Altered Myocardial Fatty Acid and Glucose Metabolism in Idiopathic Dilated Cardiomyopathy

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OBJECTIVES The purpose of this study was to determine whether patients with idiopathic dilated cardiomyopathy (IDCM) exhibit alterations in myocardial fatty acid and glucose metabolism.

BACKGROUND Alterations in myocardial metabolism have been implicated in the pathogenesis of heart failure (HF); however, studies of myocardial metabolic function in human HF have yielded conflicting results. Animal models of HF have shown a downregulation of the expression of enzymes of fatty acid beta-oxidation that recapitulates the fetal energy metabolic program, in which fatty acid metabolism is decreased and glucose metabolism is increased.

METHODS Seven patients with IDCM (mean left ventricular ejection fraction 27 ± 8%) and 12 normal controls underwent positron emission tomography for measurements of myocardial blood flow (MBF), myocardial oxygen consumption (MVO2), myocardial glucose utilization (MGU), myocardial fatty acid utilization (MFAU) and myocardial fatty acid oxidation (MFAO).

RESULTS The systolic and diastolic blood pressures, plasma substrates and insulin levels, MBF and MVO2, were similar between groups. The rates of MFAU and MFAO were significantly lower in IDCM than in the normal control group (MFAU: 134 ± 44 vs. 213 ± 49 nmol/g/min, p = 0.003; and MFAO: 113 ± 50 vs. 205 ± 49 nmol/g/min, p = 0.001) and the rates of MGU were significantly higher in IDCM than the normal control group (MGU: 247 ± 63 vs. 125 ± 64 nmol/g/min, p < 0.001).

CONCLUSIONS Patients with IDCM exhibit alterations in myocardial metabolism characterized by decreased fatty acid metabolism and increased myocardial glucose metabolism, a pattern similar to that shown in animal models of HF. Whether alterations in myocardial metabolism constitute an adaptive response or mediate the development of HF remains to be determined.

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Alterations in myocardial substrate metabolism have been implicated in the pathogenesis of contractile dysfunction and heart failure (HF) (1–3). Animal models of HF have shown that in the progression from cardiac hypertrophy to ventricular dysfunction, the expression of genes encoding for mitochondrial fatty acid beta-oxidation (FAO) enzymes is coordinately decreased, resulting in a shift in myocardial metabolism that recapitulates the fetal heart gene program, with glucose instead of fatty acids becoming the primary energy substrate (4–8).

The reactivation of the metabolic fetal gene program may have detrimental consequences on myocardial contractile function. The downregulation of mitochondrial FAO enzymes is associated with increased myocardial utilization of oxygen-sparing glycolytic pathways for the production of high-energy phosphates (4). Although this allows for reduced oxygen demands in the hypertrophied and failing heart, the reliance of the myocardium on glucose may produce a relatively energy-deficient state that over a long time may result in decreased contractile performance (1–3). Alternatively, the inability to metabolize fatty acids in the presence of excess availability may be associated with accumulation of nonoxidized toxic fatty acid derivatives, resulting in lipotoxicity and HF (9). This hypothesis is supported by the development of myocardial hypertrophy, HF and sudden cardiac death in children with genetic defects in myocardial FAO enzymes (10–12). Furthermore, myocardial FAO enzyme expression is downregulated in humans with dilated cardiomyopathy, suggesting that a gene regulatory program is responsible for the alterations in myocardial energy substrate utilization (13).

Animal studies have provided significant insight into the metabolic alterations that occur in HF; however, studies in humans have yielded conflicting results. Accordingly, we measured myocardial fatty acid and glucose metabolism by positron emission tomography (PET) in patients with idiopathic dilated cardiomyopathy (IDCM) and compared these values with those obtained in normal controls. The hypothesis of this study was that patients with IDCM exhibit alterations in myocardial metabolism that are similar...
to those shown in animal models of HF, manifested by reduced levels of myocardial fatty acid utilization (MFAU) and myocardial fatty acid oxidation (MFAO) and by increased levels of myocardial glucose utilization (MGU).

**METHODS**

**Study population.** The study population consisted of patients with IDCM and normal controls. Inclusion criteria for patients with IDCM were: 1) diagnosis of cardiomyopathy within 18 months of enrollment; 2) no evidence of coronary artery disease (CAD) as assessed by coronary angiography; and 3) global moderate-to-severe left ventricular dysfunction (global hypokinesis). Normal controls were recruited by advertisement and had no history or symptoms of cardiovascular disease. All patients and normal controls underwent a complete cardiac evaluation, including a history, physical exam and echocardiogram.

Exclusion criteria for both IDCM patients and normal controls were: 1) causes of cardiomyopathy (other than IDCM for the patients), such as valvular, restrictive or hypertrophic, or due to sarcoidosis, amyloidosis, hemochromatosis, pericardial and/or congenital heart disease; 2) smoker; 4) previous cardiac angiography; and 3) global moderate-to-severe left ventricular dysfunction (global hypokinesis). Normal controls were recruited by advertisement and had no history or symptoms of cardiovascular disease. All patients and normal controls underwent a complete cardiac evaluation, including a history, physical exam and echocardiogram.

Patients were treated with standard individualized therapy for HF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, digoxin and nitrates. After completing the imaging protocol, patients were considered for treatment with beta-blockers. All patients had been clinically stable for at least one month before completing the study protocol. Written informed consent, approved by the Human Studies Committee and the Radioactive Drug Research Committee at Washington University School of Medicine, was obtained from all study subjects.

**Imaging protocol.** **ECHOCARDIOGRAPHY.** All patients and normal controls underwent complete two-dimensional and Doppler echocardiography to determine the left ventricular ejection fraction (LVEF) and left ventricular mass index and to assess valve function (14). Normal controls also underwent exercise stress echocardiography to assess for CAD; those with an ischemic response (chest pain, electrocardiographic and/or echocardiographic ischemia) were excluded.

**CARDIAC PET.** All studies were performed on conventional commercially available tomographs (Siemens ECAT 962 HR+, Siemens Medical Systems, Iselin, New Jersey). After a 12-h overnight fast, all subjects underwent a PET imaging protocol (Fig. 1) to measure myocardial blood flow (MBF), myocardial oxygen consumption (MVO2), MFAU and MFAO, and MGU. A transmission scan was performed to correct for photon attenuation used in emission-image reconstruction. To measure MBF, an intravenous bolus of 0.40 mCi/kg (up to 25 mCi) of 15O-water was followed by 5-min dynamic data collection. To measure MVO2, an intravenous bolus of 0.40 mCi/kg of 11C-acetate was given followed by a 30-min dynamic data collection. To measure MGU, an intravenous bolus of 0.40 mCi/Kg of 11C-glucose was given followed by a 60-min dynamic data collection. MFAU and MFAO were measured using an intravenous bolus of 0.40 mCi/kg of 11C-palmitate, followed by a 30-min dynamic data collection. During the 11C-acetate, 11C-glucose and 11C-palmitate data collections, venous blood samples were obtained at predetermined intervals to measure plasma substrates (such as glucose and free fatty acids) and plasma 13CO2 values and 13C-lactate (in the case of 13C-glucose) to correct the arterial input function for compartmental modeling of the myocardial kinetics of the various metabolic tracers.

**Image analysis.** All PET-derived images were reoriented to generate standard short- and long-axis views. Myocardial time-activity curves were generated by placing a region of
interest on three to four mid-ventricular short-axis slices on the anterolateral wall (3 to 5 cm²) of composite 15O-water, 11C-acetate, 11C-glucose and 11C-palmitate images as previously described (15–19). To generate blood time-activity curves for each tracer, a small region of interest (1 cm²) was placed within the left atrial cavity on a mid-ventricular slice in the vertical long-axis orientation of each composite image. Within these regions of interest, myocardial and blood time-activity curves were generated for 15O-water, 11C-acetate, 11C-glucose and 11C-palmitate, respectively. To avoid contamination from right ventricular blood and liver radioactivity, septal and inferior regions were omitted. Subsequently, blood and myocardial time-activity curves were used in conjunction with well-established kinetic models to measure MBF (ml/g/min), MVO2, MFAU, MFAO and MGU. Blood-to-myocardium count spillover was accounted for in each of the models by estimating the spillover fraction along with the model transfer-rate constants.

**MEASUREMENT OF MBF.** By applying the image-analysis routine to the time-segmented data, we generated myocardial time-activity curves for each segment. From these data, MBF was quantified using a compartmental modeling approach previously validated (15–19).

**MEASUREMENT OF MVO2.** After we corrected PET-derived blood activity for 11CO2 contribution, blood and myocardial time-activity curves were used in conjunction with a one-compartment kinetic model to estimate the rate at which 11C-acetate is converted to 11CO2 (k2, min⁻¹). Values for MVO2 were determined using a known relationship between k2 and MVO2 (16,17).

**MEASUREMENT OF MFAU, MFAO AND MGU.** After correcting the PET-derived blood 11CO2 activity, blood and myocardial 11C-palmitate time-activity curves were used in conjunction with a four-compartment kinetic model to measure fractional myocardial palmitate extraction and oxidation (18). In a similar fashion, after correcting PET-derived blood activity for the key metabolites of 11C-glucose (11CO2 and 11C-lactate), blood and myocardial 11C-glucose time-activity curves were used in conjunction with a four-compartment kinetic model to measure fractional myocardial glucose extraction (19).

Substrate uptake (in ml/g/min) is the product of the substrate extraction fraction and MBF (Equation 1). Substrate uptake thus represents the rate at which the substrate is taken up by the myocardium, and is independent of the level of substrate in plasma. Substrate utilization (in nmol/g/min) is the product of substrate uptake and the concentration of substrate in plasma (Equation 2) and thus reflects the amount of substrate taken up by myocardium. Changes in substrate utilization may be due to changes in extraction fraction, MBF and/or plasma substrate levels.

The tracer extraction fractions are used in conjunction with MBF and plasma levels of free fatty acid or glucose to calculate the total tracer uptake and utilization (MGU and MFAU).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of IDCM Patients and Normal Controls</th>
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<tr>
<td>Normal Controls (n = 12)</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
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<tr>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
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<tr>
<td>RPP (mm Hg · beats · min⁻¹)</td>
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</tbody>
</table>

**RESULTS**

**Patient characteristics.** Seven patients with IDCM (3 women, mean age 39 ± 7 years) and 12 normal controls (9 women, mean age 26 ± 5 years) were enrolled into the study (Table 1). At the time of the initial referral to the HF clinic, all patients were in New York Heart Association (NYHA) functional class IV. However, at the time of enrollment into this study, patients were in stable HF: three were in NYHA functional class III and four were in NYHA functional class III. The mean duration of HF for the group was 15 months. Two patients had a history of hypertension, two had a history of hyperlipidemia; none had diabetes mellitus. As expected, patients with IDCM had significantly lower
LVEF and significantly higher left ventricular mass compared with the normal control group.

**Cardiac imaging studies. REST HEMODYNAMICS, PLASMA SUBSTRATES AND INSULIN LEVELS, MBF AND MVO₂.** The heart rate and the rate-pressure product were significantly higher in the IDCM group compared with the normal control group; however, the systolic and diastolic blood pressures were similar for both groups (Table 1). Plasma levels of fatty acids, glucose, and insulin, and measurements of MBF and MVO₂ were similar for both groups (Table 2).

**MYOCARDIAL FATTY ACID AND GLUCOSE METABOLISM.** Myocardial substrate uptake was significantly different between the two groups: FFA uptake was lower and glucose uptake was higher in the IDCM group (Table 2). Rates of myocardial fatty acid metabolism were significantly lower in the IDCM group compared with the normal control group (MFAU: 134 ± 44 vs. 213 ± 49 nmol/g/min, p = 0.003; MFAO: 113 ± 50 vs. 205 ± 49 nmol/g/min, p = 0.001, respectively, Fig. 2). Rates of MGU were significantly higher in the IDCM group compared with the normal control group (247 ± 63 vs. 125 ± 64 nmol/g/min, p < 0.001, respectively, Fig. 2). Thus, patients with IDCM exhibit reduced rates of myocardial fatty acid metabolism and increased rates of myocardial glucose metabolism compared with normal subjects. Moreover, these differences could not be attributed to differences in plasma substrate levels or differences in myocardial uptake of fatty acids or glucose, because these values paralleled those for MFAU, MFAO and MGU in both groups (Table 2).

**DISCUSSION**

Results of this study demonstrate that patients with IDCM exhibit a shift in myocardial substrate metabolism manifested by increased rates of myocardial glucose uptake and utilization and decreased rates of myocardial fatty acid uptake and MFAU that is paralleled by a decrease in MFAO. These changes cannot be explained by differences in plasma substrates, insulin, MBF or MVO₂. Downregulated expression of myocardial genes involved in mitochondrial FAO has been shown in animals with pressure-overload cardiac hypertrophy, in animals with HF and in pathologic specimens of humans with dilated cardiomyopathy (1,4,13). As previously shown in animal models of HF, in this study we show, in vivo, that alterations in myocardial energy metabolism also occur in humans with IDCM. Taken together, the animal and human studies show that alterations in myocardial fatty acid and glucose metabolism occur in HF. Whether these alterations represent an adaptive response of the failing heart or whether they play a

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**Table 2. Plasma Substrates and Insulin, MBF, MVO₂, and Myocardial Substrate Uptake**

<table>
<thead>
<tr>
<th>Plasma Substrates</th>
<th>Normal Controls (n = 12)</th>
<th>IDCM (n = 7)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (μmol/ml)</td>
<td>4.9 ± 0.4</td>
<td>5.0 ± 0.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>5.1 ± 3.6</td>
<td>5.2 ± 7.8</td>
<td>0.94</td>
</tr>
<tr>
<td>FFA (nmol/ml)</td>
<td>665 ± 174</td>
<td>597 ± 157</td>
<td>0.41</td>
</tr>
<tr>
<td>MBF (ml/g/min)</td>
<td>1.0 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.21</td>
</tr>
<tr>
<td>MVO₂ (nmol/g/min)</td>
<td>4934 ± 830</td>
<td>4935 ± 770</td>
<td>0.99</td>
</tr>
<tr>
<td>Myocardial FFA uptake (μl/g/min)</td>
<td>330 ± 80</td>
<td>236 ± 33</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial glucose uptake (μl/g/min)</td>
<td>26 ± 14</td>
<td>49 ± 13</td>
<td>0.003</td>
</tr>
</tbody>
</table>

FFA = free fatty acids; IDCM = idiopathic dilated cardiomyopathy; MBF = myocardial blood flow; MVO₂ = myocardial oxygen consumption.

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**Figure 2.** Myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy (IDCM). Patients with IDCM exhibited significantly lower rates of myocardial fatty acid utilization and myocardial fatty acid oxidation and significantly higher rates of myocardial glucose utilization compared with normal subjects.
pathophysiologic role remains to be determined. If these alterations represent a maladaptive response, novel treatment strategies in HF may involve metabolic manipulation.

**Myocardial metabolism in the normal and failing heart.**

During the fetal stages of the developing mammalian heart, glucose is the primary energy substrate for energy production, while FAO rates are very low (5,20–21). Shortly after birth and in the normal adult heart, a fall in plasma insulin levels, coupled with decreased availability of glucose and increased availability of fatty acids, leads to enzymatic changes, including increased expression of mitochondrial FAO enzymes that result in a parallel increase in the production of adenosine triphosphate from myocardial FAO (5). Thus, in the normal adult myocardium, mitochondrial FAO is the primary source of intracellular energy.

Animal studies have shown that myocardial energy substrate utilization is altered in association with the development of pathologic forms of ventricular hypertrophy and in the failing heart: fatty acid utilization decreases while glycolysis increases (1,4,22–25). Recent studies have shown that along with the re-expression of fetal isoforms of a variety of contractile and calcium regulatory proteins, the switch from myocardial FAO to glycolysis during the development of pressure-overload LVH and HF recapitulates the fetal heart phenotype (4,13).

Activation of the fetal gene program may initially be an adaptive structural and metabolic response of the overloaded ventricle to maximize efficiency and decrease oxygen consumption. This is supported by the known severe clinical manifestations resulting from genetic defects of myocardial FAO enzymes, including cardiomyopathy and sudden cardiac death (10–12). In the genetic form of metabolic cardiomyopathy, HF often ensues during acute illness associated with fasting, when glucose (the principal substrate) is not readily available. In these patients, the diminished rate of FAO and consequent increased reliance on glucose oxidation that is characteristic of this condition occurs in a pattern similar to that exhibited by the IDCM patients in the present study. Thus, the hypothesis is that defective myocardial FAO leads to inadequate energy production, particularly under conditions of increased work, a phenomenon that has been referred to as decreased energy reserve (2). Furthermore, the accumulation of nonoxidized fatty acid derivatives in the myocardium may lead to lipotoxicity and HF (9). Accumulation of long-chain carnitine esters has been shown to cause ventricular arrhythmias, particularly under conditions of myocardial ischemia, implying that these metabolic derangements may also play a role in sudden cardiac death associated with ventricular hypertrophy and with cardiomyopathy (12,26,27).

**Comparison of this study with previous studies of myocardial metabolic function in HF.** Numerous studies of patients with cardiomyopathy have yielded conflicting results (28–34). Early studies of myocardial metabolism assessed patients with HF by using PET to estimate the clearance rates of long-chain fatty acids tracers such as $^{11}$C-palmitate (35–38). The initial uptake of $^{11}$C-palmitate represents primarily MBF; it then clears the myocardium in a bi-exponential pattern, with the early rapid phase reflecting FAO and the slow clearance representing incorporation of the tracer into the lipid pool. By use of this method, decreased rates of MFAO were shown in patients with myocardial long-chain acyl-CoA dehydrogenase genetic defects (38). Furthermore, the extent of decreased clearance of $^{11}$C-palmitate was shown to correlate with the clinical severity.

Our group has recently validated the use of $^{11}$C-palmitate and $^{12}$C-glucose for the quantification of fatty acid and glucose metabolism, respectively, determined by compartmental modeling, a more accurate and robust technique than estimation of clearance rates (18,19). The present study was conducted using compartmental modeling to determine myocardial metabolism.

A study using iodine-123 beta-methyl-iophenyl pentadecanoic acid (a fatty acid analogue whose uptake parallels that of palmitate but is resistant to FAO) also showed impaired myocardial fatty acid uptake in patients with IDCM (34). Despite the limitations of this study (no attenuation or scatter correction, inability to quantify defects, use of a fatty acid analogue that does not undergo FAO) and despite the uncertain significance of their iodine-123 beta-methyl-iophenyl pentadecanoic acid--thallium-201 mismatch (supposedly all patients had normal coronaries), our study confirms their findings. Furthermore, the present study shows additional findings that further confirm altered myocardial metabolism in IDCM, such as decreased MFAU and MFAO, paralleled by increased MGU.

Others have used ($^{18}$F)fluoro-6-thia-heptadecanoic acid (a long-chain fatty acid analogue) and $^{18}$F-fluorodeoxyglucose (a glucose analogue) to show that patients with HF exhibit increased rates of myocardial fatty acid uptake and lower rates of myocardial glucose uptake (31–33). These findings are discrepant from those of our study, and several differences between these two studies may explain these discrepancies. First, the previous study included a heterogeneous study population composed of patients with both ischemic and nonischemic cardiomyopathy; our study included only patients with nonischemic cardiomyopathy. Second, a control population was not included in the previous study; our study included a normal control group. Third, the previous study used tracer analogues of both fatty acids and glucose. Tracer analogues afford only an indirect assessment of substrate metabolism because they are metabolized differently from the metabolite being studied. Our study used metabolic tracers of the actual substrates being evaluated (palmitate and glucose). Fourth, contrary to our study, the previous study did not assess plasma substrate levels, MBF or MVO$_2$ levels, all of which influence myocardial substrate uptake and myocardial metabolism. Finally, the results of the previous studies are in contradiction with the large scientific literature, ranging from cellular preparations to animal models of HF, and even studies of...
explained hearts of humans with cardiomyopathy that show downregulation of fatty acid metabolism and upregulation of glucose metabolism.

**Study limitations.** The goal of the present study was to show alterations in myocardial metabolism in a homogeneous group of patients with IDCM. This particular patient population was chosen to avoid the limitations of previous studies that included a heterogeneous study population. Specifically, we wanted to avoid the confounding effects that CAD, ischemic cardiomyopathy and treatment with beta-blockers have on the segmental and global measurements of MBF, MVO$_2$, and contractile and metabolic function. Although the rigorous study entry criteria limited the number of eligible patients, this group was very homogeneous and representative of patients with IDCM. Furthermore, the differences found between IDCM and normal controls were quite striking and are in agreement with those previously documented in animal models of HF, in humans with IDCM, and in humans with genetic defects of fatty acid metabolism.

The patients with IDCM were older than the normal controls. However, both groups were relatively young adults and thus their age difference is not large enough to account for the dramatic alterations in myocardial metabolism observed between these groups.

**Clinical implications of the results of this study.** The precise mechanisms leading to HF have not been well characterized. Although there is no conclusive evidence directly implicating metabolic abnormalities in the pathophysiology of HF in humans, there is strong scientific evidence, based on animal models, that this is one of several possible mechanisms. Thus, the present study shows, in agreement to what has been previously identified in animal models of HF, that myocardial fatty acid and glucose metabolism are altered in HF, suggesting that at least in human IDCM, the phenotypic manifestations match the genotypic expression seen in animal models. By use of PET-derived techniques, it is now possible to study noninvasively, in vivo, in humans, the metabolic alterations that occur in association with the transition from ventricular hypertrophy to HF. Furthermore, patients that exhibit these metabolic abnormalities can now be identified and potentially risk-stratified based on the severity of these abnormalities. Finally, this noninvasive PET-derived approach may allow identification of patients with HF whose metabolic abnormalities may be a target for metabolic modulation. One such potential target is peroxisome proliferator-activated receptor alpha, a nuclear receptor known to control the expression of myocardial FAO enzymes (39).

**Conclusions.** The precise mechanisms mediating reduced myocardial contractile performance and resulting in HF have not been well characterized. In this study, we show that patients with IDCM exhibit alterations in myocardial metabolism characterized by decreased MFAU and MFAO and by increased MGU. These findings are in agreement with those previously identified in animal models of HF, in pathologic specimens of humans with dilated cardiomyopathy and in humans with genetic defects of fatty acid metabolism, that myocardial fatty acid and glucose metabolism is altered in HF. Whether alterations in myocardial metabolism are an adaptive response or mediate the development of HF remains to be determined.

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