

ORIGINAL ARTICLE

The Effect of Oral Sucrose on Exercise Tolerance in Patients with McArdle's Disease

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ABSTRACT

BACKGROUND

Energy metabolism in muscles relies predominantly on the breakdown of glycogen early in exercise. In patients with McArdle's disease, blocked glycogenolysis in muscles results in low exercise tolerance and can lead to muscle injury, particularly in the first minutes of exercise. We hypothesized that ingesting sucrose before exercise would increase the availability of glucose and would therefore improve exercise tolerance in patients with McArdle's disease.

METHODS

In a single-blind, randomized, placebo-controlled crossover study, 12 patients with McArdle's disease drank 660 ml of a beverage that had been sweetened with artificial sweeteners (placebo) or with 75 g of sucrose after an overnight fast. Thirty to 40 minutes later, the patients rode a stationary bicycle at a constant workload for 15 minutes while the heart rate, level of perceived exertion, and venous blood glucose levels were monitored.

RESULTS

Supplemental sucrose increased the mean plasma glucose level by more than 36 mg per deciliter (2.0 mmol per liter) and resulted in a marked improvement in exercise tolerance in all patients. The mean (\pm SE) heart rate dropped by a maximum of 34 ± 3 beats per minute ($P<0.001$), and the level of perceived exertion fell dramatically when the patients ingested glucose as compared with when they received the placebo.

CONCLUSIONS

This study suggests that the ingestion of sucrose before exercise can markedly improve exercise tolerance in patients with McArdle's disease. The treatment takes effect during the time when muscle injury commonly develops in these patients. In addition to increasing the patients' exercise capacity and sense of well-being, the treatment may protect against exercise-induced rhabdomyolysis.

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McARDLE'S DISEASE IS THE MOST common disorder of muscle carbohydrate metabolism, with an estimated prevalence of about 1 case in 100,000 people. It is an autosomal recessive error of metabolism caused by mutations in the gene that codes for myophosphorylase.¹ Typically, these mutations result in the translation of a nonfunctioning enzyme and completely block the breakdown of glycogen in muscle. Muscle glycogen is an important fuel that supports nearly all muscle energy metabolism early in exercise and during high-intensity work.² Correspondingly, patients with McArdle's disease have approximately half the normal maximal work capacity,³ and muscle cramps, muscle injury, and myoglobinuria induced by sudden, vigorous exercise frequently develop.^{4,5}

Because it specifically blocks muscle glycogenolysis, McArdle's disease is a naturally occurring model that has helped elucidate the role of muscle glycogen in many physiologic processes.^{3,6-12} Though more than 200 articles on McArdle's disease have been published in the past four decades, few have dealt with attempts at treatment, and none have documented clinically relevant improvement in exercise tolerance.

A characteristic of McArdle's disease is a spontaneous "second-wind" phenomenon, in which the very activity that initially causes severe fatigue becomes easily tolerated after it has been continued for about 10 minutes.¹¹⁻¹⁴ The second wind is associated with a large decrease in heart rate and the level of perceived exertion.¹¹⁻¹³ This decrease is attributable to a substantial increase in peak oxidative capacity. The improved oxidative capacity is due to the improved delivery of extramuscular energy, particularly glucose, to working muscles, which partially compensates for the impaired glycogen breakdown.¹⁴ It has been known for several decades that the intravenous infusion of glucose bypasses the metabolic block and can improve exercise capacity in patients with McArdle's disease.^{3,14-18} The effect on exercise tolerance of oral glucose, which patients themselves can administer before exercise, has not been investigated. The effects of intravenous and oral glucose are not necessarily similar, because the absorption of glucose and the neurohormonal responses to it depend on the route of administration.¹⁹

In this study we investigated whether patients with McArdle's disease who take sucrose orally before exercise can improve work performance in the early stages of exercise — before the second wind occurs — when patients are particularly prone to

muscle cramps and injury. Sucrose, a disaccharide, is the most prevalent dietary sugar and is rapidly split into fructose and glucose after ingestion. Glucose and fructose bypass the metabolic block in McArdle's disease and act as equal contributors to glycolysis. We studied 12 patients with McArdle's disease in a single-blind, randomized, placebo-controlled, crossover study. We tested exercise tolerance during aerobic exercise on a bicycle ergometer.

METHODS

SUBJECTS

We performed the study from April 1999 to February 2002 in 12 unrelated patients (7 men and 5 women) with McArdle's disease. Their average age was 37 years (range, 22 to 57). All the patients had a history of lifelong exercise intolerance and had had repeated episodes of cramps and myoglobinuria that were triggered by sudden vigorous exercise. Plasma lactate levels dropped slightly in response to forearm exercise. The diagnosis of McArdle's disease was confirmed in each case by a muscle biopsy that showed a lack of myophosphorylase on staining and no residual myophosphorylase activity in skeletal muscle on biochemical testing. One patient was taking glimepiride for type 2 diabetes mellitus, but otherwise, none of the patients were taking any medications.

The study was approved by the scientific ethics committee in Copenhagen, Denmark, and the institutional review board of the University of Texas Southwestern Medical Center and Presbyterian Hospital, Dallas, and all patients gave written informed consent.

EXPERIMENTAL PROTOCOL

All patients reported to the laboratory between 9 a.m. and 10 a.m. after fasting overnight. Each patient was studied on three separate days. The first day was used to define the work protocols for the study, including a constant workload for 15 minutes on a bicycle ergometer (MedGraphics CPE 2000) that elicited a near-maximal heart rate and level of perceived exertion before the second wind occurred. On the other two days, the patients received, in random order, a caffeine-free soft drink (660 ml) that either was artificially sweetened or contained 75 g of sucrose. The patients consumed their drinks 30 to 40 minutes before they began exercising and were unaware of the content. Interviews conducted after ingestion showed that the patients could not distinguish between the drinks. An antecubital venous

catheter was inserted in each patient, and blood was periodically obtained for the analysis of glucose, lactate, pyruvate, ammonia, free fatty acids, and insulin. The heart rate was monitored continuously with a three-lead electrocardiograph.

The primary efficacy end points for sucrose supplementation and its relation to exercise tolerance were the level of perceived exertion and the heart rate, which correlates closely with relative work and oxidative capacity.²⁰ The level of perceived exertion was scored every minute by each patient on a Borg scale,²¹ in which a rating of 6 represents the least effort, and 20 the most. To investigate a possible dose-response effect, the patient with the lowest body weight was studied for an additional day, during which she consumed a drink that contained 37.5 g of sucrose (half the normal amount) before exercise.

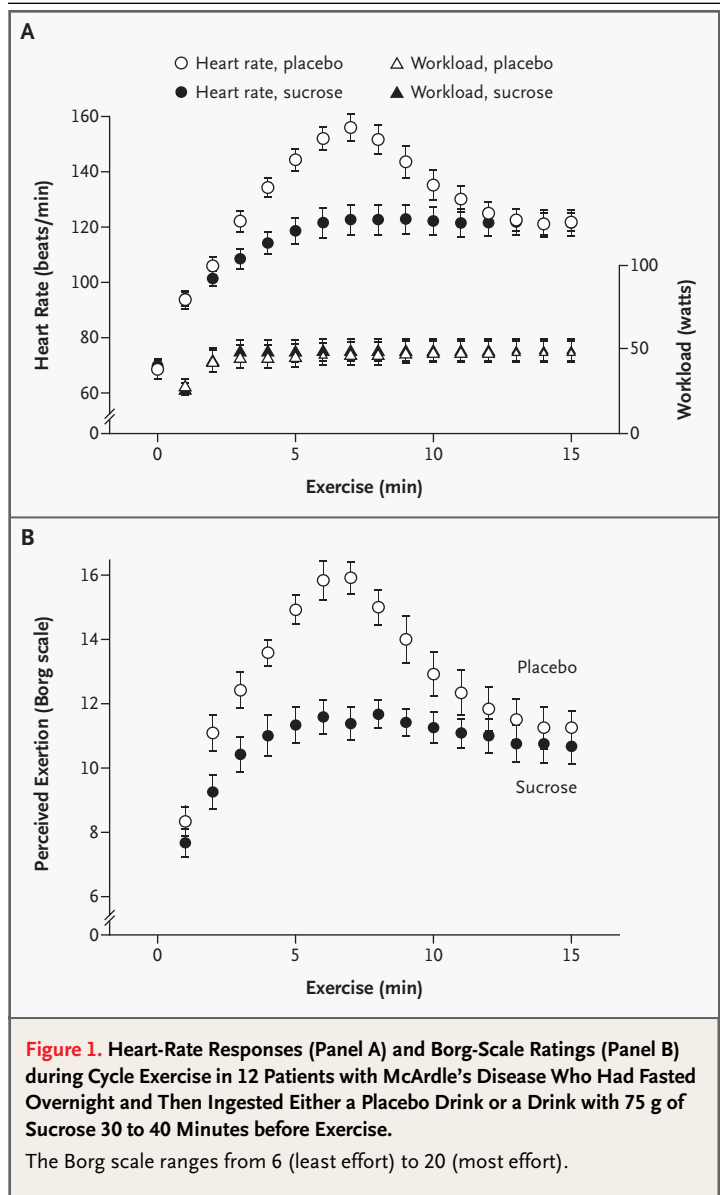
STATISTICAL ANALYSIS

Blood samples were spun in a refrigerated centrifuge and stored at -20°C until analysis. Plasma glucose, lactate, pyruvate, ammonia, and free fatty acids were measured with fluorometric assays, and insulin was measured with the use of radioimmunoassay.³ Values are reported as means ±SE. A P value of 0.05 or lower (by two-tailed testing) was considered to indicate statistical significance. Differences in the performance of the patients after ingesting sucrose and after ingesting placebo were assessed with the use of a paired Student's t-test and analysis of variance for repeated measures.

RESULTS

HEART RATE, LEVEL OF PERCEIVED EXERTION, AND WORKLOAD

After ingestion of the placebo drink, the mean peak heart rate (156±5 beats per minute) and level of perceived exertion (15.9±0.5) occurred in the seventh minute of exercise (Fig. 1) and were followed by a spontaneous second wind, with a drop in the heart rate of 35±3 beats per minute (P<0.001). After patients ingested sucrose, however, the heart rate in the seventh minute of exercise was 34±3 beats per minute lower than at the same time during exercise after ingestion of placebo (P<0.001) (Fig. 1), and the patients did not have a second wind. Accordingly, perceived exertion in the seventh minute of exercise was considerably lower after the ingestion of sucrose than after the ingestion of placebo (P<0.001). The patients were randomly assigned so that seven received sucrose first, and five received placebo first.



In four patients who received placebo supplementation and who had received sucrose in their first trial, the workload had to be decreased slightly for approximately five minutes before the second wind occurred (Fig. 1), because of the patients' near-exhaustion and the risk of muscle injury. This lower workload blunted the heart rate and level of perceived exertion and may therefore have led to an underestimation of the differences in responses to exercise between the two treatments.

In the one patient in whom half the normal dose of sucrose was tested, the peak heart rate in the seventh minute of exercise was 184 beats per minute after she ingested placebo, 142 after the ingestion

of 37.5 g of sucrose, and 116 after the ingestion of 75 g of sucrose. The second-wind phenomenon was obliterated by the high dose of sucrose but only blunted by the lower dose (Fig. 2), suggesting a dose–response relation between the heart rate during exercise and the dose of sucrose.

PLASMA LEVELS OF GLUCOSE, INSULIN, LACTATE, PYRUVATE, AMMONIA, AND FREE FATTY ACIDS

Sucrose ingestion resulted in marked hyperinsulinemia and an increase in the plasma glucose level that was more than 36 mg per deciliter (2.0 mmol per liter) greater than the level measured after patients ingested placebo (Fig. 3). Both increases were maintained throughout the exercise period ($P=0.005$). In line with the increased availability of glucose, plasma levels of lactate and pyruvate were elevated at rest after the ingestion of sucrose (Table 1). Plasma glucose, lactate, and insulin levels all fell during exercise under both conditions. The exercise-induced increase in plasma ammonia was attenuated, and the availability of free fatty acids, as inferred from the plasma levels of free fatty acids, decreased with sucrose.

DISCUSSION

Patients with McArdle's disease have an inability to break down muscle glycogen. Brief, vigorous exercise that is powered by anaerobic glycogenolysis often causes muscle pain and injury in these patients.

Glycogen is also critical for normal oxidative metabolism, and blocked glycogenolysis makes oxidative capacity depend on and fluctuate with the changing availability of bloodborne fuels. In patients with McArdle's disease, the oxidative limitation is most severe in the first seven to eight minutes of exercise, before bloodborne fuels, especially glucose and free fatty acids, become available and lead to an increase in muscle oxidative capacity and thus a second wind.⁴ During this period of profoundly limited oxidative metabolism, moderate exercise, such as brisk walking, may provoke muscle cramping and injury in these patients.

No treatment has yet been found that can alleviate symptoms, improve exercise tolerance, and provide protection against muscle injury during the early minutes of exercise in patients with McArdle's disease. Although treatment with a high-protein diet or creatine supplementation has been suggested, only minimal biochemical changes occur in the muscles with such therapy, and these effects have never been translated into clinically meaningful responses in patients with McArdle's disease.^{22–24} Attempts to boost energy metabolism within the muscles and thus exercise tolerance in such patients by treatment with D-ribose, pyridoxine, creatine, or branched-chain amino acids have also failed.^{25–28} Transfer of the intact myophosphorylase gene to myophosphorylase-deficient muscle, with the use of adenovirus as a vector, has been performed in vitro with some success,^{29,30} but this approach requires much more investigation before it can be considered for clinical use. Meanwhile, treatments need to be developed that can minimize the incidence of muscle injury and increase exercise tolerance in patients with McArdle's disease.

Our study provides evidence that sucrose ingestion before exercise markedly improves exercise tolerance in patients with McArdle's disease. The treatment is effective only during the time when patients are highly susceptible to muscle injury — that is, during the first minutes of exercise, when there is a low availability of bloodborne fuels plus an absence of glycogen-derived pyruvate, which together dramatically limit the capacity for oxidative phosphorylation.¹⁴ Treatment with sucrose virtually abolishes the spontaneous second-wind phenomenon, because the increased availability of glucose at the onset of exercise effectively induces a second wind from the start of exercise. The treatment seems to cause a markedly lower level of perceived exertion on the Borg scale and a dramatic lowering of the

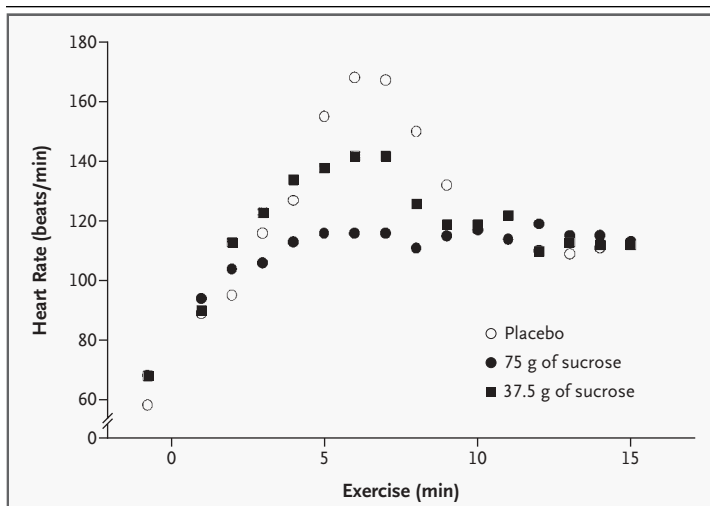


Figure 2. Heart-Rate Responses during Exercise in a 31-Year-Old Woman with McArdle's Disease Who Had Ingested a Placebo Drink, a Drink with 75 g of Sucrose, or a Drink with 37.5 g of Sucrose 30 to 40 Minutes before Exercise.

heart rate that is directly attributable to an increase in the oxidative capacity of the muscles.¹⁴

The clinical relevance of the treatment is emphasized by the fact that the participants have continued to use the treatment one to seven times a week, with consistent improvement in exercise tolerance. For ethical reasons, the patients were not encouraged to work hard enough to incur muscle damage. Nevertheless, the treatment with sucrose should help prevent muscle injury by augmenting the oxidative capacity of the muscles, thus increasing the threshold of exercise necessary to induce muscle injury.

Although the simple treatment we propose may be the single most effective treatment for patients with McArdle's disease, it has limitations. The treatment is not suited for situations that require unexpected vigorous exercise. Furthermore, the effect of the treatment is short-lived and therefore unlikely to affect endurance during long-term exercise. Repeated doses of oral glucose may lead to an intake of calories that exceeds expenditure and would inhibit lipolysis and thus the use of free fatty acids, which is probably an important fuel source during prolonged exercise in patients with McArdle's disease, as it is in healthy subjects. The treatment may increase exercise tolerance in all types of dynamic exercise, but it is unlikely to be helpful in static exercise, such as weight lifting, during which blood flow to working muscles is curtailed. Treatment with sucrose would usually be contraindicated in persons with diabetes mellitus, although we found it to be as effective in one patient with type 2 diabetes mellitus as it was in other patients. Our results with this patient, however, suggest that glucose uptake during exercise rests primarily on a contraction-induced glucose-uptake mechanism and not on insulin sensitivity.³¹

Considering the marked effect on exercise tolerance of the ingestion of sucrose before exercise begins, it is surprising that few patients have discovered this treatment on their own by trial and error. None of our patients had previously used oral sucrose loading. One patient who was not included in the study reported using oral sucrose loading and had developed a "soft-drink addiction" that had resulted in substantial weight gain. This anecdotal experience emphasizes the importance of informing patients with McArdle's disease that they should ingest sucrose only before engaging in exercise that is known from experience to elicit muscle symptoms.

We administered sucrose 30 to 40 minutes before exercise to ensure that sufficient amounts of glucose and fructose were absorbed from the intes-

tine. However, subsequent reports from our patients indicate that an interval of 15 minutes between consumption and exercise may suffice. Whether the amount of ingested sucrose should be adjusted to body weight is not clear. However, the attenuated effect of half a dose of sucrose on exercise tolerance in the patient with the lowest body weight suggests that this question warrants investigation. Nonetheless, the patients should determine the minimal dose of sucrose that will alleviate their symptoms early in exercise.

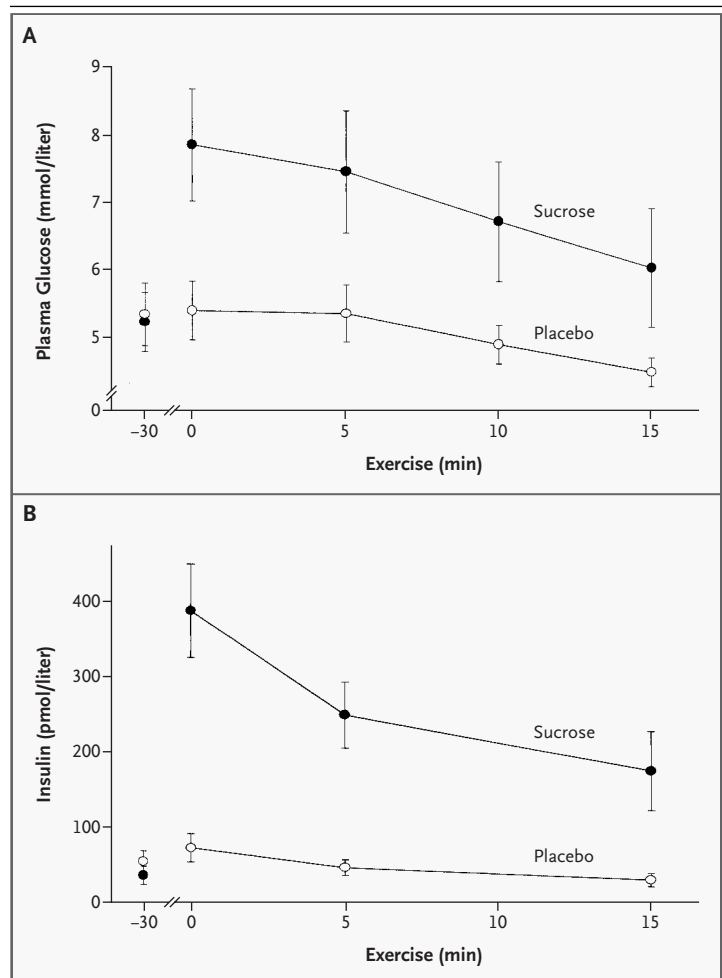


Figure 3. Mean (\pm SE) Plasma Levels of Glucose (Panel A) and Insulin (Panel B) during Cycle Exercise in Patients with McArdle's Disease Who Had Fasted Overnight and Then Ingested Either a Placebo Drink or a Drink with 75 g of Sucrose 30 to 40 Minutes before Exercise.

Glucose values represent the findings in 12 patients, and insulin values the findings in 9 patients. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for insulin to microunits per milliliter, divide by 7.175.

Table 1. Plasma Levels of Lactate, Pyruvate, Ammonia, and Free Fatty Acids Immediately before Exercise and in the 15th Minute of Cycling in Patients with McArdle's Disease.*

Variable	Lactate		Pyruvate		Ammonia		Free Fatty Acids	
	At Rest	After Exercise	At Rest	After Exercise	At Rest	After Exercise	At Rest	After Exercise
	<i>mmol/liter</i>		<i>μmol/liter</i>				<i>mmol/liter</i>	
Placebo	0.86±0.06	0.73±0.04†	64±7	64±8	99±34	231±24†	0.50±0.08	0.56±0.09
Oral sucrose	2.34±0.20‡	1.80±0.15†‡	136±22‡	128±21‡	112±28	147±22†‡	0.30±0.06‡	0.23±0.04‡

* Plus-minus values are means ±SE. All patients had fasted overnight and then ingested a drink with 75 g of sucrose or a placebo drink 30 to 40 minutes before exercise. Data on lactate and pyruvate were obtained for 12 patients, and data on ammonia and free fatty acids for 9 patients. To convert values for pyruvate to milligrams per deciliter, divide by 113.6; to convert values for ammonia to micrograms per deciliter, divide by 0.5872.

† P<0.05 for the difference from the value at rest.

‡ P<0.05 for the comparison with placebo.

It has been known for decades that intravenous glucose dramatically improves exercise tolerance in patients with McArdle's disease,^{3,14-17} so it may not seem surprising that glucose derived from ingested sucrose also has a beneficial clinical effect. However, the oral ingestion of sucrose and the intravenous administration of glucose induce different neurohormonal responses and levels of glucose availability.¹⁹ In a recent study of patients with impaired fatty-acid oxidation due to carnitine palmitoyltransferase II deficiency — a disease that, like McArdle's, can lead to exercise-induced myoglobinuria — an infusion of glucose improved exercise tolerance, whereas oral sucrose in the amount given in our study did not.¹⁹ The reason for this difference is that oral sucrose leads to lower glucose availability and more marked hyperinsulinemia than does intravenous glucose. Hyperinsulinemia inhibits muscle glycogenolysis, which is an important source of energy for patients with defects of fatty-acid oxidation.

In our study, patients with McArdle's disease had sucrose-induced hyperinsulinemia, but since muscle glycogenolysis is already blocked in this condition, the hyperinsulinemia had a negative effect only on the mobilization and utilization of fatty acids. Increased fatty-acid availability and oxidation have been postulated to have a role in the spontaneous second wind in McArdle's disease,¹¹ and free fatty acids are probably important energy sources during prolonged exercise in patients with McArdle's disease, just as they are in healthy subjects. However, our results indicate that the oxidative benefit of enhanced glucose availability mitigates any potential oxidative limitation attributable to falling fatty acid levels. This supports the view that the enhanced mobilization and utilization of glucose are critical for

the development of the spontaneous second wind in McArdle's disease.¹⁴

In muscle phosphofructokinase deficiency (Tarui's disease) — an inborn error of metabolism that is associated with a complete block in glycolysis — increased glucose availability results in an “out-of-wind” phenomenon, whereby patients have a decrease in their oxidative and exercise capacities.³² In contrast to patients with McArdle's disease or carnitine palmitoyltransferase II deficiency, patients with Tarui's disease rely almost exclusively on fatty-acid metabolism during exercise, and the out-of-wind phenomenon induced by glucose may be explained by an insulin-mediated suppression of lipolysis.^{32,33} In McArdle's disease, unlike conditions characterized by blocked muscle glycolysis or impaired fatty-acid oxidation, the beneficial effect of increased glucose availability that is induced by sucrose ingestion seems to override the detrimental effect of the ensuing hyperinsulinemia.

In McArdle's disease, blocked glycogenolysis in the muscles limits the availability of glycolytic metabolites, mainly pyruvate, that enter the tricarboxylic acid cycle oxidatively (pyruvate metabolized to acetyl coenzyme A) or expand the tricarboxylic-acid cycle (pyruvate metabolized to oxaloacetate). Limited oxidative metabolism in McArdle's disease may therefore be attributable not only to limited pyruvate oxidation itself but also to the impaired ability to augment fatty-acid oxidation when the tricarboxylic-acid cycle is not sparked by glycolytic metabolites. The sucrose-induced enhancement of exercise capacity that we observed may therefore be explained by anaplerosis of the tricarboxylic-acid cycle as well as by increased pyruvate oxidation from higher glycolytic flux under conditions of the improved avail-

ability of extramuscular glucose and fructose. Improved glycolytic flux was also evidenced by a sucrose-induced lowering of plasma ammonia levels, a direct marker of energy status during exercise in patients with McArdle's disease.³⁴

This study shows that, in patients with McArdle's disease, oral sucrose ingested before exercise alleviates the muscle symptoms and abolishes the second-wind phenomenon that occur during the early

stages of exercise, when patients are prone to muscle injury. When informing patients with McArdle's disease about such treatment, doctors should stress the importance of restricting its use to avoid unintentional weight gain.

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