Myocardial Free Fatty Acid and Glucose Use After Carvedilol Treatment in Patients With Congestive Heart Failure

Thomas R. Wallhaus, MD; Michael Taylor, PhD; Timothy R. DeGrado, PhD; Douglas C. Russell, MD, PhD; Peter Stanko, MD; Robert J. Nickles, PhD; Charles K. Stone, MD

Methods and Results—We studied the effect of carvedilol therapy on myocardial FFA and glucose use in 9 patients with stable New York Heart Association functional class III ischemic cardiomyopathy (left ventricular ejection fraction ≤35%) using myocardial positron emission tomography studies and resting echocardiograms before and 3 months after carvedilol treatment. Myocardial uptake of the novel long chain fatty acid metabolic tracer 14(R, S)-[18F]-fluoro-6-thia-heptadecanoic acid ([18F]-FTHA) was used to determine myocardial FFA use, and [18F]fluoro-2-deoxy-glucose ([18F]-FDG) was used to determine myocardial glucose use. After carvedilol treatment, the mean myocardial uptake rate for [18F]-FTHA decreased (from 20.4±8.6 to 9.7±2.3 mL · 100 g⁻¹ · min⁻¹; P<0.005), mean fatty acid use decreased (from 19.3±7.0 to 8.2±1.8 μmol/L · 100 g⁻¹ · min⁻¹; P<0.005), the mean myocardial uptake rate for [18F]-FDG was unchanged (from 1.4±0.4 to 2.4±0.8 mL · 100 g⁻¹ · min⁻¹; P=0.14), and mean glucose use was unchanged (from 11.1±3.1 to 18.7±6.0 μmol/L · 100 g⁻¹ · min⁻¹; P=0.12). Serum FFA and glucose concentrations were unchanged, and mean left ventricular ejection fraction improved (from 26±2% to 37±4%; P<0.05).

Conclusions—Carvedilol treatment in patients with heart failure results in a 57% decrease in myocardial FFA use without a significant change in glucose use. These metabolic changes could contribute to the observed improvements in energy efficiency seen in patients with heart failure. (Circulation. 2001;103:2441-2446.)

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

Significant evidence has demonstrated that β-adrenergceptor blockade in the setting of stable, chronic heart failure can result in a dramatic improvement in left ventricular function and prognosis in patients with both ischemic and nonischemic cardiomyopathy. The pathophysiological basis for these clinical benefits, perhaps surprisingly, is not clearly established. A potential rationale for the use of β-adrenergceptor blockade in heart failure is its effect to counteract the adverse metabolic effects of long-term sympathethic adrenergic system activation and the resulting increased myocardial oxygen consumption.

In heart failure, myocardial energy efficiency is reduced. It can be hypothesized that myocardial energy efficiency is reduced as a result of inappropriate, catecholamine-induced, enhanced free fatty acid (FFA) use secondary to elevated levels of serum FFAs acting as a metabolic substrate for the myocardium and within the myocardium itself by wasteful cycling of FFAs through intramyocardial lipolysis, reesterification, and suppression of glucose metabolism. β-Adrenergceptor blockade in patients with heart failure improves myocardial energy efficiency and a shift in myocardial substrate use from FFA to glucose oxidation could contribute to the energy-sparing effects of this treatment.

In the present study, we evaluated the effect of a 3-month period of carvedilol treatment on regional myocardial FFA and glucose uptake in patients with stable New York Heart Association (NYHA) functional class III ischemic cardiomyopathy using positron emission tomography (PET) imaging with both the long-chain fatty acid tracer 14(R, S)-[18F]-fluoro-6-thia-heptadecanoic acid ([18F]-FTHA) and [18F]fluoro-2-deoxy-glucose ([18F]-FDG). We hypothesized that a switch in myocardial energy substrate use from FFAs to glucose may be one potential mechanism for the improved energy efficiency seen in the treatment of patients with heart failure.
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±14</td>
</tr>
<tr>
<td>Race, white/black</td>
<td>9/9</td>
</tr>
<tr>
<td>Patients taking an ACE inhibitor</td>
<td>8/9</td>
</tr>
<tr>
<td>Patients taking digoxin</td>
<td>8/9</td>
</tr>
<tr>
<td>Patients taking cholesterol-lowering agents</td>
<td>6/9</td>
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Values are mean±SEM or No. of patients.

Methods

Patient Population

This study was reviewed and approved by the Human Subjects Committee at the University of Wisconsin at Madison. Nine patients were recruited from the University of Wisconsin Hospital and Clinics and the Madison Veterans Hospital (Table 1). All patients gave informed consent. All patients had left ventricular ejection fractions ≤35% and were on active treatment with an ACE inhibitor (if tolerated) and digitalis (unless contraindicated), with stable NYHA functional class III congestive heart failure at least 3 months before study entry. Left ventricular ejection fraction was determined by resting echocardiograms. No patient was taking β-adrenergic blocking agents at the time of study entry. Exclusion criteria included a history of diabetes mellitus, severe or unstable angina, recent myocardial infarction (<3 months), and active alcohol/drug abuse.

Carvedilol Treatment Regimen

All patients completed baseline initial [18F]-FTHA and [18F]-FDG PET scans (Figure 1). Patients then received carvedilol starting at a dose of 3.125 mg orally twice a day for 1 week. Thereafter, dosage was titrated every 2 weeks to a target dose of 25 mg twice a day before returning for follow-up [18F]-FTHA and [18F]-FDG PET scans. During this time, patients were evaluated in the clinic every 2 weeks to assess tolerance and compliance with carvedilol therapy.

[18F]-FTHA and [18F]-FDG Tracer Production

Nucleophilic aqueous [18F]-fluoride was produced by using the 11.4-MeV beam of the University of Wisconsin Radiopharmaceutical Delivery System 112 cyclotron and the high-pressure Au/Ag or Ag body [18O]H2O targets, which are described in detail elsewhere. [18F]-FTHA was synthesized as previously described. [18F]-FDG was produced using a microwave cavity-based adaptation of the Hammacher synthesis, as previously described.

PET Scanning Procedures Before and After Carvedilol

All patients completed [18F]-FTHA and [18F]-FDG PET scans on consecutive days, both before and after completion of 3-month course of carvedilol. After an overnight fast (12 hours), patients underwent a brief history and physical examination. Intravenous access was obtained with 20-gauge angiocatheters in the dorsum of the right hand and the left antecubital fossa. Blood samples were drawn to determine glucose and FFA concentrations at the beginning, midpoint, and at end of the PET scan. Serum norepinephrine and epinephrine samples were drawn just before the PET scans in the supine position, after 30 minutes of rest. Blood samples were stored at –70°C until analyzed. Patients were positioned supine in the GE Advance PET scanner (General Electric Inc), which was set to the following parameters: 15.6 cm axial field of view, 35 slices, 3.8 mm in-plane resolution, and whole body tomograph. After optimization of subject position for visualization of the entire heart, transmission scans were performed for 15 minutes using 3 rotating 68 Ge pin sources.

For the [18F]-FTHA scans, patients received a programmed infusion of 2.5 mCi of [18F]-FTHA over 10 minutes from a Harvard syringe pump using a standard 10-mL syringe. For the [18F]-FDG scans, patients received a 10-mCi bolus infusion of [18F]-FDG. Dynamic imaging was performed with a frame rate of 2 minutes for 5 scans, 5 minutes for 6 scans, and 10 minutes for 1 scan. After injecting the tracer, 2 mL of arterialized venous blood was drawn from the heated-hand intravenous catheter for 18F activity every 2 minutes for the first 20 minutes and every 5 minutes for the last 40 minutes of the scanning procedure. Samples were placed on ice and centrifuged. Standard aliquots of plasma were used to determine the time course of radioactivity concentration.

Biochemical Analysis

Serum epinephrine and norepinephrine concentrations were determined by high-pressure liquid chromatography with electrochemical detection. Nonesterified (free) fatty acid concentrations were measured by spectrophotometric enzymatic assay (Wako Chemicals). Plasma glucose concentrations were measured by a glucose oxidation assay (CX3-Delta Analyzer, Beckman Instruments, Inc).

Region of Interest Definition

To determine radiotracer time course, regions of interest were drawn within the myocardial borders in 3 contiguous midventricular transaxial slices of each subject. Myocardial slices were aligned between PET scans taken before and after carvedilol treatment, and identical regions of interest were pasted onto myocardial segments on [18F]-FTHA and [18F]-FDG scans. All 9 patients had thinned, akinetic left ventricular wall segments on echocardiography, which corresponded to metabolically inactive segments on PET images, suggesting infarcted myocardium. Regions of interest did not include these wall segments. Regions of interest were restricted to myocardial segments demonstrating relatively preserved contractility by echocardiography. PET myocardial transaxial slices were matched with the apical long-axis echocardiographic wall segments used to assess resting wall motion.

Data Analysis

Estimation of uptake rates from the PET time course data were performed with graphical analysis. The myocardial uptake rates (K) for [18F]-FTHA and [18F]-FDG were first estimated from the following relation:

(1) $$ \frac{C(T)}{C(T)} = \frac{\int_{0}^{t} C(t)dt}{K_{i} C(T)} + V_{d} $$

where C(T) indicates myocardial radioactivity, dt, derivative time; and Cp, plasma [18F] radioactivity concentration at time T. Plots of C(T)/C(T) versus C(T)/C(T) are fitted to straight lines by conventional least-squares methods, and the slopes of the best-fit lines are taken as estimates of K. The myocardial metabolic uptake (MUR) rates for each region of interest were then calculated from the K values using the following formula:

(2) $$ MUR = \frac{PK}{LC} $$

where P indicates the plasma glucose or FFA concentration and LC is the lumped constant. The mean serum fatty acid and glucose values obtained during the PET scanning procedure were used to determine P. A lumped constant of 0.67 was assumed for [18F]-FDG, and 1.0 was assumed for [18F]-FTHA.
Myocardial oxygen consumption related to FFA use was estimated before and after carvedilol treatment using the following formula:

\[(\text{FFA O}_2 \text{ consumption} = |\text{FFA utilization rate}| \times 130 \text{ ATP/mole FFA} / 2.83 \text{ ATP yield per O}_2 \text{ atom})\]

where 130 ATP/mole FFA is the amount of ATP produced per mole of FFA consumed, and 2.83 ATP yield per O atoms is the amount of ATP produced per mole of oxygen consumed.

### Echocardiographic Evaluation

Echocardiograms were obtained using a Hewlett Packard Sonos 5500 ultrasound system before and after the completion of carvedilol treatment. Left ventricular regional wall motion was assessed by an experienced echocardiographer who was blinded to the carvedilol status of the patient. Two-dimensional echocardiographic estimation of left ventricular ejection fraction was calculated using Simpson’s biplane method with the Nova Microsonics ImageVue Workstation.

### Statistical Analysis

The clinical and laboratory data of the patients are presented as mean±SEM. Uptake rate data are presented as mean±SEM. Comparing data before and after carvedilol treatment was done with a paired Student’s t test. P<0.05 was considered statistically significant.

### Results

#### Patient Characteristics

The study population was composed of 9 male patients with ischemic cardiomyopathy (Table 1). All patients received unchanged medical therapy for 3 months before enrollment. Patients were maintained on ACE inhibitors (89%), digoxin (89%), and diuretics (89%). Four patients (44%) were receiving hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), one (11%) was receiving gemfibrozil, and one was receiving an angiotensin II receptor blocker (11%). No patients were receiving β-adrenoreceptor blocking agents before the study. All patients were maintained on carvedilol treatment at 25 mg twice a day for at least 3 months (mean, 110±9 days).

#### Biochemical Data

The mean serum norepinephrine and epinephrine concentrations before carvedilol treatment were not significantly elevated and did not significantly change with carvedilol treatment (Table 2). The mean serum FFA concentration before carvedilol treatment was elevated above the published normal range (0.40 to 0.66 mmol/mL), and it did not significantly change after carvedilol treatment (0.92±0.27 mmol/L versus 0.88±0.24 mmol/L; P=NS). The mean serum glucose concentration at baseline was within the normal range, and it did not significantly change after carvedilol treatment (5.4±0.3 mmol/L versus 5.6±0.3 mmol/L; P=NS).

#### Hemodynamic and Echocardiographic Data

The mean resting heart rate decreased with carvedilol treatment (78±5 bpm versus 66±5 bpm; P<0.05), but the mean systolic blood pressure was unchanged (122±5 mm Hg versus 114±4 mm Hg; P=NS). The rate-pressure product was significantly lowered by carvedilol treatment (9457±489 mm Hg · bpm versus 7185±478 mm Hg · bpm; P<0.05); however, the calculated minute work was not significantly changed by carvedilol (221 500±2700 mm Hg · bpm/cm² versus 234 300±3700 mm Hg · bpm/cm²; P=0.58).

Left ventricular ejection fraction increased significantly (from 26±2% to 37±4%; P<0.002) after carvedilol treatment, but left ventricular diastolic volume (195±34 mL versus 170±33 mL; P=NS), systolic volume (142±29 mL versus 116±19 mL; P=NS), end-diastolic dimension (6.30±0.23 cm versus 6.14±0.53 cm; P=NS), and end-systolic dimension (5.46±0.31 cm versus 5.23±0.50 cm; P=NS) were not significantly changed by carvedilol treatment. The stroke volume index was significantly increased by carvedilol (24.1±3.1 mL/m² versus 30.6±3.8 mL/m²; P<0.05).

#### PET Images and Kinetic Analysis

**[18F]-FTHA**

[18F]-FTHA uptake was seen in the heart within 90 seconds after the start of the infusion, and it provided clear delineation of myocardial borders. An example of parametric slope images before and after carvedilol for [18F]-FTHA is shown in Figure 2 (top). The mean Kᵢ for [18F]-FTHA decreased (from 19.3±7.0 to 8.2±1.8 mmol/L · 100g⁻¹ · min⁻¹; P<0.005), and the mean myocardial fatty acid use in nonischemic segments decreased (from 19.3±7.0 to 8.2±1.8 mmol/L · 100g⁻¹ · min⁻¹; P<0.005). The change in individual and mean uptake rate constants (Kᵢ) and myocardial uptake rates (MUR) for [18F]-FTHA before and after carvedilol treatment are shown in Figure 3. All patients demonstrated a decrease in Kᵢ and MUR for [18F]-FTHA after carvedilol treatment. The estimated myocardial oxygen consumption related to FFA use decreased by 57% after carvedilol treatment (from 871±122 to 376±30 μmolO₂ consumed · 100 g⁻¹ · min⁻¹; P<0.05).

**[18F]-FDG**

As expected for fasting patients, dynamic [18F]-FDG images demonstrated low levels of myocardial [18F]-FDG uptake. An

### Table 2. Laboratory and Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Before Carvedilol</th>
<th>After Carvedilol</th>
<th>P</th>
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<tbody>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.5±0.3</td>
<td>5.72±0.4</td>
<td>0.08</td>
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<tr>
<td>Serum FFA, mmol/L</td>
<td>0.96±0.10</td>
<td>0.91±0.10</td>
<td>0.71</td>
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<tr>
<td>Serum norepinephrine concentration, pg/mL</td>
<td>467±36</td>
<td>535±117</td>
<td>0.50</td>
</tr>
<tr>
<td>Serum epinephrine concentration, pg/mL</td>
<td>39±8</td>
<td>40±8</td>
<td>0.47</td>
</tr>
<tr>
<td>Rate-pressure product, mm Hg · bpm</td>
<td>9077±531</td>
<td>7594±585</td>
<td>0.05</td>
</tr>
<tr>
<td>Minute work, mm Hg · bpm/cm²</td>
<td>221 500±2700</td>
<td>234 300±3700</td>
<td>0.58</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>25±2</td>
<td>37±3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
example of parametric slope images before and after carvedilol for \[^{18}\text{F}\]-FDG from one patient are shown in Figure 2 (bottom). The change in individual and mean uptake rate constants (K) and myocardial uptake rates (MUR) for \[^{18}\text{F}\]-FDG are shown in Figure 4. The mean K, for \[^{18}\text{F}\]-FDG was unchanged (from 1.4±0.4 to 2.4±0.8 mL · 100 g⁻¹ · min⁻¹; P=0.12), and the mean glucose use was unchanged (from 11.1±3.1 to 18.7±6.0 mmol · 100 g⁻¹ · min⁻¹; P=0.12).

Eight of the 9 patients demonstrated an increase in K uptake rates and MUR for \[^{18}\text{F}\]-FDG, whereas one patient demonstrated a decrease in K uptake rates and MUR for \[^{18}\text{F}\]-FDG.

**Discussion**

\[^{18}\text{F}\]-FTHA Imaging

In this study, carvedilol therapy administered over a 3-month period to patients with stable NYHA functional class III heart failure resulted in a 57% decrease in myocardial \[^{18}\text{F}\]-FTHA uptake rates and \[^{18}\text{F}\]-FTHA uptake rate constants (K). Because the rate of radioactivity accumulation of \[^{18}\text{F}\]-FTHA is believed to reflect the β-oxidation rate of long chain fatty acids, our results are consistent with a marked decrease in myocardial FFA oxidation after carvedilol therapy. The decrease in myocardial \[^{18}\text{F}\]-FTHA uptake does not seem to be the result of altered substrate availability given the lack of a significant change in serum FFA or glucose concentration. Instead, a consistent lowering of \[^{18}\text{F}\]-FTHA uptake rate constants (K) suggests carvedilol affects FFA uptake at the level of the myocyte. Maki et al. recently demonstrated a similar reduction in myocardial \[^{18}\text{F}\]-FTHA uptake in patients with preserved left ventricular function who were treated with insulin infusion. In contrast to our findings, however, no effect of insulin on myocardial \[^{18}\text{F}\]-FTHA uptake rate constants (K) was observed, and effects were associated with a significant lowering of serum FFA concentration. Thus, the change in myocardial \[^{18}\text{F}\]-FTHA uptake in the study by Maki et al. was related to changes in substrate availability rather than the cellular handling of the substrate.

A potential explanation for our observed decrease in \[^{18}\text{F}\]-FTHA uptake rate constants (K) after carvedilol therapy is a decrease in the activity of myocardial carnitine palmitoyl transferase I (CPT I), a key enzyme involved in mitochondrial FFA uptake. Recent work by Panchal et al., who used a canine model of heart failure, demonstrated a 28% decrease in the activity of CPT I after metoprolol treatment. Decreased

**Figure 2.** Representative parametric slope images of \[^{18}\text{F}\]-FTHA and \[^{18}\text{F}\]-FDG images before and after carvedilol treatment, with pixel values expressed in mL · 100 g⁻¹ · min⁻¹. Transaxial images of 4 midventricular slices are shown for one patient. Images are oriented with the right ventricle in the upper left hand corner of each image frame. The top 2 image sets demonstrate myocardial \[^{18}\text{F}\]-FTHA uptake before and 3 months after carvedilol treatment, respectively. A decrease in myocardial \[^{18}\text{F}\]-FTHA uptake is seen on the images taken after carvedilol treatment. The bottom 2 image sets demonstrate myocardial \[^{18}\text{F}\]-FDG uptake before and 3 months after carvedilol treatment, respectively. An increase in myocardial \[^{18}\text{F}\]-FDG uptake is seen on the images taken after carvedilol treatment.

Figure 3. K (left) and MUR (right) rates for \[^{18}\text{F}\]-FTHA before and after carvedilol treatment in individual patients. The overall decrease in K and MUR is shown by –. A decrease in both K and MUR for \[^{18}\text{F}\]-FTHA is demonstrated after 3 months of carvedilol treatment.
CPT I activity by carvedilol could account for a significant lowering of myocardial FFA oxidation, and it provides a potential mechanism for the improved energy efficiency seen in patients with heart failure who are treated with β-adrenoceptor blockade. 12 Although CPT I activity was not directly measured in our patients, DeGrado et al 10 previously demonstrated an 87% decrease in myocardial [18F]-FTHA uptake in mice treated with the CPT I inhibitor 2[5(4-chlorophenyl)pentyl] oxirane-2-carboxylate.

[18F]-FDG Imaging
No significant change in myocardial glucose use was seen in our patients. This finding is consistent with a relative switch in myocardial substrate use from FFA to glucose given the results of previous investigations demonstrating a reduction in myocardial oxygen consumption after β-blockade. 11,12 Changes in lactate oxidation by the heart could contribute to the variability seen in myocardial glucose uptake in our study. The inhibition of CPT I activity is known to increase the activity of pyruvate dehydrogenase, 7,26,28 which catalyzes the decarboxylation of pyruvate, 29 and the increased activity of this enzyme is expected to cause not only an increase in glucose oxidation, but an increase in lactate oxidation as well. 30 Because [18F]-FDG provides information only about glucose uptake, a significant increase in myocardial lactate uptake may occur in some patients, with only minor or no changes in myocardial [18F]-FDG uptake. In addition, fasted studies with [18F]-FDG result in poor myocardial count statistics and affect the ability to measure a significant change in myocardial [18F]-FDG uptake. We used the fasted state to standardize the metabolic state of patients during [18F]-FTHA and [18F]-FDG PET scans because Patlak graphical analysis requires a stable serum level of substrate during the dynamic image acquisition. We evaluated serum FFA and glucose concentrations under the conditions of fasting, Intralipid (an intravenous fatty acid solution) infusion, and after a standardized fatty meal and found the fasted state provided the most stable concentration of serum FFAs and glucose (unpublished data).

Myocardial Energy Metabolism and Heart Failure
Alterations in myocardial energy metabolism that may occur in heart failure are somewhat controversial. We recently reported evidence of increased myocardial FFA and decreased myocardial glucose use in patients with heart failure using [18F]-FTHA and [18F]-FDG. 31 These results are in agreement with the findings of previous human studies demonstrating an increase in myocardial FFA metabolism and a decrease in myocardial glucose metabolism in heart failure patients compared with controls using direct, invasive measurements of FFA and glucose metabolism. 7,32 Conversely, animal studies have suggested a switch to a more fetal form of energy metabolism in heart failure, with increased glycolysis and suppression of FFA metabolism. 33,34 Sack et al 35 showed a down-regulation of several genes involved in fatty acid metabolism in heart failure. Doenst et al 36 demonstrated an increase in glucose uptake with β-adrenergic stimulation, but other reports have not shown this increase. 37,38 One explanation for the findings of Doenst et al 36 is that an increased lactate production and release of FFA on adrenergic stimulation results in increased availability of these substrates in the heart. The preference of the heart for the oxidation of lactate and FFA may then overwhelm the stimulatory effects of epinephrine on glucose metabolism, resulting in a net decrease of glucose uptake. 36

Although FFA oxidation is the major substrate for the heart and provides the highest yield of ATP (130 ATP per mole FFA versus 38 ATP per mole glucose), the metabolism of FFA requires more oxygen than glucose. The ATP yield for FFA per oxygen atom taken up is 2.83 compared with glucose at 3.17. 22 Therefore, myocardial FFA oxidation is less energy-efficient than glucose oxidation given the need for increased oxygen consumption for the same amount of ATP produced. Using the calculated myocardial FFA and glucose use rates in our patients, the amount of ATP produced decreased by 40% after carvedilol treatment. This decrease occurred despite the lack of a change in minute work, suggesting less energy is needed to perform the same amount of myocardial work after carvedilol treatment.

Estimated myocardial oxygen consumption related to FFA use fell by 57% after carvedilol treatment. This finding is consistent with previous studies demonstrating a significant decrease in myocardial oxygen consumption and improvement in myocardial energy efficiency with β-adrenoceptor blockade. 11,12 Although the mechanism for the improved energy efficiency is proposed to be the result of a switch from myocardial FFA oxidation to glucose oxidation, 12 this was not confirmed directly in our study.

The potential of ischemia and hibernation to alter myocardial metabolism was considered given the presence of underlying coronary artery disease in our patients. In the presence of ischemia, myocardial FFA oxidation is known to be suppressed and myocardial glucose oxidation is increased. 30 It is unlikely that significant myocardial ischemia affected our results given the high baseline myocardial FFA use and significant decrease in FFA use after carvedilol treatment seen in our patients. The effect of myocardial hibernation on myocardial FFA oxidation has also been previously evaluated with [18F]-FTHA by Maki et al. 39 They found no significant difference in [18F]-FTHA uptake in viable versus normal

\[ \text{Ki (mL/min/100 g)} \]

\[ \text{Pre-Carvedilol} \]

\[ \text{Post-Carvedilol} \]

\[ \text{MUR (umol/min/100 g)} \]

\[ \text{Pre-Carvedilol} \]

\[ \text{Post-Carvedilol} \]
myocardial segments, suggesting that the presence of myocardial hibernation is unlikely to have affected our results.

**Study Limitations**

A control group was not included in this study because of overwhelming evidence supporting the use of β-blocker therapy in patients with heart failure, thus making it unethical to withhold this therapy from patients with heart failure. Establishing a direct link between the changes in substrate use and a change in myocardial energy efficiency is difficult. Although factors other than a switch in myocardial substrate use may affect energy efficiency in patients with heart failure, the 57% reduction in myocardial FFA use seen in our study almost certainly led to a significant reduction in energy consumption by the heart.

**Conclusions**

Our results demonstrate carvedilol can significantly lower myocardial FFA use by 57% in patients with stable NYHA functional class III heart failure. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency seen with β-adrenoceptor blockade in the treatment of heart failure.

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**References**

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