REVIEW ARTICLE

Malignant Hyperthermia: A Review

David J Berman[1], Kumar Belani[2]

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Abstract

Malignant hyperthermia (MH) is a complex pharmacogenetic condition associated with the development of a hypermetabolic state when exposed to specific "triggering" anesthetic medications. These inciting agents include all potent inhalational anesthetics (e.g., halothane, sevoflurane, desflurane, isoflurane) and succinylcholine. While poorly understood, mutations in the ryanodine receptor are thought to play a pathogenic role in this genetic condition: these mutations are typically inherited in an autosomal dominant fashion or may be *de novo* mutations. The mainstay of treatment for patients with a history or family history of MH is avoidance of these triggering anesthetic agents. If a crisis occurs, discontinuation of the offending agent, prompt expert consultation, and targeted therapy with dantrolene have decreased the mortality of this condition from >70 to <10%. Future directions for MH research include more accurate genetic testing, a better understanding of the disease mechanism, and continued research for the optimal management of MH crises.

Keywords: Anesthesiology, Dantrolene, Genetic disease, Hypermetabolic state, Malignant hyperthermia, Ryanodine receptor.

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Introduction

Malignant hyperthermia is a complex pharmacogenetic disorder of skeletal muscle that traditionally manifests as a hypermetabolic state (hypercarbia, tachycardia, hyperthermia, metabolic acidosis, and skeletal muscle rigidity) in a genetically susceptible individual when exposed to halogenated inhalational anesthetics or succinylcholine.[1–3] While the mechanism of this disease is not completely understood, it is theorized that exposure to triggering agents causes a significant increase in ionized calcium release from the sarcoplasmic reticulum in skeletal muscle of patients with genetic susceptibility. This results in skeletal muscle rigidity and an increase in skeletal muscle metabolism with the ensuing symptoms. While MH is generally considered a unique clinical disease, there is a wide spectrum of presentations which makes the true incidence of the condition difficult to ascertain. Presentations differ from mild self-resolving fevers in the postoperative period to severe, life-threatening hypermetabolic states with associated electrolyte derangements and arrhythmias progressing to cardiac arrest.

The main genetic mutations are centered around the ryanodine receptor and the *RYR1* gene,[4] with hundreds of mutations known to cause the MH spectrum of disorders, but other genetic mutations in other genes (*CACNA1S* and *STAC3*) have also been implicated. Certain genetic syndromes also place patients at risk for MH reactions.[5] These genetic mutations are usually inherited, typically in an autosomal dominant pattern, or may be *de novo* mutations.

Recognition of MH susceptibility and prevention of a crisis by avoidance of triggering agents is key. When a crisis occurs, the hallmarks of treatment include early detection, early administration of dantrolene, supportive care, and postcrisis care including genetic testing of the proband and first-degree relatives and avoiding triggering agents in the future. The historical mortality of MH was >70% in initial literature from decades ago, but has since declined to well under 5% today.[6,7]

[1]Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

[2]Department of Anesthesiology, University of Minnesota Medical School, Minneapolis, Minnesota, United States

Corresponding Author: David J Berman, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, Phone: +410-955-5608, e-mail: daveberman@jhmi.edu

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Disease Prevalence

Malignant hyperthermia is a worldwide disease. The prevalence is challenging to estimate, though likely falls in the range of 1:100,000 anesthetics.[8] This difficulty is due to the wide spectrum of MH manifestations, as well as the variable responses to anesthetic agents in susceptible patients. Among patients who have developed an acute MH episode in large case series, half have had exposures to anesthetics before without incident.[9,10] Previous exposures to uncomplicated anesthetics, even high numbers, do not eliminate the possibility of an MH reaction: a patient with confirmed MH (by genetic testing) was reported to the MH hotline with an acute episode after 30+ prior general anesthetics. A recent review of 370 patients with RYR1 mutations known to cause MH showed that there was an approximately 40% likelihood of developing MH with a triggering agent in a genetically susceptible individual.[11] This makes estimation of the true incidence of MH susceptibility difficult to ascertain, though it remains an uncommon condition.

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Malignant hyperthermia occurs in all ethnic groups and does not display a specific racial or ethnic predisposition. Approximately half of all reported events occur in individuals 18 or younger,[10] with males being roughly twice as likely to experience MH than females.[8,9]

Genetic Basis

The genetic basis for MH most likely involves genes controlling the amount of cytoplasmic calcium in skeletal muscles, causing muscle contraction.[12,13] Specifically, genes involved in calcium release from the sarcoplasmic reticulum are most commonly implicated in MH pathogenesis: these gene families include the ryanodine receptor (RYR1),[11,14] dihydropyridine (DHP)[15] and SH3 and cysteine-rich domains 3 (STAC3) receptors,[16] and aspartate beta-hydroxylase (ASPH) receptor. The latter receptor is also associated with exertional heat illness, an MH-like hypermetabolic state associated with high ambient temperatures and exertional rhabdomyolysis, in addition to MH susceptibility itself.[17] Another receptor on the calcium channel is the CACANA 1S, which has also been implicated in the causation of MH.[18]

While genetic testing can verify the presence of a pathogenic variant, different mutations have varying degrees of MH risk.[14] Additionally, individual patients and patients with the same mutations can have vastly different clinical scenarios despite similar anesthetic exposures.[11] This is likely due to variable penetrance and differences in expressivity of the encoded proteins, but this is an area of active exploration.

Identification of Susceptible Individuals: Family History and Related Disorders

A key step in anesthetic pre-evaluation of any patient is ascertaining a family history of problems with anesthesia, specifically focusing on adverse reactions which are genetically linked. Certain key genetic conditions (MH, pseudocholinesterase deficiency) may have broad and far-reaching implications for anesthetic management and are an important part of any pre-procedural history and physical. A history of MH or a hypermetabolic state surrounding the perioperative period should raise concern for the possibility of MH. A calculator has been proposed to help determine whether an anesthetic reaction was consistent with MH.[19] While it has not been traditionally validated in a cohort of patients with known MH, it is thought to be helpful in preoperative counseling and referring patients for testing prior to procedures. Patients with a history of unexplained fevers and/or muscle cramping in response to exertion or infection may be susceptible to MH, as these episodes may be indicative of an "awake MH" state and predispose patients to development of MH perioperatively.[20] Awake MH is thought to be a state of MH without exposure to triggering agents, which may occur in response to other systemic stressors and appears clinically similar to MH.

Certain genetic conditions are associated with an increase in susceptibility to MH.[5] These include myopathies with abnormalities in the ryanodine receptor, such as central core myopathy, multiminicore disease, King–Denborough syndrome, STAC3 myopathy, and other rare diseases. Patients with rare enzymopathies of skeletal muscle may also be at an increased risk. Patients who have experienced severe exertional or heat-related rhabdomyolysis may be at a higher risk for MH than the general population, and many advocate for treating these patients as MH-susceptible. This includes the state of "awake MH" described above. Several small case series have shown that cohorts of these patients are at a higher-than-average likelihood of possessing an MH-causative mutation of experiencing a positive caffeine-halothane contracture test.[21–25]

While muscular dystrophies are not known to have a higher rate of MH, these patients may experience rhabdomyolysis and hyperkalemia after administration of succinylcholine and volatile anesthetics. Patients with severe statin-induced myopathy, which may manifest as severe muscle pain and may be associated with rhabdomyolysis, may be at an increased risk for MH as well.[26,27] Certain other rare genetic syndromes are also associated with MH: these are discussed elsewhere.[5]

Patients with a personal or family history of suspected MH may be referred for confirmatory testing. While the full details of genetic testing are beyond the scope of this review, we will briefly mention several different testing options for patients with concern for MH susceptibility. Testing can either be done *via* genetic sequencing (obtained from a blood sample) or a muscle biopsy and performance of a contracture test. While there are benefits and downsides to both testing strategies, most patients choose to undergo genetic testing as a first approach due to ease of access. Some patients choose to forego testing altogether.

Genetic testing requires a blood test sent to a testing center, and typically evaluates for *RYR1* mutations as well as *CACNA1S* and *STAC3* genes. This testing allows for the identification of the precise mutation, allowing further targeting for testing of family members. Results typically indicate one of three possibilities—no mutations, causative mutations, and variants of unknown significance. It is important to note that patients with no known causative mutations may still be MH-susceptible, especially if they have experienced an episode concerning for MH: the sensitivity for *RYR1* sequencing is thought to be approximately 70%.[28] This is likely due to a wide variety of additional mutations, yet to be described, which may be MH-causative. Patients with a causative mutation are presumed MH-susceptible, whereas patients with variants of unknown significance should be treated as MH-susceptible until further testing is performed. Further information about genetic testing centers, insurance coverage, and a patient guide can be found on the Malignant Hyperthermia Association of the United States (MHAUS) website.[29] Whole exome sequencing may increase the future sensitivity of genetic testing for the diagnosis of MH, but that remains an area of active investigation.

Muscle biopsy testing is performed at a limited number of centers across the world, and involves a freshly collected vastus lateralis muscle biopsy specimen for testing. This testing is generally performed under local anesthesia in adults, and non-triggering general anesthetics in children. Testing is recommended for confirmation in patients who experienced an MH event (ideally after waiting several months) or for patients with a first-degree relative with MH whose genetic testing is unrevealing. This testing involves taking a muscle biopsy and exposing it to RYR1 agonists, evaluating the degree of contracture. Several protocols for testing have been developed,[30,31] with both test protocols demonstrating a high sensitivity (97–99%) and a lower specificity (78–94%). Therefore, the incidence of false-negative testing is believed to be low, but the incidence of false positive testing may be considerably higher. Interpreting these results can be challenging, but a negative testing result can be considered an appropriate rule out of MH susceptibility. Positive testing results, while potentially an uncommon false positive, generally indicate that an individual

should be treated as MH-susceptible due to the potentially fatal consequences of MH in susceptible individuals. Patients with a positive contracture test should undergo genetic testing so that family members can be tested if variants are found (Fig. 1).

Integrating the results of both contraction testing and genetic testing can be challenging, and often warrant consultation with an MH expert and/or genetic counselor. Patients who receive both negative genetic testing and contracture test should be treated as not MH-susceptible given the relative sensitivity and specificity of both tests, but the management of discordant results can be nuanced.

Anesthetic Management of the MH-susceptible Patient

The mainstays of treatment for MH-susceptible patients include avoidance of triggering agents and appropriate monitoring of vital signs during anesthesia. Avoiding triggering agents include avoidance of volatile anesthetics and succinylcholine, as well as cleaning anesthesia delivery systems to avoid inadvertent exposure from prior procedures.

The anesthesia machine should be cleaned of all traces of prior anesthetics, ideally using activated charcoal filters as recommended by MHAUS. After flushing both limbs for at least 90 seconds with high-flow oxygen, the filters are applied to both inspiratory and expiratory ports. These filters have been demonstrated to keep volatile concentrations below 5 ppm for at least 12 hours when using fresh gas flows >3 L.[32,33] If these filters are unavailable, flushing the circuit with high-flow oxygen should be performed according to machine manufacturer recommendations.[33] As rubber components of anesthesia machines can emit volatile anesthetics which have been previously absorbed, high fresh gas flows should be maintained throughout the anesthetic.[34] Alternatively, a standalone intensive care unit-style ventilator not exposed to anesthetic agents can be utilized in lieu of an anesthesia machine, and some institutions will also have one anesthesia machine saved for MH-susceptible patients which is not exposed to volatile anesthetics. A new breathing circuit should be applied, and many experts recommend changing the carbon dioxide absorbent. Volatile anesthetics should be taped to the "off" position or removed from the anesthesia machine to prevent inadvertent use.

All commonly used anesthetic agents are considered safe in MH-susceptible patients, with the exception of volatile anesthetics and succinylcholine. Equipment for the initial management of an MH crisis should be readily available in the anesthetizing location. General anesthesia with propofol infusion and non-depolarizing neuromuscular blockade, regional anesthetics, or monitored anesthesia care have all been demonstrated as safe in MH-susceptible patients, and MH susceptibility in itself has not been shown to increase postoperative adverse outcomes as compared with a non-susceptible propensity-matched cohort.[35]

Many facilities will perform MH-susceptible patients as the first procedure of the day, in order to assure adequate time to prepare the operating room and to potentially allow for extended postanesthesia care unit recovery. Dantrolene pretreatment is unnecessary per MHAUS guidelines.[36] Ambulatory surgery is routinely performed in patients who are MH-susceptible, assuming a non-triggering anesthetic and an otherwise uneventful perioperative course. These patients should be given strict return precautions if they develop an elevated temperature, muscle rigidity, or dark urine concerning for myoglobinuria.

Pregnant patients who are MH-susceptible may receive neuraxial anesthesia, and if general anesthesia is required they should be managed as per the guidelines above. If a pregnant patient's partner has MH or MH susceptibility, there is a theoretical possibility of the fetus developing MH when exposed to triggering agents although no case reports of this have been published. Therefore, patients with a partner who is MH-susceptible should be treated with MH precautions until delivery per MHAUS recommendations.[36,37]



Fig. 1: Preparation for a muscle biopsy. For the *in vitro* contracture test, biopsy of the vastus lateralis muscle is done. The muscle removed needs to be immediately stored in Kreb's oxygenated solution. A skilled surgeon that can remove the muscle without injury is required. The muscle is immediately taken to the laboratory and dissected into a minimum of six contractile strips in well-oxygenated baths. Three strips are exposed to 3% halothane and the other three to increasing concentrations of caffeine. A sustained contracture on exposure to halothane and caffeine suggests MH

Clinical Manifestations of an Acute Crisis

The initial signs of MH may occur within minutes after induction of anesthesia and exposure to triggering agents, during the maintenance phase of anesthesia, or may appear after cessation. While there are a large number of potential indicators of MH, not all patients will develop all signs.

The initial clinical sign for the development of an MH crisis is the rapid increase in end-tidal carbon dioxide ($ETCO_2$) or overbreathing the ventilator. Other initial signs include severe masseter muscle rigidity, sinus tachycardia, hypertension, or electrocardiogram findings suggestive of hyperkalemia. Hyperthermia typically follows these earlier clinical signs, and temperature elevations are drastic. Later in the course, evidence of myoglobinuria may be present if significant rhabdomyolysis has occurred. Occasionally, isolated rhabdomyolysis may present postoperatively in patients with no other evidence of MH: these episodes may be under the MH spectrum and may be underrecognized due to their lack of other clinical signs (Fig. 2).

This case demonstrates the rapid rise and fall of carbon dioxide, with a slower rise and fall of core temperature.

Laboratory evidence of an acute MH episode includes evidence of a combined respiratory/metabolic acidosis, hyperkalemia, evidence of rhabdomyolysis (increase in creatinine kinase), and potential

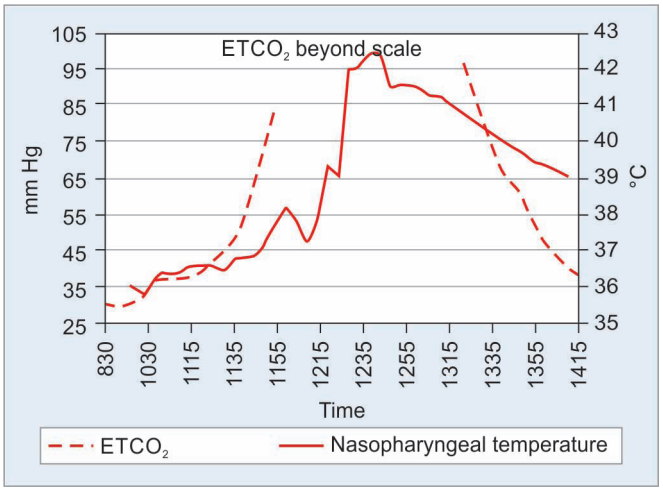


Fig. 2: End-tidal CO_2 trend and temperature in a patient with MH who received dantrolene. This case demonstrates the rapid rise and fall of carbon dioxide, with a slower rise and fall of core temperature

development of consumptive coagulopathy later in the disease course. The development of respiratory acidosis is near-universal in a large series of cases reported to the North American MH Registry, with a lower percentage also exhibiting metabolic acidemia.[10]

Common alternative diagnoses should be considered when entertaining the possibility of MH: this includes inadequate depth of anesthesia, inadvertent hypoventilation (or CO_2 rebreathing), and increased CO_2 absorption from laparoscopic or endoscopic insufflation. Postoperative fever is also a relatively common occurrence but does not generally indicate MH in the absence of other clinical signs. Other more uncommon conditions are important to consider, such as sepsis, other hypermetabolic states (thyroid storm, neuroleptic malignant syndrome, serotonin syndrome), pheochromocytoma, baclofen withdrawal, cocaine toxicity, and central nervous system-mediated fever in the setting of brain injury.

After the successful treatment of an acute event, approximately 20% of patients will experience a recrudescence defined as tachypnea, tachycardia, or hyperthermia.[38] This is the basis for the MHAUS recommendation for continued dantrolene treatment in the post-acute period.

Acute Management of MH

The most important steps for the management of an acute MH episode include prompt recognition of a crisis, discontinuing the offending agents, using charcoal filters in the anesthesia circuit, and administration of dantrolene (the antidote). The surgeon should be notified, and the procedure stopped as soon as it is safe to do so. Oxygenation and ventilation should be optimized, targeting a reduction in $ETCO_2$ and increasing inspired oxygen to 100%.

Numerous cognitive aids published by MHAUS[39] and the Stanford Emergency Manual[40] and around-the-clock help from board-certified anesthesiologists with expertise in managing MH are available *via* phone by calling the MHAUS hotline at 1-800-644-9737 (001-209-417-3722 outside the United States).

Dantrolene should be administered as soon as it is reconstituted, as each 15-minute delay in dantrolene administration is associated with a significant increase in complications.[41] With older formulations of dantrolene, reconstitution can be particularly labor-intensive: extra clinicians may be required for reconstitution. An initial loading dose of 2.5 mg/kg should be administered *via* rapid injection, ideally through a large intravenous (IV). Subsequent doses can be given every 5 minutes until a clinical response is obtained: some patients require up to 10 mg/kg to see the initial effect. Arterial access is typically obtained to allow for repeated blood gas and lab analysis, and specimens should immediately be sent for electrolytes, arterial blood gas, creatine kinase, and potentially additional labs as dictated by the clinical condition. Hyperkalemia is common and is treated with typical treatments for hyperkalemia such as calcium gluconate, insulin/dextrose, sodium bicarbonate, and albuterol. Metabolic acidosis may be treated with sodium bicarbonate, with the corollary that bicarbonate infusions will result in CO_2 production. Therefore, if bicarbonate is administered, it should be administered slowly.

Cardiac arrhythmias are common in patients experiencing an MH crisis and usually respond well to treatment and standard advanced cardiac life support maneuvers. However, the administration of calcium channel blockers is contraindicated when administering dantrolene due to worsening hyperkalemia, myocardial depression, and severe hypotension.

Rapid cooling should be initiated for severely hyperthermic patients, using cold blankets, chilled IV fluids, ice packs, and decreasing the ambient temperature of the room. Peritoneal lavage with cold saline has been advocated for the treatment of refractory hyperthermia.[42] Insertion of a urinary catheter should be performed, in order to monitor urine output and decrease the risk of myoglobinuria-associated kidney injury. Urine color monitoring should also be performed as a surrogate for the development of myoglobinuria.

In rare scenarios, extracorporeal support with the use of venoarterial extracorporeal membrane oxygenation (VA ECMO) can be performed in patients with MH who have refractory cardiac arrest despite following MHAUS protocols. There are several case reports of the strategy being used successfully.[43,44]

Post-acute Management

After the conclusion of the procedure, patients should be transferred to a monitored care setting and monitored carefully for at least 24 hours. MHAUS recommends continuing dantrolene, either as an intermittent bolus or as a continuous infusion, for at least 24 hours after the last observed sign of acute MH. Recrudescence is common[38] and may necessitate higher doses of dantrolene. Dantrolene maintenance dosing should be performed until creatine kinase downtrends, the patient is normothermic, muscle tone is no longer rigid, and the patient is stable from a metabolic perspective.

Patients with an MH event should be counseled to mention this history to all their healthcare providers and wear a medic alert bracelet. It is also recommended that inhalational anesthetics and succinylcholine be added to the patient's allergy list in the electronic medical record. Patients should be referred for confirmatory testing, and their families should similarly be referred for testing in consultation with an MH expert or a genetic counselor. MHAUS has published patient education materials detailing steps to take when determined to be MH-susceptible.[45] Patients are also recommended to avoid exercise in excessive heat, particularly with high humidity, as this may precipitate a subsequent MH crisis.

Conclusion

Malignant hyperthermia is a rare, autosomal dominant condition that presents as a hypermetabolic response after exposure to

volatile anesthetics or succinylcholine. Its pathophysiology includes abnormalities of skeletal muscle receptors, allowing excess calcium to accumulate in response to these agents. Typical signs of MH include hyperthermia, hypercarbia, tachycardia, muscle rigidity, hyperkalemia, and myoglobinuria. Prompt recognition and early dantrolene administration are key to positive outcomes, and the supplies necessary to treat MH should be immediately available wherever general anesthesia is provided.

Patients should be monitored for at least 24 hours and continued on maintenance doses of dantrolene, as recrudescence of MH is common within the first day after an event. Patients' families should be notified of the diagnosis and the need for genetic or contracture testing, and patients with a history of MH should avoid triggering agents in all future anesthetics.

Authorship Criteria

Both authors vouch that they have been involved in the following:

- Concept and design of study or acquisition of data or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be published.

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Orcid

David J Berman https://orcid.org/0000-0003-2750-4666

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