Slowed Glycogen Utilization EnhancesExercise Endurance in Patients With Heart Failure
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OBJECTIVES
The objective of the study was to investigate the impact of alteration of glycogen stores and metabolism on exercise performance in patients with heart failure.

BACKGROUND
In normal subjects, muscle glycogen depletion results in increased exertional fatigue and reduced endurance. Skeletal muscle biopsies have revealed reduced glycogen content in patients with congestive heart failure (CHF). Whether glycogen depletion contributes to reduced endurance and abnormal ventilation in these patients is unknown.

METHODS
Bicycle exercise tests with measurement of respiratory gases were performed following dietary manipulations to induce glycogen depletion (60% protein, 40% fat) and slow glycogen utilization (60% carbohydrate, 30% fat, 10% protein) in 13 patients with CHF (left ventricular ejection fraction 22 ± 6%; age 48 ± 9 years) and 7 control subjects (age 45 ± 5 years). Maximal exercise, exercise at 75% of peak workload until exhaustion and 1-min cycles of supramaximal exercise at 133% of peak were performed on three occasions over a two-week period.

RESULTS
Significant changes in resting respiratory quotients (RQs) in normal (Baseline: 0.78 ± 0.03; Depleted: 0.69 ± 0.05) and CHF subjects (Baseline: 0.84 ± 0.05; Depleted: 0.72 ± 0.05) were observed (both p < 0.05). Peak VO2 (oxygen consumption) in both groups was unchanged. The ventilatory response to exercise was analyzed by correlating CO2 production (VCO2) to minute ventilation (VE) in each test. The slopes of these correlations were not affected in either group. With glycogen depletion, exercise endurance was reduced from 17 to 6.1 min (57 ± 19%) in normal subjects versus a reduction of 9.4 to 8.1 min (11 ± 19%) in patients (p < 0.05). With slowed glycogen use, CHF patients increased exercise endurance from 9.4 to 16.5 min (65%) versus 17 to 20.6 min (18%) in normal subjects (p < 0.05).

CONCLUSIONS
Glycogen depletion minimally affects maximal exercise performance, endurance or ventilation in CHF patients, whereas slowed glycogen utilization markedly enhances exercise endurance. Therapeutic interventions that increase or slow use of glycogen stores may have clinical benefit.

Glycogen provides a ready source of energy for use during exercise (1,2). Glycogen stores are located primarily in the liver and skeletal muscle. Breakdown of glycogen in the liver frees glucose into the bloodstream. Glycogen breakdown in the muscle yields only phosphorylated glucose, which is a nondiffusible molecule and thus remains within the muscle cell as a captured source of energy.

The rate-limiting enzyme for glycogen breakdown is phosphorylase. This enzyme is activated by elevations in intracellular levels of cyclic adenosine monophosphate (cAMP), calcium and phosphate. Thus, catecholamines and muscle contraction stimulate breakdown of glycogen. The end product of glycogen metabolism is pyruvate, which can be metabolized both anaerobically and aerobically. Pyruvate can be converted in the cytosol to lactate by glycolysis or in the mitochondria to CO2 (carbon dioxide) and water via the Krebs cycle. Elevation of free fatty acids slows glycogen utilization by increasing levels of acetyl CoA (coenzyme A) and citrate, thereby inhibiting pyruvate dehydrogenase. This negative feedback inhibition leads to an increase in glucose-6-phosphate, which inhibits phosphorylase and slows glycogen breakdown (Fig. 1).

During rest, cells derive most of their fuel from substrates present in blood. During exercise, fuel combustion is determined by the intensity and duration of exercise as well as by substrate availability. In the first few minutes of exercise, muscle glycogen is the main fuel used to generate adenosine triphosphate (ATP). This is followed by blood glucose and,
during sustained exercise, by free fatty acids. Muscles rely heavily on glycogen during heavy exercise owing to its proximity.

Glycogen stores and metabolism in normal subjects affect exercise endurance (3–5). Whether abnormalities in glycogen metabolism contribute to reduced endurance in patients with heart failure has not been studied. However, abnormalities in glycogen metabolism have been described in heart failure. In a rat infarct model of congestive heart failure (CHF), Musch and colleagues (6,7) described accelerated rates of glycogen breakdown and utilization in the leg muscles of infarct rats versus sham controls. Biopsies of limb skeletal muscle in patients with CHF have demonstrated reduced glycogen levels (8). In vivo 31 phosphorus magnetic resonance spectroscopy also suggests an increased rate of glycogenolysis in patients with CHF (9). Possible mechanisms of abnormal glycogen metabolism in patients with CHF include reduced delivery of substrates due to reduction in skeletal muscle perfusion; elevated hormonal levels such as catecholamines, which will increase breakdown of glycogen; and intrinsic alteration of skeletal muscle metabolism with an increased reliance on glycolytic activity. Deconditioning also results in a greater reliance on carbohydrate metabolism.

The purpose of this study was to investigate the effect of glycogen depletion and slowed glycogen use on exercise performance in patients with CHF. We hypothesized that, in patients with CHF, glycogen depletion would minimally affect exercise performance, whereas carbohydrate loading with slowed glycogen utilization would enhance performance.

**METHODS**

**Subjects.** Seven normal subjects and 13 patients with CHF were studied (Table 1). The subjects were age-matched. Five of the patients had coronary artery disease, and eight patients had dilated cardiomyopathy. Mean ejection fraction was 21% and peak VO₂ (oxygen consumption) averaged 14 ml/kg/min. The majority of the patients had class II or III CHF. None of the patients were being treated with beta-blockers. None were diabetic. All had undergone prior exercise testing with measurement of VO₂. None of the subjects were limited by chest pain or claudication. The average age of the four men and three women who formed the control group was 45 ± 5 years. None of the normal subjects were on any medications. All had normal history and physical exams.

The protocol was approved by Columbia University’s Committee on Studies Involving Human Beings. Written informed consent was obtained from all subjects.

**Exercise protocol.** The exercise protocol consisted of three parts—maximal, submaximal and supramaximal bicycle exercise. Sixty-minute rest periods separated the studies. Before exercise, respiratory gases were collected for approximately 10 min to measure basal respiratory quotient. Routine bicycle exercise was then performed using 25-W increments to peak exercise. Submaximal exercise consisted of bicycling at 75% of peak workload until exhaustion. The duration of exercise was recorded. Supramaximal exercise consisted of 1 min of exercise at 133% of peak workload for 1 min followed by 2 min of rest. This was repeated until the subject was unable to complete a full minute of exercise. The number of full cycles was recorded.

The three-part exercise protocol was performed by the patient in the fasting state on the afternoon of day 1. On discharge to home, subjects were provided with a nutritional drink consisting of 60% protein and 40% fat. Caloric

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**Table 1. Clinical Characteristics of CHF Subjects**

<table>
<thead>
<tr>
<th>Etiology of CHF</th>
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<tbody>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>8</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48 ± 8</td>
</tr>
<tr>
<td>Gender</td>
<td>11</td>
</tr>
<tr>
<td>Men</td>
<td>11</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>21 ± 6</td>
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<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>13.7 ± 3</td>
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<tr>
<td>New York Heart Association classification</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>1</td>
</tr>
<tr>
<td>Class II</td>
<td>6</td>
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<tr>
<td>Class III</td>
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content was determined by the subject's body surface area (BSA). Approximately 1,000 calories were provided. This nutritional drink was the only food the subjects were permitted. On day 2, patients again reported in the fasting state, and the exercise protocol was repeated.

The following week, a nutritional drink was delivered the night prior to exercise. It consisted of 60% carbohydrate, 30% protein, and 10% fat. Caloric content was again determined from BSA and averaged 1,600 calories. The next morning the subjects reported to the exercise lab where a high-fat breakfast was served. Three and one-half hours later, 2,000 U of heparin IV was administered to activate lipoprotein lipase and thus increase formation of free fatty acids. Thirty minutes later the exercise was repeated.

**Breath assays.** Peroxidation of fatty acids results in increased production of alkanes, which can be measured in the breath. Alkane breath concentrations were compared in three patients in the fasting state following normal diet, with glycogen depletion, and after carbohydrate loading.

Samples of alveolar breath and unfiltered room air (10 liter/min) were collected sequentially using a transportable apparatus that captured the volatile organic compounds on an adsorptive trap containing activated carbon and molecular sieve as described previously by Phillips (10,11). The volatile organic compounds were subsequently desorbed from the adsorptive trap in a microprocessor-controlled thermal desorber and concentrated by two-stage cryofocusing in sequential cold traps at −150°C. The concentrated sample was then separated by gas chromatography and analyzed by mass spectroscopy with an ion-trap detector.

An alveolar gradient was calculated as the difference of concentration in breath minus the concentration in inspired air. A positive gradient was consistent with a metabolite manufactured in the body. A negative gradient was consistent with ingestion of an air pollutant. Positive gradients for alkanes were recorded.

**Statistical analysis.** Statistical analysis was performed using t tests, analysis of variance (ANOVA) or chi-square analysis for continuous and noncontinuous variables as appropriate. Linear regression analysis was used to correlate ventilation to CO₂ production. As the design for the study was a two-factor experiment (group and diet) with diet treated as a repeated measure (i.e., multiple measurements [within person] on the same unit), a repeated measures ANOVA was utilized, including a test for interaction effects (group × diet). Because of correlations within subject, F tests were adjusted for their degrees of freedom, via univariate methodology, including the estimation of the correlation structure (i.e., compound symmetry, autoregressive [AR(1)], unstructured, others), or by the more conservative multivariate methods. Hence, p values were generated by the most appropriate methods according to the assumptions of repeated-methods ANOVA. Unless otherwise indicated, p values were not adjusted for multiplicity of testing. Data were analyzed using SAS system software (SAS Institute, Cary, North Carolina).

**RESULTS**

**Efficacy of dietary and exercise intervention.** Resting respiratory quotients and production of exhaled breath alkanes were used to assess the effectiveness of our diet and exercise interventions in shifting substrate utilization. Resting respiratory quotient (RQ) based exclusively on metabolism of 1 g of fat is approximately 0.71. Exclusive carbohydrate metabolism would yield a resting RQ of 1.00. Resting RQs for normal subjects and CHF subjects at baseline, with glycogen depletion and with slowed glycogen utilization demonstrated significant differences (Table 2). In the glycogen-depleted state, both groups had significantly reduced RQs. This shift in RQ reflects a greater reliance on fat than on carbohydrate metabolism. Similarly, after the high-carbohydrate diet, RQs tended to be higher than the baseline values (Fig. 2).

Positive alveolar gradients for ethane (5.8 pmol/liter) and decane (0.84 pmol/liter) were present in the three patients following glycogen depletion but not in the baseline or carbohydrate-loaded state. Positive alveolar gradients for pentane production were seen in the control (0.4 pmol/liter) and glycogen-depleted (0.39 pmol/liter) states. Exhaled urea, probably representing protein metabolism, was observed only in the glycogen-depleted state (0.16 pmol/liter).

**Exercise performance.** Peak Vo₂ measured at baseline, during glycogen depletion, and with slowed glycogen utilization was unchanged in both normal and CHF subjects (Table 2). Peak Vo₂ was significantly lower in CHF subjects than in normal subjects (Fig. 3).

Exercise duration during submaximal exercise was used as a parameter of endurance. In normal subjects, glycogen
Glycogen depletion resulted in a significant deterioration of performance, with a decrease in exercise time from 17 to 6 min (57% decline) \( (p = 0.02) \). With slowed glycogen utilization there was a slight tendency to increase exercise time from 17 to 20.5 min (18% increase) \( (p = 0.1) \). In contrast, glycogen depletion minimally affected endurance in patients with CHF. Exercise time was decreased from 9.4 to 8.1 min (11% decline) \( (p = 0.07) \). However, slowed glycogen utilization significantly increased exercise duration, with exercise time increasing 9.4 to 16.5 min (65% increase) \( (p = 0.006) \) (Table 3, Fig. 4A).

With supramaximal exercise, during glycogen depletion normal subjects had a significant deterioration in the number of cycles that could be completed, from 5 to 2 \( (p = 0.003) \). Slowed glycogen utilization did not affect exercise performance, as the number of completed cycles was unchanged from baseline. In contrast, no significant change from baseline was observed during glycogen depletion in patients with CHF (6 vs. 5) \( (p = 0.17) \), whereas the number of cycles tended to increase during slowed utilization (6 vs. 8) \( (p = 0.005) \) (Table 3, Fig. 4B).

Ventilation. The ventilatory response to exercise was assessed by performing a linear regression of minute ventilation to \( \text{CO}_2 \) production and solving the equation for the ventilation at a \( \text{VCO}_2 \) of 1 liter. No significant change in ventilation was observed in either group with dietary manipulations (Table 2).

Subjective assessment of exercise intensity. When the intensity of exercise was compared to the baseline studies, all normal subjects felt that, during glycogen depletion, the exercise was much more difficult. In contrast, 11 of 13 CHF patients noted the exercise to be either of the same intensity or easier. With slowed glycogen utilization, both groups found the exercise to be the same or easier, although a larger percentage of patients felt exercise intensity was reduced (Table 4).

**DISCUSSION**

This study demonstrates that, contrary to the normal response, glycogen depletion does not affect exercise endurance in patients with CHF, whereas alteration of diet to slow glycogen utilization significantly enhances exercise endurance in these patients.

Measurement of basal RQs in normal and CHF subjects demonstrated the adequacy of our dietary interventions and...
exercise protocol in producing glycogen depletion. In both groups, RQ was significantly lower than baseline values, suggesting a shift from carbohydrate to free fatty acid metabolism. Moreover, volatile alkanes measured in the breath of CHF patients were increased in the glycogen-depleted state. This is consistent with increased peroxidation of free fatty acids (1).

In normal subjects, glycogen depletion did not affect maximal VO2 but significantly diminished exercise endurance. Subjectively, with glycogen depletion, normal subjects uniformly experienced tremendous fatigue and an increased difficulty in performing exercise. Slowed glycogen utilization tended to increase exercise endurance. The observed changes are consistent with prior reports (3–5).

In CHF subjects, alteration of glycogen metabolism did not affect peak VO2. However, in contrast to normal subjects, glycogen depletion had minimal effect on exercise endurance. Only 2 of the 13 CHF patients experienced fatigue with glycogen depletion. The majority sensed no difference between the basal and glycogen-depleted states. Further depletion of an already depleted state appears to minimally affect exercise endurance in these patients. Alternative explanations would include inability to use glycogen stores or the inadequacy of our protocol to deplete glycogen stores in these patients owing to the low exercise workloads used. The reduction in basal RQ and increased production of volatile alkanes would support a shift of metabolism from carbohydrate to free fatty acid, and thus the efficacy of our protocol to induce glycogen depletion in this patient population. Direct measurement of glycogen in muscle biopsies preceding each exercise protocol would have directly answered these questions.

Patients with CHF have an excessive ventilatory response to exercise. Glycogen depletion has variably been shown to increase ventilation in normal subjects (12). The mechanism for increased ventilation may be neurogenic, resulting from an increase in muscle fiber recruitment, as glycogen-depleted muscle fibers cannot maintain adequate tension at high power outputs. In our study, alteration of glycogen metabolism did not affect the ventilatory response to exercise in either normal subjects or CHF patients. As the changes observed in prior studies tended to be small, the absence of changes in this population may be related to the small number of subjects and/or differences in our data analysis.

Slowed utilization of glycogen stores following carbohydrate loading resulted in an impressive increase in exercise endurance in CHF subjects. Subjectively, exercise was noted by most patients to be easier. Correction of a depleted state versus less rapid use of glycogen stores or both may have resulted in these findings. Earlier studies have suggested an accelerated rate of glycogen breakdown and utilization in heart failure (6,7,9). Moreover, insulin resistance has been described in patients with CHF (13,14). Insulin resistance would impair glucose uptake, resulting in a greater reliance on glycogen metabolism with more rapid depletion of this substrate. Thus, nutritional interventions that replete and/or slow breakdown of glycogen could be beneficial for these patients.

In several studies, aerobic training has been shown to improve endurance in patients with CHF (15,16). Exercise-induced enzymatic changes in lipid metabolism lead to an increase in the supply and metabolism of free fatty acids. This shift from carbohydrate metabolism results in diminished glycogen use and increased muscle glycogen content. The improvement in endurance observed with training may in part be related to changes in glycogen content. Kemp et al. (9) demonstrated a reduction in glycogen phosphorylase activation following aerobic training in patients with CHF.

### Table 3. Exercise Performance During Submaximal and Supramaximal Exercise in the Normal and HFC Groups

<table>
<thead>
<tr>
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<th>Submaximal Exercise (min)</th>
<th>Supramaximal Exercise (n)</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>CHF</td>
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<tr>
<td>Baseline</td>
<td>17.0 ± 4.8</td>
<td>9.4 ± 4</td>
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<tr>
<td>Depleted</td>
<td>6.1 ± 1.9*</td>
<td>8.1 ± 3.1</td>
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<tr>
<td>Slowed use</td>
<td>20.5 ± 8.5</td>
<td>16.5 ± 5.6*</td>
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*p < 0.05 baseline versus depleted versus slowed use.

### Table 4. Subjective Assessment of Exercise Difficulty

<table>
<thead>
<tr>
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<th>Normal</th>
<th>CHF</th>
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<tbody>
<tr>
<td>Glycogen Depleted*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harder</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Easier</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Same</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Slowed Utilization*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harder</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Easier</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Same</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*p < 0.05. Normal subjects versus CHF patients.
Clinical implications. The ability to sustain submaximal work is critical to daily functioning and quality of life. Fatigue remains a disabling symptom in CHF. Therapeutic interventions that can improve endurance and reduce fatigue are important to the quality of life of these patients. Our study suggests that therapeutic interventions and/or simple dietary modifications that slow glycogen utilization, increase glycogen stores, or shift substrate utilization from carbohydrate to free fatty acids may increase endurance and alleviate fatigue in patients with CHF. To quote Marie Antionette, “Let them eat cake.”

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REFERENCES