Susceptibility to malignant hyperthermia (MH) is viewed as a pharmacogenetic trait dependent on exposure to inhalational anesthetics. Outside of the operating room, individuals susceptible to MH are usually asymptomatic. Events that occurred in the absence of anesthetics have been reported over the years and were originally termed awake episodes. In this issue of Anesthesiology, two cases of nonanesthetic MH-like episodes triggered by either exposure to environmental heat or infection are described. These two cases raise the question of how at risk the MH susceptible individuals actually are.

Classic MH is caused by uncontrolled intracellular Ca\(^{2+}\) release from the sarcoplasmic reticulum mediated by an overactive Ca\(^{2+}\) release channel, the ryanodine receptor 1 (RyR1) (fig. 1). A fulminating anesthetic crisis manifests with tachyarrhythmia and sweating initially, hypercapnia, tachypnea, metabolic acidosis, and rapidly increasing temperature followed by muscle rigidity and rhabdomyolysis. Complications include cardiac arrest, heat stroke, and renal failure. Prompt infusion of dantrolene to block RyR1 is mandatory therapy.

MH susceptibility is inherited in an autosomal dominant fashion in man and horse whereas in swine, it is recessive (table 1). In swine, the disorder is even named for these events, porcine stress syndrome, and the trait has been selectively bred because already heterozygous animals have muscle hypertrophy and therefore more meat. Homozygous pigs are frequently killed because already heterozygous animals have muscle hypertrophy and therefore more meat. Homozygous pigs develop MH triggered by emotional and physical exertion during long-lasting transport in hot, close confinement. The animals either die spontaneously or their meat shows a very evident hyperthermia, spontaneous colic-like episodes, or are frequent in the form of recurrent rhabdomyolysis.

In MH-susceptible individuals, 10% have compound heterozygous RyR1 mutations. In Japanese patients, 10% have compound heterozygous RyR1 mutations.8 Furthermore, a recessive RyR1 myopathy has been described recently that displays symmetrical ptosis and muscle hypotonia.9 However, in MH-susceptible Japanese patients, 10% have compound heterozygous RyR1 mutations.

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Gene Single RyR1 or CACNTAS mutation. Therefore, it is possible that RyR1 mutations without any clinical signs of myopathy, so that no generally valid conclusion can be drawn.

The causative RyR1 mutations in the MH-susceptible animals (p.R614C homozygous in swine and p.R2454G homozygous in horses) are both in hot spots of RyR1 where very frequent human MH susceptibility mutations reside. The mutations in the two children reported in this article (p.R3983C) and in another child who died of a nonanesthetic MH (p.R3983H) are in a different RyR1 part that contains an S-nitrosylation site. Therefore, it is possible that the episodes represent a distinct phenotype. Diagnostic testing may need to be rethought. The in vitro contracture test performed on excised muscle exposed to triggering agents, halothane, and caffeine. The standard protocol of the in vitro contracture test may not be ideal to determine susceptibility to spontaneous MH-like episodes. The in vitro contracture test performed on a muscle biopsy of the boy reported in this article (using 31P in vivo MRI) need to be developed.

For prevention of nonanesthetic MH, treatment with dantrolene or N-acetylcysteine might be useful (see text). We combined the entities heat stroke and exertional rhabdomyolysis with exertional heat stroke because this term takes into account the same pathogenesis. MDMA = 3,4 methylenedioxymethamphetamine; MH = malignant hyperthermia; NO = nitric oxide; RyR1 = ryanodine receptor.

### Table 1. Summary of the Current Understanding of Malignant Hyperthermia and Similar Events

<table>
<thead>
<tr>
<th></th>
<th>Classic Human MH</th>
<th>Nonanesthetic Human MH</th>
<th>Horse MH</th>
<th>Mouse MH</th>
<th>Porcine Stress Syndrome</th>
<th>Exertional Heat Stroke</th>
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</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
<td>Single RyR1 or</td>
<td>RyR1 mutation(s) and</td>
<td>RyR1</td>
<td>Homozygous RyR1 mutations</td>
<td>Caucasian ethnic origin, male sex, other genetic factors such as predominance of muscle fiber type 2 Polygenic</td>
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<td></td>
<td>CACNTAS mutation</td>
<td>congenital myopathy</td>
<td>mutation</td>
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<tr>
<td><strong>Inheritance</strong></td>
<td>Dominant</td>
<td>Unclear</td>
<td>Dominant</td>
<td>Recessive</td>
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<td>susceptibility</td>
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<td>to MH</td>
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<td><strong>Trigger</strong></td>
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<td>Extraordinary physical</td>
<td>Volatile</td>
<td>Volatile</td>
<td>Extraordinary physical</td>
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<td>anesthetics;</td>
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<td>anesthetics;</td>
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<td>preservative-free</td>
<td>especially in hot</td>
<td>physical or heat</td>
<td>mental, physical</td>
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<td></td>
<td>succinylcholine</td>
<td>surroundings; infectious fever</td>
<td>stress</td>
<td>or heat stress;</td>
<td>sorbitonergic drugs</td>
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<td><strong>Pathophysiology</strong></td>
<td>Increased</td>
<td>Increased Ca$$^{2+}$$ turnover through strong physiologic activation of skeletal muscle promoted by hyperthermia and mutated RyR1</td>
<td>Increased resting Ca$$^{2+}$$ levels, increased NO-levels, which further sensitize RyR1 to pharmacologic or physiologic triggers</td>
<td>Pathophysiologic principle as above, homozygous RyR1 mutation, therefore muscle extremely prone to both, exogenous and/or endogenous triggers</td>
<td>Uncoupling of oxidative phosphorylation, loss of cellular integrity, increased muscle metabolism promoted by overactivation of excitation-contraction coupling, heat, and mitochondrial uncoupling</td>
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<td>RyR1 to activating ligands such as halothane, sevoflurane, desflurane with uncontrolled Ca$$^{2+}$$ release from sarcoplasmic reticulum, RyR1-mediated release of endogenous pyrogen IL-1/β from B-lymphocytes</td>
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<td><strong>Acute therapy</strong></td>
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<td>Stop triggers are</td>
<td>Stop triggers are</td>
<td>Stop triggers are</td>
<td>Rehydration, correction of glucose and electrolyte levels, physical cooling, benefit of dantrolene uncLEAR</td>
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<td>intravenous</td>
<td>intravenous dantrolene, physical cooling, symptomatic therapy aiming at maintenance of adequate ventilation, circulation, and pH regulation</td>
<td>intravenous dantrolene, physical cooling, symptomatic therapy aiming at maintenance of adequate ventilation, circulation, and pH regulation</td>
<td>intravenous dantrolene, physical cooling, symptomatic therapy aiming at maintenance of adequate ventilation, circulation, and pH regulation</td>
<td>of glucose and electrolyte levels, physical cooling, benefit of dantrolene uncLEAR</td>
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</table>

For prevention of nonanesthetic MH, treatment with dantrolene or N-acetylcysteine might be useful (see text). We combined the entities heat stroke and exertional rhabdomyolysis with exertional heat stroke because this term takes into account the same pathogenesis. MDMA = 3,4 methylenedioxymethamphetamine; MH = malignant hyperthermia; NO = nitric oxide; RyR1 = ryanodine receptor.
nonanesthetic MH susceptibility. Alternatively, only one RyR1 mutation (*i.e.*, in only 16% of the tetrameric RyR1 complexes, all four RyR1 subunits are impaired) might be sufficient if combined with a second mutation that is associated with a congenital myopathy. Therefore, MH-susceptible individuals presenting with ophthalmoplegia and muscle hypotonia, hypertrophy, or spasms will be at risk for nonanesthetic MH. At least such individuals should avoid excessive heat exposure, exhausting physical exertion, high fever, and all drugs that increase heat production and reduce heat dissipation or have been reported to cause rhabdomyolysis.16 For prevention of nonanesthetic MH, treatment with dantrolene (blocks RyR1) or N-acetylcysteine (protects against oxidative damage) might be useful. In case of an episode, rapid cooling at home and during transport to the hospital could significantly contribute to RyR1 stabilization. At the hospital, dantrolene should be infused as in a typical MH crisis. Because children have less developed compensation mechanisms for increased body heat and a higher incidence of MH events than adults (1:15,000 vs. 1:100,000), their parents should be particularly careful.

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