# Nonanesthetic Malignant Hyperthermia

SUSCEPTIBILITY to malignant hyperthermia (MH) is viewed as a pharmacogenetic trait dependent on exposure to inhalational anesthetics.[1,2] 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.[3] In this issue of ANESTHESIOLOGY, two cases of nonanesthetic MH-like episodes triggered by either exposure to environmental heat or infection are described.[4] 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).[5] A fulminant 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 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 obvious, changed characteristic after slaughter that leads to the detection of the disorder.[6] Mating, fighting, heat exposure, and infection trigger episodes that may not display all elements and show delayed or abortive progression. In the very muscular affected quarter horses, nonanesthetic events are frequent in the form of recurrent rhabdomyolysis without evident hyperthermia, spontaneous colic-like episodes, or heat-induced full MH events.[7] In one mare with an especially severe phenotype, a concomitant polysaccharide storage myopathy was identified histologically postmortem.

The two unrelated children reported in this article,[4] a boy and a girl, both showed marked hypertrophy and fever-induced MH-like events or recurrent cramping with rigid gait. The boy also had bilateral ptosis and muscle hypotonia indicative of a congenital myopathy, which may have aggravated the phenotype as in the quarter horse. Although both children harbored the same RyR1 variant, p.R3983C, on one allele, the girl had a second mutation, p.D4505H, on the other allele, possibly suggesting an additive effect comparable

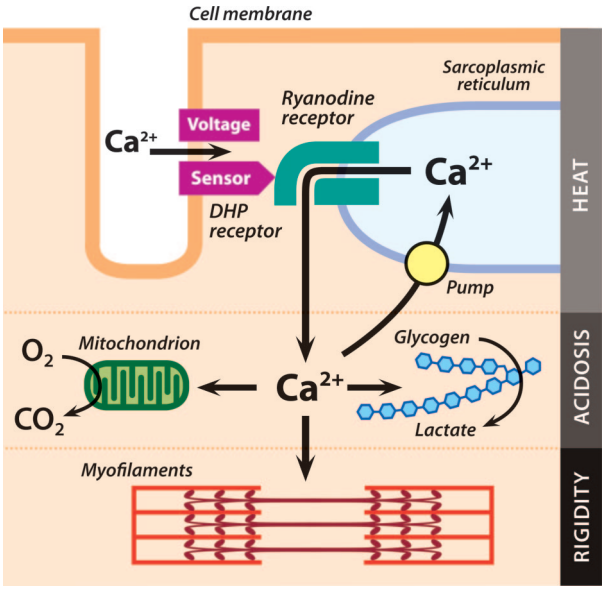


**Fig. 1.** Scheme of the subcellular structures involved in excitation-contraction coupling of skeletal muscle. The dihydropyridine receptor senses the membrane depolarization, alters its conformation, and activates the ryanodine receptor (which releases $Ca^{2+}$ from the sarcoplasmic reticulum [SR], a $Ca^{2+}$ store). $Ca^{2+}$ binds to troponin and activates the so-called contractile machinery. Interstitial and SR-luminal calcium concentrations are in the millimolar range, whereas the myoplasmic $Ca^{2+}$ concentration at rest is in the upper nanomolar to low micromolar range. The large $Ca^{2+}$ gradients are maintained by the SR $Ca^{2+}$ pump and indirectly by the sarcolemmal $Na^+/K^+$ pump (the $Na^+$ gradient drives the $Na^+/Ca^{2+}$ exchanger). In classic malignant hyperthermia, uncontrolled $Ca^{2+}$ release from the SR leads to an increased pump activity and heat production, mainly by the adenosine triphosphate-dependent $Ca^{2+}$ reuptake into the SR. To cope with the increased energy consumption, glycogen stores will be depleted for maximal adenosine triphosphate production. The myoplasmic $Ca^{2+}$ overload may also stimulate $Ca^{2+}$ sensitive proteases, liposomal enzymes, and nuclear DNases, potentially resulting in rhabdomyolysis.

with the recessive situation in porcine stress syndrome. The notion of an additive effect of RyR1 mutations with other muscle-damaging traits could be supported by a recent report of a fatal heat-induced MH event with heat stroke in a 2-yr-old child harboring two RyR1 mutations, p.R4645Q and p.L4320_R4322dup.[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

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

| | Classic Human MH | Nonanesthetic Human MH | Horse MH Mouse MH | Porcine Stress Syndrome | Exertional Heat Stroke |
|---|---|---|---|---|---|
| Gene | Single RyR1 or *CACN1AS* mutation | RyR1 mutation(s) and congenital myopathy mutation | RyR1 mutation | Homozygeous RyR1 mutations | Caucasian ethnic origin, male sex, other genetic factors such as predominance of muscle fiber type 2 |
| Inheritance | Dominant susceptibility to MH | Unclear | Dominant | Recessive | Polygenic |
| Trigger | Volatile anesthetics; preservative-free succinylcholine under debate | Extraordinary physical exercise especially in hot surroundings; infectious fever | Volatile anesthetics; physical or heat stress | Volatile anesthetics; mental, physical or heat stress; succinylcholine without precurarization | Extraordinary physical exercise, dehydration, hot surroundings; serotonergic drugs such as MDMA; muscle may be sensitized by drugs such as statins |
| Signs | Hypercapnia, combined and severe metabolic and respiratory acidosis, hyperkalemia, generalized muscle rigidity, tachyarrhythmia, hypotension, hyperthermia, skin freckling, acute renal failure, dark urine as a consequence of muscle breakdown, disseminated intravasal coagulation. | | | | Central nervous system features such as seizures, compared with a "true" MH event: gradual onset of muscle related symptoms |
| Pathophysiology | Increased sensitivity of 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$\beta$ from B-lymphocytes | Increased $Ca^{2+}$ turnover through strong physiologic activation of skeletal muscle promoted by hyperthermia and mutated RyR1 | Increased resting $Ca^{2+}$ levels, increased NO-levels, which further sensitize RyR1 to pharmacologic or physiologic triggers | Pathophysiologic principle as above, homozygous RyR1 mutation, therefore muscle extremely prone to both, exogenous and/or endogenous triggers | Uncoupling of oxidative phosphorylation, loss of cellular integrity, increased muscle metabolism promoted by overactivation of excitation-contraction coupling, heat, and mitochondrial uncoupling |
| Acute therapy | Stop triggers, intravenous dantrolene, physical cooling, symptomatic therapy aiming at maintenance of adequate ventilation, circulation, and pH regulation | | | | Rehydration, correction of glucose and electrolyte levels, physical cooling, benefit of dantrolene unclear |

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 = stick oxide; RyR1 = ryanodine receptor.

mutations without any clinical signs of myopathy,[10] 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 dominant 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)[4] and in another child who died of a nonanesthetic MH (p.R3983H)[11] are in a different RyR1 part that contains an S-nitrosylation site.[12] Therefore, it is possible that the episodes represent a distinct phenotype. Diagnostic testing may need to be rethought. The *in vitro* contracture test is 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[4] would be considered by Europeans as MH equivocal. In addition, positive *in vitro* contracture test results were found in only 24% of 45 individuals with exertional heat stroke,[13] and in 83% of 12 patients with exercise-induced rhabdomyolysis.[14] Therefore, more appropriate test protocols *in vitro* (heat, oxidative stress, and nitrogen species as triggers) or *in vivo* (using $^{31}P$ MRI)[15] need to be developed.

Which individuals should be considered at high risk for nonanesthetic MH? As long as no more specific tests for nonanesthetic MH susceptibility are available, we have to consider which individuals require counseling. Although a single RyR1 mutation predisposes to anesthesia-related MH, two mutations on different alleles seem to be required for

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),[17] their parents should be particularly careful.

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