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Josef Finsterer · Helmut Eichberger · Christa Jarius

Lactate-stress testing in 54 patients with mitochondriopathy

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Abstract Since there are only few data available about the lactate stress test in a group of patients with mitochondrial myopathy, we investigated the sensitivity of this test in a larger cohort of such patients. Serum lactate was determined before, during and after a 15 minute, constant 30 W workload on a bicycle ergometer in 47 controls, aged 15 to 72 years and 54 patients with mitochondrial myopathy, aged 15 to 74 years. Lactate's upper reference limits at rest, 5, 10, 15 minutes after starting, and 15 minutes after finishing the exercise were 2.0, 2.1, 2.1, 2.1 and 1.8 mmol/l respectively. The sensitivity of the lactate-stress test was 69%. The lactate-stress test complements electrophysiological and bioptical findings and proved to be helpful in diagnosing mitochondrial myopathy.

Key words Mitochondriopathy · Bicycle ergometer · Exercise stress test · Metabolic disorder · Lactacidosis

Introduction

Lactic acidosis may occur with a variety of metabolic defects although impairment of the oxidative phosphorylation system is by far the most common cause. In these patients moderate exercise has been shown to induce a disproportional increase of serum lactate in most of them [1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18]. This increase is due to the defective oxidative metabolism with a reactive change from aerobic to anaerobic phosphorylation of ADP and an equilibrium shift of the pyruvate/lactate reaction towards lactate [7, 9, 14, 18]. The increase of lactate during moderate exercise has been used for diagnostic purposes, but little is known about its sensitivity in a large cohort of patients with mitochondrial myopathy. This study was thus carried out: 1. to investigate the sensitivity of the lactate-stress test in a large group of patients with mitochondrial myopathy, and 2. to find out if the lactate-stress test is more sensitive in patients with abnormal EMG, ragged-red muscle fibres or proven mtDNA mutation.

J. Finsterer (✉)
Postfach 348, 1180 Wien, Austria, Europe
e-mail: fij@2nr.nkr.magwien.gv.at,
Tel.: +43-1-88000-260 or 261, Fax: +43-1-4781711

L. Boltzmann
Institute for Research in Neuromuscular Disorders,
(Director: Prof. B. Mamoli), Vienna

H. Eichberger
Institute of Anatomy, Neuromuscular Department,
University of Vienna, Vienna

C. Jarius
Institute of Neurology, University of Vienna, Vienna, Austria

Methods and materials

Lactate-stress testing was performed in 54 patients with mitochondrial myopathy (27 women, 27 men), aged 15 to 74 years, and 47 healthy, age-matched subjects (27 women, 20 men), aged 15 to 72 years. In all patients the diagnosis was based on clinical findings (fatiguibility (n = 26), reduced tendon reflexes (n = 24), cramps (n = 23), weakness (n = 21), sensory impairment (n = 19), wasting (n = 17), muscle soreness (n = 12), ptosis (n = 12), double vision (n = 11)), electrophysiological investigations and morphological muscle alterations like ragged-red fibres, subsarcolemmal accumulation of mitochondria, reduced oxidative enzyme staining, abnormally shaped mitochondria and mitochondrial cristae, paracristalline inclusions, glycogen and lipid storage (Table 1). Biochemical studies were carried out in eight patients, but failed to demonstrate decreased oxidative enzyme activity in any of them. MtDNA analysis was carried out in 21 of the patients and revealed referenced or new mutations in 14 of them (Table 1) [5].

All subjects were studied on the paddle-rate independent electronic bicycle ergometer E980 (Tunturi, Piispanristi, Finland). Subjects were advised to avoid strenuous exercise for three days before the lactate-stress test. Additionally, patients were told to rest for 30 minutes before the test. Blood was taken before starting the exercise (R1), 5, 10 and 15 minutes after starting cycling at a power of continuously 30 W (S5, S10, S15) and 15 minutes after finishing the exercise (R2) [5, 18]. Lactate was determined with the commercially available Ektachrome Clinical Chemistry Slide (LAC, Kodak, Rochester-N.Y., USA) [5]. Subjects with renal failure, malignancies, diabetes, hepatopathy and those taking biguanids, valproate, corticosteroids, ethanol, salicylate or oral contraceptives were excluded. A test result was defined as pathologic if >2 of the 5 lactate values exceeded the corresponding upper reference limits. All patients gave informed consent prior to their inclusion in the study.

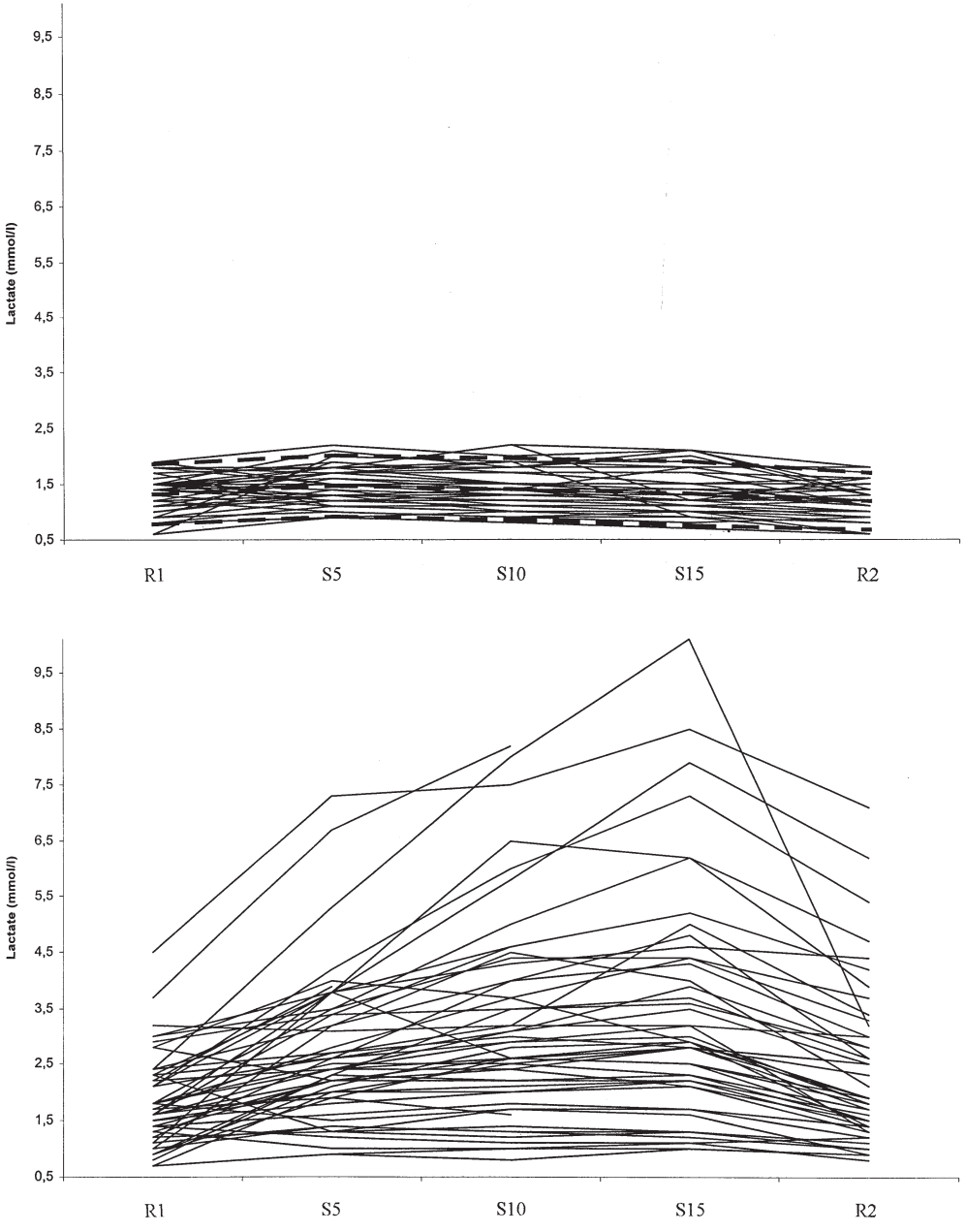

Fig. 1 Serum lactate levels at rest before the exercise (R1), 5, 10 and 15 minutes after starting the 15-minute workload at constantly 30 W on a bicycle ergometer (S5, S10, S15), and 15 minutes after finishing the workload (R2) in 47 healthy subjects (upper panel) and 54 patients with mitochondrial myopathy (lower panel). The mean ± 2 SD is additionally indicated in the control group (upper panel)

Results

Since all lactate levels were not significantly different between the genders, their data were combined. Lactate levels at R1, S5, S10, S15 and R2 were normally distributed and independent of age. Mean ±2SD of the serum lactate levels at R1, S5, S10, S15 and R2 was 2.0, 2.1, 2.1, 2.1 and 1.8 mmol/l respectively (Figure 1). Mean lactate levels at R1, S5, S10, S15 and R2 were significantly increased (all $p = 0.0001$) in patients with mitochondrial myopathy. The lactate-stress test was indicative of pathology in 37 patients (Figure 1). The sensitivity of the lactate stress test was thus 69% (Table 1). Resting lactate was normal in 35 patients (65%). In 19 patients (35%), venous lactate was increased already at rest (>2.0 mmol/l). Eighteen of these patients had also a lactate stress test indicative of pathology. In only one patient with an elevated pre-exercise lactate, the stress test remained normal. In 19 patients (54%) with normal pre-exercise lactate levels, the lactate stress test became indicative of pathology. Five patients stopped cycling prematurely because of exhaustion. In two patients, lactate further increased after exercise. Twenty-seven patients with a lactate-stress test indicative of pathology showed histochemically either generalised or checkerboard reduction of the cytochrome-c-oxidase activity (Table 1). Considering only patients with a myogenic, neurogenic or unspecifically abnormal EMG (n = 36), the sensitivity of the lactate-stress test increased to 75% (Table 1). Regarding only patients with ragged-red

Table 1 Demographics and EMG, lactate-stress test, muscle biopsy and mtDNA data in 54 patients with mitochondrial myopathy

Pat	Sex	Age	EMG	LST	RRF	ROE	AMI	mtDNA
AA	m	43	my	a	–	+	+	–
AG	m	46	my	a	+	+	+	
BM	m	48	no	a	+	+	+	G3438A
BE	f	70	no	no	+	+	+	
BM	f	15	my	no	+	+	+	–
CM	f	49	no	a	+	+	+	–
DE	m	70	n	a	+	+	+	
DA	m	69	no	a	+	+	+	C15904T
FM	m	18	my	a	–	+	–	
GO	m	51	my	a	+	+	+	
GM	f	74	no	no	–	–	–	–
GJ	m	47	n	a	+	+	+	
GJ	m	49	my	no	–	+	–	
HH	f	70	my	a	+	+	+	
HG	f	51	u	a	+	+	+	–
HH	f	42	my	a	+	+	+	
HW	m	68	u	a	+	+	+	
HS	f	72	my	a	–	+	–	
HP	f	19	my	no	–	–	+	G14771T
JE	m	50	my	a	+	+	+	
KI	f	49	no	a	+	+	+	T3197C
KR	m	51	no	a	+	+	–	
KZ	m	48	u	a	+	+	+	
KM	f	20	my	a	+	+	+	
KE	f	62	no	no	–	–	+	
KL	f	49	my	no	+	+	+	
KZ	f	46	my	a	–	–	–	
KG	f	70	nd	a	–	+	+	
LW	f	54	my	a	+	+	+	
LG	f	41	my	no	+	+	+	
LL	m	38	my	a	–	–	+	T4216C
LP	m	54	my	no	+	–	+	
LM	m	30	n	a	+	+	+	T4216C, G15812A
MS	f	42	no	a	+	+	+	
MR	m	45	my	a	–	+	–	A8344G
NI	f	26	my	no	+	+	+	3.5 kb Del
PJ	m	56	no	no	–	+	+	
PR	m	30	my	no	+	+	+	ND3
SS	f	29	no	a	+	+	+	
SE	f	56	no	a	+	+	+	
SE	f	32	n	a	+	+	+	
ST	m	62	my	a	+	+	+	–
SH	m	59	no	no	+	+	+	
SR	m	44	no	no	–	+	+	
ST	f	49	my	no	+	+	+	A8344G
SR	m	32	n	a	+	+	+	
SE	f	63	my	a	+	+	+	
SW	m	27	no	no	+	+	+	A8344G
SE	m	41	nd	no	+	+	+	T10084C
SG	f	53	n	a	+	+	+	4277, 8731, 14793
SA	m	55	n	a	+	–	+	–
SE	m	37	u	a	–	+	+	T12083G
TH	f	43	my	a	+	+	–	
WM	f	40	no	a	–	+	+	

fibres (n = 39), the sensitivity of the lactate-stress test was 72% (Table 1). Taking into account only patients with proven mtDNA mutation, the sensitivity of the test dropped to 54% (Table 1). The EMG was myogenic in 25 patients, neurogenic in seven, and unspecifically abnormal in four patients. In nine patients with normal EMG, the lactate-stress test was abnormal (Table 1).

Discussion

Lactate stress testing by means of a bicycle ergometer is one of the most powerful tools to assess the impaired oxidative metabolism in mitochondrial myopathies [1, 2, 3, 5, 6, 7, 8, 13, 15, 17, 18]. The test relies on the increase of serum lactate during moderate exercise in patients with mitochondrial myopathy. In a previous study on 30 patients, subjects had to cycle for 15 minutes at 30 W [18]. Regarding a result as pathologic only if serum lactate at rest and during exercise exceeded 1.5 and 2.0 mmol/l respectively, the sensitivity was 83%. In another study on 29 patients with mitochondrial myopathy, the workload was adjusted to a heart rate of 150 beats/minute [13]. Peak levels of >2 mmol/l were found in 19 patients. In a study on 20 patients with chronic progressive external ophthalmoplegia, tested with a similar protocol as ours, the sensitivity was 75% [3]. In a study on nine patients with mitochondrial myopathy, serum lactate increased during an increasing workload over 60 minutes in all of them [2]. In a study on four patients who had to bike with the maximal workload they could each individuallly tolerate for 20 minutes, serum lactate increased in all of them [17]. Recently we determined serum lactate levels in 26 patients with mitochondrial myopathy and 10 patients with non-mitochondrial myopathy during a 15 minute workload of 30 W on a bicycle ergometer [5]. Regarding a result as pathologic if > 2 values were increased, the sensitivity was 69% and the specificity 90%.

Contrary to previous results [3,17], serum lactate was normal at rest before the exercise in 65% of the patients tested for the present study. This might be due to the test procedure which told patients to take a rest for 30 minutes before starting the exercise and reduce physical activity within 3 days before the test. That 19 of the patients with a normal resting lactate had a pathologic increase of lactate during exercise, stresses the importance of measuring serum lactate not only at rest but also during slight exercise. An abnormal lactate stress test was not necessarily associated with a general or checkerboard reduction of oxidative enzyme staining. Normal oxidative enzyme staining might be due to the fact that organs other than the skeletal muscle are more severely affected by the im-

Pat: patient, LST: lactate-stress test, RRF: ragged-red fibres or subsarcolemmal accumulations of mitochondria, ROE: reduced oxidative enzyme staining, AMI: abnormal mitochondria, mtDNA: mtDNA mutations, m: male, f: female, my: myogenic, n: neurogenic, u: unspecifically abnormal, nd. not done, no: normal, a: abnormal, +: present, –: absent,

paired oxidative phosphorylation. To establish the correct diagnosis in these cases, biopsies of tissues other than the muscle may be helpful. In our patients the skeletal muscle was the organ most often affected. In only five of our patients there was no clinical evidence of skeletal muscle involvement. Two of these patients had an abnormal lactate-stress test and all of them had a pathologic muscle biopsy. The surprising finding that biochemical studies were normal in all eight tested patients might be due to the fact that there was only a checkerboard reduction of oxidative enzymes in these patients. The fact that not all patients with abnormal EMG, ragged-red fibres or proven mtDNA mutation also had an abnormal lactate-stress test supports the view that the diagnosis of mitochondrial myopathy requires the synopsis of clinical, serological, electrophysiological, bioptical, biochemical and genetic data.

Clinical implications of the presented results are that patients with suspected mitochondrial myopathy should undergo a lactate-stress test, even if resting lactate and electrophysiologic and bioptical investigations are normal. A normal lactate stress test, on the other hand, does not exclude mitochondrial myopathy. Particularly in patients who refuse biopsy, the lactate-stress test can be helpful to establish the diagnosis. In patients who are unable to cycle because of severe leg weakness, weight lifting with the upper limbs could be performed instead [3]. Particularly in patients with only mild symptoms and signs and normal electrophysiological findings, a pathological lactate-stress test may support the decision for or against biopsy. Limitations of the study are that biochemical investigations and mtDNA analysis were not carried out in all patients, that the reproducibility was not tested and that the workload was not adjusted to the individual workload.

In conclusion, the presented lactate-stress test proved to be helpful in diagnosing mitochondrial myopathy. The test is not more sensitive in patients with abnormal EMG, ragged-red fibres or proven mtDNA mutation. The test is simple, quick, cheap and reliable.

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