Influence of insulin and free fatty acids on contractile function in patients with chronically stunned and hibernating myocardium

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Wiggers, Henrik, Helene Norrelund, Søren Steen Nielsen, Niels H. Andersen, Jens Erik Nielsen-Kudsk, Jens S. Christiansen, Torsten T. Nielsen, Niels Møller, and Hans Erik Bøtker. Influence of insulin and free fatty acids on contractile function in patients with chronically stunned and hibernating myocardium. Am J Physiol Heart Circ Physiol 289: H938–H946, 2005. First published April 1, 2005; doi:10.1152/ajpheart.00150.2005.—It is unknown whether short-term modulation of substrate supply affects cardiac performance in heart failure patients with chronic ischemic myocardium. The aim of this study was to determine whether modulation of myocardial substrate metabolism with insulin and free fatty acids (FFAs) affects contractile function of chronically stunned (CST) and hibernating (HIB) myocardium at rest and after maximal exercise. We studied eight nondiabetic patients with ejection fraction (EF) 30 ± 4% (SE) and CST/HIB in 49 ± 6% of the left ventricle; 36 ± 6% CST and 13 ± 2% HIB as determined by 99mTc-Technetium-Sestamibi single photon emission computed tomography (SPECT) and [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET). Each patient was subjected to a 3-h infusion of 1 saline, 2 insulin-glucose (i.e., euglycemic insulin clamp; high insulin, suppressed FFA), and 3 somatostatin-heparin (suppressed insulin, high FFA). Echocardiographic endpoints were global EF and regional contractile function [maximum velocity (∵max) and strain rate (εmax)] as determined by tissue Doppler imaging at steady state and after maximal exercise. EF was similar at baseline and steady state and increased after exercise to 36 ± 5% (∵ < 0.05). Baseline regional ∵max and εmax were highest in control, intermediate in CST and HIB, and lowest in infarct regions (∵ < 0.05). Steady-state EF, ∵max, and εmax were not affected by metabolic modulation in any region. After maximal exercise, contractile function increased in control, CST, and HIB (∵ < 0.05), but not in infarct, regions. Exercise-induced contractile increments were unaffected by metabolic modulation. Metabolic modulation does not influence contractile function in CST and HIB regions. Chronic ischemic myocardium has preserved ability to adapt to extreme, short-term changes in substrate supply at rest and after maximal exercise.

glucose; hibernation; myocardial stunning

METABOLIC INTERVENTION with insulin and glucose exerts beneficial effects on myocardial function in acute ischemic states (5, 7, 9, 26). The efficacy is based on the well-known preference of the ischemic myocardium for glucose as the metabolic substrate for oxidative phosphorylation (27, 29, 47). A similar preference characterizes the failing heart, even in the absence of ischemia (8). This feature is accompanied by a downregulation of cardiac metabolic pathways controlling fatty acid oxidation (38), implying that the failing heart reverts to fetal phenotypes at molecular, cellular, and metabolic levels (37), as demonstrated in viable, dysfunctional myocardium (50). At the same time, patients in advanced stages of heart failure due to ischemic cardiomyopathy are characterized by whole body insulin resistance (44), including increased levels of circulating free fatty acids (FFAs), which may contribute to a suboptimal substrate supply to the affected myocardium. Some data suggest that whole body insulin resistance in heart failure is accompanied by myocardial insulin resistance (34), which may further compromise myocardial glucose uptake. At the same time, it has been reported that myocardial insulin sensitivity is preserved to a degree that allows an ample insulin-stimulated enhancement of glucose uptake in reversibly dysfunctional myocardium in patients with ischemic cardiomyopathy (29). Reversible myocardial dysfunction in ischemic cardiomyopathy is caused by stunning and hibernation (35, 50), but it is unknown whether modulation of fuel substrate supply in patients affects cardiac performance (23, 29, 33) and whether increased glucose supply and decreased FFA supply improve cardiac function, such that therapeutic strategies designed to enhance myocardial glucose uptake could be rational goals. The main purpose of the present work was to study whether modulation of myocardial substrate metabolism affects contractile function of chronically stunned and hibernating myocardium at rest and after maximal exercise. We selected patients with large regions of hibernating and stunned myocardium. The patients were studied in the fasting state on 3 separate days and were infused with saline, insulin-glucose (high insulin and suppressed FFA), or somatostatin-heparin (suppressed insulin and high FFA). By this approach, the myocardium is exposed to variable levels of glucose and FFA. Main outcome measures were three-dimensional global and tissue Doppler regional left ventricular function at rest and after maximal exercise.

MATERIALS AND METHODS

Patients. We included eight patients with angiographically verified ischemic cardiomyopathy and viable (chronically stunned and/or hibernating) myocardium in ≥25% of the left ventricle on 99mTc-sestamibi single-photon-emission computed tomography (SPECT) and [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET). Patients were required to have an ejection fraction (EF) ≤40%, to be stable on medical treatment, and to be in New York Heart Association (NYHA) class II or III. We excluded patients with diabetes, cardiac valve disease, congenital heart disease, atrial fibrillation, bundle branch block, serum (S)-creatinine >200 µmol/l, hy-
perkalemia, or exercise limitation due to angina pectoris or noncardiac causes.

**Design.** Before the experiments, the patients underwent exercise testing to become familiarized with the experimental setting. The patients were studied on their usual medication after an overnight fast at 8 AM. In a crossover design with the patient blinded to the type of infusion, we studied the patients in random order on 3 separate days: 1) infusion of isotonic saline at one-third of the expected/observed glucose infusion rate, 2) euglycemic insulin clamping at an insulin infusion rate of 60 mU·m⁻²·min⁻¹, with blood glucose kept at baseline levels by infusion of 20% glucose with KCl (20 mmol/l), and 3) infusion of somatostatin (300 μg/h) and heparin (bolus 400 IE, followed by 400 IE/h). We infused saline at the same rate as expected/observed in the control arm. When plasma glucose levels decreased to <4.5 mmol/l, we infused 20% glucose with KCl (20 mmol/l). In this study arm, the patients were electrocardiographically monitored. In all study arms, we made baseline echocardiographic measurements after 1 h of rest. Infusion was then started, and image acquisition was repeated during steady state, i.e., 165 min later. The patients then underwent a maximal bicycle exercise load, and echocardiography was performed after peak exercise, with the patient in the left supine position. The infusion was continued throughout this period. The local ethics committee approved the study, and informed consent was obtained from all patients.

**Echocardiography.** All echocardiographic examinations were performed by one observer on an ultrasound scanner (Vivid Five, GE Medical System, Horten, Norway) with a 2.5-MHz transducer and stored on optical disk. Echopac analysis software (GE-Vingmed Ultrasound, Horten, Norway) was used for analysis. Left ventricular volumes and EF were measured by tracing the endocardial borders, using a triplane method (1), as an average of three to five consecutive heartbeats. Regional wall motion scoring was evaluated semiquantitatively using the 16-segment model (42). We assessed left ventricular diastolic function from mitral inflow parameters (2).

**Tissue Doppler imaging.** Tissue Doppler imaging was done from the three apical standard views, as previously described in our laboratory (2). We recorded data with an average frame rate of 131 ± 4 frames/s and performed blinded analysis using Echopac analysis software. A sample region of 11 × 11 pixels was placed in the center of the basal and midventricular segments at the same distance from the mitral ring on each recording. In apical segments, we measured the most basal part. We measured peak systolic velocities (Vmax) and peak systolic strain rate (εmax) during ejection time in each of the 16 segments (2). In each segment, we measured baseline Vmax (Vmax 1) and εmax (εmax 1), the difference between steady-state and baseline Vmax (Vmax 2 - Vmax 1) and εmax (εmax 2 - εmax 1), and the difference between maximal exercise and steady-state Vmax (Vmax 3 - Vmax 2) and εmax (εmax 3 - εmax 2).

**Exercise.** The patients exercised on a bicycle ergometer in an upright position, using an individualized ramp protocol, according to the preliminary exercise test, to ensure a test duration of 7–10 min. The initial workload was increased every minute until exhaustion. Breath-by-breath gas exchange analysis was performed, and maximal O₂ consumption was determined as the highest O₂ consumption achieved during exercise (Jaeger Oxycon Delta, Erich Jaeger, Hoechberg, Germany).

**Myocardial SPECT.** ⁹⁹ᵐTc-sestamibi (700 MBq ± 10%) was injected after the patient had rested for 30 min, and image acquisition was started 60 min after radiotiotope injection. SPECT acquisition was performed using a dual-headed rotating gamma camera (FORTE, ADAC, Milpitas, CA) with a high-resolution, parallel-hole collimator. Sixty-four projections of 25 s each were obtained over a noncircular 180° arc, extending from the 45° right anterior oblique to the 45° left posterior oblique position. Attenuation correction was performed using two ¹⁵³Ga line sources (Vantage, ADAC).

**FDG gamma camera PET.** Patients were examined on a separate day and after 12 h of fasting. [¹⁸F]FDG (125 MBq) was injected 2 h after intake of 500 mg of acipimox (Olbetam) (25) and 100 ml of a 50% glucose beverage. Image acquisition was performed on a dual-headed gamma camera with a 5/8-inch (15.9-mm) crystal and molecular coincident registration (FORTE, ADAC). Attenuation correction was performed with a ¹³⁷Cs point source.

**Image analysis.** We aligned the images with the 16 echocardiographic regions and scored the regional myocardial tracer uptake of sestamibi and FDG semiquantitatively as follows: 0 for normal, 1 for mildly reduced, 2 for moderately reduced, 3 for severely reduced, and 4 for none (39, 41). Regions with normal wall motion score were classified as control. Dysfunctional segments were defined as chronically stunned (sestamibi ≤ 1 and FDG ≤ 1), hibernating (sestamibi = 2 and FDG = 0 or sestamibi = 3 and FDG = 1), or infarcted (sestamibi ≥ 2 and FDG ≥ 2) (41).

**Plasma glucose, S-insulin, S-FFA, and plasma triglycerides, metabolites, and catecholamines.** Plasma (P) glucose was measured in duplicate immediately after sampling on a glucose analyzer (Beckman Coulter, Palo Alto, CA). We determined the other substances as previously described (12, 20, 32).

**Statistical methods.** We used the statistical software program SPSS 10.0 (SPSS, Cary, NC) for statistical analyses. The Kolmogorov-Smirnov test was used to test whether variables were normally distributed; if they were not, we transformed data logarithmically. We used three-way ANOVA and Tukey’s honestly significant difference test for post hoc analysis. Values are means ± SE. P < 0.05 was considered significant.

**RESULTS**

**Patient characteristics.** Patient characteristics are shown in Table 1. All patients were men with a mean age of 65 ± 3 yr. Mean EF was 30 ± 4%, and seven of eight patients had a history of myocardial infarction. Three- vessel disease was found in seven patients and one-vessel disease in one patient. Five patients were in NYHA class II and three in class III. One patient was in Canadian Cardiovascular Society class II, and the remaining seven were in class I. All patients were treated with angiotensin-converting enzyme inhibitors, diuretics, and statins, six of eight with β-blockers, four of eight with spironolactone, and one of eight with digoxin. Mean HbA1c was 5.9 ± 0.1%, and LDL-cholesterol was 2.3 ± 0.2 mmol/l (90 ± 8 mg/dl).

**Viable and scar regions.** The mean number of SPECT viable regions per patient was 7.8 ± 1.0 (5.8 ± 1.0 chronically stunned and 2.0 ± 0.3 hibernating regions per patient). There were 5.5 ± 1.7 infarct regions per patient. Wall motion score was similar in chronically stunned and hibernating regions (2.1 ± 0.1 and 2.2 ± 0.1, P = 0.71) and higher in infarct regions (2.6 ± 0.1, P < 0.01 vs. other regions). Six segments could not be visualized echocardiographically, and in the final analysis, 122 segments were included: 22 control, 44 chronically stunned, 14 hibernating, and 42 infarct regions.

**S-insulin, S-FFA, and P-glucose.** S-insulin, S-FFA, and P-glucose in the three study arms are shown in Fig. 1. S-insulin and S-FFA levels differed between the three study arms (P < 0.001). Levels remained stable during steady state and after exercise, except for S-FFA in the somatostatin-heparin arm, which decreased after exercise (P < 0.02). P-glucose levels were higher in the somatostatin-heparin arm than during saline infusion (P < 0.01) but did not differ from insulin clamp (P = 0.25). None of the patients had episodes of hypoglycemia. In all groups, levels remained stable during steady state. During somatostatin-heparin infusion, P-glucose levels were 0.6 and 0.4 mmol/l higher at steady state than in the saline and insulin...
arms, respectively ($P < 0.05$). After exercise, P-glucose levels were higher in the somatostatin-heparin than in the insulin arm ($P < 0.05$).

Blood pressure and heart rate. Blood pressure and heart rate remained stable during the resting study period and did not differ between the study arms (Table 2).

- **P**-potassium, **P**-triglycerides, **P**-lactate, and **P**-catecholamines. **P**-potassium, **P**-triglycerides, **P**-lactate, and **P**-catecholamines are shown in Table 2. Lactate levels increased fourfold in all groups after maximal exercise. After maximal exercise, norepinephrine levels increased twofold in all groups, whereas epinephrine levels remained constant.

Exercise data. There were no differences between the control, insulin clamp, and somatostatin-heparin arms with regard to exercise time (7.8 ± 0.4, 7.7 ± 0.5, and 7.6 ± 0.3 min, $P = 0.21$), maximal workload (108 ± 11, 107 ± 11, and 107 ± 14 W, $P = 0.42$), peak heart rate (119 ± 6, 115 ± 9, and 120 ± 9 beats/min, $P = 0.23$), peak systolic blood pressure (140 ± 10, 138 ± 9, and 131 ± 11 mmHg, $P = 0.10$), or maximal O2 consumption (16.6 ± 1.2, 16.4 ± 1.0, and 16.6 ± 1.4 ml·kg$^{-1}$·min$^{-1}$, $P = 0.47$).

Global left ventricular function. Global left ventricular function (Fig. 2) did not differ between the control, insulin clamp, and somatostatin-heparin arms at baseline ($P = 0.83$). EF did not differ between baseline and steady state ($P = 0.41$) but increased significantly after stress ($P = 0.04$ vs. baseline and steady state). Metabolic modulation did not induce any significant differences in EF at steady state or after stress ($P = 0.67$).

Regional myocardial contractile function. $V_{max 1}$ and $\epsilon_{max 1}$ (i.e., at baseline) were similar for the three study arms in all regions (Figs. 3 and 4). $V_{max 1}$ and $\epsilon_{max 1}$ were highest in control ($P < 0.05$ vs. other regions), lowest in infarct ($P < 0.05$ vs. other regions), and intermediate and at the same level in chronically stunned and hibernating regions. In regions classified as chronically stunned and hibernating, there was a correlation between semiquantitative septal uptake and $V_{max}$ ($r = 0.18, P < 0.01$) and $\epsilon_{max}$ ($r = 0.16, P < 0.01$). Metabolic modulation did not induce any significant changes at steady state ($V_{max 1} - V_{max 2}$ and $\epsilon_{max 1} - \epsilon_{max 2}$) in any of the regions. $V_{max}$ increased significantly after maximal exercise in control, chronically stunned, and hibernating regions ($P < 0.001$), whereas this increase was not observed in infarct regions ($P = 0.10$). After exercise, $\epsilon_{max}$ increased in control and chronically stunned regions ($P < 0.05$) but was unaltered in hibernating ($P = 0.11$) and infarct regions ($P = 0.31$). The response to maximal exercise ($V_{max 3} - V_{max 2}$ and $\epsilon_{max 3} - \epsilon_{max 2}$) was unaffected by metabolic modulation in all regions. Echocardiography had a power to detect a significant difference between $V_{max 2}$ and $V_{max 1}$ of 0.41 cm/s in control, 0.20 cm/s in chronically stunned, 0.40 cm/s in hibernating, and 0.19 cm/s in infarct regions. For $V_{max 3}$ and $V_{max 2}$, the values were 0.41, 0.31, 0.59, and 0.22 cm/s, respectively. For $\epsilon_{max 2}$ and $\epsilon_{max 1}$, as well as $\epsilon_{max 3}$ and $\epsilon_{max 2}$, tissue Doppler echocardiography had a power to detect a significant difference of 0.20 and 0.21 s$^{-1}$ in control, 0.11 and 0.14 s$^{-1}$ in chronically stunned, 0.14 and 0.24 s$^{-1}$ in hibernating, and 0.11 and 0.11 s$^{-1}$ in infarct regions.

Diastolic left ventricular function. Metabolic intervention did not affect peak E wave ($P = 0.19$), peak A wave ($P = 0.17$), E wave-to-A wave ratio ($P = 0.24$), E wave deceleration time ($P = 0.37$), or color M-mode flow propagation velocity ($V_p$) ($P = 0.51$). There were no changes in any of these indexes over time (Table 2).

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Previous AMI</th>
<th>ECG</th>
<th>NYHA-Class/CCS-class/</th>
<th>Extent of CAD, % diameter stenosis</th>
<th>EF, %</th>
<th>EDV, ml</th>
<th>Viable Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: V_1–V_4 ST ↓ I, II, aVF</td>
<td>2/2</td>
<td>LAD_1, 100%; Cx diffuse; severe CAD; RCA_2, 100%</td>
<td>23</td>
<td>355</td>
<td>3 CST/2 HIB</td>
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<tr>
<td>2</td>
<td>67</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: V_1–V_4, III, aVF ST ↓ no leads</td>
<td>3/1</td>
<td>Diffuse, severe CAD, LAD, 90% × 3; Cx_2, 100%; OM_2, 100%; RCA_2, 100%</td>
<td>24</td>
<td>174</td>
<td>4 CST/0 HIB</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: V_3–V_4 ST ↓ no leads</td>
<td>3/1</td>
<td>LAD_1, 100%; Cx_2, 80%; RCA_1, 100%</td>
<td>16</td>
<td>225</td>
<td>3 CST/3 HIB</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: no leads ST ↓ no leads</td>
<td>2/1</td>
<td>LAD_1, 100%; Cx_1, 95%; OM_1, 100%; RCA_2, 100%</td>
<td>25</td>
<td>202</td>
<td>10 CST/2 HIB</td>
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<tr>
<td>5</td>
<td>65</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: no leads ST ↓ no leads</td>
<td>3/1</td>
<td>LAD and Cx: multiple severe stenoses; RCA, 100%, and with diffuse CAD</td>
<td>38</td>
<td>94</td>
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</tr>
<tr>
<td>6</td>
<td>52</td>
<td>Male</td>
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<td>Q waves: no leads ST ↓ no leads</td>
<td>2/1</td>
<td>RCA_1, 100%</td>
<td>40</td>
<td>113</td>
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<td>7</td>
<td>58</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: aVL, V_4 ST ↓ I, II, aVF</td>
<td>2/2</td>
<td>LAD_2, 100%; IM, 100%; Cx, diffuse CAD; RCA_3, 90%</td>
<td>31</td>
<td>170</td>
<td>9 CST/2 HIB</td>
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<td>8</td>
<td>65</td>
<td>Male</td>
<td>Yes</td>
<td>Q waves: no leads ST ↓ I, V_1–V_6</td>
<td>2/1</td>
<td>LAD multiple severe stenoses; OM_1, 100%; RCA_2, 100%</td>
<td>39</td>
<td>203</td>
<td>6 CST/2 HIB</td>
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</table>

AMI, acute myocardial infarction; LAD, left anterior descending coronary artery; CAD, coronary artery disease; CST, chronically stunned; HIB, hibernating; LAD_1 and LAD_2, segments 1 and 2 of LAD; OM_1 and OM_2, 1st and 2nd obtuse marginal branches of circumflex coronary artery (Cx); Cx_1 and Cx_2, segments 1 and 2 of Cx; RCA, right coronary artery; RCA_1 and RCA_2, segments 1 and 2 of RCA; EF, ejection fraction; EDV, end-diastolic volume; NYHA, NY Heart Association; CCS, Canadian Cardiovascular Society; IM, ramus intermedius.
DISCUSSION

The main finding of the present study is that acute modulation of circulating insulin and FFA levels does not influence myocardial contractile function in patients with chronic heart failure and large regions of dysfunctional, viable myocardium. These findings were unexpected, because interventions that switch energy substrate preference and improve coupling between glycolysis and glucose oxidation are generally considered beneficial in the failing heart, irrespective of whether ischemia is the underlying mechanism. However, our findings...
indicate a preserved ability of chronically stunned and hibernating myocardium to adapt to extreme, short-term changes in myocardial substrate supply at rest and after maximal exercise.

**Patients, design, and methods.** Although it has previously been demonstrated that wall motion may not improve with insulin infusion in patients with ischemic heart disease without heart failure (29), the effects of metabolic modulation on resting contractile function in patients with left ventricular dysfunction are not consistent (23, 29, 33). A plausible explanation is heterogeneity of the patient populations studied, i.e., inclusion of patients with relatively preserved EF (23, 29), diabetes mellitus (23), and dilated cardiomyopathy (33). Furthermore, omission of viability testing (33), episodes of hypoglycemia (23), lack of a control study arm (23), and insensitive measures of contractile function (29, 33) may contribute to the variable results. In the present study, we included nondiabetic patients with severe ischemic cardiomyopathy who were carefully characterized with respect to myocardial viability. We selected patients with large regions of viable, dysfunctional myocardium and with NYHA class II or III heart failure. We avoided hypoglycemia and included a control arm in our study design to avoid any bias due to changes in preload and the resting state on our outcome measures. Finally, we used sensitive echocardiographic techniques to detect changes in myocardial contractile function.

**Modulation of myocardial substrate supply by glucose-insulin infusion and contractile function in chronically stunned and hibernating myocardium.** Insulin decreases circulating FFA levels through inhibition of lipolysis and increases myocardial glucose uptake (4, 17, 29, 32). In patients with acute ischemia independently of its effect on substrate supply (22), improvement of myocardial contractile function or outcome observed in experimental (9, 27) and clinical settings of acute ischemia (7) is associated with decreased FFA oxidation and increased glucose uptake. These beneficial effects of increased glucose uptake in acute ischemic states demonstrate a coupling between glucose uptake and myocardial contractile function. This coupling is mediated by increased glycolytic ATP production (3, 9), which improves sarcoplasmic reticulum Ca\(^{2+}\) transport (56) and protects ion pumps (10), and by mitochondrial ATP production from glucose oxidation, which preserves a favorable myocytic energetic profile (5). In chronically stunned and hibernating myocardium, we found that contractile function was unaffected by infusion of insulin at a rate known to increase myocardial glucose uptake (4, 17, 29, 31, 54). This finding is consistent with our previous findings that dysfunction is not associated with reduced ATP levels and lactate content is negligible (55) and that oxidative metabolism is preserved or only slightly reduced (18, 21). Our results therefore support the belief that ongoing biochemical signs of myocardial ischemia represent an infrequent phenomenon in chronically stunned and hibernating myocardium. The present study shows that, in contrast to acute ischemic states but similar to observations in the normal heart (40), contractile function of chronically stunned and hibernating myocardium is not improved by an acute increase in glucose uptake.

<table>
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<tr>
<th>Table 2. Hemodynamics, diastolic function, potassium, triglycerides, lactate, and catecholamines</th>
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<td>BP, mmHg</td>
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<td>P-K+, mmol/l</td>
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<td>P-TG, mmol/l</td>
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<td>P-NE, pg/ml</td>
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<td>P-Epi, pg/ml</td>
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Values are means ± SE. BP, blood pressure; E p, color M-mode flow propagation velocity; P-K+, P-TG, P-lactate, P-NE, and P-Epi, plasma K+, triglycerides, lactate, norepinephrine; and epinephrine. \(*P < 0.05\) vs. baseline; \(\dagger P < 0.01\) vs. other study arms; \(\ddagger P < 0.001\) baseline; \(\ddagger\ddagger P < 0.001\) vs. other time points; \(\ddagger\ddagger\ddagger P < 0.001\) vs. baseline by ANOVA.

Fig. 2. Ejection fraction in the 3 study arms at baseline, at steady state, and after maximal exercise. \(*P < 0.05\) vs. baseline and steady state. There were no differences among the 3 study arms (\(P = 0.67\)).
Myocardial lipotoxicity in patients with ischemic cardiomyopathy? High FFA levels exert negative inotropic effects in experimental models of acute myocardial ischemia (9, 27) and insulin resistance (58) and reduce the ischemic threshold in patients with angina pectoris (16). FFA may compromise contractile function, because loss of coupling between FFA uptake and oxidation leads to intracellular accumulation of nonoxidized fatty acid derivatives (58). The effects of elevated circulating FFA levels on contractile function in patients with stable chronic heart failure and viable, dysfunctional myocardial regions were assessed during saline infusion, euglycemic insulin clamp, and somatostatin-heparin pretreatment. Regional peak systolic velocity ($V_{\text{max}}$) and strain rate ($\varepsilon_{\text{max}}$) were evaluated during ejection and steady state.

***Fig. 3. Regional peak systolic velocity ($V_{\text{max}}$) during ejection time at baseline ($V_{\text{max}1}$), change in $V_{\text{max}}$ between baseline and steady state ($V_{\text{max}1} - V_{\text{max}2}$), and change in $V_{\text{max}}$ between steady state and maximal exercise ($V_{\text{max}3} - V_{\text{max}2}$) during saline infusion (○), euglycemic insulin clamp (●), and somatostatin-heparin (□). $V_{\text{max}}$ was highest in control ($P < 0.05$ vs. other categories), lowest in infarct ($P < 0.05$ vs. other categories), and intermediate and at the same level in chronically stunned and hibernating regions. After maximal exercise, $V_{\text{max}}$ increased significantly in control, chronically stunned, and hibernating regions ($P < 0.001$), whereas no change was observed in infarct regions. Metabolic modulation did not affect $V_{\text{max}2} - V_{\text{max}1}$ and $V_{\text{max}3} - V_{\text{max}2}$ in any region. *$P < 0.001$ vs. steady state.

***Fig. 4. Regional peak systolic strain rate ($\varepsilon_{\text{max}}$) during ejection. See Fig. 3 legend for details. $\varepsilon_{\text{max}1}$ was highest in control ($P < 0.05$ vs. other categories), lowest in infarct ($P < 0.05$ vs. other regions), and intermediate and at the same level in chronically stunned and hibernating regions. After maximal exercise, $\varepsilon_{\text{max}}$ increased significantly in control and chronically stunned regions ($P < 0.05$), whereas no change was observed in hibernating and infarct regions. Metabolic modulation did not affect $\varepsilon_{\text{max}2} - \varepsilon_{\text{max}1}$ and $\varepsilon_{\text{max}3} - \varepsilon_{\text{max}2}$ in any region. *$P < 0.05$ vs. steady state.
diagram are unknown. We hypothesized that acute lipotoxicity could be induced or chronic lipotoxicity could be unmasked during massive FFA exposure. Pancreatic insulin release was completely suppressed by somatostatin, and heparin was infused to mobilize lipoprotein lipase and achieve very high FFA levels. Myocardial glucose uptake measured by quantitative PET decreases from 25 μmol·100 g⁻¹·min⁻¹ in the fasting state to <2 μmol·100 g⁻¹·min⁻¹ during somatostatin-heparin infusion (4), indicating a major reliance on FFA uptake and oxidation for energy generation during such pronounced FFA exposure. We observed no deterioration of cardiac contractile function in chronically stunned, hibernating, or control regions. Our results show that chronically stunned and hibernating regions of nondiabetic patients with ischemic cardiomyopathy can resist the potential lipotoxic effects induced by 3 h of very high FFA exposure.

Preserved capacity of viable, dysfunctional myocardium to adapt to changes in myocardial substrate supply at rest and during exercise. A global preference for glucose as the substrate for energy generation accompanied by a downregulation of FFA uptake and metabolism is observed in patients with ischemic heart disease (47, 48) and heart failure (8, 37, 38). Myocardial ischemia is observed in human chronically stunned and hibernating myocardium during episodes of stress (50, 53), but it is uncertain whether substrate metabolism in control regions at rest differs from that at submaximal workload (17, 18, 21, 28, 29, 31, 54). Whereas the normal human heart is able to adapt to differences in substrate supply (45), chronically stunned and hibernating myocardium have been proposed to be dependent on high rates of anaerobic glycolysis as an adaptive metabolic mechanism to preserve function and to avoid cellular degeneration during superimposed stress (11, 51). We found that viable, dysfunctional myocardium could increase contractile function after maximal exercise similar to control regions, despite profound changes in substrate levels. In a chronic animal model, hibernating myocardium retained the ability to increase function during stress without any metabolic evidence of ischemia, suggesting that adaptive mechanisms prevent the development of ischemia during submaximal workloads (14). The present study shows that chronically stunned and hibernating myocardium possess a preserved ability to adapt to differences in the metabolic environment and to withstand extreme short-term changes in substrate supply, even at increased workloads, without any critical reliance on high glucose uptake rates. Whether this ability represents preserved normal metabolism or is part of a protective and adaptive metabolic response remains unknown.

Clinical implications. Our results indicate that short-term interventions specifically targeting intermediary metabolism result in no clinically important improvement of contractile function in patients with chronically stunned and hibernating myocardium. The efficacy of glucose-insulin infusion observed in some (7, 26, 30), but not all (49), studies of acute ischemic and postoperative states may in part be related to an anti-inflammatory, rather than a metabolic, effect (6). It remains to be studied whether long-term metabolic intervention is beneficial and whether patients with diabetes or acute decompensated heart failure can benefit from such treatment.

The subdivision of viable heart muscle into chronically stunned and hibernating myocardium may be of minor importance in the decision to revascularize or not revascularize heart failure patients, and these two classifications share a number of pathophysiological and clinical aspects (35, 50). However, there are data to suggest differences between myocardium classified as chronically stunned and as hibernating by perfusion/metabolic imaging. Haas et al. (19) studied the time course of improvement of dysfunctional myocardium after revascularization. Dysfunctional regions with normal perfusion and metabolism (i.e., “stunning”) differed from regions with reduced perfusion and preserved metabolism (“mismatch regions”) with respect to the degree and time course of functional recovery after coronary artery bypass surgery. Schwarz et al. (43) studied biopsies from dysfunctional myocardium in patients with variable durations of chronic ischemia. Morphological tissue analysis identified different histological changes between dysfunctional segments with preserved perfusion and FDG uptake (stunning) and mismatch (“hibernation”) with use of FDG PET or sestamibi SPECT. A number of experimental studies by Fallavollita et al. (13, 15) and Thijsse et al. (46) support the belief that chronically stunned myocardium over time progresses to a state of hibernation. Together, these observations suggest some differences between myocardium classified as chronically stunned and as hibernating. This led us to subclassify the viable, dysfunctional regions, although this distinction, from a clinical point of view, may be of minor importance.

Study limitations. We did not study the relation between O₂ consumption and left ventricular performance, i.e., myocardial efficiency, which theoretically could improve, although function was unchanged. Myocardial substrate uptake was not quantified during the different metabolic interventions of the present study. Previous studies using PET and invasive techniques have documented that modulation of myocardial FFA and glucose uptake can be achieved by the interventions used in our design (4, 17, 29, 31, 54). Anticongestive medication affects myocardial substrate metabolism (52) and could bias metabolic interventions. We found it unethical to withdraw well-documented medical therapy from these patients and ensured that interventions were performed in addition to optimized medication, which remained constant throughout the study period. We cannot exclude the possibility that higher insulin infusion rates could have additional beneficial effects. However, the rate chosen in the present study ensured an insulin infusion rate >6 U/h, which is comparable or even higher than that in most previous clinical studies documenting a beneficial effect in postoperative or acute ischemic states (7, 26, 29, 30, 33). We documented that circulating FFAs were totally suppressed and that we achieved plasma insulin levels in the supraphysiological range.

Recovery of function after revascularization in chronically stunned and hibernating myocardium was not confirmed, and it can be argued that the absence of contractile response to metabolic modulation was due to degeneration of the sarcomere (11, 50, 51), resulting in the inability of the myocyte to respond to an improvement in the metabolic status of the cell. However, function improved during stress in these regions, demonstrating a contractile reserve.

In the present study, we scored sestamibi and FDG images semiquantitatively. We previously validated sestamibi SPECT without attenuation correction against [¹³N]ammonia PET and obtained different results in only 8% of segments (39). An even better correlation would be expected in the present study between...
perfusion measured by sestamibi SPECT and the “gold standard” \[^{13}N\]\text{ammonia PET}, because we performed attenuation correction of sestamibi uptake. We therefore believe that the estimates of perfusion and viability status used in the present study are valid. It is not likely that differences in wall thickening contributed to the differences in tracer uptake between chronically stunned and hibernating myocardium, because the wall motion score was similar in the two types of regions.

The possibility of a type 2 statistical error must be considered. We used a crossover design and sensitive, reproducible (2) echocardiographic techniques with paired measurements of regional contractile function. This approach eliminated interpatient and minimized intrapatient variation and resulted in a low variability between \(V_{\text{max}2}\) and \(V_{\text{max}1}\), \(\epsilon_{\text{max}2}\) and \(\epsilon_{\text{max}1}\), \(V_{\text{max}3}\) and \(V_{\text{max}2}\), and \(\epsilon_{\text{max}3}\) and \(\epsilon_{\text{max}2}\) (Figs. 3 and 4). It is possible that the echocardiographic techniques used to assess regional function were insensitive to subtle changes in contractile function. However, our data consistently demonstrated that global and regional measures of contractility, as well as hemodynamics, were unaffected by modulation of substrate supply, supporting the belief that short-term metabolic modulation has no clinically important effect.


**Conclusions.** Contractile dysfunction of chronically stunned and hibernating myocardium in nondiabetic patients with chronic heart failure remains unchanged during extreme acute changes in FFA and insulin levels at rest and during exercise. In support of the belief that short-term metabolic modulation has no clinically important effect.

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