

Effects of Graded Exercise on Leg Exchange of Energy Substrates in Malignant Hyperthermia Susceptible Subjects

Hans Rutberg, M.D., Ph.D.,* Erik Håkanson, M.D., Ph.D.,* George M. Hall, M.B., B.S., Ph.D., F.F.A.R.C.S.,†
Lennart Jorfeldt, M.D., Ph.D.‡

It has been speculated that, in malignant hyperthermia-susceptible (MHS) individuals, an abnormality of sympathetic activity is seen during stressful situations, such as exercise. The authors investigated whether muscle metabolism in eight MHS subjects, at rest and during moderate and heavy short-term exercise, is different than that in normals. Leg exchange of energy substrates (glucose, lactate, and glycerol) was quantified by measuring leg blood flow and arterial-venous concentration differences. Muscle biopsies were also performed, and ATP, glycogen, and lactate were analyzed. Catecholamines and oxygen uptake were also measured. The study was performed at rest with subjects in the supine position and during two periods (40% and 80% of the subjects maximal oxygen uptake, respectively) on a bicycle ergometer. The principal finding of the study was that there was no major difference in oxygen uptake or leg exchange of glucose, lactate, and glycerol between MHS-subjects and previously standard normals during different grades of exercise. Furthermore, muscle metabolites and plasma catecholamines did not differ between the groups. This study indicates a normal sympathetic activity and muscle metabolism in MHS subjects during rest, as well as during moderate and severe exercise. The authors' results do not support the opinion that persons with positive *in vitro* tests for MH should restrict their physical activity. (Key words: Hyperthermia: exercise test; malignant. Metabolism: free fatty acids; glucose; glycogen; lactate; oxygen consumption. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

MALIGNANT HYPERTHERMIA (MH) in humans is a rare syndrome induced by a variety of drugs, including volatile anesthetics and depolarizing muscle relaxants, *i.e.*, succinylcholine. The syndrome is characterized by a hypermetabolic reaction in skeletal muscle.^{1,2}

The syndrome also occurs in certain breeds of pigs where various forms of stress, such as exercise and heat, can induce the MH reaction.³ Several authors have speculated that severe exercise or emotional stress may

induce the MH-syndrome in humans.⁴⁻⁶ In normal humans, severe physical exercise induces a eight-fold increase in systemic oxygen uptake and an even more marked rise in leg oxygen uptake.^{7,8} Furthermore, since mechanical efficiency during exercise is only about 25%, a great part of the work performed results in heat production. Exercise also induces a marked increase in sympathetic activity demonstrated by high catecholamine levels.⁹

It has been proposed that there is an abnormality of sympathetic activity in malignant hyperthermia-susceptible (MHS) individuals during stressful situations, such as exercise.^{10,11} This was suggested by slightly higher concentrations of plasma-free fatty acids (FFA) and blood lactate during exercise, as compared to controls. Furthermore, preliminary data from muscle biopsies in unstressed anesthetized MHS-subjects showed a higher glycolytic activity, possibly indicating a higher level of sympathetic activity.¹²

The present study was designed to investigate whether muscle metabolism in MHS subjects, at rest and during moderate and heavy short-term exercise, is different than that in normal subjects. Leg uptake and release of energy substrates was quantified by measuring leg blood flow and arterial-venous concentration differences of energy substrates. Muscle biopsies were also performed during the three conditions of the study, and arterial catecholamines were measured as indicators of sympathetic activity.

Material and Methods

The investigation was performed in Linköping and approved by the Local Ethics Committee. All subjects were informed of the nature, purpose, and possible risks of the study before they consented to participate.

Eight MHS subjects, seven male and one female, were investigated. They were all found to be susceptible to malignant hyperthermia by *in vitro* tests with exposure of muscle biopsies to halothane and to caffeine.¹³ Three subjects had sustained a clinical episode of MH. The tests were performed at the MH investigation unit, University of Lund. As a control group, eight healthy male military conscripts were studied. Data for the two groups are presented in table I. The control group has been presented previously.⁸

* Associate Professor of Anaesthesia. Department of Anaesthesia. University Hospital, S-581 85 Linköping, Sweden.

† Reader in Anaesthesia, Royal Postgraduate Medical School, Hammersmith Hospital.

‡ Professor of Clinical Physiology, Department of Clinical Physiology, University Hospital, Linköping, Sweden.

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Address reprint requests to Dr. Rutberg: Department of Anaesthesia, University Hospital, S-581 85 Linköping, Sweden.

TABLE 1. Age, Height, Weight, Maximal Oxygen Uptake ($\dot{V}O_2$ max), Workload at 40% ($W_{40\%}$) and 80% ($W_{80\%}$) of $\dot{V}O_2$ max and Heart Rate

No	Sex	Age (Yr)	Height (cm)	Weight (kg)	V'O ₂ max (l/min)	Workload (Watts)		Heart rate		
						W _{40%}	W _{80%}	At Rest	W _{40%}	W _{80%}
MHS = subjects										
1	♂	17	185	63	3.7	100	210	60	142	188
2	♀	47	168	75	2.3	60	110	78	158	173
3	♂	47	173	81	2.9	60	130	56	118	167
4	♂	40	169	72	3.2	70	150	52	154	158
5	♂	40	167	72	2.3	50	130	70	118	164
6	♂	46	180	76	2.8	60	160	76	126	164
7	♂	28	180	70	3.0	70	160	58	117	175
8	♂	31	181	85	3.4	90	190	68	128	160
Mean ± SEM		37 ± 4*	175 ± 3	74.3 ± 2.4	3.0 ± 0.2	70 ± 6	155 ± 12	65 ± 3	136 ± 6*	169 ± 3
Control = subjects										
1	♂	23	186	72	4.2	110	230	55	115	155
2	♂	21	185	85	3.0	70	160	74	107	152
3	♂	21	181	68	2.8	70	150	66	90	126
4	♂	20	182	75	3.2	80	170	62	110	168
5	♂	21	174	62	3.2	80	180	60	120	170
6	♂	21	175	73	2.5	60	130	64	100	134
7	♂	21	181	82	3.1	70	170	74	110	166
8	♂	20	173	65	3.0	70	160	70	118	180
Mean ± SEM		21 ± 1	180 ± 2	72.7 ± 2.8	3.1 ± 0.2	76 ± 5	169 ± 10	66 ± 2	109 ± 4	156 ± 7

* $P < 0.01$ between MHS and control.

PROCEDURE

All studies were begun between 9 A.M. and noon, either after an overnight fast or 6 h after a light breakfast. No smoking was permitted during the previous 12 h, and no alcohol was consumed during the previous 48 h.

Catheters with an external diameter of 1.2 mm were inserted percutaneously into both femoral veins and one femoral artery under local anesthesia (bupivacaine 0.5%). The tips of the catheters were located at the level of the inguinal ligament. Patency of the catheters was maintained by intermittent flushing with physiological saline. The study was performed with the subjects resting in the supine position 10–15 min after catheter insertion, and during two periods of exercise of 15 min duration each, separated by 20 min rest in the supine position. The exercise was performed while sitting on an electrically braked bicycle ergometer. The workloads chosen corresponded to approximately 40% and 80% of the subjects' maximal oxygen uptake. This had been calculated according to Astrand and Ryhming¹⁴ from a submaximal exercise test performed earlier.

Leg blood flow was determined using a dye dilution technique based on constant infusion of indocyanine green (Cardio-green®) into the femoral artery.¹⁵ All blood samples for assay of metabolites were taken in duplicate from the artery and simultaneously from the ipsilateral femoral vein. Hormone analyses were performed on arterial blood. Muscle biopsies were taken

from the lateral part of quadriceps femoris with a Bergström-Stille needle¹⁶ and immediately frozen in liquid nitrogen. The patient's ECG was monitored continuously. Systemic oxygen uptake was measured at rest and during exercise.

ANALYSES

Blood samples for analyses of oxygen saturation and hemoglobin concentration were drawn into siliconized glass syringes. The oxygen content of the samples was calculated after determination of the oxygen saturation of the hemoglobin (OSM2, Radiometer, Copenhagen, Denmark), the hemoglobin concentration using the cyanmethemoglobin technique (International Committee for standardization in Haematology, 1967), and P_{O_2} . Hematocrit was determined using a microcapillary hematocrit centrifuge and corrected for trapped plasma.¹⁷

All blood samples for assay of metabolites were immediately precipitated with ice-cold perchloric acid. After centrifugation, the protein-free extract was frozen (-80°C) pending analysis. The analyses were performed by microfluorimetry: D-glucose by modification for fluorimetry of the hexokinase method described by Schmidt¹⁸ and Barthelma and Czok,¹⁹ and lactate and glycerol as described previously.²⁰ Free fatty acids (FFA) were analysed according to Ho.²¹ The coefficients of variation for the individual determinations were as follows: glucose 1%, lactate 1.6%, glycerol 2.8%, and FFA 7%.

TABLE 2. Leg Blood Flow, Leg Oxygen Uptake, Systemic Oxygen Uptake, Carbon Dioxide Production, and Mechanical Efficiency at Rest and During Exercise ($W_{40\%}$ and $W_{80\%}$) (Mean \pm SEM)

Variables	Rest		Exercise $W_{40\%}$		Exercise $W_{80\%}$	
	MHS	Control	MHS	Control	MHS	Control
Leg blood flow (l/min)	0.4 ± 0.05	0.5 ± 0.05	2.5 ± 0.30	2.6 ± 0.16	4.1 ± 0.38	4.5 ± 0.40
Leg oxygen uptake (mmol/min)	1.0 ± 0.13	0.9 ± 0.09	16.8 ± 2.20	16.0 ± 0.93	30.9 ± 3.56	32.3 ± 3.38
Systemic oxygen uptake (ml/min)	290.3 ± 9.9	267.3 ± 6.6	1184.4 ± 47.8	1143.3 ± 60.1	2069.1 ± 126.4	2127.1 ± 132.3
Carbon dioxide production (ml/min)	$245.7 \pm 12.3^*$	207.1 ± 6.8	1074.8 ± 61.1	972.5 ± 47.7	2065.3 ± 133.3	1962.9 ± 108.6
Leg mechanical efficiency (%)	—	—	28.1 ± 1.8	33.3 ± 2.0	32.8 ± 2.5	36.6 ± 2.3
Systemic mechanical efficiency (%)	—	—	$21.2 \pm 1.2^*$	25.6 ± 1.0	25.7 ± 1.1	26.8 ± 1.1

* $P < 0.05$ between MHS and control.

The muscle biopsies were analyzed for ATP, creatine phosphate, creatine, glucose-6-phosphate, glycogen, lactate, and citrate.²² Plasma catecholamines were determined by HPLC.²³

Oxygen consumption was measured for 10 min at rest and for 3 min at the end of both exercise periods with the Douglas bag procedure. The expired air was analyzed on a mass spectrometer.

Mechanical efficiency (ME, %) was calculated from the formula: $ME = \text{mechanical work performed} \times 100 \div 60 \div 20500 \times (\text{total} - \text{basal oxygen uptake})$ where 20500 (J/l) is the calorific coefficient for oxygen. Mechanical work is expressed in W and oxygen uptake in l/min.

For statistical analysis, one-way analysis of variance was used. Tests were made at the 1% and 5% level. Data are presented as mean \pm SEM.

Results

The MHS-subjects were significantly older than the controls ($P < 0.01$). Height and weight did not differ between the groups.

HEMODYNAMICS AND OXYGEN UPTAKE

There was no significant difference between the groups with respect to heart rate at rest. On the moderate workload, the MHS group demonstrated a higher heart rate ($P < 0.01$). There were no differences between the two groups for leg blood flow, leg oxygen uptake, or systemic oxygen uptake. Carbon dioxide production was significantly higher in the MHS subjects at rest, but, during exercise, no difference was seen between the groups. See tables 1 and 2 for results.

ARTERIAL CONCENTRATIONS OF METABOLITES AND HORMONES

Blood glucose at rest and during the moderate workload was approximately 12% higher in the MHS subjects ($P < 0.05$). Both groups demonstrated a marked increase in the lactate concentration, but no differences were observed between them. Glycerol concentrations were significantly higher in the MHS group at rest and during exercise, whereas FFA concentrations did not differ at rest and during moderate work. During heavy

TABLE 3. Arterial Concentrations of Glucose, Lactate, Glycerol, FFA, Epinephrine, and Norepinephrine at Rest and During Graded Exercise ($W_{40\%}$ and $W_{80\%}$) (Mean \pm SEM)

Variables	Rest		Exercise $W_{40\%}$		Exercise $W_{80\%}$	
	MHS	Control	MHS	Control	MHS	Control
Glucose (mmol/l)	$5.1 \pm 0.2^*$	4.5 ± 0.2	$5.2 \pm 0.1^*$	4.7 ± 0.1	5.1 ± 0.1	5.0 ± 0.2
Lactate (mmol/l)	0.50 ± 0.07	0.41 ± 0.03	1.31 ± 0.39	0.94 ± 0.15	4.32 ± 0.56	3.50 ± 0.68
Glycerol (mmol/l)	$0.07 \pm 0.008^*$	0.05 ± 0.004	$0.15 \pm 0.01^\dagger$	0.10 ± 0.01	$0.13 \pm 0.01^*$	0.10 ± 0.01
FFA (mmol/l)	0.53 ± 0.04	0.48 ± 0.05	0.52 ± 0.02	0.53 ± 0.05	$0.31 \pm 0.02^*$	0.43 ± 0.04
Epinephrine (nmol/l)	0.36 ± 0.1	0.53 ± 0.07	0.69 ± 0.14	1.02 ± 0.09	2.49 ± 1.03	2.3 ± 0.39
Norepinephrine (nmol/l)	1.6 ± 0.2	1.4 ± 0.1	5.7 ± 0.9	4.3 ± 0.6	16.7 ± 2.5	15.0 ± 3.1

* $P < 0.05$ between MHS and control.† $P < 0.01$ between MHS and control.

TABLE 4. Leg Uptake or Release (-) of Glucose, Lactate and Glycerol at Rest and During Graded Exercise (W_{40%} and W_{80%}) (Mean \pm SEM mmol/min)

Variables	Rest		Exercise W _{40%}		Exercise W _{80%}	
	MHS	Control	MHS	Control	MHS	Control
Glucose	0.06 \pm 0.02	-0.08 \pm 0.09	0.01 \pm 0.07	0.02 \pm 0.10	0.60 \pm 0.11	0.65 \pm 0.31
Lactate	-0.05 \pm 0.01	-0.02 \pm 0.01	-0.32 \pm 0.11	-0.22 \pm 0.12	-1.76 \pm 0.19	-1.75 \pm 0.57
Glycerol	-0.02 \pm 0.01	-0.02 \pm 0.04	-0.05 \pm 0.03	-0.002 \pm 0.01	0.01 \pm 0.02	-0.01 \pm 0.02

exercise, significantly lower FFA values were seen in the MHS group. Both epinephrine and norepinephrine concentrations increased markedly during exercise in both groups, without significant differences between them (table 3).

LEG EXCHANGE OF METABOLITES

No differences between the MHS subjects and controls were observed for uptake or release in any of the measured energy metabolites (table 4).

MUSCLE METABOLITES

No significant differences were seen in muscle metabolites between the two groups (table 5).

MECHANICAL EFFICIENCY

Leg mechanical efficiency did not differ between the groups, whereas systemic mechanical efficiency was lower in the MHS group on the moderate workload ($P < 0.05$) (table 2).

Discussion

Physical exercise is associated with increased sympathetic activity.^{9,24} In the current study by choosing workloads that were set to 40% and 80% of the subject's estimated oxygen uptake both aerobic and anaerobic metabolism were studied.

The principal finding of the present study was that no major difference in the metabolic response (oxygen up-

take, leg exchange of substrates, muscle metabolites, and catecholamines) to different grades of exercise between MHS individuals and controls was observed.

Although the general pattern of reaction to exercise was similar, there were minor differences between the groups. These differences were, however, small and inconsistent, and could partly be explained by the fact that the groups were not fully matched for physical fitness, age, and sex. In spite of these slight differences between the control group and the study group, we chose, for ethical reasons, to use this previously described control group, since the investigation was extensive and invasive.

The circulatory and metabolic response to exercise is influenced by the work load, both in absolute and relative terms, and might also be influenced by anthropometric variables. With reference to absolute and relative workloads, the patient group and the control group demonstrated no major differences, although the higher heart rate in the patient group during exercise (significant at W 40%) might indicate a somewhat higher relative work load.

Ayling *et al.*²⁵ reported a more marked increase in circulating norepinephrine in MHS subjects when exposed to cold compared to a control group. However, as the authors suggest, it might be shivering rather than MH that explains the difference between the two groups. An increase in sympathetic activity is also seen during MH-episodes, both in pigs and humans.^{5,26,27} Whether this is a primary phenomenon or a consequence of the metabolic derangements in MH-crisis is

TABLE 5. Concentrations of Energy-rich Muscle Metabolites at Rest and During Graded Exercise (W_{40%} and W_{80%}) (Mean \pm SEM mmol/kg Dry Muscle)

Variables	Rest		Exercise W _{40%}		Exercise W _{80%}	
	MHS	Control	MHS	Control	MHS	Control
Glycogen	325 \pm 44	400 \pm 52	258 \pm 24	330 \pm 43	160 \pm 46	286 \pm 55
Glucose-6-phosphate	1.7 \pm 0.2	1.4 \pm 0.3	2.8 \pm 0.2	2.4 \pm 0.5	4.2 \pm 0.4	3.5 \pm 0.4
Lactate	5.0 \pm 2.1	4.6 \pm 1.1	4.2 \pm 0.8	6.9 \pm 1.6	35.9 \pm 7.8	26.3 \pm 7.4
Citrate	0.28 \pm 0.05	0.19 \pm 0.02	0.57 \pm 0.07	0.38 \pm 0.08	0.94 \pm 0.16	0.64 \pm 0.11
ATP	22.3 \pm 0.8	25.2 \pm 1.1	22.4 \pm 0.8	24.5 \pm 1.1	22.8 \pm 1.1	24.3 \pm 0.8
CP	76.5 \pm 5.1	76.9 \pm 9.8	66.4 \pm 5.5	59.4 \pm 8.5	42.5 \pm 9.0	45.8 \pm 8.3
Creatine	69.4 \pm 11.1	62.7 \pm 1.9	82.3 \pm 9.3	82.8 \pm 10.7	124.9 \pm 13.2	93.2 \pm 11.8

not clear.¹ Furthermore, it has been speculated that MHS individuals have an increased sympathetic activity during exercise, since higher levels of plasma cyclic-AMP and free fatty acids have been observed.^{11,28}

In the current investigation, the patients were studied at a fixed relative workload, since this gives a far smaller inter-individual variation in sympathetic nervous activity than at a fixed absolute workload.²⁴ Our finding of normal plasma catecholamine concentrations at rest and a normal increase in catecholamines during exercise in MHS subjects in the current study agrees with the results presented by Reynolds *et al.*²⁹ Thus, our results do not support there being an abnormal sympathetic activity in malignant hyperthermia susceptible individuals not experiencing MH, as proposed by Campbell *et al.*¹¹ The latter authors based their hypothesis on relatively small differences in plasma FFA and blood lactate concentrations between MHS individuals and controls. Furthermore, urinary catecholamines in their study did not differ between the groups.

We found a sevenfold increase in systemic oxygen uptake during heavy exercise, and no differences between the groups were observed, either at rest or during exercise. Furthermore the mechanical efficiency which directly relates the oxygen consumption to the work performed did not demonstrate any difference between the groups at the higher workload, and only a minor difference at W 40%. These results that MHS subjects expend the same amount of energy in performance of the same work as controls agree with previous findings.¹¹

During exercise, leg metabolism is dominated by muscle tissue, and any abnormalities in muscle metabolism would thus be demonstrated by differences between the groups in leg oxygen uptake. There was an approximately 30-fold increase in leg oxygen uptake in both groups at W 80% exercise level, far exceeding the rise in systemic oxygen uptake. At rest and at lower degrees of exercise, muscle mainly oxidizes FFA,³⁰ whereas glucose utilization increases with increasing workload.³¹ In the current study, there were no significant differences between the groups in leg oxygen uptake, leg mechanical efficiency, or leg exchange of glucose, lactate, and glycerol, and, thus, there was no evidence of abnormal local energy exchange in the MHS group.

Lower muscle glycogen and ATP levels and higher muscle lactate levels have previously been reported in unstressed MHS subjects under anesthesia.¹² This finding was, however, not confirmed in our study.

In conclusion, our study indicates that sympathetic activity, as assessed by plasma catecholamine concentra-

tions, and muscle metabolism are normal in MHS subjects during severe exercise. Our results do not support the opinion that subjects with positive *in vitro* tests for MH should restrict their physical activity.

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