Effect of Changes in Fat Availability on Exercise Capacity in McArdle Disease

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**Background:** The major fuel for exercising muscle at low exercise intensities is fat.

**Objective:** To investigate the role of fat metabolism in McArdle disease (also known as glycogen storage disease type V), an inborn error of muscle glycogenolysis, by manipulating free fatty acid availability for oxidation during exercise.

**Design:** Randomized, placebo-controlled, crossover trial.

**Setting:** Hospitalized care.

**Patients:** Ten patients (8 men and 2 women) with McArdle disease.

**Interventions:** Patients cycled at a constant workload corresponding to 70% of their maximum oxygen consumption. In random order and on separate days, patients received nicotinic acid (a known blocker of lipolysis) to decrease the availability of free fatty acids or 20% Intralipid infusion to increase free fatty acid availability during exercise. Results were compared with placebo (isotonic sodium chloride solution infusion) and glucose infusion trials.

**Main Outcome Measures:** Exercise tolerance was assessed by heart rate response to exercise during different infusions.

**Results:** Free fatty acid levels more than tripled by Intralipid infusion and were halved by nicotinic acid administration. Heart rate was significantly higher during exercise in the Intralipid infusion and nicotinic acid trials compared with the placebo and glucose infusion trials, an effect that was observed before and after the patients had experienced the second wind phenomenon.

**Conclusions:** Lipids are an important source of fuel for exercising muscle in McArdle disease, but maximal rates of fat oxidation seem limited and cannot be increased above physiologically normal rates during exercise. This limitation is probably caused by a metabolic bottleneck in the tricarboxylic acid cycle due to impaired glycolytic flux in McArdle disease. Therapies aimed at enhancing fat use in McArdle disease should be combined with interventions targeting expansion of the tricarboxylic acid cycle.

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**MUSCLE GLYCOGEN** IS AN important fuel for contracting muscle early in exercise and at high exercise intensities. McArdle disease (also known as glycogen storage disease type V) is an inborn error of muscle metabolism caused by mutations in the myophosphorylase gene (PYGM) (OMIM_232600). Myophosphorylase activity is typically absent such that muscle glycogen breakdown is completely blocked in this condition. Accordingly, the work capacity of these patients is generally reduced to one-fourth to one-half of normal levels. Muscle cramps, provoked by sudden vigorous exercise, are common. The cramps can result in muscle injury as reflected by almost constantly elevated creatine kinase levels and by recurrent episodes of myoglobinuria.

McArdle disease has supplied important insights into the role of muscle glycogen for energy metabolism during exercise. A remaining question that has not been studied (to our knowledge) is the role of fat metabolism in McArdle disease. Ideally, patients with this disease should compensate for their blocked glycogen metabolism by increasing fat combustion. Patients with McArdle disease have a higher sympathoadrenal response to exercise, which must increase lipolysis. Using stable isotope techniques to study palmitate turnover, it has recently been shown that mobilization and oxidation of free fatty acids (FFAs) during exercise are increased in McArdle disease. Although
helpful, higher fat combustion far from rescues the energy crisis that occurs during exercise in McArdle disease, and the question remains why patients do not increase their fat combustion even more to compensate for blocked muscle glycogenolysis. It was previously proposed that a shortage of tricarboxylic acid (TCA) cycle intermediates in McArdle disease may be rate limiting for fat oxidation. McArdle disease provides a good model to study the interplay between muscle glycogen and fat metabolism during exercise. To study this further, we manipulated FFA availability for oxidation during exercise in 10 patients with McArdle disease by decreasing FFA availability via administration of nicotinic acid or by increasing FFA availability via infusion of lipids intravenously. This not only will provide important insights into the pattern of substrate mobilization in the disease, which may facilitate development of therapies, but also may improve our understanding of the relative roles of fat and muscle glycogen during exercise in the healthy individual.

METHODS

SUBJECTS

We studied 10 patients (8 men and 2 women) with McArdle disease recruited from Denmark and the United States. Their mean (SE) age was 35 (2) years (age range, 20-43 years). All patients had a typical history of exercise intolerance and successive episodes of myoglobinuria. Diagnoses were confirmed by demonstration of absent myophosphorylase activity in muscle or by genetic testing for PYGM. No subject took any medication.

The Ethics Committee of Copenhagen had approved the study. The subjects were informed of the nature and risk of the study and gave written consent to participate.

EXPERIMENTAL PROTOCOL

All participants were studied in the same laboratory at the Neuromuscular Research Unit at Righospitalet, Copenhagen, Denmark, and they reported to the laboratory between 9 and 10 AM. The patients exercised on a stationary cycle ergometer (CPE; MedGraphics, St Paul, Minnesota) operated via a cardiopulmonary exercise test system (CPX/D; MedGraphics) that continuously measured gas exchanges, workload, and heart rate. On the first day, patients performed an incremental exercise test to exhaustion to determine each subject’s maximum oxygen consumption. Workload increments were adjusted so that the duration of the test was kept between 12 and 15 minutes. The findings were used to identify the level of constant workload that was to be used in studies.

On the following 4 days, the patients exercised each day for 20 minutes at a constant workload corresponding to approximately 70% of their maximum oxygen consumption. Based on our clinical experience in McArdle disease, physiologic responses and creatine kinase values are unaffected if moderate, short-term aerobic exercise is performed on consecutive days. Before the experiment, an antecubital venous catheter was inserted in each subject for blood sampling, and a second antecubital catheter was placed in the contralateral arm for infusion studies. During exercise, heart rate was scored every minute, and gas exchanges and blood samples for measurements of glucose, lactate, and insulin levels and FFAs were obtained every 5 minutes.

A different treatment was given each day in random order. We administered nicotinic acid (a known blocker of lipolysis) to decrease the availability of fat for combustion and Intralipid (Fresenius Kabi AB, Uppala, Sweden) infusion to increase the availability. The results were compared with a placebo trial in which patients received a 50-mL bolus of isotonic sodium chloride solution before exercise, followed by isotonic sodium chloride solution infusion (360 mL/h) during exercise, and these results were compared with those of a glucose infusion trial in which patients received 10% glucose (a 30-mL bolus) 5 minutes before cycling, followed by infusion of 10% glucose (360 mL/h) during exercise. In the Intralipid infusion trial, patients received infusion of 20% Intralipid at an infusion rate of 100 mL/h. One liter of Intralipid contains purified soybean oil (200 g), purified egg phospholipids (12 g), glycerol anhydrous (22 g), and water for injection in a sufficient quantity to equal 1 L. Using sodium hydroxide, the pH was adjusted to approximately 8. Energy content per liter was 8.4 mJ (2000 kcal). Infusion was started 30 minutes before exercise to enhance fat availability when exercise started and was continued at an unchanged infusion rate during exercise. Heparin sodium (1000 U) was injected intravenously 30 minutes and 5 minutes before exercise to further enhance lipolysis. In the nicotinic acid trial, patients ingested nicotinic acid (2.5-5 mg/kg of body weight) 60 minutes before exercise, and they ingested 1.25 to 2.5 mg/kg of body weight 30 minutes before and at the onset of exercise.

Patients were blinded to the content of infusions, and infusion sets were covered during the experiments. The patients could not be blinded to the nicotinic acid trial. From the information provided in the consent forms and from the flushing induced by nicotinic acid, the patients knew that they had received nicotinic acid. It was also the only treatment that was administered orally.

ANALYSES

Venous blood was sampled in syringes containing 0.33M EDTA (10 µL/mL of blood) spun in a refrigerated centrifuge and stored at −20°C until analysis. Blood samples were analyzed for lactate and plasma glucose levels (model 2300 STAT plus; YSI Inc, Yellow Springs, Ohio). Free fatty acid levels were analyzed on an automated fluorometer (Cobas Fara; Roche, Basel, Switzerland). The insulin level was measured by radioimmunoassay. The primary end point was heart rate (in beats per minute) during exercise. Values are expressed as mean (SE). Two-tailed P < .05 was considered statistically significant. Differences among treatments were assessed by paired t test.

RESULTS

EFFECTS ON HEART RATE

Fuel availability is different before and after the second wind phenomenon in patients with McArdle disease. Therefore, it is logical to describe the response to changes in fat availability among patients in the first half of the exercise period, before and during the second wind, and in the last half of the exercise period during the metabolic steady-state period after the second wind has taken effect. During the first 10 minutes of exercise, heart rate peaked in the sixth minute of exercise in the placebo, nicotinic acid, and Intralipid infusion trials (Figure 1). Peak heart rates were higher in the nicotinic acid trial (144 [4] beats/min) and the Intralipid infusion trial (136 [6] beats/min) vs the
placebo trial (130 [4] beats/min) ($P < .01$). In all 3 trials, the peak heart rate was followed by a spontaneous second wind of similar magnitude. In contrast, glucose infusion almost abolished the second wind such that the heart rate was significantly lower than that in the other 3 trials from 5 to 10 minutes of exercise. In the first half of the exercise period, the heart rate was on average 15 (1) beats/min higher in the nicotinic acid trial vs the placebo trial ($P < .01$) and 8 (3) beats/min higher in the Intralipid infusion trial vs the placebo trial ($P < .01$), whereas the heart rate was 10 (2) beats/min lower in the glucose infusion trial vs the placebo trial ($P < .01$).

In the second half of the exercise period, the heart rate was consistently 11 (1) beats/min higher in the nicotinic acid trial and 9.0 (0.2) beats/min higher in the Intralipid infusion trial vs the placebo trial ($P < .01$). The heart rate was slightly lower during the glucose infusion trial (2.5 [0.2]) vs the placebo trial ($P < .01$). Nicotinic acid produced a resting tachycardia of 6 (2) beats/min, but after considering this, heart rates were still significantly higher during exercise in the nicotinic acid trial vs the placebo trial.

**PLASMA METABOLITES AND INSULIN**

The fat availability manipulations were successful according to plasma FFA levels because FFA levels more than tripled by Intralipid infusion and decreased to less than half of normal values by nicotinic acid administration (Figure 2). Free fatty acid levels were comparable in the placebo and glucose infusion trials.

Plasma glucose concentration was almost tripled by glucose infusion. In the other trials, plasma glucose concentrations did not change significantly during the study and did not differ between trials, although levels tended to be higher in the nicotinic acid trial. In line with this trend, plasma lactate levels were higher before and during exercise in the nicotinic acid trial compared with the placebo and Intralipid infusion trials. Plasma lactate levels dropped in the nicotinic acid and placebo trials with exercise but continued to increase in the glucose infusion trial.
As expected, glucose infusion induced hyperinsulinemia. Plasma insulin levels were comparable in the placebo and Intralipid infusion trials but were slightly increased in the nicotinic acid trial ($P = .05$). This is in accord with higher lactate levels and the trend toward higher glucose levels in this trial.

**COMMENT**

At low and moderate work intensities in healthy subjects, the major fuel for exercising muscle is fat.\(^{11,12}\) Oxidation of fat is not compromised directly by the enzyme defect in McArdle disease, and fat could be hypothesized to serve as an alternative fuel to muscle glycogen in this condition. Therefore, we investigated fat metabolism in McArdle disease by increasing FFA availability during exercise via Intralipid infusion or by decreasing the availability via administration of nicotinic acid, a known blocker of lipolysis. The main findings of the study are that blocking FFA availability with nicotinic acid has a detrimental effect on exercise performance in patients, indicating that spontaneous lipid oxidation during exercise is an important fuel source for working muscle in this condition. Although lipid metabolism is important to support energy metabolism in patients with McArdle disease, increased FFA availability did not augment fat oxidation in our patients with McArdle disease and cannot compensate for blocked muscle glycogenolysis. The findings indicate that therapies aimed at enhancing fat utilization in McArdle disease, without improving limitations in carbohydrate metabolism, will probably fail to work.

Using stable isotope techniques to measure fat turnover, it was recently shown that patients with McArdle disease have normal fat oxidation at rest but that fat oxidation is enhanced during exercise.\(^{8}\) Although fat oxidation was augmented and FFA availability was abundant in patients in that study, fat oxidation did not increase sufficiently to rescue the energy deficit imposed on the muscle by myophosphorylase deficiency. This finding points to a ceiling effect of maximal fat oxidation, which likely is caused by limitations in substrate flux of the TCA cycle due to low glycolytic flux in McArdle disease.\(^{8}\) This is different from fat oxidation in healthy subjects, in whom fat oxidation increases in parallel with increasing FFA concentrations during sustained exercise.\(^{13}\) The basic metabolic observation of enhanced fat oxidation during exercise, which is insufficient to restore normal energy status in working muscle of patients with McArdle disease, is compatible with the present interventional finding of no improvement in exercise tolerance when increasing fat availability by Intralipid infusion. Therefore, substrate availability does not determine the level of fat oxidation during exercise in McArdle disease. In fact, exercise tolerance fell during lipid infusion, which probably relates to a direct inhibitory effect of FFA levels on glucose transport into working muscle cells, as patients with McArdle disease rely heavily on extramuscular glucose as a fuel.\(^{14}\) High FFA levels interfere with glucose uptake in muscle and may have a role in development of insulin insensitivity seen in type 2 diabetes mellitus.\(^{15-16}\)

The inability to spontaneously augment fat oxidation during exercise or to benefit from fat supplements, as indicated by the present study, points to a metabolic bottleneck in fat metabolism that likely resides in the TCA cycle. The TCA cycle intermediates in working muscle are low in patients with McArdle disease.\(^{17}\) The level of TCA cycle intermediates may influence TCA cycle flux, and an increase in TCA intermediates is necessary for enhanced aerobic function and contractile performance.\(^{17-21}\) In McArdle disease, expansion of TCA cycle flux (anaplerosis) seems to be a crucial step for improving aerobic capacity.

The second wind phenomenon is pathognomonic for McArdle disease\(^ {22}\) and is associated with a large spontaneous decrease in heart rate and perceived exertion after 6 to 8 minutes of exercise. The phenomenon is caused by increased oxidative capacity due to improved delivery and oxidation of extramuscular fuels to working muscles. It was previously shown that improvement in glucose oxidation is essential for eliciting the second wind.\(^ {2}\) The present study indicates that spontaneous lipid oxidation is also an important energy component fueling myophosphorylase-deficient muscles before the second wind because exercise tolerance is severely impaired by nicotinic acid in this period. We know from stable isotope investigations that fat oxidation may also contribute to the second wind in parallel with improvements in the oxidation of extramuscular glucose.\(^ {3}\) However, the present study shows that lipid infusion (unlike glucose infusion) cannot diminish the magnitude of the second wind phenomenon.

Fat metabolism in McArdle disease, as assessed by manipulating fat availability, has been studied in 5 earlier case studies. In 3 studies\(^{23-25}\) in which patients with McArdle disease were fasting, improvement in ventilatory response, exercise capacity, or cardiac output relative to oxygen uptake was observed and was attributed to better fat oxidation because fasting promotes fat utilization. However, the effect of fasting on exercise capacity in McArdle disease has not been studied in detail, to our knowledge. In another study, a long-term ketogenic diet seemed to help exercise tolerance in one patient,\(^ {26}\) and a 3-day fat-rich diet was claimed to improve tolerance to submaximal exercise in another patient.\(^ {27}\) Controlled studies on the effect of fasting or lipid-promoting diets in larger numbers of patients with McArdle disease are warranted to test the results of these case studies.

Lipid infusion had no effect on exercise capacity in phosphoglycerate mutase deficiency of distal muscle glycolysis.\(^ {28}\) This is not surprising because this defect always leaves some residual enzyme activity, and exercise capacity is near normal. Therefore, glycolysis is normal in muscle of patients with this deficiency at submaximal exercise intensities (levels at which fat oxidation is important). In muscle phosphofructokinase deficiency, lipid and glucose infusions have the opposite effect on exercise capacity compared with that in McArdle disease.\(^ {29}\) Like patients with McArdle disease, patients with muscle phosphofructokinase deficiency have complete enzymatic block, and symptoms closely mimic those of McArdle disease except that patients have no second wind.
phenomenon. In muscle phosphofructokinase deficiency, glycolysis is blocked not only from glycosyl units derived from muscle glycogenolysis but also from exogenously supplied glucose (in contrast to patients with McArdle disease). Therefore, lipids represent the primary fuel available for muscular work in this condition. Accordingly, oxidative capacity is significantly improved by lipid infusion, while glucose infusion produces an “out-of-wind phenomenon.” The detrimental effects of high FFA levels on glucose transport across the sarcolemma that affects patients with McArdle disease are inapplicable in patients with muscle phosphofructokinase deficiency because glucose cannot be used as a fuel.

Lipids are an important source of fuel for exercising muscle and even more so in patients with McArdle disease, in whom muscle glycogenolysis is blocked. However, our results indicate that maximal rates of fat oxidation are limited and cannot be increased above physiologically normal rates during exercise in this condition. This limitation is probably caused by a metabolic bottleneck in the TCA cycle due to impaired glycolytic flux in McArdle disease. Our results indicate that future dietary therapies in McArdle disease should be aimed at expanding the TCA pool by delivery of glycolytic substrates, which should also increase the capacity for fat oxidation.

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