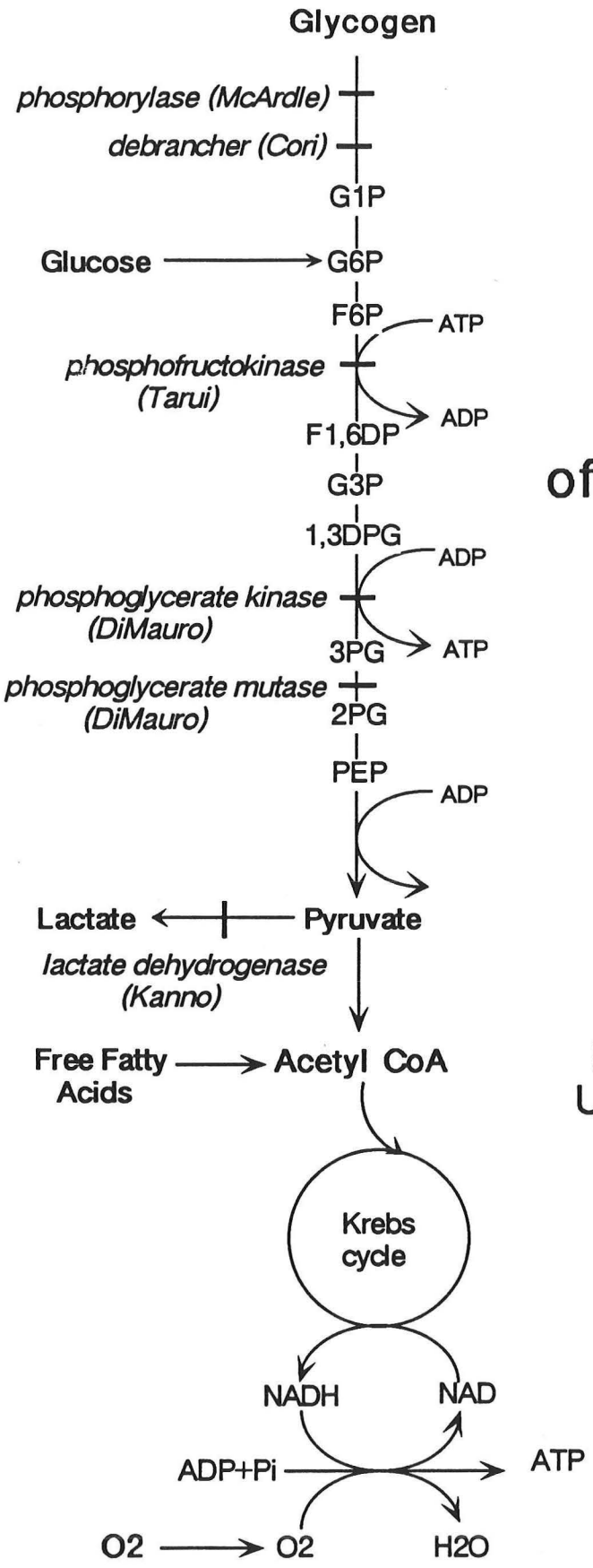

McArdle's Disease and Related Disorders of Muscle Glycogenolysis

Internal Medicine Grand Rounds
U.T. Southwestern Medical Center
May 31, 1990

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McARDLE'S DISEASE AND RELATED DISORDERS OF MUSCLE GLYCOGENOLYSIS

In 1951, Brian McArdle described George W., a 30 year old man with a life long history of exercise intolerance marked by muscle pain brought on by mild exertion and which progressed when exercise was prolonged to weakness and stiffness of active muscles (1). The patient had no abnormalities on physical examination. Specifically muscle muscle power and tone were judged to be normal. However, employing exercise testing, McArdle reproduced the patient's symptoms of abnormal fatigability and muscle cramping and recognized these symptoms to be similar to the consequences of experimental iodoacetate poisoning. Iodoacetate inhibits glycogenolysis at the level of glyceraldehyde phosphate dehydrogenase (GAPDH). As demonstrated by Lundsgaard, stimulation of iodoacetate-treated frog muscle results in an abnormally rapid decline in muscle contractile force, the development of an electrically silent muscle contracture similar to rigor, and a lack of the normal increase in lactate concentration in the bathing medium. McArdle demonstrated in his patient a similar "gross defect in the breakdown of glycogen to lactic acid in muscles" characterized by a failure of increase in blood lactate with intense aerobic and ischemic forearm exercise (Hollings test). McArdle further demonstrated in the patient a normal hyperglycemic response to adrenalin implying normal hepatic glycogenolysis and found normal lactate production in red cells. These results suggested that metabolic defect affected "chiefly if not entirely the skeletal muscles."

The abnormality responsible for "McArdle's disease" (McArdle had postulated a defect in GAPDH) was recognized eight years later as deficiency of muscle glycogen phosphorylase by Mommaerts and coworkers (2) and Schmidt and coworkers (3, 4) and later the same defect was confirmed in McArdle's original patient. These later reports recognized other typical features of the disorder: the common occurrence of exertional myoglobinuria and familial occurrence compatible with autosomal recessive inheritance. Myophosphorylase deficiency was thus the first clearly defined metabolic myopathy and the prototype of inherited defects in muscle energy metabolism. Since then a number of related enzyme defects involving glycogenolysis in skeletal muscle with similar symptomatology have been described: muscle phosphofructokinase deficiency (Tarui, 1964), muscle lactate dehydrogenase deficiency (Kanno, 1980), phosphoglycerate mutase deficiency (DiMauro, 1981), and phosphoglycerate kinase deficiency (DiMauro, 1983).

CLINICAL FEATURES OF McARDLE'S DISEASE

Skeletal muscle disorders (myopathies) classically are associated with progressive, predominantly proximal weakness. In contrast, patients with McArdle's disease and related disorders which impair energy availability, usually have normal examinations at rest but complain of *exercise intolerance* in which *symptoms are related specifically to the increased energy demands of exercise.* This patten of symptoms is the hallmark of muscle energy defects. The ability to identify affected patients depends upon recognition of the typical clinical history.

TABLE 1: MYOPHOSPHORYLASE DEFICIENCY: CLINICAL FEATURES

	# of cases/all cases	%
Exercise intolerance	108/112	96
Myoglobinuria	56/112	50
+renal failure	15/56	27
Fixed weakness	32/112	28
Wasting	13/112	12
Seizures	5/112	4
Age at onset (years):		
< 15	94/110	85
15-30	10/110	9
>30	6/110	6
Age at diagnosis (years):		
<10	5/111	4
10-30	55/111	50
30-50	30/111	27
>50	21/111	19
Positive family history	51/97	53

Data based on 112 cases; M=79, F=33. From DiMauro and Bresolin, Myology, vol 2,1986, p. 1586.

Symptoms of abnormal fatigability usually are life long and parents may report that affected children were unable to keep up with their peers and were the first to tire on family outings. Pain and cramps are less prominent and myoglobinuria is not a feature of the disease at this age and the disorder is virtually never recognized before the second decade (unless older siblings have already been diagnosed). In the second decade and beyond patients typically complain of muscle aching and weakness with exercise and, when exercise is continued despite these premonitory symptoms, muscle stiffness, cramping, and rhabdomyolysis with myoglobinuria. The types of exercise which are particularly likely to produce symptoms and most commonly are associated with muscle cramping and myoglobinuria are: 1) intense isometric exercise (eg. arm wrestling, trying to push a stalled car) which may trigger symptoms after only brief effort; or 2) brief maximal dynamic exercise (running the bases in baseball, flurry of swimming triggered by anxiety or horseplay) - running a distance of about 60 yards typically produces symptoms. The cramp (contracture) is directly related to the intense exercise; the muscle is shortened, hard, usually intensely painful, and is unable to be lengthened for minutes to hours. These cramps are the *direct consequence of exertion* and are not to be confused with spontaneous cramps which occur at rest, often during sleep, or cramps which occur with over-shortening of a muscle without intense effort. As initially recognized by McArdle, unlike ordinary cramps, the muscle shortening is electrically silent implying that it relates not to recurrent sarcolemmal activation (as is typical of spontaneous cramps) but to persistent calcium mediated interaction of actin and myosin due to calcium ingress (?sacolemmal, sarcoplasmic reticulum injury) or to impaired calcium reuptake by SR due to the cellular energy deficit (5, 6).

Episodes of exertional myoglobinuria occur in at least 50% of patients with McArdle's disease and commonly these episodes bring the patients to medical attention.

In approximately 30% of our patients, however, the initial episode of pigmenturia was interpreted as denoting renal or hepatic disease. The usual reasons for failure to identify the true cause of the symptoms were not recognizing the role of exercise in triggering the episode and failure to obtain a serum creatine kinase level. In approximately 25% of the patients reviewed by DiMauro and Bresolin, myoglobinuria was complicated by acute renal failure.

Exercise tolerance commonly varies from day to day and within a single period of exercise. The classic example is the "second wind" phenomenon first recognized by Pearson and coworkers (7). Typically patients note that muscle fatigue occurs in the first few minutes of exercise necessitating stopping and resting. This pattern of fatigue may recur several times, but after this "warm up" period, exercise suddenly becomes much easier so the activity (walking, mowing the lawn, etc) can be continued without further interruption. The mechanism of the second wind is increased delivery of blood borne fuels to working muscle related to increased mobilization of extramuscular fuels, increased blood flow or both (8, 9).

Though exercise intolerance is the dominant manifestation of McArdle's disease, a significant minority of patients develop variable, predominantly proximal *weakness.* Usually this occurs later in life (5th decade and beyond) but occasionally younger patients are affected (6). Its pathogenesis is unknown. Proposed mechanisms include: 1) incomplete recovery from recurrent muscle injury (10); 2) a consequence of the oxidation of amino acids by myophosphorylase deficient muscle as alternate energy substrates, thus compromising protein metabolism (11); 3) interference with muscle contractile function by excessive accumulation of muscle glycogen (12). The finding of focal muscle injury and atrophy as has been demonstrated by MRI imaging in a few patients seems most consistent with the first mechanism (10).

Though the clinical presentation described by McArdle is typical, clinical variants of myophosphorylase deficiency have been described: 1) patients in whom the onset of otherwise typical exercise intolerance is greatly delayed (13); 2) atypical adult presentations of patients in whom symptoms of abnormal exercise tolerance seem unusually trivial (14) or in whom muscle weakness is especially prominent, sometimes in the absence of preceding dramatic exercise intolerance (15, 16, 17); 3) atypical childhood forms presenting as fatal hypotonia and ventilatory failure in early infancy (18, 19, 20) or as congenital myopathy (21, 22). The biochemical basis of these clinical variants is unknown. There also are reports of rare patients heterozygous for myophosphorylase deficiency with residual phosphorylase in the range of 20-30% who apparently have symptoms attributable to impaired glycogenolysis (23, 24). Manifesting heterozygotes represents an alternative explanation for the report of apparent dominantly inherited McArdle's disease (25).

LABORATORY AND DIAGNOSIC FEATURES

Elevation in serum creatine kinase (CK) was present in more than 90% of cases in whom the determination was made in the review of DiMauro and Bresolin. This of course is the case in those who have had recent myoglobinuria (in whom dramatic CK elevations in the 10's or 100's of thousands may be seen) but substantial elevations in the range of 3-10 times the upper limit of normal are commonly present in the absence of obvious

dramatic muscle injury. This apparently relates to the fact that highly focal exertional muscle necrosis is extremely common in such patients as shown by screening MR imaging.

A more diagnostic laboratory abnormality is failure of increase in blood lactate with exercise as demonstrated initially by McArdle. The test most commonly is conducted under ischemic conditions. The protocol utilized in my laboratory is the following: an intracath is placed in an anticubital vein and a resting (pre exercise) sample is obtained. A blood pressure cuff is then inflated above arterial pressure and the patient exercises maximally using a hand ergometer squeezing at a rate of 30/minute until fatigued (normal subjects typically can perform such maximal ischemic exercise for 1-2 minutes, McArdle subjects fatigue within a minute). The cuff is then rapidly deflated and serial blood samples are obtained immediately and at 1, 2, 5, 10. and 20 minutes post exercise. To eliminate or minimize lactate production by red cells, the blood is mixed with ice cold perchloric acid (to deproteinize the sample) or, as a minimum, is placed immediately on ice for speedy transport to the laboratory for assay. Added precision is achieved by recording the force of initial maximal voluntary contraction and by monitoring the strength of successive contractions. A complication of this test is induction of a muscle contracture in affected patients. This is especially likely if ischemia is maintained after exercise is completed.

TABLE 2: MYOPHOSPHORYLASE DEFICIENCY: LABORATORY DATA

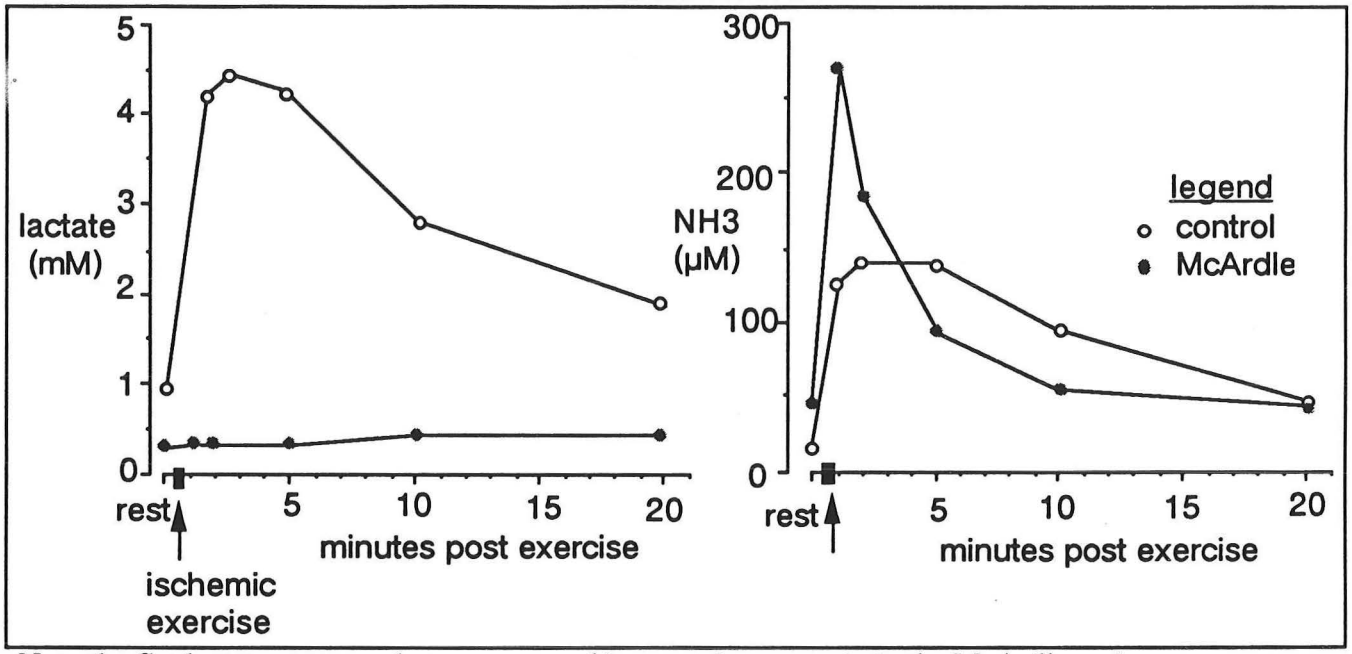
	Incidence	%
Increased serum CK at rest	62/67	93
Ischemic exercise - venous lactate response:		
no rise	51/55	93
decreased rise	4/55	7
Abnormal EMG at rest	29/59	49
Abnormal ECG	8/34	24
Muscle glycogen concentration (%)		
<1.5	9/63	14
1.5-3.0	30/63	48
>3.0	24/63	38
Muscle phosphorylase activity		
undetectable	56/74	76
residual	18/74	24

From DiMauro and Bresolin, Myology, vol 2, 1986, p. 1588

A three fold increase in lactate with ischemic exercise generally is considered normal. In our hands, venous lactate in normal subjects increases from a mean of 1 mM at rest to 4.5 mM 1-2 minutes post ischemic exercise (figure 1). The typical response in McArdle's a completely flat lactate curve. A small percentage of patients have a detectable though subnormal increase presumably attributable to a partial enzyme deficiency. It has been recognized that patients with McArdle's disease and related muscle glycolytic defects not only fail to produce lactate, but also have an exaggerated increase in venous ammonia related to increased accumulation and deamination of AMP (via AMP deaminase) in exercise (26, 27, 28, 29). The ammonia determination is an important confirmation which permits identification of a low lactate response attributable to poor effort since this will

results as well in a subnormal ammonia response (30). However an exception is the rare occurrence of coexisting myoadenylate deaminase deficiency (which blocks the increase in ammonia) and McArdle's disease (31).

FIGURE I: VENOUS LACTATE, AMMONIA RESPONSE TO ISCHEMIC FOREARM EXERCISE IN McARDLE'S DISEASE



Note the flat lactate response but exaggerated increase in ammonia in the McArdle patient compared to the mean value for healthy control subjects.

A positive ischemic lactate test indicates the presence of a defect in glycogenolysis and the need for definitive biochemical testing as achieved by muscle biopsy. Histochemical determination on fresh frozen muscle generally is adequate for the diagnosis of phosphorylase deficiency though quantitative biochemical measurement of enzyme activity is preferable. Typically there is no detectable phosphorylase activity (in > 75% of cases). In the remainder a small percentage of residual phosphorylase (usually 2-5% of normal) has been reported. The molecular basis of these partial defects has not been elucidated but limited data suggests these patients have less severe exercise intolerance. Routine performance of the phosphorylase histochemical stain has permitted recognition of the disorder in patients in whom the diagnosis was not suspected due to atypical clinical presentations (17). Muscle biopsy typically reveals excess glycogen stores which accumulate as subsarcolemmal, PAS positive blebs. Quantitative determination of glycogen generally reveals levels to be increased from 2 to 3 fold normal.

MOLECULAR BASIS OF PHOSPHORYASE DEFICIENCY

As suggested by McArdle's original report, the clinical manifestations are confined to skeletal muscle and the enzymatic defect is complete only in skeletal muscle.

Phosphorylase exists as multiple isozymes with distinct isoforms present in liver, heart and skeletal muscle. The muscle form alone is expressed in skeletal muscle accounting for the complete absence of enzymatic activity in this tissue (though histochemically detectable activity is present in smooth muscle of blood vessels). The muscle form of phosphorylase is expressed as well in heart and brain. Cardiac muscle has three isoenzymes as shown by activity analysis after acrylamide gel electrophoresis (19). There is a band corresponding to the muscle form, a heart form and a hybrid of the two. Evaluation of the heart in a patient with typical McArdle's disease and a child with a fatal infantile variant of the disorder revealed a partial defect in phosphorylase manifest by loss of the muscle and muscle/heart hybrid forms of the enzyme. The isozyme pattern of human brain has not been evaluated in detail but studies with antibody directed at the muscle form of the enzyme indicate inhibition of 20-30% of enzymatic activity, compatible with expression of the muscle isoform in brain and the presence of a partial defect in brain in myophosphorylase deficiency. mRNA analyses reveal similar findings (32). No clinical features attributable to the partial defect in heart have been identified. There is evidence of increased incidence of seizures in patients with McArdle's disease but whether this relates specifically to loss of the muscle isoform in brain is unknown. Though phosphorylase is absent from mature muscle in McArdle's disease, activity can be demonstrated histochemically in regenerating muscle fibers and in muscle culture. This initially puzzling finding was explained by the demonstration of a "fetal" isoenzyme which differs electrophoretically and immunologically from mature muscle phosphorylase (33, 34). This provided evidence that muscle undergoes a developmentally regulated change in isozyme composition during myogenesis.

TABLE 3: BIOCHEMISTRY OF MYOPHOSPHORYLASE DEFICIENCY

	#/total	%	no enzyme activity	residual enzyme activity (%)
SDH-PAGE:				
absent protein	35/42	83	35/35	
markedly reduced protein	6/42	14	5/6	1/6 (4%)
normal protein	1/42	2		1/1 (0.33%)
ELISA:				
absent CRM	41/48	85	41/41	
detectable but decreased CRM	6/48	13	5/6	1/6
slightly decreased CRM	1/48	2		1/1

SDH-PAGE = sodium dodecylsulfate polyacrylamide gel electrophoresis; ELISA = enzyme linked immunosorbent assay (using antibody to purified human muscle phosphorylase; from Servidei et al, Ann Neurol 24:774, 1988

The gene encoding human muscle phosphorylase has been mapped to the long arm of chromosome 11 (35) and has been cloned and sequenced (36). Southern blot analysis of DNA isolated from white blood cells in 4 McArdle patients studied by Gautron and coworkers (37) and 11 patients studied by Servidei and coworkers (38) have failed to reveal major deletion or rearrangements of the phosphoylase gene as compared with controls. While the precise genetic defect(s) remain to be discovered, it is clear that

McArdle's disease is biochemically heterogeneous. In some patients, no enzyme protein can be detected electrophoretically (39), chromatographically (40) or immunologically (41, 42, 43). In others, an enzymatically inactive protein can be found electrophoretically (39) or immunologically (42, 43, 44).

Servidei, DiMauro and coworkers have evaluated 48 biopsies from patients with McArdle's disease (table 3). The clinical and laboratory features of these patients corresponded closely the review of cases previously published from this laboratory (45). Using SDS polyacrylamide electrophoresis, 35 of the 42 studied biopsies showed complete absence of the band corresponding to normal phosphorylase, implying that the protein was not expressed. 6 of 42 showed a faint band consistent with a markedly reduced phosphorylase protein. Five of these six had no detectable enzymatic activity implying that the residual protein was catalytically inactive. The remaining patient had approximately 4% of normal enzymatic activity. A single patient had an apparently normal level of phosphorylase by SDS-PAGE, but residual enzyme activity was less than 1% of normal. ELISA studies were performed using antibody (rabbit) raised to phosphorylase purified from postmortem human skeletal muscle on these and 6 additional patients with similar results (table 3). These studies indicated that the vast majority of patients with phosphorylase deficiency have no residual enzymatic activity and no or only trace amounts of residual phosphorylase protein as assessed electrophoretically or immunologically. RNA analysis in myophosphorylase deficiency has revealed further biochemical heterogeneity. Gauton and coworkers studied eight patients, all with enzymatically and electrophoretically absent myophosphorylase. In 5 of these patients, no myophosphorylase mRNA was detectable, but in the remaining 3, a reduced amount of normal length mRNA was present. Servidei and coworkers studies performed similar studies in 4 patients (table 4)

TABLE 4: CLINICAL AND BIOCHEMICAL FEATURES INCLUDING mRNA ANALYSIS IN 4 PATIENTS

Patient	Sex,age	Exercise intolerance	Cramps	Pigment-uria	Weakness	Glycogen	CRM	mRNA
WR	M,65	+	-	-	+	2.06	absent	normal
RL	M,25	+	+	+	-	2.42	absent	short
KE	M,12	+	-	-	-	3.03	decreased	normal
DB	M,31	±	+	-	-	2.50	ND	absent

Glycogen concentration expressed in gm/100 gm muscle wet wt (normal control approximately 1), CRM = cross reacting material. From Servidei et al, Ann Neurol 24:774, 1988

These investigators found one patient each with normal and absent mRNA in patients proven (Table 3, WR) or presumed (DB) to have no immunologically detectable myophosphorylase. In addition one patient (RL) with no cross reacting material had an abnormally short mRNA. In addition they studied one patient with detectable CRM in whom the myophosphoylase mRNA or normal size was present. On the basis of these results, Servidei et al have postulated the existence of at least 5 biochemical varieties of myophosphorylase deficiency (table 5).

TABLE 5: POSSIBLE MOLECULAR MUTATIONS IN McARDLE'S DISEASE

	PHOSPHORYLASE PROTEIN AND mRNA	Reported cases	Reference	POSTULATED MUTATION
I	Normal protein concentration, normal-length mRNA			Point mutation at site essential for binding or regulation
II	Decreased protein concentration, normal-length mRNA	1/4	a	Point mutation giving unstable protein or mRNA, or decreased transcription
III	No protein, normal-length mRNA	1/4 3/8	a b	Nonsense mutation terminating protein early, or frameshift mutation changing protein sequence
IV	No protein, short mRNA	1/4	a	Point mutation giving cryptic splice-site or intragenic deletion
V	No protein, no mRNA	1/4 5/8	a b	Gene deletion or regulatory mutation

from a) Servidei et al, Ann Neurol 24:774, 1988; b) Gautron et al, J Clin Invest 79:275, 1987.

ROLE OF GLYCOGEN IN MUSCLE ENERGY METABOLISM - IMPLICATIONS OF GLYCOGEN UNAVAILABILITY

The end result of the absence of muscle phosphorylase is the selective loss of glycogen as a fuel for muscle energy metabolism. Glycogen is a branched polysaccharide made up of D-glucose residues in α 1-4 glucosidic bonds branched at intervals of 12-18 residues by α 1-6 glycosidic linkages. Approximately 93% of glucosidic linkages are 1-4, 7% 1-6. The highly branched structure increases glycogen solubility and provides multiple sites for rapid enzymatic degradation. Glycogen is stored in muscle cytoplasm as aggregates which by EM appear as electron dense granules in the subsarcolemmal and intermyofibrillar spaces, particularly in the I bands. These glycogen aggregates are closely associated with the enzymes involved in glycogen synthesis and degradation (glycogen synthetase, glycogen phosphorylase and the kinases/phosphatases involved in the interconversion of these enzymes between active/inactive forms.

The glycogen concentration of normal human muscle is approximately 1% wet weight (approximately 50 mM of glucosyl residues/gm). In a normal 70 kg man, there is thus 350 to 400 gm of muscle glycogen compared to approximately 70 to 80 gm stored in liver. Additionally about 20 gm of glucose is found in blood. Compared to other bodily energy stores, the caloric value of carbohydrate is small - approximately 2,000 kilocalories compared to about 140,000 kilocalories stored as lipid in non-obese man (46).

Glycogen phosphorylase catalyzes phosphorolysis of α 1,4 linkages of glycogen, Debrancher catalyzes two reactions: 1) transfer of a maltotriosyl unit from a donor to an acceptor chain of the glycogen molecule followed by 2) hydrolysis of the α 1,6 glycosidic link. Glycogen phosphorylase was the first enzyme in which enzymatic regulation through phosphorylation-dephosphoryla was demonstrated (47). Phosphorylase b (less active) is converted to phosphorylase a (active) by the phosphorylase kinase catalyzed transfer of the

terminal phosphate of ATP to a specific serine residue of each phosphorylase b subunit. Phosphorylase kinase in turn exists in phosphorylated and non-phosphorylated forms, the interconversion catalyzed by a cyclic AMP dependent protein kinase. Additionally phosphoylase kinase is activated by the increased levels of cytoplasmic calcium which occur with muscle activity. Phosphorylase kinase contains as one of its subunits calmodulin which mediates this calcium effect. Calcium activated phosphorylase kinase in muscle also has been shown to phosphorylate a specific serine residue of glycogen synthase converting it to its relatively inactive form. Thus muscle calcium transients couple muscle excitation to contraction and at the same time stimulate glycogen breakdown (and inhibit its synthesis) during muscular activity. The intercoversion of phosphorylase b to a is probably not paramount in the regulation of glycogen degradation in skeletal muscle however. Phosphorylase b is catalytically active in the presence of levels of inorganic phosphate and AMP found in working muscle and experimental studies in man suggest that alterations in these modulators (especially Pi) of phosphorylase activity may be of greater importance than interconversion of phosphorylase b to a in the regulation of glycogen breakdown in muscle (48).

TABLE 6: FUEL STORAGE, POWER OUTPUT AND ACCELERATION

Anaerobic Processes	Available Energy (mol ATP)	Work time at 70% max (min)	Max power (mM ATP/ kg d.m./sec)	Time to reach max power	O_2 need (O_2/ATP)
ATP	0.02	0.03	11.2	< 1 sec	0
PCr	0.34	0.5	8.6	< 1 sec	0
CHO → lactate	0.7-5.2	0.9-6.9	5.2	< 5 sec	0
Aerobic Processes					
CHO → CO_2+H_2O	70	93	2.7	3 min	0.167
FFA → CO_2+H_2O	8000	10600	1.4	30 min	0.177

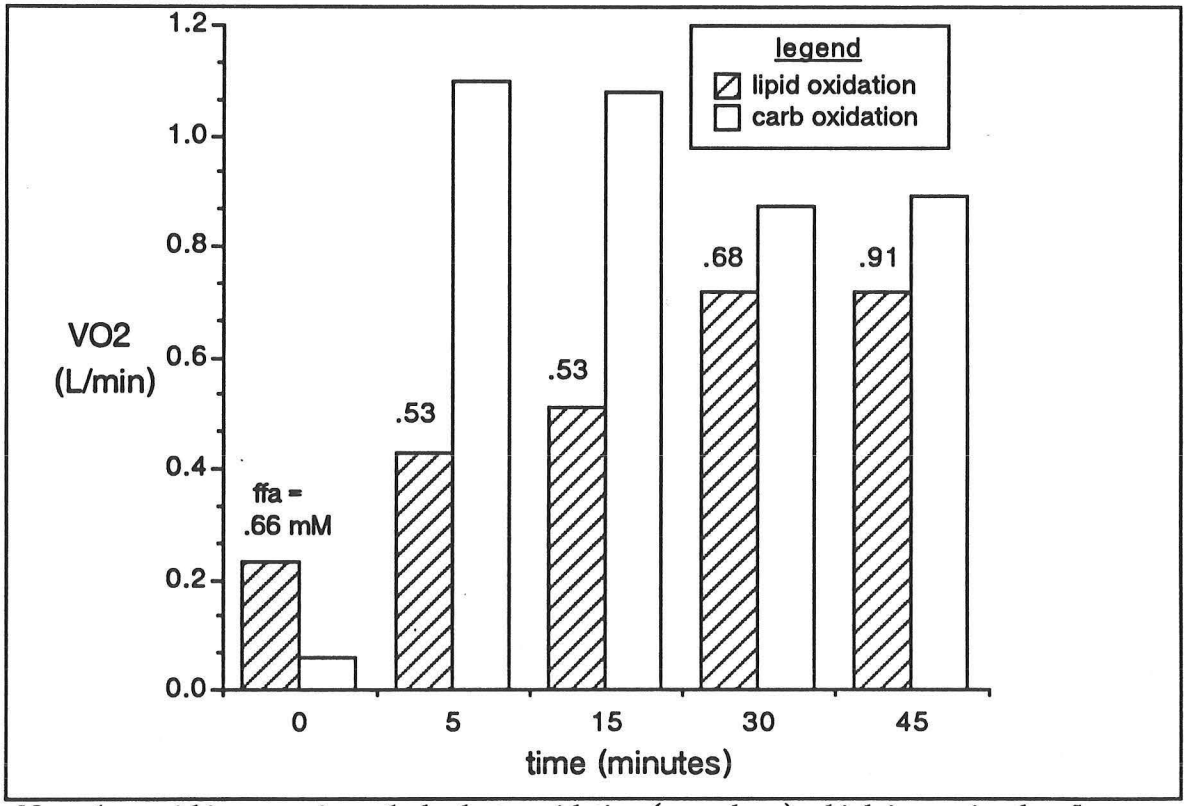
Available energy was calculated from 20 kg muscle with a glycogen content of 70 mmol/kg w wt, from liver glycogen store of 500 mmol and from a fat depot of 15 kg. Work time was calculated from VO_2max of 4.01 L/min. Maximal power of anaerobic energy stores was calculated from Hultman and Sjöholm (1983). Maximal aerobic power was calculated assuming VO_2max of 4.01 of which 72% is used by working legs (Jorfeldt and Wahren, 1971) and working muscle mass of 20 kg (= 4.7 kg d.m.). The maximal power output of FFA oxidation was assumed to correspond to 50% of total aerobic power. From Sahlin (49).

Skeletal muscle lacks the enzyme glucose-6-phosphatase and consequently is unable to convert glucose-6-phosphate to glucose. Thus unlike glycogen in liver, muscle glycogen is relatively spared during starvation indicating that its preservation for muscle energy metabolism takes precedent over supplying other body carbohydrate needs during fasting. Muscle glycogen is degraded *anaerobically* (glycogen → lactate) during ischemic exercise and in circumstances in which muscle energy utilization exceeds oxidative energy production (eg. at the onset of exercise and during exercise which approaches or exceeds maximal oxidative capacity.) The advantages of anaerobic glycogenolysis include the ability to support high rates of ATP resynthesis (high power output) and the ability to achieve these high rates of power output rapidly (seconds). Glycogen is the most abundant anaerobic fuel, providing 2-10 times the energy available from phosphocreatine (table 6).

The loss of glycogen as an anaerobic fuel explains the rapid fatigue and contractures that result from intense isometric contractions in patients with McArdle's disease.

The common relationship between glycogen utilization and lactate formation in skeletal muscle has to the widely held assumption that glycogen is used predominantly or exclusively as an anaerobic fuel. In fact glycogen is also a crucial *aerobic* fuel (glycogen → CO2 + H2O) Complete oxidation of glycogen increases the yield of energy available from anaerobic glycogenolysis more than an order of magnitude. Though lipid is a far more abundant oxidative fuel and is required for normal endurance exercise, muscle glycogen is superior to lipid in several ways. First, glycogen is a more readily available oxidative fuel and thus is able to achieve more rapidly than lipid a maximal rate of oxidative phosphorylation (49). This fact is evident by examining the relative contribution to oxygen uptake of lipid versus carbohydrate oxidation as estimated by indirect calorimetry (figure 3) At an exercise workload corresponding to approximately 50% of VO2max, the large increase in oxygen uptake from rest to 5 minutes of exercise is met almost exclusively by carbohydrate (glycogen) oxidation. In contrast lipid oxidation increases more gradually, attributable to the slow rate of mobilization and hence availability of fatty acids as compared to muscle glycogen (figure 2).

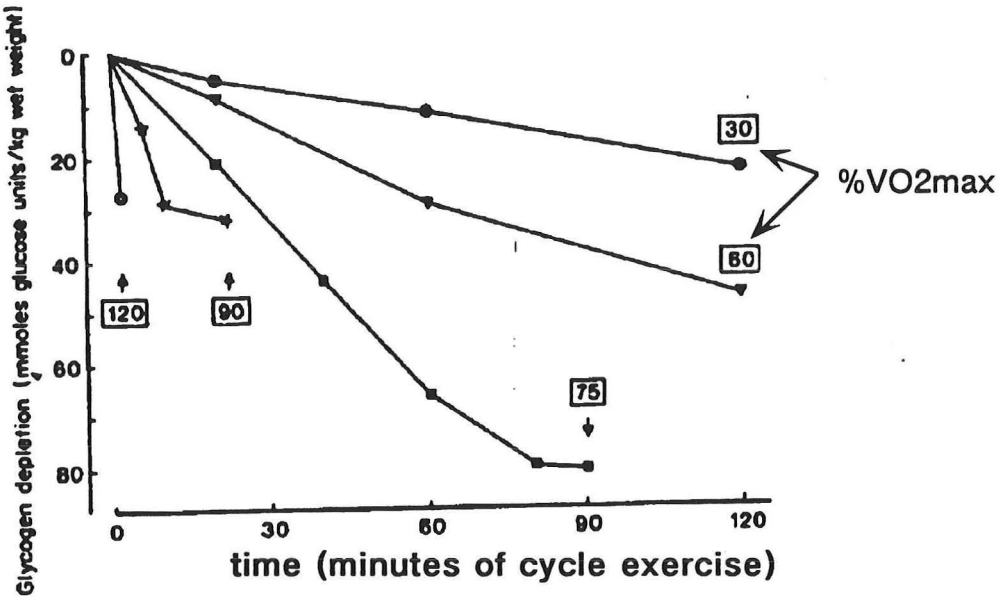
FIGURE 2: CARBOHYDRATE RELATIVE TO LIPID OXIDATION DURING EXERCISE AT 50% OF VO2MAX



Note the rapid increase in carbohydrate oxidation (open bars) which is maximal at 5 minutes and declines thereafter as lipid (FFA) oxidation (hatched bars) more gradually increases. Corresponding plasma levels of FFA are indicated at the top of the hatched bars.

The fraction of carbohydrate oxidized during dynamic exercise increases (as indicated by the progressive rise in the respiratory exchange ratio, RER) with increasing exercise intensity implying that glycogen is superior to lipid as a fuel of maximal oxidative metabolism in skeletal muscle. Thus there is a progressive shift from predominant oxidation of lipids (associated with RER = 0.7) at rest to the virtual exclusive oxidation of carbohydrate (RER = 1.0) with near maximal levels of dynamic exercise (49, 50). The role of muscle glycogen as the dominant source of oxidizable carbohydrate in working muscle was indicated by a series of classic experiments performed by Scandinavian investigators employing serial needle biopsies of muscle in the course of exercise of varying intensities (figure 3) (51, 52, 53, 54).

FIGURE 3 GLYCOGEN DEPLETION DURING CYCLE EXERCISE



The boxed numbers denote % of VO2max; the last point indicated with exercise at 75, 90 and 120% VO2max corresponds to the point of fatigue. From Saltin and Karlsson (1971), "Muscle metabolism during exercise," Plenum, New York, pp 395-400.

These studies revealed that exercise workloads associated with little or no lactate production (i.e. <70-75% VO2max) resulted in progressive depletion of muscle glycogen stores consistent with the complete oxidation of glycogen to CO2 and H2O. The importance of the aerobic utilization of glycogen was indicated further by the fact that, at high submaximal levels of exercise (70-80% VO2max), the point of muscle fatigue correlated closely with virtual depletion of glycogen stores. Correspondingly, the length of time that exercise could be continued at 70% VO2max was shown to correlate directly with initial concentrations of muscle glycogen. The biochemical mechanisms underlying the requirement of glycogen to support maximal oxidative metabolism are incompletely understood. Available data are consistent with the premise that maximal oxygen utilization in exercise normally is limited by oxygen availability; and glycogen is the single most

efficient source of ATP production relative to oxygen consumption. Thus the molar ratio of ATP produced to O2 consumed is 6.2 for glycogen, 6.0 for glucose and 5.6 for palmitate (55).

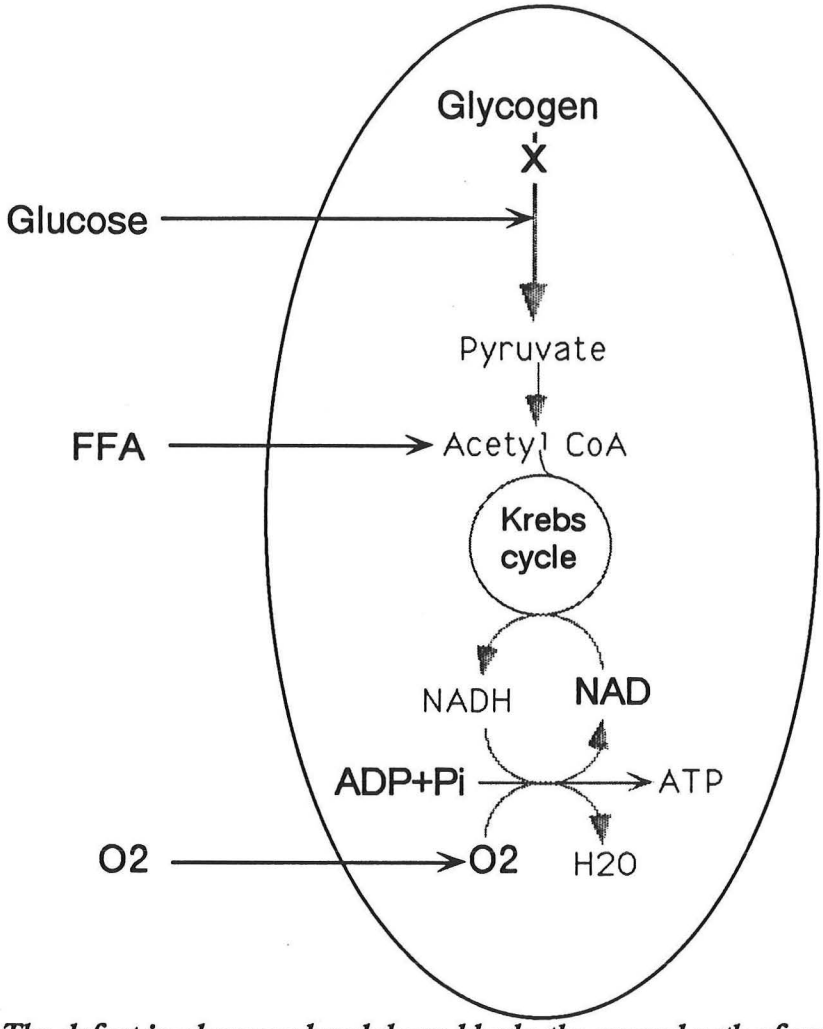
These considerations suggest that intolerance of dynamic exercise in myophosphorylase deficiency relates to an important extent to the block in the *aerobic* metabolism of glycogen. Studies of VO2max in patients with McArdle's disease confirm that VO2 max is approximately 1/3 to 1/2 that of normal healthy subjects (56, 57, 58) and is low even when compared to patients with exertional myalgia unrelated to an underlying defect in muscle metabolism (table 7). Low VO2 max is associated with a low maximal RER indicating reduced availability of oxidizable carbohydrate compared to heathy subjects and patients with myalgia. The physiologic expression of is indicated by the relationship, VO2max = maximal cardiac output (Q) X maximal systemic arteriovenous O2 difference (a-v O2 diff). Thus oxygen uptake is the product of oxygen delivery by the circulation (i.e. Q) and oxygen extraction by metabolizing tissues (systemic a-v O2 diff) which in exercise is predominantly active muscle. Maximal cardiac output in patients we have studied is similar to that of healthy subjects implying that oxygen delivery is not limiting to VO2 (59, 60, 61). In contrast, maximal systemic a-v O2 difference is markedly attenuated (58, 61). The normal oxygen content of arterial blood (assuming normal oxygen carrying capacity) is approximately 20ml O2/100 ml blood, i.e. 20 ml/dl. From rest to maximal exercise, a-v O2 difference typically increases from 5 ml/dl to more than 15 ml/dl. In contrast to the normal more than 3 fold increase, a-v O2 diff in McArdle patients exercised 2-4 hours after a normal meal typically increased only about 50%. These results suggest that a complete block in glycogen availability results in a substrate-limited impairment of cellular oxidative metabolism and hence limited ability to extract oxygen from circulating blood.

TABLE 7: OXIDATIVE METABOLISM IN MAXIMAL CYCLE EXERCISE IN McARDLE'S DISEASE

Subjects	VO2	VE/VO2	RER	HR
MEN				
Healthy (n=8)	40.8±1.6	45.4±2.1	1.14±.02	188±4
Myalgia (n=6)	27.0±1.6	40.1±2.0	1.09±.02	164±4
McArdle's disease				
1	12	37.8	0.92	141
2	15	39.4	0.96	176
3	17	44.4	0.96	146
mean ± SE	14.7±1.4	40.5±2.0	0.95±.01	154±11
WOMEN				
Healthy	31.7±2.1	45.9±4.0	1.14±0.3	187±4
Myalgia	21.6±2.4	47.0±2.0	1.10±.04	170±7
McArdle's disease	11.8	49	0.98	169

VO2 = oxygen uptake, ml/kg/min; VE/VO2 = ratio of pulmonary ventilation to oxygen uptake; RER = respiratory exchange ratio; HR = heart rate, beats per minute. From Haller, et al, Ann Neurol 17:196, 1985.

FIGURE 4: POSTULATED BASIS OF SUBSTRATE-LIMITED OXIDATIVE METABOLISM IN McARDLE'S DISEASE

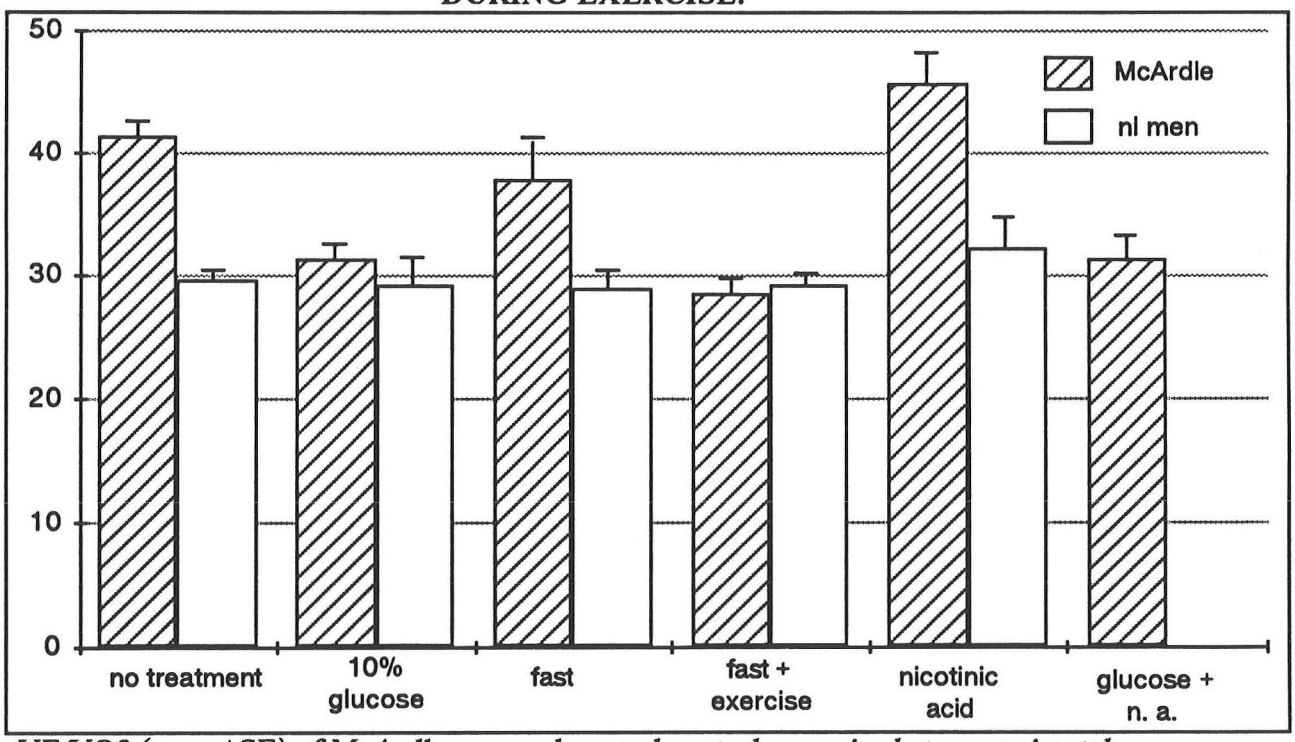


The defect in glycogen breakdown blocks the normal path of acetyl CoA production from glycogen in heavy exercise, thus 1) limiting the availability of acetyl units for incorporation in the Krebs cycle; 2) impairing mitochondrial production of NADH; and 3) thereby limiting oxidative phosphorylation and oxygen uptake.

Substrate-limited oxidative metabolism is the basis of the "second wind" phenomenon. The term was coined by Pearson to characterize the dramatic increase in exercise capacity that may occur in McArdle patients spontaneously or in response to carbohydrate or lipid infusions (7). Subsequent studies identified increased blood levels of FFA, increased muscle blood flow or both as the major factors associated with a spontaneous "second wind " (8, 9). The common denominator of the "second wind" - whether achieved spontaneously, by substrate infusions (eg. glucose, fructose, lactate, triglyceride emulsion) (7), by interventions that promote substrate mobilization (glucagon, epinephrine, heparin), augment blood flow (epinephrine, prior exercise)(9), or increase cellular fuel transport (insulin) (3)- is apparently an increased cellular supply of oxidizable substrate and presumably an augmented rate of ATP production via oxidative phosphorylation. This concept is supported by the finding that VO2max typically is increased 20-30% by infusions of alternate oxidative fuel and decreased by interventions

(eg nicotinic acid) which reduce fuel mobilization (58, 61, 62). Maximal cardiac output in McArdle patients is unchanged by altered fuel availability but maximal a-v O2 difference increases with infusions of glucose, lactate and triglyceride consistent with augmented substrate availability for oxidative phosphorylation. We have proposed the scheme outlined in figure 4 to account for these results (62). This hypothesis indicates that, in the presence of the complete block in glycogen breakdown, the rate of production of acetyl CoA is limited. The availability of acetyl CoA in turn limits oxidative metabolism by reducing the flux of Krebs cycle intermediates and thus the production of reducing equivalents (NADH) for oxidation via the respiratory chain. As a result, the provision of reduced cytochrome c for oxidation via cytochrome c oxidase,the terminal reaction of the electron transport chain is attenuated, thus limiting oxidative phosphorylation and oxygen extraction by working muscle. Blood borne substrates such as glucose and FFA improve exercise tolerance by increasing the production of acetyl CoA and thus the rate of Krebs cycle flux and oxidative phosphorylation. This hypothesis predicts that the normal increase in muscle NADH which accompanies high intense exercise would fail to occur in McArdle's disease (63). Recent data indicate the NADH in fact does fail to increase in maximal ischemic or cycle aerobic exercise in McArdle patients (61, 64).

FIGURE 5: VENTILATION RELATIVE TO OXYGEN UPTAKE (VE/VO2) DURING EXERCISE.



VE/VO2 (mean±SE) of McArdle men and normal controls exercised at approximately 50% of VO2max under conditions of varying muscle energy substrate availability. No treatment = 2-4 hrs after a normal meal; 10% glucose infusion; fast = after 12-14 hr fast; fast+ exercise = after 45 minutes of submaximal exercise in the fasting state to increase FFA availability; nicotinic acid = 600-800 mg orally to inhibit lipolysis; glucose + n.a. = glucose infusion after nicotinic acid. Differences between McArdle and control means are statistically significant during "no treatment" ($p<0.001$), fasting ($p<0.05$), and nicotinic acid ($p<0.01$). From Haller and Lewis, Neurology 36:717, 1986.

CARDIOPULMONARY REGULATION IN EXERCISE IN McARDLE'S DISEASE

Impaired muscle oxidative metabolism likely is central to the altered heart rate, cardiac output, blood flow and ventilatory responses which have been recognized in exercise in patients with McArdle's disease (1, 8, 9, 56, 65). The enormous capacity of skeletal muscle to increase its oxidative needs from rest to maximal exercise requires cardiopulmonary responses that are closely coordinated to skeletal muscle needs for oxygen and for removal of metabolic end products. In his initial report, McArdle recognized that his patient respiration and heart rate were more rapid than would be expected for the amount of work performed and that muscle blood flow after ischemic exercise was exaggerated compared to a control subject. These observations have been confirmed and extended by subsequent investigations. Porte and coworkers, for example, found that with fatiguing exercise, a McArdle patient's heart rate and ventilation were greater than normal and that heart rate and ventilation fell substantially with similar exercise during spontaneous or induced second wind. They concluded that "lack of substrate seems to cause a disproportionate increase in heart rate and alveolar hyperventilation by mechanisms that are unknown. The stimulus to ventilation is presumably neural because the known humoral stimuli of arterial oxygen and carbon dioxide tensions and pH cannot account for the level of ventilation; it is presumably peripheral because ventilation increased early in exercise before the patient noticed pain or discomfort" (8).

We have found similar exaggerated ventilatory responses in McArdle patients during exercise (66). In normal subjects, ventilation during submaximal exercise increases in direct proportion to the increase in workload and oxygen uptake. As a result, below the anaerobic threshold (i.e. approx 75% VO2max), the ratio VE/VO2 remains relatively constant at approximately 30 (figure 5). In contrast, in McArdle's disease ventilation during submaximal exercise commonly is exaggerated relative to workload and VO2 and VE/VO2 is high (figure 5 and table 8). Increased ventilation raised the production of CO2 and increases arterial pH. Since lactate is not produced in exercise, frank respiratory alkalosis occurs and may be a factor contributing to symptoms of lightheadedness and frank syncope or seizures in the course of exercise as has been reported in a number of patients (40, 43, 67, 68, 69). Administration of glucose did not alter VO2 at the same workload in our study (table 8), but significantly lowered ventilation and the ratio of ventilation to O2 and CO2. There was a trend to lower VCO2 which did not reach statistical significance but R and venous pH fell significantly.

Modification of substrate availability by other means also altered the ventilatory response to exercise and hence VE/VO2 in McArdle patients. Increasing the availability of FFA or glucose normalized ventilation while reducing FFA availability by means of the antilipolytic agent, nicotinic acid, potentiated the exaggerated ventilatory response. Blood borne metabolites, namely CO2 and H^+ ions, generally are considered of major importance in mediating exercise hyperpnea. Our observations that increased substrate availability lowers ventilation relative to CO2 production in conjunction with a fall in pH indicate other factors are responsible and are consistent with a reflex ventilatory drive arising from metabolically sensitive neural afferents in working muscle (70, 71).

TABLE 8: GAS EXCHANGE DURING SUBMAXIMAL EXERCISE IN McARDLE'S DISEASE

	Work	VE	VO2	VCO2	VE/VO2	VE/VCO2	R	venous pH	venous PCO2	venous pO2
no treatment	30 ±10	42 ±2.8	0.94 ±0.13	0.96 ±.09	44.8 ±2.7	44 ±1.5	1.02 ±0.05	7.38 ±0.02	42 ±4	28 ±6
glucose	30 ±10	*31.1 ±3.6	0.93 ±0.15	0.86 ±0.10	*33.4 ±1.8	*39.5 ±1.2	*.85 ±1.2	*7.35 ±0.01	46 ±1	27 ±5

*cycle exercise performed by four McArdle men at approximately 50% of VO2max (workload = 30±10 watts) before (no treatment) and after glucose infusion; VE = ventilation in L/min; VO2 = oxygen uptake in L/min; VCO2 = carbon dioxide production in L/min; R = VCO2/VO2; pH, PCO2 and PO2 determined in venous blood. Values represent mean ±SE; * = difference between no treatment and glucose condition is statistically significant (p<0.05) From Haller and Lewis, Neurology 36:717, 1986.*

TABLE 9: CARDIOVASCULAR RESPONSE TO MAXIMAL EXERCISE

Subjects	Cardiac output (Q)	ΔQ/ΔVO2	systemic a-vO2 difference	HR
MEN				
Healthy (n=8)	248±14	4.8±0.2	16.6±0.5	188±4
Myalgia (n=6)	203±16	5.6±0.2	13.9±0.6	164±4
McArdle's disease				
1	173	13.9	6.5	141
2	192	11.1	7.8	176
3	150	7.8	11.3	146
mean ± SE	172±12	10.8±1.9	8.5±1.4	154±11
WOMEN				
Healthy	211±6	5.0±0.4	15.1±0.8	187±4
Myalgia	169±16	5.4±0.2	12.8±0.4	170±7
McArdle's disease	193	13.7	6.1	169

Q = cardiac output (ml/kg/min); ΔQ/ΔVO2 = increase in cardiac output relative to the increase in oxygen uptake from rest to exercise; systemic a-v O2 difference = systemic arteriovenous oxygen difference (ml/dl); HR = heart rate (beats/min); from Haller et al, Ann Neurol 17:196, 1985.

OXYGEN TRANSPORT IN McARDLE'S DISEASE

Abnormal oxygen transport also characterizes exercise in McArdle's disease. A nearly 1:1 ratio between oxygen transport and utilization in exercise illustrates the normal tight gearing of oxygen delivery to muscle oxidative rate. Assuming normal oxygen carrying capacity (i.e. approx. 20ml O2/dl oxygenated blood), 5 liters of cardiac output are required to transport 1 liter of oxygen in exercise. In normal individuals, cardiac output increases 5-6 liters for each liter of increased oxygen uptake from rest to exercise (i.e. $\Delta Q/\Delta VO2 \approx 5$) with only minor variation with respect to age, sex, body weight, level of

conditioning, or active muscle mass. Mechanisms responsible for matching O2 transport (i.e. cardiac output, Q) and O2 utilization include activation of brainstem cardiovascular centers a) in parallel with activation of motor units via the corticospinal tract, i.e. "central command;" and b) reflexly via unmyelinated afferent fibers that arise in skeletal muscle and are sensitive to metabolites produced during muscle contraction (72).

In McArdle's disease the increase in cardiac output per liter of oxygen uptake during exercise is 2-3 times normal while maximal systemic a-vO2 difference is markedly low (table 9) (58, 59, 61, 73). This cardiac response to exercise is inconsistent with primary cardiac disease or cardiac deconditioning. Severe myocardial or valvular disease typically produces a hypokinetic circulation in exercise with low maximal cardiac stroke volume and cardiac output, with normal or high maximal systemic a-vO2 diff. Deconditioning due to physical inactivity lowers maximal cardiac output and stroke volume but maintains a normal relationship between Q and VO2 in exercise.

The excessive cardiac output response to dynamic exercise is associated with exaggerated increases in mean arterial pressure despite an abnormally large reduction in systemic vascular resistance (62). A primary increase in cardiac output would be required to produce higher than normal blood pressure whereas a lower than normal blood pressure would be expected if the excessive cardiac output response were due simply to baroreceptor mediated response to a significant fall in arterial pressure. The steep reduction in systemic resistance suggests that increased cardiac output is combined with exaggerated metabolic vasodilation in working muscle. This is compatible with the finding of an exaggerated hyperemic response to ischemic exercise in McArdle's original paper and to the later finding of Barcroft, Greenwood, McArdle and coworkers of increased hyperemia after aerobic exercise as well (1, 65). Studies of leg blood flow during cycle exercise in McArdle patients indicate that blood flow to working muscle is increased relative to metabolic rate (74). These data are consistent with the hypothesis that blood flow in active muscle is increased relative to metabolic rate both due to increased systemic oxygen transport and due to exaggerated metabolic vasodilation. A close relationship between the underlying oxidative defect and disordered oxygen transport is indicated by the fact that increased availability of blood borne oxidative substrate normalizes the relationship between cardiac output and systemic oxygen uptake and between leg blood flow and oxygen utilization (61, 74).

ABNORMAL FATIGABILITY IN McARDLE'S DISEASE: PHYSIOLOGIC AND METABOLIC CORRELATES

Characteristic of McArdle's disease is abnormally rapid fatigue (inability to maintain contractile force) which leads to a muscle contracture if exercise is continued. Clinical evidence strongly indicates the presence of an imbalance between energy supply and demand, but the precise metabolic factors responsible for these phenomena are unknown. Muscle contraction and ion transport underlying muscle activation and relaxation are coupled to ATP hydrolysis via specific ATPases (figure 6). Initial speculation was that abnormal fatigability and muscle contracture was the result of depletion of ATP leading to insufficient ATP available to support these reactions. Good evidence exists that adenine nucleotide breakdown is exaggerated in McArdle's disease as

indicated by increased levels of venous ammonia, inosine and hypoxanthine with exercise (26, 27, 28, 29, 75). The presumed enzymatic mechanism is the following:

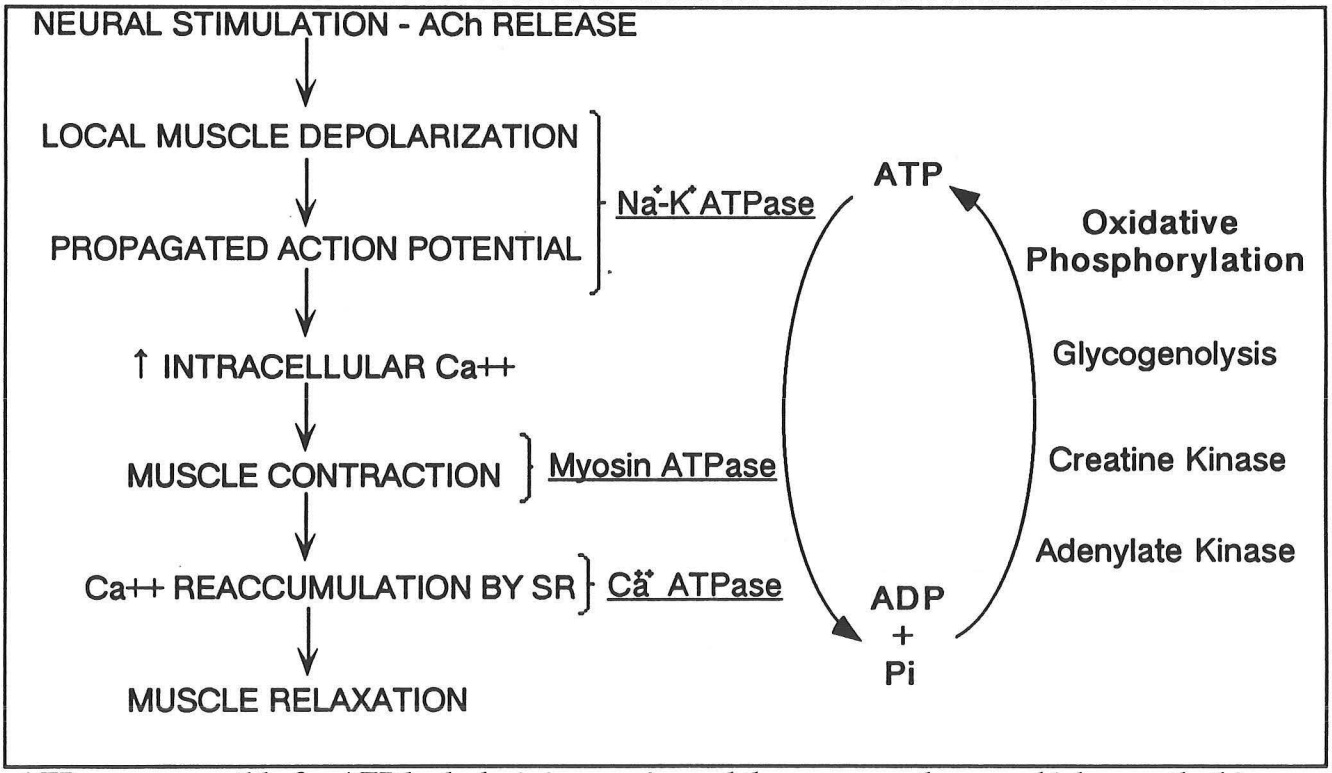
$$2ATP \xrightarrow{ATPase} 2ADP + 2Pi$$

$$2ADP \xleftrightarrow{myokinase} ATP + AMP$$

$$AMP \xrightarrow{adenylate\ deaminase} IMP + NH3$$

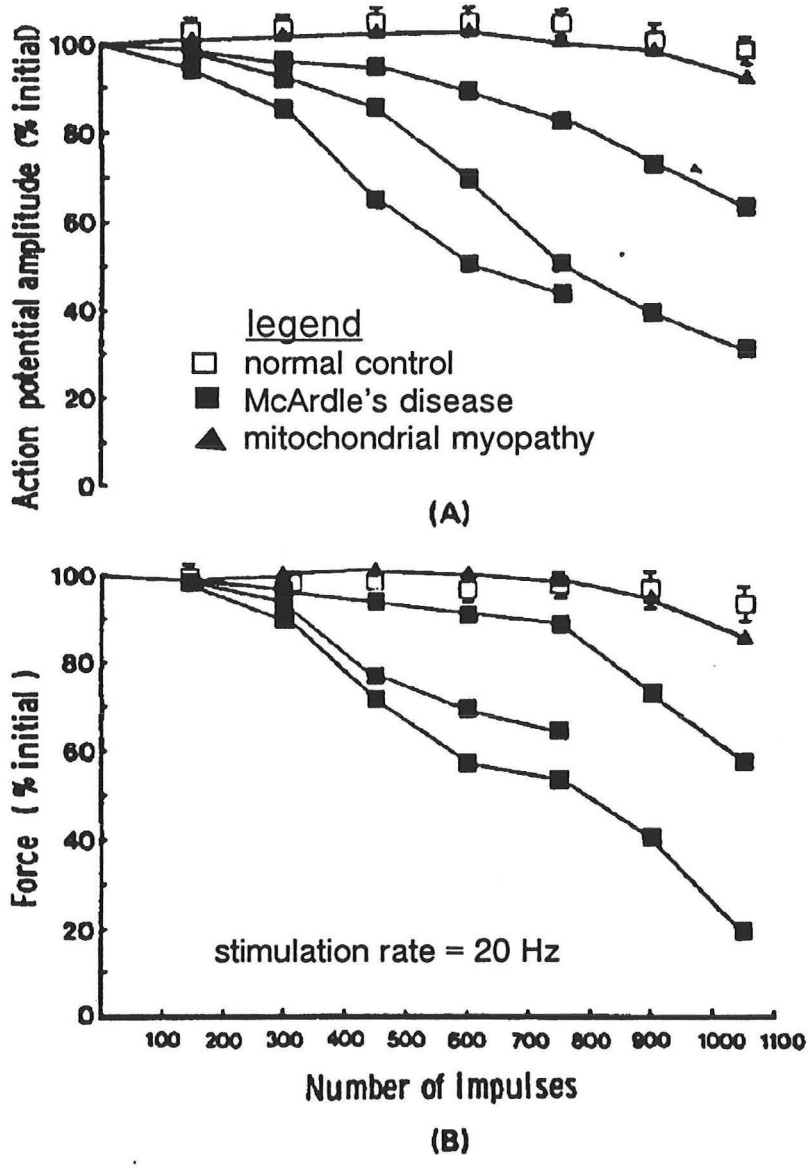
However direct measurement of ATP by means of needle biopsy or 31P-NMR have failed to demonstrate a significant decline in cellular ATP (5, 76, 77, 78, 79, 80). The seemingly discrepant ATP and ammonia data can be reconciled when on considers that ATP is present in millimolar concentrations where as ammonia levels are almost two orders of magnitude less. Thus a minor fall in ATP is sufficient to account for dramatic increases in ammonia, inosine and hypoxanthine. Even if cellular ATP levels are slightly less than normal, ATP concentrations remain more than an order of magnitude higher than that which would be expected to impair muscle contraction. The possibility that depletion of a crucial subcellular pool of ATP is responsible for premature fatigue (5) cannot be entirely excluded though this explanation seems unlikely .

FIGURE 6: MUSCLE FUNCTIONAL AND ENERGETIC RELATIONSHIPS IN EXERCISE



ATPases responsible for ATP hydrolysis in exercise and the energy pathways which resynthethize ATP. Note that both ADP and inorganic phosphate (Pi) are utilized in oxidative phosphorylation and glycogenolysis. In the creatine kinase and the coupled myokinase/adenylate kinase reactions there is a net accumulation of Pi.

FIGURE 7: CONTRACTILE FATIGUE AND MEMBRANE EXCITABLITY IN McARDLE'S DISEASE



Force fatigue and failure of excitation during electrical stimulation at 20 Hz with local ischemic of the adductor pollicis muscle in 5 normal subjects (open squares), 3 patients with McArdle's disease (closed squares) and 1 patient with a mitochondrial myopathy (closed triangle). (A) action potential amplitude as a percent of the initial. (B) Force as a function of the number of impulses delivered to the ulnar nerve at the wrist. From Edwards et al, Disorders of the Motor Unit, D.L Schotland ed., John Wiley, 1982, pp 715-728.

We have proposed that premature fatigue in McArdle's disease is attributable to the accumulation of hydrolysis products of ATP, ADP and inorganic phosphate (Pi), to levels which impair cellular energy utilization (62). 31P NMR studies indicate that ADP and Pi increase abnormally relative to work performed in McArdle's disease as a consequence of the block in glycogenolysis and impaired oxidative phosphorylation (78, 81). High levels of ADP and Pi reduce the free energy of hydrolysis of ATP and may contribute to fatigue by end product inhibition of the myosin, Ca^{++}, and Na^+/K^+ ATPases. Experimental studies in skinned muscle fibers and 31P-NMR studies in healthy humans have shown a close correlation between the accumulation of Pi and H^+ and a decrease in force of muscle contractions attributable to inhibition of actin-myosin interaction (82, 83, 84, 85, 86). In these studies, the fall in pH denoting the increase in $[H^+]$, greatly potentiates the Pi mediated fall in muscle isometric tension. In NMR studies, fatigue correlates specifically with the increase in diprotonated phosphate ($H_2PO_4^-$) but this mechanism cannot apply to McArdle's disease since hydrogen ions do not accumulate due to the block in lactate formation.

Consideration of the exertional muscle symptoms in McArdle patients suggests that the mechanism of muscle fatigue in these patients may differ from that in healthy humans. Ischemic exercise in McArdle patients results in a progressive decline in membrane excitability manifest by a fall in the compound muscle action potential (87, 88, 89, 90) which is not present in normal subjects (figure 7). The decline in muscle excitability in turn closely parallels the fall in muscle force generation. A possible mechanism of membrane inexcitability in McArdle's disease is the accumulation of extracellular K^+. Muscle activation is associated with cellular loss of K^+ and accumulation of Na^+. Levels of muscle ADP and Pi inhibitory to the Na^+/K^+ pump would impair K^+ reuptake, thereby promoting membrane depolarization and ultimate inactivation of the regenerative membrane action potential. Clearly a loss of membrane excitability cannot account for all of the symptoms in McArdle's disease however. Loss of membrane excitability typically results in flaccid weakness and thus does not explain the typical muscle contracture. ADP or Pi mediated inhibition of Ca^{++}ATPase or myosin ATPase may be involved in this process (61, 62).

TREATMENT OF McARDLES DISEASE

Management of patients with McArdle's disease includes education regarding the cause and possible consequences of the disease. Patients should be counseled regarding factors which normally promote muscle glycogen utilization and which thus predispose to exertional muscle injury (table 10) as well as factors which normally tend to spare muscle glycogen and thus are likely to be associated with improved exercise intolerance. Warm-up exercise to promote FFA mobilization and increase blood flow to working muscle is an important prelude to all physical exertion. Regular low level exercise (eg walking a a well tolerated pace) promotes physical conditioning which may have long term benefits by increasing lipid-oxidizing capacity of muscle. In healthy subjects improved fitness increases the oxidation of lipid relative to carbohydrate in exercise (i.e. spares glycogen).

The use of pharmacologic agents, special diets or dietary supplements to augment the availability of oxidative fuels generally has been disappointing or equivocally

successful. There is little rationale for a high carbohydrate diet. Although glucose can be oxidized by muscle in McArdle's disease, its potential benefit is offset by homeostatic mechanisms that maintain blood glucose in a narrow range and by the corresponding lowering of plasma fatty acid levels. The net effect of a carbohydrate meal is often a lowering of exercise capacity. Intravenous glucose resulting in substantial elevation in blood glucose levels, presumably thereby increasing glucose transport into muscle, can acutely improve exercise capacity, but has little therapeutic implication outside a hospital or clinic setting. Glucagon, by augmenting hepatic glycogenolysis, has also been found to improve exercise capacity acutely (91, 92) but there seems little rationale for its chronic use (93, 94).

TABLE 10: VARIABLES IN MUSCLE LIPID-CARBOHYDRATE UTILIZATION

	Factors Promoting Glycogen Use	Mechanism
Dietary	high-carbohydrate diet, recent carbohydrate meal	inhibits lipolysis, lowers blood levels of FFA
Exercise Pattern	a)isometric, ischemic b)rapid transition from rest to high intensity dynamic exercise	a) requires anaerobic glycogenolysis b) promotes glycogen oxidation
Physical Conditioning	low level of physical conditioning	low levels of lipid oxidizing enzymes, increased metabolism of carb relative to lipid at a given work load
	Factors Promoting Lipid (FFA) Use	
Dietary	fasting or high fat diet	increases levels of circulating FFA
Exercise pattern	prolonged, submaximal	promotes fat mobilization, increases glucose transport, promotes physical conditioning
Physical Conditioning	high level of physical conditioning	high levels of lipid oxidizing enzymes, increased metabolism of lipid relative to carb at a given work load

Medium-chain triglyceride diets increase hepatic production of ketones which can be oxidized by skeletal muscle. Increased exercise tolerance has been achieved in some patients but others tolerate the diet poorly, complaining of nausea, diarrhea and meager if any improvement in exercise capacity. Long-chain free fatty acids represent the dominant available oxidative fuel in glycolytic defects, but "high fat" diets have not provided major benefits (95). Epinephrine acutely increases exercise capacity, an effect attributed both to augmented lipolysis and to increased blood flow. The finding of net uptake in amino acids in a McArdle patient compared to controls (96) suggests the possibility that amino acids

serve as alternative oxidative fuels in this disorder. Slonim found improved exercise capacity in McArdle patients receiving a high protein diet in addition to regular exercise (11). Whether the exercise or the diet was the more crucial variable is uncertain, but it seem prudent to insure that patient include adequate protein in their diet.

MUSCLE GLYCOLYTIC DISORDERS WHICH MAY MIMIC McARDLE'S DISEASE

A number of inborn errors of metabolism affecting muscle glycogenolysis have now been described (title page). Those which most closely mimic McArdle's disease are muscle phosphofructokinase deficiency (Tarui's disease) and the recently described distal defects of glycolysis, phosphoglycerate kinase, phosphoglycerate mutase and lactate dehydrogenase deficiency. Glycogen debrancher deficiency rarely is associated with dramatic exercise intolerance, typically is not associated with exertional myoglobinuria and contractures and so is not included in the following discussion. Phosphorylase kinase deficiency affecting skeletal muscle has been recognized but the clinical features and their relationship to the enzyme defect remains to be clarified. In two patients we have evaluated with this defect, cycle exercise including lactate production was normal implying that glycogen breakdown was not dramatically impaired.

Muscle phosphofructokinase deficiency (PFKD) was first recognized by Tarui and coworkers in three siblings who had easy fatigability and stiffness in vigorously exercised muscles (97). Following an ischemic exercise test in which a failure to produce lactate was documented, one of the patients developed pigmenturia. These authors demonstrated a virtually complete absence of the enzyme in skeletal muscle and a partial deficiency of red cell PFK. A subsequent case was reported by Layzer, Rowland and Ranney with similar symptoms including multiple episodes of exertional pigmenturia (98). In this report, the frequent association of nausea with exertional muscle pain and fatigue was noted. In addition this patient was of Ashkenazi Jewish heritage as has been the rule in subsequently recognized cases in North America and Europe (99). The classical syndrome is related to the absence of functional activity of the M form of PFK and is associated with muscle (exertional fatigue, pain, injury), hematologic (hemolysis, erythrocytosis) and general metabolic (hyperuricemia, symptomatic gout) symptoms (92, 99, 100).

Like McArdle patients, PFKD patients have lifelong symptoms of easy fatigue with exertional weakness, pain and contractures in association with evidence of muscle injury as indicated by elevated serum creatine kinase and, in some cases, exertional pigmenturia (myoglobinuria). These symptoms are virtually identical to McArdle's disease. Like McArdle's disease, PFKD is associated with anaerobic and oxidative defects attributable to the unavailability of glycogen; attenuated increases in oxygen extraction in working muscle consistent with substrate-limited oxidative phosphorylase; and exaggerated cardiopulmonary responses to exercise (61). Perhaps noteworthy is the fact that muscle symptoms and exercise abnormalities do not seem more severe than in McArdle disease since glucose as well as glycogen utilization is blocked. This can be interpreted to indicate the primacy of muscle glycogen as a muscle carbohydrate fuel. More difficult to explain is the presence of some evidence that symptoms of muscle

involvement may actually be less severe in PFKD than McArdle's disease. For example, the incidence of myoglobinuria and associated renal failure are apparently much higher (2-5 fold) in McArdle disease (99).

TABLE 11: COMPARISON OF McARDLE'S AND TARUI'S DISEASES

	McArdle's Disease	Tarui's Disease
biochemical defect	muscle phosphorylase (chromosome 11)	muscle phosphofructokinase (chromosome 1)
substrate blocked	glycogen	glycogen + glucose
inheritance	autosomal recessive	autosomal recessive
racial predilection	no	Ashkenazi
muscle symptoms	exercise intolerance exertional muscle contracture exertional myoglobinuria second wind ± weakness	exercise intolerance exertional muscle contracture exertional myoglobinuria ±second wind ± weakness
laboratory	ischemic exercise → no lactate, high ammonia elevated serum creatine kinase ± hyperuricemia	ischemic exercise → no lactate, high ammonia elevated serum creatine kinase ± hyperuricemia increased total bililrubin, retic count
other		partial defect in red cells/hemolysis
muscle metabolites at fatigue	↑ADP, ↑Pi, ↓H^+	↑ADP, ↓Pi, ↓H^+

Muscle glycogen deposition is increased (usually 2-4% of wet wt) similar to McArdle patients. However the accumulation of an abnormal polysaccharide which is diastase resistant, resembling amylopectin has been found in some biopsies and is postulated to accumulate due to activation of glycogen synthase by G-6-P. The enzyme defect is virtually complete though immunologic cross reacting M subunit typically is detectable (101, 102, 103). In cultured muscle enzyme activity reappears as a result of the expression of P and L forms of PFK. In contrast to McArdle disease in which hexose phosphates are virtually undetectable in muscle, patients with PFKD may have increased G-I-P, G-6-P, and F-6-P at rest and, as indicated by 31P-NMR, there is marked increase in phosphate monoester (i.e. hexose phosphates) in exercise and a delayed disappearance of this peak during rest after exercise (79). As a result, the increase in inorganic phosphate in exercise is greatly attenuated in PFKD compared to McArdle's disease. The similarity in patterns of muscle fatigue despite differing levels of Pi implies that factors other than increased Pi are responsible for the abnormal fatigability common to the two disorders. A factor which may be responsible is an exaggerated accumulation in ADP in both conditions (61).

Distal blocks in muscle glycogenolysis. Only a handful of cases of phophoglycerate kinase (104, 105, 106, 107), phosphoglycerate mutase (106, 108, 109, 110), or muscle lactate dehydrogenase deficiency (111, 112, 113) have been described. In each, the block in glycogenolysis is less complete than in McArdle's disease and PFK deficiency. As an apparent consequence exercise intolerance is less prominent. Specifically

oxidative capacity is virtually normal consistent with the capacity to provide adequate amounts of pyruvate and thus acetyl CoA for terminal oxidation (110, 113). Correspondingly, oxygen transport is normally coupled to oxygen utilization in exercise (113). In each case, however, extreme exertion is capable of triggering rhabdomyolysis with myoglobinuria. This suggests that during exercise that normally demands maximal power output, glycogenolysis in these disorders is inadequate to match anaerobic energy demand.

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