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Exercise responses in patients with an enzyme deficiency in the mitochondrial respiratory chain

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Exercise responses in patients with an enzyme deficiency in the mitochondrial respiratory chain. J.M. Bogaard, H.F.M. Busch, H.R. Scholte, H. Stam, A. Versprille.

ABSTRACT: Responses to exercise were obtained in six patients with a biochemically diagnosed enzyme deficiency at the level of NADH-CoQ reductase. The responses were compared with those of a control group, consisting of fourteen patients with inexplicable dyspnoea or muscle pain during exercise, for which no firm diagnosis could be established and of which the exercise responses were in the normal range. Metabolic, ventilatory and cardiological variables such as oxygen uptake ($\dot{V}O_2$), minute ventilation ($\dot{V}E$), respiratory exchange ratio (R), heart rate (HR) and difference in blood lactate or base-excess (BE) between rest and maximal workload were measured during cycle ergometry from samples obtained in the last minutes of four minute periods, in which the load increased stepwise by 30 W per four minutes. The threshold of lactate metabolism (T_{lact}) was assumed to be equal to the threshold determined both by the $\dot{V}O_2$ at which the $\dot{V}E$ *versus* $\dot{V}O_2$ response started to deviate from a straight line and the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) showed a minimum (T_{vent}). T_{vent} was estimated from the mean of these values, obtained by linear and parabolic regression analysis respectively. In the patient group, mean values for symptom limited maximal $\dot{V}O_2$ ($\dot{V}O_{2,max,sl}$; % of $\dot{V}O_{2,max,ref}$), T_{vent} (% of $\dot{V}O_{2,max,ref}$) and R at maximal workload were 43, 17 and 1.23 against 85, 47 and 1.06 for the same variables in the control group, respectively. The differences were highly significant ($p<0.001$; $p<0.005$ for mean R difference). Mean maximal HR and mean change in blood lactate or BE were not significantly different in the two groups. Considering the physiological mechanisms influencing the exercise responses, including the threshold of lactate metabolism, we hypothesize that the limited work performance in the patient group is given by a limitation of the oxidative capacity of the respiratory chain by the enzyme deficiency, giving an early energy supply by anaerobic glycolysis. Our investigation stresses the validity of exercise testing as an investigative strategy in neuromuscular disorders.

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During exercise tests of normals, when applying progressively increasing workloads, a threshold was found in various metabolic and ventilatory variables at about 50–70% of $\dot{V}O_{2,max}$.

The increase in ventilation became proportionally greater than the increase in oxygen uptake ($\dot{V}O_2$) and followed the increase in CO_2 production ($\dot{V}CO_2$) [1–4]. Consequently, the respiratory exchange ratio (R) and the ventilatory equivalent for oxygen ($\dot{V}E$) also started to increase. This threshold did not indicate the start of lactate production but can be considered as the $\dot{V}O_2$ at which the lactate efflux from exercising muscle started to exceed the rate of removal by oxidative processes [5, 6].

The lactate threshold (T_{lact}) was independent of ramp slope of increase in workload [7, 8]. Experimental evidence was found for the coincidence of T_{lact} and the threshold derived from the discontinuity in the ventilation response (T_{vent}) [2, 4, 8–11].

In studies of pulmonary and cardiovascular function the interpretation of T_{lact} (T_{vent}) is often based on the balance between oxygen requirement and oxygen availability [1, 3, 4, 11]. If, however, the T_{lact} is functionally defined as an imbalance between lactate influx and oxidative removal by the body, other mechanisms besides O_2 supply might influence its value.

This was emphasized by a number of investigators, who explained that a single mechanism in terms of muscular oxygen supply and requirement implies an oversimplification of all the mechanisms behind the threshold of anaerobic metabolism [5, 12–15].

Also, mitochondrial enzyme deficiencies may cause a rate limitation of mitochondrial oxidative phosphorylation and so decrease the threshold at which anaerobic glycolysis starts to contribute in the energy delivering metabolic processes.

We have performed exercise testing in six patients

Table 1. - Individual data and mean and ±1 SD for the group of patients for symptom limited $\dot{V}O_{2,max,sl}$ (% reference); ventilatory threshold (T_{vent}) in % of reference $\dot{V}O_{2,max}$; actual maximal heart rate and % of reference; maximal ventilation ($\dot{V}E$) in % of MVV_{30}, maximal R and change in lactate or base excess at maximal workload with respect to resting condition. Also the mean and 1 SD for the same variables from the control group are presented, together with the level of significance with respect to the patient data.

Patient	Sex	Age	Height m	Weight kg	$\dot{V}O_{2,max}$ mmol·min^{-1}	$\dot{V}O_{2,max}$ % ref	T_{vent} % $\dot{V}O_{2,max,ref}$	HR_{max} min^{-1}	HR_{max} % max,ref	$\dot{V}E_{max}$ l·min^{-1}	$\dot{V}E_{max}$ % MVV_{30}	R_{max}	ΔLact(BE) mmol·l^{-1}
CMZ	f	13	1.53	45	53.6	59	16	207	105	55	88	1.20	10
ADD	m	15	1.84	65	57.1	39	21	189	96	48	50	1.25	13
CB	f	15	1.58	48	33.5	35	0	155	78	37	60	1.14	6
JJ	m	22	1.78	64	48.2	35	12	180	93	64	58	1.39	6
HJB	f	32	1.61	62	48.7	49	30	168	91	46	58	1.16	4
FVV	m	27	1.71	56	45.1	40	24	144	76	44	68	1.26	8
mean		20.7	1.68	56.7	47.8	43	17		90	49	64	1.23	8
SD		7.7	0.12	8.5	8.0	9.4	10.5		11.1	9.4	13.2	0.09	3.3
Controls		n=14;	11M, 3F										
mean		32.8	1.74	69.3	105.4	85.3	47.0		95.0	78.0	90.0	1.06	8.0
SD (range)		13.2	0.07	11.7	27.2	15.1	11.1		7.8	24.1	9.8	0.09	2.7
p significance of differences						<0.001	<0.001		NS		<0.001	<0.005	NS

with symptoms of early fatigue during exercise, in which biochemically a mitochondrial enzyme deficiency could be detected. The exercise responses will be interpreted in terms of current hypotheses, explaining the threshold of lactate metabolism.

Patients and methods

Patients

The anthropometric data of the patients are shown in table 1. In all patients a mitochondrial enzyme deficiency at the level of NADH-CoQ reductase was detected. In patients JJ and CB a hereditary connection was present because both belonged to the same family.

Control group

Our control group consisted of fourteen patients, admitted to our laboratory for subjective complaints such as dyspnoea (n = 13) or muscle pain (n = 1) during exercise.

Clinical anamnesis and pulmonary, cardiovascular and neurological function revealed no abnormalities at rest. The exercise responses of ventilatory, metabolic and circulatory variables were in the normal range. Therefore these responses were used as a reference for the responses of our patients with mitochondrial enzyme deficiency. Mean values for the anthropometric data are given in table 1.

Biochemical analysis

Muscle biopsies were taken from the M. quadriceps under local analgesia. Small parts of the biopsy were frozen for histopathological routine investigation, and for the assay of carnitine and marker enzyme activities. The biggest part was immediately used for the isolation of mitochondria, which were used for the study of oxidative phophorylation with several substrates reducing the respiratory chain before NAD^+ (pyruvate + malate, glutamate + malate), at NAD^+ and CoQ (palmitoylcarnitine + malate), at CoQ (succinate + rotenone) and at cytochrome ç (ascorbate + N,N,N',N'-tetramethyl-p-Phenylenediamine). The rate of oxygen uptake by the isolated mitochondria was stimulated by ADP in the presence of glucose and hexokinase and was recorded at 25°C by polarographic oxygen tension measurement in the sample [16]. The energy production was determined by assay of the glucose-6-P formed. More details and the methods used are given elsewhere [16–18]. The muscle biopsies were processed according to accepted procedures for morphological and histochemical investigations.

Exercise protocol

Metabolic, ventilatory and circulatory variables were measured in the last minute of four minute

periods with constant workload, increasing stepwise per period.

The load increased 30 W every four minutes, which is comparable with the increase reported by other authors [3, 19, 20]. The test was stopped when the patient was exhausted or intimated a subjective feeling of excessive fatigue. Other reasons were risk factors *e.g.* systolic blood pressure (upper limit 33 kPa), which urged us in one patient (FVV) to terminate a test.

The ergometer-workload was largely independent of pedalling frequency (hyperbolic type, Lode, Groningen, The Netherlands) and ventilation was measured in the expiratory line with a Lilly type pneumotachometer, which was linear up to 750 $l \cdot min^{-1}$ (Jaeger, Würzburg, Western-Germany). Volume was obtained as integrated flow. Volume calibration was done with a 1 *l* syringe and correction factors were applied for calculation of volume at the appropriate conditions of temperature and humidity. The patients breathed via a low resistance two way valve (Jaeger, Würzburg) into a mixing box of three litres, from which mixed expired gases were sampled. Concentrations of CO_2 and O_2 were measured with an infrared-analyser (Jaeger, Würzburg) and a paramagnetic analyser (Taylor Servomex, OA 150) respectively. The oxygen analyser was adapted for our purpose by Mijnhardt, Odijk, The Netherlands. In four patients (CMZ, CB, JJ, HJB) lactate was determined at rest and at the symptom limited maximal $\dot{V}O_2$ ($\dot{V}O_{2,max,sl}$) from venous blood (brachial vein). In the other cases arterial blood was sampled, via a small catheter in the brachial artery, and blood gas variables were estimated with an automated blood gas analyser (ABL3, Radiometer, Denmark).

Our investigation was aimed at the detection of the lactate threshold *c.q.* ventilatory threshold (T_{vent}). We used the procedure, described by ORR *et al.* [21] and performed linear regression analysis on the apparently linear first part of the $\dot{V}E$ response and the second part of the curve. T_{vent} was derived from the intersection of both lines. Another marker for T_{vent} gives the minimum of the ($\dot{V}E/\dot{V}O_2$) *versus* $\dot{V}O_2$ response. This value was derived by parabolic regression analysis on the data around this minimum. For the linear regression analysis of the individual segments two to five data were used and for the parabolic regression analysis three to six data. For the final T_{vent} estimates the mean of those two estimates was taken.

Moreover, the relationship between $\dot{V}O_{2,max,sl}$ and lactate at maximal workload was compared with data, obtained both in our control group and in another study, in which a group of patients with heart disease, sedentary normals and well trained individuals was investigated [4].

Reference values for the variables, obtained during the tests, were obtained from JONES *et al.* [19]. The significance of differences was derived from a t-test for differences between means of groups of unequal size [22].

Results

Biochemical, histochemical and morphological analysis

The mitochondria of the patients showed a defect in the mitochondrial respiratory chain at the level of NADH-CoQ reductase. The substrates which reduced the respiratory chain before NAD^+ were oxidized (in the presence of ADP) at markedly reduced rates. With glutamate plus malate the oxygen uptake rates were 10–35 nanoatoms oxygen ($mg \cdot min^{-1}$) protein compared with 59–170 in seventeen controls. The oxidation rates of pyruvate plus malate were reduced likewise. The rates with succinate plus rotenone were in the range of 41–166, which was in the range of the controls, (72–196). The P/O ratios (moles glucose-6-P formed/atom oxygen consumed) were normal. The mitochondrial inner membranes were perfectly closed as indicated by the low activity of Mg^{2+}-ATPase, and the high stimulation of this activity by uncoupler. These activities were in the control range, as was the oxidation rate of U-^{14} C-palmitate in the presence of carnitine, which indicated an adequate amount of NAD^+ and coenzyme A in the mitochondrial matrix. No other deficiency was found in the mitochondrial oxidative phosphorylation (succinate-cytochrome ç reductase, cytochrome ç oxidase, adenine nucleotide translocator).

The number and distribution of the different fibre types was found to be normal. In patient CB the mitochondrial density appeared to be approximately doubled with respect to normal. In the other patients no deviations with respect to the normal range were present.

Exercise responses

In table 1 the variables, obtained from the exercise tests, at first admission, are summarized. For the patient group individual data are presented, together with the mean values and SD's of the whole group. For the control group only the mean values and SD's are presented.

$\dot{V}O_{2,max,sl}$ in the patient group was half the value of the control group, the T_{vent} was even lower. Both differences were highly significant ($p < 0.001$). T_{vent}, as measured from the $\dot{V}E/\dot{V}O_2$ response was on average nearly equal (mean difference 0.4% $\dot{V}O_{2,max,ref}$, SE 2.6%) to the same estimate, as derived from the $\dot{V}E$ response. Maximal heart rate (HR) was not significantly different between both groups as was also found for the increase in lactate concentration, of which the mean values were equal. The respiratory exchange ratio (R) at maximal workload appeared to be significantly larger ($p < 0.005$) in the patient group. The only variable which was significantly lower ($p < 0.001$) in the patient group was maximal minute ventilation ($\dot{V}E$) in % of maximal voluntary ventilation at a frequency of 30 per min (MVV_{30}).

Two patients (CB and FVV) stopped at a heart rate lower than 80% of predicted maximum. FVV reached

that heart rate at a systolic blood pressure which markedly exceeded 33 kPa (37 kPa). In these patients R_{max} (1.14 and 1.26) and increase in lactate concentration (6 and 8 mmol·l^{-1} respectively) indicated that their subjective feeling of exhaustion coincided with a marked lactate production and therefore muscle fatigue. From our data we considered $\dot{V}O_{2,max,sl}$ in the patient group as really symptom limited maximal

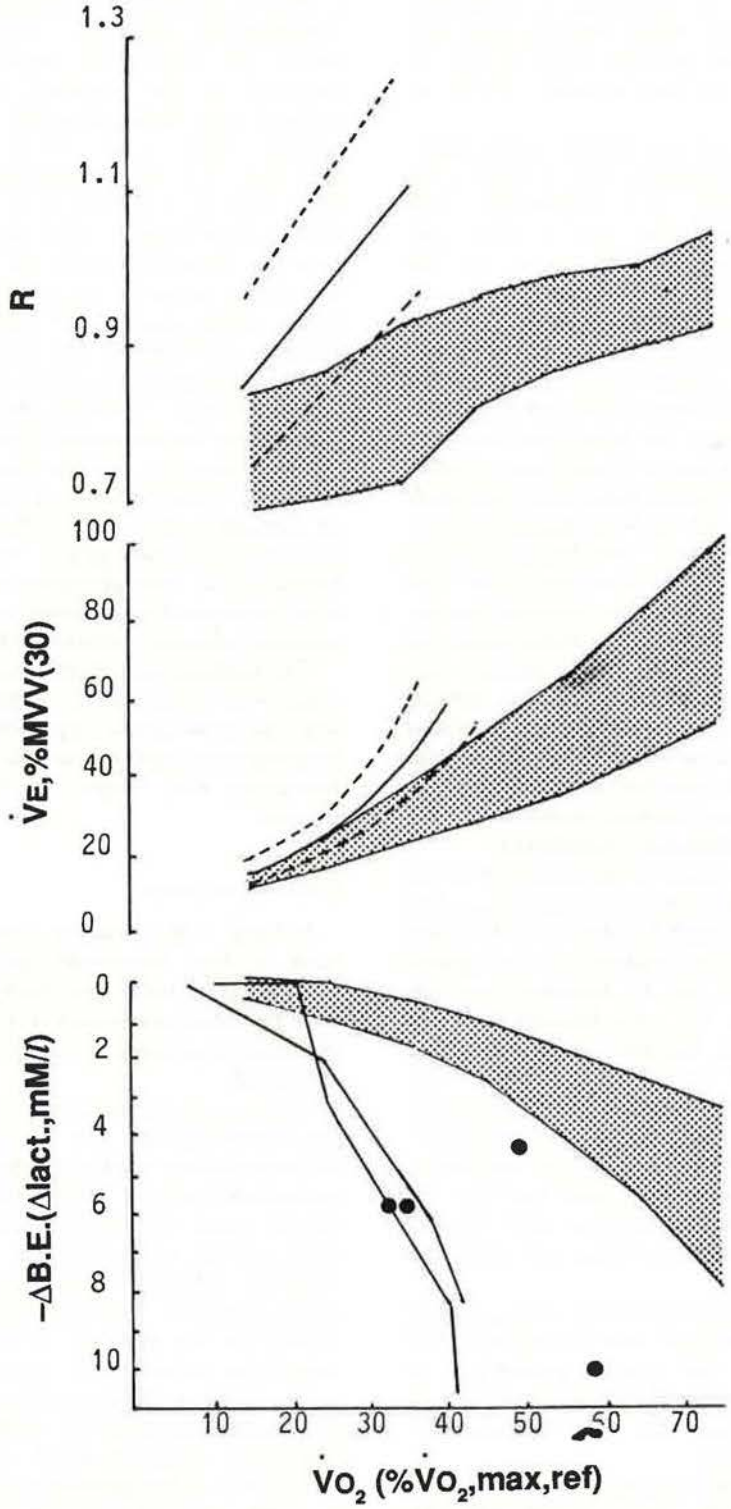

Fig. 1. Mean and ±1 SD range of the respiratory exchange ratio (R), ventilation ($\dot{V}_E$) in % of maximal voluntary ventilation at a frequency of 30 per min (MVV_{30}) and change in lactate concentration or base excess (BE) in the control group, as indicated by shaded areas. Also the mean ±1 SD range for R and $\dot{V}_E$ (%MVV_{30}) in the six patients with a mitochondrial myopathy is indicated together with the lactate (BE) change for two patients and this change at maximal workload in the remaining four.

oxygen uptake. The number of workloads applied varied from one (patient CB) to three in the patient group and from four to nine in the control group.

In figure 1 responses of R, $\dot{V}E$ in % of MVV_{30} and lactate or -base excess (-BE) are presented against $\dot{V}O_2$ in % of predicted maximum, both for our control group and for the patients. For the control group the shaded areas indicate the mean ± 1 SD range. For the patient group the same is indicated with respect to R and $\dot{V}E$ in % MVV_{30}. In two patients (ADD, FVV) the BE response is given as detected from blood gas analysis at each workload. In the remaining patients only the lactate at symptom limited maximal $\dot{V}O_2$ is indicated.

All patient responses differ markedly from those of the control group. The early occurring lactate threshold, as can be derived from the lower figure, causes the CO_2 flux to the lungs and so R to increase much more steeply than in the control group. Despite the smoothing by averaging the fourteen responses in the control group a threshold of lactate metabolism is shown by the R response. For the patients, no threshold could be detected in the mean R response which showed an early and abrupt increase at low workloads. Although the patients reach lower $\dot{V}E$ values in % of MVV_{30} at their $\dot{V}O_{2,max,sl}$ it is clearly shown that $\dot{V}E$ already increases more than for the control group at low workloads.

The early occurring lactate acidosis for the patients also becomes clear if the lactate increase at $\dot{V}O_{2,max,sl}$, together with that for the control group is presented along with data from WASSERMAN and coworkers [4], (fig. 2). Our patient responses compare with those from Wasserman's group with heart disease. The control data coincide roughly with Wasserman's data for his group of sedentary normals.

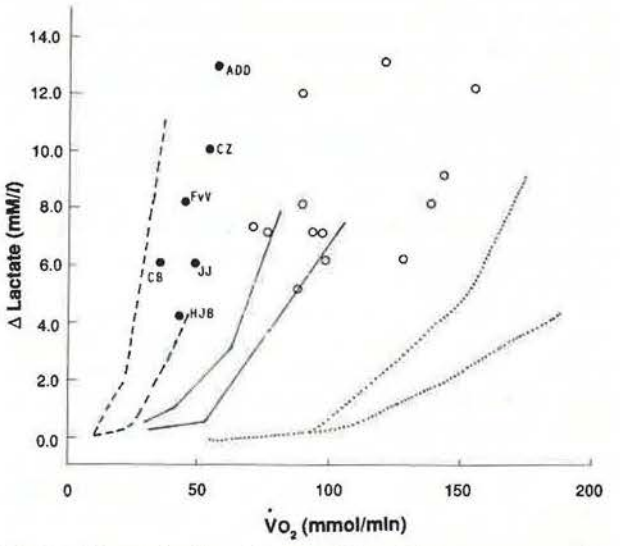

Fig. 2. Change in blood lactate (BE) with respect to resting condition, at $\dot{V}O_{2,max}$. Patients with mitochondrial myopathy (●); control group (○). Ranges for patients with heart disease (- - -), sedentary normals (——) and well trained individuals (.....) from WASSERMAN *et al.* [4].

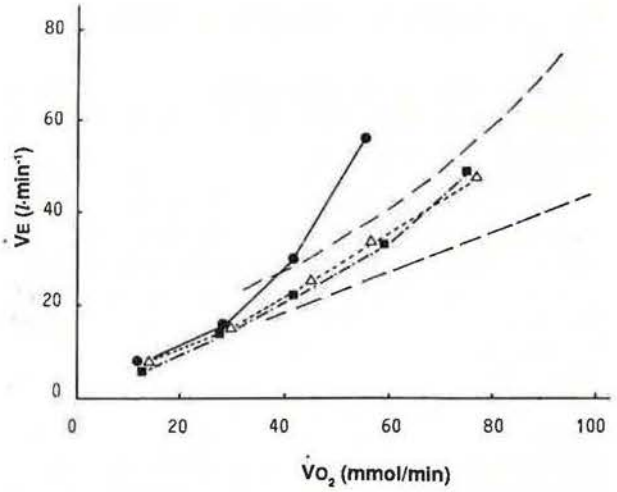

Fig. 3. Ventilation response of patient CZ before (——) and at two successive measurements with three months intervals after treatment with riboflavin (-.-.-., ----, respectively). Normal range of responses from JONES *et al.* [19].

Although our patient data are only derived from measurements at first admission, in some cases exercise responses were used as a criterion for the evaluation of therapy.

In one patient (CZ) the condition drastically improved after treatment with riboflavin. The improvement could be concluded both from the clinical picture and from the change in the exercise responses. Her case has been described in detail elsewhere [23].

In figure 3 the ventilation responses are shown, together with the range of normal responses [19], before and at two successive measurements after treatment. In the three successive measurements $\dot{V}O_{2,max,sl}$ in % of reference and R at maximal workload were 54, 71 and 76 and 1.20, 1.07 and 1.05, respectively [23]. The figure shows the shift of the threshold of lactate acidosis to larger $\dot{V}O_2$ values after treatment.

Discussion

Besides analysis of maximum values for ventilatory, metabolic and cardiovascular variables during exercise testing, the level of $\dot{V}O_2$, at which lactate efflux from exercising muscle starts to exceed the oxidative removal of the body, is also of diagnostic importance. In clinical function testing this level is often associated with the start of anaerobic metabolism, supplementing energy to the oxidative processes, from which the term 'anaerobic threshold' is derived.

We determined exercise responses in six patients with a muscle mitochondrial deficiency limited work performance. The differences between these responses and those of a control group will be discussed both with respect to maximum values, attained for ventilatory, metabolic and cardiovascular variables, and to the level of $\dot{V}O_2$ at which blood lactate started to increase markedly.

The exercise protocol; estimation of exercise variables

For the analysis of discontinuities in the exercise responses, associated with the threshold of lactate increase (T_{lact}) steady state approaches, as well as ramp slopes up to 50 W per min, are equally valid, if variables are plotted against $\dot{V}O_2$ [7]. Although higher ramp slopes shorten the exercise test and so are more 'patient friendly' we preferred a steady state approach in order to be able to compare actual values with reference data [19, 20]. WASSERMAN *et al.* [3] argued that a steady state is reached within four minutes, the time duration of each step in our protocol, for not too heavy loads. This is in accordance with more recent studies on $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}O_2$ kinetics [11]. The Scandinavian protocols, as mentioned by JONES *et al.* [19] use workloads of 5–8 minutes duration. At the heavier loads above T_{vent} a true steady state is not fully reached because of the on-going lactate accumulation [11].

At the onset of lactic acidosis the increased CO_2 flux appears to parallel the increase in ventilation, causing isocapnic buffering [2–4]. From this mechanism stems the estimation of T_{lact} by T_{vent}. Although deviations between lactate and ventilatory thresholds are reported, for instance after endurance training [24], the approximation of the T_{lact} by T_{vent} is experimentally well established [2, 4, 8–11]. The physiological mechanisms, however, relating the $\dot{V}E$ response to the metabolic acidosis are not yet clear and most probably include metabolic, neurogenic and humoral influences [2, 25]. WASSERMAN *et al.* [3] and ORR *et al.* [21] stated that the most sensitive index of the anaerobic threshold, as assessed by gas exchange, is the disproportionate increase in $\dot{V}E$ for an increment in $\dot{V}O_2$. We applied the approach, suggested by ORR *et al.* and performed linear regression analysis on the curve parts before and after T_{vent}. Moreover, a parabolic regression analysis was applied to the ($\dot{V}E/\dot{V}O_2$) *versus* $\dot{V}O_2$ response, in order to find its minimum. As a final T_{vent} we used the mean of those estimates in order to compensate, as accurately as possible, for random fluctuations that influence T_{vent} estimations by hand.

Because, certainly in the children, not in all cases an arterial line was inserted, we used either changes in venous lactate or base-excess to determine blood lactate increase. These changes are, however, comparable [3, 26] as are the lactate concentrations of arterial and venous blood from non-exercising muscle [27].

Comparison of patient-responses with those of the control group

Our control group consisted of patients in whom extensive functional investigations in resting conditions and exercise responses, revealed no functional abnormalities. Although, in the strict sense, they were not normal volunteers, we used their responses as reference because they underwent exactly the same exercise protocol. Maximal $\dot{V}O_2$, maximal heart rate, maximal $\dot{V}E$ in % of maximum voluntary ventilation at a rate of 30 per min and lactate increase with respect to resting values indicate (table 1) that on average the control group attained maximal workload. The mean response of R and the mean $\dot{V}E$ at 85% $\dot{V}O_{2,max,ref}$ were not appreciably different from reference values described recently for fifty healthy men who underwent a comparable protocol [20]. Most probably $\dot{V}O_{2,max,sl}$ was limited either by physical condition or by ending the test before complete exhaustion, which is the usual regime in our laboratory. The similar lactate increase at $\dot{V}O_{2,max}$ in the control group and patient group indicates a corresponding subjective work performance.

Because in the patients with mitochondrial myopathy the duration of the test was shorter, the rate of the lactate accumulation was larger, resulting in the significantly larger R values at maximal exercise. The lower $\dot{V}O_{2,max}$ in the patient group is associated with a lowered T_{vent}, indicating an early occurrence of lactate acidosis. Although the rate of increase in $\dot{V}E$ is larger in the patient group than that in the control group (fig. 1), maximal $\dot{V}E$ in % of MVV_{30} was significantly lower. We cannot explain this difference. The maximal heart rate in the patient group was no different from the control group.

Interpretation of the lactate threshold

In clinical exercise testing emphasis was often given to the interpretation of the lactate or ventilation threshold as the threshold of anaerobic metabolism. The physiological concept, explaining the existence of an anaerobic threshold, may be defined as an 'oxygen availability concept' [1, 4, 8, 26]. According to this concept, an imbalance between the O_2 supply and O_2 requirement in exercising muscle, where oxygen requirement is greater than oxygen supply, will result in a net increase in anaerobic oxidation in the cytosol of the cell with pyruvate conversion to lactate. Evidence for this hypothesis mostly comes from clinical physiological investigations in patients in whom the oxygen transport capacity is limited. T_{vent} was found to be lowered in cardiac patients [4, 28, 29] and the decrease was related to the degree of circulatory impairment [29]. Anaemia [4, 30, 31] and lowered inspiratory oxygen concentrations [32] also caused a lowered T_{vent}.

Lactate production and removal processes in the body, such as oxidation in muscles, heart, liver and kidneys, and gluconeogenesis, however, determine the disproportionate rise in muscle and blood lactate at higher exercise levels. So the lactate threshold has to be considered with respect to energetics in the total body. This implies a number of other factors which influence it [5, 12, 14, 15] *e.g.* the composition of the skeletal muscles with respect to fibre types (slow- and fast-twitch red fibres, type I and IIa, and fast-twitch white fibres, type IIb) and the density and biochemical composition of skeletal muscle mitochondria.

A recent investigation [13] showed that lactate

accumulation occurred in canine red gracilis muscle, performing work by external twitching, at local oxygen tension (Po_2) above the critical mitochondrial O_2 tension. It was concluded that, in this specific situation, lactate accumulation was not simply due to an O_2 limit on mitochondrial ATP production.

Because our patients differed from normals almost exclusively due to a mitchondrial enzyme deficiency, this aspect will be discussed in more detail.

Enzyme activities and exercise tolerance

Studies, on changes in endurance capacity under influence of various types of training activities, indicate a relationship between composition, activity and density of enzymes and physical performance [5, 12, 14]. HOLLOSZY [5] mentions two-fold increases in enzyme activities both for animal experiments (rats) and human studies on endurance. Such a rise was also confirmed by adaptive increase in mitochondrial respiratory enzyme levels in humans. Although after endurance training $\dot{V}o_2$ was unchanged as a function of workload, lactate accumulation at each $\dot{V}o_2$ level decreased, shifting the lactate threshold to a higher $\dot{V}o_2$. DAVIES *et al.* [10] found the same after endurance training of middle aged man but mentioned also an increased capillary proliferation of skeletal muscle and so a more efficient blood supply to the tissue as one of the possible mechanisms.

In our patients we found five had a normal mitochondrial density of skeletal muscle. In only one patient (CB) was the density doubled, so a diminished mitochondrial density can certainly be excluded as a mechanism for the limited performance.

An analysis of the enzyme activities revealed a marked deficiency only at the level of NADH-CoQ reductase in the respiratory chain. In two patients (ADD, FVV) an abnormally high systolic blood pressure was found at maximal exercise, 250 and 280 mmHg respectively, which caused us to stop the test in patient FVV.

We found no evidence for an impaired O_2 supply of working skeletal muscle or for an impaired distribution of blood flow to organs (liver, kidneys, heart) involved in oxidative removal of produced lactate. A hypothesis for the limited work performance in our patients is given by a limitation of the oxidative capacity of the respiratory chain by the enzyme deficiency, causing an early energy supply by anaerobic glycolysis. In patient CZ the substantial improvement of the physical condition by a large dose of riboflavin may well be due to an increased activity of the flavine mononucleotide-containing NADH-CoQ reductase [23]. The changes in the exercise responses remained highly significant even after correction for the growth of the child between the tests [33].

Conclusion

In addition to investigations, stressing the relationship between mitochondrial activities and endurance [5, 14] we have found a severely limited exercise performance in patients with a mitochondrial enzyme deficiency, in which the exercise response was even comparable with that of patients with severe cardiovascular impairment. In three of our patients (CMZ, CB, HB) the exercise responses led to a biochemical analysis of a muscle biopsy from which a mitochondrial myopathy was diagnosed. Our investigation strengthens the importance of the recognition of metabolic disturbances by means of clinical exercise testing and stresses, as previously mentioned [6], the validity of exercise tests as an investigative strategy in neuromuscular disorders.

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RÉSUMÉ: La réponse à l'exercice a été obtenue chez six malades atteints d'une carence enzymatique diagnostiquée biochimiquement au niveau de la réductase NADH-CoQ. Les réponses ont été comparées avec celles d'un groupe de contrôle, comprenant quatorze patients ayant une dyspnée d'effort unexplicable ou des douleurs musculaires durant l'exercice pour lesquelles on n'a pu établir aucun diagnostic sûr et dont les réponses à l'exercice se trouvaient dans l'éventail normal. Les variables métaboliques, ventilatoires et cardiologiques tels l'absorption d'oxygène ($\dot{V}O_2$), la ventilation minute ($\dot{V}E$), le taux d'échange respiratoire (R), la fréquence cardiaque (HR) et la différence de lactate du sang ou d'excès-base (BE) entre le repos et l'effort maximum ont été mesureés au cours de l'ergométrie cyclique à partir d'échantillons obtenus durant la dernière minute de périodes de quatre minutes chacune et durant lesquelles l'effort a été accru par paliers à raison de 30 W toutes les quatre minutes. Le seuil du métabolisme des lactates (T_{lact}) a été supposé être égal à celui déterminé à la fois par la $\dot{V}O_2$ (niveau où la réponse $\dot{V}E$ *versus* $\dot{V}O_2$ a commencé alors à dévier de sa ligne droite et où l'équivalent ventilatoire pour l'oxygène ($\dot{V}E/\dot{V}O_2$) a exhibé une valeur minimum (T_{vent})). T_{vent} a été estimé à partir de la moyenne de ces valeurs, obtenues par des analyses de régression respectivement linéaire et parabolique. Pour le groupe de patients, les valeurs moyennes pour la $\dot{V}O_2$ maximum à symptômes limités ($\dot{V}O_{2,max,sl}$), % $\dot{V}O_{2,max,ref}$), T_{vent} (% de $\dot{V}O_{2,max,ref}$) et pour R à l'effort maximum ont été de 43, 17 et 1,23 contre 85, 47 et 1,06 respectivement pour les mêmes variables dans le groupe de contrôle. Les différences étaient très significatives ($p<0,001$; $p<0,005$ pour la différence moyenne R). La moyenne maximum HR et le changement moyen de lactate du sang ou de BE ne différaient pas de façon significative entre les deux groupes. Etant donné les mécanismes physiologiques qui influent sur la réponse à l'exercice y compris le seuil du métabolisme de lactates, nous émettons l'hypothèse que le rendement limité de travail dans le groupe de patients s'explique par une limitation de la capacité oxyditive du système respiratoire due à la carence enzymatique, ce qui donne un approvisionnement énergétique précoce par glycolyse anaérobique. Notre enquête souligne la valeur des tests d'exercice en tant que stratégie investigatrice dans le cas des maladies neuromusculaires.