

Evidence for Susceptibility to Malignant Hyperthermia in Patients with Exercise-induced Rhabdomyolysis

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Background: **Malignant hyperthermia (MH), heat stroke, and exercise-induced rhabdomyolysis (ER) were suspected to be related syndromes. However, it is not known whether individuals with history of ER have an increased incidence of susceptibility to MH. To establish an association between ER and susceptibility to MH, the authors determined the MH status in patients with a history of MH-like episodes induced by physical stress.**

Methods: **Twelve unrelated patients with ER, 18 patients with anesthesia-induced MH, and 28 controls were investigated with the *in vitro* contracture test (IVCT) according to the European MH Group protocol and the ryanodine contracture test. In addition, all patients were screened for genetic mutations, and histology was performed on muscle specimens.**

Results: **Ten ER patients had positive IVCT results, one patient had a negative test result, and one patient showed equivocal responses. Samples from patients with positive IVCT results showed pronounced contractures after exposition to ryanodine, as opposed to specimens from patients with negative IVCT results, which developed contractures slowly. Three ER patients had mutations at the ryanodine receptor gene. All anesthesia-induced MH patients had positive IVCT results, two of them presented the C1840T mutation. The control patients had normal contracture test results and no typical MH mutations. Histologic examination determined no specific myopathies in any patient.**

Conclusions: **Regarding these results, the authors recommend performing muscle biopsies for histologic examination and IVCT in patients with ER. In addition, the patient should be seen by a neurologist and screened for genetic abnormalities to shed light on the genetics of MH.**

MALIGNANT hyperthermia (MH) is a disorder of the Ca^{2+}-release channel or the ryanodine receptor at the skeletal muscle sarcoplasmic reticulum with an autosomal dominant trait. The clinical syndrome is characterized by a hypermetabolic state with muscle rigidity, metabolic acidosis, hypercapnia, tachycardia, and fever as a response to certain anesthetic agents, *i.e.*, halogenated volatile anesthetics and depolarizing muscle relaxants.[1] Moreover, it has been suggested that MH might be triggered by physical exercise and emotional stress,[2–4] an event well known in genetically determined breeds of swine.[1] Numerous articles were published presenting cases of exercise-induced MH–like episodes after physical strain, excitement, and environmental heat.[5–11] Therefore, it has been suggested that MH, heat stroke, and exercise-induced rhabdomyolysis (ER) might be related syndromes.[2,4] It is unknown, whether individuals with a history of ER present with an increased incidence for susceptibility to MH (MHS).

To examine the association between ER in humans and MHS, we performed *in vitro* contracture tests in patients with a history of MH-like episodes induced by different forms of physical stress apart from anesthetic procedures. The results from these investigations were compared with the data from patients with anesthesia-induced MH (A-MH) and control patients.

Methods

Patients

Between May 1991 and May 1999, 12 unrelated patients with severe ER, intense muscle cramping, or aching in their history were investigated in our laboratory for MHS (table 1). A detailed description of the clinical courses of these patients can be found on the Journal's Web site (www.anesthesiology.org). In brief, a 12-yr-old boy had experienced recurrent episodes of myoglobinuria and muscle cramping after physical exercise classes at school (patient no. 1). Another patient, a soldier who had collapsed after a 10-km brisk walk during military training, developed fever and rhabdomyolysis, and creatine kinase values increased to 19.040 U/l (patient no. 2; the complete history of this patient was presented recently[13]). Three patients presented with elevated creatine kinase values and myoglobinuria after extreme exercise for body building (patients no. 3–5), and seven patients had clinical symptoms of rhabdomyolysis after cycling (patient no. 6) or sports training (patients no. 7–12). None of the patients' symptoms was associated with exertional heat exposure.

All patients were male, and none showed signs of a chronic or acute infection. They were not on any medication, drugs or alcohol, or dietary supplements on a regular basis. There was no history of muscle diseases or

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Table 1. Biometric Data from Patients with Exercise-Induced MH: Symptoms after Exercise and Results from Examination on Skeletal Muscle Preparations and Mutation Screening

Patient No.	Age (yr)	Clinical Symptoms after Different Forms of Exercise	CK at Rest (U/l)	MH Status	Muscle Histology	Mutation
1	12	Myoglobinuria; muscle aching‡	53	MHS	Normal	C487T
2*	22	Myoglobinuria; fever 41°C; CK = 19.040 U/l; unconsciousness§	22	MHEh	Normal	—
3	25	Rhabdomyolysis; muscle cramping; CK = 7.000 U/l‖	46	MHS	Normal	—
4	45	Rhabdomyolysis; CK = 1.792 U/l‖	66	MHS	Nonspecific††	—
5	37	Myoglobinuria‖	60	MHS	Nonspecific‡‡	—
6	30	Muscle cramping; CK = 1.470 U/l#	329	MHS	Normal	—
7	37	Rhabdomyolysis; muscle cramping and aching; CK = 3.400 U/l**	307	MHS	Nonspecific‡‡	—
8	33	Rhabdomyolysis; CK = 2.466 U/l; muscle aching**	164	MHN	Normal	—
9	25	CK = 800 U/l; muscle cramping**	263	MHS	Nonspecific‡‡§§	—
10	17	Muscle cramping and aching; CK = 1.450 U/l; rhabdomyolysis**	57	MHS	Normal	—
11†	37	Recurrent episodes of fever; myoglobinuria; muscle aching**	44	MHS	Normal	G7297A
12	18	Myoglobinuria; muscle aching**	406	MHS	Nonspecific‡‡	G1021A

* The complete history of patient 2 was presented in reference 13. † The complete history of patient 11 was presented in reference 28. ‡ After physical exercise class at school. § After military training. ‖ After extreme bodybuilding. # After cycling. ** After sports training. †† Internal nuclei. ‡‡ Muscle fiber type II hypertrophy. §§ Muscle fiber type I hypertrophy.

MH = malignant hyperthermia; CK = creatine kinase; MHS = MH susceptible; MHEh = MH equivocal for halothane; MHN = MH normal.

anesthetic complications in either the patients themselves or their families. Five of these patients had undergone anesthesia before (in four cases, volatile anesthetics were used), but no MH-like episodes had to be coped with.

To compare the test data from the patients with exercise-induced rhabdomyolysis with normative data, a group of 18 patients with A-MH in their own or the family history were investigated. The scores from the Clinical Grading Scale[15] of these patients ranged between 15 and 55; two A-MH patients were so-called probands, with a personally experienced MH event and a Clinical Grading Scale score greater than 50. Twenty-eight patients without MH, neuromuscular diseases, or exercise-related MH symptoms in their history underwent biopsy during surgery of the hip and served as controls.

Study Design and Procedures

After obtaining approval from the ethics committee of the University Hospital Eppendorf, written informed consent for the investigations was obtained from all patients. The time interval between the patient experiencing ER or an A-MH episode was in all cases longer than 3 months. Adult muscle bundles from the vastus lateralis were excised during regional anesthesia (3-in-1 nerve block) and in children during trigger-free general anesthesia. Two or three muscle bundles were excised carefully and subsequently placed in Krebs Ringer solution (NaCl 118.1 mM, KCl 3.4 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 0.8 mM, KH_2PO_4 1.2 mM, $NaHCO_3$ 25.0 mM, glucose 11.1 mM) equilibrated with carbogen (95% oxygen, 5% carbon dioxide). Apart from these specimens, an additional small muscle sample (weight, approximately 250 mg) was taken for evaluation of histomorphologic changes (morphometry, immunhistochemistry, fiber size, ratio analysis, *etc.*), and a blood sample was drawn for genetic screening.

In Vitro *Contracture Tests and Muscle Histology*

The muscle bundles of each patient were dissected into 6–10 strips (length, 15–25 mm; width, 2–3 mm; weight, 120–250 mg). Only viable muscle samples (twitch response to supramaximal stimulation more than or equal to 10 mN) were used for the *in vitro* contracture test (IVCT) and classification according to the European MH Group protocol.[16] Each patient was tested with a minimum of two samples with each drug. The IVCT gave halothane and caffeine thresholds for each patient as follows: positive test = muscle contractures more than or equal to 2 mN at a caffeine concentration of 2.0 mM or less and a halothane threshold concentration at 0.44 mM or less; negative test = muscle contractures more than or equal to 2 mN at a caffeine concentration of 3.0 mM or more and a halothane threshold concentration exceeding 0.44 mM; and equivocal results = abnormal contracture responses to either halothane or caffeine.

After contracture testing, viable muscle specimens surplus to diagnostic requirements were subjected to the *in vitro* contracture test with ryanodine as described previously.[17,18] Ryanodine was administered as bolus dose at a concentration of 1 μM to the tissue bath. The contracture course after ryanodine administration was characterized by different contracture levels: (1) onset time

of contracture; (2) time to achieve a contracture level of 2 mN; (3) time to reach a contracture level of 10 mN; and (4) contracture maximum. The *in vitro* effects on contracture development were observed for at least 60 min.

An additional small muscle sample was excised from each patient for pathologic examination. In all specimens, histologic, histochemical, immunohistochemical, and morphometric (fiber size, ratio analysis, dystrophinopathies, *etc.*) investigations were performed to detect muscular alterations.

Genetic Analysis

Constitutional DNA was obtained from 10 ml blood leukocytes and subjected to polymerase chain reaction (PCR) as described previously,[19] with the aid of primers specific for exons 2, 6, 9, 11, 14, 39, 45, and 46 of the skeletal muscle ryanodine receptor gene (*RYR1*). Two methods were applied to screen for known and new mutations in these *RYR1*-gene exons, where mutations have been reported before, *i.e.*, single-strand conformation polymorphism and direct sequencing of several amplified products spanning the selected coding regions of the gene. The single-strand conformation polymorphism was performed according to the method by Singh *et al.*[20] except that silver staining was conducted on polyacrylamide gels to monitor the single strands instead of the incorporation of P^{32} and autoradiography. PCR products corresponding to aberrant bands and all of the PCR products were sequenced using an automated fluorescence system (ABI, Prism 310; Perkin Elmer, USA) to confirm the wild type and the sequences of the mutation sites. In a few cases, restriction digestion of the PCR products with specific enzymes was used to confirm results.

Statistical Analysis

The data are presented as medians and ranges or as mean ± SD. The effects of halothane, caffeine, and ryanodine were assessed with repeated-measures analysis of variance. If applicable, subsequent comparisons were performed with the aid of the Scheffé *post hoc* method. The remaining data were compared using the *t* test or the Mann–Whitney test. Results were considered significant if *P* values were less than 0.05.

Results

The individual results of the patients with ER as well as the biometric data of all patients (patients with A-MH and controls) are presented in tables 1 and 2. Patients' characteristics showed significant differences regarding age, which can be attributed to the criteria of patient selection (*i.e.*, hip surgery in the control group), and creatine kinase values.

Table 2. Characteristics of All Patients

Group	ER	A-MH	Control
n	12	18	28
Age (yr)	28 ± 10*	31 ± 13*	63 ± 15
Height (cm)	178 ± 7	172 ± 13	168 ± 8
Weight (kg)	77 ± 13	71 ± 12	72 ± 14
CK (U/l)	155 ± 135*	106 ± 110*	63 ± 29
MHS	10	18	0
MHN	1	0	28
MHE	1	0	0

* $P < 0.05$ *versus* control.

ER = exercise-induced malignant hyperthermia; A-MH = anesthesia-induced malignant hyperthermia; CK = creatine kinase in serum; MHS = malignant hyperthermia susceptible; MHN = malignant hyperthermia normal; MHE = malignant hyperthermia equivocal.

Muscle preparations from 11 ER patients and all preparations from A-MH patients showed significant contractures after administration of halothane (fig. 1A). None of the preparations from control patients developed contractures. The results of the caffeine contracture test were comparable (fig. 1B). Ten of 12 muscle specimens from the ER patients and all A-MH specimens produced significant contractures. Control preparations developed contractures at caffeine concentrations of 4.0 or 32.0 mM, which is defined to be a normal reaction. Regarding these results, 10 ER patients were diagnosed as MHS according to the European MH Group criteria, one patient showed normal contracture results (MHN), and one patient was classified as MH equivocal for halothane (MHEh). All A-MH patients were diagnosed as MHS, and all control patients as MHN.

After administration of ryanodine, all muscle specimens developed contractures (fig. 2). However, contracture development was significantly accelerated and more intense in the positive and equivocal response specimens as compared with the MHN and control specimens. All contracture levels were reached significantly faster in the positive and equivocal IVCT specimens, and the contracture maximum was significantly higher than in the MHN and control preparations. These data confirm the results from the standard IVCT with halothane and caffeine as described in previous investigations.[17,18]

Muscle histology revealed no specific myopathologic alterations in any of the three groups. Histologic examination showed normal findings in seven patients in the ER group, and five specimens presented unspecific muscular alterations, *e.g.*, internal nuclei, fiber type II hypertrophy, and a combination of fiber type I and II hypertrophy (table 1). Similar results could be obtained from the A-MH patients (unspecific muscular alterations in four patients) and the controls (five patients with myopathologic changes).

In the ER group, genetic mutation screening disclosed a formerly unknown mutation at C487T in patient no. 1, a G7297A mutation in patient no. 11, and a G1021A mutation in patient no. 12 (table 1). In the A-MH group, the C1840T mutation was found in two patients. All of

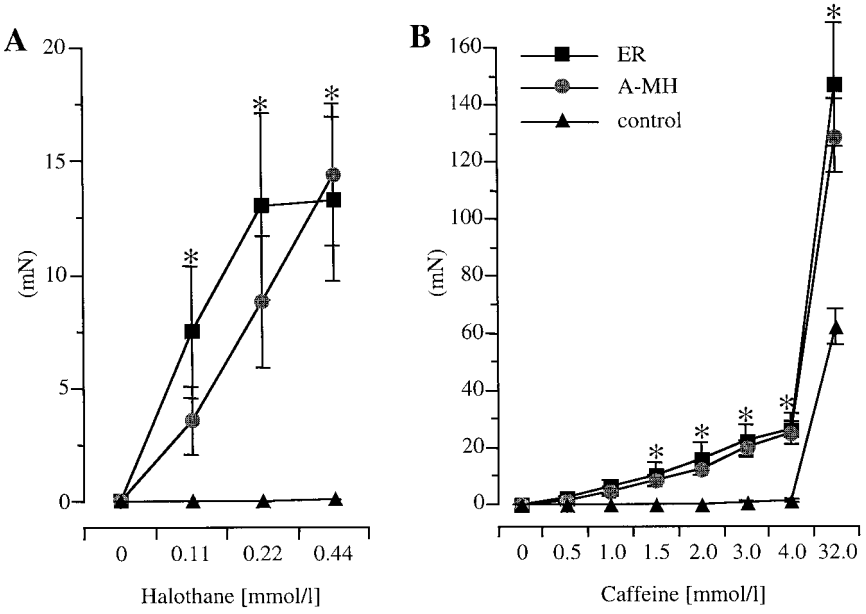

Fig. 1. Contracture course after administration of halothane (*A*) and caffeine (*B*) in skeletal muscle specimens from patients with exercise-induced malignant hyperthermia (ER), patients with anesthesia-induced malignant hyperthermia (A-MH), and control patients. $P < 0.05$ *versus* control.

these mutations are characteristic for MH at the ryanodine receptor gene. In contrast, no mutations were found in the control patients.

Discussion

In 10 of 12 patients with ER, the standard IVCT with halothane and caffeine produced abnormal contracture responses. One patient had an equivocal response. All of these patients showed pathologic results in the ryanodine contracture test. Only one patient had normal contracture test results. All A-MH patients were classified as MHS and had pathologic contracture responses to ryanodine. In contrast, the control patients showed normal results. The results of this investigation demonstrate that MH has to be coped with by anesthesiologists, and even internists, neurologists, intensive care and other specialists need to be informed about MH and concerned with the clinical expression of the syndrome.

We would like to stress that we did not perform a controlled exercise study. Results presented here describe patient data gathered from individuals seen in our MH laboratory. These persons experienced the top of their individual physical capacity during work or leisure activities followed by MH-like symptoms. It is still unknown why some patients who are susceptible to MH have an increased risk for ER and other MH-like symptoms. Explanations that have been presented for the great variability regarding the MH syndrome include the genetic heterogeneity[21] or alterations in the sympathetic nervous system[22,23] and the serotonin system.[24] All patients with ER were investigated before this study by neurologists and internists. None of them presented any relevant diseases or infections or took any medication or

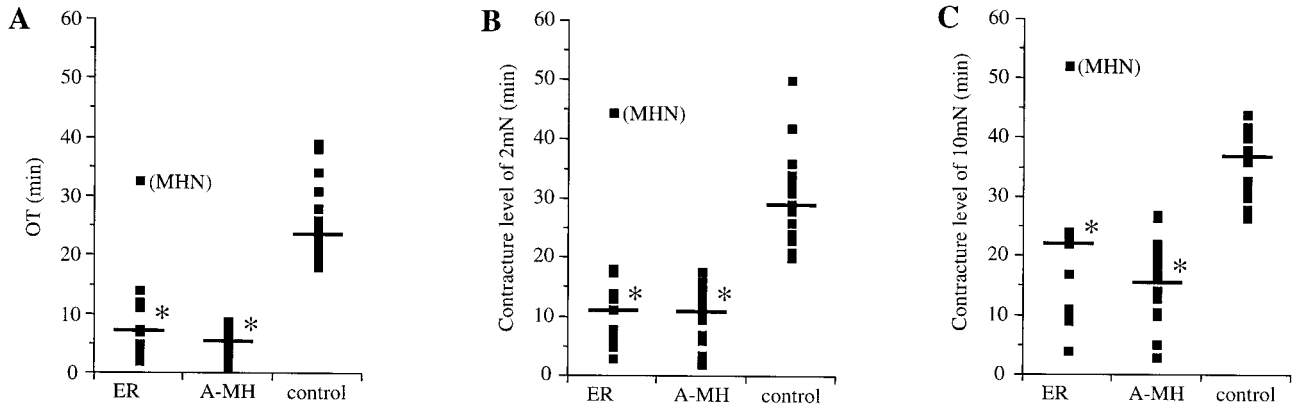

Fig. 2. Contracture course after bolus administration of 1 μM ryanodine in skeletal muscle specimens from patients with exercise-induced malignant hyperthermia (ER), patients with anesthesia-induced malignant hyperthermia (A-MH), and control patients. Data are shown as medians (line) and individual data (■) in minutes at onset of contracture development (OT; *A*), at contracture levels 2 mN (*B*) and 10 mN (*C*). *$P < 0.05$ *versus* control. MHN = malignant hyperthermia normal.

a regular basis. Additionally, abuse of alcohol or other drugs could be ruled out.

In susceptible swine, MH can be easily triggered by stress such as exercise and overheating. Molecular genetic analysis in these animals showed a single-point mutation (C1843T mutation) in the porcine skeletal muscle ryanodine receptor gene on chromosome 6, which is associated with the MH phenotype. The corresponding mutation in the human ryanodine receptor (*RYR1*) gene on chromosome 19q13.1–13.2 region has been identified as a C1840T mutation.[21] However, close to 30 different single-point mutations have been identified in the *RYR1* gene in MH families, and linkage to DNA markers from chromosomes 1, 3, 5, 7, and 17 with the human MHS phenotype has been revealed.[21] In humans, MH follows an autosomal dominant trait, whereas a recessive trait in swine has been proven. Therefore, it has been suggested that genetic differences in humans and swine might be the underlying cause for distinct properties or sensitivity for MH triggers. Different genetic mutations at the human *RYR1* gene might be responsible for an increased sensitivity to stress. However, in this study only 3 of 12 patients presented different mutations associated with the MH phenotype. Regarding these results, it seems to be very unlikely that specific mutations may account for stress sensitivity. It must be kept in mind that the patients have been screened for known mutations only. To completely understand the complex relation between ER and underlying mutations of the *RYR1* gene, a full gene analysis at the cDNA and genomic levels is definitely required.

Numerous case reports about MH-like episodes in humans after stressful situations were presented in the last years.[5–13] It remains unclear whether these responses were provoked by a sympathetic overactivity or increased catecholamine levels. Measurement of plasma catecholamine levels during exercise showed no differences between MHS and MHN individuals.[25–27] *In vitro* tests using skeletal muscle specimens from MHS humans proved that adrenaline, noradrenaline, and isoprenaline had no effect, whereas ephedrine increased halothane-induced contractures.[28] A point of objection concerning these results would be that the investigations were conducted only on subjects who were classified as MHS but did not present any MH-like episodes after physical strain in their history. The aim would be to reconsider the findings after examining MHS patients with ER who probably will present different results. This train of thought is supported by the case of a patient that was recently published.[29] This patient presented recurrent episodes of fever and fatigue associated with muscle cramping and aching after exercise or emotional stress. The patient underwent muscle biopsy for histologic examination and IVCT and was diagnosed as MHS. Mutation screening disclosed a substitution of A for G7297, which was shown to be associated with MHS. To estimate altered catecholamine levels and hemodynamic function, this patient was subjected to exercise on a bicycle ergometer, thus experiencing defined strain according to a concept that had been designed especially for this investigation. The results were overwhelming, showing a remarkable increase in catecholamine levels as well as severe alterations in hemodynamic functions during the study period. These results were attributed to an alteration in the sympathetic system. It has also been suggested that some MHS patients might have a primarily altered sympathetic system leading to a higher sensitivity to physical or emotional stress.

The results of the presented study stress the importance of performing not only histologic examinations but also the IVCT as well as genetic mutation screening in patients with unexplained ER. The aim is to develop standardized test protocols for exercise studies and to select MHS patients with a history of stress intolerance for these investigations that might prove to be very precious for our understanding of trigger mechanisms in MH. Prior studies systematically investigated the effects of different forms and intensities of exercise in MHS patients in comparison to MHN.[26,27,30,31] However, only minor differences between MHS and MHN patients in response to mild exercise were found.

The IVCT according to the European test protocol has a sensitivity of approximately 100% but a specificity of only 93.6%.[16] Assuming a low prevalence of MH in the general population, the predictive value of a positive test result might not be very high. On the other hand, it is tempting to speculate that the prevalence of MH is much higher than previously assumed. However, the clinical implications of the results in the ER patients are not clear to date and need to be studied in a larger population.

In conclusion, we recommend performing a muscle biopsy for histology and the IVCT in all patients with severe clinical episodes resembling exercise-induced MH. Genetic screening should be performed to achieve more insights into the genetics of MH. A well-designed, prospective, controlled multicenter evaluation throughout Europe and North America would be helpful in obtaining more information on the incidence of MH in individuals with ER. Furthermore, such multicenter studies could be the basis for the development and standardization of a common protocol for exercise investigations, as proposed by several investigators.[26,29,31]

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