Heart Failure

Relationship Between Coronary Microvascular Dysfunction and Cardiac Energetics Impairment in Type 1 Diabetes Mellitus

G. Nallur Shivu, MRCP; T.T. Phan, MRCP; K. Abozguia, MRCP; I. Ahmed, MRCP; A. Wagenmakers, PhD; A. Henning, PhD; P. Narendran, MRCP, PhD; M. Stevens, MD; M. Frenneaux, MD, FRCP

Background—Asymptomatic subjects with diabetes mellitus have an impaired cardiac energetics status that may play a significant role in the development of heart failure. In the present study, we assessed the role of microvascular dysfunction in the development of impaired cardiac energetics in subjects with type 1 diabetes mellitus.

Methods and Results—Twenty-five asymptomatic subjects with type 1 diabetes mellitus (mean age ±1 SD 33±8 years) and 26 age-, sex-, and body mass index–matched healthy control subjects (32±8 years old) were recruited into the study. The type 1 diabetes mellitus subjects were divided into 2 age-matched groups (newly diagnosed [<5 years] and longer-duration [≥10 years] diabetes) to assess the impact of microvascular disease. All subjects had an echocardiogram and an exercise ECG performed, followed by magnetic resonance spectroscopy and stress magnetic resonance imaging.

Compared with healthy control subjects, the phosphocreatine/γ-ATP ratio was reduced significantly both in subjects with longer-term (2.1±0.5 versus 1.5±0.4, P<0.000) and newly diagnosed (2.1±0.5 versus 1.6±0.2, P<0.000) diabetes. The phosphocreatine/γ-ATP ratio was similar in newly diagnosed diabetes subjects and those with longer-term disease (1.6±0.2 versus 1.5±0.4, P=0.32). The mean myocardial perfusion reserve index in the longer-term type 1 diabetes mellitus subjects was significantly lower than in healthy control subjects (1.7±0.6 versus 2.3±0.4, P=0.005). On univariate analysis, there was no significant correlation of phosphocreatine/γ-ATP ratio with myocardial perfusion reserve index (r=0.21, P=0.26).

Conclusions—We demonstrate that young subjects with uncomplicated type 1 diabetes mellitus have impaired myocardial energetics irrespective of the duration of diabetes and that the impaired cardiac energetics status is independent of coronary microvascular function. We postulate that impairment of cardiac energetics in these subjects primarily results from metabolic dysfunction rather than microvascular impairment. (Circulation. 2010;121:1209-1215.)

Key Words: diabetes mellitus ■ cardiomyopathy ■ spectroscopy ■ magnetic resonance imaging

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and dyslipidemia. The prevalence of diabetes is increasing rapidly throughout the Western world.1-3 Heart failure occurs more frequently in diabetes4 and is commonly due to epicardial coronary artery disease (CAD), hypertension, or both.5-7 There is a markedly increased mortality associated with CAD and heart failure in patients with type 1 diabetes mellitus (T1DM).8 However, in some patients, left ventricular (LV) dysfunction occurs in the absence of significant epicardial CAD or hypertension.9 This indicates that diabetes mellitus may have a direct effect on the heart that can contribute to the development of LV dysfunction. The impact of diabetes mellitus on the heart can occur via various mechanisms, including unrecognized hypertension, large- and small-vessel microvascular disease, energetics impairment, autonomic neuropathy, and oxidant stress. Asymptomatic subjects with type 2 diabetes mellitus have impaired cardiac energetics status, as reflected in a reduced phosphocreatine/γ-ATP ratio on cardiac magnetic resonance spectroscopy (MRS).10 Impairment of cardiac energetics status potentially plays a significant role in the development of contractile dysfunction. Although microvascular ischemia potentially may contribute to impairment of energetics, a primary disturbance of energetics status unrelated to ischemia and due to the metabolic effects of diabetes is also likely.

Clinical Perspective on p 1215

The primary aim of the present study was to confirm the presence of cardiac energetics impairment in uncomplicated T1DM and to establish its relationship to coronary
microvascular dysfunction. For this purpose, we recruited a cohort of healthy young T1DM subjects with no history of hypertension, primary hyperlipidemia, renal disease, or coronary heart disease. To tease out the potential pathophysiological mechanisms in the development of cardiac energetics impairment, we studied 2 age-matched groups of T1DM subjects. The first group (newly diagnosed with T1DM) had been diagnosed for less than 5 years and hence were unlikely to have microvascular disease; the second group (longer-term T1DM) had been diagnosed for more than 10 years and were thus likely to have a certain degree of microvascular dysfunction. We used MRS to determine cardiac energetics status and used stress magnetic resonance imaging (MRI) to compute the myocardial perfusion reserve index (MPRI), which is a measure of coronary microvascular function.

**Methods**

Fifty-one subjects who met the inclusion criteria and provided informed consent were recruited from the Heart of England NHS Foundation Trust and University Hospital Birmingham NHS Trust, Birmingham, United Kingdom. Healthy control subjects (HCs) were recruited by general advertisements at the University of Birmingham and through blood banks. All investigations were undertaken at the University of Birmingham, and the project was approved by the Multicenter Regional Ethics Committee in Birmingham. Data on LV torsion in these subjects have been published by our group previously.11

**Subjects**

We recruited 26 subjects with T1DM (according to the World Health Organization definition) without a history of chest pain or breathlessness; 1 subject dropped out of the study. All patients had no evidence of coronary heart disease or heart failure on the basis of history, 12-lead ECG, a normal ejection fraction on echocardiography, and metabolic exercise testing. Subjects were divided into predefined age-matched subgroups based on duration of their diabetes, as defined above: Those who were newly diagnosed (10 subjects, age 32±10 years) and those with longer-term disease (15 subjects, age 33±6 years).

**Healthy Control Subjects**

Twenty-six age-, sex-, and body mass index–matched control subjects with no cardiac history or diabetes mellitus were recruited. All HCs underwent a normal 12-lead ECG, echocardiogram, and metabolic exercise test. Subjects fasted overnight, and blood samples were taken on the morning of the study. After this, a light breakfast was given, and patients were allowed to take their morning dose of insulin. Subjects then underwent cardiac MRI/MRS, echocardiography, and exercise ECG. Stress MRI was performed only in a subgroup of HCs (8 subjects).

**Echocardiography**

Echocardiography was performed with participants in the left lateral decubitus position with a Vivid 7 (GE Healthcare, Waukesha, Wis) echocardiographic machine and a 2.5-MHz transducer. Standard echocardiographic views were obtained from parasternal and apical windows. The ejection fraction was calculated with the Simpson rule.12

**Metabolic Exercise Testing**

Subjects underwent a symptom-limited erect treadmill exercise testing with a standard ramp protocol with simultaneous respiratory gas analysis on a Schiller CS-200 Ergo-Spiro exercise machine. Peak oxygen consumption (VO_2max) was defined as the highest value of oxygen consumption measured during the exercise period. Blood pressure and ECG were monitored throughout testing. Subjects were encouraged to exercise to exhaustion with a minimal requirement of a respiratory exchange ratio >1.

**31P Cardiac MRS**

In vivo myocardial energetics status was measured with a Philips Achieva 3T scanner (Philips Healthcare, Best, the Netherlands), as previously validated and described by our group.13 A linearly polarized transmit-and-receive 31P coil with a diameter of 14 cm was used. MRS was performed with the image-selected in vivo spectroscopy method. The size of voxel of acquisition was kept constant at 89.54 mL (44×55×37 mm^3) so that comparisons could be made between different subjects. The repetition time was 10 000 ms with 136 averages and 512 samples. Acquisition was ECG gated, and the trigger delay was measured by subtracting 250 to 300 from the total length of the cardiac cycle, which left 250 to 300 ms of the cardiac cycle for spectral acquisition (acquisition time was 170 ms). Total scan time was 23 minutes.

**Stress MRI**

Cardiac MRI was performed on a 3T Philips Achieva MRI scanner with a dedicated SENSE cardiac coil (Philips). The subject was positioned in the scanner with the heart at the isocenter of the magnet. Survey images were obtained, followed by first-pass images after gadolinium contrast injection (0.1 mL/kg body weight, 4 mL/s). For perfusion images, a single-shot turbo field echo SENSE pulse sequence was used with 3 slices per heart beat. Slice thickness was 8 mm, with a gap of 12 mm between slices. The field of view was 400 mm with a matrix of 152×109. Repetition time was 3.5 ms with an echo time of 1.05 ms. The LV was imaged by tracking the entry of contrast first into the right ventricle and then the LV cavity, followed by illumination of the LV myocardium as the contrast passed through the coronary arterial tree (Figure 1). After a gap of 20 minutes to allow the contrast to be eliminated completely from the myocardium, adenosine infusion was started at a rate of 140 mg·kg⁻¹·min⁻¹. At 3 minutes of infusion, stress first-pass images were obtained after injection of further gadolinium contrast (0.1 mL/kg) in a similar fashion and at the same short-axis levels. The ECG was monitored continuously and blood pressure recorded every minute during the stress scan.

**Analysis**

**Magnetic Resonance Spectroscopy**

Spectra were analyzed and quantified on jMRUI software with AMARES, a time-domain–fitting program.14 Postprocessing was performed with 15-Hz gaussian line broadening and Fourier transformation. Phase correction was performed with phosphocreatine (PCr) peak as the reference peak. Quantification was performed with AMARES with the use of a prior knowledge file to preselect the peaks. Concentrations of PCr, ATP, and 2,3-diphosphoglycerate were calculated as the area under the peaks. PCr/ATP ratio was determined after the ATP peak was corrected for blood contamination as described previously.15 We have previously published the reproducibility data in HC subjects.13 The MRS was repeated twice in 5 patients with diabetes mellitus to test the variability of the PCr/ATP ratio. Bland-Altman plots demonstrated a variability of 0.13±0.28 (bias ±1.96 SD) with a mean PCr/ATP ratio of 1.6 and 1.5. The quality (signal-to-noise ratio) of spectra in all subjects was further assessed by Cramer-Rao lower bounds (expressed as mean±SD).13,17 The lower bounds were 8±4% for PCr peak and 11±4% for the γ-ATP peak in the control population and 8±2% for PCr peak and 11±3% for the γ-ATP peak in the patient population. These figures indicate that the spectra were of good quality and suggest good reproducibility of PCr/ATP ratios in both HC subjects and patients in the present study.
Myocardial Perfusion Reserve Index

The MPRI, which is a measure of coronary microvascular function, was computed from the stress MRI images. The images were analyzed on ViewForum software version 5.0 (Philips). Initially, image alignment was performed to reduce the motion of the heart in different cardiac cycles. Next, the endocardial and epicardial borders were traced and propagated throughout all the images. A sample volume was placed in the LV cavity as a comparison for signal intensity of blood. Signal-intensity curves were obtained from the software, and the peak upslope of the LV myocardial illumination was computed in relation to the LV cavity illumination. A similar analysis was performed on all 3 short-axis images at rest and peak stress. The MPRI was obtained from the ratio of LV relative peak upslope at stress compared with rest.

Statistical Analysis

The main aim of the present study was to assess the impact of microvascular disease on the development of impaired cardiac energetics in patients with T1DM. Continuous variables are expressed as mean±SD. We used generalized estimating equations (independent working correlation matrix structure) with age, sex, body mass index, and subgroups as covariates to determine the statistical difference between means. P<0.05 was considered to indicate statistical significance. Variances of data sets were determined with an F test. Pearson correlation coefficient (r) was used to describe the relationship between variables. SPSS (version 15.0; SPSS Inc, Chicago, Ill) was used to perform the statistical operations.

Results

Baseline characteristics and results are summarized in Table 1. LV ejection fraction was similar in the longer-term diabetes subjects, newly diagnosed subjects, and HC subjects. All of the diastolic parameters listed in Table 1 (E/A ratio, isovolumic relaxation time, and E/E') were within the normal range, with no statistical difference between subject groups.

Magnetic Resonance Spectroscopy

Typical cardiac spectra in T1DM subjects and HCs are shown in Figure 2. The PCr/γ-ATP ratio was reduced significantly compared with HCs in both longer-term and newly diagnosed diabetes mellitus (Table 1). The PCr/γ-ATP ratio was similar in those with newly diagnosed diabetes and those with longer-term diabetes mellitus (Table 1). When the subject groups were divided by retinopathy status (obtained by use of retinal photography), subjects with retinopathy (9 with background retinopathy, 2 with proliferative retinopathy, and 2 with maculopathy) had similar PCr/γ-ATP ratios as those without retinopathy (Table 2).

Myocardial Perfusion Reserve Index

Mean MPRI in the longer-term T1DM group was significantly lower than in HCs (Table 1). MPRI in newly diagnosed T1DM subjects was nonsignificantly higher than in those with longer-term diabetes (Table 1). When the subject groups were divided into those with and without coronary microvascular dysfunction (MPRI of 1.5 was considered the lower limit of normal, which was 2 SDs below the mean for HCs), patients with and without coronary microvascular dysfunction had similar PCr/γ-ATP ratios (Table 2). Moreover, those with and without coronary microvascular dysfunction had significantly lower PCr/γ-ATP ratios than HCs (Table 2).

Correlation

There was no significant correlation of PCr/γ-ATP ratio with MPRI (r=0.21, \( P=0.26 \)), hemoglobin A1c (r=−0.27, \( P<0.05 \)), free fatty acids (FFAs; \( r=−0.11, P=0.45 \)), or triglycerides (r=0.09, \( P=0.54 \)).

Discussion

In the present study, we have shown that cardiac energetics as determined by PCr/γ-ATP ratio are reduced in young subjects with uncomplicated T1DM in the absence of ischemic heart disease, irrespective of the duration of diabetes or the presence of coronary microvascular dysfunction or other microvascular disease (retinopathy or nephropathy). Cardiac energetics did not correlate with coronary microvascular dysfunction, which suggests a primary metabolic role in the development of impaired energetics in these individuals.
Previous studies have demonstrated altered cardiac energetics in asymptomatic T1DM patients and patients with type 2 diabetes mellitus. The present findings confirm those results. However, in the present study, we have extended those findings by exploring the potential pathophysiology of this deficit. Subjects were characterized for the presence of macrovascular and microvascular disease by exercise testing and stress MRI.

![Typical spectra in T1DM](Typical_spectra_in_T1DM.png)

![Typical spectra in HC](Typical_spectra_in_HC.png)

**Figure 2.** Typical spectra in T1DM and HC. 2,3-DPG indicates 2,3-diphosphoglycerate.
It has been demonstrated previously that impaired cardiac energetics plays a key pathophysiological role in the development of heart failure and that the energetic abnormality usually precedes the onset of contractile dysfunction. However, the key underlying mechanisms for this energetic impairment are not well known. Diabetes mellitus is associated with decreased glucose transport, glycolysis, and oxidation. The reduced uptake of glucose via GLUT4 receptors decreases the availability of glucose in the myocardium. In normal hearts, 60% to 90% of the energy is derived from fatty acid oxidation. In diabetes mellitus, this can increase to 90% to 100%. The increased utilization of FFAs to generate energy is demonstrated in positron emission tomography studies. Increased FFA uptake results in lipid accumulation in the subjects with diabetes mellitus (0.3 ± 0.18 versus 0.23 ± 0.11 mmol/L, P = 0.07). This increased FFA in the plasma coupled with increased FFA uptake could be an important factor resulting in impairment of cardiac energetics. In addition, FFAs are increased in newly diagnosed subjects, which may explain the reduced PCr/γ-ATP ratio in these individuals.

The increased FFA uptake results in lipid accumulation in spite of increased FFA oxidation. Lipid accumulation can worsen myocardial insulin resistance, which in turn worsens glucose uptake. Furthermore, increased FFA oxidation produces more reactive oxygen species, which can oxidize lipids and proteins, resulting in cell damage. Reactive oxygen species impair mitochondrial coupling, which results in a decrease in ATP production.

Myocardial energetics impairment might also occur secondary to ischemia caused by microvascular disease. It is well known that development of microvascular disease is directly related to diabetes duration and glycemic control in T1DM. Indeed, the longer-term T1DM subjects in the present study had a lower MPRI than the newly diagnosed subjects or HCs. MPRI is a good indicator of coronary microvascular function. The present study demonstrates a lack of association between coronary microvascular dysfunction and energetics impairment. Moreover, cardiac energetics impairment was present even in the newly diagnosed diabetes patients (although to a slightly lesser degree), which implicates metabolic impairment as the probable important mechanism. Hence, microvascular disease did not appear to account for the development of cardiac energetics impairment in diabetes.

Previous studies in type 2 diabetes mellitus have demonstrated that impaired cardiac energetics could contribute to the development of diastolic dysfunction in these subjects. In the present study, we demonstrated that cardiac energetics impairment was present even in newly diagnosed diabetes patients. This substantiates the fact that energetics impairment precedes the onset of contractile dysfunction, as shown in previous animal studies.

Interestingly, we found that there was a significantly lower VO2max in the longer-term T1DM subjects than in the newly diagnosed T1DM subjects and HCs. Previous studies have shown that reduced exercise capacity in type 2 diabetes mellitus is related to subclinical LV dysfunction, diabetes control, and heart rate recovery. In the present study, most of the T1DM subjects had impaired cardiac energetics; however, myocardial perfusion was impaired only in the subjects with longer-term diabetes mellitus. It is therefore tempting to speculate that a combination of energetics and perfusion abnormalities could have resulted in reduced VO2max in the longer-term T1DM subjects. Skeletal muscle perfusion abnormalities could also contribute to the reduced exercise capacity, although this was not measured in the present study.

**Clinical Implications**

Development of heart failure in diabetes is a complex mechanism and is affected by many secondary factors, such as hypertension, CAD, renal disease, and hyperlipidemia. In the present study, we have demonstrated cardiac energetics impairment in uncomplicated diabetes, proving that diabetes has a direct effect on the myocardium. This impairment occurs early in the disease process, and intervention at this stage to improve myocardial energetics status may be an important method of reducing cardiovascular complications. Metabolic modulation has assumed importance recently in the management of patients with CAD and heart failure. Because subjects with diabetes have a metabolic profile similar to these patients, meta-

---

**Table 2. Cardiac Energetics in Subgroups of Subjects With Various Complications**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complications Absent (n)</th>
<th>Complications Present (n)</th>
<th>HC (n)</th>
<th>P*</th>
<th>P†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCr/γ-ATP ratio</td>
<td>1.6 ± 0.4 (12)</td>
<td>1.4 ± 0.4 (13)</td>
<td>2.1 ± 0.5 (26)</td>
<td>0.001</td>
<td>&lt;0.000</td>
<td>0.143</td>
</tr>
<tr>
<td>MPRI</td>
<td></td>
<td></td>
<td>2.1 ± 0.5 (26)</td>
<td></td>
<td>&lt;0.000</td>
<td>0.184</td>
</tr>
</tbody>
</table>

*Comparison between HCs and complications absent.
†Comparison between HCs and complications present.
‡Comparison between complications absent and present.
bolic agents could potentially be used to prevent heart failure in diabetes; however, large-scale studies are required to substantiate this. Alternatively, intensive metabolic control early in T1DM can achieve long-term benefits in reducing cardiovascular complications.36

Study Limitations
The principal limitation of the study was the small sample size of the study population. Additionally, this was a cross-sectional study, which therefore yields no information on the ultimate outcome of these subclinical deficits.

Sources of Funding
This project was supported by the British Heart Foundation. Dr Wagenmakers is the recipient of a BBSRC case studentship, a Wellcome Trust infrastructure grant, a British Heart Foundation grant, and a BBSRC doctoral training grant. Dr Frenneaux received a British Heart Foundation Programme grant.

Disclosures
Dr Henning has served on speakers’ bureaus teaching cardiac MRS techniques. Dr Stevens received research support from Lilly Pharmaceutical Co. Dr Frenneaux received honoraria from Medtronic, St. Jude, and Biotronik, and has served as a consultant/advisory board member for Medtronic, St. Jude, and Biotronik. The remaining authors report no conflicts.

References
Development of heart failure in diabetes mellitus is a complex mechanism and is affected by many secondary factors, such as hypertension, coronary artery disease, renal disease, and hyperlipidemia. In this study, we have demonstrated cardiac energetics impairment in uncomplicated diabetes, proving that diabetes has a direct effect on the myocardium. We have also shown that microvascular disease probably does not play a significant role in the development of energetics impairment. This energetics impairment occurs early in the disease process, and intervention at this stage to improve myocardial energetics status may be an important method of reducing cardiovascular complications. Metabolic modulation has assumed importance recently in the management of patients with coronary artery disease and heart failure. Because subjects with diabetes mellitus have a metabolic profile similar to these patients, metabolic agents potentially could be used to prevent heart failure in diabetes mellitus; however, large-scale studies are required to substantiate this. Alternatively, intensive metabolic control early in type 1 diabetes mellitus can achieve long-term benefits in reducing cardiovascular complications.
Relationship Between Coronary Microvascular Dysfunction and Cardiac Energetics
Impairment in Type 1 Diabetes Mellitus

Circulation. 2010;121:1209-1215; originally published online March 1, 2010;
doi: 10.1161/CIRCULATIONAHA.109.873273
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/10/1209