

# Effect of Fuels on Exercise Capacity in Muscle Phosphoglycerate Mutase Deficiency

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**Background:** Muscle phosphoglycerate mutase deficiency (PGAMD) is a rare, recessively inherited metabolic myopathy that affects one of the last steps of glycolysis. Clinically, PGAMD resembles muscle phosphorylase deficiency (McArdle disease) and phosphofructokinase deficiency (PFKD). However, it is unknown whether PGAMD is associated with a second-wind phenomenon during exercise, as in McArdle disease, and whether patients with PGAMD, like patients with PFKD and McArdle disease, benefit from supplementation with fuels that bypass the metabolic block.

**Objective:** To investigate whether fuels that bypass the metabolic block can improve exercise capacity or whether exercise capacity improves during sustained exercise.

**Design:** Single-blind, placebo-controlled investigation of the effects of glucose, lactate, and intralipid on work capacity in patients with PGAMD.

**Setting:** National University Hospital, University of Copenhagen, and Neuromuscular Center, Institute for Exercise and Environmental Medicine.

**Patients:** Two unrelated men (21 and 26 years old) with PGAMD who since their teens had experienced muscle cramps, muscle pain, and episodes of myoglobinuria provoked by brief vigorous exercise, 4 patients with McArdle disease (mean  $\pm$  SD age, 32  $\pm$  5 years) with 0% residual phos-

phorylase activity in muscle, and 6 healthy, untrained male volunteers (mean  $\pm$  SD age, 23  $\pm$  1 years) were studied.

**Interventions:** Using constant and variable workload protocols on a cycle ergometer, it was investigated whether a spontaneous second wind occurs during exercise in patients with PGAMD, and using a constant workload protocol followed by an incremental load to exhaustion, it was tested whether infusion of lactate, glucose, or intralipid alters the exercise tolerance in PGAMD.

**Main Outcome Measures:** Whether a second wind occurs during exercise and whether fuels that bypass the metabolic block can improve exercise and oxidative capacity.

**Results:** In contrast to patients with McArdle disease, with whom they share many clinical features, in patients with PGAMD, cycle exercise and oxidative capacity are virtually normal, a second wind does not occur, and lipid and lactate supplements do not improve exercise capacity.

**Conclusion:** Although the clinical manifestations of PGAMD mimic McArdle disease with respect to the presence of exertional muscle cramps, rhabdomyolysis, and myoglobinuria, this study shows that cycle exercise responses are strikingly different.

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**M**USCLE PHOSPHOGLYCERATE mutase deficiency (PGAMD) is a rare, recessively inherited metabolic myopathy that affects one of the last steps of glycolysis.<sup>1</sup> The condition is associated with exercise-induced cramps and myoglobinuria, elicited by brief vigorous exercise.<sup>1-4</sup> The enzymatic defect in PGAMD is attributable to mutations in the M isoform of the *PGAM* gene. Residual PGAM activity in the muscles of patients (typically 2%-6%) is due to activity of the B-isoform.<sup>2,4</sup>

Clinically, PGAMD resembles muscle phosphorylase deficiency (McArdle dis-

ease) and phosphofructokinase deficiency (PFKD). Patients with McArdle disease and PFKD have complete enzymatic blocks; consequently, their exercise and oxidative capacity improves considerably when fuels that bypass the metabolic block are administered.<sup>5-7</sup> In PGAMD, it is unknown whether such fuels can improve exercise capacity or whether exercise capacity improves during sustained exercise, as is typical with the spontaneous second wind in patients with McArdle disease.<sup>8</sup> We investigated this in 2 patients with PGAMD and compared findings with those in healthy patients and patients with McArdle disease.

## METHODS

### PATIENTS

We studied 2 unrelated men (21 and 26 years old) with PGAMD who since their teens had experienced muscle cramps, muscle pain, and episodes of myoglobinuria provoked by brief vigorous exercise. Ischemic forearm exercise evoked blunted increases in venous plasma lactate levels and exaggerated increases in plasma ammonium levels. Both had tubular aggregates in muscle. The parents of one patient were first cousins. Both had a selective PGAM deficiency in muscle (approximately 3% of normal). Four patients with McArdle disease (mean  $\pm$  SD age, 32  $\pm$  5 years) with 0% residual phosphorylase activity in muscle and 6 healthy, untrained male volunteers (mean  $\pm$  SD age, 23  $\pm$  1 years) were also studied. In all of the patients, neurological examination results were normal.

### EXPERIMENTAL PROTOCOLS

#### Maximal Work Capacity

Peak oxygen uptake ( $\dot{V}O_2\text{max}$ ) and cardiac output ( $\dot{Q}$ ), assessed by the acetylene-rebreathing method, were determined as previously described.<sup>9</sup> Peak arteriovenous oxygen difference (a measure of the integrity of muscle oxidative phosphorylation) was determined as the quotient  $\dot{V}O_2/\dot{Q}$ .<sup>9</sup>

#### Second-Wind Protocol

The 2 patients with PGAMD and the 3 patients with McArdle disease were studied with an exercise protocol that we have used to delineate the second-wind phenomenon in McArdle disease.<sup>5</sup> In short, initial peak work and oxidative capacity was determined in the first 6 to 8 minutes of cycle exercise. The workload was then reduced for 5 to 10 minutes in the period when patients with McArdle disease develop a second wind and increased again to determine peak exercise capacity at 20 minutes of exercise. A bolus infusion of 100 mL of 50% glucose was administered to determine the presence of a glucose-induced second wind.<sup>5</sup> Exercise was stopped at 25 minutes.

### FUEL SUPPLEMENTATION

One patient with PGAMD was given an infusion of saline, lactate, intralipid, or glucose on separate days. The patient cycled at 65% of  $\dot{V}O_2\text{max}$  (100 W) for 20 minutes followed by incremental exercise to exhaustion. A group of 6 healthy age-matched men and 1 patient with McArdle disease performed the same exercise protocol during saline (healthy patients and patient with McArdle disease) or glucose (patient with McArdle disease) infusions. Infusions were blinded to the subjects and were started 2 minutes before exercise and primed by a bolus (glucose, 50 mL of a 10% solution; lactate, 50 mL of a 200mM solution; saline, 50 mL; and intralipid, 10 mL with heparin added to promote lipolysis). Constant-rate infusions, using the same solutions as the bolus, were 5 mL/min for glucose, lactate, and saline and 1 mL/min for intralipid.

### PHOSPHOROUS MAGNETIC RESONANCE SPECTROSCOPY OF MUSCLE

Phosphorous magnetic resonance spectroscopy (MRS) of the tibialis anterior muscle was performed in the patients with

Table. Exercise Findings in Studied Subjects\*

Variable	Patients With PGAMD (n = 2)	Patients With McArdle Disease (n = 4)	Healthy Subjects (n = 6)
Workload, W	165 $\pm$ 7	52 $\pm$ 10	244 $\pm$ 30
$\dot{V}O_2\text{max}$ , mL $\cdot$ min <sup>-1</sup> $\cdot$ kg <sup>-1</sup>	35 $\pm$ 2	14 $\pm$ 1	50 $\pm$ 4
$\dot{Q}/\dot{V}O_2$ , L/min	4.1 $\pm$ 0.1	11.7 $\pm$ 2.0	4.7 $\pm$ 0.6
A - $\dot{V}O_2$ , mL/dL†	15.4 $\pm$ 1.6	7.2 $\pm$ 1.1	16.7 $\pm$ 2.1
Heart rate, beats/min	171 $\pm$ 3	170 $\pm$ 13	194 $\pm$ 5
Plasma lactate, mg/dL	34.2 $\pm$ 1.8	6.3 $\pm$ 0.9	47.8 $\pm$ 8.1

Abbreviations: A -  $\dot{V}O_2$ , arteriovenous difference in oxygen; PGAMD, phosphoglycerate mutase deficiency;  $\dot{Q}/\dot{V}O_2$ , cardiac output as a function of  $\dot{V}O_2$ ;  $\dot{V}O_2\text{max}$ , peak oxygen uptake.

SI conversion factor: To convert plasma lactate to millimoles per liter, multiply by 0.111.

\*Values are given as mean  $\pm$  SD.

†Expressed as milliliters of oxygen per deciliters of blood.

PGAMD at rest and during exercise (intermittent static contractions at 1 Hz) at moderate (30% of maximal voluntary contraction) and high-intensity (45% of maximal voluntary contraction) exercise. Phosphorous MRS recordings were performed as previously described.<sup>10</sup>

## RESULTS

### MAXIMAL WORK CAPACITY

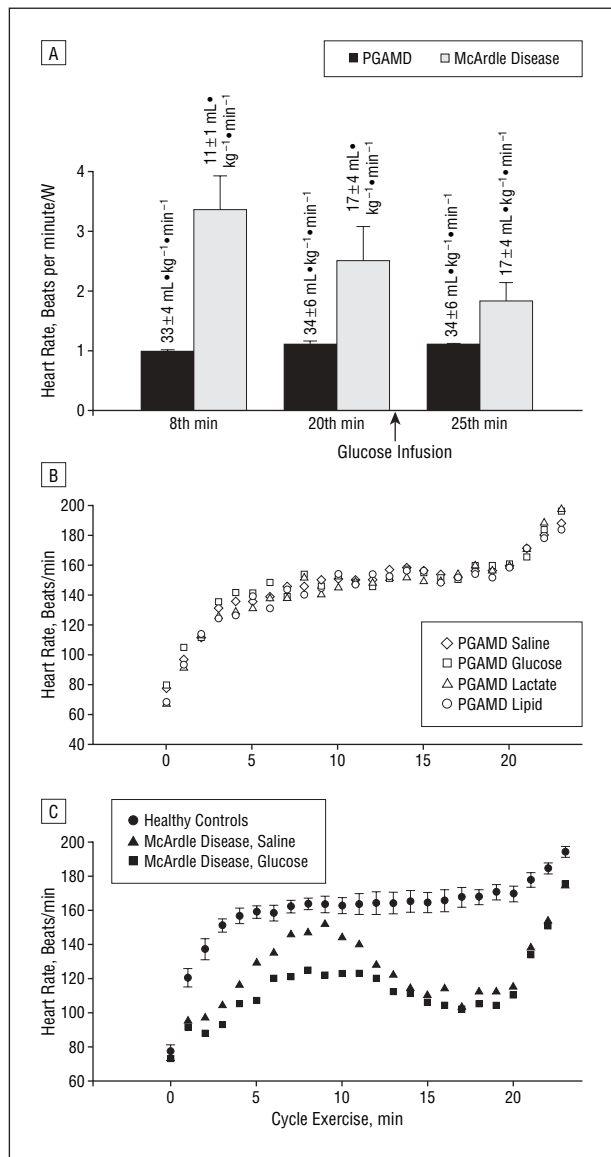
During maximal work, patients with PGAMD had a normal oxygen extraction capacity (peak arteriovenous difference in oxygen), a normal relationship between blood flow and  $\dot{V}O_2$  ( $\dot{Q}/\dot{V}O_2$ ), near-normal lactate levels, and a  $\dot{V}O_2\text{max}$  that was 70% of controls (ie, in the low normal range) (**Table**). In contrast, patients with McArdle disease had a  $\dot{V}O_2\text{max}$  that was one third of normal, impaired oxygen extraction capacity, a high  $\dot{Q}$  relative to  $\dot{V}O_2$ , and a decrease (mean  $\pm$  SD, 1.8  $\pm$  0.9 mg/dL [0.2  $\pm$  0.1 mmol/L]) in plasma lactate levels with exercise.

### SPONTANEOUS SECOND WIND

During the variable workload protocol, peak exercise capacity did not change in patients with PGAMD as it did in patients with McArdle disease, thus demonstrating absence of a spontaneous or glucose-induced second wind in PGAMD (**Figure 1A**). Similarly, during saline infusions, the heart rate was stable during constant workload exercise in patients with PGAMD and healthy subjects, in contrast to the characteristic decrease in heart rate with a spontaneous second wind observed in patients with McArdle disease (**Figure 1B and C**).

### FUEL SUPPLEMENTATION

Lactate, glucose, and intralipid infusions more than doubled plasma levels of these substrates in the patients with PGAMD but did not affect exercise capacity based on  $\dot{V}O_2\text{max}$  and heart rate responses (**Figure 1B**). In contrast, a glucose infusion induced a new second wind during both the vari-

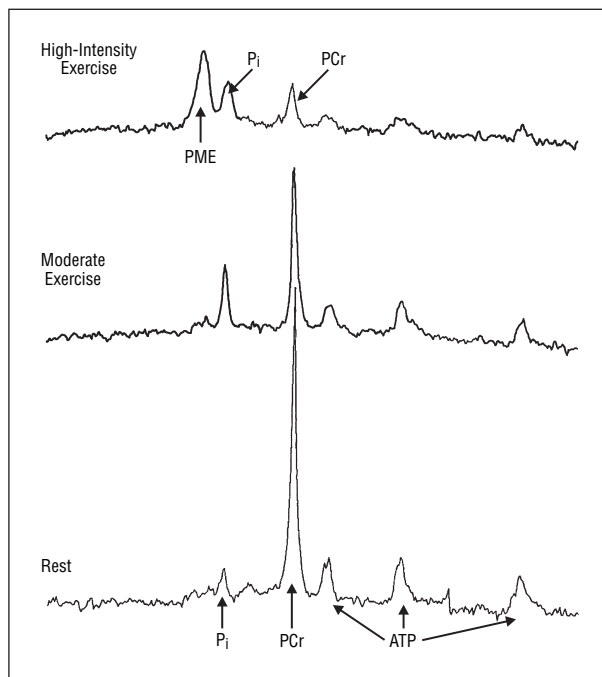


**Figure 1.** A, Heart rate as a function of workload (beats per minute per watt) in 2 patients with phosphoglycerate mutase deficiency (PGAMD) and 3 patients with McArdle disease during peak exercise in the 8th, 20th, and 25th minute of cycle exercise. Patients received a glucose infusion from the 20th minute of exercise. Numbers over the bars indicate oxygen uptake. B, Heart responses during 20 minutes of constant work at approximately 65% of peak oxygen uptake ( $\dot{V}O_{2max}$ ) followed by an incremental workload to exhaustion in a patient with PGAMD during intravenous infusions with saline, lactate, glucose, and lipids. C, Heart responses during 20 minutes of constant work at approximately 65% of  $\dot{V}O_{2max}$  followed by an incremental workload to exhaustion in a patient with McArdle disease during saline and glucose infusions and in 6 age-matched, healthy subjects during saline infusion. Error bars indicate standard deviation.

able (Figure 1A) and constant (Figure 1C) workload protocols in patients with McArdle disease. Plasma lactate levels at the end of the saline infusion protocol were similar in the patients with PGAMD (58.56 mg/dL [6.5 mmol/L]) and the 6 healthy subjects (mean  $\pm$  SD, 60.36  $\pm$  6.31 mg/dL [6.7  $\pm$  0.7 mmol/L]).

### PHOSPHOROUS MRS OF MUSCLE

Phosphorous MRS findings in the 2 patients with PGAMD were normal at rest and were similar during



**Figure 2.** Phosphorous magnetic resonance spectroscopy of the tibialis anterior muscle in one of the patients with phosphoglycerate mutase deficiency at rest, during moderate exercise, and during high-intensity exercise. PCr indicates phosphocreatine;  $P_i$ , inorganic phosphate; PME, phosphomonoester; and ATP, adenosine triphosphate.

exercise, as illustrated in 1 patient (Figure 2). A large peak at 10.7 ppm appeared during high-intensity exercise, reflecting monophosphorylated carbohydrate intermediates (phosphomonoesters [PMEs]). The PME peak did not develop during moderate work but developed during 5½ minutes of exercise to exhaustion at the high work intensity so that the PME concentration reached 18 mmol/L. At exhaustion, the inorganic phosphate peak had increased from 1.5 to 12 mmol/L, the phosphocreatine peak had decreased from 22 to 4.5 mmol/L, and the adenosine triphosphate peak had decreased from 7.5 to 3 mmol/L. As estimated from the chemical shift of inorganic phosphate, the pH dropped from 7.05 at rest to 6.5 at exhaustion. The adenosine triphosphate and pH values did not change in the muscle during moderate work.

### COMMENT

Although the clinical manifestations of PGAMD mimic McArdle disease with respect to the presence of exertional muscle cramps, rhabdomyolysis, and myoglobinuria, this study shows that cycle exercise responses are strikingly different. The principal findings are that (1) patients with PGAMD have near-normal maximal oxidative capacity; (2) they produce almost normal amounts of lactate during dynamic and static intermittent exercise; (3) they do not experience a second wind during exercise, either spontaneously or induced by fuels that bypass the metabolic block; (4) glucose infusion does not impair exercise capacity as it does in patients with PFKD; and (5) PMEs accumulate in muscle exclusively during high-intensity exercise.

The relatively preserved capacity for dynamic exercise in patients with PGAMD undoubtedly relates to the residual enzyme activity that provides sufficient glycolytic flux to meet muscle oxidative requirements at near-maximal work intensities. Accordingly, patients with PGAMD had normal increases in plasma lactate levels and normal phosphorous MRS-assessed acidification of muscle during maximal exercise. Normal lactate responses to maximal cycle exercise and a near-normal work capacity have previously been reported in 1 patient with PGAMD.<sup>3</sup> Normal glycolytic flux during submaximal exercise was further evidenced by the absence of PMEs in muscle during moderate exercise intensity, as assessed by phosphorous MRS.

The glycolytic flux necessary to provide sufficient pyruvate to meet oxidative requirements of working muscle is modest compared with that required for sustaining peak rates of adenosine triphosphate production during maximal exercise.<sup>5</sup> The complete enzymatic blocks present in patients with McArdle disease and PFKD significantly limit peak rates of muscle oxidative phosphorylation. Consequently, muscle oxidative capacity in these conditions depends on the availability of bloodborne fuels that can bypass the metabolic blocks. Therefore, patients with McArdle disease and PFKD experience variations in exercise capacity according to the availability of these fuels,<sup>5,6</sup> epitomized by the second-wind phenomenon in McArdle disease<sup>8</sup> and the out-of-wind phenomenon in PFKD.<sup>7</sup> Our results indicate that the residual PGAM activity in PGAMD is sufficient to maintain a glycolysis that meets oxidative requirements and thus eliminates spontaneous fluctuations in exercise capacity (no spontaneous second wind) and fluctuations in exercise capacity induced by supplementation with free fatty acids, lactate, and glucose (no substrate-induced second wind or out of wind). The fact that symptoms of muscle contracture and rhabdomyolysis occur in patients with PGAMD only with intense exercise implicates the metabolic consequences of limited substrate-level phosphorylation during anaerobic glycolysis in the genesis of these symptoms.

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