control and stenosis measurements were analyzed using a one-tail paired t test. To determine the stability of the preparation and reproducibility of the measurements, control data were analyzed using an analysis of variance for each experiment. A value of p<0.05 was considered significant.

Results

Figure 2 illustrates a typical control spectrum after processing and demonstrates the resonances of ATP, PCr, and a combined PME/P peak. The sequence of spectra in Figure 3 illustrates the changes seen with graded ischemia. In this animal, as the distal LAD pressure was reduced from a control value of 90 to 60 mm Hg and then to 30 mm Hg, the PCr peak progressively fell and the Pi peak progressively increased in magnitude. The Pi peak also shifted upfield (to the right), consistent with intracellular acidosis. ATP signals did not change despite the changes in PCr and Pi.
Multiple control measurements of regional myocardial blood flow, PCr/ATP, and PCr/P, did not vary significantly within any experiment. Figure 4 illustrates the sequence of events during a typical 3-hour experiment. Control measurements at time 0 (LAD pressure=64 mm Hg) were followed by a mild coronary stenosis (time 27 minutes, LAD pressure=44 mm Hg) that did not result in significant alterations in myocardial blood flow or metabolites. After return to control, a severe reduction in

**Figure 2.** A representative $^3$P spectrum obtained in 2 minutes under control conditions demonstrating the resonances of the α, β, and γ phosphates of ATP, the resonance of phosphocreatine (PCr), and a combined resonance of phosphomonoesters (PME, primarily 2,3-diphosphoglycerate of chamber blood) and inorganic phosphate (Pi).

**Figure 3.** Three spectra acquired under control conditions (bottom), with left anterior descending coronary artery pressure of 60 mm Hg (middle) or 30 mm Hg (top). With decreasing blood flow, the phosphocreatine (PCr) resonance decreases and the inorganic phosphate (Pi) resonance increases. The vertical line above the phosphomonoesters (PME)/Pi peak indicates the chemical shift under control conditions and illustrates the upfield shift of the Pi peak during ischemia.
blood flow at 62 minutes (LAD pressure=30 mm Hg) was accompanied by marked reductions in metabolites. Following this ischemic period, the control measurements at 80 minutes demonstrated a slightly elevated value of PCr/ATP. This overshoot of the PCr concentration following reflow after significant ischemia has been previously reported.1-5 The experiment then continued with a period of moderate ischemia (time 100 minutes, LAD pressure=37 mm Hg), followed by repeat control measurements at 175 minutes with normal coronary pressures of 64 mm Hg.

High Energy Phosphates as a Function of Regional Myocardial Blood Flow

Figure 5 shows the relation of normalized ATP, \( P_i \), and PCr concentrations to regional myocardial blood flow for five experiments. ATP (Figure 5, top) did not change significantly as blood flow was reduced. \( P_i \) (Figure 5, middle) was significantly and inversely correlated to myocardial blood flow and increased 72% when subendocardial blood flow was 50% of control (\( p<0.05 \)). As with \( P_i \), significant changes in PCr occurred at blood flows of 50% or less (\( p<0.05 \)). The correlation coefficients for \( P_i \) and PCr as functions of subendocardial blood flow were 0.70 (\( p<0.05 \)) and 0.76 (\( p<0.05 \)), respectively. Correlations between metabolite concentrations and subepicardial blood flow were lower than for subendocardial or transmural blood flow.

Subendocardial blood flow correlated best with the ratio of PCr/\( P_i \), which was a highly sensitive metabolic measure of graded regional ischemia. Figure 6 shows that PCr/\( P_i \) declined by 25% below control values when blood flow was diminished by 21% (\( p<0.05 \)) and reached 50% of control values when blood flow was reduced by 52%. Changes in PCr/\( P_i \) were more closely related to endocardial blood flow (\( r=0.94, p<0.05 \)) than to epicardial blood flow (\( r=0.74, p<0.05 \)). In contrast to PCr/\( P_i \), PCr/ATP was maintained at blood flows above 50% of control but declined at flows below this threshold (Figure 7) with a slope similar to that seen with PCr/\( P_i \). A 77% reduction in endocardial blood flow was required to reduce PCr/ATP to 50% of control.

A significant upfield chemical shift of \( P_i \), indicating a fall of intracellular pH, occurred when regional
endocardial blood flow fell to 50% of control (Figure 8). There was substantial scatter in the chemical shift data, thus making any individual measure of pH unreliable as an indicator of acidosis during ischemia. However, the most severe (80%) reduction in flow caused a mean upfield shift of 0.47 ppm, corresponding to a fall of pH of 0.4 pH units.

High Energy Phosphates as a Function of Coronary Pressure

The pressure gradient index was highly correlated to endocardial blood flow ($r=0.80$, $p<0.05$) (Figure 9), thus validating its use as an indicator of the degree of stenosis in this preparation. The relations of ATP, $P_i$, and PCr to the PGI were similar to the relations seen with blood flow. ATP did not change significantly with ischemia, while changes in $P_i$ and PCr were correlated with the degree of stenosis ($r=0.60$ and $r=0.71$, $p<0.05$, respectively).

As the degree of coronary stenosis increased, PCr/ $P_i$ showed a linear correlation with PGI ($r=0.80$, $p<0.05$). When the pressure gradient across the stenosis was half of the aortic pressure (PGI=0.5), PCr/ $P_i$ fell to 36% of control. Similarly, PCr/ATP decreased almost linearly with the PGI ($r=0.77$, $p<0.05$) and did not exhibit the threshold phenomenon seen with endocardial blood flow measurements. The chemical shift of $P_i$ was only modestly, although still significantly, correlated with the PGI ($r=0.55$, $p<0.05$).

Discussion

Effects of Ischemia on PCr and $P_i$

Previous investigators have measured high energy phosphate compounds in isolated perfused heart preparations during graded reductions in coronary flow. Lavanchy et al.21 noted major changes in high energy phosphates when coronary flow was severely

*Figure 6. Phosphocreatine-to-inorganic phosphate (PCr/$P_i$) as a fraction of control measurements as a function of relative subendocardial blood flow for five animals. Top panel shows the group data with a linear fit, $PCr/P_i=0.91*BF+0.06$, ($r=0.94$), where $BF$ is blood flow. Bottom panel shows the individual animal data points. The fall of PCr/$P_i$, with 20% reductions in flow is demonstrated in both graphs.

*Figure 7. Phosphocreatine-to-ATP ratio (PCr/ATP) as a fraction of control measurements as a function of relative subendocardial blood flow for five animals. PCr/ ATP is modeled with both linear and third-order polynomial fits and does not decline significantly until subendocardial blood flow is reduced by 50%. Equations for the fits shown are $PCr/ATP=0.58*BF+0.43$, ($r=0.81$), and $PCr/ATP=-2.67*(BF)^3+2.84*BF-0.04$, ($r=0.88$), where BF is blood flow.

*Figure 8. The chemical shift of inorganic phosphate ($P_i$, in ppm) as a function of relative subendocardial blood flow for five animals. The linear fit ($P_i$ chemical shift= $0.53*BF+4.66$, ($r=0.70$) yields a calculated pH fall of approximately 0.4 pH units at 20% of control blood flow.
Thus, a reduction of PCr/Pj reflects an impairment in oxidative metabolism of the myocardium. The changes of ADP or the phosphorylation potential have been implicated as modulators of the rate of oxygen consumption and the rate of ATP synthesis. The ability to gauge ADP concentration via the PCr/Pj ratio is important because ADP, ATP/ADP, and the cytosolic phosphorylation potential are closely related to the ATP/ADP ratio occurring below coronary flow rates of 7.2 ml/min/g (a rate that is at the lower end of normal for a working glucose perfused rat heart). In their studies, the onset or magnitude of the decrease in phosphorylation potential did not appear to be different to that of PCr or Pj and, therefore, was not a more sensitive marker of ischemia. However, it is difficult to relate the findings of these studies to our own. There are important physiological distinctions between glucose perfused isolated hearts undergoing global ischemia and an in vivo preparation with regional ischemia, including differences in substrate utilization, loading conditions, flow rates, and external regulatory mechanisms that may influence the relations being examined.

The phosphorylation potential is an important measure of the energy status of the cell and can be used to determine the adequacy of energy reserves for vital cell functions. However, 31P NMR cannot detect the low cytosolic concentrations of ADP, thus preventing calculation of the phosphorylation potential. Chance et al. have suggested that the PCr/Pi ratio is closely related to the ATP/ADP ratio and provides a more readily measurable estimate of the changes of ADP or the phosphorylation potential. The ability to gauge ADP concentration via the ratio of PCr/Pi is important because ADP, ATP/ADP, and the phosphorylation potential have each been implicated as modulators of the rate of oxygen consumption and the rate of ATP synthesis. Thus, a reduction of PCr/Pi reflects an impairment in oxidative metabolism of the myocardium.

Effects of Ischemia on ATP

Previous NMR studies of ATP levels during graded ischemia were performed by Clarke and Willis, who found a slight rise in [ATP] as flow was reduced in their glucose perfused isolated rat hearts. In contrast, enzymatic assays of freeze-clamped cardiac biopsies from dog heart in vivo studies have shown reductions in [ATP] during severe ischemia. After 5 minutes of partial ischemia, Mori et al. found that the ATP concentration fell approximately 20% as coronary blood flow (measured by electromagnetic flowmeter) was reduced by 50–75%. However, the relation between [ATP] and tissue blood flow was unclear because myocardial blood flow in the tissue samples was not measured.

Biopsy samples of myocardium obtained after 1/2 or 5 hours of partial coronary stenosis by Neill and Ingwall demonstrated modest and stable reductions of [ATP] with tissue blood flows greater than 0.3 ml/mg/min. In contrast, with flows less than 0.3 ml/mg/min, [ATP] fell progressively over 5 hours. However, ATP concentrations were not determined for the shorter ischemic times used in our study.

Thus, while there is some variability among the observations in these studies of different species, preparations, and measurement techniques, a common finding is that ATP appears to be relatively preserved at modest reductions in blood flow but is progressively reduced with severe ischemia.

In comparison to these findings, we noted stability of ATP levels over a wide range of coronary stenoses. This indicates that the myocardium was able to maintain an energy supply/demand balance in the face of moderate ischemia. As oxygen availability is limited by ischemia, the supply of ATP from oxidative phosphorylation becomes limited. Transiently, ATP can be generated from PCr through the creatine kinase reaction. Furthermore, additional ATP can be generated by increased glycolysis (perhaps mediated by ADP). An additional method of maintaining energy balance is for the myocardium to downregulate its energy requirements by decreasing contractility.
While the relative contributions of each of these mechanisms cannot be determined from our study, they were sufficient to maintain ATP at these levels and durations of ischemia.

Effects of Ischemia on pH

The reduction in myocardial pH during ischemia has been previously suggested to be a sensitive response to global ischemia. In perfused hearts, Lavanchy et al.21 noted significant reductions in pH (7.1 to 6.9) at levels of blood flow that did not affect PCr or P_i. Similarly, Clarke and Willis1 measured changes in pH occurring with smaller reductions in flow than were required to depress high energy phosphates. Thus, glucose perfused hearts readily develop acidosis during ischemia, possibly due to the use of glucose as a sole substrate. In contrast, in our study, pH changes did not precede changes in high energy phosphates. This finding likely reflects the greater reliance of the heart on fatty acid metabolism in vivo.

Effects of Ischemia on Metabolites and Function

The changes in high energy phosphates and pH during graded regional ischemia may have significant implications for the regulation of myocardial function. Maintenance of [ATP] during ischemia is, to some degree, due to decreased utilization of ATP because of reduced contractility. Although not firmly established, it is quite possible that myocardial dysfunction during ischemia is mediated by changes in P_i, and/or pH.22-30 These changes can affect actomyosin cross-bridge formation31 as well as calcium homeostasis both inside the cell and across the cell membranes.32

The relation between graded ischemia and myocardial function in perfused hearts has been examined by several investigators.1,2,11 In contrast to the small changes in metabolites associated with flow reductions, a linear correlation between coronary flow and myocardial contractility over a wide range of coronary flows has been described. The interpretation of these results is complicated by the high flow rates characteristic of perfused hearts. In vivo canine studies by several groups19,33 have examined the changes in segmental wall thickening with graded ischemia. Gallagher et al.34 using normalized data for subendocardial blood flow, noted significant reductions in wall thickening with flows below 60% of control. Furthermore, the relation between flow and function observed by Gallagher et al paralleled the relation between flow and PCr/P_i in our study. While a close linkage between metabolism and function is indirectly suggested by these data, this relation must be confirmed by simultaneous measurements in an in vivo animal preparation.

Limitations

There are several methodological issues in this study that may have affected our results. First, the closer relation between high energy phosphates and subendocardial compared with subepicardial blood flow are, in part, a function of the NMR acquisition parameters. Other studies, as well as our own regional blood flow measurements, have demonstrated that coronary artery stenosis reduces subendocardial blood flow more than subepicardial blood flow.35 Thus, metabolism in the subendocardium should be more sensitive to coronary stenosis. The acquisition parameters in this study were therefore chosen to obtain a greater proportion of signal from the subendocardium than in an experiment with a 90° pulse at the subepicardium. Hence, the spectra were relatively, although not primarily, weighted to the subendocardium, also resulting in increased signal contamination from chamber blood 2,3-DPG.

Secondly, the actual volume and location of tissue contributing to the spectra could not be precisely defined using a surface coil. While use of an open-chest preparation eliminated the problem of contamination by noncardiac tissues, potential contamination by signal from nons ischemic tissue remained a concern. This was avoided by placing a small surface coil in the center of a large ischemic region and obtaining samples for blood flow measurements in the region below the surface coil. Since this region contributed most of the signal to the spectra, the degree of contamination by tissue at the edge or outside the coil was minimal. Furthermore, the effect of contamination would have been to underestimate the degree of metabolic abnormalities during ischemia and thus diminish the observed metabolic changes.

Thirdly, the resonance in the PME region due to 2,3-DPG made the measurement of P_i intensity and chemical shift difficult under control conditions. To limit errors, standardized protocols for peak identification were used for all experiments and measurements. During regional ischemia, the P_i resonance was easily identified. However, the contribution of overlapping signal from 2,3-DPG, and the heterogeneity of pH in the ischemic region, cannot be estimated.

Summary

This study has defined the changes in high energy phosphates produced by graded regional ischemia in an in vivo porcine model of partial coronary stenosis. The ratio of PCr/P_i, reflecting the phosphorylation potential of the cell, was found to be a sensitive marker of ischemia. Its fall with subendocardial blood flow reductions of only 20% indicated that the energy status of the myocardium is closely coupled to myocardial blood flow. ATP remained constant, reflecting the ability of the cell to maintain energy supply/demand balance during graded regional ischemia. Myocardial pH fell with moderate ischemia (blood flow<50% of control), presumably due to increased glycolysis. Thus, the status of high energy phosphates may play an important role in the early mechanical and electrical changes seen with ischemia.36 In addition, noninva-
sive measurement of the PCr/Pi ratio may be useful as a sensitivity marker of mild regional ischemia.

References


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