Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Malignant Hyperthermia Susceptibility and Related Diseases

Ronald S. Litman, D.O., Sarah M. Griggs, B.S., James J. Dowling, M.D., Ph.D., Sheila Riazi, M.D.

MALIGNANT hyperthermia (MH) is an inherited disorder of skeletal muscle that manifests clinically as a hypermetabolic crisis when a susceptible individual receives a halogenated inhalational anesthetic agent or succinylcholine.[1–3] The clinical signs that ensue from this exposure in susceptible individuals include hypercapnia, masseter muscle and/or generalized muscle rigidity, acidosis, peaked T waves that indicate hyperkalemia, and hyperthermia and are caused by the dysregulated entry of myoplasmic calcium, which results in a hypermetabolic cascade involving sustained muscular contractures, depletion of adenosine triphosphate, and muscle cell death.[4] The inheritance of pathogenic variants (*i.e.*, mutations) in three genes are primarily associated with MH susceptibility and account for the genetic basis of approximately 70% of patients investigated (fig. 1). The majority of MH–associated variants are found within the *RYR1* gene that encodes the skeletal muscle ryanodine receptor type I protein.[2,5–7] This protein regulates the movement of calcium from the sarcoplasmic reticulum into the intracellular space of the muscle cell. In MH–susceptible individuals, abnormalities of the ryanodine receptor result in the accumulation of excessive myoplasmic calcium in the presence of one of the anesthetic triggering agents. Nearly 700 variants have been identified in *RYR1*; however, only 35 have been functionally validated as MH–causative pathogenic variants (an up-to-date list as well as the criteria for causality may be found at the European Malignant Hyperthermia Group website).[8] The remainder await validation studies.

The most common *RYR1* variants that confer susceptibility to MH result from gain-of-function mutations in specific amino acids and regions of the RYR1 protein. These mutations may arise *de novo* or may be inherited, and the MH phenotype manifests variable expressivity and incomplete penetrance. Inheritance of MH causative pathogenic variants is suspected in individuals with a history of a likely MH clinical event or in those patients with a family history of MH susceptibility or a likely MH event. The mainstay of prevention of MH is the identification of these genetically susceptible individuals so that clinicians can then avoid triggering anesthetic agents.

There is a wide range of both dominant and recessive disorders associated with *RYR1* pathogenic variants, and many of these inherited myopathies and related conditions have been linked with MH susceptibility.[9–11] Therefore, in clinical anesthesia practice, MH susceptibility has often been assumed in patients with nonspecific muscle weakness but without a definitive diagnosis. This shotgun approach is less than ideal because most causes of muscle weakness are not associated with MH susceptibility, and this process then only results in the inaccurate labeling of patients (and their families) who would otherwise be able to safely receive volatile anesthetic agents and succinylcholine.

In this article, we build upon and summarize a body of data that have linked specific genotypic or phenotypic findings with susceptibility to MH and offer suggestions to anesthesiologists about the types of patients that should or should not receive a trigger-free general anesthetic. We discuss anesthetic management of certain congenital myopathies that may predispose to MH–like symptoms during general anesthesia, and we offer an approach to the anesthetic management of the undiagnosed patient with muscle weakness.

Diseases Associated with MH Susceptibility

The most common diseases associated with MH susceptibility are those associated with known *RYR1*-associated phenotypes, the "ryanodinopathies" (table 1). Not all patients with one of these clinical phenotypes or a proven *RYR1* myopathy will assuredly be susceptible to MH, but because MH susceptibility and myopathy co-occur in a relatively large percentage of individuals with an *RYR1* pathogenic variant (estimated to be at least 30% of individuals with *RYR1*

Corresponding articles on pages 8 and 168. Figure 1 was enhanced by Sara Jarret, C.M.I.

Submitted for publication October 2, 2016. Accepted for publication April 7, 2017. From the Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (R.S.L., S.M.G.); Division of Neurology, Hospital for Sick Children, Toronto, Ontario, Canada (J.J.D.); and Department of Anesthesia and Pain Management, University Health Network, University of Toronto, Toronto, Ontario, Canada (S.R.).

Anesthesiology 2018; 128:159-67

<zdoi;10.1097/ALN.0000000000001877>

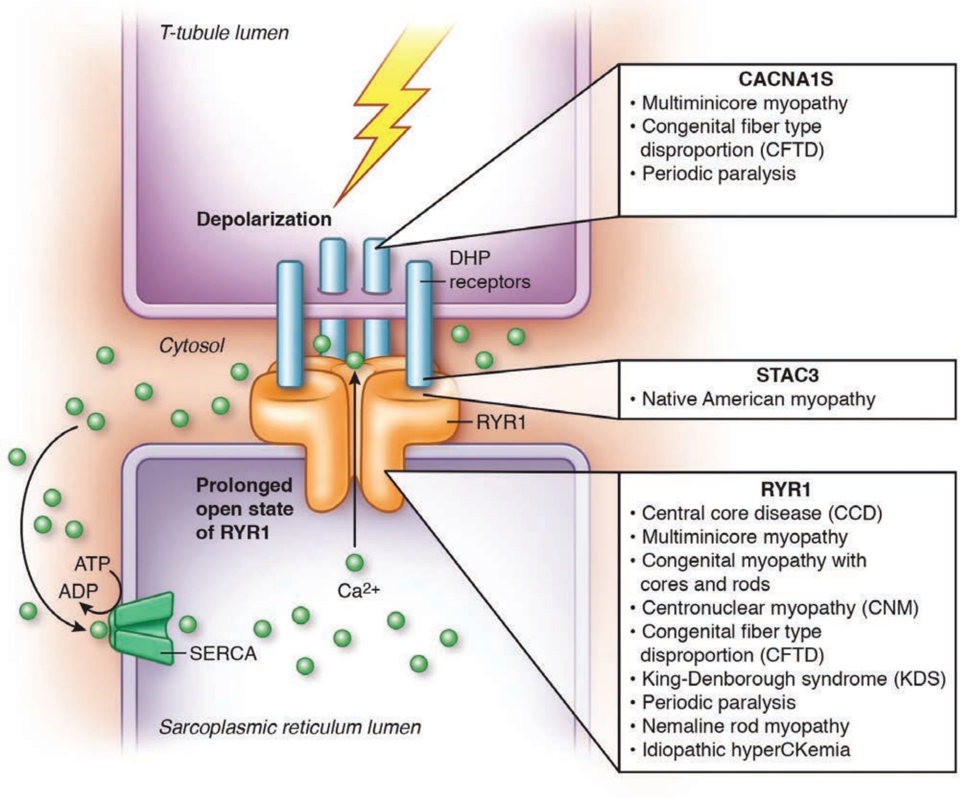

Fig. 1. Depiction of the skeletal muscle cell excitation–contraction complex and the different pathologic variants that may result in malignant hyperthermia susceptibility. ADP = adenosine diphosphate; ATP = adenosine triphosphate; CCD = central core disease; CFTD = congenital fiber type disproportion; CNM = centronuclear myopathy; DHP = dihydropyridine; KDS = King–Denborough syndrome; SERCA = sarcoplasmic/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase.

myopathies),[12] they should be considered MH–susceptible unless proven negative by a specialized MH contracture biopsy.*[17,18] In addition, it must be stressed that the clinical spectrum of the ryanodinopathies is broad, often changes with the age of the patient, and is potentially variable even within the same family where the causative pathogenic variants are the same.[10]

Patients with an *RYR1* pathogenic variant, whether or not they exhibit MH susceptibility, may appear clinically normal and may not demonstrate typical phenotypic findings of a neuromuscular disease. In fact, most patients who have demonstrated clinical MH and who have an *RYR1* variant have no overt clinical phenotype.[19–21] Some may even demonstrate enhanced muscle mass and above average athletic skills.[22] A subset of these phenotypically normal patients may develop rhabdomyolysis in response to certain conditions such as heat, exercise, administration of statin medications, or viral illness.[23–32] It is estimated that MH–related *RYR1* pathogenic variants may account for between 20 and 30% of cases of heat- or exercise-induced rhabdomyolysis.[4] Some of these patients may demonstrate an elevated baseline serum creatine kinase level,[6] and some may exhibit bleeding tendencies.[33] Patients without a phenotypic or genotypic diagnosis that have demonstrated exaggerated or frequent muscle breakdown under normal or atypical conditions should be assumed to have an underlying *RYR1* pathogenic variant that confers MH susceptibility, should not receive anesthetic triggering agents, and should undergo diagnostic neuromuscular and genetic evaluation.[34–38]

Some patients with an *RYR1* variant demonstrate a clinically evident myopathy of varying degrees in the absence of administration of anesthetic triggering agents.[39,40] In fact, *RYR1* variants are the most common cause of nondystrophic muscle disease in children.[4] Histopathologic phenotypes that have been associated with *RYR1* variants include central core disease,[40,41] multiminicore myopathy,[40,42–45] congenital myopathy with cores and rods,[46,47] centronuclear

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*MH contracture testing is considered the "gold standard" for diagnosis of an individual's MH susceptibility and is the only way to rule out MH susceptibility. In North America, it is referred to as the caffeine–halothane contracture test (CHCT), and in Europe, it is referred to as the *in vitro* contracture test (IVCT). Although there are minor differences in methodology, both contracture tests are based on the contractile response of the individual's fresh muscle tissue when it is bathed in caffeine and halothane. The sensitivity (true negative) of the CHCT is 97% (95% CI, 84 to 100%),[13] and the sensitivity of the IVCT conducted according to the European Malignant Hyperthermia Group protocol has been reevaluated as 100%.[14] Therefore, patients who have tested negative by CHCT or IVCT are ruled out for MH susceptibility and may safely receive triggering agents.[15,16]

Table 1. Phenotypes Associated with MH Susceptibility

Phenotype	Clinical Characteristics	Genotype	Association with MH
Normal	No apparent muscle symptoms.	Dominant *RYR1* or (dominant and recessive) *CACNA1S* variants.	Based on clinical MH episodes in patient or family and findings of pathogenic *RYR1* variants.
CCD	Congenital myopathy characterized by nonspecific motor developmental delays and weakness and varying degrees of clinical involvement and progression.	Dominant (and heterozygous *de novo*) *RYR1* variants.	Based on presence of *RYR1* variants and pedigree analyses of families with CCD and MH episodes.[7,42,45]
Multiminicore myopathy	Congenital myopathy characterized by generalized muscle weakness and amyotrophy, which may progress slowly or remain stable; may have ophthalmoparesis.	Recessive *RYR1* and recessive *CACNA1S* variants.	Reports of MH episodes in these patients.[12]
Congenital myopathy with cores and rods	Varying degrees of severity of hypotonia during infancy.	Most typically dominant *de novo RYR1* variants, as well as variants in NEB, ACTA1, and TPM2.	Compound heterozygosity (triplet of *RYR1* variants in one allele and fourth *RYR1* variant on the other allele) resulted in a complex phenotype of malignant hyperthermia and core myopathy.[47]
Centronuclear myopathy	Muscle weakness that may begin at birth and affect different muscle groups; may have ophthalmoparesis.	Variants in *DNM2*, *MTM1*, *BIN1*, *CCDC78*, *DNM2*, *TTN*, *SPEG*, and *RYR1.*	MH episodes likely only in patients with *RYR1* variants (and possibly *CACNA1S*, though these patients also typically have cores) and not in other subtypes.[9] There are no reports of MH in patients with centronuclear myopathy, but precautions are advisable because of possible *RYR1* variant before genetic testing is performed.
Congenital fiber type disproportion	Nonprogressive or slowly progressive myopathy with weakness and hypotonia during infancy. Clinical features include failure to thrive, developmental delays of gross motor skills, limb weakness, joint contractures and scoliosis.	Variants in *ACTA1*, *SEPN1*, *LMNA*, *RYR1*, *MYH7*, *CACNA1S*, or *TPM3*.	One study reported between 10 and 20% of congenital fiber-type disproportion is caused by variants in *RYR1*.[49] There are no reports of MH in patients with congenital fiber-type disproportion, but precautions are advisable because of possible *RYR1* variant before genetic testing is performed.
KDS	Congenital myopathy characterized by skeletal abnormalities and dysmorphic features.	Reported cases of KDS with and without variants in *RYR1*.	Multiple reports of MH in patients with KDS. Subsequent finding of *RYR1* variants in KDS patients.[50–52]
Periodic paralysis	Periods of extreme muscle weakness or paralysis based on fluctuating serum potassium levels.	Variants in *RYR1*, *CACNA1S*, or *SCN4A*.	Consider MH–susceptible if *RYR1*, *CACNA1S*, or unknown genotype.[4,62–65]
Nemaline rod myopathy	Primarily proximal muscle weakness, delayed motor development beginning in early childhood, variable in severity and progression.	Mainly associated with variants in *ACTA1*, *NEB*, *TPM3*, *TPM2*, *TNNT1*, and *CFL2*. Rarely associated with *RYR1*.[54]	Consider MH–susceptible if *RYR1* or unknown genotype.
Native American myopathy	Myopathy characterized by congenital weakness, arthrogryposis, cleft palate, ptosis, myopathic facies, short stature, kyphoscoliosis, and talipes deformities.	Variants in the *STAC3* gene.	Case reports and pedigrees reporting association with MH.[66,68]
Idiopathic hyperCKemia	Persistent elevations in serum creatine kinase levels without evidence of other neuromuscular disease.	Associated with many different entities such as undiagnosed Duchenne, variants in *CAV3*, *RYR1*, and others.	Reports of patients with hyperCKemia and *RYR1* variants have developed clinical MH.[36,37]

CCD = central core disease; KDS = King–Denborough syndrome; MH = malignant hyperthermia.

myopathy,[48] and congenital fiber type disproportion.[49] Importantly, however, patients with *RYR1* variants may have histopathologic findings that change with age and also may only have nonspecific myopathic or dystrophic changes. Patients with an *RYR1* variant may manifest King–Denborough syndrome, an extremely rare but classically described condition that is characterized by dysmorphic features, abnormal gait, and MH susceptibility.[50–53]

For the various histopathologic subtypes of congenital myopathy, only those individuals with an *RYR1* variant (as well as CACNA1S and STAC3, see below) are linked to MH susceptibility. However, many of these patients have been phenotyped (*i.e.*, histologic findings on muscle biopsy plus clinical characteristics) without confirmatory genetic analysis and thus are also considered MH–susceptible before genetic testing studies. Conversely, patients with these phenotypes and a confirmed causative variant other than *RYR1* are not considered MH–susceptible. As an example, a patient with nemaline myopathy associated with a confirmed *RYR1* variant is considered MH–susceptible,[54] whereas a patient with the same disease caused by a variant of *NEB* or *ACTA1* (among others) would not be considered MH–susceptible and does not need MH precautions.

It is well known that patients with acute or progressive muscle atrophy (*i.e.*, congenital myopathy patients and many individuals with other forms of muscle disease) may demonstrate exaggerated release of myoplasmic potassium after administration of succinylcholine.[55,56] Although these patients should not receive succinylcholine, it is not for the purpose of avoiding MH. This is discussed more fully below.

Less common loci of causality of MH susceptibility (approximately 2% of cases) are variants in the α-1 subunit of the dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor (*CACNA1S*), also part of the excitation–contraction complex in skeletal muscle. MH causative variants in *CACNA1S* have been associated with a normal clinical phenotype,[57–59] as well as with congenital myopathies that resemble some subtypes of *RYR1* myopathy[60,61] and dynamic phenotypes like potassium-related periodic paralysis.[62,63] Patients with periodic paralysis without genetic confirmation and those with a documented MH–causative *RYR1* or *CACNA1S* variant should be considered MH–susceptible. It is not yet clear whether patients with recessive *CACNA1S*-related myopathies will be at risk of MH and for now should be considered MH–susceptible until further data are available.[61] Periodic paralysis is also associated with variants in *SCN4A*, which is not associated with MH susceptibility.[64,65]

Last, MH susceptibility is associated with pathologic variants in the *STAC3* gene. These variants are manifested most commonly as Native American myopathy,[66–68] a rare disorder found in the Lumbee Native Americans of North Carolina. More recently, individuals with MH outside of the Lumbee population have also been reported to have *STAC3* variants, but the exact association between *STAC3*, MH susceptibility, and the other features of Native American Myopathy are not yet clear.

In the modern era of increasingly accessible genetic analysis, we can now more precisely associate certain diseases with MH susceptibility based on the presence of similar variants that alter the contractile apparatus and its response to exposure to anesthetic triggering agents. However, there is no definitive method by which to characterize with certainty the link between an inherited condition and MH susceptibility. Therefore, patients with a personal or family history of an MH–like event related to the administration of general anesthesia and who have demonstrated the presence of an *RYR1*, *CACNA1S*, or *STAC3* gene variant should be considered MH–susceptible unless proven negative by contracture biopsy. Patients with associated phenotypes that have not been characterized by genotype should also be considered MH–susceptible until found to have an unrelated variant that is not associated with MH susceptibility.

Diseases Associated with Non-MH Anesthetic-induced Rhabdomyolysis

Some myopathic conditions have been associated with the development of fatal or life-threatening rhabdomyolysis upon exposure to volatile anesthetic agents or succinylcholine (table 2). The most common of these conditions are Duchenne and Becker muscular dystrophy. Although rhabdomyolysis with hyperkalemia can be a feature of MH, the MH syndrome usually manifests signs of hypermetabolism, such as respiratory acidosis, metabolic acidosis, and excessive heat production. The development of life-threatening rhabdomyolysis with hyperkalemia after administration of succinylcholine to patients with Duchenne or Becker muscular dystrophy is well documented;[69] therefore, succinylcholine is contraindicated in patients with these disorders and other conditions with acute or progressive muscle atrophy (*e.g.*, acute burns, stroke, and others).[55] The use of volatile anesthetics without succinylcholine have been reported to cause non–MH–related rhabdomyolysis and hyperkalemia in patients with these dystrophies,[70–75] and even though published case series have documented the safe administration of volatile agents to patients with Duchenne and Becker dystrophy,[76,77] some authors and patient organizations have advocated the strict avoidance of volatile anesthetics in this patient population.[78–81] Conversely, the use of intravenous anesthesia alone has been implicated in the development of heart failure related to preexisting disease in patients with Duchenne dystrophy.[82,83] Thus, existing and potential comorbidities (*i.e.*, cardiac and respiratory dysfunction) in this patient population may also be important factors that determine overall perioperative outcomes.[84] Other myopathies reported to be associated with rhabdomyolysis around the time of administration of general anesthesia include carnitine palmitoyltransferase type 2 deficiency[85,86] and merosin-deficient congenital muscular dystrophy.[87,88] There is currently insufficient evidence to make firm suggestions for avoidance of MH–triggering anesthetics in patients with these phenotypic entities.

There exist a number of case reports that describe distinct phenotypic entities that have, on occasion, demonstrated MH or an MH–like syndrome (*i.e.*, hyperthermia, rhabdomyolysis, and others) in response to volatile anesthetic agents. Invariably, these reports do not contain enough information to confirm a clinical diagnosis of MH, and there is not an established genetic link between the phenotype and an MH–associated genotype. For these reasons, we do not consider them to have a known or suggested association with MH susceptibility. They include Schwartz–Jampel syndrome,

Table 2. Diseases Associated with Non-MH Anesthetic-induced Rhabdomyolysis

Disease	Clinical Characteristics	Genetics	Association with MH
DMD	Progressive proximal muscular weakness with cardiac involvement.	Dystrophin (*DMD*) variants (X-linked).	No association with MH, but fatal and life-threatening hyperkalemia reported with administration of succinylcholine and volatile agents.[69]
Becker muscular dystrophy	Less severe form of muscular dystrophy than Duchenne; characterized by muscle wasting and weakness at variable ages.	Dystrophin (*DMD*) variants (X-linked).	No association with MH, but fatal and life-threatening hyperkalemia reported with administration of succinylcholine and volatile agents.[74,75]
CPT2 deficiency	Recurrent episodes of rhabdomyolysis triggered by prolonged exercise, fasting, or febrile illness.	Variants in *S113L*, *P50H*, *Q413fs-F448L.*	One report of a child with CPT2 deficiency that developed rhabdomyolysis after exposure to a volatile anesthetic agent.[86] In a population of MH–susceptible individuals, none had CPT2 deficiency.[85]
Merosin-deficient congenital muscular dystrophy	Congenital muscular dystrophy characterized by muscle weakness apparent at birth.	Recessive variants in *LAMA2*.	One report of an MH–like episode after a nontriggering anesthetic.[87] There is no evidence of a link to MH susceptibility.

CPT2 = carnitine palmitoyltransferase type 2; DMD = Duchenne muscular dystrophy; MH = malignant hyperthermia; Non-MH = nonmalignant hyperthermia.

Noonan syndrome, arthrogryposis multiplex congenita, all mitochondrial myopathies, osteogenesis imperfecta, and Freeman–Sheldon syndrome.[89–94]

Approach to Undiagnosed Hypotonic Patients

One of the most vexing clinical situations faced by anesthesiologists is how to determine the MH–susceptibility status of a hypotonic and/or weak patient that has not yet received a phenotypic or genotypic diagnosis. Although the clinical spectrum of the ryanodinopathies is extensive,[95] it would be unreasonably cautious to consider all hypotonic patients (and their extended families) to be MH–susceptible because most hypotonia in children is central in origin.[96] Because *RYR1* variants presently constitute the most common nondystrophic type of congenital muscle disease, we suggest that genetic testing be performed before muscle biopsy because current recommendations for the evaluation of congenital myopathies and congenital muscular dystrophies are now favoring genetic testing before biopsy in the diagnostic process.[97] However, in the absence of a diagnosis, patients should be considered MH–susceptible when they possess any of the following clinical characteristics: (1) statement from the patient's primary physician or other healthcare worker that they or a closely related family member are suspected to have an *RYR1*-, *CACNA1S*-, or *STAC3*-related myopathy based on their medical history or physical findings; (2) personal or closely related family history of suspected MH during general anesthesia with triggering agents in the absence of a negative contracture biopsy (*i.e.*, caffeine–halothane contracture test or *in vitro* contracture test); or (3) personal or closely related family history of frequent exaggerated episodes of creatine kinase increase, rigidity, or evidence of rhabdomyolysis in response to exercise, heat exposure, or statin administration.

Ideally, infants with hypotonia should have a neurologic consultation before the administration of general anesthesia to provide the anesthesia team with the best possible information about their diagnosis and risk of MH susceptibility. In neonates with hypotonia, nearly all underlying diagnoses are not associated with an increased risk of MH. Most cases of neonatal hypotonia are caused by central nervous system dysfunction such as hypoxic ischemic encephalopathy or chromosomal syndromes such as trisomy 21, and these conditions are distinguishable from myopathies by history and examination. In the setting of weakness in an older child where a muscle disease may be suspected, nontriggering agents may be considered until the appropriate diagnosis has been established or when *RYR1*, *CACNA1S*, and *STAC3* mutations have been excluded. However, the extensive clinical experience of the authors has shown that these conservative measures are unnecessary because of the paucity of cases of intraoperative MH in these undiagnosed children when triggering anesthetics are used.

Anesthesiologists should be well versed about the anesthetic implications of the diagnoses and should consult with an MH expert from the Malignant Hyperthermia Association of the United States to determine the risk of MH with triggering agents. The decision about the most appropriate anesthetic technique should be discussed beforehand with the surgical team as well as with the patient, and/or their parents when applicable, especially when the diagnosis is unknown.

Who Needs a Nontriggering Technique?

In this review, we attempted to develop a categorization scheme that uses phenotypic and genotypic classifications to determine the types of diseases that are linked with MH susceptibility (table 3). Nearly all of the diseases associated with MH susceptibility can reasonably be assumed to be due to pathogenic variants in *RYR1*, with a few additional patients having variants

Table 3. Who Needs a Nontriggering Technique?

The following types of patients should be considered malignant hyperthermia (MH)–susceptible and should not receive anesthetic triggering agents (*i.e.*, volatile inhalational anesthetics and succinylcholine) unless proven not MH–susceptible by a negative specialized contracture biopsy test in an approved MH biopsy center (http://www.mhaus.org/testing/muscle-biopsy-chct/chct-muscle-biopsy-testing-centers/; accessed August 28, 2017):

- Any patient with a personal or closely related family history of a clinical MH–like event while anesthetized with triggering agents.
- Any patient with a personal or closely related family history of a previous MH–like event (*e.g.*, rhabdomyolysis, masseter or generalized rigidity, acidosis, and others) without exposure to triggering agents. Historically these events have been related to environmentally hot conditions, exercise, or administration of statin medications.
- Any patient with a personal or closely related family history of a suspected or confirmed pathogenic variant of *RYR1*, *CACNA1S*, or *STAC3*, regardless of their past history of uncomplicated administration of triggering anesthetics. Family members of these probands that do not harbor the same pathogenic variant are not considered MH–susceptible. Individuals with an *RYR1* variant that has not been strictly characterized as pathogenic according to the European Malignant Hyperthermia Group criteria are assessed for MH susceptibility on a case-by-case basis, taking into account other pertinent factors in the history and physical examination, such as evidence of previous MH in the patient or their closely related family members, and input from experts in the genetic testing of MH.[13]
- Prior to confirmatory genetic testing, patients with personal or closely related family history of congenital muscle weakness consistent with phenotypes associated with known MH–causative pathogenic variants. These include central core disease, King–Denborough syndrome, multiminicore myopathy, congenital myopathy with cores and rods, centronuclear myopathy, congenital fiber type disproportion, and Native American myopathy.

MH = malignant hyperthermia.

of *CACNA1S* and *STAC3* that are also associated with MH susceptibility. Although the preponderance of patients with MH susceptibility may appear phenotypically normal, MH is associated with certain defined clinical phenotypes related to *RYR1* variants including but not limited to central core disease, multiminicore myopathy, congenital myopathy with cores and rods, congenital fiber type disproportion, centronuclear myopathy, and, rarely, King–Denborough syndrome. An increased incidence of MH susceptibility has also been noted in patients that have experienced exaggerated and repeated (and sometimes fatal[38]) rhabdomyolysis as a result of heat, exercise, or statin administration. A unique situation that may occasionally be encountered is a patient with a proven *RYR1* variant that has not been strictly characterized as causative according to the European Malignant Hyperthermia Group criteria. The MH susceptibility status of these patients should be made on a case-by-case basis, taking into account other pertinent factors in the history and physical examination, such as evidence of previous MH in the patient or their family and input from experts in the genetic testing for MH.[14]

Until further knowledge in this area has accumulated, there will be areas of uncertainty where anesthesiologists will have to use their contextual clinical judgment regarding whether to proceed with a nontriggering technique without definitive cause, thus labeling the patient and their family as MH–susceptible for an indefinite period. For example, in Brody myopathy with fast-twitch skeletal muscle sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase mutations,[98] there is only slight evidence of a possible link between the disease and MH susceptibility,[99] but the pathophysiologic aspects of the disease would suggest that anesthetic triggering agents may cause an abnormal increase in myoplasmic calcium, triggering an MH–like event. In cases like this, avoidance of triggering agents is probably the safest approach, even though a definitive link is unproven. A more common example where anesthesiologists must use their contextual judgment is when a healthy patient presents with a vague history of a relative who developed hyperthermia in the perioperative period, often in the distant past, and no medical records about that relative's episode are available. This situation should prompt a thorough, yet time-sensitive review of the medical history of the family in an attempt to search for comorbidities, other complications or MH–like episodes during anesthesia, and occurrences of previous anesthetics with and without triggering agents. Administration of both triggering and nontriggering agents may be reasonably justifiable, depending on the individual circumstances.

Other degenerative primary muscle disorders, such as Duchenne or Becker muscular dystrophy, are associated with development of life-threatening rhabdomyolysis during or immediately after exposure to triggering agents, but this response does not represent classic MH because of the lack of concomitant hypermetabolic symptoms. These patients should not receive succinylcholine or inhaled anesthetic agents unless indicated for unavoidable clinical reasons.

Acknowledgements

The authors gratefully acknowledge the assistance of the anonymous reviewers, who greatly enhanced the quality of this paper, and Henry Rosenberg, M.D., director of medical education and clinical research, Saint Barnabas Medical Center, Livingston, New Jersey, for his lifelong dedication to helping patients with MH, and for his unselfish collegiality that made possible the academic careers of many MH researchers and educators, and resulted in the publication of this paper.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Litman: Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, Pennsylvania 19104. Litmanr@email.chop.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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