31P Magnetic Resonance Spectroscopy in Dilated Cardiomyopathy and Coronary Artery Disease

Altered Cardiac High-Energy Phosphate Metabolism in Heart Failure

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Background. The purpose of this work was to further define the value of cardiac 31P magnetic resonance (MR) spectroscopy for patients with coronary artery disease and dilated cardiomyopathy.

Methods and Results. Blood-corrected and T1-corrected 31P MR spectra of anteroseptal myocardium were obtained at rest using image-selected in vivo spectroscopy localization, a selected volume of 85±12 cm3, and a field strength of 1.5 T. Nineteen volunteers had a creatine phosphate (CP)/ATP ratio of 1.95±0.45 (mean±SD) and a PDE/ATP ratio of 1.06±0.53; in four patients with left anterior descending coronary artery (LAD) stenosis, six patients with chronic anterior wall infarction, and four patients with chronic posterior wall infarction, CP/ATP and phosphodiester (PDE)/ATP ratios did not differ from those in volunteers. Twenty-five measurements of 19 patients with dilated cardiomyopathy yielded a CP/ATP of 1.78±0.51 and a PDE/ATP of 0.98±0.56 (p=NS versus volunteers). When these patients were grouped according to the severity of heart failure, however, CP/ATP was 1.94±0.43 in mild (p=NS versus volunteers) and 1.44±0.52 in severe DCM (p<0.05), respectively. No correlation was found between CP/ATP and left ventricular ejection fraction or fractional shortening, but correlation of CP/ATP with the New York Heart Association (NYHA) class was significant (r=0.60, p<0.005). Six patients with dilated cardiomyopathy were studied repeatedly before and after 12±6 weeks of drug treatment leading to clinical recompensation with improvement of the NYHA status by 0.8±0.3 classes. Concomitantly, CP/ATP increased from 1.51±0.32 to 2.15±0.27 (p<0.01), whereas PDE/ATP did not change significantly.

Conclusions. Cardiac high-energy phosphate metabolism at rest is normal in LAD stenosis and chronic myocardial infarction in the absence of heart failure. The CP/ATP ratio has low specificity for the diagnosis of dilated cardiomyopathy. However, CP/ATP correlated with the clinical severity of heart failure and may improve during clinical recompensation. (Circulation 1992;86:1810–1818)

KEY WORDS • magnetic resonance spectroscopy • high-energy phosphates • cardiomyopathies • coronary artery disease • heart failure • energy metabolism

The value of 31P magnetic resonance (MR) spectroscopy for studying the substantial changes of high-energy phosphate metabolites in hearts subjected to acute ischemia and reperfusion has been extensively demonstrated in a number of animal studies.1,2 In addition, chronic alterations of energy metabolism in residual intact myocardial tissue evoked by a model of chronic myocardial infarction in rat were recently reported.3 Clinical 31P MR studies of acutely or chronically ischemic myocardium, however, have so far been few,4,5 and the value of 31P MR spectroscopy for patients with coronary artery disease (CAD) remains to be further defined.

Various animal models of congestive heart failure and cardiac hypertrophy have shown alterations in energy metabolism occurring in concert with reductions of mechanical function,6–8 and reduced high-energy phosphate levels have been proposed as a major mechanism responsible for the occurrence of heart failure (see Reference 9 for a review). Clinical studies based on myocardial biopsy specimens from patients with dilated cardiomyopathy (DCM) using conventional analytical biochemistry techniques10 reported reduced myocardial ATP concentrations correlating with the extent of mechanical dysfunction. Studies on human cardiac energy metabolism using 31P MR spectroscopy in patients with DCM have reported unchanged11 or reduced12 creatine phosphate (CP)/ATP ratios.

Thus, the purpose of this study was twofold: First, we sought to define changes of energy metabolism occurring at rest in patients with CAD, specifically in those with left anterior descending coronary artery (LAD) stenosis, chronic anterior wall infarction (AWI), and posterior wall infarction (AWI). Second, to clarify con-
TABLE 1. Characteristics of Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Time after MI</th>
<th>Angiography/ventriculography</th>
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<tbody>
<tr>
<td>20</td>
<td>LAD</td>
<td>67</td>
<td>M</td>
<td>...</td>
<td>LAD 90%, Rd, 95%, Rd, 95%,Cx 90%, RCA 100%, EF 56%</td>
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<tr>
<td>21</td>
<td>LAD</td>
<td>62</td>
<td>M</td>
<td>...</td>
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</tr>
<tr>
<td>45</td>
<td>LAD</td>
<td>66</td>
<td>M</td>
<td>...</td>
<td>LAD 95%, Cx 60%, RCA 70% EF 54%</td>
</tr>
<tr>
<td>50</td>
<td>LAD</td>
<td>58</td>
<td>M</td>
<td>...</td>
<td>LAD 95%, EF 89%</td>
</tr>
<tr>
<td>7</td>
<td>AWI</td>
<td>54</td>
<td>M</td>
<td>6 Years</td>
<td>LAD 100%, ant. hypokinesia, EF 68%</td>
</tr>
<tr>
<td>11</td>
<td>AWI</td>
<td>62</td>
<td>M</td>
<td>3 Weeks</td>
<td>LAD 70%, left perstol. 70%, ant. hypokinesia, EF 75%</td>
</tr>
<tr>
<td>14</td>
<td>AWI</td>
<td>61</td>
<td>M</td>
<td>2 Weeks</td>
<td>LAD 100%, Cx 95%, RCA 100%, ant/inf. hypokinesia, EF 30%</td>
</tr>
<tr>
<td>24</td>
<td>AWI</td>
<td>54</td>
<td>M</td>
<td>2 Weeks</td>
<td>LAD 95%, intern. 80%, Rm, 95%, RCA 80%, ant. hypokinesia, EF 89%</td>
</tr>
<tr>
<td>30</td>
<td>AWI</td>
<td>55</td>
<td>M</td>
<td>2 Weeks</td>
<td>LAD 95%, ant. akinesia, EF 42%</td>
</tr>
<tr>
<td>36</td>
<td>AWI</td>
<td>63</td>
<td>M</td>
<td>3 Weeks</td>
<td>LAD 95%, antero septal hypokinesia, EF 83%</td>
</tr>
<tr>
<td>4</td>
<td>PWI</td>
<td>54</td>
<td>M</td>
<td>5 Months</td>
<td>Cx 100%, RCA 95%, inf. hypokinesia, EF 58%</td>
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<tr>
<td>5</td>
<td>PWI</td>
<td>50</td>
<td>M</td>
<td>2 Weeks</td>
<td>RCA 100%, Cx 30%, inf. akinesia, EF 55%</td>
</tr>
<tr>
<td>19</td>
<td>PWI</td>
<td>56</td>
<td>M</td>
<td>4 Weeks</td>
<td>Cx 100%, inf. hypokinesia, EF 54%</td>
</tr>
<tr>
<td>46</td>
<td>PWI</td>
<td>67</td>
<td>M</td>
<td>6 Weeks</td>
<td>Cx 100%, inf. akinesia, EF 56%</td>
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</tbody>
</table>

MI, myocardial infarction; LAD, left anterior descending coronary artery; AWI, anterior wall infarction; PWI, posterior wall infarction; Rd, Rd, first and second diagonal branch of LAD; Cx, circumflex artery; RCA, right coronary artery; EF, ejection fraction; ant., anterior; post., posterolateral; inf., inferior; interm., intermediate; Rm, first marginal branch of Cx.

Conflicting results from other groups, we evaluated whether 31P MR is a sensitive technique for the detection of DCM. Furthermore, we examined whether alterations of energy metabolism in DCM correlate with the clinical severity of heart failure, as estimated by the New York Heart Association (NYHA) classification independent of functional parameters, and whether depressed energy metabolism can improve with medical therapy leading to clinical recompensation.

Methods

Characteristics of Volunteers and Patient Groups

All studies were approved by the Ethics Committee of the University of Würzburg. Nineteen volunteers with a mean age of 24±2 years (range, 20–29 years) served as a control group. All volunteers were apparently healthy individuals with no signs of heart disease at rest and during exercise. The 33 patients (mean age, 54 years; range, 28–67 years) were divided into 14 with CAD and 19 with DCM. Those with CAD (Table 1) were further subdivided as follows.

Four patients (all men; mean age, 63 years; range, 58–67 years; LAD group) had an LAD stenosis of ≥70%. Three of four reported a typical history of chest pain. All patients received nitrates and acetylsalicylic acid, three received a ß-blocking agent, two received a Ca2+ channel blocker, two an angiotensin-converting enzyme (ACE) inhibitor, one digitalis, and one a diuretic. The LAD lesion was demonstrated by coronary angiography by an independent cardiologist. This group was examined to visualize energy metabolism at rest in myocardium supplied by a highly stenotic coronary artery. Patients in this group were allowed to have significant stenoses of the circumflex (Cx) and/or right coronary artery (RCA) in addition to the LAD lesion but were not included if left ventriculographic and/or ECG evidence of previous infarction was found.

Six patients (all men; mean age, 58 years; range, 54–63 years; AWI group) were examined who had a previous anterior wall myocardial infarction (between 2 weeks and 6 years previously). In all patients, this was evidenced by anterior wall motion abnormalities upon left ventriculography. In addition, in every patient, previous serum chemistry changes (creatinine kinase [CK]-MB) and/or ECG findings indicated the presence of myocardial infarction. All patients received nitrates, four received a Ca2+ channel blocker, three a ß-blocker, three acetylsalicylic acid, three a diuretic agent, one an ACE inhibitor, and one digitalis. The LAD lesion responsible for the AWI was demonstrated by coronary angiography. This group was examined to visualize energy metabolism in scar tissue and in residual myocardium immediately adjacent to the infarct scar. Patients in this group were allowed to have significant stenosis of the Cx and/or RCA in addition to the LAD lesion and were also allowed to have other wall motion abnormalities in addition to the anterior hypokinesia or akinesia.

Four patients (all men; mean age, 57 years; range, 50–67 years; PWI group) were examined who had a previous posterior wall myocardial infarction (between 2 weeks and 5 months previously). In all patients, this was evidenced by inferior wall motion abnormalities upon left ventriculography. In addition, in every patient, previous serum chemistry changes (CK-MB) and/or ECG findings indicated the presence of infarction. All patients received nitrates, three received acetylsalicylic acid, two a ß-blocker, and two a diuretic agent. The RCA or Cx lesion responsible for the PWI was demonstrated by coronary angiography. Because this group was examined to visualize energy metabolism in residual intact myocardium in a region remote from the infarct scar, patients were included only if normal LAD morphology and normal anterior wall motion was found. None of the patients with CAD (LAD, AWI, or PWI) had any clinical signs of heart failure.

Table 2 shows characteristics of the 19 patients with DCM. Seventeen were men, two women; mean age was 51±10 years (range, 28–64 years). The presumed pathogenesis of DCM was alcoholic in seven, postmyocarditis in three, and idiopathic in nine. In all patients, left ventricular (LV) fractional shortening (FS) averag-
ing 16 ± 9% was determined echocardiographically in the parasternal-long axis view close to the time of spectroscopy (± 2 days). In 17 of 19 patients, LV ejection fraction (EF) averaging 33 ± 14% was determined by radiocontrast left ventriculography or radionuclide scan. In all DCM patients, the presence of CAD was ruled out by demonstrating normal coronary anatomy in the absence of LV dysfunction by coronary angiography. In addition, none of the DCM patients had chest pain or signs of myocardial infarction on ECG readings. At the day of spectroscopy, the clinical status of each patient was evaluated by an independent cardiologist before spectroscopy was performed, and patients were graded according to the NYHA classification for heart failure. At the time of study, 16 patients received a diuretic, 16 received digitalis, 16 an ACE inhibitor, two a class I (mexiletine and propafenone) and one a class III (amiodarone) antiarrhythmic drug, and two acetylsalicylic acid. Table 3 describes NYHA classes and treatment regimen of six patients with DCM who were studied before and 12 ± 6 weeks (range, 3–20 weeks) after drug therapy. The mean age of this subgroup was 54 ± 11 years (range, 37–64 years). All patients received diuretics and ACE inhibitors, five received digitalis, and four were treated with 50 mg/day of the β-blocker metoprolol. In all patients, the clinical status improved by at least 0.5 NYHA classes (mean, 0.8 ± 0.3) during treatment. Serial measurements of LV function were not made.

**MR Data Acquisition and Processing**

Measurements were taken with a 1.5-T (resonance frequencies, 63.83 MHz for 1H, 27.16 MHz for 31P) whole-body Philips Gyroscan MR system with an effective bore size of 65 cm. A single custom-made 15-cm-diameter surface coil tunable to 1H and 31P (double-tuned coil) served as both transmitter and receiver coil. To minimize motion artifacts, subjects were examined in prone position with the chest wall lying above the surface coil.

Before each measurement, shimming on the proton signal was performed, yielding line widths of <0.7 ppm (<45 Hz) for H2O; spectroscopy was not performed if 1H line width could not be reduced below 0.7 ppm. Localization was then carried out by the image-selected in vivo spectroscopy (ISIS) technique. First, nine T1-weighted, spin-echo multislice 1H images of the heart were recorded with a pulse repetition time (TR) equal to one RR interval, an echo time of 30 ms, and a slice thickness of 15 mm, confirming the correct position of the surface coil relative to the heart. On the basis of these scout images, the ISIS volume was positioned over the anterosepal region of the heart, as illustrated by an example shown in Figure 1. Volume size for spectroscopy ranged from 46 to 117 cm3 (mean, 84 ± 12 cm3). Adiabatic pulses were used and yielded flip angles of 180° throughout the selected volume. The acquisition was ECG triggered. TR was equal to two RR intervals, 15 or 24 seconds; correspondingly, the number of averages was 1,024, 128, or 96; 32%, 36%, and 24% of measurements in volunteers, CAD patients, and DCM patients, respectively, were performed with a short TR (two RR intervals). Total scan time/spectrum was = 32 minutes, and total patient examination time was 45–60 minutes. For the six patients with DCM studied sequentially, the same TR was used for both examinations. CP/ATP ratios were corrected for partial saturation based on T1 measurements in volunteers as previously described: T1,8 of γ-ATP, CP, and phosphodiestere (PDE) were 5.4 ± 0.5, 6.1 ± 0.5, and 5.0 ± 1.0 seconds, respectively. This assumes that T1,8 do not change in the presence of cardiac disease. The quality of volume selection by ISIS was tested in phantom experiments in which a cube (volume, 64 ml) filled with hypophosphoric acid (H3PO4) was placed in a cylinder (15 cm in diameter and height) containing orthophosphoric acid (H3PO4). When the ISIS volume was localized with the cube containing H3PO4 and TR was varied from 2 to 20 seconds, the H3PO4 resonance area was reduced by 91.3% (TR, 2 seconds) to 91.9% (TR, 20 seconds) compared with nonlocalized spectra. Thus, localized spectra were contaminated by signal from surrounding

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cause</th>
<th>Age (years)</th>
<th>Sex</th>
<th>NYHA class</th>
<th>EF (%)†</th>
<th>FS (%)†</th>
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<td>M</td>
<td>III</td>
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<td>11</td>
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<tr>
<td>8</td>
<td>Myocarditis</td>
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<td>M</td>
<td>III</td>
<td>38</td>
<td>8</td>
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<tr>
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<td>40</td>
<td>M</td>
<td>II–III</td>
<td>30</td>
<td>18</td>
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<tr>
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<td>47</td>
<td>F</td>
<td>II–III</td>
<td>46 (rn)</td>
<td>16</td>
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<tr>
<td>23</td>
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<td>51</td>
<td>M</td>
<td>II</td>
<td>19 (rn)</td>
<td>8</td>
</tr>
<tr>
<td>26</td>
<td>Idiopathic</td>
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<td>M</td>
<td>II–III</td>
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<tr>
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<td>49</td>
<td>M</td>
<td>II–III</td>
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<td>41</td>
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<tr>
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<td>59</td>
<td>M</td>
<td>III</td>
<td>6</td>
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</tr>
<tr>
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<td>Idiopathic</td>
<td>55</td>
<td>F</td>
<td>II</td>
<td>60</td>
<td>30</td>
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<tr>
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<td>Alcoholic</td>
<td>64</td>
<td>M</td>
<td>III–IV</td>
<td>12</td>
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<tr>
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<td>28</td>
<td>M</td>
<td>III–IV</td>
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<td>M</td>
<td>II</td>
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<td>III–IV</td>
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<td>M</td>
<td>II</td>
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<td>13</td>
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<tr>
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<td>Idiopathic</td>
<td>56</td>
<td>M</td>
<td>III</td>
<td>34</td>
<td>23</td>
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</tbody>
</table>

**NYHA, New York Heart Association; EF, ejection fraction; FS, fractional shortening.**

†By echocardiography.
volume by <10% regardless of TR. 31P spectra were processed with zero shift, direct current correction (30%), exponential multiplication (7 Hz), and individual phase correction. Peak areas for 2,3-diphosphoglycerate (2,3-DPG), PDE, CP, [γ-P], [α-P], and [β-P]ATP (Figure 2) were obtained by Lorentzian line fits in the time domain as previously described14 using 400 iterations. Preliminary work indicated that peak areas differed by <3% after 300 iterations were applied. For comparison of spectra from different subjects, the CP/[γ-P]ATP ratio and PDE/[γ-P]ATP ratio were calculated. Because of bandwidth limitations of the transmitter, we chose to use the [γ-P] instead of the [β-P] resonance of ATP. The CP/ATP ratio is regarded as an index of the energetic state of the heart (see Reference 9 for review); furthermore, it has been suggested that changes of the PDE/ATP ratio may indicate cardiomyocyte membrane damage in DCM.11

When ISIS is used as a single-volume technique, all 31P spectra exhibit resonances corresponding to 2,3-DPG. We therefore corrected spectra for blood contamination. 31P spectra of venous blood freshly drawn from 19 volunteers (temperature, 37°C; TR, 2.4 seconds; number of acquisitions, 1,032) gave a [γ-P]ATP/2,3-DPG area ratio of 0.11±0.02 (SD), corresponding to a molar ratio of 0.22. Literature values reported using routine chemistry are somewhat higher (0.30±0.02, SEM).15,16 The PDE/2,3-DPG area ratio in blood was 0.19±0.03. Thus, for blood correction, the [γ-P]ATP resonance area of cardiac spectra was reduced by 11% of the 2,3-DPG resonance area, and the PDE resonance was reduced by 19% of the 2,3-DPG area. The average [γ-P]ATP/2,3-DPG ratio in all cardiac spectra was 0.73±0.41 and was 0.87±0.44 in volunteers, 0.75±0.48 in CAD, and 0.68±0.41 in DCM (p=NS, volunteers versus CAD and DCM, respectively), indicating that the degree of blood contamination tended to be greater in DCM but was not significantly different.

Statistical Analysis

CP/ATP and PDE/ATP ratios calculated for each metabolite were averaged to yield mean±SD values. Data from the various groups and subgroups were compared by factorial ANOVA17 with statistically significant differences detected by Scheffe’s F test. The correlations among CP/ATP ratios and NYHA class, EF, and FS were analyzed by linear regression analysis.17 Changes of heart rate and high-energy phosphate ratios during treatment in patients with DCM were compared by paired t test.17 Calculations were aided by the StatView SE+Graphics Professional, Graphic, Statistics Utility (BrainPower Inc., Calabasas, Calif.). Values of p<0.05 were considered significant.

Results

Volunteers

Figure 2A shows a typical 31P spectrum from a volunteer. The average ratio of T1 and blood-corrected CP/ATP was 1.95±0.45, and PDE/ATP was 1.06±0.53 (Figure 3). Values without blood correction were CP/ATP, 1.64±0.26 and PDE/ATP, 1.17±0.45; thus, blood correction increased the CP/ATP ratio by 19% and decreased the PDE/ATP ratio by 9%. On the basis of 31P metabolite ratios measured in blood from volunteers, we calculated that, on average, 17±8% of the ATP resonance area and 28±17% of the PDE reso-
nance area could be attributed to blood contamination of the ISIS volume.

Coronary Artery Disease

Examples of $^{31}$P spectra from one patient with LAD stenosis, one with AWI, and one with PWI are shown in Figures 2B–2D. Compared with the volunteer, none of the spectra appear to be grossly altered apart from various degrees of blood contamination. Mean $T_1$ and blood-corrected metabolite ratios are given in Figure 3. The figure demonstrates that neither the CP/ATP nor the PDE/ATP ratio showed any significant change in patients with CAD, although there may be a slight tendency for reduced CP/ATP in AWI and PWI. Thus, no significant abnormalities of energy metabolism at rest could be detected in patients with LAD stenosis, AWI, and PWI.

Dilated Cardiomyopathy

Figure 4 (left panel) shows the spectrum of a 37-year old patient with DCM who was in NYHA class III heart failure. In this spectrum, the CP/ATP ratio is reduced (1.56), and the PDE/ATP ratio is elevated (2.26). Figure 3 gives mean values of $T_1$ and blood-corrected metabolite ratios for all 25 measurements of 19 patients with DCM. The CP/ATP ratio showed a trend toward a decrease (1.78±0.51) but was not significantly different from volunteers (1.95±0.45). The PDE/ATP ratio (0.98±0.56) was similar to values from volunteers (1.06±0.53). Thus, as a group including all clinical stages, patients with DCM could not be distinguished from volunteers on the basis of $^{31}$P MR data. When patients were grouped according to the clinical severity of heart failure, however, a different picture evolved. As depicted in Figure 3, CP/ATP ratios were unchanged (1.94±0.43) in patients with mild (NYHA <III) but significantly reduced (1.44±0.52; $p<0.05$) in severe (NYHA ≥III) DCM. Figure 5 shows that the CP/ATP ratio decreased progressively in relation to the severity of heart failure; CP/ATP values were 2.14±0.32 ($n=9$), 1.71±0.46 ($n=8$), 1.61±0.31 ($n=4$), and 1.26±0.68 ($n=4$) for NYHA classes II, III, and IV, respectively. Furthermore, linear regression between NYHA class and CP/ATP was highly significant ($r=0.60$, $p<0.005$). In contrast, the PDE/ATP ratio bore no correlation with the clinical severity of heart failure (Figures 3 and 5), and linear regression was not significant ($r=0.16$, $p=0.43$). Similarly, we failed to detect a significant correlation between the indexes of LV performance (EF and FS) and CP/ATP or PDE/ATP ratios. Linear regression yielded CP/ATP=0.009EF+1.38 ($r=0.25$, $p=0.34$); CP/ATP=−0.001FS+1.68 ($r=0.02$, $p=0.94$); PDE/ATP=0.007EF+0.79 ($r=0.17$, $p=0.52$); and PDE/ATP=−0.004FS+1.06 ($r=0.07$, $p=0.76$). Correlations did not improve when EF values >40% or FS values >20% were excluded from the regression.

Finally, a subgroup of six patients with DCM was examined sequentially before and after 12±6 weeks of drug therapy (see “Methods” and Table 3). The six patients improved by 0.8±0.3 NYHA classes during treatment. Figure 4 shows spectra of a patient before and after therapy. The increase of CP/ATP and the decrease of PDE/ATP occurring with therapy are apparent. Figure 6 shows the changes of CP/ATP and PDE/ATP during treatment. The initial CP/ATP ratio

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Cardiac $^{31}$P magnetic resonance spectra from a volunteer (panel A) and from patients with LAD stenosis (panel B), chronic anterior (panel C), and chronic posterior wall infarction (panel D). Compared with the volunteer, none of the patient spectra appear to be grossly altered apart from various degrees of blood contamination. CP, creatine phosphate; PDE, phosphodiesters; 2/3 DPG, 2,3-diphosphoglycerate.

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** (Left panel) shows the spectrum of a 37-year old patient with DCM who was in NYHA class III heart failure. In this spectrum, the CP/ATP ratio is reduced (1.56), and the PDE/ATP ratio is elevated (2.26). Figure 3 gives mean values of $T_1$, and blood-corrected metabolite ratios for all 25 measurements of 19 patients with DCM. The CP/ATP ratio showed a trend toward a decrease (1.78±0.51) but was not significantly different from volunteers (1.95±0.45). The PDE/ATP ratio (0.98±0.56) was similar to values from volunteers (1.06±0.53). Thus, as a group including all clinical stages, patients with DCM could not be distinguished from volunteers on the basis of $^{31}$P MR data. When patients were grouped according to the clinical severity of heart failure, however, a different picture evolved. As depicted in Figure 3, CP/ATP ratios were unchanged (1.94±0.43) in patients with mild (NYHA <III) but significantly reduced (1.44±0.52; $p<0.05$) in severe (NYHA ≥III) DCM. Figure 5 shows that the CP/ATP ratio decreased progressively in relation to the severity of heart failure; CP/ATP values were 2.14±0.32 ($n=9$), 1.71±0.46 ($n=8$), 1.61±0.31 ($n=4$), and 1.26±0.68 ($n=4$) for NYHA classes II, III, and IV, respectively. Furthermore, linear regression between NYHA class and CP/ATP was highly significant ($r=0.60$, $p<0.005$). In contrast, the PDE/ATP ratio bore no correlation with the clinical severity of heart failure (Figures 3 and 5), and linear regression was not significant ($r=0.16$, $p=0.43$). Similarly, we failed to detect a significant correlation between the indexes of LV performance (EF and FS) and CP/ATP or PDE/ATP ratios. Linear regression yielded CP/ATP=0.009EF+1.38 ($r=0.25$, $p=0.34$); CP/ATP=−0.001FS+1.68 ($r=0.02$, $p=0.94$); PDE/ATP=0.007EF+0.79 ($r=0.17$, $p=0.52$); and PDE/ATP=−0.004FS+1.06 ($r=0.07$, $p=0.76$). Correlations did not improve when EF values >40% or FS values >20% were excluded from the regression.

Finally, a subgroup of six patients with DCM was examined sequentially before and after 12±6 weeks of drug therapy (see "Methods" and Table 3). The six patients improved by 0.8±0.3 NYHA classes during treatment. Figure 4 shows spectra of a patient before and after therapy. The increase of CP/ATP and the decrease of PDE/ATP occurring with therapy are apparent. Figure 6 shows the changes of CP/ATP and PDE/ATP during treatment. The initial CP/ATP ratio
FIGURE 3. Bar graphs showing mean creatine phosphate (CP)/ATP (top panel) and phosphodiester (PDE)/ATP (bottom panel) ratios of volunteers (Vol) and patient groups. LAD, left anterior descending coronary artery stenosis; AWI, chronic anterior wall infarction; PWI, chronic posterior wall infarction; DCM, dilated cardiomyopathy; DCMm and DCMs, mild and severe DCM, respectively. Data are mean±SD.

was 1.51±0.32 and increased in all six patients after therapy to a value of 2.15±0.27; this increase was statistically significant (p<0.01). The PDE/ATP ratio was 1.14±0.76 before and 0.94±0.56 after treatment; there was a decrease in four and an increase in two patients; changes with therapy were not significant.

Thus, in patients with DCM, the CP/ATP ratio but not the PDE/ATP ratio was inversely correlated to the severity of heart failure and could be improved by chronic drug therapy. Only the more severe cases of DCM showed abnormal CP/ATP, which bore no correlation with parameters of LV function.

Discussion

Volunteers

In this report, we measured cardiac anteroseptal CP/ATP and PDE/ATP ratios using ISIS as a single-volume technique. CP/ATP values obtained for volunteers (T1-corrected, 1.64±0.26 [SD]) are comparable to results reported from other groups. Uncorrected CP/ATP was 1.55±0.20 (SD),18 1.33±0.19 (SEM),11 1.6±0.4 (SD),5 and 1.58±1.69,19 T1-corrected CP/ATP was 1.72±0.15 (SEM) or 1.64±0.08 (SEM).12 After spectra were corrected for the presence of blood, the volunteer CP/ATP ratio increased to 1.95±0.45, i.e., by 19%. Reported blood20,21 and blood- and T1-corrected CP/ATP ratios are 1.71±0.12 (SEM),20 1.5±0.2 (SD),21 1.80±0.06 (SEM)12 and 2.0±0.4 (SD).22 These values are all comparable and are also close to numbers reported for blood-perfused animal hearts.23-25 Thus, although our volunteer group was not age-matched, there are no indications that an age dependence of the CP/ATP ratio exists that could influence our findings. Few studies have reported on the PDE/ATP ratio, and the available data show considerable scatter: 1.76±0.22 (SEM),12 0.29±0.08 (SEM),11 0.84±0.08 (SEM),26 or 1.06±0.53 (SD), as reported here. The reasons for substantially differing PDE/ATP ratios in these studies remain unclear at present, although a partial explanation may be varying acquisition delays.12 From our measurements of the PDE/2,3-DPG ratio in blood, we calculate that 26% of the cardiac PDE peak arose from blood contamination, and thus, only 74% of the PDE

FIGURE 4. 31P magnetic resonance spectra of a patient with dilated cardiomyopathy before (left panel) and 18 weeks after (right panel) treatment with digitalis, diuretics, ACE inhibitors, and β-blockers. As the clinical status was improved from New York Heart Association class III to II, creatine phosphate (CP)/ATP ratio was increased, and in this case, phosphodiester (PDE)/ATP was reduced. Also, in this case, 2,3-diphosphoglycerate (2/3 DPG) was decreased after therapy, indicating reduced signal from blood. For all patients, however, the amount of blood contamination was similar before and after therapy. γ [γ-P]ATP, α, [α-P]ATP.

FIGURE 5. Scatterplots showing creatine phosphate (CP)/ ATP (left panel) and phosphodiester (PDE)/ATP (right panel) in patients with dilated cardiomyopathy graded according to the New York Heart Association (NYHA) classification. For each NYHA class, raw and mean data are shown. Correlation between the NYHA grade and CP/ATP was highly significant (r=0.60; p<0.005).
signal originated from heart muscle. Therefore, PDE/ATP ratios may also vary depending on the degree of blood contamination. Because all published values were obtained at 1.5–2 T, the well-described field dependence of PDE\textsuperscript{27,28} should not be a major factor influencing PDE/ATP ratios.

Coronary Artery Disease

In patients with LAD stenosis, we studied energy metabolism of myocardium supplied by a highly stenotic coronary artery at rest. Normal metabolite ratios indicate that alterations of energy metabolism do not occur under these conditions. This is in agreement with the findings of Weiss et al\textsuperscript{4} who reported normal CP/ATP in anterior myocardium supplied by a stenotic LAD. In addition, these authors demonstrated that the CP/ATP ratio decreased significantly during exercise. We also found normal CP/ATP and PDE/ATP in patients with AWI and PWI. In AWI, because of a relatively large selected volume (up to 114 cm\textsuperscript{3}), we obtained signal from residual myocardium adjacent to the infarct zone and from scar tissue. Since myocardial scar tissue presumably contains little or almost no ATP, however, the acquired signal most likely arose almost exclusively from residual intact myocardium. In PWI patients, spectra from residual intact myocardium remote from the infarct scar were acquired. Normal metabolite ratios in AWI and PWI patients indicate that energy metabolism at rest is unaltered in residual myocardium. It remains to be determined whether such patients will show altered energy metabolism during exercise. To date, there are no other studies examining anterior wall \textsuperscript{31}P spectra after PWI. One study by Bottomley et al\textsuperscript{5} has reported reduced CP/inorganic phosphate (P\textsubscript{i}) and increased P\textsubscript{i}/ATP ratios in some spectra obtained from patients examined 5–9 days after AWI. In our spectra, we were unable to resolve the P\textsubscript{i} resonance from the overlapping 2,3-DPG resonances and thus could not evaluate changes of the P\textsubscript{i} resonance. Hardy et al\textsuperscript{12} have reported reduced CP/ATP (1.53±0.07 versus 1.80±0.06 in volunteers, SEM) in patients with congestive heart failure resulting from severe multivessel CAD (presumably patients who had myocardial infarctions months to years before), but none of our patients with myocardial infarction and normal CP/ATP ratios had signs of failure. Systematic sequential studies of the changes in energy metabolism after myocardial infarction in conjunction with invasive and noninvasive evaluation of altered hemodynamics (remodeling) are needed to further clarify these points.

Dilated Cardiomyopathy

In this study, we report that as a group including all clinical stages, the CP/ATP ratio in patients with DCM tended to be lower (1.78±0.51, SD) but was not significantly decreased compared with volunteers (1.95±0.45). When patients were subdivided according to the clinical severity of heart failure, however, the CP/ATP ratio was progressively reduced. There was no significant change in patients with mild heart failure, but there was a marked reduction of CP/ATP in advanced stages of heart failure. CP/ATP ratios showed a highly significant correlation with the NYHA class (p<0.005). No correlation could be detected between measurements of LV function (FS, EF) and CP/ATP or PDE/ATP ratios. The presence of a correlation of CP/ATP with the clinical status in the absence of a correlation with direct functional indexes may be related to the fact that not all DCM patients with low EFs immediately develop the full clinical syndrome of heart failure. The clinical syndrome of severe heart failure is characterized by neurohumoral activation, and it is likely that this was the case in DCM patients with severe heart failure, whereas DCM patients with discrete signs of heart failure have only slightly elevated catecholamine, renin, and vasopressin levels.\textsuperscript{29,30} Changes in high-energy phosphate metabolism of the heart may therefore be dependent in part on the full clinical syndrome of congestive heart failure, including neurohumoral activation and sodium and water retention. Our findings are in line with the few reports available on this issue. Hardy et al\textsuperscript{12} reported reduced CP/ATP (1.41±0.12 versus 1.80±0.06 in volunteers, SEM) in patients with DCM and overt cardiac failure; these authors also were unable to demonstrate a correlation of LVEF and CP/ATP or PDE/ATP. Reduced CP/ATP ratios have also been described by Luyten et al\textsuperscript{22} (0.56±0.16, SD) and Rajagopalan et al\textsuperscript{31} (0.9) in patients with severe DCM. In the first study available on human DCM, Whitman et al\textsuperscript{23} reported on an infant with severe DCM in whom the CP/ATP ratio increased from 1.3 to 2.0 upon intravenous infusion of glucose. Similar to our findings, in patients with DCM not classified for the severity of heart failure, Schaefer et al\textsuperscript{11} found a trend toward a decrease of the CP/ATP ratio (0.70±0.12 versus 0.89±0.08 in volunteers, SEM), which was not significant. Reduced CP/ATP is probably linked to the

\begin{figure}
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\includegraphics[width=\textwidth]{figure6.png}
\caption{Graphs showing creatine phosphate (CP)/ATP (left panel) and phosphodiesters PDE/ATP (right panel) ratios before and after 12±6 weeks of drug therapy in six patients with dilated cardiomyopathy. There was a significant increase of CP/ATP from 1.51±0.32 to 2.15±0.27 (*p<0.01).}
\end{figure}
presence of heart failure by a common mechanism nonspecific for DCM: In patients with aortic stenosis or aortic incompetence, Conway et al\textsuperscript{21} reported reduced CP/ATP (1.10±0.32, SD) in the presence but normal CP/ATP (1.56±0.15) in the absence of heart failure. CP/ATP was also reduced (1.53±0.07 versus 1.80±0.06 in volunteers, SEM) in cardiac failure resulting from ischemic heart disease.\textsuperscript{12}

To the best of our knowledge, this is the first report on patients with DCM and clinical heart failure that demonstrates changes of the CP/ATP ratio during medical treatment leading to clinical recompensation. We found that concomitantly with the improvement of NYHA class (by 0.8±0.3 classes), the CP/ATP ratio increased from 1.51±0.32 to 2.15±0.27 (p<0.05). This indicates that cardiac energy metabolism improved in parallel with the clinical status. The most likely explanation of improved high-energy phosphate metabolism is an improved hemodynamic milieu with reductions in both preload and afterload, probably caused by ACE inhibition and diuretics. Purely speculatively, there may also be a direct beneficial effect of either the ACE inhibitor and/or the \( \beta \)-blocker; both classes of agents have been shown to protect cardiac energy metabolism during metabolic stress.\textsuperscript{33,34} Controlled studies with larger patient numbers are needed to further elucidate these points.

We do not believe that changes in energy metabolism are an artifact of changes in selected spectroscopic volumes: Spectra were corrected for the presence of blood, and in addition, the ATP/2,3-DPG ratio of cardiac spectra was 0.53±0.19 before and 0.46±0.25 (\( p=\text{NS} \)) after therapy, indicating that the percentage of selected volume contaminated by blood was similar before and after treatment. Thus, we assume that spectral changes observed with treatment were a result of intrinsic metabolic recovery of myocardial tissue. At the time of spectroscopy, heart rate was slightly, although significantly, higher before (91±7 beats per minute) than after (82±9 beats per minute) treatment (\( p<0.05 \)). Thus, changes in CP/ATP may result in part from reduced work load after therapy. Experimentally, however, blood-perfused hearts show little variation of high-energy phosphate ratios with changing work load conditions.\textsuperscript{35}

Our findings do not allow us to discriminate whether the observed changes of CP/ATP in severe DCM are a cause for or only an epiphenomenon of heart failure. However, a number of studies using various models of cardiac hypertrophy and failure\textsuperscript{3,7,8,36,37} have uniformly demonstrated reduced CP/ATP ratios occurring simultaneously with the depression of cardiac contractile function, suggesting an essential role for energy metabolism in the development of heart failure. One mechanism for reduced CP/ATP in heart failure is probably depletion of the total creatine pool: Nascimben et al\textsuperscript{38} reported a 57% reduction of total creatine in patients with DCM.

In our study, no significant alterations of the PDE/ATP ratio were observed in patients with DCM. This is in agreement with Hardy et al\textsuperscript{22} but in disagreement with others who observed increased PDE/ATP.\textsuperscript{11,26} We could not reproduce the correlation of PDE/ATP and LVEF reported by Auffermann et al.\textsuperscript{29} Although increased PDE/ATP ratios were attributed to increased membrane damage,\textsuperscript{39} Luyten et al\textsuperscript{22} recently showed that increased PDE/ATP was entirely attributable to increased blood contamination of spectra in DCM. We could not reproduce this finding, because PDE/ATP ratios were not elevated in DCM. Our findings indicate that the PDE/ATP ratio is not a useful parameter for characterizing patients with DCM.

**Limitations**

Using ISIS as a single-volume technique, we had to use relatively large selected volumes for the spectroscopy protocol. Multiple voxel techniques, currently unavailable for all but a few clinical MR systems, allow for smaller selected volumes and, thus, better spatial resolution with, possibly, determination of endocardial/epicardial gradients of energy metabolism as well as determination of intracellular P\textsubscript{i} and pH.\textsuperscript{22,40} Also, at present, the technique does not allow absolute quantification of CP and ATP. Thus, although CP/ATP ratios were unchanged after myocardial infarction and in mild DCM, we would not be able to detect simultaneous proportional reductions of both CP and ATP. Possible solutions to overcome this problem may be on the way.\textsuperscript{41} Furthermore, we varied the ISIS volume between 46 and 114 ml; using computer simulation, Lawry et al\textsuperscript{42} have shown that, in an ISIS experiment, the degree of contamination from signal outside the selected volume may depend on the size of the selected volume itself. We selected the ISIS volume to include as much heart muscle as possible and cannot exclude the possibility that such effects might constitute an error source. It should also be mentioned that all spectra were obtained at rest, and establishment of routine exercise standards should greatly enhance the sensitivity of the technique for detecting diseased myocardium.\textsuperscript{43,44} Finally, the approach of blood-correcting spectra, which is at present taken by most groups using cardiac \( ^{31} \)P MR spectroscopy, may have certain limitations: first, blood \( ^{31} \)P-observable metabolites may undergo changes with disease states\textsuperscript{45}; second, the Pi resonance is included in the area of the 2,3-DPG peaks, and if Pi is increased in DCM, overcorrection of the CP/ATP ratio might occur; third, the blood ATP/2,3-DPG ratio may change with the degree of oxygen saturation\textsuperscript{45} and may, thus, vary depending on the degree of right versus left chamber blood contamination. Although we would not expect any of these factors to profoundly change our results, an exact evaluation is problematic at present.

In summary, we found unchanged myocardial high-energy phosphate metabolism at rest in patients with CAD. Alterations in energy metabolism do occur in advanced but not in mild cases of DCM; such changes correlate with the severity of heart failure and can be improved with treatment leading to clinical recompensation.

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