Reduced Myocardial Creatine Kinase Flux in Human Myocardial Infarction
An In Vivo Phosphorus Magnetic Resonance Spectroscopy Study

Paul A. Bottomley, PhD; Katherine C. Wu, MD; Gary Gerstenblith, MD; Steven P. Schulman, MD; Angela Steinberg, RN; Robert G. Weiss, MD

Background—Energy metabolism is essential for myocellular viability. The high-energy phosphates adenosine triphosphate (ATP) and phosphocreatine (PCr) are reduced in human myocardial infarction (MI), reflecting myocyte loss and/or decreased intracellular ATP generation by creatine kinase (CK), the prime energy reserve of the heart. The pseudo-first-order CK rate constant, k, measures intracellular CK reaction kinetics and is independent of myocyte number within sampled tissue. CK flux is defined as the product of [PCr] and k. CK flux and k have never been measured in human MI.

Methods and Results—Myocardial CK metabolite concentrations, k, and CK flux were measured noninvasively in 15 patients 7 weeks to 16 years after anterior MI using phosphorus magnetic resonance spectroscopy. In patients, mean myocardial [ATP] and [PCr] were 39% to 44% lower than in 15 control subjects (PCr = 5.4 ± 1.2 versus 9.6 ± 1.1 μmol/g wet weight in MI versus control subjects, respectively, P < 0.001; ATP = 3.4 ± 1.1 versus 5.5 ± 1.3 μmol/g wet weight, P < 0.001). The myocardial CK rate constant, k, was normal in MI subjects (0.31 ± 0.08 s⁻¹) compared with control subjects (0.33 ± 0.07 s⁻¹), as was PCr/ATP (1.74 ± 0.27 in MI versus 1.87 ± 0.45). However, CK flux was halved in MI to 1.7 ± 0.5 versus 3.3 ± 0.8 μmol/g/ s⁻¹; P < 0.001.

Conclusions—These first observations of CK kinetics in prior human MI demonstrate that CK ATP supply is significantly reduced as a result of substrate depletion, likely attributable to myocyte loss. That k and PCr/ATP are unchanged in MI is consistent with the preservation of intracellular CK metabolism in surviving myocytes. Importantly, the results support therapies that primarily ameliorate the effects of tissue and substrate loss after MI and those that reduce energy demand rather than those that increase energy transfer or workload in surviving tissue. (Circulation. 2009;119:1918-1924.)

Key Words: adenosine triphosphate ■ creatine kinase ■ magnetic resonance spectroscopy ■ metabolism ■ myocardial infarction

A denosine triphosphate (ATP) is essential for normal cardiac function, including myofibrillar contraction, ion transport, and myocyte viability.¹ ATP is generated at the myofibrils by the creatine kinase (CK) reaction, which transfers a high-energy phosphoryl group from phosphocreatine (PCr) to adenosine diphosphate.² The movement of phosphoryl groups through CK, or CK flux, serves as the primary energy reserve in cardiac muscle and acts as both a spatial and temporal ATP buffer.³ The CK flux is defined as the product of the PCr concentration with the pseudo–first-order forward reaction rate constant, k (s⁻¹). This rate constant can be interpreted as the fraction of the PCr pool turning over to create ATP each second. As a measure of the intracellular function of the CK reaction, k is independent of the number of myocytes within the studied sample.

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Conventional quantitative phosphorus (³¹P) magnetic resonance spectroscopy (MRS) provides noninvasive in vivo measures of cardiac concentrations of the high-energy phosphates ATP and PCr.⁴⁻⁸ Although CK flux can be measured by saturation transfer ³¹P MRS methods,⁹⁻¹¹ they were impractical in humans until recently because of the inefficiency of the saturation transfer protocol, the need to provide spatial localization for a noninvasive clinical setting, and the need to combine the protocol with noninvasive metabolite concentration measurements in the same examination. We recently introduced the 4-angle saturation transfer (FAST) method to measure reaction rate constants with about an order-of-magnitude faster scan time than the standard method.¹² FAST enables direct, noninvasive, localized measurements of the...
myocardial CK pseudo–first-order rate constant, k, in addition to the CK flux, when combined with concentration-referenced metabolite quantification methods performed during the same MRS examination. Using this technique, we reported a 50% reduction in CK flux in patients with nonischemic dilated cardiomyopathy and mild to moderate chronic heart failure (CHF), as well as a 65% decrease in cardiac PCR and ATP concentrations compared with concentrations in healthy control subjects. This decrease may be due to myocardial CK flux, to myofibrils in surviving myocytes. We therefore used the FAST saturation transfer technique to test the hypothesis that CK flux and/or k are reduced in patients with prior myocardial infarction (MI) compared with healthy control subjects. We report here, for the first time, CK flux and its determinants k and [PCr], as well as [ATP] in the anterior LV wall of these patients.

Methods

Study Protocol
All human studies were approved by The Johns Hopkins Institutional Review Board for human investigation. All subjects gave informed consent after receiving an explanation of the study and protocol. Fifteen patients 31 to 83 years of age (mean, 57 ± 16 years; median, 57 years; 4 women) with a history of anterior, anteroseptal, anterolateral, or anteropapillary MI and echocardiographic anterior wall motion abnormalities were studied at rest on a General Electric 1.5-T magnetic resonance imaging (MRI/MRS system (General Electric Healthcare Technologies, Waukesha, Wis) 7 weeks to 16 years after MI (mean, 6.4 ± 6.0 years; median, 2.4 years; n = 14; 1 MI of unknown age). All patients were candidates for prophylactic implantable cardioverter-defibrillators. Fifteen healthy subjects 31 to 60 years of age (mean, 41 ± 7 years; P = 0.002 versus patients; median, 41 years; 3 women) with no history of heart disease, hypertension, or diabetes mellitus served as control subjects.

Owing to the duration of the MRS examination, a separate MRI examination that incorporated cine, myocardial tagging, and late-gadolinium-enhancement (LGE) MRI protocols was performed on a 77% water content, the same as in MI (edema resolves by 4 weeks after MI)22. Second, concentrations were determined from the MRS protocol14,16 thus comprises (1) conventional spillover-proton (H) MRI acquired with the body coil of the scanner to position the anterior myocardium over the coil and for shimming; (2) acquisition of the 31P FAST data sets localized by 1-dimensional chemical shift imaging (32 transaxial 1-cm-thick slices; TR = 1 second, NEX = 12, α = 60°; and NEX = 24, α = 15° with chemical selective saturation at ±2.7 ppm); (3) acquisition of a fifth 31P 1-dimensional chemical shift imaging set with saturation turned off (α = 60°; NEX = 12; gated with TR of ~1 second) for phosphate metabolite quantification; and (4) acquisition of a sixth 31P 1-dimensional chemical shift imaging data set with the 31P coil (α = 60°; NEX = 4; gated with TR of ~2 seconds) to provide a water concentration reference for metabolite quantification. The total MRS examination time was ~70 minutes. After the patient’s MRS examination, steps 3 and 4 were repeated, fully relaxed (TR = 4 seconds for H; TR = 8 seconds for 31P), on a phosphate reference phantom to calibrate the ratio of phosphate to proton signal for determining concentration from steps 3 and 4.

Data Analysis
Cine MRI was processed with the GE scanner’s CINE TOOL software to obtain LV ejection fraction (EF), cardiac volume, and mass by standard methods. Infarct size, measured in grams, was determined from the size of the region exhibiting LGE, defined as the region exhibiting an elevated signal intensity, compared with the peak remote signal.19 The peak remote signal was determined by tracing the endocardial and epicardial borders in each short-axis cross section and defining an ~50-mm2 region of interest within normal, artifact-free, remote myocardium. The areas of LGE with signal intensities greater than the peak remote signal in each involved slice were added to obtain the total infarct size. In addition, the transmural fraction of tissue occupied by hyperenhancing infarction that was present in the tissue sampled by 31P MRS was estimated by comparing LGE images with the scout images acquired during 31P MRS. Each short-axis LGE image was divided into 12 sectors, and the 2 pairs of sectors adjacent to the anterior right ventricular insertion site were used to assess the transmurality of the infarct in the anteroseptal region sampled by 31P MRS as identified in the scout images.

The forward CK pseudo–first-order rate constant, k (s−1), was calculated from the saturation spillover-corrected Equations 5, 6, and 9 of Reference 15 based on the amplitude of the PCr signal in spectra acquired from MRS protocol steps 2 and 3 as a function of depth through the chest and anterior myocardium. These k values are directly comparable to those published earlier using the same technique. We also report rates, k*, that are corrected in accordance with the latest numerical analysis of errors caused by spillover irradiation:20

\[ k* = k - (k' - 0.0534k - 0.0354)(0.2025Q + 0.0098Q - 0.2585) \]

where Q is the ratio of PCr measured in the FAST experiment with control saturation to that measured with no saturating radiation whatsoever.

The 31P MRS protocol provided sufficient data to enable the metabolite concentrations [PCr] and [ATP] (brackets denote tissue concentrations in units of μmol/g wet weight of tissue) to be determined noninvasively 2 ways. First, the concentrations were calculated from the ratio of the corresponding metabolite peak areas acquired in step 3 to the water signal from step 4 multiplied by the 31P calibration factor and the cardiac tissue water proton concentration.6 The latter was taken as 86 mol/kg tissue wet weight based on a 77% water content, the same as in MI (edema resolves by 4 to 5 weeks after MI). Second, concentrations were determined from the ratio of the saturation- and blood ATP–corrected metabolite signals to the signal from the phosphate reference phantom.4 For both methods, the metabolite signal areas were determined by gaussian fitting and corrected for blood ATP and partial saturation using standard blood 2,3-diphosphoglycerate-to-ATP ratios and relaxation times,23,24 assumed unchanged in these patients. The 2 concentration estimates, which are not independent because they use the same 31P measurements, were then averaged to obtain a single concentration.
value at each depth in the chest and anterior myocardium for each subject. The forward CK flux is then determined from the product \( k \times [\text{PCr}] \) (in \( \mu\text{mol/g wet weight per second} \)) at each depth. Flux, \( k \), and \([\text{PCr}]\) values for the anterior myocardial wall are averaged from the 2 to 3 adjacent MRS slices intersecting the anterior myocardium, as identified from the corresponding scout MRI.

Results are presented as mean±SD. Statistical significance was evaluated by 2-tailed independent \( t \) testing or by paired \( t \) testing when explicitly noted. Correlation coefficients for functional, morphological, temporal, and metabolic measures were calculated in the 15 patients, and the significance of the correlations was determined from them. A value of \( P<0.05 \) was considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Patients had evidence of LV remodeling after MI with mean LV EFs by MRI of 30±9%, mean LV end-diastolic and end-systolic volumes of 231±53 and 165±51 mL, respectively, and LV masses of 142±58 g. Cine MRI and myocardial tagging confirmed the presence of anterior wall dysfunction (akinesia, dyskinesia) in all patients. Mean infarct mass by LGE MRI was 48±23 g, corresponding to 29±12% of the total LV mass.

Figure 1 shows typical scout MRI (Figure 1a) and localized \(^{31}\text{P}\) saturation transfer MRS results from a healthy control subject (Figure 1b) and from a patient with a 12-year-old anterior-apical MI (Figure 1c), along with short-axis LGE images in which the infarct is rendered bright from the mid LV extending distally to the apex (Figure 1e). In the \(^{31}\text{P}\) spectra (Figure 1b and 1c), the reduction in \([\text{PCr}]\) height with \(^\gamma\text{-ATP}\) saturated (right) compared with control irradiation (left) is proportional to the CK pseudo-first-order rate constant, \( k \). In the control subject (Figure 1b), this reduction corresponds to more than one third of the PCr turning over per second, with \( k=0.38\text{ s}^{-1} \). Myocardial \([\text{PCr}]\) was measured at 10.4 \( \mu\text{mol/g wet weight} \), yielding a forward CK flux of 3.9 \( \mu\text{mol(g} \cdot \text{s})^{-1} \). The same \( k \) was measured in spectra from 2 adjacent slices in the MI patient (Figure 1c). However, the lower signal-to-noise ratio in the patient spectra reflects a reduced metabolite concentration of 6.9 \( \mu\text{mol/g} \) for myocardial \([\text{PCr}]\). Consequently, the forward flux for generating ATP via CK is reduced to 2.6 \( \mu\text{mol(g} \cdot \text{s})^{-1} \) in this subject.

The measured \(^{31}\text{P}\) MRS \([\text{PCr}]/\text{ATP}\) ratio, \([\text{PCr}]\), and CK flux averaged across the anterior myocardium of MI patients and control subjects are plotted in Figure 2. Mean \([\text{PCr}]\) shows a highly significant reduction in the anterior myocardium of MI patients to 56% of that in healthy subjects \((P<0.001)\). [ATP] is similarly reduced to 61% \((P<0.001\) versus control subjects). If treated separately, the water and the phosphate reference calculations of \([\text{PCr}]\) and [ATP] yield results for control subjects that do not differ significantly \((P=0.1,\text{ paired } t\text{ test})\) as noted previously, and both methods separately yield similar highly significant reductions in [PCr] and [ATP] to 47% to 66% in MI \((P<0.001\) versus control subjects). Despite the reduction in [PCr] and [ATP], neither the average \([\text{PCr}]/\text{ATP}\) ratio nor \( k \) in MI patients differs statistically significantly from healthy subjects, although \([\text{PCr}]/\text{ATP}\) trends lower. Although \( k \) is unchanged, the CK flux, which is the product of the reduced [PCr] and \( k \), is halved in MI compared with control subjects \((P<0.001)\). The mean metabolite concentrations, ratios, reaction rates, and CK fluxes are summarized in the Table.

We also compared metabolic measures in adjacent superficial and deeper myocardial slices and found the same results, with an \( \approx50\% \) reduction in \([\text{PCr}]\) at both levels in MI patients. Thus, in MI patients, [PCr] was 6.5±1.4 and 5.0±1.8 \( \mu\text{mol/g} \) in the superficial and deeper myocardial slices, respectively, versus 10.5±1.7 and 9.2±1.8 \( \mu\text{mol/g} \) in control subjects \((P<0.001)\). Nevertheless, the CK reaction rate, \( k \), in the same sections did not differ significantly between MI patients and control subjects (from superficial to deeper myocardium, \( k=0.32±0.16 \) and 0.36±0.20 \text{ s}^{-1} \), respectively, in MI versus 0.33±0.12 and 0.38±0.17 \text{ s}^{-1} \) in control subjects). Thus, CK flux was reduced in the anterior wall of patients with MI in proportion to the reduction in metabolite pools (PCr and ATP) with no significant reduction in \( k \), interpreted as the fraction of PCr pool exchanging with ATP.
ATP each second. Use of the equation\textsuperscript{20} given above for correcting k did not affect these results (k* in the Table).

The fraction of hyperenhancing tissue or infarct transmurality present in the apical anteroseptal region sampled by \textsuperscript{31}P MRS as estimated from the LGE images was 61±23%. As depicted in Figure 3, this is comparable to, although somewhat larger than, the degree of [PCr] and [ATP] depletion (46±12%, \(P=0.04\); 41±20%, \(P=0.06\), respectively).

Regional metabolic measures from the anterior wall generally did not correlate with global measures of cardiac mass, chamber size, or EF. Cardiac [PCr] correlated modestly with LV EF (\(r=0.57\), \(P=0.03\); Figure 4). No other significant correlations were found between anterior myocardial \textsuperscript{31}P MRS indexes ([PCr], [ATP], PCr/ATP, k, CK flux) and global functional or morphological MRI measures of lesion and chamber volumes (LV EF, LV end-diastolic volume, LV end-systolic volume, lesion mass, lesion percent of the LV, lesion age) in patients, or between \textsuperscript{31}P MRS indexes and age in control subjects. However, trends at the 0.05<\(P<0.1\) level were evident in correlations between both [PCr] and CK flux and LV end-systolic volume (\(r=0.46\) and \(r=0.49\), respectively) and between [ATP] and LV EF (\(r=0.47\)) in patients.

**Discussion**

This is the first study of CK flux, the prime energy reserve of the heart, in humans after MI. The primary finding is that a significant reduction in CK flux occurs, caused by a decrease in [PCr] in these patients studied 7 weeks to 16 years after MI but that the fraction of the PCr pool exchanging with ATP each second, k, is not changed compared with healthy control subjects. [ATP] is also decreased in patients with prior infarction, whereas the PCr/ATP ratio is not changed. These observations of reduced [ATP] and [PCr] with preserved k and PCr/ATP are consistent with metabolite loss in infarcted areas, but and preservation of nearly normal metabolism in residual noninfarcted tissues within the region interrogated by \textsuperscript{31}P MRS.

Our finding that PCr/ATP is not altered in patients with prior anterior MI is consistent with the first, albeit limited, human cardiac in vivo \textsuperscript{31}P MRS measurements in MI patients\textsuperscript{26} and several subsequent studies in larger patient groups.\textsuperscript{27,28} However, reductions in cardiac PCr/ATP at the \(P<0.05\) level are reported in some studies of MI\textsuperscript{5,29,30} The associations of other conditions that may reduce myocardial PCr/ATP such as dilated cardiomyopathy,\textsuperscript{23,27} LV hypertrophy,\textsuperscript{8,17,31–34} and/or CHF\textsuperscript{16,23,27,31} are possible confounding factors in these reports. More recently, myocardial PCr/ATP was reported to be 50% lower in the immediate border zone.

**Table. Summary of \textsuperscript{31}P MRS Findings**

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=15)</th>
<th>Patients (n=15)</th>
<th>(P) (Patients Versus Control Subjects)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCr/ATP</td>
<td>1.87±0.45</td>
<td>1.74±0.27</td>
<td>0.32</td>
</tr>
<tr>
<td>[PCr], (\mu\text{mol/g wet weight})</td>
<td>9.6±1.1</td>
<td>5.4±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[ATP], (\mu\text{mol/g wet weight})</td>
<td>5.5±1.3</td>
<td>3.36±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>k, s(^{-1})</td>
<td>0.33±0.07</td>
<td>0.31±0.08</td>
<td>0.47</td>
</tr>
<tr>
<td>CK flux, (\mu\text{mol(g.s)}^{-1})</td>
<td>3.2±0.8</td>
<td>1.7±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>k*, s(^{-1})</td>
<td>0.34±0.07</td>
<td>0.31±0.08</td>
<td>0.37</td>
</tr>
<tr>
<td>CK flux, (\mu\text{mol(g.s)}^{-1})</td>
<td>3.3±0.8</td>
<td>1.7±0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Two tailed, equal variance.
‡Computed using k*.

**Figure 2.** The average myocardial PCr/ATP ratio, [PCr], k, and CK flux (left to right) measured by \textsuperscript{31}P MRS in the anterior myocardium of MI patients (†) and control subjects (•). Crosses denote mean values with error bars (±1 SD; \(P<0.001\) for [PCr] and CK flux in MI vs control subjects).

**Figure 3.** The mean fraction of hyperenhancing tissue or infarct transmurality, as a percentage of anteroseptal LV wall (black bar, left axis), in the apical anteroseptal region sampled by \textsuperscript{31}P MRS and the anteroseptal LV [PCr] and [ATP] reductions, as a percentage of mean values in healthy subjects (right axis; error bars designate 1 SD). The reduction in cardiac high-energy phosphates does not exceed the estimate of infarct content in the anteroseptal region, suggesting that the metabolite loss is due primarily to tissue loss and infarction (\(P=0.04\) for [PCr] and \(P=0.06\) for [ATP] vs infarct transmurality).
of a porcine infarct model compared with that in remote uninvolved myocardium, suggesting that local energy defects may exist in the immediate peri-infarct region and contribute to local dysfunction. Unlike human studies, which must be performed noninvasively, the porcine myocardium was sampled with a small $^3$P detection coil applied directly to the infarct border, yielding much smaller sampling volumes (0.18 mL) than those presently achievable in human studies. Thus, at present, we can conclude that bulk myocardial PCr/ATP in the relatively large sampling volume achievable in humans with the present methodology is only minimally reduced, if at all, in the anterior myocardial wall of these patients with prior anterior MI.

Concentration measurements offer additional insight into cardiac metabolism because an unchanged PCr/ATP ratio may be due to unaltered [PCr] and [ATP] or to significant but similar changes in both metabolites. Our findings that [PCr] and [ATP] are significantly reduced but to similar extents in anterior MI are consistent with mean reductions of 56% to 68% of normal values for [ATP] and [PCr], respectively, observed by noninvasive $^3$P MRS in patients with prior anterior MI and fixed defects on radionuclide images, with metabolic function. We have previously reported both k and CK flux, the product of k and [PCr], in the normal human heart at rest and stress, in patients with nonischemic dilated cardiomyopathy with CHF, and in nonischemic dilated cardiomyopathy and CHF. Statistical comparisons are as published ($P<0.001$ vs $k=0.32\pm0.07$ $s^{-1}$ and CK flux $=3.2\pm0.9$ $\mumol/\text{g} \cdot \text{s}^{-1}$) in 16 normal control subjects at rest;† $P<0.001$ and $P=0.01$ in 14 resting control subjects$^{17}$ with $k=0.32\pm0.06$ $s^{-1}$ and CK flux $=3.1\pm0.9$ $\mumol/\text{g} \cdot \text{s}^{-1}$ and from the current study ($P<0.001$; the Table).

Figure 5. a, Comparison of FAST CK reaction rate constants, k, and (b) forward CK flux measured by FAST $^3$P MRS from current (hatched bars) and prior studies of normal subjects during a 200% dobutamine-induced increase in cardiac workload ("stress"), in LV hypertrophy without and with CHF, and in nonischemic dilated cardiomyopathy and CHF. Statistical comparisons are as published ($P<0.001$ vs $k=0.32\pm0.07$ $s^{-1}$ and CK flux $=3.2\pm0.9$ $\mumol/\text{g} \cdot \text{s}^{-1}$) in 16 normal control subjects at rest;† $P<0.001$ and $P=0.01$ in 14 resting control subjects$^{17}$ with $k=0.32\pm0.06$ $s^{-1}$ and CK flux $=3.1\pm0.9$ $\mumol/\text{g} \cdot \text{s}^{-1}$ and from the current study ($P<0.001$; the Table).
CK flux—by nearly 50% in our study and by 30% in the infarcted swine without CHF.

The CK reaction is important to energy metabolism because of its ability to rapidly buffer ATP and its putative role in shuttling high-energy phosphate in the form of PCr between the mitochondria, where ATP is produced by oxidative phosphorylation, and the myofibrils, where it is consumed for contraction. The 50% reduction in CK flux to 1.7±0.5 μmol(g · s)⁻¹ (the Table) observed here in patients with prior MI is comparable to values of 1.6±0.6 and 1.1±0.4 μmol(g · s)⁻¹ measured in CHF patients with nonischemic global cardiomyopathies. For those CHF patients, it was noted that reductions to such levels may limit energy supply if CK is essential as a spatial/temporal energy buffer during periods of peak energy demand during the cardiac cycle and/or stress.

In general, reductions in myocardial CK flux can be due to a loss of total enzyme activity, altered intracellular substrate levels or ratios, or allosteric modifications of the enzyme. At this time, no in vivo method exists for resolving bulk tissue changes in ATP and PCr concentrations caused by myocyte loss from those resulting from altered intracellular metabolite levels in surviving cells. However, k, as a measure of intracellular metabolic function, is not confounded by myocyte loss because it measures only the surviving cells that contribute to the ³¹P MRS signal. Thus, the observation that k, interpreted as the fraction of the intracellular PCr pool exchanging with ATP each second, is unaltered in patients with prior MI 7 weeks to 16 years after MI (the Table) supports a hypothesis that intracellular CK reaction kinetics are essentially normal in the surviving myocytes. Our observation that myocardial PCr/ATP ratios are also preserved supports this view as well, considering that the observed macroscopic-level [PCr] and [ATP] reductions do not necessarily reflect depletion of intracellular [PCr] and [ATP] in surviving myocytes and that intracellular ATP levels are highly regulated and maintained. Therefore, the tissue reductions seen in [PCr] and [ATP] by ³¹P MRS are most likely attributable to a proportionate loss of myocytes, with the consequent macroscopic reduction in PCr substrate being responsible for the observed reduction in the CK flux in the region sampled.

Study Limitations

The main limitation in applying ³¹P MRS to relate metabolism and function in patients is its relatively low sensitivity and spatial resolution, for which higher-field MRI/MRS scanners are a possible remedy. To date, this has generally limited clinical studies to anterior LV regions that are larger than those accessible to invasive studies in animal models, including the peri-infarct area, as noted above. Indeed, additional signal contributions from surrounding normal myocardium may explain the difference between the 61% infarction estimate by MRI and the 46% metabolite loss seen by ³¹P MRS (Figure 3). Thus, the local reductions in metabolite concentrations and CK flux are likely even larger than the changes reported here.

Note also that although it is possible to improve spatial resolution by signal averaging to improve sensitivity, this inevitably reduces the number of different ³¹P MRS experiments that can be accommodated within a total examination time that is tolerable for most patients, ~1 hour. Loss of even 1 of the 6 spectral acquisitions in the present study would sacrifice a measure of either the concentration or the reaction kinetics. For the present work, separate MRI/MRS examinations were performed to acquire all of the metabolic, functional, and viability measures, so a precise match between the MRI and the metabolic data was not feasible. Nevertheless, patients on average had large anterior MI's representing ~30% of the entire LV mass, and on the basis of scout MRI scans obtained in both studies, the infarcted region was interrogated by ³¹P MRS.

Because no significant correlation was found between [ATP], [PCr], PCr/ATP, or CK flux and age in control subjects and because k was the same in both patients and control subjects and did not correlate with age, we do not expect that age confounds the primary findings. Indeed, none of the metabolic measures listed in the Table are altered by >8% if the youngest control subjects and oldest patients are excluded to render either no significant difference in age or the same mean age for both groups. This includes the P values that do not change, except for [ATP] for which P=0.002 in MI versus control subjects (for 8 patients 45±10 years of age versus 8 control subjects 45±7 years of age).

Clinical Implications

These results demonstrate that the primary effect of MI on CK metabolism is reduced CK flux as a result of substrate depletion in the infarcted area, whereas the CK reaction rate constant remains intact. The substrate loss causes a reduction in the ATP delivered by CK that is comparable to that previously reported in dilated and hypertrophic cardiomyopathies. The findings that k and PCr/ATP are normal in patients 7 weeks or longer after MI are consistent with the hypothesis that CK metabolism is essentially intact in surviving myocytes. Importantly, the results support therapies that primarily ameliorate the effects of tissue loss on substrate depletion and those that reduce energy demand in the postinfarcted heart rather than those that affect energy transfer, which does not appear to be significantly depressed in surviving myocytes, or those that increase demand in the surviving tissue.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Contractile dysfunction in patients with myocardial infarction (MI) may be due to cell loss, abnormal metabolism in surviving tissue, or a mix of both. The creatine kinase (CK) reaction serves as the major energy reserve of the heart, providing adenosine triphosphate (ATP) via phosphocreatine (PCr) to fuel contractile function. The CK forward pseudo–first-rate constant for generating ATP is a measure of intracellular metabolism and is independent of the number of myocytes. To determine whether intracellular CK metabolism is preserved after MI, we used, for the first time, a new magnetic resonance spectroscopy technique to directly measure the CK reaction rate constant, forward CK flux, PCr, and ATP concentrations in patients with prior anterior MI. We found that the primary effect of MI on CK metabolism is a reduction in PCr and ATP, which reduces the forward CK flux for generating ATP in the infarcted area. However, the CK reaction rate constant and the PCr/ATP ratio remain essentially intact. The results are consistent with metabolite loss in infarcted areas but preservation of near-normal intracellular metabolism in residual noninfarcted tissue. Importantly, the results support therapies that primarily ameliorate the effects of tissue loss on metabolite depletion and those that reduce energy demand after MI rather than those that affect energy transfer, which does not appear to be significantly depressed in surviving myocytes, or those that increase the energy demand on the surviving tissue.
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