



# Current Concepts In the Understanding of Malignant Hyperthermia

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**M**alignant hyperthermia (MH) is a pharmacogenetic disorder triggered by exposure to halogenated volatile anesthetic gases and succinylcholine. The underlying mechanism for this potentially deadly condition involves the unregulated release of calcium from the sarcoplasmic reticulum into the myoplasm. The ryanodine receptor protein encoded by the *RYR1* gene on chromosome 19q.13.1 forms the calcium channel (Figure 1).



Exposure to anesthetic-triggering agents and, in rare cases, to physical exertion in the presence of high environmental temperature stimulates the unregulated release of calcium through the channel.<sup>1</sup> This release can precipitate a metabolic chain reaction with generalized muscle contraction (rigidity) accompanied by the byproducts of metabolism: heat, carbon dioxide, and acidosis. The ensuing hypermetabolic state culminates in the exhaustion of the myocyte's ability to maintain cellular integrity, resulting in rhabdomyolysis, hyperkalemia, and combined metabolic respiratory acidosis.

The only effective treatment for an MH crisis is the administration of dantrolene sodium,<sup>2</sup> a hydantoin derivative first developed as a muscle relaxant. Dr. Keith Ellis discovered that dantrolene acted on the intrinsic mechanism of skeletal muscle contraction and had no effect on cardiac or smooth muscle.<sup>3</sup> The exact mechanism of action is unknown, except that the drug binds to the ryanodine receptor and interferes with the release of calcium into the myoplasm.

Determination of the incidence and prevalence of MH has been difficult. The disease itself is rare and may go unrecognized and, although the autosomal dominant pattern of inheritance imparts a 50% chance of passing the mutated gene to the offspring, the phenotypic manifestation is characterized by reduced penetrance and variable expressivity. The incidence of MH is reported to range from 1 in 3,000 to 1 in 50,000 anesthetics, with an occurrence among children of 1 in 5,000 to 1 in 10,000 anesthetics and adults of 1 in 50,000 anesthetics.<sup>4,5</sup> Two studies examining MH in the United States found an estimated incidence rate of 11 MH patients per 1 million hospital discharges from

hospitals participating in the Nationwide Inpatient Sample (NIS) from 2000 to 2005 and a prevalence of 3.8 per 100,000 surgical patient discharges from pediatric hospitals participating in the Kids' Inpatient Database (KID) for the years 2000, 2003, and 2006.<sup>6,7</sup> A more recent study examining the KID database from 2000 to 2009 for pediatric patients with an International Classification of Diseases, Ninth Revision (ICD-9) code for MH and surgery found an MH prevalence of 1 in 10,000 surgical patients.<sup>8</sup> One study examining MH in New York hospitals found a prevalence of 1 in 100,000 due to anesthesia in surgical patients.<sup>9</sup> These differing results exemplify how the population being scrutinized can have a major influence in the final analysis. Therefore, the best approach to understanding the prevalence of MH is that it is a potentially lethal condition in every anesthetized patient until proven otherwise (Table 1).

Screening can be conducted using the clinical grading scale to evaluate the likelihood that a past or present intraoperative event truly represents an MH crisis. A presumptive diagnosis of a patient having experienced an MH crisis is based on 6 physiologic processes and independent variables, such as reversal of MH signs and symptoms with the administration of dantrolene or creatine kinase greater than 20,000 units/L with the use of succinylcholine or greater than 10,000 units/L without the use of succinylcholine.<sup>10</sup> A raw score is calculated and matched to the raw score range, which has a corresponding MH rank for different raw score values. The lowest raw score range is 0, which is equivalent to an MH rank of 1, meaning the description of the event has an "almost never" likelihood of being an MH crisis. A raw score range above 50 has an MH rank of 6, translating to a description of an event that is "almost certain" to be consistent with an MH crisis.<sup>10</sup>

## Testing

The gold standard for testing individuals at risk for MH or confirming a clinical diagnosis of MH is the caffeine halothane contracture test (CHCT) or the in vitro contracture test (IVCT in Europe). Eligible candidates undergo a muscle biopsy that obtains 2 g of tissue from one of the quadriceps muscles using a nontriggering anesthetic technique and conducting the contracture test within 5 hours of harvesting the specimen.<sup>4</sup> The procedure is performed 3 times for each test agent according to the standardized protocol of the North American Malignant Hyperthermia Group (NAMHG).<sup>11</sup> Two sets of 3 muscle fascicles are dissected from the muscle specimen.<sup>11</sup> Each fascicle is mounted in a separate bath of carbogenated Krebs-Ringer's solution and exposed separately to 3% halothane and increasing concentrations of caffeine.<sup>11</sup> A supramaximal electrical stimulation is applied to the muscle strip after exposure to halothane and after each change in concentration of caffeine.<sup>11</sup> A force transducer is used to measure the isometric contraction. The sensitivity is



**Figure 1. Structural rendering of the ryanodine receptor protein.**

approximately 97% and specificity is 78%.<sup>12</sup> However, the IVCT using the European Malignant Hyperthermia Group's protocol has a sensitivity of 99% and a specificity of 93.6%.<sup>13</sup> The difference in specificity may be due to the single exposure to 3% halothane used in the NAMHG protocol.<sup>12</sup>

Patients who have experienced a clinical episode of MH or significant rhabdomyolysis must wait at least 2 to 3 months to allow time for the muscles to completely recover.<sup>4</sup> (Only 4 centers in the United States offer the test: the University of Minnesota, Wake Forest University, the Uniformed Services University of the Health Sciences, and the University of California, Davis; 1 center in Canada, Toronto General Hospital, does, as well. In Europe, there are 22 MH centers, mainly in Germany [6], France [3] and Italy [3].)

Molecular genetic testing remains a noninvasive and less-costly alternative to a muscle biopsy. The test often is used to confirm MH susceptibility (MHS) after muscle testing. Patients with a convincing history, such as a high clinical grading scale score, post-mortem DNA testing for a suspected MH-related death, or a first-degree relative of a proband with a clinical history of MH, are eligible for genetic testing.<sup>4</sup> However, unlike the muscle contracture test, a negative test does not exclude MHS. The protocol requires collection of a blood or tissue sample containing the patient's DNA and delivery to a genetics laboratory for analysis, such as Prevention Genetics, LLC, in Marshfield, Wisconsin, or the DNA Diagnostics Center, in Pittsburgh.

To date, 2 genes have been identified as causal for MH: *RYR1* and *CACNA1S*, which codes for the  $\alpha 1$ -subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel.<sup>4</sup> *RYR1* accounts for 70% to 80% of MHS patients, whereas *CACNA1S* accounts for 1%.<sup>4</sup> Although more than 70% of individuals with a confirmed diagnosis of MH carry a DNA variant, genetic testing can identify only 25% to 30% of those with MHS.<sup>4</sup> This statement may seem confusing, but reflects the real problem of having identified over 300 DNA variants for *RYR1*, but having only officially listed 32 as "causal" for MH. Most of the variants either represent polymorphisms or have unknown significance. The task at hand is to define the significance of these DNA variants in order to increase the sensitivity of genetic testing. Therefore, the test cannot be used for screening. It is most valuable when there has been either a positive contracture test or a "very likely" or higher classification of an MH episode. Also, patients found to have a variant of unknown significance present a clinical dilemma for their physician in regard to their MH status or may find themselves arbitrarily classified as MH-susceptible based on possession of an *RYR1* variant.

It should be noted that there tends to be a 10% discordance between the results of a muscle contracture test and a genetic test, which has yet to be explained.<sup>14</sup> The cost of muscle contracture testing

**Table 1. Signs of MH**

<b>Tachycardia: early, nonspecific</b>
<b>Increasing EtCO<sub>2</sub> temporarily responsive (early) or unresponsive (late) to increases in minute ventilation</b>
<b>Trunk or total body rigidity</b>
<b>Masseter muscle rigidity—"Jaws of Steel"—correlated with other signs of MH</b>
<b>Mixed respiratory/metabolic acidosis</b>
<b>Rise in temperature, especially when rapid and unexplainable (late sign)</b>
<b>Myoglobinuria</b>

**EtCO<sub>2</sub>**, end-tidal carbon dioxide; **MH**, malignant hyperthermia

and the low yield of genetic studies require careful consideration of candidates who will benefit the most from either test. Candidates should be evaluated by a knowledgeable physician or genetic counselor before testing. (Consultants are available through the Malignant Hyperthermia Association of the United States.)

In addition to diagnostic testing, the patient's medical history may provide insight into whether he or she is at risk for MH. A variety of myopathies are associated with MHS. Patients with central core disease, multiminicore disease (MmD), and King-Denborough syndrome are well documented to be at risk for an MH crisis.<sup>15</sup> A classic finding of both central core disease and MmD are characteristic cores in muscle biopsy specimens. All 3 conditions represent congenital myopathies associated with an *RYR1* defect.<sup>15</sup> Duchenne muscular dystrophy and mitochondrial disorders are not associated with mutations in *RYR1*, unlike many other myopathies. The pathophysiology of Duchenne and mitochondrial myopathies do not directly involve the ryanodine receptor. The important concept is that these patients may be at risk for an MH-like crisis from exposure to volatile halogenated gases and succinylcholine resulting in rhabdomyolysis and hyperkalemia through a similar mechanism without sharing a common genetic link.<sup>16,17</sup>

**Table 2. Acute Management Of an MH Crisis<sup>a</sup>**

Declare crisis: Call for help, MH cart
Notify surgical team: Determine best time to abort procedure, assist with active cooling of patient
Stop exposure to triggering agents: Discontinue volatile agents, hyperventilate with high fresh gas flows using 100% oxygen. <i>Do not change anesthesia machine.</i>
Switch to nontriggering anesthetic technique: total IV anesthesia.
Administer 2.5 mg/kg of dantrolene in repeated doses based on clinical and laboratory response. Ryanodex is supplied in 20 mL vials containing 250 mg dantrolene sodium and 125 mg mannitol; generic dantrolene vials contain 20 mg of dantrolene and 3 g of mannitol. <i>Mix with only preservative-free sterile water.</i>
Obtain additional peripheral or central venous access as indicated.
Place arterial catheter for continuous monitoring of hemodynamics and vascular access for frequent blood sampling.
Place Foley catheter to monitor urine output.
Initiate and continue active cooling of patient as indicated.
Address metabolic and electrolyte derangements.
Transfer to intensive care unit for further treatment and continuation of dantrolene.
Call MH Hotline: (800) 644-9737 for emergency assistance.

MH, malignant hyperthermia

<sup>a</sup> www.mhaus.org/testing/centers. Accessed January 16, 2014.

## Clinical Presentation

The importance of early recognition and treatment is reflected in previous studies of MH crises and patient outcomes. One of the earliest and most specific signs for MH has been an increase in end-tidal carbon dioxide despite increases in minute ventilation. Along with generalized muscle rigidity, the 2 signs are strongly indicative that the patient is experiencing an MH crisis. Ironically, hyperthermia is not the earliest sign, which may be delayed. Once body temperature begins to rise, the rate of increase can be as much as 1°C to 2°C every 5 minutes if unchecked. A retrospective study demonstrated a 3-fold increase in complications associated with each 2°C increase in maximum temperature; a 30-minute delay in dantrolene administration resulted in a 1.6-fold increase in complications.<sup>17</sup>

Review of the North American Malignant Hyperthermia Registry between 1987 and 2006 illustrated the increased risk for cardiac arrest/death due to a longer period between anesthetic induction and maximum end-tidal carbon dioxide (216 vs. 87 min).<sup>17</sup> Blood gas indices, maximum recorded temperature, and total dose of dantrolene administered were markedly abnormal in the 4 patients who died and represented the cases with delayed presentation or recognition and therefore a delayed response to treatment.<sup>17</sup> In a retrospective study by Litman et al, 10 cases of MH were identified in the postoperative period, approximately 40 minutes after cessation of anesthetic gases.<sup>18</sup> These were stated to be true, but quite rare, occurrences of MH.

## Managing an MH Crisis

The anesthetic management of an MH crisis is among the most intense clinical challenges an anesthesia provider can encounter (Table 2). Initial steps involve stopping the delivery of the triggering agent, such as sevoflurane, isoflurane, or desflurane (Figure 2). High fresh gas flow rates with 100% oxygen should be instituted to purge the anesthesia machine of any anesthetic gases as quickly as possible without disconnecting the patient. In addition, the surgeon and the rest of the team should be alerted to the crisis.

Dantrolene should be administered as soon as possible. The initial dose of dantrolene is 2.5 mg/kg, repeated as needed to control signs of the crisis. This in itself is a time-consuming task: gathering the vials, each containing only 20 mg of dantrolene and 3 g of mannitol, mixing with 60 mL of preservative-free sterile water, aspirating back into the 60-mL syringe, and injecting into the largest, free-flowing peripheral IV or central venous line. Also, placement of activated charcoal filters is recommended on the inspiratory and expiratory ports of the anesthesia machine to facilitate removal of triggering anesthetic gases from both the machine and patient (Figure 3). Assistance will be needed for obtaining additional IV and arterial access, placing a Foley catheter, and actively cooling the patient to a temperature of 38°C.



**Figure 2. Malignant hyperthermia is a pharmacogenetic disorder caused by halogenated volatile anesthetic gases and succinylcholine.**

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Assessing response to therapy will require frequent blood sampling to ensure correction of metabolic derangements and to follow indicators of the severity of rhabdomyolysis, such as creatine kinase. Recrudescence is always a danger after successful treatment and therefore requires the patient to continue therapy in the ICU for at least 24 to 36 hours.

MH-susceptible patients may be anesthetized safely using a nontriggering anesthetic, such as regional or IV anesthesia. However, procedures requiring controlled ventilation may require the patient to be intubated. Intubation requires preparing an anesthesia machine by purging the system of residual volatile anesthetic agent with high fresh gas flows, while ventilating a 2- or 3-L breathing bag and/or replacing components of the breathing system with autoclaved or new parts and finally changing the patient breathing circuit. The last step should be performed immediately after the patient arrives in the operating room or procedure area. Preparation of the anesthesia machine should commence as soon as possible, as it is a labor-intensive process requiring as long as 104 minutes.<sup>19</sup> A review article by Kim and Nemergut provides a table summarizing the steps involved in flushing different anesthesia machines.<sup>20</sup> Additional information concerning anesthesia machine preparation can be found on the website of the Malignant Hyperthermia Association of the United States (at [www.MHAUS.org/healthcare-professionals/mhaus-recommendations/anesthesia-workstation-preparation](http://www.MHAUS.org/healthcare-professionals/mhaus-recommendations/anesthesia-workstation-preparation)) or on those of the respective manufacturers.

The introduction of a new activated charcoal filter (Vapor-Clean, Dynasthetics) has refocused attention



**Figure 3. Placement of activated charcoal filters at the inspiratory and expiratory ports can help remove traces of the triggering anesthetic gas.**

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on eliminating anesthetic gases using activated charcoal.<sup>21</sup> These yellow filters are placed on the inspiratory and expiratory ports of the anesthesia machine. The filters have been demonstrated to reduce the concentrations of sevoflurane, isoflurane, and desflurane to 5 ppm or lower within 2 minutes for 90 minutes.<sup>21</sup> A study by Bilmen and Gillies demonstrated the effectiveness of these filters for 12 hours. They recommend using one filter on the inspiratory limb, flushing the anesthesia machine for 90 seconds with high fresh gas flows for 10 Lpm, replacing the breathing circuit and soda lime canister, and continuing with high fresh gas flows for at least 90 minutes before removing the filter or keeping the filter in place and reducing the gas flow to 3 Lpm.<sup>22</sup> Also important, the vaporizers should be taped or removed to avoid inadvertent use, which might overwhelm the absorptive capacity of the filters.

In addition, the FDA recently approved Ryanodex (Eagle Pharmaceuticals), a new formulation of dantrolene incorporating nanosuspension technology. The new drug is packaged in 250 mg vials as a lyophilized powder requiring 5 mL of preservative-free sterile water for reconstitution, yielding a 50 mg/mL concentration. Also, the new formulation contains 125 mg per vial of mannitol as opposed to 3 g per vial of mannitol and 20 mg of dantrolene. Ten seconds of vigorous

**Table 3. Cases of Awake MH**

Anecdotal cases: heat exposure with exercise misdiagnosed as heat stroke.

Subset of those with MH susceptibility can develop MH without anesthesia; have *RYR1* variant.

In 7 pediatric patients with susceptibility to MH who had awake MH event and subsequently died, findings included viral illness, high environmental temperature, and physical or emotional stress.

Based on references 24-26.

agitation is stated to yield a uniform orange-colored suspension ready for immediate use or storage for up to 6 hours. This would enable an anesthesia provider to deliver the first dantrolene dose of 2.5 mg/kg in a 100 kg patient with only one vial and minimal effort in comparison to previous formulations. Administration of dantrolene is stated to be compatible with IV infusion of 0.9% sodium chloride injection, or 5% dextrose injection, but not for reconstitution. Manufacturer warnings and precautions and adverse reactions are the same as for other preparations of dantrolene and specifically refer to the drug's pH of approximately 10.3 and ability to induce muscle weakness. Unfortunately, at the time of this review the drug had just been released for clinical use so little is known about its real-world application and effectiveness.

### Awake MH

There have been anecdotal reports of patients experiencing MH or MH-like signs without anesthesia (Table 3). These patients will usually trigger upon exposure to heat in conjunction with exercise and may be misdiagnosed as having simple heat stroke. In some cases of so-called "awake MH," the patient may have an underlying myopathy, as well as a ryanodine receptor mutation. Gronert et al. reported the first confirmed case of awake MH in 1980.<sup>23</sup> The patient was a 42-year-old man who experienced periodic body cramps with high fevers. A positive muscle biopsy proved him to have MHS. His daily activities included self-monitoring for signs and symptoms of MH and self-treatment with oral dantrolene. Additionally, after undergoing a nontriggering anesthetic technique for surgery, he experienced fevers postoperatively, which were successfully treated with dantrolene.

Increasing evidence indicates that a subset of MHS individuals can develop signs of MH without anesthesia. A more recent case involved a 6-year-old boy who died of fulminant MH.<sup>24</sup> The child developed lower extremity rigidity, trismus, and fever to 108.9°F after playing in a splash pool. He was rushed to the hospital and emergently intubated on arrival with succinylcholine for respiratory distress and questionable seizure activity. He experienced cardiac arrest, which was unresponsive to treatment. A postmortem DNA analysis demonstrated a novel *RYR1* variant. The father shared the same genetic defect and was found by muscle contracture testing to be strongly positive for MHS; he also was diagnosed with central core disease.

A review article reported the deaths of 7 MHS pediatric patients who experienced an awake MH event.<sup>25</sup> Many of these children had been diagnosed clinically and had a positive muscle contracture test and a positive test for a causal genetic mutation. Testing of family members with the same *RYR1* variants were found to have positive contracture tests consistent with MHS or in vitro testing demonstrating a 2-fold increase in response to caffeine exposure.

The common findings among these children were viral illnesses, high environmental temperatures, and stress at the time of the awake MH event and death. These findings seem to corroborate the effect of stress in an earlier report of awake MH episodes in male patients with confirmed MHS.<sup>26</sup> It was noted that "extreme physical or emotional stress or fatigue resulted in aching joints, malaise, fevers of 40°C or more, and soaking sweats."

Comparison of the experiences of awake MH individuals to those cited in a paper on postoperative MH may suggest a link between awake MH and the occurrence of MH in the postoperative period. A retrospective study identified 10 patients having experienced MH out of 528 suspected cases, leading to the conclusion that postoperative MH does occur in a rare subset of MHS patients, with a prevalence of 1.9% in the study population.<sup>27</sup> All 10 patients had received a volatile anesthetic agent and 5 had received succinylcholine. The case duration was from 35 to 660 minutes. All patients experienced an MH episode within 40 minutes, however the majority of patients demonstrated signs and symptoms within 15 minutes. The times were measured from when the anesthesiologist turned off the anesthetic agent to when the patient manifested signs of MH in the postanesthesia care unit.

Studies of MH-susceptible swine have found them to trigger because of emotional or physical stress, and some have hypothesized that the same may be the case in humans, although that contention has not been studied or proven. A notable difference is that MH-susceptible swine are homozygous for a single mutation in the *RYR1* gene, while almost all humans are heterozygous and many different mutations or DNA variants have been linked to MH susceptibility. However, the role of stressors, such as return of muscle

activity in conjunction with residual anesthetic levels in the immediate postoperative period, pain, and temperature instability, may offer some insight into a shared mechanism for awake MH and postoperative MH. The stress placed by any one or combination of factors may be sufficient to trigger MH or may add to the existing stressors to overcome the threshold for sparking a crisis.<sup>26-28</sup> More studies are needed to verify or refute if a relationship exists between these 2 rare subtypes.

## Conclusion

MH is a rare and potentially fatal pharmacogenetic disorder. Susceptibility to malignant hyperthermia is commonly discovered after an MH crisis is triggered by exposure to halogenated volatile anesthetic agents or succinylcholine. The clinical grading score is a useful tool for making a clinical assessment of whether a patient has experienced MH. However, the gold standard for testing is the CHCT. For those individuals who are biologically related to a proband, the genetic test offers a minimally invasive, low-cost alternative to the muscle biopsy. Because *RYR1* is so large, and

there are so many DNA variants that have yet to be characterized, more research is necessary to clarify who is—and is not—at risk for MH. A recent article by Gonsalves et al examined the exome sequencing data of 870 volunteers in the ClinSeq study.<sup>29</sup> Of 4 *RYR1* variants predicted to be pathogenic for MHS, 3 were found in 3 participants without medical or family histories of MHS. The study found a prevalence of 1 in 340 control patients for the pathologic *RYR1* mutations. The essential question now emerging, not only for MH but many other disorders, is when does a DNA variant lead to clinical manifestations of a disorder? For those patients already identified, anesthesia care can be safely managed with a nontriggering anesthetic technique, a well-prepared anesthesia machine and/or the use of activated charcoal filters. The relation of MH susceptibility to heat and exercise is a phenomenon that is suggestive but requires more study. The FDA approval of Ryanodex may alleviate many of the logistic headaches and simplify the treatment of MH. The phenomenon of awake MH is still being investigated and may in the future require changes in practice to anticipate, prevent, and manage such cases.

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