Suppression of circulating free fatty acids with acipimox in chronic heart failure patients changes whole body metabolism but does not affect cardiac function

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WHOLE BODY AND CARDIAC METABOLISM are abnormal in patients with chronic heart failure (HF) and correlate with a poor prognosis (2, 16, 28). In HF, cardiac glucose metabolism is increased, fatty acid handling and mitochondrial enzymes are down regulated (7, 8, 13, 23), and high-energy phosphate metabolism is reduced (27). It is debated whether these changes are causally involved in the progression of HF or represent an epiphenomenon secondary to the disease process itself (17, 32). Insulin resistance and high levels of circulating free fatty acids (FFAs) increase myocardial FFA uptake and may cause lipotoxicity and the progression of HF. Optimizing myocardial energy metabolism by targeting abnormal whole body metabolism and thereby decreasing cardiac FFAs and increasing glucose metabolism may therefore constitute a principle for treatment of patients with HF (21). Positive results have been reported in studies of glucagon-like peptide-1 (25), trimetazidine (10, 31), and perhexiline (12), but most studies conducted have been small, unrandomized, and open labeled (10, 25). We did not detect any acute effects of total suppression of circulating FFAs in HF patients with large areas of chronically stunned and hibernating myocardium (34), whereas others (30) have reported a decrease in stroke volume and myocardial efficiency. The proposed mechanism in prior positive studies have been effects on cardiac metabolism through increased insulin sensitivity (31), myocardial glucose uptake (18), decreased myocyte FFA mitochondrial transportation (12), or energy generation (10, 31). The aim of this randomized, double-blinded crossover, proof of concept study was to investigate the cardiac and whole body metabolic effects of 28 days of reduction of circulating FFAs in patients with HF and coronary artery disease. Suppression of circulating FFAs was performed using acipimox, which is a nicotinic acid derivate that causes the acute inhibition of lipolysis in adipose tissue (5). Acipimox suppresses FFA oxidation and increases glucose oxidation in the healthy human heart (11).

METHODS

Patients. We included 24 patients with ischemic heart disease and HF who were in New York Heart Association (NYHA) classes II and III, had a left ventricular (LV) ejection fraction (EF) of <40%, were between 30 and 80 yr of age, and were stable on optimized medication. We excluded patients with diabetes, reduced renal function (creatinine clearance of <40 ml/min) (6), acute myocardial infarction within the last 3 mo, significant cardiac valve disease, disability, or prior malignant disease.

Design. In a double-blinded placebo-controlled crossover design, patients were examined in an out-hospital setting. All patients were studied in random order during two separate 28-day periods at least 28 days apart. Patients received 250 mg acipimox and placebo by oral capsule 4 times/day for 28 ± 2 days. According to the protocol, the dose was reduced to 250 mg acipimox 1 time/day in one patient due to a creatinine clearance of <80 ml/min. The pharmacy at Aarhus University Hospital performed the randomization and kept the randomization list until data analysis was completed. Examinations were started in the morning after an overnight fast. Treatment was started when baseline testing was completed. At baseline and after 28 days,
patients were studied by echocardiography, 6-min hall walk tests, cardiopulmonary exercise testing, and cardiac output (CO) measurements, and we obtained NH3-terminal pro-brain natriuretic peptide (NT-pro-BNP) and metabolic profiles. Compliance was ensured by self-reported pill intake and by counting leftover medicine and was above 90%. The study protocol was approved by the local ethics committee. Informed written consent was obtained from all patients.

Clinical trial registration information can be found at http://ClinicalTrials.gov (identifier: NCT00549614). The study was monitored according to the standards in Good Clinical Practice.

**Clamp/calorimetry substudy.** On day 27, in 12 of 24 consecutive patients, indirect calorimetry and a hyperinsulinemic-euglycemic clamp were performed. Indirect calorimetry was performed both before and during the hyperinsulinemic-euglycemic clamp.

Safety measures. Patients were contacted by phone twice during the first 48 h of treatment and were evaluated clinically and biochemically after 7 days. Pulse, blood pressure, ECG, creatinine, and NT-pro-BNP were recorded at baseline, after 7 days, and after 28 days.

**Echocardiography.** Echocardiographic measurements were performed by one observer on an ultrasound scanner (Vivid Seven, GE Medical System, Horten, Norway) with a 2.5-MHz transducer and stored on the hospital server as previously described (34). Echopac analysis software (GE-Vingmed Ultrasound) was used for analysis. LVEF was assessed tracing the endocardial borders using a triplane model as previously described (34). By tissue-Doppler imaging, we measured peak systolic velocities and peak systolic strain rate during ejection time (34). Measurements were performed at rest and after maximal exercise. We assessed LV diastolic function from the following mitral inflow components: E wave, A wave, and E-to-A ratio. E wave deceleration time, and isovolumetric relaxation time; these parameters were recorded. Parameters were estimated as averages of three consecutive heart beats.

Cardiopulmonary exercise testing and CO measurements. All patients were familiar with the experimental setting before exercise testing. A staged bicycle exercise test with stages lasting 1 min and increments of 10 W/min was performed. At rest and at peak exercise, O2 uptake, saturation, cardiac index, stroke volume, and pulse were measured using the Innocor rebreathing system (Innovision, Odense, Denmark). This device derives CO and related parameters noninvasively by the Fick principle using an inert soluble gas and an insoluble gas. ECG, blood pressure, and heart rate are registered simultaneously. Four patients did not participate in the exercise test [abdominal aortic aneurism (n = 1), stenosis in the left main coronary artery (n = 1), debilitating gout (n = 1), and refused (n = 1)].

Six-minute hall walk test. Patients performed a 6-min hall walk test at baseline and at 28 days. The test was carried out on a straight 50-m indoor course.

**Metabolic parameters and BNP.** NT-pro-BNP, fasting venous plasma glucose, insulin, and FFAs were measured at baseline, after 7 days, and after 28 days. As a marker of insulin resistance, we used homeostasis model assessment (HOMA-IR) (15). Blood samples were immediately cooled, spun, and stored at −80°C until analysis (19). Fasting plasma glucose, FFAs, insulin, and NT-pro-BNP were determined as previously described (19).

**Myocardial single photon emission computed tomography/positron emission tomography.** 99mTc-Sestamibi and FDG α-camera positron emission tomography (PET) were performed as previously described (34). We aligned the Sestamibi and FDG images with the 16 echocardiographic regions and classified regions as control, viable, or scar (34). Among the final study population, four patients did not undergo single photon emission computed tomography (SPECT)/PET after completion of the protocol [myocardial infarction (n = 1), amiodarone-induced thyrotoxicosis and atrial fibrillation (n = 1), claustrophobia (n = 1), and refusal (n = 1)].

Clamp. Twelve consecutive patients (patients 1–12) participated in a substudy aimed at determining metabolic effects. These patients were examined on day 27 after an overnight fast at 8 AM. During the first 3 h, fasting substrate metabolism was investigated (basal); from 3 to 5 h, substrate metabolism was investigated during a euglycemic hyperinsulinemic clamp (clamp). During the clamp, patients had infusions of insulin and glucose. Insulin was infused at a steady rate (0.6 mU·kg⁻¹·min⁻¹). A glucose infusion (20%) was titrated to maintain plasma glucose values of ~5.0 mmol/l. The M value is the infusion rate of exogenous glucose necessary to maintain euglycemia during the last 30 min of the clamp.

Calorimetry. The same patients who participated in the clamp substudy performed 30 min of indirect calorimetry twice on day 27 after 2.5 and 4.5 h, as previously described (19). Energy expenditure and respiratory quotient at rest were calculated from the measurements of gas exchange. Oxidative rates of glucose and lipid were calculated after being corrected for protein oxidation. Protein oxidation was estimated by the urinary excretion rate of urea. Net lipid and glucose oxidation rates were calculated from the above measurements.

**Statistics.** Values (day 28 vs. baseline) for changes in LVEF, maximal O2 consumption (VO2max), cardiac index, maximal workload, and BNP were obtained, and these were compared using a Student’s paired t-test. Baseline and day 28 values were compared using a two-way ANOVA model (time and intervention). Grubbs’ test was used to identify one outlier in whom FFAs had increased threefold during both placebo and acipimox treatment. Tissue Doppler images were analyzed using a three-way ANOVA model (intervention, patient, and region). Data are reported as means ± SE.
RESULTS

Study population. We included 23 men and 1 woman, but 5 patients did not complete the protocol. Three patients, all receiving placebo, were excluded during the first treatment arm. The causes were vertigo, abdominal pain, and unstable angina pectoris. One patient discontinued treatment in the second treatment period (placebo) due to dyspepsia, and one patient who received placebo in the first treatment period was excluded during the washout period due to the progression of HF and chronic obstructive pulmonary disease. One patient whose FFA levels more than tripled during treatment [increase from baseline: 280% (acipimox) and 232% (placebo)] was identified as an outlier and was excluded from analysis. The final study population included 18 patients. When the outlier was identified as an outlier and was excluded from analysis. The final study population included 18 patients. When the outlier was included in post hoc analysis, P values did not change from significant to nonsignificant or vice versa. Among the 12 patients participating in the clamp/calorimetry substudy, 8 patients completed both study arms. Results from 7 patients are reported below since the outlier participated in this substudy.

Patient characteristics. Mean LVEF at baseline was 26% ± 2% [NYHA classes II (n = 13) and III (n = 5)]. Medical treatments included angiotensin-converting enzyme inhibitors/ANG II receptor blockers (n = 18, 100%), β-blockers (n = 18, 100%), aldosterone antagonists (n = 10, 56%), loop diuretics (n = 14, 78%), aspirin (n = 18, 100%), and statins (n = 17, 94%). Patients were 59 ± 2 yr of age and had a body mass index of 27 ± 1 kg/m² (weight: 89 ± 4 kg). Body weight did not change significantly in either study arm, and changes did not differ (data not shown).

Safety. During acipimox, 8 of 19 patients suffered adverse events. The corresponding number during placebo was seven patients. Adverse events were in generally mild and self-limiting. The most common reported event was flushing within the first week in seven patients receiving acipimox versus none during placebo.

Metabolic effects. At baseline, no significant differences were detected between study arms in fasting venous FFAs (acipimox vs. placebo: 0.35 ± 0.04 and 0.30 ± 0.04 mmol/L, P = 0.19). The treatment effect on FFA differed [acipimox vs. placebo (day 28 – day 0): −0.10 ± 0.03 vs. +0.01 ± 0.03 mmol/L, P < 0.01; Fig. 1]. This corresponds to a relative change in FFAs with acipimox versus placebo of −27 ± 9% versus +11 ± 12% (P < 0.01). Fasting venous plasma glucose, fasting serum insulin, and HOMA-IR did not differ at baseline between the first and second study periods, i.e., there was no carryover effect, and was not affected by treatment (Fig. 1). At baseline, patients were insulin resistant with a HOMA-IR of 2.7 (3).

Clamp/calorimetry substudy. In the seven patients who completed the hyperinsulinemic euglycemic clamp, M values did not differ [acipimox vs. placebo (day 28): 7.3 ± 1.3 vs. 7.5 ± 1.6 mg·kg⁻¹·min⁻¹, P = 0.93]. A trend toward an increased respiratory quotient was observed after an overnight fast [acipimox vs. placebo (day 28): 0.87 ± 0.2 vs. +0.82 ± 0.2, P = 0.13]. Trends in both glucose and lipid utilization rates indicated an altered whole body metabolic state after treatment with acipimox (Table 1), in which the contribution of glucose oxidation to resting energy expenditure was increased and lipid oxidation was decreased. The reason for nonsignificance is probably reduced power due to an unexpectedly high dropout rate among the 12 patients scheduled to undergo a study of whole body metabolism. In support of an altered whole body metabolic state, acipimox abandoned the physiological response to hyperinsulinemia. Significant differences in the effect of insulin treatment (clamp – basal levels) on glucose and FFA oxidation existed between groups (Table 1) due to already

Table 1. Indirect calorimetry in 7 patients after 27 days

<table>
<thead>
<tr>
<th></th>
<th>Acipimox Basal</th>
<th>Placebo Basal</th>
<th>P value</th>
<th>Acipimox Clamp</th>
<th>Placebo Clamp</th>
<th>P value</th>
<th>Acipimox Basal – Clamp</th>
<th>Placebo Basal – Clamp</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory quotient</td>
<td>0.87 ± 0.2</td>
<td>0.82 ± 0.2</td>
<td>0.13</td>
<td>0.84 ± 0.1</td>
<td>0.86 ± 0.2</td>
<td>0.42</td>
<td>0.03 ± 0.02</td>
<td>+0.04 ± 0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EE</td>
<td>3.317 ± 873</td>
<td>3.024 ± 1.120</td>
<td>0.86</td>
<td>3.364 ± 918</td>
<td>2.934 ± 1.017</td>
<td>0.79</td>
<td>+47 ± 79</td>
<td>−90 ± 110</td>
<td>0.41</td>
</tr>
<tr>
<td>Glucose oxidation, mg·kg⁻¹·min⁻¹</td>
<td>2.9 ± 0.9</td>
<td>1.5 ± 0.4</td>
<td>0.25</td>
<td>2.7 ± 1.0</td>
<td>2.1 ± 0.6</td>
<td>0.70</td>
<td>−0.3 ± 0.3</td>
<td>+0.6 ± 0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>%EE</td>
<td>45 ± 4</td>
<td>31 ± 7</td>
<td>0.18</td>
<td>36 ± 4</td>
<td>42 ± 6</td>
<td>0.40</td>
<td>−9 ± 5</td>
<td>+10 ± 3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lipid oxidation, mg·kg⁻¹·min⁻¹</td>
<td>1.1 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>0.89</td>
<td>1.3 ± 0.5</td>
<td>1.0 ± 0.5</td>
<td>0.69</td>
<td>+0.1 ± 0.1</td>
<td>−0.3 ± 0.2</td>
<td>0.12</td>
</tr>
<tr>
<td>%EE</td>
<td>33 ± 8</td>
<td>47 ± 8</td>
<td>0.25</td>
<td>41 ± 6</td>
<td>37 ± 7</td>
<td>0.63</td>
<td>+8 ± 5</td>
<td>−9 ± 3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are means ± SE. There was a trend toward a predominantly glucose-dependent energy substrate supply and a significantly different response to insulin. EE, energy expenditure.

Table 2. Exercise data after 28 days

<table>
<thead>
<tr>
<th></th>
<th>Acipimox Baseline</th>
<th>Rest</th>
<th>Peak exercise</th>
<th>Placebo Baseline</th>
<th>Rest</th>
<th>Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>110 ± 4</td>
<td>68 ± 2</td>
<td>118 ± 13</td>
<td>111 ± 13</td>
<td>118 ± 13</td>
<td>111 ± 13</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>107 ± 4</td>
<td>69 ± 2</td>
<td>111 ± 13</td>
<td>111 ± 13</td>
<td>118 ± 13</td>
<td>111 ± 13</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>4 ± 0.4</td>
<td>4 ± 0.3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>Exercise capacity, W</td>
<td>4 ± 0.4</td>
<td>4 ± 0.3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>O₂ consumption, ml kg⁻¹·min⁻¹</td>
<td>2.4 ± 0.2</td>
<td>2.2 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>1,396 ± 137</td>
<td>1,485 ± 106</td>
<td>962 ± 220*</td>
<td>1,476 ± 112</td>
<td>1,384 ± 145</td>
<td>916 ± 119*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVEF, left ventricular ejection fraction. *P < 0.05, peak vs. rest.
high basal levels of glucose oxidation and low basal levels of FFA oxidation during acipimox treatment. Patient characteristics in this subgroup of patients did not significantly differ from the whole study population.

**SPECT/PET.** In 14 patients, data were available from myocardial SPECT and $^{99m}$Tc-Sestamibi and FDG $\gamma$-camera PET examinations. Three regions could not be classified due to poor image quality. The remaining 219 regions were classified as scarred (88 regions, 35%), hibernating (27 regions, 11%), stunned (68 regions, 27%), and control (70 regions, 28%).

**Echocardiography.** LVEF did not differ at baseline [acipimox vs. placebo (day 0): 27 ± 2% and 26 ± 2%, P = 0.47], and treatments effects were equal [acipimox vs. placebo (day 28 – day 0): +1 ± 2% and +0 ± 1%, P = 0.83]. There was a significant difference in LVEF measured during rest and after maximal exercise (Table 2), but not between treatment groups. Echocardiographic measures of diastolic function did not significantly differ between groups (Table 3). We investigated changes in regional contractile function in control, viable, and scarred myocardium as determined by SPECT/PET imaging. Using Doppler-tissue velocity imaging, we found no impact of acipimox on regional peak systolic velocities (Fig. 2) or peak systolic strain rate at rest or after maximal exercise (data not shown).

**Exercise.** Fourteen patients completed the exercise test. At baseline and after 28 days, there were no significant differences between groups in LVEF, systolic blood pressure, heart rate, exercise capacity, VO$_{2}$max, stroke volume, cardiac index, and systemic vascular resistance at rest or during exercise (day 28 values are shown in Table 2).

**Six-minute hall walk test.** The distances covered at baseline were similar (acipimox vs. placebo: 541 ± 17 and 523 ± 23 m, P = 0.96), and there were no significant treatment effects [acipimox vs. placebo (day 28 – day 0): 12 ± 7 and –4 ± 16 m, P = 0.47].

**Blood pressure and heart rate.** Heart rate was equal at baseline (acipimox vs. placebo: 68 ± 16 and 62 ± 2 beats/min, P = 0.42). There were no treatment effects on heart rate [acipimox vs. placebo (day 28 – day 0): 1 ± 1 and 1 ± 1 beats/min, P = 0.87]. Mean arterial blood pressure did not differ at baseline (acipimox vs. placebo: 83 ± 2 and 87 ± 3 mmHg, P = 0.21). There were no treatment effects on mean arterial blood pressure [acipimox vs. placebo (day 28 – day 0): –1 ± 3 and –5 ± 2 mmHg, P = 0.20].

**DISCUSSION**

The present study provides data on cardiac and whole body effects of acipimox and the most pronounced long-term reduction in circulating FFAs reported in HF patients. Our findings show that contractile function of the failing heart readily adapts to a 27% reduction in circulating FFAs since we detected no effects of FFA suppression on systolic or diastolic function at rest, NT-pro-BNP, or EF and CO during maximal exercise. Acipimox did not affect insulin resistance, as determined by hyperinsulinemic euglycemic clamp M values or HOMA-IR, but had whole body effects in terms of increased glucose and reduced lipid utilization rates.

**Circulating FFAs in HF.** Patients with HF develop insulin resistance with increased levels of circulating FFAs, glucose, and insulin. Most PET studies (9, 14, 29) have shown that these changes at whole body levels are accompanied by changes in myocardial substrate uptake in terms of increased glucose and decreased FFA uptake. Whether this switch in substrate preference is caused by intrinsic metabolic changes in the myocardium, indirect changes due to altered metabolic milieu, or myocardial insulin resistance, if such exists, has not been settled. Key issues are whether changes in cardiac metabolism are causally involved in the process of HF and whether they are adaptive, maladaptive, or both. Previous studies addressing the acute effects of FFA suppression have reported that contractile function and hemodynamics are preserved (34) or slightly decreased (30). In the present study, circulating FFAs were moderately suppressed. However, a reduction in circulating FFAs over weeks has not previously been reported with other metabolic interventions in HF (10, 12, 25, 31). Our results show that a longer-term reduction of the myocardial FFA
supply in stable HF patients with acipimox does not change cardiac function at rest and during exercise. We observed a decrease in FFAs of 0.10 mmol/L. We did not measure myocardial glucose uptake in this study, but other studies (4, 20, 24) have shown that a similar decrease in plasma FFAs corresponds to a substantial increase in myocardial glucose uptake, since the circulating FFA concentration is the main determinant of myocardial glucose uptake. It is possible that a further reduction in circulating FFAs could have beneficial effects, but, at present, no such treatment is available. Our findings let us suggest that the failing heart has preserved metabolic flexibility and seems to be able to adapt to moderate changes in substrate availability. The present study therefore questions a strategy of moderately altering substrate availability as a therapeutic target in the treatment of HF. However, these results apply only for acipimox. Other agents targeting metabolism and/or myocardial substrate utilization may exert different effects.

Modulation of FFA intracellular metabolism in HF. In previous HF studies, the metabolic modulation of other targets of myocardial metabolism have been studied. The results of metabolic modulation in humans have been variable (10, 25, 30, 31, 34). Perhexiline, an inhibitor of mitochondrial FFA uptake, has been shown to improve LVEF in a population consisting of mixed cardiomyopathies (12). Renewed interest in this drug recently appeared as careful dose titration seems to prevent the hepatotoxicity and neurotoxaphies previously limiting its use. Most reproducible results have been obtained using trimetazidine (10, 31). A study (31) has reported a beneficial effect on LVEF occurring despite only a minor 10% decrease in the myocardial β-oxidative rate. Since an increase in whole body insulin sensitivity was observed, the authors hypothesized that the beneficial effect was achieved through unspecific extracardiac changes. In the present study, insulin resistance was not affected by acipimox and FFA suppression, and, although speculative, it could account for the lack of effect observed. Targeting whole body metabolism and the cardiac FFA supply alone without treating insulin resistance, cardiac energy generation, or transfer (17) was insufficient to achieve any clinical significant cardiac effects in stable HF patients.

Limitations. Fatty acid utilization is unaltered or slightly decreased in early stages of HF but decreases substantially in advanced stages of HF (22, 29). We did not include patients in NYHA class IV, and it is possible that this patient group responds differently to suppression of FFAs due to a more deranged whole body and myocardial metabolism.

Patients with HF and overt diabetes might respond differently to treatment due to a more deranged metabolism, although some studies (12, 25) have reported that the effect of metabolic modulation is independent of metabolic status. All study patients received β-blocker therapy, which decreases myocardial FFA uptake (33) and therefore may blunt the effects of reducing circulating FFAs. Future studies should address whether the modulation of myocardial FFAs has beneficial effects in HF patients who do not tolerate β-blocking agents.

Even though acipimox inhibits lipolysis, it is known that this drug may lead to a substantial variation in circulation FFA levels. To minimize this variation, we chose to give the drug 4 times/day and achieved a significant reduction in circulating FFAs in the morning during fasting. Higher levels might occur during daytime and sleep, and it is possible that pharmacokinetic features of acipimox might account for the lack of effect.

We did not document changes in myocardial substrate uptake, but the effects of lowering circulating FFAs on myocardial FFA and glucose uptake are well known from previous studies (4, 14).

Patients were treated for 28 days, and we cannot exclude that a longer intervention period could affect our outcome measures differently. The present study is, to our knowledge, the first study in HF patients that achieved a reduction in circulating FFAs beyond acute changes.

Our power calculation was based on a desire to identify changes in LVEF of >3.3 percentage points (based on $2\alpha = 0.05$ and $1 - \beta = 0.80$). We had expected that 20 patients would complete the examinations. However, fewer patients than expected completed the already small study, thus increasing the possibility of type 2 statistical errors. It is conceivable that the echocardiographic techniques used to assess regional function were too insensitive to detect subtle changes in contractile function. However, our data consistently demonstrated that global and measures of regional contractility as well as hemodynamics were unaffected by the modulation of substrate supply, supporting that there was no clinically important effect.

It should be emphasized that these results apply only for acipimox treatment. Other metabolically active treatments have shown promise in prior trials. Whether any of these treatments are beneficial in HF needs to be elucidated in larger, long-term trials.

Conclusions. Acipimox caused minor changes in whole body metabolism and decreased the FFA supply, but a long-term reduction in circulating FFAs with acipimox did not change systolic or diastolic cardiac function or exercise capacity in patients with HF.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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