Free Fatty Acid Depletion Acutely Decreases Cardiac Work and Efficiency in Cardiomyopathic Heart Failure

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Background—Metabolic modulators that enhance myocardial glucose metabolism by inhibiting free fatty acid (FFA) metabolism may improve cardiac function in heart failure patients. We studied the effect of acute FFA withdrawal on cardiac function in patients with heart failure caused by idiopathic dilated cardiomyopathy (IDCM).

Methods and Results—Eighteen fasting nondiabetic patients with IDCM (14 men, 4 women, aged 58.8±8.0 years, ejection fraction 33±8.8%) and 8 matched healthy controls underwent examination of myocardial perfusion and oxidative and FFA metabolism, before and after acute reduction of serum FFA concentrations by acipimox, an inhibitor of lipolysis. Metabolism was monitored by positron emission tomography and [15O]H2O, [11C]acetate, and [11C]palmitate. Left ventricular function and myocardial work were echocardiographically measured, and efficiency of forward work was calculated. Acipimox decreased myocardial FFA uptake by >80% in both groups. Rate-pressure product and myocardial perfusion remained unchanged, whereas stroke volume decreased similarly in both groups. In the healthy controls, reduced cardiac work was accompanied by decreased oxidative metabolism (from 0.071±0.019 to 0.055±0.016 min⁻¹, P<0.01). In IDCM patients, cardiac work fell, whereas oxidative metabolism remained unchanged and efficiency fell (from 35.4±12.6 to 31.6±13.3 mm Hg · L · g⁻¹ · P<0.05).

Conclusions—Acutely decreased serum FFA depresses cardiac work. In healthy hearts, this is accompanied by parallel decrease in oxidative metabolism, and myocardial efficiency is preserved. In failing hearts, FFA depletion did not downregulate oxidative metabolism, and myocardial efficiency deteriorated. Thus, failing hearts are unexpectedly more dependent than healthy hearts on FFA availability. We propose that both glucose and fatty acid oxidation are required for optimal function of the failing heart. (Circulation. 2006;114:2130-2137.)

Key Words: cardiomyopathy | fatty acids | heart failure | metabolism

The heart is unique among organ systems in its continuous need for high-energy phosphates to maintain contractile function. It can switch between different substrates depending on substrate availability, hormonal milieu, oxygen availability, and metabolic demands.1 Myocardial glucose and free fatty acid (FFA) metabolism are tightly coupled, with increased FFA metabolism inhibiting myocardial glucose metabolism and vice versa.2 We have previously demonstrated that limitation of FFA availability by acipimox, an inhibitor of lipolysis, increases myocardial glucose uptake to the same extent as euglycemic hyperinsulinemia.3

Experimental4,5 and preliminary clinical6,7 studies have demonstrated that metabolic modulators that enhance myocardial glucose metabolism directly or indirectly by inhibiting FFA metabolism may be beneficial to the failing heart. This is linked to the fact that glucose is a more energy-efficient fuel than FFA.1 Although the maximum oxygen saving that can be calculated from a total switch from oxidation of FFA as sole fuel to total glucose oxidation is only just over 11%,1 experimental data show that increasing circulating FFA levels within the physiological range increases oxygen uptake by 27%.8 High FFA concentrations in human heart failure are associated with increased levels of mitochondrial uncoupling proteins,9 which can produce substantial oxygen waste.4 Furthermore, a metabolic switch from predominant myocardial FFA to glucose metabolism may partly explain beneficial effects of β-blockade in heart failure patients.4,10 Thus, a reduction of circulating FFA levels is expected to become an effective treatment for human heart failure.4,9 Specifically, an

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acutefailure(suchasischemicheartdisease,primarystvalvulardisease,or
Exclusion criteria included diabetes(type I,II)andsecondaryheart
Medications, % (n/N) All but one of the patients (17/18) were on
least 3 months before the study day. The mean New York Heart
Clinically stable, and were receiving stable medical therapy for at
1). All patients had at least a 10-month history of IDCM, were
enrolled in the study after a screening visit consisting of a medical

Study Subjects
Eighteen patients with IDCM and 8 healthy control patients were
invited to participate in the study. They had to be functioning
clinical status, and were receiving stable medical therapy for at
least 3 months before the study day. The mean New York Heart
Association (NYHA) functional class was 2.2 in the patient group.
All but one of the patients (17/18) were on β-blocker medication.
Exclusion criteria included diabetes (type I, II) and secondary heart
failure (such as ischemic heart disease, primary valvular disease, or

Methods

Eighteen patients with IDCM and 8 healthy control patients were
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Clinical status, and were receiving stable medical therapy for at
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Association (NYHA) functional class was 2.2 in the patient group.
All but one of the patients (17/18) were on β-blocker medication.
Exclusion criteria included diabetes (type I, II) and secondary heart
failure (such as ischemic heart disease, primary valvular disease, or

TABLE 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IDCM Patients (n=18)</th>
<th>Healthy Controls (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59±7.8</td>
<td>55±12</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>14/4</td>
<td>6/2</td>
</tr>
<tr>
<td>Current smokers, n/N</td>
<td>6/18</td>
<td>0/8</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>≥2.2±0.3</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension, n/N</td>
<td>5/18</td>
<td>0/8</td>
</tr>
<tr>
<td>Hypercholesterolemia, n/N</td>
<td>10/18</td>
<td>0/8</td>
</tr>
<tr>
<td>Body mass index, kg · m⁻²</td>
<td>28±4.7</td>
<td>26±4.8</td>
</tr>
<tr>
<td>Medications, % (n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>89 (16/18)</td>
<td>...</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>94 (17/18)</td>
<td>...</td>
</tr>
<tr>
<td>Diuretics</td>
<td>56 (10/18)</td>
<td>...</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28 (5/18)</td>
<td>...</td>
</tr>
<tr>
<td>Angiotensin II blocker</td>
<td>17 (3/18)</td>
<td>...</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>33±9.1</td>
<td>66±5.8*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>74±10</td>
<td>54±4.4*</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>61±10</td>
<td>34±3.5*</td>
</tr>
<tr>
<td>LV mass index, g · m⁻²</td>
<td>142±36</td>
<td>75±12*</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>2.1±0.3</td>
<td>2.0±0.5</td>
</tr>
</tbody>
</table>

 Values are mean±SDunless otherwise indicated.

*P<0.0001 between the groups.

Figure 1. Detailed study protocol. For further details see text.

Study Design
All patients were instructed to follow their normal medication
regimen on the study day. The detailed imaging protocol is displayed
in Figure 1. Myocardial perfusion and oxidative and FFA metabo-
lost were measured with PET and [¹¹C]acetate, and
[¹¹C]palmitate, respectively. Cardiac dimensions and function were
measured by echocardiography. Volumes were performed
first in the fasting state (after 10 to 12 hours of fasting) and
repeated after acute reduction of serum FFA levels by acipimox (250 mg
orally twice, 1 hour between doses: Olbetam, Pharmacia). ECG,
heart rate, and blood pressure were monitored throughout the studies.
Plasma glucose levels were determined just before [¹¹C]palmitate
scan, and FFA levels were determined during (0, 15, 30 minutes)
[¹¹C]palmitate scan. In addition, fasting plasma lactate and serum
insulin levels were measured. Insulin sensitivity was estimated with
the homeostasis model assessment (HOMA index), which is known
correlate well with the whole-body glucose uptake values mea-
sured with euglycemic hyperinsulinemia.16,17

Echocardiograms
All echocardiograms and all analyses were performed by the same
experienced investigator (E.E.) using a commercially available
ultrasound scanner (Acuson Sequoia 512, Siemens, Mountain View,
Calif). Standard views of the LV were assessed by 2-dimensional
and M-mode techniques. LVEDD and LVESD, interventricular
septal and posterior wall thicknesses, and LVEF were measured
according to the American Society of Echocardiography recom-
dinations.19 LV mass was calculated by using the cube formula and
the correction formula proposed by Devereux et al.19 LV mass
was divided by body surface area to yield LV mass index. The LV stroke
volume was measured from the LV outflow tract with the use of
pulsed Doppler measurements. Mitral regurgitation was identified by
color flow Doppler. A standard 0-to-4 scoring system, where 0
indicates none or trivial and 4 indicates severe regurgitation, was
used. Forward LV work was calculated as: systolic blood pressure

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**Measurement of Myocardial Perfusion and Oxidative and FFA Metabolism**

The positron-emitting tracers $[^1^5^O]H_2O$, $[^1^1^C]acetate$, and $[^1^1^C]palmitate$ were produced as previously described.$^{20-22}$ The subjects were in a supine position in the GE Advance whole body PET scanner (General Electric, Milwaukee, Wis). Correct positioning of the patient was ascertained on a rectilinear transmission scan followed by a transmission scan for photon attenuation correction. Myocardial perfusion was measured with an intravenous bolus of $[^1^5^O]H_2O$ with simultaneous start of an approximately 5-minute dynamic emission scan ($14\times5$, $3\times10$, $3\times20$, $4\times30$ seconds). Thereafter, myocardial oxidative metabolism was measured with an intravenous bolus of $[^1^1^C]acetate$ with simultaneous start of a 29-minute dynamic emission scan ($10\times10$, $1\times60$, $5\times100$, $5\times120$, $2\times240$ seconds). While waiting for tracer decay, subjects underwent echocardiographic examination. After repeated transmission scans for myocardial FFA uptake and oxidation measurement, the subjects received an intravenous bolus of $[^1^1^C]palmitate$ with simultaneous start of a 30-minute dynamic emission scan ($5\times60$, $10\times30$, $2\times60$, $9\times120$ seconds). All PET data were corrected for dead time, decay, and measured photon attenuation. Images were processed with the standard reconstruction algorithm.

**Calculation of Myocardial Perfusion, Oxidative Metabolism, and Estimate of Efficiency**

In the perfusion study, regions of interest (ROIs) were drawn on the LV myocardium on an average of 4 midventricular transaxial planes covering the septum, anterior wall, lateral wall, and the whole LV myocardium. An average of the lateral and anterior wall ROIs was used to represent the LV. Regional myocardial perfusion was calculated with a single compartment model.$^{23}$ An LV cavity ROI was drawn and used as the input function for determination of the LV time–activity curve.$^{24}$ In the myocardial $[^1^1^C]acetate$ studies, one ROI covering the whole LV myocardium (“horseshoe” ROI) was drawn on an average of 4 midventricular transaxial planes. Monoexponential fitting was applied and $[^1^1^C]acetate$ clearance rate ($K_{ mono}$) was calculated. Myocardial efficiency of forward work (the relationship between forward work and oxidative metabolism) was estimated as: forward LV work per gram/global LV $K_{ mono}$.

**Calculation of Myocardial FFA Uptake Index and β-Oxidation Rate Constant**

To calculate myocardial FFA uptake index, ROIs were drawn on 4 midventricular transaxial planes covering the whole LV wall ("horseshoe" ROI). An additional small circular ROI was placed in the middle of the LV cavity and was used to calculate the input function. A $[^1^1^C]palmitate$ uptake index in the myocardium was calculated by dividing the myocardial activity at 7.5 minutes by the integral of the plasma time–activity curve.$^{20}$ The myocardial FFA uptake index was calculated by multiplying the $[^1^1^C]palmitate$ uptake index by the mean serum FFA concentration during the $[^1^1^C]palmitate$ scan. The myocardial $[^1^1^C]palmitate$ β-oxidation rate constant was calculated as previously described.$^{20}$ Biexponential curve was fitted on the early part of the downsloping phase of the time–activity curve.$^{20}$

**Biochemical Analysis**

Plasma glucose was determined by a glucose oxidase method (GM7 Analysers, Analox Instruments, Hammersmith, UK). Serum-free insulin concentrations were measured by using a double-antibody radioimmunoassay (Insulin RIA kit, Pharmacia, Uppsala, Sweden) after precipitation with polyelectrolyte glycol. The HOMA index was calculated as (fasting serum insulin × fasting plasma glucose)/22.5.$^{25}$ Serum FFAs were determined with an enzymatic colorimetric method (Nefra C Test, Wako Chemicals GmbH, Neuss, Germany). Plasma lactate was determined by enzymatic analysis.$^{26}$

**Statistical Analysis**

Values are expressed as mean±SD. To compare results between healthy and failing hearts, the unpaired Student $t$ test was applied in normally distributed parameters, and the Wilcoxon rank-sum exact test was applied in non-normally distributed parameters. The paired Student $t$ test was used for intragroup comparisons between parameters before and after acipimox administration. Linear regression analysis (Pearson and Spearman when appropriate) was used to calculate correlations between continuous variables in patients and healthy volunteers. A probability value <0.05 was considered statistically significant. All statistical tests were 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.

**Results**

**Biochemical and Hemodynamic Parameters**

At baseline, biochemical parameters were similar between the groups (Table 2). After acipimox administration, serum FFA levels decreased strikingly and similarly in the both groups as expected (from 0.65±0.23 to 0.098±0.040 mmol·L$^{-1}$, $P$<0.001, and from 0.62±0.12 to 0.074±0.045 mmol·L$^{-1}$, respectively. Biochemical and Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Fasting</th>
<th>Acipimox</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$fS$ FFA, mmol·L$^{-1}$</td>
<td>0.65±0.23</td>
<td>0.098±0.040</td>
<td>−84*</td>
</tr>
<tr>
<td>$fP$ Glucose, mmol·L$^{-1}$</td>
<td>6.0±0.6</td>
<td>5.5±0.6</td>
<td>−7.7†</td>
</tr>
<tr>
<td>$fS$ Insulin, mU·L$^{-1}$</td>
<td>11.2±8.2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>$fP$ Lactate, mmol·L$^{-1}$</td>
<td>1.1±0.3</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic</th>
<th>Fasting</th>
<th>Acipimox</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, 1·min$^{-1}$</td>
<td>63±10</td>
<td>63±10</td>
<td>+0.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118±16</td>
<td>119±15</td>
<td>+1.0</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70±14</td>
<td>72±13</td>
<td>+2.7</td>
</tr>
<tr>
<td>Rate–pressure product, mm Hg·min$^{-1}$</td>
<td>7534±1728</td>
<td>7528±1520</td>
<td>+1.3</td>
</tr>
</tbody>
</table>

Data are presented as the mean±SD. *$P$<0.001 vs baseline, †$P$<0.01 vs baseline, ‡$P$<0.001 between groups.
groups the marked suppression of FFA uptake with a modest
administration (black bars) in IDCM patients and controls. Note in both
patients and controls, respectively). Glucose levels
tended to decrease in the control group (P<0.01) between the groups (Figure 3A).
Myocardial FFA uptake was similar in both groups at baseline as well as the response to acipimox administration were comparable between the groups (Figure 2). Acipimox reduced myocardial FFA uptake strikingly in both groups as expected (from 5.58±2.02 to 1.02±0.39 μmol · 100 g⁻¹ · min⁻¹, P<0.0001, and from 6.17±1.07 to 0.98±0.61 μmol · 100 g⁻¹ · min⁻¹, P<0.02, not significant between the groups)
Myocardial β-oxidation rate constant, in turn, increased significantly in both groups (from 0.040±0.009 to 0.049±0.011 min⁻¹, P<0.002, and from 0.039±0.005 to 0.044±0.007 min⁻¹, P<0.05, patients and controls, respectively, not significant between the groups).

Myocardial FFA Uptake and β-Oxidation Rate Constant
Myocardial FFA uptake and β-oxidation rate constant at baseline as well as the response to acipimox administration were comparable between the groups (Figure 2). Acipimox reduced myocardial FFA uptake strikingly in both groups as expected (from 5.58±2.02 to 1.02±0.39 μmol · 100 g⁻¹ · min⁻¹, P<0.0001, and from 6.17±1.07 to 0.98±0.61 μmol · 100 g⁻¹ · min⁻¹, P<0.02, not significant between the groups).

Myocardial Perfusion, Oxidative Metabolism, Work, and Estimate of Efficiency
Myocardial perfusion was similar in both groups at baseline and remained unchanged after acipimox administration (Table 3). At baseline, LV oxidative metabolism, stroke volume, and total cardiac work were similar between the groups. Myocardial work per gram of tissue (2.14±0.72 versus 3.74±3.35 mm Hg · L · g⁻¹ · min⁻¹, P<0.001) as well as efficiency of forward work (35.4±12.3 versus 54.3±8.9 mm Hg · L · g⁻¹, P<0.001) were clearly lower in the patient group as compared with controls (Table 3).

After acipimox administration, LV oxidative metabolism decreased in the control group (−22%, P<0.01 versus baseline), but it remained unchanged in the patient group (+1.5%, not significant). The different responses to acipimox were significant (P<0.01) between the groups (Figure 3A).

In both groups, acipimox decreased stroke volume (−7.9% in patients and −8.4% in controls, not significant between the groups) and cardiac output (−11% in both groups). In the control group, the efficiency of forward work tended to increase (+18%, P=0.082 versus baseline), whereas in IDCM patients efficiency decreased significantly (−11%, P<0.05 versus baseline). Thus, the response of cardiac efficiency to acipimox in patients was different from that in healthy controls (P<0.01 for change between the groups, Figure 3B).

To investigate further the potential contributing factors to the effects of FFA withdrawal, the association of efficiency

![Figure 2. Myocardial (A) FFA uptake and (B) β-oxidation rate constant in fasting state (white bars) and after acipimox administration (black bars) in IDCM patients and controls. Note in both groups the marked suppression of FFA uptake with a modest increase in the β-oxidation rate constant.](http://circ.ahajournals.org/)

**Table 3. Myocardial Perfusion, Oxidative Metabolism, Work, and Efficiency of Forward Work**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients</th>
<th></th>
<th>Change, %</th>
<th>Controls</th>
<th></th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
<td>Acipimox</td>
<td></td>
<td>Fasting</td>
<td>Acipimox</td>
<td></td>
</tr>
<tr>
<td>Basal perfusion, mL · g⁻¹ · min⁻¹</td>
<td>0.77±0.23</td>
<td>0.71±0.15</td>
<td>−4.6</td>
<td>0.85±0.31</td>
<td>0.74±0.14</td>
<td>−1.6</td>
</tr>
<tr>
<td>LV Kmono, min⁻¹</td>
<td>0.062±0.015</td>
<td>0.063±0.018</td>
<td>+1.5</td>
<td>0.071±0.019</td>
<td>0.055±0.016†</td>
<td>−22‡</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>74.8±19.1</td>
<td>69.4±22.1</td>
<td>−7.9§</td>
<td>84.5±9.4</td>
<td>77.7±15.2</td>
<td>−8.4</td>
</tr>
<tr>
<td>Cardiac output, L · min⁻¹</td>
<td>4.95±1.12</td>
<td>4.39±1.31</td>
<td>−11§</td>
<td>4.55±0.75</td>
<td>4.10±1.18</td>
<td>−11</td>
</tr>
<tr>
<td>LV work power, mm Hg · L · min⁻¹</td>
<td>584±154</td>
<td>527±197</td>
<td>−9.8</td>
<td>537±119</td>
<td>492±159</td>
<td>−9.2</td>
</tr>
<tr>
<td>LV work power/g, mm Hg · L · g⁻¹ · min⁻¹</td>
<td>2.14±0.72*</td>
<td>1.91±0.77*</td>
<td>−9.8</td>
<td>3.74±0.94</td>
<td>3.35±0.78</td>
<td>−9.2</td>
</tr>
<tr>
<td>Efficiency, mm Hg · L · g⁻¹</td>
<td>35.4±12.3</td>
<td>31.6±13.3</td>
<td>−11§</td>
<td>54.3±8.9</td>
<td>62.8±12.1</td>
<td>+18‡</td>
</tr>
</tbody>
</table>

Data are presented as the mean±SD. LV Kmono indicates index of myocardial oxidative metabolism from [¹⁴C]acetate study.

* P<0.001 between groups, †P<0.01 vs baseline, ‡P<0.01 vs change in the patient group, §P<0.05 vs baseline.
with measured parameters was studied. In patients in whom efficiency decreased more strikingly (more than median, n=9), myocardial FFA uptake was significantly lower during FFA deprivation (0.86±0.44 versus 1.18±0.26 minutes⁻¹, P<0.05). In addition, the increase in β-oxidation rate constant was more striking, though only of borderline statistical significance (37±26 versus 13±22%, P=0.056), in those patients with more pronounced decrease in efficiency (Table 4). Fasting lactate levels were significantly lower (P<0.05) and HOMA index tended to be lower (P=0.08) in patients with greater depression in efficiency in response to FFA limitation. β₁-Adrenoceptor occupancy or the severity of LV dysfunction did not correlate with response to FFA deprivation (data not shown). In the control group (but not the cardiomyopathic group), the HOMA index correlated positively with changes in stroke volume (R=0.75, P<0.05, Figure 4A) and the efficiency of forward work (R=0.75, P<0.05, Figure 4B).

**Discussion**

The main and unexpected finding of the present study is that acute suppression of FFA availability in patients with cardiomyopathic heart failure leads to further depression of cardiac work, with unchanged rates of oxidative metabolism, so that myocardial efficiency of forward work deteriorates further (Table 3, Figure 3). In contrast and as expected from current physiological understanding, acute suppression of FFA metabolism in the healthy heart saves oxygen without any decrease in myocardial efficiency (Figure 3), which is probably explained by switching substrate metabolism toward the more energy-efficient glucose. In the healthy hearts, the acute FFA depletion reduced the oxygen demand by 22% (Figure 3), similar to the 27% oxygen saving noted in mice. Thus, the unexpected results of the present study argue against the important hypothesis that switching myocardial substrate metabolism acutely from FFA to glucose may be beneficial for the failing heart. It is worth noting, however, that conclusions only on acute but not long-term metabolic modulation can be made on the basis of this study.

**FFA Oxidation**

Sack and coworkers demonstrated that, in severely failing human hearts (mean EF, 21%), myocardial FFA oxidation enzyme genes are downregulated. However, the present study suggests that, in modestly severe heart failure, myocardial FFA oxidation enzymes can be acutely upregulated when

**TABLE 4. Comparison Between IDCM Patients With Efficiency Decrease After Acipimox Administration**

<table>
<thead>
<tr>
<th></th>
<th>Efficiency Decrease &gt;10% (n=9)</th>
<th>Efficiency Decrease &lt;10% (n=9)</th>
<th>P Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV FFA uptake index, fasting, μmol · 100 g⁻¹ · min⁻¹</td>
<td>4.88±1.21</td>
<td>6.27±2.48</td>
<td>0.15</td>
</tr>
<tr>
<td>LV FFA uptake index, acipimox, μmol · 100 g⁻¹ · min⁻¹</td>
<td>0.86±0.44</td>
<td>1.18±0.26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Change in LV FFA uptake index, %</td>
<td>-82±9.7</td>
<td>-79±7.7</td>
<td>0.47</td>
</tr>
<tr>
<td>LV FFA β-oxidation rate constant, fasting, min⁻¹</td>
<td>0.034±0.006</td>
<td>0.046±0.008</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>LV FFA β-oxidation rate constant, acipimox, min⁻¹</td>
<td>0.047±0.014</td>
<td>0.051±0.009</td>
<td>0.60</td>
</tr>
<tr>
<td>Change in β-oxidation rate constant, %</td>
<td>37±26</td>
<td>13±22</td>
<td>0.056</td>
</tr>
<tr>
<td>Fasting serum insulin, mU · L⁻¹</td>
<td>7.6±2.9</td>
<td>15±10</td>
<td>0.10</td>
</tr>
<tr>
<td>HOMA index</td>
<td>2.0±1.0</td>
<td>4.1±3.0</td>
<td>0.081</td>
</tr>
<tr>
<td>Fasting plasma lactate, mmol · L⁻¹</td>
<td>1.0±0.2</td>
<td>1.2±0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>β₁-Adrenoceptor occupancy, %</td>
<td>93±7.1</td>
<td>84±18</td>
<td>0.20</td>
</tr>
<tr>
<td>EF, fasting, %</td>
<td>36±7.5</td>
<td>31±10</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values are mean±SD.
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Figure 4. The association between HOMA index and the change in (A) stroke volume and (B) efficiency of forward work after acipimox administration in healthy volunteers. Note a correlation between an increased HOMA index and changes in stroke volume and efficiency. There were no such correlations in IDCM patients.

FFA levels are suppressed, because the relative increase in β-oxidation rate was similar in IDCM patients and healthy volunteers in response to acipimox administration. Thus, although myocardial contractile function and oxidative metabolism are uncoupled after acute substrate deprivation, the failing heart can preserve ability to upregulate oxidative FFA metabolism. It is important to note, however, that the calculated myocardial β-oxidation rate constant only indicates the fraction of the intracellular available FFA pool that is entering β-oxidation, not the absolute amount of FFA oxidized. It is likely that, given the striking suppression of FFA uptake, the absolute FFA oxidation is also decreased.

Interestingly, in patients in whom decreased efficiency was most prominent, the myocardial FFA uptake after acipimox was lower and the increase in β-oxidation fraction was more marked when compared with patients with a lesser decrease in efficiency (Table 4). Furthermore, fasting lactate levels, and therefore the availability of lactate as an alternative fuel, were lower in the former group. These findings further support the proposal that the failing heart of this degree of severity is more rather than less dependent on an adequate availability of FFA as substrate.

Substrate Switching

The present results contrast with those of experimental studies in animals in which acute4 or short periods5 of enhancement of myocardial glucose metabolism improved cardiac function. In patients, Wiggers et al28 demonstrated that acute decreases or increases in FFA availability did not influence contractile function in chronically stunned and hibernating human myocardium, with sustained ability to adapt to extreme short-term changes in substrate supply both at rest and after maximal exercise. The degree of heart failure, as judged by the EFs, did not change during substrate switches. The differing results may be related to the different diseases (ischemic dysfunction versus IDCM). In addition, our study had a larger patient population in which myocardial substrate metabolism was quantified with more comprehensive parameters of oxidative metabolism and myocardial efficiency.

Treatment with β-blockers induces a switch from myocardial FFA toward glucose metabolism.4,10 It can be hypothesized that no additional benefit could be achieved by limiting FFA availability in heart failure patients in whom myocardial FFA uptake was already suppressed by β-blockade. However, in the present study, the degree of β-blockade, as estimated by β1-adrenoceptor occupancy, varied strikingly within the patient group without any clear association with the response to acipimox administration (Table 4).

Theoretically, it could be postulated that insulin resistance, a common comorbidity in heart failure,29,30 could explain the inability of the failing heart to acutely switch from FFAs to glucose when FFA availability is limited. However, the HOMA index, an indicator of insulin resistance, tended to be lower in our patients with more severe deterioration of myocardial efficiency. Furthermore, in the nonfailing control group the HOMA index correlated positively with the change in stroke volume and efficiency of forward work after acipimox administration (Figure 4). This accords with the results of Peterson et al31 in obese young women and suggests that limiting FFA availability may increase myocardial efficiency in nonfailing hearts with insulin resistance.

Limitations

Because of the very demanding study protocol, we could not include a measurement of myocardial glucose oxidation, as the protocol was already long and tedious (Figure 1). However, the unchanged rates of oxidation after acipimox in the cardiomyopathic group without any increase in the HOMA index in patients with the greater decrease in efficiency (Table 4) suggests that there was a reciprocal increase in glucose oxidation. We previously demonstrated that acipimox produces an increase in myocardial glucose uptake equal to that observed during glucose-insulin clamping.3 Furthermore, in knockout models, when FFA uptake by the heart is reduced, uptake of glucose increases.32,33 Of interest, prolonged sustained deprivation of FFA as fuel was associated with cardiac abnormalities in both mouse models. A second limitation is that measurements in the fasting state and after acipimox administration were not performed in a randomized order. This would require a 2-day study protocol, and the metabolic as well as hemodynamic state of patients with moderate heart failure might vary significantly from day to day. Therefore, we preferred this study design as an adequate compromise to test the hypothesis of the study. Third, despite...
the present robust analysis of the palmitate kinetics, the absolute amount of FFA oxidized could not be measured. The estimated myocardial β-oxidation rate constant merely indicates the fraction of intracellular available FFA pool that is entering β-oxidation. Fourth, the controls and patient groups could, by definition, not be properly matched, especially with regard to disease states and medications (Table 1). Fifth, our results pertain to a group of cardiomyopathic patients with moderate heart failure (mean EF, 36%). In more severe failure, the balance between glucose and FFA metabolism may change to be more in favor of glucose.4,27,34 However, in that case, the adverse effects of acute FFA deprivation should be more rather than less marked.

Conclusions

The results of the present study demonstrate that acute FFA deprivation in patients with cardiomyopathic heart failure, in contrast to healthy controls, uncouples cardiac contractile function from oxidative metabolism, which explains the decreased cardiac efficiency. These findings may indicate that the cardiomyopathic myocyte has lost its ability to adapt to acute extreme substrate level changes when necessary. Although metabolic modulation has raised a great deal of interest as an alternative or additional form of therapy in the failing heart,4–6 the results of the present study suggest that indirect stimulation of myocardial glucose metabolism by acutely limiting FFA availability would not be a promising form of therapy in heart failure due to IDCm. Whether chronic administration of other inhibitors of FFA oxidation, beyond the 8 weeks of benefit already shown in one human study with perhexiline,6 could beneficially influence myocardial efficiency of work and clinical outcome in IDCm patients remains to be demonstrated.

Our results are, at first sight, counterintuitive in view of the current evidence favoring the concept that acute inhibition of myocardial fatty acid oxidation can rapidly improve LV function and mechanical efficiency in heart failure.4 Of interest though, even in chronic heart failure, cautions have been expressed about therapy involving chronic alteration of metabolic pathways with the theoretical risk of cardiac dysfunction.35 Rather, our data provide the first evidence in humans for the hypothesis that “the heart functions best when it oxidizes two substrates simultaneously”.36 We suggest that there is an obligatory role for oxidative metabolism of FFA in the failing cardiomyopathic heart.

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Disclosures

None.

References

CLINICAL PERSPECTIVE

Experimental and preliminary clinical studies have demonstrated that metabolic modulators that enhance myocardial glucose metabolism directly or indirectly by inhibiting free fatty acid (FFA) metabolism may be beneficial to the failing heart. Thus, a reduction of circulating FFA levels was expected to become an effective treatment for human heart failure. The main purpose of this study was to test the hypothesis that acute FFA depletion would result in an increased myocardial efficiency of forward work in patients with heart failure caused by idiopathic dilated cardiomyopathy (IDCM).

Unexpectedly, the results of the present study demonstrate that acute FFA deprivation in patients with IDCM, in contrast to healthy controls, uncouples cardiac contractile function from oxidative metabolism so that myocardial efficiency deteriorates further. Thus, the results of the present study argue against the hypothesis that limiting FFA availability may be beneficial for the cardiomyopathic heart failure. Whether chronic administration of other inhibitors of FFA oxidation could beneficially influence myocardial efficiency of work and clinical outcome in IDCM patients remains to be demonstrated.
Free Fatty Acid Depletion Acutely Decreases Cardiac Work and Efficiency in Cardiomyopathic Heart Failure

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