Trimetazidine, a Metabolic Modulator, Has Cardiac and Extracardiac Benefits in Idiopathic Dilated Cardiomyopathy

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Background—The anti-ischemic agent trimetazidine improves ejection fraction in heart failure that is hypothetically linked to inhibitory effects on cardiac free fatty acid (FFA) oxidation. However, FFA oxidation remains unmeasured in humans. We investigated the effects of trimetazidine on cardiac perfusion, efficiency of work, and FFA oxidation in idiopathic dilated cardiomyopathy.

Methods and Results—Nineteen nondiabetic patients with idiopathic dilated cardiomyopathy on standard medication were randomized to single-blind trimetazidine (n=12) or placebo (n=7) for 3 months. Myocardial perfusion, FFA, and total oxidative metabolism were measured using positron emission tomography with [15O]H2O, [11C]acetate, and [11C]palmitate. Cardiac function was assessed echocardiographically; insulin sensitivity was assessed by the homeostasis model assessment index. Trimetazidine increased ejection fraction from 30.9±8.5% to 34.8±12% (P=0.027 versus placebo). Myocardial FFA uptake was unchanged, and β-oxidation rate constant decreased only 10%. Myocardial perfusion, oxidative metabolism, and work efficiency remained unchanged. Trimetazidine decreased insulin resistance (glucose: 5.9±0.7 versus 5.5±0.6 mmol/L, P=0.047; insulin: 10±6.9 versus 7.6±3.6 mU/L, P=0.031; homeostasis model assessment index: 2.75±2.28 versus 1.89±1.06, P=0.027). The degree of β-blockade and trimetazidine interacted positively on ejection fraction. Plasma high-density lipoprotein concentrations increased 11% (P<0.001).

Conclusions—In idiopathic dilated cardiomyopathy with heart failure, trimetazidine increased cardiac function and had both cardiac and extracardiac metabolic effects. Cardiac FFA oxidation modestly decreased and myocardial oxidative rate was unchanged, implying increased oxidation of glucose. Trimetazidine improved whole-body insulin sensitivity and glucose control in these insulin-resistant idiopathic dilated cardiomyopathy patients, thus hypothetically countering the myocardial damage of insulin resistance. Additionally, the trimetazidine-induced increase in ejection fraction was associated with greater β1-adrenoceptor occupancy, suggesting a synergistic mechanism. (Circulation. 2008;118:1250-1258.)

Key Words: fatty acids ■ heart failure ■ metabolism ■ positron emission tomography ■ trimetazidine

Chronic heart failure (HF) is a common cause of mortality and morbidity with increasing prevalence and healthcare costs. Our study was focused specifically on patients with idiopathic dilated cardiomyopathy (IDCM), one of the more common causes of systolic HF. Despite recent therapeutic advances, many patients with IDCM remain highly symptomatic with a poor prognosis.

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Metabolic modulators such as trimetazidine and perhexiline have raised considerable interest as additional forms of HF therapy. In a recent open-label study, trimetazidine improved functional class and ejection fraction (EF) in a range of patients with HF.1 The concept that such agents may optimize myocardial energy metabolism and allow more efficient production of energy from glucose than from free fatty acids (FFA) is “unique and conceptually appealing.”2 Some problems, however, hamper the applicability of this hypothesis to the therapy of IDCM. First, no data are available to show decreased FFA oxidation in humans with HF. Rather, it is assumed that because a metabolic modulator such as trimetazidine acts in healthy rodent hearts by partially inhibiting long-chain 3-ketoacyl coenzyme A thiolase,3 the last enzyme involved in mitochondrial fatty acid β-oxidation,
similar effects would be found in failing human hearts.\textsuperscript{1,2,4} Second, patients with IDCM may already have substantially downregulated FFA and upregulated glucose metabolism,\textsuperscript{5} especially when medicated with $\beta$-blockers that also induce myocardial metabolic switching from FFA to glucose oxidation.\textsuperscript{6,7} Third, in our recent study, when this hypothesis was tested by acutely decreasing the availability of FFA by administering acipimox\textsuperscript{8} to patients with IDCM, myocardial efficiency of work deteriorated further. Thus, acute limitation of FFA availability does not induce positive effects on cardiac performance in patients with HF.

Trimetazidine improves EF in patients with HF with or without diabetes\textsuperscript{1,4,9–11} and increases the ratios of phospho-creatine to adenosine triphosphate.\textsuperscript{12} In isolated working rat hearts, trimetazidine decreases the rate of palmitate oxidation up to 50%.\textsuperscript{3} However, no data are currently available on the effect of trimetazidine on myocardial FFA oxidative metabolism or the efficiency of work in patients with HF. Therefore, we used positron emission tomography (PET) combined with echocardiography to measure myocardial efficiency\textsuperscript{13,14} and substrate metabolism rates\textsuperscript{15} before and during treatment with trimetazidine in patients with IDCM and HF. To the best of our knowledge, this is the first study to test the hypothesis that trimetazidine improves cardiac function in IDCM by reducing FFA oxidation. We also reasoned that trimetazidine could improve insulin resistance in HF by extracardiac inhibition of FFA oxidation.\textsuperscript{16} A third specific goal was to investigate whether the effects of trimetazidine on cardiac function were additive to those of $\beta$-blockers.

### Methods

#### Study Subjects

Nineteen IDCM patients were enrolled in the study after a screening visit that included an oral glucose tolerance test. All patients had at least a 10-month history of IDCM with an EF <47%, were clinically stable (New York Heart Association class 2.2±0.3), and were receiving stable medical therapy for at least 3 months before the study. Eighteen patients were on $\beta$-blocker medication. Exclusion criteria included diabetes (type I or II) and HF secondary to a known cause (such as ischemic heart disease, primary valvular disease, or chronic alcoholism). Ischemic heart disease was ruled out by angiography (12 of 19), perfusion imaging (2 of 19), or exercise test (5 of 19). The study protocol was approved by the local ethics committee, and all subjects gave written informed consent.

#### Intervention

After baseline investigations, patients were randomly assigned to receive either trimetazidine (35 mg BID, Vastarel, Laboratoires Servier France, Neuilly-sur-Seine, France; n=12) or placebo (n=7) in a single-blind manner in addition to their previous standard medication. The characteristics of the patient groups at baseline are summarized in Table 1. The groups were comparable in age, body mass index, and New York Heart Association functional class. At baseline, EF, left ventricular (LV) dimensions, and LV mass index were similar, whereas LV mass was significantly higher in the trimetazidine group. Both patient groups followed similar medication regimens. Clinical status and ECG were controlled, and blood samples were collected 1 and 2 months later. After 3 months of treatment, PET imaging and echocardiography were repeated. The compliance assessed by pill counting was >95% in both groups.

#### Positron Emission Tomography

Myocardial perfusion and oxidative and FFA metabolism were measured with $[{\text{15}}\text{O}]\text{H}_2\text{O}, [{\text{11}}\text{C}]\text{acetate},$ and $[{\text{11}}\text{C}]\text{palmitate}$ as PET tracers.\textsuperscript{6} Echocardiographic examinations were performed between $[{\text{11}}\text{C}]\text{acetate}$ and $[{\text{11}}\text{C}]\text{palmitate}$ scans, ECG, heart rate, and blood pressure were monitored throughout the sessions. Echocardiographic evaluation was as before.\textsuperscript{6} Systemic vascular resistance (SVR) was calculated as follows: $\text{SVR} = \text{MABP} / (\text{SV} \times \text{HR})$, where MABP is mean arterial blood pressure, $\text{SV}$ is stroke volume, and HR is heart rate. Relative wall thickness (WT) was calculated as follows: $\text{WT} = (2 \times \text{diastolic PW}) / \text{LVEDD}$, where LVEDD is LV end-diastolic dimension and PW is the posterior wall. Wall stress (WS) was calculated from the following: $\text{WS} = [(\text{BP} \times \text{LVESD/2}) /[2 \times (\text{systolic IVC} + \text{systolic PW/2})]$], where LVESD is LV end-systolic dimension and IVC is interventricular septum.

#### Measurement of Myocardial Perfusion, Oxidative and FFA Metabolism

The positron-emitting tracers $[{\text{15}}\text{O}]\text{H}_2\text{O}, [{\text{11}}\text{C}]\text{acetate},$ and $[{\text{11}}\text{C}]\text{palmitate}$ were produced and used as previously described.\textsuperscript{8,17–19} All PET data were corrected for dead time, decay, and measured photon attenuation. Images were processed with standard reconstruction algorithms.

#### Calculation of Myocardial Perfusion, Oxidative Metabolism, and Efficiency

Regional myocardial perfusion was calculated from a single-compartment model\textsuperscript{10} as previously described.\textsuperscript{8} In $[{\text{11}}\text{C}]\text{acetate}$ PET studies, one region of interest (“horsehoe” region of interest) was drawn to cover the whole LV myocardium on an average of 4 midventricular transaxial planes. Monoexponential fitting was applied, and $[{\text{11}}\text{C}]\text{acetate}$ clearance rate ($K_{\text{clear}}$) was calculated. Myocardial efficiency of forward work (the relationship between forward

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### Table 1. Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Trimetazidine Group (n=12)</th>
<th>Placebo Group (n=7)</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>59±8.8</td>
<td>57±7.3</td>
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<tr>
<td>Sex, M/F</td>
<td>10/2</td>
<td>5/2</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>27.4±5.3</td>
<td>29.8±3.6</td>
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<td>Rhythm, sinus/AF</td>
<td>7/5</td>
<td>5/2</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.2±0.3</td>
<td>2.2±0.4</td>
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<tr>
<td>Hypertension, n</td>
<td>3/12</td>
<td>2/7</td>
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<tr>
<td><strong>Echocardiographic data</strong></td>
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<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>31±8.5</td>
<td>38±8.4</td>
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<td>LV mass, g</td>
<td>312±80*</td>
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<tr>
<td>LV mass index</td>
<td>153±41</td>
<td>124±18</td>
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<tr>
<td>LVEDD, mm</td>
<td>75±11</td>
<td>71±8</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>63±11</td>
<td>58±8</td>
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<td>$\beta$-Blocker</td>
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<td>7/7</td>
</tr>
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<td>Diuretic</td>
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<td>4/7</td>
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<td>Digoxin</td>
<td>4/12</td>
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</tr>
<tr>
<td>Angiotensin II blocker</td>
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<td>1/7</td>
</tr>
<tr>
<td>Statins</td>
<td>4/12</td>
<td>2/7</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation, NYHA, New York Heart Association; LVEDD, LV end-diastolic dimension; and LVESD, LV end-systolic dimension. Values are mean±SD.

*p=0.031 vs placebo group.

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work and oxygen consumption) was estimated as follows: forward LV work per gram divided by global LV $K_{\text{mono}}$.

### Calculation of Myocardial FFA Uptake Index and $\beta$-Oxidation Rate Constant

These calculations were done as described previously.8

### Biochemical Analyses

Plasma glucose and lactate, serum free insulin, serum FFA, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured as previously described.9 Plasma HDL cholesterol was measured with the Roche enzymatic method for direct determination of HDL cholesterol on a Roche Modular P-analyzer (Roche, Mannheim, Germany). In addition, HDL cholesterol, LDL cholesterol, and HDL3 cholesterol also were determined using sequential polyethylene glycol precipitation21 followed by enzymatic cholesterol determination (Olympus System Reagent, Olympus Diagnostica GmbH, Hamburg, Germany). Homeostasis model assessment index was calculated as $(fS-\text{Insu})/fP-Glu \times 22.5$, where $fS-\text{Insu}$ indicates fasting insulin and $fP-Glu$ indicates fasting plasma glucose.22 The low-density lipoprotein cholesterol concentration was calculated from the Friedewald formula.23 The extent of $\beta$-blockade was estimated with a $\beta$-adrenoceptor occupancy test.24 Malondialdehyde concentration was measured as serum total (free and protein-bound) malondialdehyde as the 2,4-dinitrophenylhydrazine derivative by high-performance liquid chromatography with 1,1,3,3-tetraethoxypropane as the standard.26 Human adipocyte fatty acid–binding protein was measured by a sandwich enzyme immunoassay (Human FABP4 ELISA, D-69120, Heidelberg, Germany). Lipoprotein(a) concentration was analyzed by a turbidimetric immunosassay (Wako Chemicals, Neuss, Germany). Plasminogen activator inhibitor was determined by an indirect enzymatic chromogenic assay (Trinity Biotech plc, Bray, Co Wicklow, Ireland).

### Statistical Analysis

Values are expressed as mean±SD. Paired Student $t$ test was used in normally distributed and signed-rank test was used in nonnormally distributed parameters to compare intragroup differences between baseline and follow-up. Linear regression analysis adjusted for baseline value and body mass index was used to compare the effects of trimetazidine and placebo on biochemical, echocardiographic, and PET parameters. Pearson (in normally distributed parameters) or Spearman (in nonnormally distributed parameters) correlation was used to calculate associations between continuous variables. A value of $P<0.05$ was considered statistically significant. All statistical tests were 2 sided and performed with SAS/STAT statistical analysis system (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
plasma glucose concentrations decreased by 6% (placebo group (Table 2). In the trimetazidine group, fasting baseline and remained unchanged during the therapy in the Biochemical variables were similar between the groups at baseline and follow-up investigations. In 1 patient, the daily medications of these 2 patients were modified between the groups, a trend was found for decreased homeostasis model assessment index in the trimetazidine group after therapy (P=0.093).

Hemodynamic variables, body weight, and body mass index (29.8 to 29.5 kg/m² in the placebo group, 27.4 to 27.5 kg/m² in the trimetazidine group) were similar between the groups at baseline and remained unchanged during treatment with trimetazidine and placebo. Systemic vascular resistance was unchanged in both groups, and no association with insulin resistance was detected (data not shown).

Myocardial Perfusion, Oxidative Metabolism, Work, and Efficiency of Forward Work
Myocardial perfusion and LV oxidative metabolism were comparable between the groups at baseline and remained unchanged in both groups during the medication (Table 3). Stroke volume, myocardial work per gram of tissue, and

Results

Intervention
All patients completed the 3-month course of treatment. Side effects in the trimetazidine group were limited to transient diarrhea in the beginning of the treatment in 2 subjects. No changes were observed in the safety laboratory samples (eg, liver laboratory tests) in either group. Two patients in the placebo group were hospitalized during the study: 1 as a result of worsening of HF symptoms and 1 for pneumonia. The medications of these 2 patients were modified between baseline and follow-up investigations. In 1 patient, the daily dose of furosemide was increased by 80 mg; in the other, the angiotensin-converting enzyme inhibitor was withdrawn because of low blood pressure. No medication changes occurred in other subjects in either group.

Biochemical and Hemodynamic Variables
Biochemical variables were similar between the groups at baseline and remained unchanged during the therapy in the placebo group (Table 2). In the trimetazidine group, fasting plasma glucose concentrations decreased by 6% (P=0.047; 90% confidence interval [CI] for the difference, 0.1 to 0.7) and serum insulin concentrations decreased by 16% (P=0.031; 90% CI for the difference, 0.4 to 4.4) during treatment compared with baseline; thus, homeostasis model assessment index decreased by 20% (P=0.027; 90% CI for the difference, 0.2 to 1.5). Moreover, fasting plasma HDL concentrations increased by 11% (P<0.001; 90% CI for the difference, 0.10 to 0.21) during treatment with trimetazidine, and further HDL analyzes revealed that both HDL₂ and HDL₃ levels increased significantly (P=0.041; 90% CI for the difference, 0.01 to 0.07; and P=0.036; 90% CI for the difference, 0.01 to 0.09, respectively). Fasting serum FFA, plasma lactate, fatty acid–binding protein, malondialdehyde, lipoprotein(a), and plasminogen activator inhibitor levels were unchanged. Between the groups, a trend was found for decreased homeostasis model assessment index in the trimetazidine group after therapy (P=0.093).

<table>
<thead>
<tr>
<th>IVS, mm</th>
<th>8.5±2.0</th>
<th>10±1.4‡</th>
<th>8.4±1.1</th>
<th>8.4±0.5</th>
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<tbody>
<tr>
<td>PW, mm</td>
<td>9.1±2.3</td>
<td>9.4±1.8</td>
<td>8.0±1.3</td>
<td>8.0±0.8</td>
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<tr>
<td>Relative wall thickness</td>
<td>0.25±0.076</td>
<td>0.26±0.056</td>
<td>0.23±0.057</td>
<td>0.23±0.036</td>
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<td>LVM, g</td>
<td>312±80</td>
<td>341±81*</td>
<td>252±28</td>
<td>255±34</td>
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<td>LVM index, g/m²</td>
<td>153±41</td>
<td>166±42*</td>
<td>124±18</td>
<td>125±15</td>
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<td>LVEDD (M-mode), mm</td>
<td>75±11</td>
<td>74±9.0</td>
<td>71±7.6</td>
<td>70±6.4</td>
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<tr>
<td>LVESD (M-mode), mm</td>
<td>63±11</td>
<td>61±10</td>
<td>58±7.7</td>
<td>58±6.2</td>
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<td>LVEDV (2D), mL</td>
<td>276±111</td>
<td>296±129</td>
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<tr>
<td>LVESV (2D), mL</td>
<td>197±102</td>
<td>204±131</td>
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<td>186±76*</td>
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<td>Fractional shortening, %</td>
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<td>18±5.8*</td>
<td>18±3.7</td>
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<td>Wall stress, mm Hg</td>
<td>158±48</td>
<td>138±38*</td>
<td>164±44</td>
<td>152±33</td>
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<td>Stroke volume, mL</td>
<td>77±12</td>
<td>84±26</td>
<td>71±27</td>
<td>77±25</td>
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<td>Cardiac output, L/min</td>
<td>5.18±1.00</td>
<td>5.03±1.04</td>
<td>4.36±1.22</td>
<td>4.89±1.26</td>
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<tr>
<td>EF, %</td>
<td>30.9±8.5</td>
<td>34.8±12†</td>
<td>37.5±8.4</td>
<td>31.9±12</td>
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<td>Basal perfusion, mL·g⁻¹·min⁻¹</td>
<td>0.73±0.19</td>
<td>0.69±0.12</td>
<td>0.80±0.30</td>
<td>0.87±0.36</td>
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<tr>
<td>LV V̇O₂max, min⁻¹</td>
<td>0.061±0.015</td>
<td>0.056±0.011</td>
<td>0.063±0.017</td>
<td>0.065±0.026</td>
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<tr>
<td>LV work power, mm Hg·L·min⁻¹</td>
<td>611±161</td>
<td>599±151</td>
<td>521±127</td>
<td>570±172</td>
</tr>
<tr>
<td>LV work power/g, mm Hg·L·g⁻¹·min⁻¹</td>
<td>2.11±0.81</td>
<td>1.85±0.62</td>
<td>2.10±0.58</td>
<td>2.30±0.94</td>
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<tr>
<td>Efficiency, mm Hg·L·g⁻¹</td>
<td>35.4±13.4</td>
<td>34.1±11.8</td>
<td>34.5±10.2</td>
<td>35.6±8.52</td>
</tr>
</tbody>
</table>

IVS indicates interventricular septum; PW, posterior wall; LVM, LV mass; LVEDD, LV end-diastolic dimension; LVESD, LV end-diastolic volume; 2D, 2 dimensional; and LVESV, LV end-systolic volume; Data are presented as mean±SD.

*P<0.05 vs baseline (see exact P values in the text).
†P=0.027 vs the change in the placebo group.
‡P=0.002 vs the change in the placebo group.
efficiency were similar between the groups at baseline and did not change after trimetazidine or placebo medication (Table 3).

Myocardial FFA Uptake and $\beta$-Oxidation Rate Constant
Myocardial FFA uptake and $\beta$-oxidation rate constant were comparable between the groups at baseline (Figure 1). During trimetazidine, myocardial $\beta$-oxidation rate constant decreased significantly compared with baseline (from $0.037 \pm 0.009$ to $0.033 \pm 0.007$ minute$^{-1}$; $P=0.034$; 90% CI for the difference, 0.001 to 0.007; 10% reduction calculated from the individual means) and remained unchanged in the placebo group. Trimetazidine or placebo did not change myocardial FFA uptake index.

Echocardiographic Results
In the trimetazidine group, EF was increased by 15% during the treatment (from $30.9 \pm 8.5\%$ to $34.8 \pm 12\%$), whereas in the placebo group, it decreased by 17% (from $37.5 \pm 8.4\%$ to $31.9 \pm 12\%$; $P=0.027$; 90% CI for the difference between groups, 3.0 to 18; Figure 2 and Table 3). In the trimetazidine group, the extent of $\beta_1$-adrenoceptor occupancy positively correlated with the relative change in EF ($R=0.75$, $P=0.005$; Figure 3A), whereas a similar association was not seen in the placebo group ($R=-0.57$, $P=0.18$; Figure 3B). Furthermore, in the trimetazidine group, interventricular septum increased compared with the placebo group ($P=0.002$; 90% CI for the difference, 0.7 to 2.1). However, no significant differences were detected in changes in relative wall thickness, LV mass, LV mass index, or LV volumes between the groups.

In the trimetazidine group, LV mass ($P=0.039$; 90% CI for the difference, 6.7 to 50) and LV mass index ($P=0.043$; 90% CI for the difference, 3.0 to 25) increased, whereas LV volumes remained unchanged compared with baseline. Furthermore, fractional shortening increased ($P=0.023$; 90% CI for the difference, 0.6 to 3.2) and wall stress decreased...
with baseline. In the placebo group, all the above-mentioned parameters remained unchanged except for LV end-systolic volume, which increased significantly compared with baseline ($P=0.047$; 90% CI for difference, 5.6 to 45).

**Discussion**

Although trimetazidine has been studied extensively in HF predominantly of ischemic origin, our study has 4 major novel features. First, we report for the first time that in human HF the expected primary target for trimetazidine, namely myocardial FFA oxidative metabolism, was reduced by only 10%. This raises the possibility of additional mechanisms of action such as whole-body metabolic effects with increased insulin sensitivity, suggesting decreased whole-body FFA oxidation in IDCM, as found by Fragasso et al in diabetic ischemic patients. Second, ours is the only study showing that trimetazidine can improve LV function in chronic HF caused by IDCM in which overt myocardial ischemia has been excluded. Third, the positive effects of trimetazidine on LV function were especially evident in patients with a high degree of β-blockade as estimated by a β1-adrenoceptor occupancy test, strongly suggesting an additive effect of these 2 modalities of therapy. Fourth, trimetazidine unexpectedly improved the lipid profile by increasing HDL cholesterol levels by 11%.

Because HF is an “energy-deprived” state, the energy-saving hypothesis is attractive. Could the reduction in FFA oxidation by only 10% support this hypothesis by switching from FFA to glucose oxidation? Completely changing from total FFA oxidation to only glucose (ie, becoming totally reliant on glucose for energy metabolism) would spare only 11% of the myocardial oxygen uptake. Thus, myocardial energy-saving metabolic switching from FFA to glucose is an unlikely main mechanism of trimetazidine action in the conditions of our study. However, we cannot exclude that partial inhibition of FFA oxidation might become a more powerful metabolic tool during oxygen wastage, as could occur during exercise and other adrenergic stresses in HF patients. Even if substantial adrenergic FFA-induced uncoupling and oxygen wastage were to occur to increase oxygen uptake by, for example, 40%, reducing it by 10% would still leave FFA accounting for 36% of the increased oxygen uptake. Thus, the energy-saving hypothesis becomes an unlikely mechanism.

An alternative hypothesis emphasizes a shift in the myocardial energy substrate preference from fatty acid toward...
glucose metabolism. Even the modest 10% decrease in FFA oxidation could significantly increase glycolytic flow through pyruvate dehydrogenase by the Randle mechanism and by anaplerosis of pyruvate to oxaloacetate and malate. The latter process could occur without change in the rate of acetate oxidation, our index of myocardial oxidative metabolism. Without direct measurement of pyruvate fates, the significance of these 2 routes of enhanced pyruvate entry into the citrate cycle remains speculative. However, increased oxidative glycolysis is likely as FFA falls, and the evidence of a preserved washout rate of acetate in this study supports the occurrence of the above metabolic shift. The consequences could include lessened harmful proton production and increased production of membrane-protective glycolytic ATP. These notions raise the interesting possibility that if carnitine palmitoyltransferase (CPT-1) inhibition by perhexiline or malonyl CoA was added to the modest inhibitory effects of trimetazidine, there could be an additional reinforcement in compensatory oxidative glycolysis.

The metabolic-shift hypothesis may also be supported by our data with β-blockade. In some, but not all studies, β-blockers have induced myocardial metabolic shift from FFA to glucose oxidation, as suggested here for trimetazidine. We demonstrate that beneficial effects of trimetazidine treatment on LV function were observed in patients who were almost all receiving β-blocking agents (Table 1). Our novel finding was that the increase in EF achieved by trimetazidine therapy was associated with greater β1-adrenoceptor occupancy (Figure 3), suggesting synergistic clinical effects of β-blockade and trimetazidine.Trimetazidine and β-blockers partially inhibit different enzymes in the FFA path, so their metabolic effects could be additive. Specifically, whereas trimetazidine did not change total myocardial oxidative metabolism, β-blockade did, and that change was accompanied by increased efficiency of work.

The basic mechanism that we favor is that both trimetazidine and β-blockade may improve insulin resistance, a well-established feature of HF and an independent risk factor for HF mortality. We found that trimetazidine improves whole-body insulin sensitivity and glucose control in insulin-resistant IDCM patients, extending to this condition the observation reported in diabetic patients with ischemic HF. This is of particular note given the high prevalence of diabetes in IDCM patients. In addition, insulin resistance increases myocardial FFA uptake and oxidation, and myocardial insulin resistance, ie, decreased myocardial glucose uptake, may worsen the energy depletion state, compromising cardiac function, as supported by its negative correlation with the LVEF. Conversely, enhanced glucose metabolism improves cardiac function in animal models and prevents the development of systolic dysfunction in patients with diabetes. Furthermore, improvement in whole-body insulin sensitivity by trimetazidine is accompanied by a metabolic shift from FFA to glucose oxidation in skeletal muscle during euglycemic hyperinsulinemia in diabetic HF patients. Overall, we postulate that such extracardiac metabolic changes may indirectly improve myocardial glucose metabolism and glycolysis, amplifying the effects mediated by the modest decrease in FFA oxidation observed in the cardiac tissue. Of note, the substrate shift should not be drastic because excess rapid deprivation of FFA is potentially harmful in HF, as shown in our previous study, whereas modest FFA inhibition, together with increased insulin sensitivity, as in the present study, appears more physiological and beneficial.

To the best of our knowledge, this data set provides the first evidence of a substantial trimetazidine-induced rise in HDL cholesterol levels. Overall, HDL levels were increased by 11%. This change was approximately equally distributed between the 2 main HDL subfractions. This result is important because HDL is 1 major marker of metabolic and cardiovascular risk and epidemiologically both HDL and LDL exert a powerful antioxidative and protective effect.

The mechanisms explaining such findings by trimetazidine cannot be deduced from the present study but may be linked to the improved whole-body glucose homeostasis (although we could not demonstrate any association between these parameters in the present study). Trimetazidine-induced rise in HDL is potentially beneficial, but one should be very cautious in this interpretation because pharmacologically elevated HDL cholesterol levels do not necessarily reflect increased reverse cholesterol transport, enhanced antioxidative capacity, and consequently decreased atherogenesis.

**Study Limitations**

The study was only single blinded. However, the echocardiographer was blinded to the patients’ medications, and PET image analysis was performed mechanically by using the same regions of interest at baseline and follow-up, eliminating any influence of the analyst. The number of patients studied was small (19 patients) because of demanding imaging procedures but was large enough to identify significant changes in metabolic parameters in the repeated imaging setup. Because of practical limitations, myocardial glucose metabolism measurements could not be included in the present protocol because it would have required a 2-day study. All measurements were done only at rest. Further studies are warranted to study the effect of trimetazidine on myocardial glucose metabolism and to test exercise effects. In the mathematical models applied in the present study, complete quantification of various steps of FFA metabolism cannot be performed. In our model, the absolute mass of oxidized FFA cannot be measured. Rather, the estimated myocardial β-oxidation rate indicates the fraction of the intracellular FFA pool that is entering β-oxidation. However, the analysis used is very simple, robust, and reproducible. It requires neither metabolite analysis nor error-sensitive multiparameter curve fitting.

**Conclusions**

In patients with HF caused by IDCM, trimetazidine has positive cardiac and extracardiac effects. Modest inhibitory effects on FFA oxidation make the energy-sparing hypothesis unlikely and the metabolic-shift hypothesis more likely. Part of the positive effects of trimetazidine on cardiac function may be related to improved glucose homeostasis and insulin sensitivity. β-Blockade and trimetazidine have synergistic positive effects on the EF. Unexpectedly and importantly, HDL cholesterol increased. These findings suggest that further studies in HF testing combinations of metabolic modu-
lators active at different sites and during exercise are warranted.

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Disclosures
None.

References

CLINICAL PERSPECTIVE

Metabolic modulators such as trimetazidine have raised considerable interest as additional forms of heart failure therapy. The concept that such agents may optimize myocardial energy metabolism and allow more efficient production of energy from glucose than from free fatty acids is appealing. Trimetazidine has been studied extensively in heart failure predominantly of ischemic origin. We extend the previous findings by showing that trimetazidine (1) improves left ventricular function in patients with chronic heart failure caused by nonischemic dilated cardiomyopathy; (2) reduces myocardial free fatty acid oxidation by only 10% in the failing human heart, raising the possibility of additional mechanisms of action; (3) has whole-body metabolic effects, with increased insulin sensitivity potentially linked to decreased whole-body free fatty acid oxidation; and (4) unexpectedly improves circulating lipid profile by increasing high-density lipoprotein cholesterol levels by 11%. The trimetazidine-induced improvement in left ventricular function is linked to the degree of β-blockade, suggesting an additive effect of these 2 therapies. Thus, trimetazidine has both cardiac and extracardiac positive effects. Further studies in heart failure testing combinations of metabolic modulators active at different sites and during exercise are warranted.
Trimetazidine, a Metabolic Modulator, Has Cardiac and Extracardiac Benefits in Idiopathic Dilated Cardiomyopathy
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