

A Nonischemic Forearm Exercise Test for McArdle Disease

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Ischemic forearm exercise invariably causes muscle cramps and pain in patients with glycolytic defects. We investigated an alternative diagnostic exercise test that may be better tolerated. Nine patients with McArdle disease, one with the partial glycolytic defect phosphoglycerate mutase deficiency, and nine matched, healthy subjects performed the classic ischemic forearm protocol and an identical protocol without ischemia. Blood was sampled in the median cubital vein of the exercised arm. Plasma lactate level increased similarly in healthy subjects during ischemic ($\Delta 5.1 \pm 0.7 \text{ mmol L}^{-1}$) and non-ischemic ($\Delta 4.4 \pm 0.3$) tests and decreased similarly in McArdle patients ($\Delta -0.10 \pm 0.02$ vs $\Delta -0.40 \pm 0.10 \text{ mmol L}^{-1}$). Postexercise peak lactate to ammonia ratios clearly separated patients and healthy controls in ischemic (McArdle, 4 ± 2 [range, 1–12]; partial glycolytic defect phosphoglycerate mutase deficiency, 6; healthy, 33 ± 4 [range, 17–56]) and non-ischemic (McArdle, 5 ± 1 [range, 1–10]; partial glycolytic defect phosphoglycerate mutase deficiency, 5; healthy, 42 ± 3 [range, 35–56]) protocols. Similar differences in lactate to ammonia ratio between patients and healthy subjects were observed in two other work protocols using intermittent handgrip contraction at 50% and static handgrip exercise at 30% of maximal voluntary contraction force. All patients developed pain and cramps during the ischemic test, and four had to abort the test prematurely. No patient experienced cramps in the non-ischemic test, and all completed the test. The findings indicate that the diagnostic ischemic forearm test for glycolytic disorders should be replaced by an aerobic forearm test.

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Myophosphorylase deficiency (McArdle disease) was the first metabolic myopathy to be recognized, when Dr Brian McArdle described the first case in a 30-year-old man with lifelong exercise intolerance and exercise-induced muscle stiffness.¹ In a clever experiment, he showed that the concentration of plasma lactate decreased in venous effluent blood from a forearm that had exercised with blocked circulation. He noticed that the metabolic changes and the muscle contractures that this ischemic exercise evoked in the patient were similar to that found by Henriques and Lundgaard² who studied frog muscle poisoned with sodium iodoacetate, a drug that blocks glycolysis. He quite accurately concluded that the patient had a disorder of glycogen breakdown that specifically affected skeletal muscle.

McArdle disease is the most common of the glycolytic muscle disorders with an estimated prevalence of approximately 1 per 100,000. Because muscle glycogen is a crucial fuel early in exercise and during high work intensities,³ the patients have a low maximal work capacity of approximately half normal⁴ and develop mus-

cle cramps, particularly early in vigorous exercise.^{5,6} These cramps can be severe and result in muscle injury, as reflected in a constantly elevated creatine kinase level and occasionally severe rhabdomyolysis that can lead to renal failure.^{5,6}

The ischemic forearm exercise test is a simple, very sensitive, and specific test for disorders of muscle glycolysis, when plasma ammonia and lactate levels are measured.^{7–9} Ammonia production is enhanced in glycolytic disorders and blunted in healthy subjects whose exercise effort is poor.^{6,8,10} The ischemic forearm exercise test is useful to screen patients before more invasive or expensive investigations (ie, muscle histology, genetic and biochemical analyses) are made. The test has been described extensively in neuromuscular and pediatric textbooks.^{6,8,11,12} It is well known, however, that the test invariably causes muscle cramps and pain in the exercised arm of patients with disorders of muscle carbohydrate metabolism, symptoms that may progress to rhabdomyolysis of the exercised arm.^{13,14} Even for healthy subjects, the test may be unpleasant.

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In this study, we investigated whether the ischemic forearm exercise test can be replaced by a safer aerobic exercise test, without losing diagnostic power. We tested this by performing the classic ischemic test and three other aerobic or semiaerobic forearm exercise tests in nine patients with McArdle disease, one patient with the partial glycolytic disorder muscle phosphoglycerate mutase deficiency (PGAMD), and nine healthy, sedentary subjects.

Subjects and Methods

Subjects

Nine patients with McArdle disease, one patient with muscle PGAMD, and nine healthy, sedentary volunteers participated. Healthy subjects and McArdle patients were matched for age, weight, and height (Table 1).

All McArdle patients had lifelong exercise intolerance and exercise-induced cramps. All patients had experienced repeated episodes of rhabdomyolysis with myoglobinuria induced by short-duration, high-intensity exercise. The PGAMD patient had an almost normal exercise tolerance, but muscle cramps were induced by sudden vigorous exercise. Diagnosis in all patients was confirmed by biochemical analyses of muscle showing absent myophosphorylase activity in eight McArdle patients, a residual phosphoglycerate mutase activity of 2.4% of normal in the PGAMD patient,¹⁵ and a residual myophosphorylase activity of 2% in a McArdle patient. Enzymatic activities of all other glycolytic enzymes were normal in the patients. One McArdle patient also had myoadenylate deaminase deficiency (MADD) as evidenced by histochemical staining and genetic analysis demonstrating the common homozygous C→T point mutation at nucleotide 34 in the second exon of the *MAD* gene. None of the subjects took any medication.

The protocol was approved by the Scientific-Ethical Committee for Copenhagen (approval no. KF-02-101/97). Informed consent was obtained from each subject.

Experimental Protocol

PREEXPERIMENTAL MEASUREMENTS. The maximal voluntary contraction (MVC) force during handgrip was determined three times. All subjects had venous catheters inserted bilaterally in the median cubital vein. The largest circumfer-

ence of the forearm and the skin fold thickness in the same place were measured to get an estimate of forearm muscle volume. The skin fold was measured on the flexor and extensor side with a caliper (John Bull, UK). An estimate of the skinless forearm cross-section area was calculated by subtracting the calculated skin area from the total cross-section area of the forearm.

EXERCISE PROTOCOLS. The subjects performed the following exercise protocols in randomized order. (1) Protocol 1: the "classic" ischemic forearm exercise test, in which the subject squeezes the handgrip dynamometer at intended maximal MVC during each contraction (contraction, 1 second; rest, 1 second). The exercise lasts 1 minute and is performed during blocked blood circulation by inflating a blood pressure cuff on the upper arm to 250mm Hg. Immediately after exercise, the cuff is released. (2) Protocol 2: identical to protocol 1, except that a cuff did not block blood circulation. (3) Protocol 3: rhythmic (0.5Hz) handgrip exercise at 50% of MVC for 2 minutes without blocked blood circulation. (4) Protocol 4: static handgrip at 30% of MVC for 2 minutes with no cuff.

After each exercise session, the subjects rested for 45 minutes before the next protocol was performed in the contralateral arm. The experimental design made it necessary to exercise the same arm twice. Tests were always alternated between arms, so that an interval of at least 1.5 hours elapsed before the same arm was retested. During 30% MVC static exercise, blood flow to the working muscle is partially blocked by the tension development in the contracting muscle¹⁶ and therefore this test is semiischemic.

Muscle discomfort during the tests was monitored by assessment of muscle cramps/stiffness and the need to abort the test because of painful cramps.

HANDGRIP SETUP. In each exercise protocol, subjects were seated, with the arm being studied supported by a wedge-shaped pillow on an adjustable table. The handle of the handgrip dynamometer (19117 Smedley Hand Dynamometer; modified by Stoelting, Wood Dale, Illinois) was placed in a vertical position so that the forearm was in a midposition between pronation and supination and the elbow in a flexion angle of 110 to 120 degrees. The handgrip was fixed securely to the table to avoid movement during exercise. The

Table 1. Characteristics of Study Subjects

Subject Type	Gender (F/M)	Age (yr)	Weight (kg)	Height (cm)	MVC (right arm/left arm), kg	Lean Forearm Cross Section Area (right arm/left arm), cm ²
McArdle (n = 7)	4/3	36 ± 4	80 ± 7	171 ± 3	34 ± 6/32 ± 6	28 ± 4/24 ± 4
Partial McArdle (n = 1)	0/1	41	98	183	57/ND	ND
McArdle + MADD (n = 1)	0/1	31	105	188	22/19	27/19
PGAMD (n = 1)	0/1	28	74	168	39/35	26/23
Healthy (n = 9)	4/5	34 ± 3	77 ± 5	175 ± 3	45 ± 4/40 ± 4	28 ± 3/27 ± 3

Values are mean ± SE. There were no significant differences between McArdle patients and healthy subjects.

MVC = maximal voluntary handgrip; MADD = myoadenylate deaminase deficiency; PGAMD = phosphoglycerate mutase deficiency; ND = not determined.

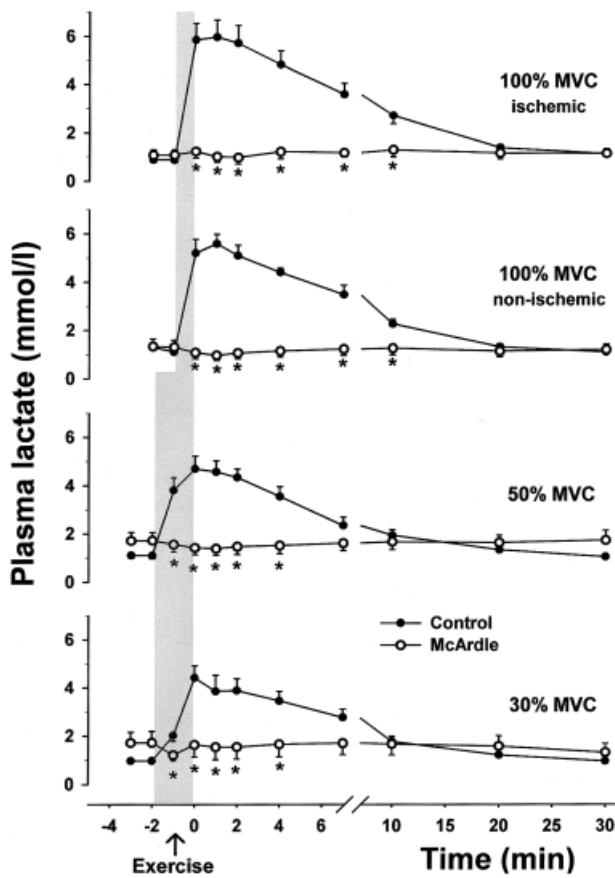


Fig 1. Plasma lactate levels before, during, and after handgrip exercise in seven patients with McArdle disease and nine healthy subjects (Control). Handgrip every other second was performed for 1 minute at 100% of intended maximal voluntary contraction (MVC) force with and without ischemia or for 2 minutes at 50% MVC without ischemia. In a fourth protocol, static handgrip at 30% of MVC was performed for 2 minutes. Values are means \pm SE. Where not shown, SEs are within symbol size. (asterisks) Difference ($p < 0.05$) between McArdle and healthy subjects.

handgrip dynamometer with transducer was connected to a voltmeter to provide visual feedback to the exercising subject. A PowerLab recording unit (ADInstruments Pty, Castle Hill, Australia) digitalized the voltmeter signal. Handgrip force was calculated as the integral of the force-time product ($\text{kg} \times \text{sec}$) for each contraction by a CHART software system (ADInstruments Pty, Castle Hill, Australia).

BLOOD FLOW. Arterial blood flow was measured after each blood sample by pulsed duplex ultrasound technique in the brachial artery 10cm proximal to the elbow joint. Because of movement artifacts, flow could not be measured during exercise. The blood flow was measured immediately after exercise in all subjects. A Hewlett-Packard (Corvallis, OR) computer sonography system (M2410B) equipped with a linear array 5 to 7MHz transducer with 5MHz pulsed Doppler was used. Blood flow was calculated from the measured time-averaged mean velocity of blood and the cross-section area of the vessel lumen.

BLOOD SAMPLING AND ANALYSIS. At rest, and during exercise and recovery, effluent cubital venous blood from the exercised arm was sampled for determination of lactate, ammonia, pH, and $p\text{CO}_2$ at the times depicted in Figures 1 and 2. Two blood samples were obtained at each time point, one for blood gas analyses (1ml) and one for analyses of lactate and ammonia (2ml). Syringes for blood gas analyses were pretreated with dry lithium heparin, and the other syringe was pretreated with EDTA. Blood gases were determined on an ABL blood gas analyzer 650 (Radiometer, Rodovre, Denmark) during the experiment. The other blood sample was spun at 4°C . Plasma was transferred to tubes on dry ice before storage at -80°C until analysis. Lactate and ammonia were analyzed by fluorometric methods on a Cobas AS Fara II (Roche, Basel, Switzerland).

STATISTICAL ANALYSES. Differences between McArdle patients and healthy subjects and differences with time were evaluated with a Student's t test and a two-way analysis of variance test, respectively. p value less than 0.05 was considered significant. All values are expressed as means \pm standard error.

Fig 2. Plasma ammonia before, during, and after handgrip exercise in seven patients with McArdle disease and nine healthy subjects (Control). For further explanations, please see the legend to Figure 1. MVC = maximal voluntary contraction.

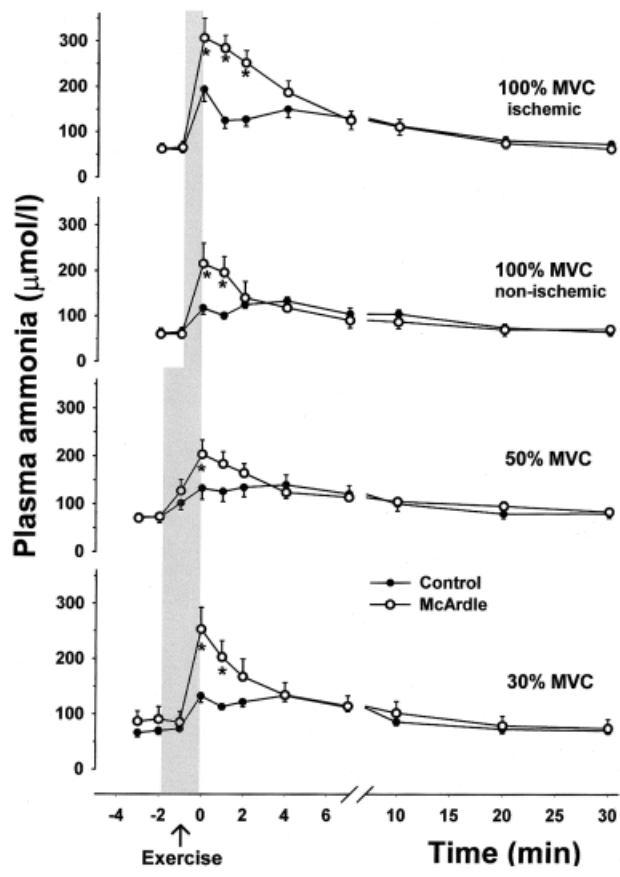


Table 2. Lactate to Ammonia Ratio in Venous Effluent Plasma Immediately at the End of Handgrip Exercise in Study Subjects

Subject Type	100% MVC Non Ischemic	100% MVC Ischemic	50% MVC	30% MVC
McArdle (n = 7)	5 ± 1 ^a (1–10)	4 ± 2 ^a (1–12)	7 ± 2 ^a (3–14)	8 ± 2 ^a (2–16)
Partial McArdle (n = 1)	3	5	ND	ND
McArdle + MADD (n = 1)	19	20	20	22
PGAMD (n = 1)	5	6	13	4
Healthy (n = 9)	42 ± 3 (35–56)	33 ± 4 (17–56)	34 ± 4 (21–54)	34 ± 3 (17–45)

Values are mean ± SE.

^aSignificant difference between McArdle patients and healthy subjects ($p < 0.05$).

MVC = maximal voluntary handgrip; MADD = myoadenylate deaminase deficiency; PGAMD = phosphoglycerate mutase deficiency; ND = not determined.

Results

All data from the PGAMD patient, the McArdle patient with combined MADD, and the McArdle patient with a residual activity of myophosphorylase are provided exclusively in Tables 1 to 3. Grouped data from the remaining seven McArdle patients and the nine healthy subjects are provided in Figures 1 to 3 and Tables 1 to 3.

Plasma Lactate and Ammonia

Resting plasma lactate and ammonia concentrations did not differ among groups. Plasma lactate level always decreased during exercise in McArdle patients with complete deficiency of myophosphorylase, whereas plasma lactate level consistently increased in other subjects. In healthy subjects, increases in lactate were similar (five to sixfold over basal) in ischemic and non-ischemic protocols at 100% MVC. At the lower exercise intensities in healthy subjects, plasma lactate level increased 4.5-fold over basal. Exercise-induced in-

creases in plasma lactate level were blunted in the PGAMD patient and the McArdle patient with 2% residual myophosphorylase activity (see Figs 1 and 2; Tables 2 and 3).

Except for the McArdle patient with MADD, in whom plasma ammonia did not change with exercise, exercise-induced increases in plasma ammonia were consistently higher in all patients with glycolytic disorders compared with healthy subjects. Using the peak lactate to ammonia ratio as the diagnostic parameter for all patients studied with isolated glycolytic disorders, we found that the specificity and sensitivity of all tests were 100%. The lactate to ammonia ratio in the McArdle + MADD patient overlapped slightly with healthy subjects in the ischemic 100% MVC and 30% MVC protocols. As shown in Table 2, the clearest separation in lactate to ammonia ratio between patients and healthy subjects was obtained with the non-ischemic protocol at 100% MVC.

Table 3. Resting Values and Peak Changes (Δ) from Rest to Immediately after Handgrip Exercise in Cubital Venous Plasma Lactate, Ammonia, pH, and pCO₂, in Brachial Artery Blood Flow and Average Force Output during the Whole Exercise Period

100% of MVC	Lactate (mmol/L) Rest (Δ)	Ammonia (μ mol/L) Rest (Δ)	pH Rest (Δ)	pCO ₂ (kPal) Rest (Δ)	Flow (ml/min) Rest (Δ)	Force (kg × sec)
Nonischemic						
McArdle (n = 7)	1.3 ± 0.3 (−0.4 ± 0.1) ^{a,b}	59 ± 9 (157 ± 39) ^{a,b}	7.37 ± 0.01 ^b (0.03 ± 0.02)	6.2 ± 0.2 (−0.7 ± 0.1) ^b	145 ± 24 (553 ± 65) ^{a,b}	508 ± 78 ^b
Partial McArdle (n = 1)	0.9 (0.8)	13 (375)	ND (ND)	ND (ND)	ND (ND)	707
McArdle + MADD (n = 1)	1.4 (−0.3)	54 (−11)	7.36 (0)	5.8 (−1)	188 (561)	355
PGAMD (n = 1)	0.74 (2.2)	27 (557)	7.35 (−0.11)	6.4 (2.8)	117 (317)	663
Healthy (n = 9)	1.1 ± 0.1 (4.4 ± 0.3) ^a	64 ± 10 (69 ± 10) ^a	7.36 ± 1.01 (−0.16 ± 0.0) ^a	6.6 ± 0.2 (3.7 ± 0.4) ^a	125 ± 22 (344 ± 55) ^a	820 ± 60
Ischemic						
McArdle (n = 7)	1.1 ± 0.2 (−0.1 ± 0.1) ^b	64 ± 13 (243 ± 4) ^{a,b}	7.38 ± 0.01 ^b (0.02 ± 0.02)	5.8 ± 0.2 (0.3 ± 0.2) ^b	139 ± 17 (606 ± 73) ^a	451 ± 78 ^b
Partial McArdle (n = 1)	1.3 (0.6)	80 (295)	ND (ND)	ND (ND)	ND (ND)	589
McArdle + MADD (n = 1)	1.6 (−0.5)	65 (5)	7.39 (0)	5.2 (−0.1)	174 (672)	446
PGAMD (n = 1)	0.8 (2.2)	46 (439)	7.34 (−0.11)	6.7 (3)	108 (518)	547
Healthy (n = 9)	0.9 ± 0.1 (5.1 ± 0.7) ^a	61 ± 5 (132 ± 27) ^a	7.36 ± 0.01 (−0.19 ± 0.02)	6.1 ± 0.5 (5 ± 0.7) ^a	124 ± 12 (563 ± 52) ^a	746 ± 57

Values are mean ± SE.

^aSignificant difference between rest and peak value ($p < 0.05$).

^bSignificant difference between McArdle patients and healthy subjects ($p < 0.05$).

MVC = maximal voluntary handgrip; MADD = myoadenylate deaminase deficiency; PGAMD = phosphoglycerate mutase deficiency; ND = not determined.

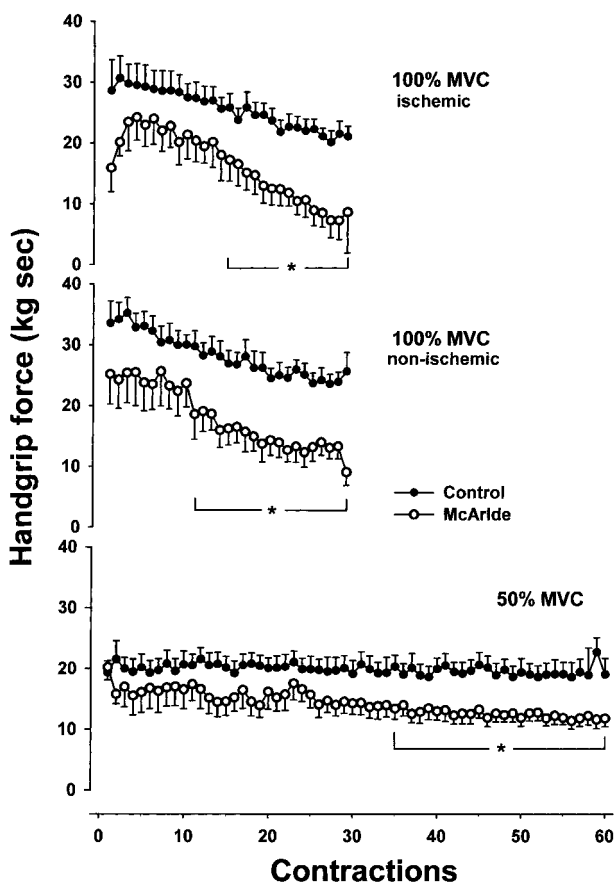


Fig 3. Force of handgrip contractions in seven patients with McArdle disease and nine healthy subjects (Control). Handgrip every other second was performed for 1 minute at 100% of intended maximal voluntary contraction (MVC) force with and without ischemia or for 2 minutes at 50% MVC without ischemia. Values are means \pm SE. (asterisk) Difference ($p < 0.05$) between McArdle and healthy subjects.

Handgrip Force, Lean Forearm Cross-section Area, Arterial Blood Flow, and Muscle Symptoms

MVC tended ($p = 0.09$) to be lower in McArdle patients compared with healthy subjects, but lean forearm cross-section area did not differ among groups (see Table 1). In dynamic exercise protocols, all patients fatigued more than healthy subjects, and as a result overall work performance was significantly lower in McArdle patients (see Fig 3; Table 3).

Resting arm blood flow was similar in all subjects. In the non-ischemic 100% MVC handgrip protocol, flow immediately after exercise was significantly higher in McArdle versus healthy subjects (Table 3), and similar findings were observed in the non-ischemic protocol at 50% MVC (data not shown). In ischemic and semi-ischemic protocols, flow rates increased to the same extent in all groups. The PGAMD patient had an exercise-induced flow response that was similar to healthy controls.

In all patients, the ischemic test was associated with cramps or 5 to 30 minutes of stiffness or pain in muscles of the exercised hand and forearm. Four McArdle patients aborted the test after 21 to 25 contractions because of painful cramps. In the non-ischemic 100% MVC test, all subjects completed the test, no one experienced cramps, and only one McArdle patient and the PGAMD patient experienced slight temporary discomfort in the exercised hand. During the 30% MVC protocol, one McArdle patient experienced cramps in the forearm, and the PGAMD patient experienced slight stiffness of the exercised hand. The 50% MVC protocol elicited discomfort in the exercised hand during the second exercise minute in three McArdle patients, and cramps and premature stop of the test in one McArdle patient.

Blood $p\text{CO}_2$ and $p\text{H}$

In 100% MVC protocols, venous effluent blood pH increased or remained unchanged, and venous $p\text{CO}_2$ did not change significantly with exercise in McArdle patients. In contrast, venous pH decreased and $p\text{CO}_2$ increased markedly after exercise in healthy subjects and the PGAMD patient. Similar intergroup differences were observed in the 50 and 30% MVC protocols (data not shown) (see Table 3).

Discussion

The ischemic forearm exercise test, originally developed by Dr McArdle in 1951, is a simple, sensitive diagnostic screening test for muscle glycolytic disorders. Patients with muscle glycolytic disorders, however, invariably experience muscle cramps and pain when examined with the test, symptoms that may result in overt rhabdomyolysis.^{13,14} The objective of this study was to investigate alternative diagnostic forearm exercise protocols that may be better tolerated than the ischemic test. The principal new finding of the study is that aerobic forearm exercise tests have the same diagnostic power as the classic ischemic test for muscle glycolytic disorders and that muscle cramps, pain, and potential muscle injury are virtually eliminated by the aerobic tests. The results suggest that use of the ischemic exercise test to evaluate muscle glycolytic disorders should be replaced with an aerobic exercise test. Furthermore, this study suggests that an aerobic forearm exercise test may also be a useful and safe diagnostic test for patients with partial defects of muscle glycolysis and provides the first direct evidence of enhanced exercise-induced limb blood flow in McArdle disease.

A diagnostic aerobic forearm exercise test for muscle glycolytic disorders has not been evaluated before. Hogrel and colleagues have reported results for a forearm test, which they have termed "non-ischemic."¹⁷ In that test, patients performed isometric handgrip exer-

cise at 70% MVC. Such exercise is, in fact, ischemic because at this level of static exercise, muscle blood flow is blocked completely by the tension developed in the contracting muscle.¹⁶ Thus, the major difference between the study of Hogrel and colleagues and the original ischemic test was that their patients exercised for only 30 seconds. Furthermore, their findings were not compared with the original ischemic test, and muscle symptoms evoked by the ischemic test at 70% MVC were not assessed systematically.¹⁷

Although our data suggest that all three alternative protocols presented in this study are diagnostic for glycolytic disorders, we recommend that the aerobic forearm test at 100% MVC should be used as the routine diagnostic test for patients with suspected disorders of muscle carbohydrate metabolism. The reasons are that (1) the test is identical to the one investigators are familiar with, except that cuff inflation is not used; (2) the intended maximal handgrip exercise means that work intensity does not necessarily have to be monitored as in the work protocols based on a percentage of MVC; and (3) it appears that the aerobic 100% MVC test provides the highest sensitivity and specificity for glycolytic disorders of muscle metabolism and is best tolerated.

Our findings also suggest that an aerobic forearm exercise test is warranted in patients with partial defects of muscle glycolysis, who typically have a higher work capacity, but suffer the same exercise-induced cramps and potential muscle injury as the McArdle patients with absent myophosphorylase activity.^{15,18-22} The findings in the PGAMD patient and the McArdle patient with residual myophosphorylase activity indicate that a non-ischemic forearm exercise test is better tolerated and has an excellent diagnostic power for these conditions as well.

Venous effluent levels of plasma lactate and ammonia typically have been assessed 10 to 30 minutes after the ischemic exercise test.^{9,13,20,23} However, as shown in this study, the diagnostic changes in plasma lactate and ammonia levels always occur within the first 2 minutes after exercise. Therefore, the forearm exercise test can be simplified, not only by excluding the use of a blood pressure cuff during exercise, but also by limiting sampling of blood to the first minutes after exercise.

This study shows that exercise-induced changes in venous pH and pCO₂ are clearly different in McArdle patients with complete block of glycogenolysis compared with that in subjects with intact or some residual glycolytic capacity (see Table 3). The consistent small alkalosis occurring in venous effluent blood of McArdle patients is related to the abolished lactic acid production and the proton-consuming phosphocreatine breakdown in muscle. The virtually unchanged pCO₂ in blood from exercising muscle in McArdle patients is

related to their lower work performance, higher blood flow, and absent muscle acidosis that shifts the HCO₃⁻/CO₂ equilibrium in the direction of CO₂.

The prevalence of MADD is 1 to 2%. The condition most likely does not cause disease,^{6,24} but may, however, cause diagnostic problems when using the forearm exercise test. A flat or blunted lactate response during the forearm exercise test associated with an absent increase in plasma ammonia may be interpreted as caused by a low work effort, and therefore patients with combined glycolytic disorders and MADD may be misdiagnosed by the forearm exercise test. In these cases, it is important to quantify work performance to be able to determine whether the responses were caused by a glycolytic defect or low work performance. Combined McArdle disease and MADD, as in the patient in this study, is rare, but other cases have been reported.²⁵⁻²⁷

Muscle blood flow in exercise has not been studied in great detail in patients with glycolytic disorders. Jehenson and colleagues found an impairment of the exercise-induced increase in muscle blood flow in five McArdle patients.²⁸ Muscle perfusion was assessed by positron emission tomography with the oxygen-15-labeled technique. However, work performance in McArdle and healthy subjects was not adequately controlled, and differences in MVC and arm muscle mass were not measured. In fact, there is evidence to suggest that the circulatory response to exercise is severely exaggerated in complete blocks of muscle glycolysis or glycogenolysis. In McArdle and phosphofructokinase deficiency patients, cardiac output is grossly elevated during cycle exercise relative to workload, indicating a hyperkinetic circulation in working muscle.^{4,29,30} Greater than normal increases in limb blood flow in McArdle disease also have been suggested by older studies.^{1,31,32} This study provides the first systematic documentation of enhanced exercise-induced limb blood flow in McArdle disease. The higher blood flow in McArdle patients occurred in aerobic protocols even though power output was 32 to 40% less than that performed by healthy subjects, which emphasizes the hyperkinetic circulatory response in these patients.

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