Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 40, No. 7, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02160-5

Absolute Concentrations of High-Energy Phosphate Metabolites in Normal, Hypertrophied, and Failing Human Myocardium Measured Noninvasively With ^{31}P-SLOOP Magnetic Resonance Spectroscopy

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OBJECTIVES The purpose of the present study was to measure absolute concentrations of phosphocreatine (PCr) and adenosine triphosphate (ATP) in normal, hypertrophied, and failing human heart.

BACKGROUND Conflicting evidence exists on the extent of changes of high-energy phosphate metabolites in hypertrophied and failing human heart. Previous reports using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) have quantified metabolites in relative terms only. However, this analysis cannot detect simultaneous reductions.

METHODS Four groups of subjects (n = 10 each), were studied: volunteers and patients with hypertensive heart disease (HHD), aortic stenosis, and dilated cardiomyopathy (DCM). Left ventricular (LV) function and mass were measured by cine magnetic resonance imaging. Absolute and relative concentrations of PCr and ATP were determined by ^{31}P-MRS with spatial localization with optimum pointspread function.

RESULTS Left ventricular ejection fraction remained normal in HHD and aortic stenosis, but was severely reduced to 18% in DCM; LV mass was increased by 55%, 79%, and 68% respectively. In volunteers, PCr and ATP concentrations were 8.82 ± 1.30 mmol/kg wet weight and 5.69 ± 1.02 mmol/kg wet weight, and the PCr/ATP ratio was 1.59 ± 0.33. High-energy phosphate levels were unaltered in HHD. In aortic stenosis, PCr was decreased by 28%, whereas ATP remained constant. In DCM, PCr was reduced by 51%, ATP by 35%, and reduction of the PCr/ATP ratio by 25% was of borderline significance (p = 0.06). Significant correlations were observed among energetic and functional variables, with the closest relations for PCr.

CONCLUSIONS In human heart failure due to DCM, both PCr and ATP are significantly reduced. Ratios of PCr to ATP underestimate changes of high-energy phosphate levels. (J Am Coll Cardiol 2002;40:1267–74) © 2002 by the American College of Cardiology Foundation

In normal myocardium, the concentrations of the high-energy phosphate compounds adenosine triphosphate (ATP) and phosphocreatine (PCr) are tightly controlled over a range of performance, because ATP production by mitochondrial oxidative phosphorylation is closely coupled to ATP utilization by cytosolic adenosine triphosphatases (1). Adenosine triphosphate is the direct energy source for energy-consuming reactions in the cell, while PCr acts as an energy storage compound, and, in addition, as an energy transport molecule in the "creatine kinase-PCr energy shuttle" (2). A number of experimental studies have demonstrated that high-energy phosphate metabolism is deranged in hypertrophied and failing myocardium (see [3,4] for a review). Previous clinical studies using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) to measure PCr/ATP ratios in human myocardium (5–16) have shown that this ratio is reduced in hypertrophied (16) and, even more so, in failing human myocardium (7,9,11). However, the PCr/ATP ratio is only an indirect measure of myocardial energetics, because two mechanisms can independently lead to its reduction (see [4] for review): 1) imbalance of myocardial oxygen supply and demand (i.e., ischemia) (17), and 2) reduction of the total creatine pool, a phenomenon known to occur in heart failure (18,19). Furthermore, simultaneous decreases of both PCr and ATP remain undetected when PCr/ATP ratios are used to estimate the energetic state of the injured heart.

More recently, measurement of absolute concentrations of high-energy phosphate metabolites in human heart has become feasible (20,21). We have previously reported on a new method for absolute quantification of myocardial high-energy phosphate concentrations, ^{31}P-MRS with spatial localization with optimum pointspread function (SLOOP) (22). This method is based on a three-dimensional model that takes into account anatomic compartments determined from segmentation of ^{1}H magnetic resonance images, B_1 field maps, flip angles, and concentration calibrations.

In the present report, we employed the new tool of ^{31}P-SLOOP MRS to measure absolute concentrations of

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Manuscript received December 12, 2001; revised manuscript received May 23, 2002, accepted June 27, 2002.

Abbreviations and Acronyms

ATP = adenosine triphosphate
AVD = aortic valve disease
DCM = dilated cardiomyopathy
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
HHD = hypertensive heart disease
LV = left ventricle/ventricular
MRI = magnetic resonance imaging
NYHA = New York Heart Association
PCr = phosphocreatine
^{31}P-MRS = phosphorus-31 magnetic resonance spectroscopy
SLOOP = spatial localization with optimum pointspread function

myocardial high-energy phosphate metabolites in normal, hypertrophied, and failing myocardium. Our hypothesis was that absolute concentrations of ATP and PCr are reduced in hypertrophied and failing human myocardium and that, therefore, PCr/ATP ratios underestimate the true extent of energetic imbalance. Preliminary accounts of this work have appeared (23,24).

METHODS

Volunteers. The control group consisted of 10 age-matched, healthy volunteers (6 male, 4 female, age range 31 to 83 years, mean 59.2 ± 14.9 years) with no history of heart disease and normal cardiac function as measured by magnetic resonance imaging (MRI). Another group of 4 healthy volunteers (3 female, mean age 27.8 ± 4.3 years) had a repeated examination by MRS to determine intrasubject variability of the MRS measurement method (SLOOP).

Patients. Three evenly sized groups of patients were studied. There were no significant differences for height and weight among the patient groups. Ten patients had hypertensive heart disease (HHD) (7 male, 3 female, age range 39 to 73 years, mean 60 ± 11 years). Inclusion criteria were a history of hypertension for more than two years and a significant (more than two standard deviations above the mean value of the volunteer group) increase of left ventricular (LV) mass, as determined by MRI. Left ventricular ejection fraction (EF) was normal, and none of the patients complained of shortness of breath (New York Heart Association [NYHA] functional class 0). Ten patients had aortic valve stenosis (6 male, 4 female, age range 43 to 82 years, mean 67.6 ± 10.9 years). Inclusion criteria were severe aortic stenosis (aortic valve area <0.70 cm^2) and planned surgical valve replacement. Left ventricular EF in all patients was >40%. Of 10 patients, 3 had mild (grade I) aortic regurgitation. Seven patients were in NYHA functional class II and three patients in NYHA functional class III. Ten patients had dilated cardiomyopathy (DCM) (6 male, 4 female, age range 32 to 68 years, mean 55.3 ± 11.2 years). Inclusion criterion was reduction of LV EF <40%, as determined by cine MRI. One patient was in NYHA functional class II, and nine patients were in NYHA functional class III. Ischemic heart disease was ruled out in all groups by cardiac catheterization.

None of the patients had a pacemaker, a history of metal fragments, implants, or vascular clips, severe arrhythmias, unstable angina pectoris, or claustrophobia. Written, informed consent was obtained from all patients and volunteers after the nature of the examination was fully explained, and the study was approved by the local ethics committee.

MRI. Magnetic resonance imaging was performed on a 1.5-T scanner (Magnetom VISION, Siemens, Erlangen, Germany). Subjects were studied in supine position using a phased-array body coil. Short- and long-axis cine MRI was performed using an electrocardiogram-triggered cine gradient echo two-dimensional sequence. Slice thickness was 8 mm, interslice gap 2 mm, using a breathhold technique in end-expiratory position with a repetition time of 100 ms, an echo delay time of 4.8 ms, and a flip angle of 30°. For functional analysis, all short-axis slices from the base to the apex were analyzed using Argus software, version VB31B (Siemens, Erlangen, Germany) as previously described (25,26). The following parameters were determined: LV end-diastolic volume (EDV) (in ml), LV end-systolic volume (ESV) (in ml), LV EF (in %), and LV mass (in g).

^{31}P-MRS. The ^{31}P-MRS measurements were performed on the same 1.5-T scanner using the SLOOP technique as recently described (22). Briefly, patients were positioned in prone position on a commercially available, double resonant ^{31}P/^{1}H-surface coil to reduce breathing artifacts. For absolute quantification, an external reference containing 20 ml 3.4 M phenyl phosphonic acid was placed below the coil. Anatomic information was obtained acquiring short-axis ^{1}H-images with a two-dimensional gradient echo sequence technique (field of view 400 × 400 mm^2, 30 contiguous slices, slice thickness 8 mm). After an automatic phase-sensitive map-shim, a phosphorus-31 three-dimensional chemical shift imaging sequence was started (double-oblique orientation, field of view 400 × 400 × 320 mm^3, 16 × 16 × 8 phase encoding steps). To increase the signal-to-noise ratio, nuclear Overhauser enhancement was employed (27). Total examination time ranged from 45 to 60 min, depending on the heart rate. A Sun Sparc Station 20 (Sun Microsystems, Grasbrunn, Germany) was used for postprocessing as previously described (22). The short-axis images were manually segmented. Briefly, the SLOOP program was run to reconstruct local spectra, taking into account the B_1-field strength, the flip angle, and standard T_1 values (28). The resonance amplitudes in the local spectra were fitted using the advanced method for accurate, robust, and efficient spectral fitting (29). The amplitude of the resonance of gamma ATP was taken as the value for ATP. In addition, nuclear Overhauser enhancement effects were considered as previously described (23). Owing to the optimal adaptation of voxel shape to anatomic regions, no blood correction was necessary. The localization criterion of

Table 1. LV EDV, ESV, SV, CO, EF, Mass and Heart Rate in Volunteers, Patients with HHD, AVD, and DCM

	VOL	HHD	AVD	DCM
LV EDV (ml)	102 ± 15	117 ± 27	128 ± 39	336 ± 76*
LV ESV (ml)	31 ± 10	39 ± 11	53 ± 30	274 ± 76*
LV SV (ml)	71 ± 8	78 ± 20	74 ± 17	68 ± 18
CO (l/min)	4.9 ± 0.9	5.2 ± 1.4	5.8 ± 1.3	5.2 ± 2.0
LV EF (%)	69 ± 6	67 ± 6	60 ± 11	18 ± 6*
LV mass (g)	140 ± 24	217 ± 68*	250 ± 41*	235 ± 46*
Heart rate (beats/min)	75 ± 14	74 ± 10	81 ± 17	92 ± 15

All data presented as mean ± SD. *$p < 0.01$ control (VOL) versus patient groups (HHD, AVD, DCM).

AVD = aortic valve disease; CO = cardiac output; DCM = dilated cardiomyopathy; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HHD = hypertensive heart disease; LV = left ventricular; SV = stroke volume; VOL = volunteers.

the compartment "LV myocardium" was calculated for contamination from blood or chest wall for every examination as described (22).

Statistics. All data are presented as mean ± SD. For statistical analysis, analysis of variance was used to test for differences among all groups of subjects. Where analysis of variance indicated significant group differences, Scheffé F test was then used to test for differences between individual groups, and a p value of <0.05 was considered statistically significant.

RESULTS

Myocardial function and mass. Left ventricular volumes and mass of volunteers and patients are summarized in Table 1. In volunteers, measurements were in agreement with previously published values (25,26,30). Left ventricular EDV and ESV were unchanged in patients with HHD and aortic valve disease (AVD) but were significantly elevated in DCM (3.3-fold for EDV and 8.8-fold for ESV compared with volunteers). This clearly demonstrates that substantial LV dilation occurred in DCM but not in the other groups of patients. For all groups, stroke volume and cardiac output, studied under resting conditions, were normal, attesting to the fact that all patients were compensated at rest. Left ventricular EF (69 ± 6% in volunteers) was normal in patients with HHD and tended to be reduced in AVD. In DCM, a substantial reduction of EF was found (18 ± 6%), attesting to severe LV dysfunction. Left ventricular mass was significantly increased in all patient groups (by 55%, 79%, and 68% for HHD, AVD, and DCM, respectively), demonstrating the presence of LV concentric (HHD, AVD, unchanged LV volumes) and eccentric (DCM, increased LV volumes) hypertrophy.

Cardiac high-energy phosphate metabolism. Representative ^{31}P-SLOOP MRS spectra are shown in Figure 1. The line width of PCr peaks was comparable in all four groups (data not shown). Figure 2 demonstrates individual and mean values for absolute concentrations of PCr and ATP as well as for PCr/ATP ratios. In volunteers, the PCr concentration was 8.8 ± 1.3 mmol/kg heart weight, ATP was 5.7 ± 1.0 mmol/kg, and PCr/ATP ratios were 1.59 ± 0.33. Intrasubject variability was 4.8% and 7.0% for PCr and ATP, respectively. In patients with HHD, PCr and ATP concentrations as well as PCr/ATP ratios remained at normal levels. In patients with aortic stenosis, PCr concentrations (by 28%; 6.3 ± 1.5 mmol/kg; $p < 0.05$ vs. volunteers) were significantly reduced, whereas PCr/ATP ratios (1.30 ± 0.20) and ATP concentrations (4.9 ± 0.9 mmol/kg) showed a trend for a reduction (by 19% and 14%, respectively). In patients with DCM, a highly significant reduction of PCr concentrations (by 51%; 4.3 ± 1.2; $p < 0.005$ vs. volunteers) was recorded. Furthermore, myocardial ATP concentrations were also found to be significantly reduced, on average by 35% (3.7 ± 0.5 mmol/kg; $p < 0.017$ vs. volunteers). On the other hand, the observed decrease of the PCr/ATP ratio (by 25%) was of borderline statistical significance ($p = 0.06$ vs. volunteers).

Correlations among cardiac function, clinical status, and energetics. Figure 3 shows correlations among functional and energetic variables. Left ventricular EF correlated significantly with PCr, ATP, and PCr/ATP ratios, but the closest relationship was found for PCr and the weakest for PCr/ATP ratios. The same pattern was observed for the correlation of EDV and ESV (PCr: $r = -0.69$, $p < 0.0001$; ATP: $r = -0.56$, $p < 0.001$; PCr/ATP: $r = -0.43$, $p < 0.01$) with the three energetic parameters. The correlations of LV mass and energetic parameters were generally weaker than those of energetics and volumes/EF, with PCr concentrations showing the highest ($r = -0.46$, $p < 0.01$), PCr/ATP intermediate ($r = -0.37$, $p < 0.017$), and ATP the lowest, in fact nonsignificant, correlation ($r = 0.31$, $p = 0.053$). Thus, absolute concentrations showed closer correlations with indices of cardiac dysfunction and dilation than PCr/ATP ratios. Furthermore, LV mass was not a strong predictor of changes in absolute or relative levels of cardiac high-energy phosphates.

For subjects in NYHA functional classes 0 (volunteers and hypertension), II, and III, PCr levels were 8.38 ± 1.54, 6.78 ± 1.11 ($p < 0.05$ NYHA II vs. III), and 4.23 ± 1.01 ($p < 0.05$ NYHA II or III vs. NYHA 0), respectively; ATP levels were 5.63 ± 1.04, 5.03 ± 0.81 ($p < 0.05$ NYHA II vs. III), and 3.58 ± 0.64 ($p < 0.05$ NYHA III vs. NYHA 0), respectively; and PCr/ATP ratios were 1.57± 0.34, 1.36 ± 0.22, and 1.21 ± 0.30 ($p < 0.05$ NYHA III vs. NYHA 0), respectively. Thus, energetic variables also correlated with the clinical status.

DISCUSSION

In the present report, we demonstrate that absolute myocardial concentrations of PCr are reduced in patients with aortic stenosis and that absolute concentrations of both PCr and ATP are decreased in DCM. Furthermore, both PCr and ATP concentrations correlated significantly with LV volumes, EF, and clinical status.

Volunteers. In volunteers, cardiac volumes and masses were all within the range reported previously for larger

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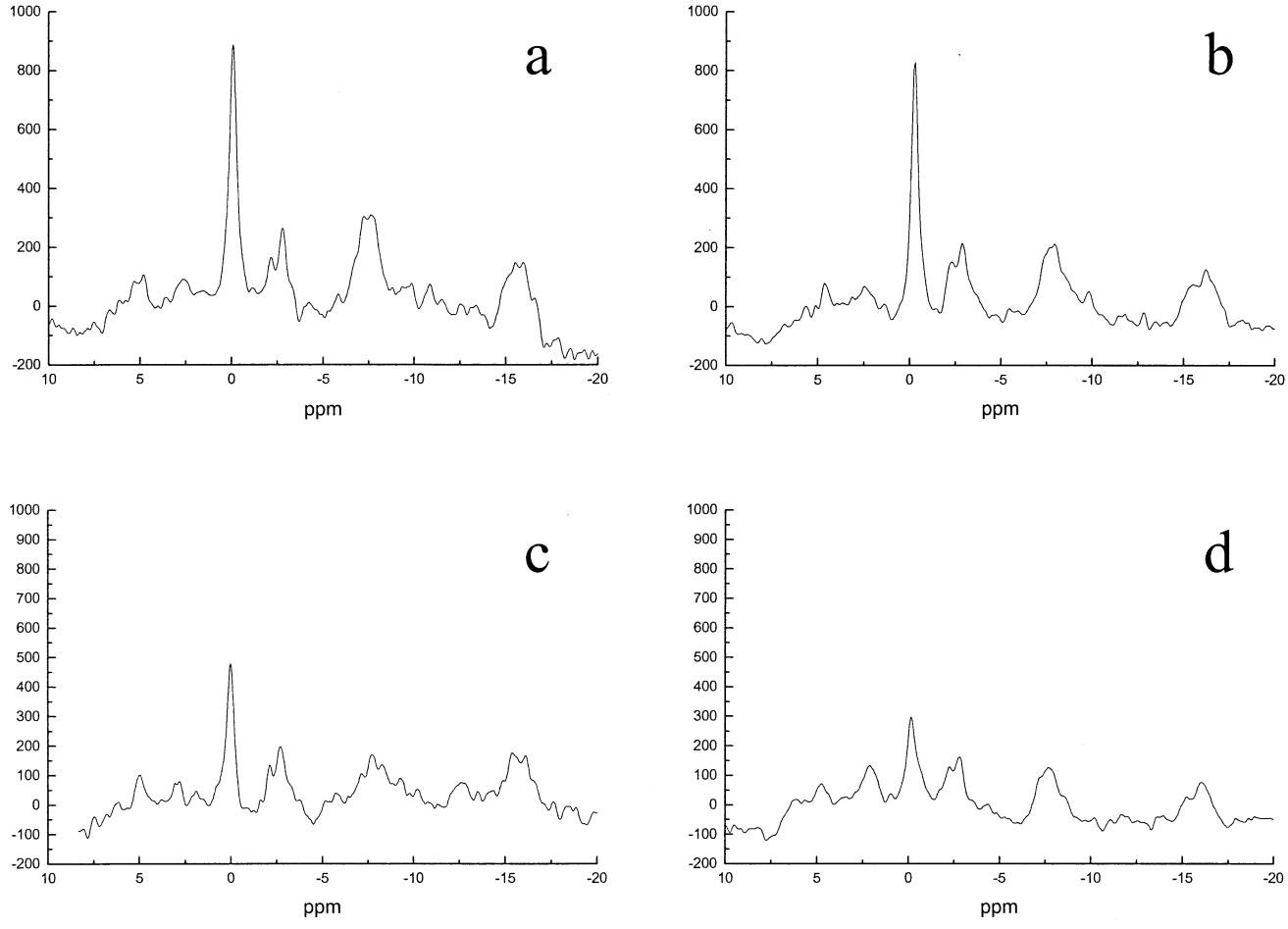

Figure 1. ^{31}P-spatial localization with optimum pointspread function spectra obtained from left ventricular myocardium. **(a)** Healthy volunteer; **(b)** hypertensive heart disease; **(c)** aortic valve disease; **(d)** dilated cardiomyopathy. Concentrations for phosphocreatine (PCr) and adenosintriphosphate (ATP) and PCr/ATP ratios were as follows: **(a)** 9.4, 5.7, 1.65; **(b)** 9.5, 6.0, 1.58; **(c)** 5.9, 4.5, 1.31; **(d)** 2.8, 2.6, 1.08.

groups of normal subjects (25,26). Using SLOOP, we determined the PCr concentration as 8.8 ± 1.3 mmol/kg heart weight and ATP as 5.7 ± 1.0 mmol/kg. Previous MRS studies of volunteers reported PCr values ranging between 7.9 and 13.5 mmol/kg heart weight and ATP values ranging from 4.8 to 8.2 mmol/kg (20–22,31,32). The measurements reported for intrastudy variability using SLOOP here are based on a small volunteer group. Nevertheless, the values reported compare favorably with the only previous report on intrasubject variability using quantitative MRS methods (31) (4% to 7% vs. 18% to 25% for PCr and ATP). The lower variability of PCr values compared with ATP is most likely due to the increased signal-to-noise ratio of PCr amplitudes.

HHD. In the patients with long-standing hypertension, substantial LV hypertrophy was present, as attested to by a 55% increase in myocardial mass, but LV EF and volumes were normal. Previously, Okada et al. (31) reported on eight patients with HHD and, in agreement with our findings, found that PCr/ATP ratios as well as absolute levels of PCr and ATP remained unchanged. On the other hand, Lamb et al. (16) found PCr/ATP ratios in hypertensive patients to be reduced by 14% and 18% both at rest and during exercise, respectively. Whether in human HHD, PCr concentrations remain at normal levels or are slightly reduced, our data indicate that, in human myocardium, significant LV hypertrophy is not always associated with reduced PCr content.

Aortic stenosis. In patients with aortic stenosis, substantial LV hypertrophy was present with a 79% increase in myocardial mass, whereas LV volumes and EF were still unchanged. Phosphocreatine levels were reduced by 28%; ATP levels (−14%) only showed a trend for a reduction. Absolute levels of high-energy phosphates in aortic stenosis have previously been examined using only invasive myocardial biopsy measurements. Here, significant changes of high-energy phosphates as well as of total creatine content have been reported (33–35). In the present study, PCr/ATP ratios (−19%) showed a trend for reduction, which did not reach statistical significance. Previous studies demonstrated reductions of PCr/ATP ratios in patients with AVD. However, patients with more severe, decompensated stages were included in these studies (11,14,36). Using quantitative MRS techniques, analysis of absolute PCr levels allows one to detect significant changes of energy metabolism even

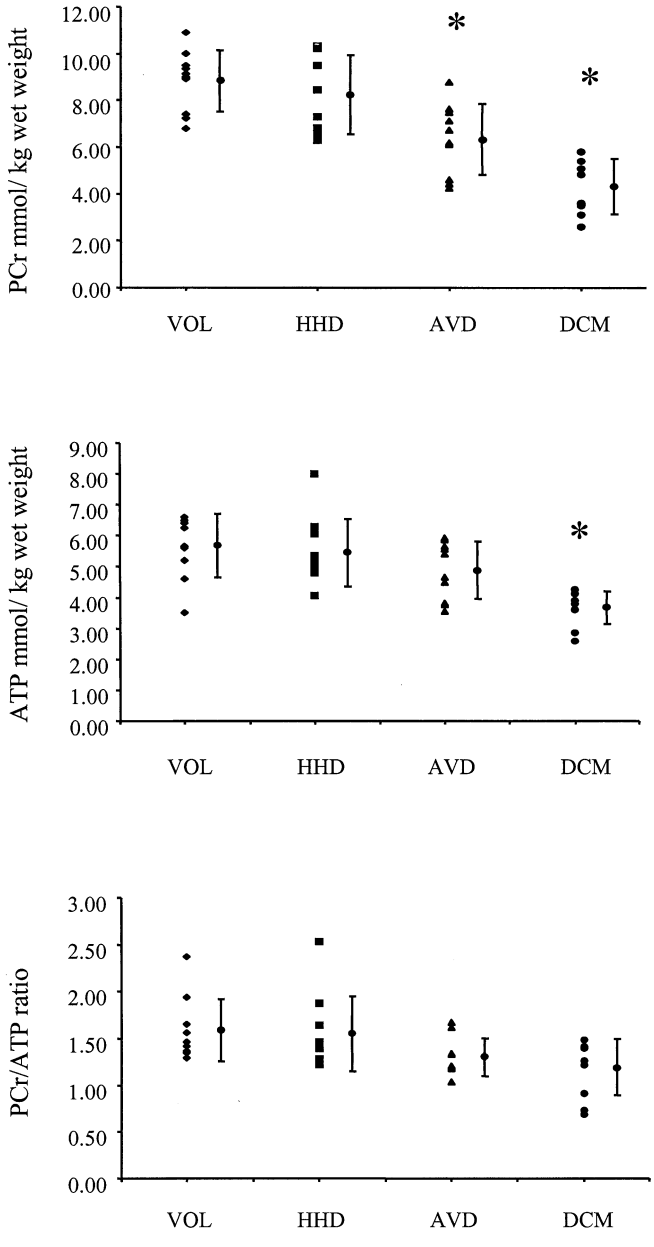

Figure 2. Absolute and relative concentrations of phosphocreatine (PCr) and adenosine triphosphate (ATP) in volunteers (VOL) and in patients with hypertensive heart disease (HHD), aortic valve disease (AVD), and dilated cardiomyopathy (DCM). Individual as well as mean ± SD values are shown for each group. Analysis of variance results were as follows: **PCr**: VOL vs. HHD $p = 0.85$, VOL vs. AVD $p = 0.01$*, VOL vs. DCM $p < 0.000001$*; HHD vs. AVD $p = 0.04$*, HHD vs. DCM $p < 0.00001$*, AVD vs. DCM $p < 0.03$*. **ATP**: VOL vs. HHD $p = 0.96$, VOL vs. AVD $p = 0.29$, VOL vs. DCM $p < 0.0003$*; HHD vs. AVD $p = 0.58$, HHD vs. DCM $p < 0.002$*, AVD vs. DCM $p = 0.052$. **PCr/ATP ratio**: VOL vs. HHD $p = 0.99$, VOL vs. AVD $p = 0.26$, VOL vs. DCM $p = 0.06$, HHD vs. AVD $p = 0.39$, HHD vs. DCM $p = 0.11$, AVD vs. DCM $p = 0.89$.

when LV function is still preserved. It is intriguing, and the reasons remain unclear, why, for a similar extent of myocardial hypertrophy, energetic changes do (aortic stenosis) or do not (HHD) occur in human myocardium, resulting in a poor correlation of LV mass and cardiac energetics. The mechanisms behind these differential responses of human cardiac energetics to different types of myocardial hypertrophy clearly necessitate further study.

Heart failure/DCM. In patients with DCM, severe systolic dysfunction was attested to by a decrease of LV EF to 18 ± 6%, and several-fold increases of LV ESV and EDV, while a 68% increase of LV mass indicated eccentric LV hypertrophy. Previous MRS studies of absolute concentrations in human heart failure are unavailable, but a number of reports have examined high-energy phosphates in biopsies taken from patients with DCM. Nascimben et al. (18) found total creatine levels to be reduced by 51% in agreement with the reduction of PCr levels by 51% in our own observations. Reductions of ATP levels by 39% (35% in our study) have been observed (37). Only one previous study (38) found no change of ATP levels in failing human myocardium, but in that study absolute ATP levels were low for both volunteers and patients. Moreover, Bashore et al. (39) found significant linear correlations between ATP levels and indices of systolic and diastolic function. Experimental studies (40), analyzing changes of high-energy phosphate metabolism during development of heart failure, observed progressive reductions of both ATP (by up to 20%) and total creatine content (by up to 41%). Thus, our data allow us to make two important observations: 1) in severe heart failure due to DCM, absolute ATP concentrations are significantly reduced; and 2) because simultaneous reductions of both ATP and PCr occur, the PCr/ATP ratio, measured by "conventional" MRS, significantly underestimates true changes of PCr concentrations in heart failure, in our study by 26%.

Study limitations. Spatial localization with optimum pointspread function determines high-energy phosphate concentrations in relation to myocardial mass. The biochemically relevant denominator would be total cardiomyocyte volume. Intuitively, it is unlikely, that the observed magnitude of changes of PCr and ATP concentrations in heart failure is due to decreases in cardiomyocyte volume, but unfortunately, current literature data are unavailable on quantification of total cardiomyocyte volume fraction in human cardiac hypertrophy and failure. Previous experimental studies using other MRS methodologies have shown agreement of in vivo MRS and in vitro biopsy measurements. For the SLOOP method, such experimental validation is still outstanding. Importantly, however, the determined values for volunteers are in close agreement with published biopsy measurements (4,22).

Also, one should be aware that thinner myocardial walls may lead to systematically different partial volume effects, in particular in patients with DCM compared with normal volunteers. As SLOOP determines the localization criterion, the maximum contamination by other compartments can be analyzed. When we performed this analysis, no significant differences for contamination by chest wall muscle or chamber blood were found between volunteers and the three patients groups (data not shown). Otherwise the

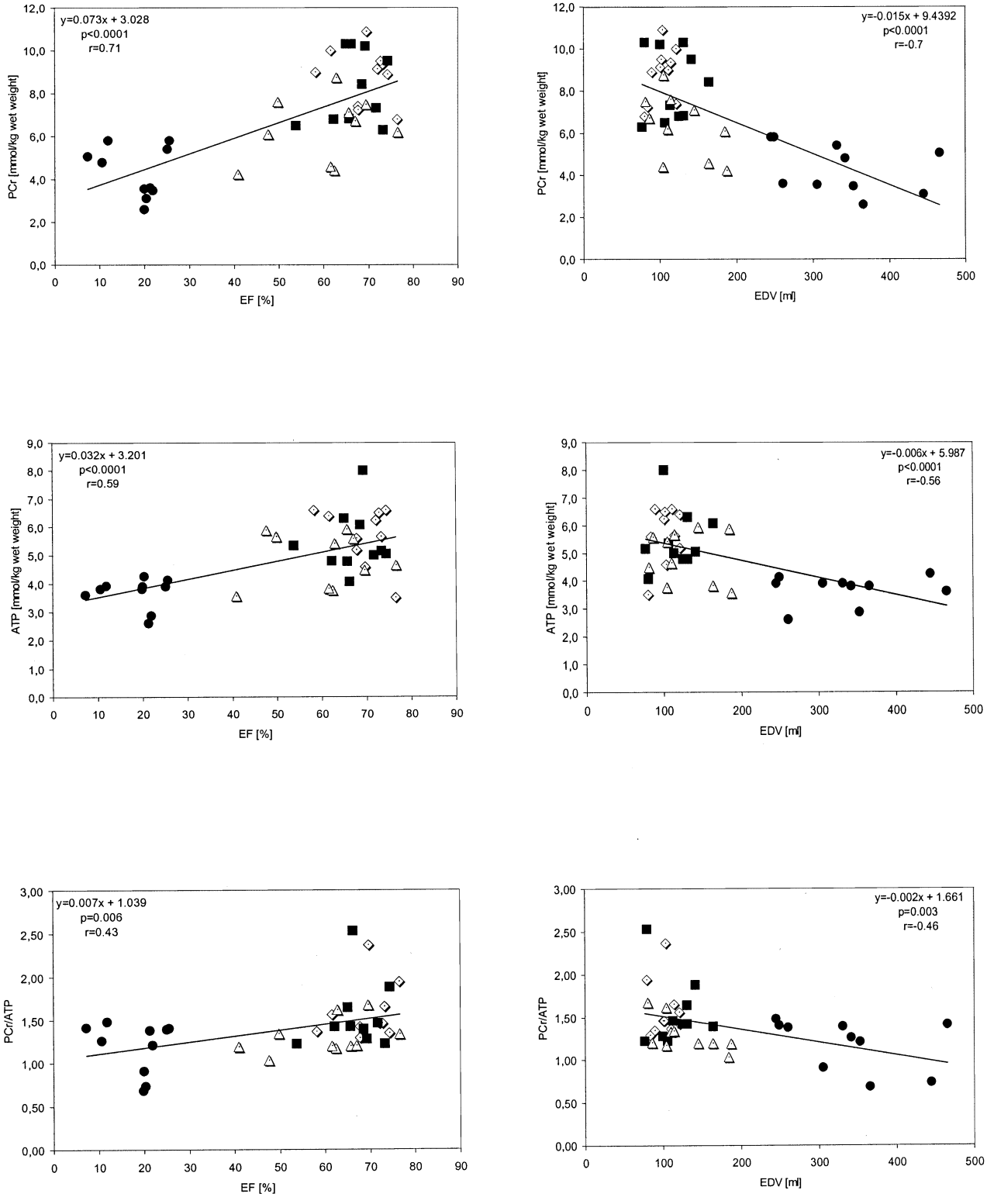

Figure 3. Correlations among functional and metabolic variables in volunteers (VOL) and in patients with hypertensive heart disease (HHD), aortic valve disease (AVD), and dilated cardiomyopathy (DCM). Correlations are shown for phosphocreatine (PCr) concentration and adenosintriphosphate (ATP) concentration, and PCr/ATP ratios with ejection fraction (EF) **(left column)** and end-diastolic volume (EDV) **(right column)**. **Diamonds** = VOL; **squares** = HHD; **triangles** = AVD; **circles** = DCM.

particular phase cancellation properties of the SLOOP reconstruction may slightly alleviate but certainly not circumvent this difficulty. This question cannot be fully assessed until a substantially higher spatial resolution is achievable, for instance at higher magnetic fields.

Although measurement of absolute concentrations of

high-energy phosphate metabolites is a significant step forward, for a complete causal analysis, we must be able to measure ATP turnover rates and calculate free ADP concentrations and the free energy change of ATP hydrolysis (delta G) (4,41,42). Therefore, simultaneous measurement of myocardial total creatine content is required. This may be achievable by a combination of ^{31}P-MRS and ^{1}H-MRS. Such measurements will be the focus of our (43) and other groups' (e.g., 44) future work, and should finally answer the question of the true functional role of myocardial high-energy phosphate metabolism in human heart failure.

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