Metabolic Modulation With Perhexiline in Chronic Heart Failure
A Randomized, Controlled Trial of Short-Term Use of a Novel Treatment

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Background—Chronic heart failure (CHF) is a major cause of morbidity and mortality that requires a novel approach to therapy. Perhexiline is an antianginal drug that augments glucose metabolism by blocking muscle mitochondrial free fatty acid uptake, thereby increasing metabolic efficiency. We assessed the effects of perhexiline treatment in CHF patients.

Methods and Results—In a double-blind fashion, we randomly assigned patients with optimally medicated CHF to either perhexiline (n=28) or placebo (n=28). The primary end point was peak exercise oxygen consumption (V̇O₂max), an important prognostic marker. In addition, the effect of perhexiline on myocardial function and quality of life was assessed. Quantitative stress echocardiography with tissue Doppler measurements was used to assess regional myocardial function in patients with ischemic CHF. 31P magnetic resonance spectroscopy was used to assess the effect of perhexiline on skeletal muscle energetics in patients with nonischemic CHF. Treatment with perhexiline led to significant improvements in V̇O₂max (16.1 ± 0.6 to 18.8 ± 1.1 mL · kg⁻¹ · min⁻¹; P<0.001), quality of life (Minnesota score reduction from 45 ± 5 to 34 ± 5; P=0.04), and left ventricular ejection fraction (24 ± 1% to 34 ± 2%; P<0.001). Perhexiline treatment also increased resting and peak dobutamine stress regional myocardial function (by 15% and 24%, respectively) and normalized skeletal muscle phosphocreatine recovery after exercise. There were no adverse effects during the treatment period.

Conclusions—In patients with CHF, metabolic modulation with perhexiline improved V̇O₂max, left ventricular ejection fraction, symptoms, resting and peak stress myocardial function, and skeletal muscle energetics. Perhexiline may therefore represent a novel treatment for CHF with a good safety profile, provided that the dosage is adjusted according to plasma levels. (Circulation. 2005;112:3280-3288.)

Key Words: heart failure • metabolism • exercise • fatty acids • glucose

Despite considerable advances in neurohumoral modulation therapy, chronic heart failure (CHF) remains a significant and increasing cause of mortality and morbidity. Indeed, recent attempts to improve outcomes in CHF patients with additional blockade have demonstrated little incremental benefit.¹⁻³ There is, therefore, an urgent need for novel therapeutic approaches.

In CHF, both exercise capacity and oxygen consumption during peak exertion (V̇O₂max) are reduced because of abnormal cardiac and skeletal muscle function.⁴⁻⁵ Impairment of V̇O₂max is correlated with functional status and prognosis.⁶⁻⁷ Angiotensin-converting enzyme inhibitors, an established treatment for CHF, have been shown previously to improve V̇O₂max.⁸⁻⁹ A potential therapeutic strategy directly aimed at improving cardiac and skeletal muscle function without increasing myocardial oxygen utilization has theoretical advantages as a potential novel therapeutic strategy and may be expected to increase V̇O₂max.

One of the major determinants of the efficiency of muscle oxygen utilization is the metabolic substrate used. In the healthy adult, free fatty acids (FFAs) are the predominant substrate (~70%) used by cardiac muscle.¹⁰⁻¹¹ Although simple stoichiometry would predict that FA utilization would require ~12% more oxygen per unit of ATP generation, in
fact, the oxygen uptake when FAs are oxidized is substantially higher. This may be due to the observation that activation of the peroxisome proliferator–activated receptor-α by FAs upregulates mitochondrial uncoupling protein expression.

Perhexiline maleate is an antifungal drug that potently inhibits the mitochondrial FFA uptake enzymes carnitine palmitoyl transferase-1 (CPT-1) and CPT-2, thereby shifting muscle substrate utilization from FFAs toward glucose. It is not negatively inotropic and does not alter systemic vascular resistance at therapeutic plasma levels.

We investigated whether perhexiline-induced shifts in metabolism would lead to improved exercise capacity, quality of life, myocardial function, and skeletal muscle energetics in CHF.

**Methods**

**Study Design**

This double-blind, randomized, placebo-controlled study was approved by the local research ethics committee, and all patients provided written, informed consent. Fifty-six patients with CHF were recruited. Entry criteria were as follows: Left ventricular ejection fraction (LVEF) <40% on echocardiography and optimally medicated CHF with New York Heart Association class II or III symptoms. Cardiopulmonary exercise testing with respiratory gas analysis, completion of the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and 2D echocardiography were performed at baseline for all patients.

Patients were allocated to 1 of 2 groups, ischemic or nonischemic, depending on the presence or absence of significant coronary artery disease during coronary angiography. The ischemic group (n=30) underwent dobutamine stress echocardiography at baseline. The nonischemic group (n=26) underwent 31P magnetic resonance spectroscopy (MRS) to measure skeletal muscle mitochondrial function.

**All Patients**

**Cardiopulmonary Exercise Test**

Incremental exercise testing with assessment of respiratory gas exchange was performed on a treadmill according to the Weber protocol. Breath-by-breath respiratory gases were measured during exercise with a Pulmolab EX670 mass spectrometer, which was calibrated before every study. Raw data were averaged to 30-second intervals, and V02max during peak exercise was obtained. ECGs and blood pressure were monitored throughout. Exercise was terminated at the subject’s request because of fatigue or breathlessness.

**Minnesota Living With Heart Failure Questionnaire**

Quality of life was assessed with the standard 21-question MLHFQ. This is a well-validated measure of symptoms in CHF. Each question was scored from 0 to 5, and the sum of the scores was calculated, whereby a higher score indicated a poorer quality of life. All patients completed the questionnaires alone and without assistance.

**Resting Echocardiography**

Echocardiography was performed with patients in the left lateral decubitus position with a Vingmed System V echocardiographic machine and a 2.5-MHz transducer. Measurements were averaged for 2 beats. Resting scans were acquired in standard echocardiographic windows for LVEF, transmitral Doppler, and resting tissue Doppler. LV volumes were obtained by biplane echocardiography, and LVEF was derived from a modified Simpson’s formula.

Tissue Doppler echocardiography was performed because it allows objective assessment of regional wall motion and is superior to conventional gray-scale echocardiography when used in conjunction with dobutamine stress. At baseline, a pulsed tissue Doppler recording of lateral mitral annular motion was recorded for estimation of LV pressure. Peak systolic velocity was measured as an indicator of LV long-axis function.

We also measured the ratio of the peak E wave from transmitral valve Doppler recordings versus the E wave from pulsed tissue Doppler recordings of the lateral mitral annulus (E/Ea), which is a noninvasive indicator of LV end-diastolic pressure.

**Ischemic Group**

**Dobutamine Stress Echocardiography**

After baseline echocardiographic studies were completed, dobutamine was infused with a syringe driver at 5 μg·kg⁻¹·min⁻¹ and increased at 3-minute intervals to 10, 20, 30, and 40 μg·kg⁻¹·min⁻¹. As much as 1 mg atropine was given if the hemodynamic response was submaximal. ECGs and blood pressures were monitored at each stage. End points for termination of the test were attainment of ≥85% of the target heart rate (220−patient age), evidence of ischemia, or severe side effects from dobutamine.

Tissue Doppler images were stored digitally during the last 90 seconds of each stage. Data from all stages were analyzed offline as the mean of 2 beats by a blinded observer using Echopac software. Results for peak systolic velocity were expressed at rest, during low-dose dobutamine (10 μg·kg⁻¹·min⁻¹), and at peak-dose dobutamine (the last stage before the infusion was terminated, which may have included the addition of atropine). Velocities were measured in 15 LV segments representing areas supplied by all 3 major coronary arteries, as described in detail elsewhere. These included basal, midposterior, lateral, inferior, septal, and anterior segments. Apical segments were not used owing to poor reproducibility of data within those segments.

**Nonischemic Group**

**31P Magnetic Resonance Spectroscopy**

Patients with CHF have delayed recovery of skeletal muscle phosphocreatine after exercise. 31P MRS allows changes in skeletal muscle intracellular high-energy phosphate compounds and pH to be measured noninvasively. At the end of exercise, because glycogenolysis has stopped and phosphocreatine resynthesis is purely oxidative, analysis of phosphocreatine recovery provides information about skeletal muscle mitochondrial function. To determine the effect of perhexiline on muscle energetics, MRS of calf muscle before, during, and after local exercise was performed with a 2-T superconducting whole-body magnet interfaced to a Bruker Avance spectrometer, as described in detail elsewhere.

Subjects were positioned within the magnet in the supine position with a 6-cm-diameter surface coil under the maximal circumference of the right calf muscle. 31P MR spectra were collected at rest, during exercise, and during recovery. After spectral acquisition at rest, a standardized exercise protocol was used that involved plantar flexion at 0.5 Hz lifting 10% of lean body mass a distance of 7 cm. This work load was continued for 4 minutes and then incremented by 2% of lean body mass for every subsequent minute until fatigue or phosphocreatine hydrolysis reached 50% of the resting level. Recovery spectra were subsequently acquired for 11 minutes.

Phosphocreatine concentrations were quantified by a time-domain–fitting routine (VARPRO). Phosphocreatine recovery halftime after exercise, a marker of skeletal muscle mitochondrial function.

**TABLE 1. Dose Adjustments**

<table>
<thead>
<tr>
<th>Perhexiline Concentration, mg/L</th>
<th>Recommended New Daily Dosage</th>
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<tbody>
<tr>
<td>&lt;0.15</td>
<td>Double daily dose</td>
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<tr>
<td>0.15 to 0.59</td>
<td>No change</td>
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<td>0.6 to 0.89</td>
<td>Reduce by 25%</td>
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<td>0.9 to 1.19</td>
<td>Halve daily dose</td>
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<tr>
<td>&gt;1.2</td>
<td>Cease for 1 week, then reduce daily dose to 25% of previous dose</td>
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TABLE 2. Patient Baseline Characteristics and Treatments

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<tr>
<th></th>
<th>Placebo, Entire Group</th>
<th>Placebo, Ischemic Group</th>
<th>Perhexiline, Entire Group</th>
<th>Perhexiline, Ischemic Group</th>
<th>Placebo, Nonischemic Group</th>
<th>Perhexiline, Nonischemic Group</th>
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<td>n</td>
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<td>Dose, mg</td>
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<td>Amiodarone</td>
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<td>Insulin</td>
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<td>Statins</td>
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<td>11</td>
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<td>Serum perhexiline levels, mg/L</td>
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<td>Week 1</td>
<td>0</td>
<td>0.50±0.09</td>
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<td>0.44±0.08</td>
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<td>0.57±0.19</td>
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<td>Week 4</td>
<td>0</td>
<td>0.49±0.09</td>
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<td>0.34±0.07</td>
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<td>0.67±0.20</td>
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<td>Week 8</td>
<td>0</td>
<td>0.47±0.10</td>
<td>0</td>
<td>0.50±0.07</td>
<td>0</td>
<td>0.43±0.12</td>
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<td>Placebo/perhexiline dose achieved, mg/d</td>
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<td>Week 1</td>
<td>288±20</td>
<td>228±17</td>
<td>269±28</td>
<td>240±21</td>
<td>304±25</td>
<td>213±25</td>
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<tr>
<td>Week 4</td>
<td>323±34</td>
<td>226±28</td>
<td>306±50</td>
<td>240±47</td>
<td>327±26</td>
<td>209±26</td>
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<td>Week 8</td>
<td>314±28</td>
<td>228±27</td>
<td>284±47</td>
<td>233±45</td>
<td>342±30</td>
<td>222±30</td>
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</tbody>
</table>

ACE indicates angiotensin-converting enzyme. Other abbreviations are as defined in text.

Function independent of skeletal muscle mass and exercise intensity, was calculated as previously described.24

Intervention

After baseline studies, patients were randomized in a double-blind fashion to receive either perhexiline (n=28) or placebo (n=28) 100 mg BID. Blood was obtained at 1, 4, and 8 weeks after initiation of the drug for measurements of serum perhexiline levels, with subsequent dose titration to prevent toxicity. Dose adjustments were advised by an unblinded physician according to a protocol devised by Horowitz et al.26 as shown in Table 1.

Identical dosage adjustments were also made for randomly allocated placebo-treated patients by the unblinded observer to ensure that blinding of the investigators was maintained. After 8 weeks of treatment, patients were reevaluated as described earlier.

Statistics

The primary end point for this study was predefined as VO2max with the following secondary end points: MLHFQ score, LVEF, E:EA, myocardial velocities at rest and during pharmacological stress, and phosphocreatine recovery half-times. Patients in both ischemic and nonischemic groups were randomized separately but with similar protocols to allow for pre hoc analysis of the primary end point for both the combined group and the 2 etiologic groups. The study had a 95% power to detect a 2 mL·kg⁻¹·min⁻¹ increase in VO2max in...
Volumes were reduced by 20% in the perhexiline group ($P<0.001$) but were unchanged in the placebo group (Table 3). Long-axis systolic function increased by 24%, reflecting an improvement in subendocardial function, and there was a 24% reduction in the E:EA, reflecting a reduction in LV end-diastolic pressure after treatment with perhexiline (Figure 2).

Symptoms improved in patients taking perhexiline. ML-HFQ scores were reduced by 24% after treatment in the perhexiline group ($P=0.04$) but remained unchanged in the placebo group (Figure 3). Mean New York Heart Association class improved by 21% in the perhexiline group with no change in the placebo group (Table 3; $P=0.02$).

Within the ischemic cohort, there was no significant difference in heart rate at rest or during dobutamine stress in either group (Table 3). However, mean peak systolic velocity increased by 15% ($P=0.007$) at rest and by 24% ($P=0.003$) at the peak dobutamine dose after perhexiline treatment (Figure 4).

Examples of skeletal muscle $^{31}$P MR spectra are shown in Figure 5. In patients with nonischemic CHF, perhexiline shortened skeletal muscle phosphocreatine recovery by 34% ($P<0.05$), bringing it to within the normal range for healthy adults (14 to 50 seconds), whereas it was unchanged in the placebo group (Figure 5).$^{21}$

**Discussion**

In the present study, we found that addition of perhexiline to optimal contemporary medical therapy in patients with moderate to severely symptomatic CHF increased $V_O^{\text{max}}$ by 17% (almost 3 mL · kg$^{-1}$ · min$^{-1}$), LVEF by 42%, long-axis systolic function by 20%, and myocardial function at rest by 15% and during stress by 24%. Treatment with perhexiline also reduced patient-reported symptom score by 24% and normalized skeletal muscle energetics. This was achieved in the absence of significant side effects. Until now, no clinical studies have examined the potential benefits of metabolic drugs in both ischemic and nonischemic CHF in a randomized, controlled fashion, nor with this range of clinically and prognostically important end points.

The mechanism for the improvement seen in myocardial function with perhexiline is likely to be related to inhibition of FFA uptake and a metabolic shift toward the use of glucose and lactate. This may restore insulin sensitivity in the failing heart and make it more oxygen-efficient. In addition to requiring more oxygen than glucose to generate energy, excessive FFA metabolism has other potentially detrimental effects on the heart. FFA metabolism is known to uncouple oxidative phosphorylation from electron transport and suppresses glucose oxidation through a direct inhibitory action on the glycolytic pathway.$^{27}$ This inhibition causes increased lactate and proton accumulation within myocardial cells,$^{28}$ leading to a fall in intracellular pH that causes a reduction in contractile function.$^{29}$ Furthermore, FFA metabolite accumulation has been shown to reduce the ventricular arrhythmia threshold$^{30}$ and induce diastolic dysfunction.$^{31}$ Initial studies suggested that perhexiline had calcium channel–blocking properties,$^{32,33}$ but subsequent studies showed that this was only observed at very high plasma concentrations.$^{33,34}$ In a

**Results**

All patients completed the 8-week course of treatment. There were no deaths during the study period. Side effects in the perhexiline group were restricted to transient nausea and dizziness during the first week of treatment (n=3). The perhexiline and placebo groups were well matched for baseline characteristics and treatment (Table 2).

$V_O^{\text{max}}$ at baseline was similar in the perhexiline and placebo groups (Figure 1). After treatment, $V_O^{\text{max}}$ was unchanged in the placebo group but had increased by 17% (2.7±0.8 mL · kg$^{-1}$ · min$^{-1}$) in the perhexiline group ($P<0.001$). The increases in $V_O^{\text{max}}$ in the ischemic and nonischemic groups were 2.9±1.2 ($P=0.008$) and 2.5±0.4 ($P=0.03$) mL · kg$^{-1}$ · min$^{-1}$, respectively.

Mean LVEF increased by 10±2 absolute percentage points after treatment in the perhexiline group ($P<0.001$) but was unchanged in the placebo group (Figure 1). LV end-systolic
TABLE 3. Primary and Secondary End Points

<table>
<thead>
<tr>
<th>Placebo Group</th>
<th>Perhexiline Group</th>
<th>P</th>
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<tbody>
<tr>
<td>VO₂max, mL/kg/min</td>
<td>16.3±0.8</td>
<td>16.1±0.6</td>
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<tr>
<td>After</td>
<td>16.0±0.9</td>
<td>18.8±1.1</td>
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<tr>
<td>Exercise time, min</td>
<td>9.9±1.2</td>
<td>10.5±1.2</td>
</tr>
<tr>
<td>Before</td>
<td>10.9±0.9</td>
<td>12.3±1.1</td>
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<tr>
<td>Respiratory exchange ratio during peak exercise*</td>
<td>1.1±0.02</td>
<td>1.1±0.03</td>
</tr>
<tr>
<td>Before</td>
<td>1.1±0.02</td>
<td>1.1±0.03</td>
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<tr>
<td>NYHA class</td>
<td>2.2±0.1</td>
<td>2.4±0.1</td>
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<tr>
<td>Before</td>
<td>2.1±0.1</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>Resting blood pressure, mm Hg</td>
<td>111/63±5/3</td>
<td>116/69±7/4</td>
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<tr>
<td>Before</td>
<td>113/67±5/4</td>
<td>113/67±7/4</td>
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<tr>
<td>Peak exercise blood pressure, mm Hg</td>
<td>141/69±5/4</td>
<td>141/75±9/3</td>
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<td>Before</td>
<td>137/88±7/4</td>
<td>142/70±9/5</td>
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<td>Resting heart rate, min⁻¹</td>
<td>76±4</td>
<td>73±3</td>
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<td>Before</td>
<td>78±4</td>
<td>73±3</td>
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<td>Peak exercise heart rate, min⁻¹</td>
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<td>MLHFO score</td>
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<td>Before</td>
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<td>LV end-diastolic volume, mL</td>
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<td>LVEF, %</td>
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<td>Long-axis function, cm/s</td>
<td>6.4±0.6</td>
<td>5.8±0.4</td>
</tr>
<tr>
<td>Before</td>
<td>6.4±0.5</td>
<td>7.2±0.6</td>
</tr>
<tr>
<td>E-EA ratio</td>
<td>8.3±1.0</td>
<td>8.6±0.6</td>
</tr>
<tr>
<td>Before</td>
<td>8.9±1.8</td>
<td>6.5±0.9</td>
</tr>
<tr>
<td>PCr half-time, s</td>
<td>58±10</td>
<td>67±15</td>
</tr>
<tr>
<td>Before</td>
<td>73±24</td>
<td>44±7</td>
</tr>
<tr>
<td>Dobutamine stress echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>67±5</td>
<td>57±2</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3. Continued

<table>
<thead>
<tr>
<th>Placebo Group</th>
<th>Perhexiline Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>After</td>
<td>66±6</td>
<td>53±2</td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>86±8</td>
<td>78±7</td>
</tr>
<tr>
<td>After</td>
<td>74±6</td>
<td>65±6</td>
</tr>
<tr>
<td>Peak dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>130±5</td>
<td>126±4</td>
</tr>
<tr>
<td>After</td>
<td>128±5</td>
<td>122±3</td>
</tr>
<tr>
<td>Mean peak systolic velocity (15 segments)</td>
<td>Rest</td>
<td>3.5±0.2</td>
</tr>
<tr>
<td>Before</td>
<td>3.4±0.2</td>
<td>3.8±0.2</td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>4.6±0.3</td>
<td>4.7±0.3</td>
</tr>
<tr>
<td>After</td>
<td>4.8±0.3</td>
<td>5.0±0.5</td>
</tr>
<tr>
<td>Peak dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>6.4±0.4</td>
<td>6.6±0.5</td>
</tr>
<tr>
<td>After</td>
<td>5.8±0.4</td>
<td>8.2±0.8</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; PCr, phosphocreatine. Other abbreviations are as defined in text. All P values refer to ANCOVA of the differential effect of perhexiline vs placebo. *Ratio of CO₂ emission/oxygen consumption.

Figure 2. Effect of perhexiline treatment on long-axis function (peak systolic velocity of the lateral mitral valve annulus at rest; A) and E-EA ratios (B). P=0.04 (long-axis function), P=0.02 (E-EA ratio). Abbreviations are as defined in text.
non–heart failure population, no effect was observed on systemic vascular resistance at therapeutic plasma concentrations.\textsuperscript{17} We, however, cannot exclude an effect on systemic vascular resistance in this study.

"Metabolic" agents have been investigated as antianginal drugs, but data relating to their potential use in CHF are scarce. Small studies have suggested that increasing glucose metabolism leads to an improvement in myocardial function. Trimetazidine, an inhibitor of FFA \( \beta \)-oxidation, improved wall-motion scores on stress echocardiography\textsuperscript{35} and myocardial function\textsuperscript{36} in ischemic LV dysfunction. More recently, in a long-term, open-label study, trimetazidine improved LV systolic function and caused reverse LV remodeling in patients with mild ischemic heart failure.\textsuperscript{37} However, these patients were not only mildly symptomatic but also suboptimally medically treated. Etomoxir, a potent CPT-1 inhibitor, improved LVEF and peak exercise cardiac output in a small, open-label study in CHF.\textsuperscript{38}

\textsuperscript{31}P MRS was included in the study design to determine whether perhexiline treatment also improved skeletal muscle energetics. Phosphocreatine recovery half-times are a measure of skeletal muscle mitochondrial function independent of muscle bulk and work load.\textsuperscript{25} The faster phosphocreatine recovery after exercise in the perhexiline-treated patients suggested an improvement in skeletal muscle mitochondrial oxidative function. This may reflect an
Improvement in the clinical syndrome and/or be a direct consequence of the metabolic substrate shift in skeletal muscle.

The antianginal efficacy of perhexiline is well documented.\textsuperscript{39,40} However, use of the drug declined because of reports of hepatotoxicity and peripheral neuropathy. It is now apparent that the risk of toxicity was related to the ability to metabolize the drug. “Slow hydroxylators,” with a genetic variant of the cytochrome P450-2D6, are particularly prone to progressive drug accumulation. In the absence of dosage adjustment, prolonged, elevated levels lead to phospholipid accumulation,\textsuperscript{42} which may also occur with other CPT inhibitors, such as amiodarone.\textsuperscript{41} The risk of developing hepatoneurotoxicity with perhexiline is markedly reduced by monitoring and maintaining serum levels between 0.15 and 0.6 mg/L.\textsuperscript{26} None of our patients developed abnormal liver function test results or neuropathy as a consequence of perhexiline treatment followed by close serum-level monitoring and titration.

The present study has several limitations. First, although larger than any other studies with metabolic agents and conducted in a randomized, controlled, double-blinded fashion with multiple clinically important end points, the study was relatively small with a total of 56 patients. Nevertheless, in both the subgroups and the entire group, the results were highly significant. Moreover, improvements were consistent across clinical, echocardiographic, and biochemical parameters. Second, the study duration was only 8 weeks. In light of previous safety concerns with perhexiline, the risk of phospholipidosis requires further monitoring in longer studies. Nevertheless, pharmacological studies have identified the optimal plasma therapeutic range for perhexiline, and by using an inexpensive and effective blood test, side effects associated with this drug are virtually eliminated.\textsuperscript{33,35,43}

The results of the current study therefore establish that perhexiline exerts significant benefits on $\dot{V}O_{2max}$, LVEF, symptomatic status, LV function at rest and during peak stress, and skeletal muscle energy metabolism in patients with stable CHF. The improvement in $\dot{V}O_{2max}$, which was larger than that seen in patients treated with angiotensin-converting enzyme inhibitors,\textsuperscript{8,9} occurred in addition to optimal medical therapy. The improvement was also greater than that reported with biventricular pacing.\textsuperscript{44} Because this study included

**Figure 5.** A, $^{31}$P MR spectra of the right calf muscle at rest, during exercise, and after exercise. PCr indicates phosphocreatine; Pi, inorganic phosphate; $\gamma$, $\alpha$, $\beta$, the 3 phosphate groups of ATP. PCr levels at each stage of exercise are acquired by measuring the area under the PCr peaks. Note that the PCr peak reduces in magnitude as exercise is performed, indicating gradual depletion of PCr, and recovers after exercise is stopped. B, Perhexiline treatment improved skeletal muscle PCr recovery in CHF patients. $P<0.05$. 

Rest | Exercise begins | Peak exercise | End recovery
--- | --- | --- | ---

[Graph showing PCr levels during rest, exercise, and recovery following perhexiline treatment.]
patients without significant coronary artery disease, the ben-
efﬁt cannot therefore be ascribed purely to an anti-ischemic
mechanism. This study therefore provides a general rationale
to investigate the potential beneﬁts of novel metabolic agents
for CHF therapy. Furthermore, it speciﬁcally provides the ra
nionale for the initiation of large-scale, longer-term studies
into the efﬁcacy and safety of perhexiline and subsequently
its potential revalidation for the novel application of CHF.

Acknowledgments
This study was supported by grants received from the British Heart
Foundation. The investigators thank Dr John Williams for the
perhexiline assays and for his independent supervision of dosage
adjustments.

Disclosure
Swedish Orphan (UK), which markets perhexiline as an orphan drug
in Europe, provided the placebo tablets free of charge. J.H. is
coordinating a clinical trial investigating the effects of perhexiline on
inoperable aortic stenosis, which is partly funded by Sigma Pharma-
cueticals, which produces perhexiline in Australia. After results of
this study were obtained, we applied for a patent for the use of
perhexiline in heart failure.

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_Circulation_. 2005;112:3280-3288
doi: 10.1161/CIRCULATIONAHA.105.551457

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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