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ORIGINAL ARTICLE
Metabolism

Decreased High-Energy Phosphate Ratios in the Myocardium of Men with Diabetes Mellitus Type I

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ABSTRACT

Aims/hypothesis: To investigate whether alterations in high-energy phosphates occur in the myocardium of persons with diabetes mellitus type I.

Microvascular abnormalities and dysfunction via thickening of the basement membrane are known to occur in diabetic patients. Myocardial high-energy phosphates have been shown to be reduced by ischemia, and alterations of the cardiac metabolism are the primary consequence of myocardial ischemia.

Methods: The present study involved 34 male patients (mean age 35.5 ± 10.1) with diabetes mellitus type I and 35 healthy male volunteers (mean age 36 ± 8.6) as age-matched controls. Phosphorus-31 magnetic resonance spectroscopic imaging of the heart was performed in all subjects using a 1.5-T whole-body magnetic resonance scanner. The ratios of phosphocreatine (PCr) to β-adenosine-triphosphate (β-ATP) were calculated. Moreover, echocardiographic evaluation and stress tests were performed in all individuals.

Results: The myocardium of patients with diabetes mellitus type I showed significantly decreased ratios of PCr to β-ATP compared with healthy controls in the left ventricle (1.90 ± 0.4 vs. 2.15 ± 0.3, $p < 0.05$*). We found a moderate negative correlation between the ratio of PCr to β-ATP in the left ventricle and both,*

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the diastolic left ventricular function (E/A; $r = -0.41$*) and the glycohemoglobin* A_{1c} *(*$GHbA_{1c}$*;* $r = -0.42$*).*

Conclusion: This study demonstrates for the first time a decreased ratio of PCr to β-ATP in the myocardium of persons with diabetes mellitus type I without a known history of coronary heart disease.

Key Words: *Phosphorus-31 magnetic resonance spectroscopy; Diabetes mellitus type I; Myocardium*

INTRODUCTION

Diabetes mellitus is an independent risk factor for cardiovascular disease (CVD), conferring a risk of two to five times that of nondiabetic individuals. Atherosclerosis accounts for about 80% of all deaths from diabetes, of which three-quarters are from coronary artery disease.[1] Therefore, early diagnosis of diabetic coronary angiopathy and diabetic cardiomyopathy is of major clinical interest.

Various biochemical tests have been proposed to identify diabetic patients at risk. To delineate these biochemical predictors, increasing interest has emerged in the use of noninvasive biophysical measurements of the vasculature. Although noninvasive measurements from different vessels, such as brachial artery flow-mediated dilatation (FMD) or carotid artery intima–media thickness (IMT), may be associated with changes in the coronary vasculature, the pathophysiological mechanisms involved may not mirror the process taking place in coronary vessels.[2] Therefore, the use of techniques that directly deal with the heart are preferred.

Phosphorus-31 magnetic resonance spectroscopic imaging (^{31}P MRSI) permits noninvasive quantification of cardiac high-energy phosphates without requiring external radioactive tracers. The quantification of cardiac high-energy phosphate metabolism is determined by the ratio of phosphocreatine (PCr) to β-adenosine-triphosphate (β-ATP).[3] Normal high-energy PCr metabolism is essential for the physiological function of the cardiac muscle. In earlier studies, Weiss et al. showed a decreased ratio of PCr to β-ATP during exercise stress in patients with severe coronary artery disease,[4] and recently, Buchthal et al. showed a decreased ratio of PCr to β-ATP in patients with no significant CVD.[5] In patients with heart failure and dilated cardiomyopathy, this decreased PCr to β-ATP ratio was evident even at rest.[6,7]

Microvascular abnormalities and dysfunction via thickening of the basal membrane are current features of diabetes mellitus, and alterations of the cardiac metabolism are the primary consequence of myocardial ischemia. Therefore, we used spatially localized ^{31}P MRSI to test the hypothesis that high-energy phosphates, as measured by the cardiac PCr to β-ATP ratio, are altered in patients with diabetes mellitus type I.

METHODS

Patients and Volunteers

The group of patients with diabetes mellitus type I consisted of 34 male patients, 24–56 years old (35.5 ± 10.1, mean ± SD) with a 4–42 years (18 ± 8.7, mean ± SD) history of disease, meeting World Health Organization criteria of diabetes mellitus type I.[8] None of these patients had a history of angina pectoris, previous CVD, or any other severe illness. Other than insulin, no patient took any other medication regularly.

The control group consisted of 35 normal male patients 23–57 years old (36 ± 8.6, mean ± SD), none of whom had any clinical history of heart disease or hypertension, and none receiving any vasoactive or lipid-lowering medication regularly.

There were no significant differences in cigarette smoking habits, consumption of alcohol, or aspirin use between the two groups. People in both groups who had any metal parts in their body, such as cardiac pace makers, wire-cerclages, or metal splinters, were excluded from the study.

All subjects gave informed consent for the study, which was approved by the ethical committee of the medical faculty of the University of Innsbruck.

Biochemical Methods

All laboratory specimens were drawn after a 12-hr fast at 8 AM. Fasting plasma glucose was determined by the glucose oxidase method (Boehringer). Glycohemoglobin A_{1c} ($GHbA_{1c}$) was determined by affinity chromatog-

raphy (Isolab). Serum total cholesterol and triglycerides were assayed by automated enzymatic methods (Boehringer). Serum HDL cholesterol was determined enzymatically after precipitation of LDL and VLDL lipoproteins with dextran sulfate/$MgCl_2$. LDL cholesterol was calculated using the Friedewald formula, as follows: LDL cholesterol = total cholesterol − HDL cholesterol − 0.2 × total triglycerides. All measurements were performed at the Department of Laboratory Medicine of the Innsbruck University, Clinic for Internal Medicine.

Magnetic Resonance Protocol

The magnetic resonance (MR) protocol consisted of cine MR imaging and ^{31}P MR spectroscopic imaging of the heart. The MR measurements were performed using a 1.5-T whole-body MR scanner (Magneton Vision, Siemens Erlangen, Germany) and a circular polarized double resonator surface coil permitting the transmission and the reception of ^{1}H resonances at 63.5 MHz and ^{31}P resonances at 25.8 MHz. The transmitter coil had a diameter of 21 cm, the receiver coil a diameter of 14 cm.

All examinations were performed with patients in a supine position. Both cine MRI and ^{31}P MRSI were acquired using electrocardiographic triggering. Cine MRI was based on a flash sequence with a repetition time (TR) of 60 msec, an echo time (TE) of 6.8 msec, a slice thickness of 8 mm, a field of view (FoV), and a matrix of 256 × 128 and used for a better localization of the voxels. Five transverse slices covered the left ventricle. The cardiac phases were imaged in intervals of 60 msec between two R waves. The number of imaged cardiac phases and, therefore, the acquisition time was dependent on the length of the R–R interval.

For ^{31}P MRSI, we used a transversal 2-dimensional chemical shift imaging sequence with a thickness of 40 mm, a TE of 3 msec, a flip angle of 90°, an FoV of 320 mm. Since the spectroscopic measurement was triggered on ECG, the TR varied from subject to subject in a range from 676 to 1274 msec. Spectroscopic data were collected during 16 acquisitions for each 8 × 8 phase-encoding step with a trigger delay of 100 msec (Fig. 1a). Spectroscopic measurements were enhanced by the nuclear Overhauser effect (NOE), achieved by a Gauss pulse with a length of 5.12 msec.

For the spectral post-processing procedure, the standard software package (LUISE, Siemens, Erlangen, Germany) was applied. After Fourier transformation, Gauss filtering in the time domain, and phase- and baseline-correction of the spectral raw data, the peaks were identified and semiautomatically fitted for the integrals under the curve in the frequency domain. The integrals of PCr, β-adenosinetriphosphate (β-ATP), and 2,3-diphosphoglycerate (2,3-DPG) were determined. Before the inverse Fourier transformation in the two *k*-space directions, raw data were interpolated to a matrix of 32 × 32 by using zero-filling[9] (Fig. 1b). The correction for T1 saturation effects caused by variations in acquisition time due to ECG gating was performed by using the method and the longitudinal T1 relaxation times for PCr (4.28 sec) and β-ATP (2.99 sec) that were previously published by van Dobbenburgh et al.[10] The spectroscopic data were then corrected for NOE enhancement with the help of previously published enhancement factors.[11] The signal intensities of β-ATP were corrected for blood contamination. According to a previous publication, the 3-DPG intensities of 2,3-DPG were used for correction with a blood 3-DPG/β-ATP ratio of 2.38, since the 2-DPG intensities might be contaminated by inorganic phosphate.[10] The anatomical landmarks for positioning were the anterior septum and the adjacent left ventricular (LV) myocardium as shown in Fig. 1a–c. For each subject, a mean PCr to β-ATP value was determined by including two rows of voxels that were derived from the left ventricle and were nearest to the coil. The voxels of the last two rows were excluded from statistical evaluation, since the PCr peak was quite low in these voxels probably due to a low signal-to-noise ratio or substantial blood contamination (Fig. 1c).

Echocardiographic Examination

Each patient and control subject underwent echocardiography using an Acuson ultrasound imaging system (Acuson, Sequoa C256, Mountain View, CA, USA) equipped with a 3.5 MHz-transducer (harmonic imaging). Parasternal long- and short-axis, as well as apical two-, four- and long-axis chamber views, were obtained. Left ventricular volumes and ejection fractions (EF) were measured by the area–length-method (modified Simpsons method). The thickness of the LV posterior wall and interventricular septum were used to calculate the LV muscle mass (Penn-formula).

Left ventricular diastolic filling was evaluated by pulsed Doppler echocardiography by determination of the early (E) to atrial (A) peak ratio.

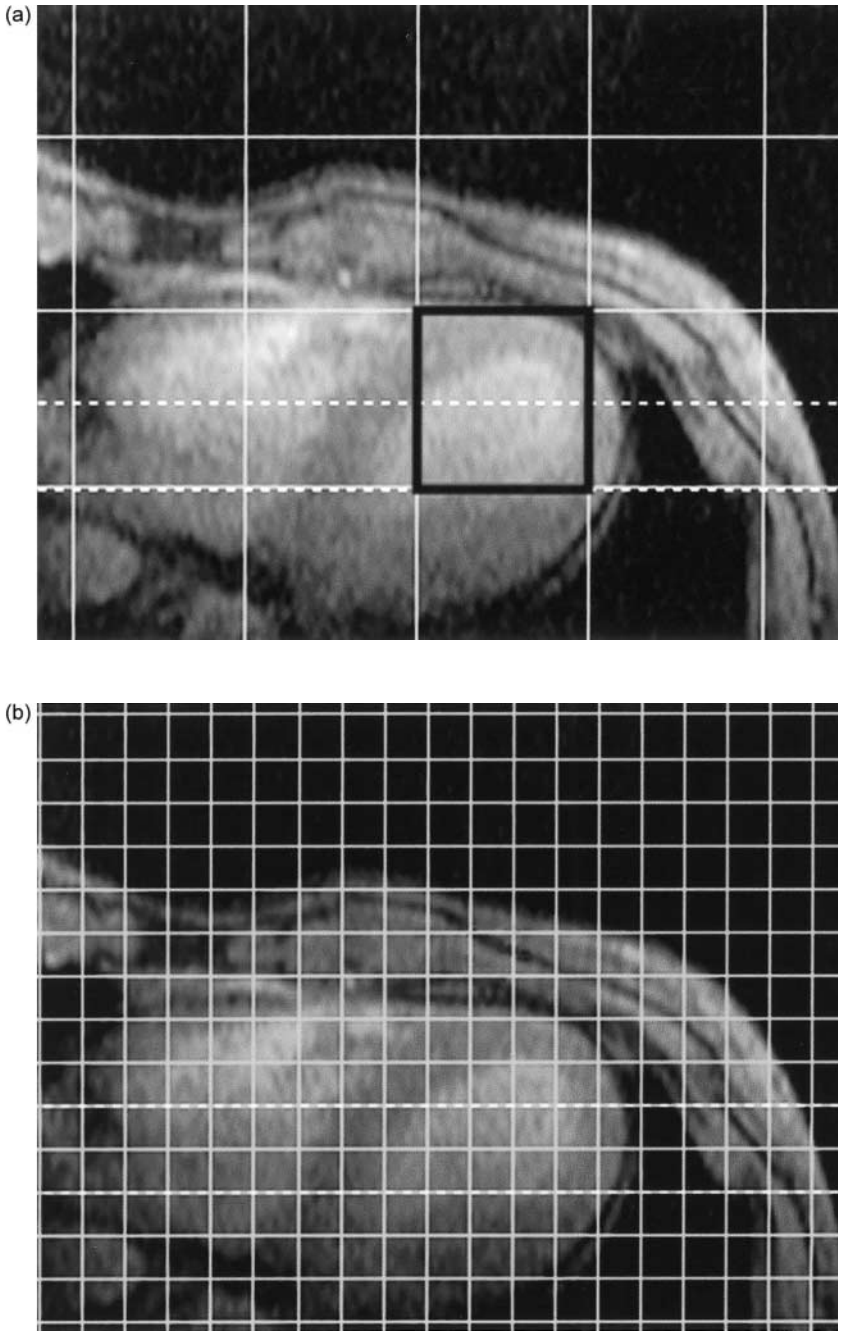

Figure 1. (a) The grid of the ^{31}P MRSI sequence measured with 8×8 phase encoding steps was superposed on the cine MR images in order to accurately determine the origin of the MR spectra. The gray frame indicates the voxel, which was positioned in the left ventricle. (b) The spectral raw data were calculated to a higher spatial resolution (32×32) by using zero-filling. This procedure resulted in a partition of each independently measured voxel in 16 voxels. This means that the voxel positioned in the left ventricle provided 16 spectra as shown in (c). (c) The voxel positioned in the left ventricle was divided into 16 voxels by using zero-filling. In each of the 16 voxels, the PCr to β-ATP ratio was calculated. As demonstrated, the PCr peaks appear quite low in the two last rows. Therefore, the mean PCr to β-ATP ratio of the left ventricle was determined by averaging the two first rows, positioned nearest to the surface coil.

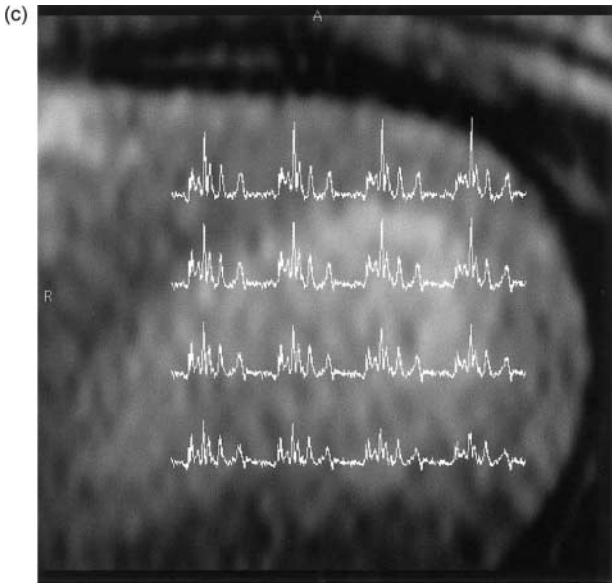

Figure 1. Continued.

Exercise Protocol

A modified Bruce protocol was used on an electrically braked bicycle ergometer.[12] Both standard blood pressure and 12-lead electrocardiographic (ECG) monitoring were performed (Marquette Electronics Inc., Bitz, Germany). Patients were encouraged to exercise until exhausted under physician supervision.

Statistical Analysis

The statistical evaluation was performed by using SPSS 10.0 for windows (SPSS Inc., Chicago, Illinois, USA). Since the Kolgomorov–Smirnov test revealed normal distribution for most of our data, unpaired *t*-tests were used for further evaluation. The significance level was set at $p < 0.05$. The Person test was used for assessment of correlations. A correlation coefficient r ranging from 0.41 to 0.6 was defined as moderate, from 0.61 to 0.8 as good, and from 0.81 to 1 as excellent.

RESULTS

Laboratory Findings and Clinical Characteristics

The clinical characteristics of the diabetic and control subjects are shown in Table 1. No significant differences were seen between the age-matched groups relative to smoking habits, serum cholesterol concentrations, body mass index, or regular sport activities. The fasting glucose levels and the $GHbA_{1c}$ are shown in Table 1. Between $GHbA_{1c}$ and the ratio of PCr to β-ATP, we found a moderate negative correlation ($r = -0.42$). As a

Table 1

Clinical and Demographic Data of the Diabetic and Control Subjects

Patient Characteristics	Diabetes Mellitus Type I ($n = 34$)	Controls ($n = 35$)
Mean age (years) ± SD	35.5 ± 10.1	36 ± 8.6
Duration of diabetes (years)	18 ± 8.7	—
PCr/β-ATP	1.90 ± 0.4*	2.15 ± 0.3
$GHbA_{1c}$ (%)	7.56 ± 1.04*	5.39 ± 0.31
Fasting serum glucose concentration (mg/dL)	153 ± 69*	88 ± 14
Body mass index (kg/m^2)	23.8 ± 2.5	24.1 ± 2.8
No. (%) of smokers	20	24
No. (%) with known CVD family history	26	32
Cholesterol (mg/dL)	190 ± 33	196 ± 38
LDL cholesterol (mg/dL)	100 ± 33*	115 ± 37
HDL cholesterol (mg/dL)	59 ± 13*	30 ± 10
Triglycerides (mg/dL)	93 ± 35*	108 ± 36

*Significant difference between the two groups ($p < 0.05$).

marker for a systemic microvascular disease, we investigated the urinary albumin/creatinine ratio. According to the guidelines, a urinary albumin/creatinine ratio above 30 mg/g suggests that microalbuminuria is probably present. In our study, the mean urinary albumin/creatinine ratio was 12.9 ± 20.8. There was no significant correlation between the urinary albumin/creatinine ratio and the PCr to β-ATP ratio in the myocardium of diabetic patients.

The lipid-profile of both groups is also shown in Table 1. The favorable lipid-profile of the patients with diabetes mellitus type I, i.e., higher HDL, lower LDL, and triglycerides, compared with the healthy controls are consistent with previously described findings.[13]

^{31}P MRSI

Figure 2 shows a representative example of a ^{31}P MR spectrum acquired from a diabetic person (a) and a healthy control person (b). The mean myocardial PCr to β-ATP ratio was significantly decreased in the left ventricle of patients with diabetes mellitus type I. The mean myocardial PCr to β-ATP ratio of diabetics in the left ventricle was 1.90 ± 0.4 vs. 2.15 ± 0.3 in normal volunteers ($p < 0.05$) (Fig. 2a and b).

Echocardiographic Examination

The echocardiographic characteristics of the study population are reported in Table 2. We found significantly decreased EF in the diabetes mellitus type I group (59.4 ± 5.6 vs. 64.7 ± 4.6, $p < 0.001$), and the E/A ratio was also significantly reduced (1.1 ± 0.3 vs. 1.4 ± 0.3, $p < 0.001$). We found a moderate negative correlation between the ratio of PCr to β-ATP in the left ventricle and the E/A ratio ($r = -0.41$). There was no significant difference in the LV mass between both groups (108.1 ± 22 vs. 105.6 ± 16.9, NS).

Exercise Capacity

The results of the exercise test are shown in Table 2. We found a significantly decreased maximal exercise capacity in the diabetes mellitus type I group (112.7% ± 18 vs. 125.1% ± 20, $p < 0.001$). Interestingly, there was no significant difference between the two groups relative to resting heart rate and the resting blood pressure (systolic and diastolic). Also, none of the patients developed significant ST-segment changes or angina pectoris during exercise. There was no correlation between the exercise test tolerance and the PCr/ATP ratio.

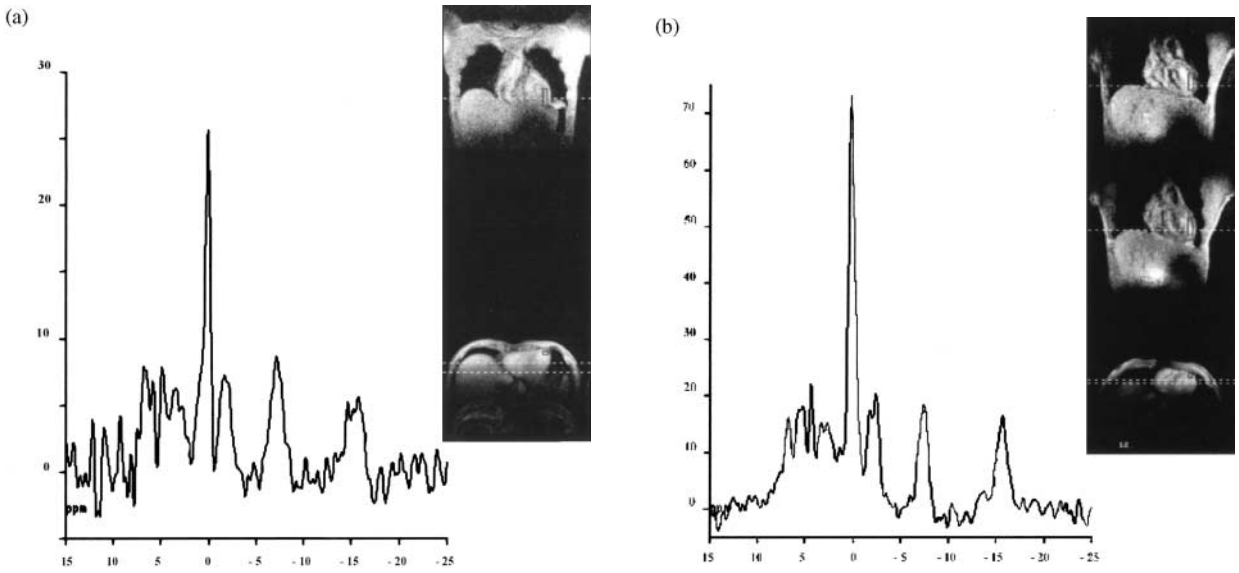

Figure 2. Comparison of selected ^{31}P MRSI-spectra from the myocardium of a representative experiment from the left ventricle of a patient with diabetes mellitus type I (a) and a control person (b). PCr was taken as 0 ppm, the peak of β-ATP is about −15 ppm. The PCr to β-ATP ratios were measured from the integrated areas of the PCr and β-ATP peaks.

Table 2

Endocardiographic and Exercise Test Characteristics

Echocardiographic and Exercise Test Characteristics	Diabetes Mellitus Type I ($n = 34$)	Controls ($n = 35$)
EF (%)	59.4 ± 5.6*	64.7 ± 4.6
LV mass (g/m^2)	108.1 ± 22	105.6 ± 16.9
E/A	1.1 ± 0.3*	1.4 ± 0.3
Resting heart rate (bpm)	81.3 ± 8.6	79 ± 9.2
Resting blood pressure—systolic (mm Hg)	122 ± 14	117 ± 8.5
Resting blood pressure—diastolic (mm Hg)	77.1 ± 15.9	75.5 ± 11.2
Maximum exercise capacity (%)	112.7 ± 18*	125.1 ± 20.2
Significant ST—segment changes	—	—
Angina pectoris	—	—

*Significant difference between the two groups ($p < 0.001$).

DISCUSSION

Diabetic patients are generally at an increased risk for CVD, even under intensive and optimized glycemic control.[14] While in type 2 diabetes, cardiovascular disorders are frequently already present at diagnosis, the cardiologist generally sees the patient with diabetes mellitus type I years after the initial diagnosis. This late cardiologic consultation is surprising because diabetes mellitus is associated with several genetically linked risk factors and reveals a two to four time greater cardiovascular risk for any given classical risk factor.[1] The early identification of patients with diabetes mellitus type I at an increased risk for developing cardiovascular complications is of great clinical importance because not only glycemic control, but also life-style and pharmacological interventions need to be intensified.

^{31}P MRSI is a well-established noninvasive technique in experimental research of regional myocardial ischemia obtained by occlusion of one of the coronary arteries,[15,16] and it permits in vivo monitoring of high-energy phosphate metabolism in the myocardium. Until now, to our knowledge, ^{31}P MRSI has been used to investigate the hearts of patients with severe CVD,[4,17] heart failure,[7] dilated cardiomyopathy,[6,7] hypertensive heart disease,[18] LV hypertrophy,[19] subacute myocardial infarction,[20] and stunned myocardium.[21] In a recent study, Buchthal et al. showed a decreased ratio of PCr to β-ATP in patients with no significant CVD.[5] In all of these studies, the myocardial metabolism was mainly characterized by the ratio of PCr to β-ATP. Neubauer et al. set a cut-off for the PCr to β-ATP in patients with dilated cardiomyopathy at 1.6 which discriminated patients with high and low mortality.[22]

In our study, the PCr to β-ATP values of patients with diabetes and healthy volunteers were in the same range as recently published for healthy volunteers.[22–24] According to previous studies, our spectroscopic data were corrected for partial saturation effects, NOE enhancement, and blood contamination.[23] In contrast to all previous cardiac ^{31}P MRS studies, we used Fourier interpolation for the spectroscopic data, which appears a useful tool improving quantitative evaluation of MRSI, signal-to-noise ratio, and acquisition time.[9] If using FOI, less phase encoding steps are required. This means a dramatic (almost four times) reduction in the measurement time. Therefore, FOI helps to examine more patients and also critical patients. Nevertheless, we detected a statistically significant difference in cardiac high-energy phosphate metabolism between our groups. The patients with diabetes exhibited decreased PCr to β-ATP ratios in the left ventricle that may indicate commencing pathologic alterations of cardiac metabolism.

Our data show, for the first time, a decreased PCr to β-ATP ratio in the myocardium of patients with an increased risk for CVD, but no known clinically manifest CVD. Corresponding to our spectroscopic data, we observed a significantly decreased E/A-ratio in patients with diabetes mellitus type I compared with normal persons. These observations are in context with the echocardiographic data from Jermendy et al., showing diastolic disorders in diabetic patients without heart disease and clinical symptoms.[25]

In principle, our results might be explained on one hand by diabetic angiopathy (micro- and/or macroangiopathy) and, on the other, by the glycosylation of

myocardial proteins or interstitial fibrosis leading to diabetic cardiomyopathy. It is also likely that the combination of these factors is responsible for the reduced high-energy phosphates. It is still not known whether a parallel reduction in both PCr and ATP concentrations (although at different rates) leads to the decreased PCr to β-ATP ratio in men with diabetes mellitus type I, or whether the depletion of PCr is primarily responsible for this altered PCr to β-ATP ratio. The second assumption is supported by data from Farrall et al.,[26] who showed that PCr is very responsive to metabolic changes during ischemia. Moreover, it is remarkable that our diabetic patients received an early insulin therapy and were under intensive glycemic control as indicated by the $GHbA_{1c}$ values (Table 1). We suppose that our findings would be more pronounced in diabetic patients with a poor glycemic control. This suggestion is supported by the moderate negative correlation between left ventricle PCr to β-ATP values and $GHbA_{1c}$ detected in our study.

Our observations also raise the question of whether alterations of the cardiac high-energy metabolism in patients with diabetes mellitus type I are related to reduced myocardial glucose utilization or reduced insulin stimulation of metabolic pathways regulating general tissue glucose utilization, including the myocardium. Until now, myocardial glucose utilization has mainly been assessed by 2-fluoro-2-desoxy-D-glucose (FDG) and positron emission tomography (PET).[27–29]

Previously published data regarding ^{31}P MRSI and CVD or heart failure support our results, since it is known that both microvascular abnormalities and dysfunction via thickening of the basal membrane and diabetic cardiomyopathy in the absence of discernable coronary artery disease occur in diabetic patients.[30] Further, it is known that the prevalence of asymptomatic myocardial ischemia is higher in diabetics.[31] Also, the recent study from Abaci et al.[32] suggesting that coronary collateral vessel development is diminished in patients with diabetes supports our findings of reduced high-energy phosphates in diabetic patients. Pitkaenen et al.[33] showed that the coronary flow reserve is reduced in young men with diabetes mellitus type I, and Nitenberg et al.[34] additionally demonstrated impaired endothelium-dependent coronary vasodilatation during papaverine and acetylcholine infusion in patients with diabetes mellitus type I and angiographically normal coronary arteries.

In normal human myocardium, metabolism under resting conditions is primarily oxidative and depends on various substrates such as free fatty acids (FFA), glucose, lactate, pyruvate, and ketones. The hormonal factors that regulate myocardial substrate utilization are complex and depend on substrate intake and integrity of feedback mechanisms regulating hormone release.[35] A decrease in glucose oxidation was shown to be associated with an increase in the myocardial PCr/β-ATP ratio.[36] Vom Dahl et al.[29] showed that in young patients with diabetes mellitus type I, metabolic standardization and supplementation with insulin during an insulin–glucose clamp is associated with myocardial glucose uptake similar to that observed in the normal heart. In contrast to the skeletal muscle, where experimental data showed that glucose transport is rate-limiting at physiological glucose concentrations,[37] in the heart studies suggest that glucose phosphorylation is rate-limiting for glucose uptake.[38] In summary, PET studies in diabetic patients demonstrate that myocardial glucose uptake is normalized by insulin therapy under conditions of euglycemia. However, under metabolic conditions comparable to those in poorly controlled patients with diabetes mellitus, PET studies indicate deregulation of myocardial glucose metabolism that could contribute to chronic LV dysfunction and other adverse cardiovascular events.[39]

In our study, we must address an important limitation. It is known that chemical shift imaging techniques are confounded by the so-called "voxel bleeding," meaning a signal contamination from adjacent voxels.[17] In order to minimize voxel bleeding and to avoid signal contribution from the thoracic muscle, volunteers were examined in supine position in order to create a small gap between the myocardium and the chest wall. Moreover, skeletal muscle is characterized by PCr to β-ATP ratios of about 5–6. Our LV PCr to β-ATP ratios are clearly lower compared to skeletal muscle and in line with previously published cardiac PCr to β-ATP ratios.[22–24] In contrast to previous one-dimensional cardiac ^{31}P MRSI studies, we used a transversal MRSI slab with a thickness of 40 mm.[40] Consequently, we might have minimized the signal contribution from the liver.

In conclusion, the present data suggest that ^{31}P MRSI makes it possible to detect in vivo decreased ratios of PCr to β-ATP in the myocardium of diabetic men without any known history of CVD, even when they are under intensive glycemic control. As a noninvasive method for investigating the myocardial high-energy phosphate metabolism, ^{31}P MRSI may be a suitable method to control the course of diabetic coronary angiopathy and cardiomyopathy. Further studies must be performed to validate the use of heart ^{31}P MRSI with other, routinely

used, techniques. Moreover, a larger study investigating the time course of the myocardial ratio of PCr to β-ATP as a function of the duration of diabetes mellitus type I, should be undertaken.

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