Mitral Regurgitation
Impaired Systolic Function, Eccentric Hypertrophy, and Increased Severity Are Linked to Lower Phosphocreatine/ATP Ratios in Humans

Michael A. Conway, MD, MSc, MRCP; Paul A. Bottomley, PhD; Ronald Ouwerkerk, PhD; George K. Radda, DPhil, FRS; Bheeshma Rajagopalan, DPhil, FRCP

Background—A number of phosphorus (31P) magnetic resonance spectroscopy (MRS) studies link alterations of high-energy phosphate metabolism in valvular disease and cardiomyopathy to the clinical severity of heart failure. However, correlations between MRS and indexes of ventricular dysfunction are inconclusive to date. We examined whether changes in 31P MRS are associated with the impaired contractility, which predisposes to chronic congestive heart failure in patients with mitral regurgitation.

Methods and Results—Thirteen normal control subjects and 22 patients with echocardiographically characterized chronic mitral regurgitation were studied by 31P MRS. The apical phosphocreatine-to-ATP ratio (PCr/ATP) was lower in severe disease \( (P < .02) \) and those on therapy \( (n = 13, 1.29 \pm 0.29, P < .01) \) in contrast to control subjects \( (n = 13, 1.61 \pm 0.3) \). Compared to those with mild mitral regurgitation, patients with more severe incompetence had lower mean myocardial PCr/ATP ratios \( \text{mild, } n = 6, 1.73 (0.17), P < .05 \) and \( P < .01 \); \( \text{moderate, } n = 5, 1.49 (0.18), P < .05 \); and \( P < .05 \); and severe, \( n = 11, 1.29 (0.32), P < .01 \). PCr/ATP in those referred for mitral valve replacement was lower \( (n = 8, 1.17 \pm 0.23) \) although not significantly decreased compared with the ratio among subjects on medical therapy alone \( (n = 5, 1.48 \pm 0.29, P < .01) \). PCr/ATP correlated with the end-systolic diameter \( (r^2 = .7, P < .001) \), end-diastolic diameter \( (r^2 = .32, P < .05) \), left ventricular wall thickness \( (r^2 = .38, P < .01) \), left atrial dimension \( (r^2 = .36, P < .05) \), and derived measurements such as the percent fractional shortening \( (r^2 = .5, P < .01) \), and left ventricular mass/body surface area \( (r^2 = .5, P < .001) \) but not with wall stress.

Conclusions—These results demonstrate that abnormalities of PCr/ATP in mitral regurgitation are related to disease severity as measured by dimensional indexes of left ventricular dilatation. They suggest that impaired high-energy phosphate metabolism is a marker of hypertrophy and heart failure. (Circulation. 1998;97:1716-1723.)

Key Words: mitral valve ■ spectroscopy ■ heart failure ■ echocardiography ■ myocardium

The mechanisms underlying deterioration of myocardial contractility in conditions such as MR (mitral incompetence) are poorly understood. Abnormal high-energy phosphorus and other metabolism appears to play a role, and several recent reports using 31P MRS describe altered PCr/ATP among patients with aortic valve disease, cardiomyopathy, ischemia, and other disorders affecting the myocardium. Disease severity was characterized from the degree of impairment, echocardiographic abnormalities, and changes in PCr/ATP.

Methods
Subjects
Twenty-two patients (age range, 17 to 78 years; mean ± SD, 54.6 ± 17 years; height, 173 ± 11 cm; weight, 66.4 ± 12.9 kg; BSA, 1.76 ± 0.2 m²; 17 men, 5 women) with MR were compared with 13 age- and sex-matched normal control subjects. To limit the effects of confounding factors, all patients fulfilled the following criteria: (1) they had clinically stable MR for at least 3 months, (2) they were able to tolerate lying prone, (3) they were in sinus rhythm \( (n = 16) \) and well-controlled atrial fibrillation \( (n = 6) \) and did not suffer from lung disease, pulmonary or systemic hypertension, acute or healed myocardial infarction, angina pectoris, significant aortic valve disease, or LV dilatation caused by idiopathic, myocarditic, or ischemic cardiomyopathy. Disease severity was characterized from the degree of dyspnea (NYHA classes I through IV) at the time of the MRS study. Patients were recruited and studied randomly as they presented within a month of referral or soon after annual outpatient review. Patients with mild incompetence had been referred with palpitations or a clinically detected mitral murmur.

The symptomatic status and echocardiographic severity of the patients with MR are listed in Table 1.
TABLE 1. Symptomatic Status and Echocardiographic Severity of MR

<table>
<thead>
<tr>
<th>Symptom Grade (NYHA)</th>
<th>Severity of MR</th>
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<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>12</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
</tr>
<tr>
<td>Treated CHF</td>
<td>5</td>
</tr>
<tr>
<td>MVR*</td>
<td>8</td>
</tr>
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</table>

CHF indicates congestive heart failure.

*One man died postoperatively owing to LV dysfunction.
of the signal from combined 2,3 DPG resonances (at 5.3 and 6.2 ppm) was equal to or greater than that of the γATP and (2) the amplitude of the 3 phosphoglycerate was equal to or lower than that of the 2 phosphoglycerate.29 Such corrections were applied to cardiac spectra from five normal control subjects and five patients with MR (moderate 5 1; severe 5 4). (This suggests that the presence of prominent blood signals is not a particular feature of dilated cardiomyopathy and is likely to reflect the depth and position of the sampling volume in a proportion of both the control subjects and valvular heart disease patients.) Data are presented as mean ± SD and compared by use of both the basic Student unpaired t test and the Welch modified two-sample t test. The comparison of PCr/ATP with the grade of mitral incompetence was examined with ANOVA. Normal distribution of the data was checked with the Kolmogorov Smirnov test. The nonparametric Spearman test was applied when the data were not normally distributed, eg, wall stress. Simple correlations were examined, and values of $P$, .05 and $r^2$, .45 were accepted as significant and as evidence favoring a relationship. There were no significant differences in myocardial PCr/ATP measured by CSI and PMRFI either before or after saturation and blood correction (uncorrected control subjects: CSI, $n = 8$, 1.66 ± 0.38 versus PMRFI, $n = 5$, 1.52 ± 0.14). The individual ratios for patients are tabulated in Table 2 (from which the correction factors can be derived), and both the uncorrected and saturation corrected mean values are presented in Tables 3 and 4.

### Results

#### Steady-State High-Energy Phosphorus Metabolism in Mitral Incompetence

Representative 1D CSI spectra from a control and patients with normal and reduced PCr/ATP are illustrated in Figure 3. A midplateau PMRFI heart spectrum of one patient with severe MR is also shown. The amplitude and area of PCr relative to ATP are highest in the normal and mild MR spectra. To determine whether myocardial high-energy phos-
Regurgitation (n = 11, 1.29). Within the current study group, patients with severe
dysfunction may determine the extent to which metabolism becomes deranged over time. Compared
with the ratio in patients with mild MR (1.73 ± 0.17, P < .05, P < .01), patients with moderate (1.49 ± 0.18, P < .05) and
severe (1.29 ± 0.32, P < .01) incompetence had lower PCr/ATP, suggesting that the degree of leakage is related to
intracellular high-energy phosphate changes. However, normal ratios are not exclusive to patients with mild
and moderate disease, as evidenced by the normal values in some cases with severe valve leakage (Table 2).

PCr/ATP: MR Compared With Control Subjects
Some previous reports suggest that LV metabolism may be different among MR patients compared with control subjects.30,31 Within the current study group, patients with severe regurgitation (n = 11, 1.29 ± 0.3, P < .02), dyspneic subjects (n = 10, 1.21 ± 0.24, P < .003), and those on therapy for heart failure (n = 13, 1.29 ± 0.29, P < .01) had significantly lower ratios compared with control subjects (n = 13, 1.61 ± 0.3). However, the control ratio was not significantly different from the ratio in patients classified echocardiographically with mild or moderate disease, among patients without dyspnea, or in those who did not require treatment for heart failure. These data are presented in Tables 3 and 4.

PCr/ATP: Mild Versus Moderate Versus Severe MR
The severity of incompetence may determine the extent to which metabolism becomes deranged over time. Compared with the ratio in patients with mild MR (1.73 ± 0.17, P < .05, P < .01), patients with moderate (1.49 ± 0.18, P < .05) and severe (1.29 ± 0.32, P < .01) incompetence had lower PCr/ATP, suggesting that the degree of leakage is related to intracellular high-energy phosphate changes. However, normal ratios are not exclusive to patients with mild and moderate disease, as evidenced by the normal values in some cases with severe valve leakage (Table 2).

PCr/ATP Versus Measured Echocardiographic Parameters
To explore possible structural or functional correlates of the above finding, the relationship between individual PCr/ATP and standard echocardiographic indexes of LA, LV dimensions, and LV Th was examined. Figure 4 shows PCr/ATP compared with ESD, EDD, and Th. PCr/ATP was closely related to ESD (r² = .7, P < .001), and a significant relationship with other parameters was also identified (Th: r² = .38, P < .01; EDD: r² = .32, P < .05; and LA: r² = .36, P < .05).

PCr/ATP Versus Derived Echocardiographic Measurements
Correlation was found between the metabolic ratio and both the LVM/BSA (r² = .52, P < .0001) and FS% (r² = .5, P < .001), but the measured wall stress was not related to PCr/ATP (r² = .14, P = NS) even when tested with the nonparametric Spearman test (Table 5).

<table>
<thead>
<tr>
<th>TABLE 4. Comparison of Mean Biochemical and Echocardiographic Measurements in Treated Compared With Untreated Patients in Relation to Symptoms of Dyspnea and According to Whether They Underwent MVR</th>
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</thead>
<tbody>
<tr>
<td><strong>PCr/ATP</strong></td>
</tr>
<tr>
<td>PCr/ATP</td>
</tr>
<tr>
<td>Sat corr</td>
</tr>
<tr>
<td>EDD, cm</td>
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<tr>
<td>ESD, cm</td>
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<tr>
<td>Th, cm</td>
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<tr>
<td>LA, cm</td>
</tr>
<tr>
<td>FS %</td>
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<tr>
<td>LVM/BSA, g/cm²</td>
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<tr>
<td>WS, dynes/cm²</td>
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</tbody>
</table>

*SOB indicates shortness of breath/dyspnea; Sat corr, saturation corrected; Med, medical; and Rx, treatment.

PCr/ATP: Mild Versus Moderate Versus Severe MR
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<th>TABLE 5. Intercorrelation of Echocardiographic and Biochemical Measurements: Best-Fit Simple Regressions (r²)</th>
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<tbody>
<tr>
<td><strong>ESD</strong></td>
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<tr>
<td>EDD</td>
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<tr>
<td>ESD</td>
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<td>Th</td>
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<tr>
<td>FS %</td>
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<tr>
<td>LVM/BSA</td>
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<tr>
<td>WS</td>
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<tr>
<td>LA</td>
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</tbody>
</table>

*WS indicates wall stress; Sat corr, saturation corrected. Correlations are not presented for parameters in which there is a common measurement in the numerator and denominator, eg, EDD and LVM/BSA.

*P < .05; † P < .01; ‡ P < .001; § P < .0001.
**PCr/ATP and Clinical Variables: Dyspnea, Antifailure Therapy, Referral for MVR**

Twelve patients reported no limitation caused by dyspnea at the time of the MRS study and had higher PCr/ATP (1.66 ± 0.2) compared with the symptomatic subjects (1.21 ± 0.24, \(P < .001\)). The findings were similar on separation of the patients into groups according to whether or not antifailure therapy was required. Those on regular oral antifailure treatment (\(n = 13\), 8 of whom subsequently underwent MVR) had lower PCr/ATP (1.29 ± 0.29) compared with the untreated group (\(n = 9\), 1.69 ± 0.15, \(P < .001\)). PCr/ATP of subjects treated both medically and referred for MVR within 2 months was lower than that of those on medical therapy alone, but the difference did not achieve conventional statistical significance (1.17 ± 0.23, \(n = 8\) versus 1.48 ± 0.29, \(n = 5\); Table 4).

**Discussion**

In the current study, intracellular myocardial biochemistry of the LV free wall and apex of the heart with mitral incompetence was examined by use of an index based on measurements of phosphate atomic nuclei in PCr and ATP. The findings show that patients have normal PCr/ATP when MR is mild but develop reduced PCr/ATP with severe disease, indicative of a reduced potential for maintaining the ATP supply for muscular contraction. Patients with symptoms of heart failure and those receiving antifailure therapy also exhibited lower PCr/ATP compared with the asymptomatic and untreated groups. The latter observations are consistent with previous studies of steady state high-energy phosphorus metabolism in valvular heart disease and heart failure caused by cardiomyopathy.

The clearest correlation between a simple echocardiographic measurement and the biochemical index is PCr/ATP versus ESD. Patients whose LVs are larger than normal at end systole have decreased PCr compared with ATP concentrations, and the greater the dilatation, the lower the ratio. This finding is consistent with the significant correlation between PCr/ATP and FS\%. Such observations suggest that the prevailing PCr/ATP may be linked to factors determining the efficiency of contractility. Hence, it represents a potential biochemical marker of LV function.

The biochemical index also links LV growth to the changes in PCr/ATP. Mass is derived using cubed EDD and LV myocardial thickness and is subject not only to the variability in these measurements but also to patient size and the effects of conditions that increase wall thickness such as hypertension. The measurements presented were adjusted for BSA, and confounding conditions were excluded during patient recruitment, thereby supporting the proposal that increased LVM is associated with an altered PCr/ATP, as has been shown with animal models.

Correlation of derived echocardiographic measurements such as FS\% and LVM/BSA with PCr/ATP reflects the relationship with the measured echocardiographic parameters from which these are calculated. Our data show no correlation between the biochemical ratio and the calculated wall stress.

The altered PCr/ATP reflects altered homeostasis of high-energy phosphorus metabolism in MR. The abnormality results perhaps from one or more of the many biochemical mechanisms that maintain efficient cellular contractility.

**Figure 1.** $^1$H MRI of the heart and chest wall. A spectrum from the inner row of the free wall and apex of the heart (section 5) using the Glinfit integration program is also shown. RV indicates right ventricle; Sep, septum; Adipose, adipose tissue; and Pi, inorganic phosphate.

**Figure 2.** Relaxed and fully saturated spectra of the combined chest wall and heart from a patient with valvular incompetence.
Recently, Massie et al.\textsuperscript{35} showed that the proportion of glucose that the heart oxidizes is higher in pigs with LV hypertrophy. They argued that a different substrate preference could offer a partial explanation for the lower PCr/ATP in LV hypertrophy because a low ratio has been observed when glucose is the sole substrate in perfused hearts.\textsuperscript{36} However, as they pointed out, the relevance of their finding to humans in whom a mixture of substrates is available remains uncertain. Reduction of PCr/ATP may be determined by chronic myocardial hypoperfusion, but it is unlikely that decreased PCr/ATP and impaired systolic function among patients with chronic stable regurgitation is analogous to the PCr depletion that occurs during global myocardial ischemia in the isolated heart preparation.\textsuperscript{34} In contrast, intracellular biochemical changes associated with concentric hypertrophy may depend more on perfusion to the endocardium (especially rate related).\textsuperscript{33,37,38} Altered biochemistry is reported by other investigators who studied patients with mitral valve prolapse. The arterial and coronary sinus blood lactate levels were increased\textsuperscript{39} in a group with mitral valve prolapse, and right ventricular endomyocardial biopsies\textsuperscript{31} demonstrated evidence of mitochondrial degeneration. However, some investigators (eg, Chidsey et al\textsuperscript{39}) have reported normal high-energy phosphorus metabolism in the papillary muscle of patients with MR compared with myocardial tissue from congenital heart disease patients.

Our findings demonstrate that deteriorating myocardial function in mitral incompetence is associated with altered PCr/ATP. The mechanism of this may be inefficient creatine phosphorylation by creatine kinase\textsuperscript{40,41} and decreased intracellular creatine.\textsuperscript{2} Because creatine uptake into muscle occurs through specific sodium-dependent membrane transport that requires energy,\textsuperscript{42} this process may be particularly susceptible to abnormal myocardial energy demand and may represent an adaptive change.

The present metabolic findings are relevant not only to the understanding of myocardial metabolism but also to the possible role of $^{31}$P MRS as a technique for investigating and clinically managing patients with valvular heart disease. We have previously proposed that serial noninvasive biochemical monitoring represents a potentially important investigation for improving management decisions relating to valve surgery.\textsuperscript{7} This applies particularly to MR, a condition in which the optimal timing of MVR is often difficult to choose. Our study identified a close relationship between $^{31}$P MRS measurements and systolic function. The latter, as measured by echocardiography, determines morbidity and mortality both with and without surgery.\textsuperscript{33–45} The link between systolic function and PCr/ATP presents a further biochemical marker for these epidemiological observations. In support of the observations, low PCr/ATP has been found to be associated with increased mortality in patients with dilated cardiomyopathy.\textsuperscript{46}

The current measurements were made at 1.9 to 2.0 T with two currently accepted techniques from patients who were carefully chosen on the basis of clinical criteria and from whom metabolic measurements could be made with good $^{31}$P MRS signal-to-noise ratios. Standard corrections were applied, and data adjustment for partial saturation and blood contamina-
tion was performed. High magnetic field strengths of ≥4 T offer further potential for increasing the sensitivity and scope of such studies. MR was assessed here with echocardiography but ultimately could be evaluated during combined conventional tagging MRI and MRS examination.

In conclusion, 31P MRS demonstrates altered PCr/ATP in patients with MR. Lower PCr/ATP ratios are linked to echocardiographic indexes of severity, including systolic function and eccentric hypertrophy, and to symptoms of heart failure. The findings may reflect altered creatine homeostasis and may be helpful in the management of patients awaiting MVR.

Acknowledgments

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