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Modified Exercise Test in Screening for Mitochondrial Myopathies – Adjustment of Workload in Relation to Muscle Strength

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Key Words
Subanaerobic threshold exercise test · Lactate stress test · Bicycle ergometer · Mitochondrial myopathy

Abstract
The aim of this study was to evaluate the usefulness of a modification of the bicycle ergometer test, the subanaerobic threshold exercise test (SATET), as a screening test for patients with mitochondrial myopathies. Since the original SATET is frequently found to be strenuous for weak patients, a new variable (relative muscle strength) was added to the workload formula. Plasma lactate levels were recorded at rest, then after 5 and 15 min of cycling on an ergometer, with constant workload. Nine patients with mitochondrial myopathy, 10 patients with other neuromuscular diseases and 9 healthy but sedentary volunteers undertook the test. An upper reference limit after exercise for plasma lactate was settled at 2.9 mmol/l. The modified SATET showed a sensitivity of 78% and a specificity compared to the healthy subjects of 100%. Compared to patients with other neuromuscular diseases, the specificity was lower (60%). All subjects completed the test without severe fatigue or pain.

Exercise intolerance is frequently a feature of mitochondrial myopathies [1] but may be experienced by several other categories of patients with neuromuscular disorders or in patients with generalized myalgia (i.e. fibromyalgia or chronic fatigue syndrome). Since the ultimate diagnosis of mitochondrial myopathy includes muscle biopsy, a need for a non-invasive and reliable screening test is obvious. The fact that patients with mitochondrial myopathies mostly show an increase in plasma lactate at low workload is used in a screening test, the SATET (subanaerobic threshold exercise test) [2]. However, we have experienced that the SATET is strenuous for a significant proportion of weak patients. Thus, we have modified the test by reducing the workload in relation to muscle strength loss. This modified test was shown to be well tolerated by the patients.

Methods

The test was performed by 9 patients with mitochondrial myopathy (8 female, 1 male) aged 35–70 years, 10 patients with other neuromuscular disease (8 female, 2 male) aged 29–66 years and 9 healthy but sedentary subjects (7 female, 2 male) aged 37–69 years (table 1). All patients were known and diagnosed at the Neuromuscular Centre. The healthy subjects and the patients with other neuromus-

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Table 1. Patient data: age, sex, maximal isometric quadriceps muscle strength, plasma lactate after 15 min of cycling (C15), diagnosis and diagnostic criteria

No.	Age	Sex	Quadriceps strength N	Lactate at C15 mmol/l	Diagnosis
Mitochondrial myopathy					
1	34	F	228	5.2	CPEO, mtDNA deletion, muscle biopsy shows RRFs
2	38	F	110	6.2	CPEO, mtDNA deletion, muscle biopsy shows RRFs
3	40	F	303	3.0	CPEO, mtDNA deletion, muscle biopsy shows RRFs
4	41	F	171	3.8	MELAS, point mutation A3243G
5	53	F	136	2.2	Mitochondrial encephalomyopathy, point mutation G8328A
6	56	F	118	2.6	Mitochondrial encephalomyopathy, muscle biopsy shows RRFs
7	57	F	248	4.3	CPEO, mtDNA deletion, muscle biopsy shows RRFs
8	70	F	253	9.0	MELAS, point mutation T582C, muscle biopsy shows RRFs
9	55	M	159	8.6	Mitochondrial encephalomyopathy, muscle biopsy shows RRFs
Other neuromuscular diseases					
1	29	F	246	4.4	SMA, type 3 (DNA verified)
2	41	F	200	2.0	FSHD (DNA verified)
3	43	F	124	3.6	FSHD, typical clinical presentation, also mother and son
4	43	F	61	2.9	FSHD, typical clinical presentation, no family history
5	61	F	185	5.1	Dystrophin deficiency carrier for Duchenne muscular dystrophy
6	62	F	166	2.5	Nemalin body myopathy, muscle biopsy proven, family history
7	64	F	199	6.1	FSHD, typical clinical presentation, also daughter and grandson
8	66	F	167	2.8	FSHD (DNA verified)
9	56	M	102	1.4	SMA, type 3, clinical and neurophysiological support
10	41	M	288	1.4	FSHD (DNA verified)

RRFs = Ragged red fibres; CPEO = chronic progressive external ophthalmoplegia; MELAS = mitochondrial myopathy, encephalopathy, lactacidosis, stroke-like episodes; SMA = spinal muscular atrophy; FSHD = facioscapulohumeral muscular dystrophy.

cular diseases were matched for age and gender to the group with mitochondrial myopathy.

All subjects were studied on a bicycle ergometer (Monark 239E, Varberg, Sweden). Muscle strength of the knee extensor (non-dominant side) was obtained in the patients with mitochondrial myopathy and other neuromuscular diseases. Maximal strength (brake test) was measured in triplicate using a hand-held myometer (Penny & Giles Transducers, Christchurch, UK) at 30 min prior to the cycle test. The mean of the two highest values was used in the calculation formula. The healthy subjects made a similar maximum knee extensor effort on a Cybex Orthotron (Lumex Inc., New York, N.Y., USA).

A venous catheter was inserted, and blood samples were drawn at rest before cycling commenced, then after 5 min (C5) and 15 min (C15) of cycling, for plasma lactate analysis. A constant workload was individually determined. The following formula was used to calculate workload: workload (W) = weight (kg) × coefficient of age (W/kg) × 90% × knee extensor strength (N)/normal knee extensor strength (N).

The coefficient of age was acquired from Nashef and Lane [2] and Reinhardt et al. [3]. The normal value of muscle strength was acquired from Bäckman et al. [4]. No reduction of workload was made for the healthy subjects.

The upper reference limit of plasma lactate at C15 was calculated as mean value + 2 SD of healthy subjects. Significances of group mean difference values were calculated with Student's t test for independent samples. All tests were two-tailed and conducted at a significance level of 0.01.

Results

All subjects managed to complete the test without strenuous effort. The mean C15 plasma lactate level in healthy subjects was 2.0 (SD 0.46) mmol/l (table 2). The upper reference limit of lactate was thus calculated to be 2.9 mmol/l (mean + 2 SD). Seven of the 9 patients with mitochondrial myopathy recorded pathological lactate values at C15 (mean value 5.0, range 2.2–9.0; fig. 1). In comparison to the healthy controls, the lactate levels of the group with mitochondrial myopathy were significantly increased at all points of time ($p = 0.005$; $p = 0.003$; $p = 0.007$). Six of 10 patients with other neuromuscular dis-

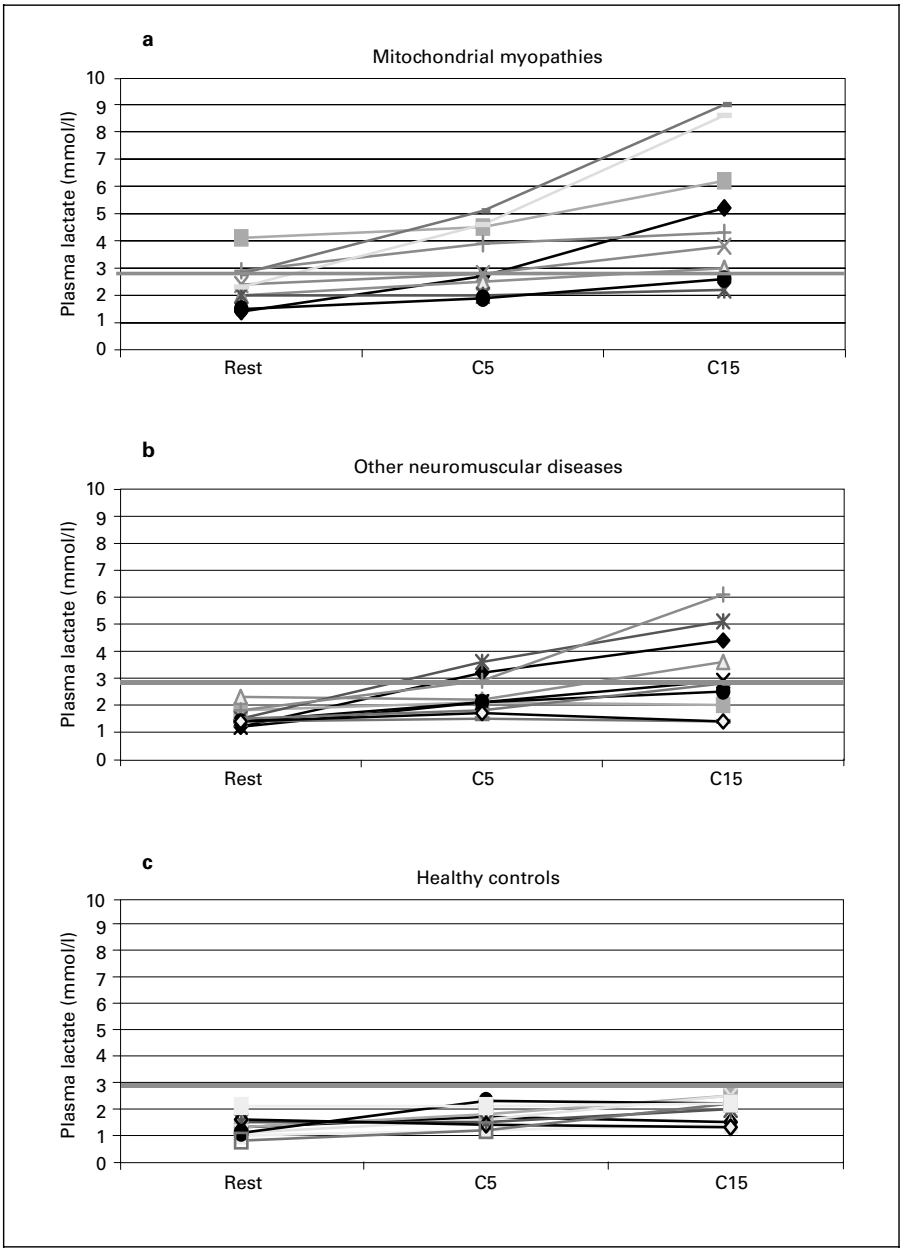

Fig. 1. Individual values of plasma lactate (rest, C5 and C15) in patients with mitochondrial myopathy (**a**), patients with other neuromuscular diseases (**b**) and healthy controls (**c**). The normal upper limit of lactate at C15 was 2.9 mmol/l.

Table 2. Plasma lactate (mmol/l): mean and standard deviation (in parentheses) from the recordings at rest, C5 and C15 in patients with mitochondrial myopathy, patients with other neuromuscular diseases and healthy controls

	Mitochondrial myopathies	Other neuromuscular diseases	Healthy controls
Rest	2.4 (0.82)	1.6 (0.33)	1.3 (0.39)
C5	3.3 (1.21)	2.3 (0.69)	1.6 (0.38)
C15	5.0 (2.50)	3.2 (1.57)	2.0 (0.46)

eases recorded lactate levels ≤2.9 mmol/l at C15, while the remaining 4 patients recorded pathological values (mean 3.2, range 1.4–6.1). All healthy subjects had a plasma lactate level less than 2.9 mmol/l at C15 (mean 2.0, range 1.2–2.6). The sensitivity of the test for detection of mitochondrial myopathy was 78%. The specificity was 100% compared to the healthy controls and 60% compared to the patients with other neuromuscular diseases. No correlation was found between maximal muscle strength prior to the test and lactate levels at C15.

Discussion

A modification of a bicycle test (SATET) [2] used in screening for patients with suspected mitochondrial myopathy has been evaluated. Our experience after many years of applying the original SATET was that the patients quite often suffered from muscle exhaustion and pain during and after the test. It can be considered likely that factors other than age, gender and weight such as muscle strength and mass, the normal activity pattern and the lung function of the patient have an influence on the test result. We have found that by reducing the workload in relation to muscle strength loss we have developed a test that is well tolerated by this patient group, a test that is less demanding for the patient but still sensitive enough to detect muscle disease. The modified test discriminates well the unhealthy from the healthy. The fairly low sensitivity compared to the healthy state (78%) indicates that there are patients with mitochondrial myopathy without hyperlactataemia. At the same time there are patients with other neuromuscular diseases who develop high lactate levels, i.e. a false-positive result. This modified SATET discriminates well those patients with muscle disease, but is however not disease specific.

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