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

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**Background**—Use of β-adrenoreceptor blockade in the treatment of heart failure has been associated with a reduction in myocardial oxygen consumption and an improvement in myocardial energy efficiency. One potential mechanism for this beneficial effect is a shift in myocardial substrate use from increased free fatty acid (FFA) oxidation to increased glucose oxidation.

**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 \(\leq 35\%\)) 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 \(14(R, S)-[^{18}F]\)-fluoro-6-thia-heptadecanoic acid (\([^{18}F]\)-FTHA) was used to determine myocardial FFA use, and \([^{18}F]\)-fluoro-2-deoxy-glucose (\([^{18}F]\)-FDG) was used to determine myocardial glucose use. After carvedilol treatment, the mean myocardial uptake rate for \([^{18}F]\)-FTHA decreased (from 20.4±8.6 to 9.7±2.3 \(\text{mL} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}\); \(P<0.005\)), mean fatty acid use decreased (from 19.3±7.0 to 8.2±1.8 \(\mu\text{molL} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}\); \(P<0.005\)), the mean myocardial uptake rate for \([^{18}F]\)-FDG was unchanged (from 1.4±0.4 to 2.4±0.8 \(\mu\text{molL} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}\); \(P=0.14\)), and mean glucose use was unchanged (from 11.1±3.1 to 18.7±6.0 \(\mu\text{molL} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}\); \(P=0.12\)). 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-adrenoreceptor 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.1–4 The pathophysiological basis for these clinical benefits, perhaps surprisingly, is not clearly established. A potential rationale for the use of β-adrenoreceptor blockade in heart failure is its effect to counteract the adverse metabolic effects of long-term sympathetic adrenergic system activation5 and the resulting increased myocardial oxygen consumption.6

In heart failure, myocardial energy efficiency is reduced.7 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.5,8–10 β-Adrenoreceptor blockade in patients with heart failure improves myocardial energy efficiency,11–16 and a shift in myocardial substrate use from FFA to glucose oxidation12 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 \(14(R, S)-[^{18}F]\)-fluoro-6-thia-heptadecanoic acid (\([^{18}F]\)-FTHA) and \([^{18}F]\)-fluoro-2-deoxy-glucose (\([^{18}F]\)-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.
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-mL 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_i) for [18F]-FTHA and [18F]-FDG were first estimated from the following relation:

\[
(1) \quad \text{MUR} = \frac{\text{PK}_i}{\text{LC}}
\]

where MUR indicates myocardial metabolic uptake (μmol per g per minute); P_i, plasma [18F] radioactivity concentration at time T; C_i(T)/C_p(T) versus C_p(T)/dt/C_p(T) are fitted to straight lines by graphical analysis. The myocardial metabolic uptake (MUR) rates for each region of interest were then calculated from the K_i values using the following formula:

\[
(2) \quad \text{MUR} = \frac{\text{PK}_i}{\text{LC}}
\]

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:

\[ \text{FFA O}_2 \text{ consumption} = \left( \frac{\text{FFA utilization rate}}{100 \text{ g}^{-1} \cdot \text{min}^{-1}} \right) \times 130 \text{ ATP/mole FFA} \]

where 130 ATP/mole FFA is the amount of ATP produced per mole of FFA consumed, and 2.83 ATP yield per O\textsubscript{2} atom is the amount of ATP produced per mole of oxygen consumed.\textsuperscript{22}

**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\textsuperscript{23} 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 \( \beta \)-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),\textsuperscript{24} 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/cm\textsuperscript{2} versus 234 300±3700 mm Hg · bpm/cm\textsuperscript{2}; \( P=0.58 \)).

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 volume (6.30±0.23 cm versus 6.14±0.53 cm; \( P=NS \)), and end-systolic volume (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/m\textsuperscript{2} versus 30.6±3.8 mL/m\textsuperscript{2}; \( P<0.05 \)).

**PET Images and Kinetic Analysis**

\( ^{[\text{18F}]\text{-FTHA}} \)

\( ^{[\text{18F}]\text{-FTHA}} \) 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 \( ^{[\text{18F}]\text{-FTHA}} \) is shown in Figure 2 (top). The mean \( K_i \) for \( ^{[\text{18F}]\text{-FTHA}} \) decreased (from 871±63 min\textsuperscript{-1} to 585±37 min\textsuperscript{-1}; \( P<0.005 \)). The change in individual and mean uptake rate constants (\( K_i \)) and myocardial uptake rates (MUR) for \( ^{[\text{18F}]\text{-FTHA}} \) before and after carvedilol treatment are shown in Figure 3. All patients demonstrated a decrease in \( K_i \) and MUR for \( ^{[\text{18F}]\text{-FTHA}} \) before and after carvedilol treatment. The estimated myocardial oxygen consumption related to FFA use decreased by 57% after carvedilol treatment (from 871±62 to 376±30 mmol/L · O\textsubscript{2} consumed · 100 g\textsuperscript{-1} · min\textsuperscript{-1}; \( P<0.05 \)).

\( ^{[\text{18F}]\text{-FDG}} \)

As expected for fasting patients, dynamic \( ^{[\text{18F}]\text{-FDG}} \) images demonstrated low levels of myocardial \( ^{[\text{18F}]\text{-FDG}} \) uptake. An
example of parametric slope images before and after carvedilol for \[^{18}F\]-FDG from one patient are shown in Figure 2 (bottom). The change in individual and mean uptake rate constants (K_i) and myocardial uptake rates (MUR) for \[^{18}F\]-FDG are shown in Figure 4. The mean K_i for \[^{18}F\]-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_i uptake rates and MUR for \[^{18}F\]-FDG, whereas one patient demonstrated a decrease in K_i uptake rates and MUR for \[^{18}F\]-FDG.

Discussion

\[^{18}F\]-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 \[^{18}F\]-FTHA uptake rates and \[^{18}F\]-FTHA uptake rate constants (K_i). Because the rate of radioactivity accumulation of \[^{18}F\]-FTHA is believed to reflect the β-oxidation rate of long chain fatty acids,\(^{18}\) our results are consistent with a marked decrease in myocardial FFA oxidation after carvedilol therapy. The decrease in myocardial \[^{18}F\]-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 \[^{18}F\]-FTHA uptake rate constants (K_i) suggests carvedilol affects FFA uptake at the level of the myocyte. Maki et al\(^{25}\) recently demonstrated a similar reduction in myocardial \[^{18}F\]-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 \[^{18}F\]-FTHA uptake rate constants (K_i) was observed, and effects were associated with a significant lowering of serum FFA concentration. Thus, the change in myocardial \[^{18}F\]-FTHA uptake in the study by Maki et al\(^{25}\) was related to changes in substrate availability rather than the cellular handling of the substrate.

A potential explanation for our observed decrease in \[^{18}F\]-FTHA uptake rate constants (K_i) 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.\(^{26}\) Recent work by Panchal et al\(^{27}\) who used a canine model of heart failure, demonstrated a 28% decrease in the activity of CPT I after metoprolol treatment. Decreased
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-adrenergoreceptor blockade. Although CPT I activity was not directly measured in our patients, DeGrado et al 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.

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, which catalyzes the decarboxylation of pyruvate, 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. 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 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. 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.

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. Sack et al demonstrated a down-regulation of several genes involved in fatty acid metabolism in heart failure. Doenst et al demonstrated an increase in glucose uptake with β-adrenergic stimulation, but other reports have not shown this increase. One explanation for the findings of Doenst et al 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.

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. 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-adrenergoreceptor blockade. Although the mechanism for the improved energy efficiency is proposed to be the result of a switch from myocardial FFA oxidation to glucose oxidation, 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. 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. They found no significant difference in [18F]-FTHA uptake in viable versus normal...
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-adrenergic blockade in the treatment of heart failure.

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