

Chapter 29 – Malignant Hyperthermia


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Malignant hyperthermia (MH), an eerie and erratic metabolic mayhem, is a clinical syndrome that in its classic form occurs during anesthesia with a potent volatile agent such as halothane and the depolarizing muscle relaxant succinylcholine, producing rapidly increasing temperature (by as much as 1° C/5 min) and extreme acidosis. The effects result from loss of control of intracellular calcium levels and compensatory acute, uncontrolled increases in skeletal muscle metabolism that may proceed to severe rhabdomyolysis. Initially, the mortality rate was 70%; earlier diagnosis and use of dantrolene have reduced it to less than 5%. MH now occurs in muted forms because of diminished use of succinylcholine, diagnostic awareness, early detection through end-expired carbon dioxide, use of less potent triggers, and use of drugs that attenuate its onset. Wilson and colleagues^[1] first used the term *malignant hyperthermia* in print in 1966. A Danish survey^[2] indicates an incidence of fulminant MH of one case per 250,000 anesthetics. However, considering only potent anesthetics and succinylcholine, one case of fulminant MH occurred per 62,000 anesthetics. The incidence of suspected MH was one case per 16,000 anesthetics or one case per 4,200 anesthetics involving potent volatile agents in combination with succinylcholine.

Public education and communication are provided by a layman's organization, Malignant Hyperthermia Association of the United States (MHAUS, 11 E. State Street, P.O. Box 1069, Sherburne, New York 13460-1069; telephone: 1-607-674-7901; fax: 1-607-674-7910; email: mhaus@norwich.net; web site: www.mhaus.org ) and by a medical professional's 24-hour, 7-day telephone service for emergency consultation, the MH Hotline (1-800-MHYPHER, or 1-800-644-9737). The professional subsidiary of MHAUS, the North American MH Registry, collates findings from biopsy centers in Canada and the United States and provides access to specific patient data through the Hotline or its Director, Dr. Barbara Broom (North American MH Registry of MHAUS, Room 7449, Department of Anesthesiology, Children's Hospital, University of Pittsburgh, 3705 Fifth Avenue at DeSoto St., Pittsburgh, Pennsylvania, 15213-2583; telephone: 1-888-274-7899; fax: 1-412-692-8658; email: bwb@pitt.edu).

Of the three forms of the ryanodine receptor, RYR1, RYR2, and RYR3, only mutations in RYR1 have been linked to MH. The genetics of MH and the related abnormal function of RYR1 are being investigated at the molecular biologic level, with the porcine model providing intricate detail. Equivalent parallels in humans are limited by scarcer material for scientific study and the difficulty in identifying underlying sources of abnormal responses, complicated by the fact that phenotypes vary within a genotype (i.e., discordance between genetic results and MH testing by contracture studies). Dantrolene remains essential in therapy, although its mechanism of action is elusive. Standardization of in vitro MH muscle contracture testing with two slightly different protocols, the European (contracture test [IVCT]) and the North American (caffeine-halothane contracture test [CHCT]), has resulted in sufficiently large databases to confirm sensitivity and specificity. Diagnostic challenges

occur with intra-anesthetic changes that mimic MH, particularly in its earlier manifestations.

HISTORY

Between 1915 and 1925, one family experienced three anesthetic-induced MH deaths featuring rigidity and hyperthermia and was puzzled for decades regarding the cause of these deaths. Susceptibility was eventually confirmed in three descendants.^[3] In 1929, Ombrédanne^[4] described anesthesia-induced postoperative hyperthermia and pallor in children with significant mortality (i.e., Ombrédanne's syndrome) but did not detect familial relationships. Critical worldwide insight into MH began in 1960, when Denborough and Lovell^[5] described a 21-year-old Australian with an open leg fracture who was more anxious about anesthesia than about surgery because 10 of his relatives had died during or after anesthesia. Lovell initially anesthetized him with the then-new agent halothane, halted it when signs of MH appeared, and subsequently used spinal anesthesia. Further evaluations of affected families came from George Locher in Wausau, Wisconsin, in conjunction with Beverly Britt in Toronto, Canada. Direct skeletal muscle involvement rather than central loss of temperature control was established by recognition of increased muscle metabolism or muscle rigidity early in the syndrome, low-threshold contracture responses,^[6] and elevated values for creatine kinase (CK).

Swine inbred for muscle development (e.g., Landrace, Pietrain, Poland China) provide an excellent animal model. The single-point mutation producing porcine MH is probably caused by the random occurrence of the altered *RYR1* allele, followed by deliberate inbreeding for desirable traits. International sharing of breeding stock accounts for its worldwide spread. Affected swine are detected by testing for the ubiquitous Arg615Cys mutation. The experimental model evolved from earlier reports describing unsuitable pork^[7]; the stresses of the abattoir result in accelerated metabolism and rapid deterioration of the muscle, resulting in pale, soft, exudative pork.^[8] Its incidence increased with breeding patterns designed to produce rapid growth rate, superior muscling, and hybrid vigor, although the drawback is a link with stress susceptibility. This increased incidence led to the term *porcine stress syndrome*.^[9] Any stresses, such as separation, shipping, weaning, fighting, coitus, or preparation for slaughter, can lead to increased metabolism, acidosis, rigidity, fever, and death.

In 1966, Hall and coworkers^[10] reported MH induced by halothane and succinylcholine in stress-susceptible swine. The human and porcine forms are virtually identical in comparisons of the clinical and laboratory changes of anesthesia-induced MH.^[11] In 1975, Harrison^[12] described the efficacy of dantrolene in preventing and treating porcine MH, which was confirmed in humans by a multihospital evaluation of dantrolene used to treat unanticipated anesthetic-induced episodes.^[13] MH in swine is a manifestation of a generalized susceptibility to stress. Stress-induced awake triggering is common in MH-susceptible swine but uncommon in MH-susceptible humans.

MH presents several paradoxes. Anesthetics are inconsistent in their ability to trigger MH and are frequently ineffective in triggering episodes in affected humans^[14]; this may be related to delay of the response by various depressants and nondepolarizing muscle

relaxants.^[15] Conversely, "safe" anesthetics, which are more appropriately described as those less likely to trigger MH, can still be associated with apparent MH episodes; these have always responded appropriately to dantrolene.^[16] Susceptible individuals appear normal in regard to structure and function until they are stressed, complicating detection of the condition. Detection requires an anesthetic challenge, an invasive and destructive muscle biopsy with contracture responses to caffeine or halothane, or genetic investigation for causative mutations.

PATHOPHYSIOLOGY AND MOLECULAR BIOLOGY

MH is a myopathy, usually subclinical, that features an acute loss of control of intracellular calcium ions (Ca^{2+}). Normal muscle contraction is initiated at the neuromuscular junction (i.e., the motor end plate). Acetylcholine is released from the terminals of motor neurons and diffuses a short distance to the postsynaptic membrane, where binding to nicotinic cholinergic receptors triggers a wave of depolarization referred to as an *excitatory postsynaptic potential* (EPSP) that leads to action potentials that propagate to transverse tubules (T tubules). The T tubules act as conduits to bring action potentials deep within the myofibrils, where their excitatory signal is transduced to the junctional face of sarcoplasmic reticulum (SR) within the muscle cells to initiate release of Ca^{2+} stored within the SR terminal cisternae. In skeletal muscle, the release of SR Ca^{2+} is an essential step for contraction. The whole process, from T-tubule depolarization to release of SR Ca^{2+} , is called excitation-contraction (EC) coupling. Knowledge of the molecular events contributing to EC coupling is essential to understanding the cause of MH.

Skeletal EC coupling begins deep within the T-tubule membrane at high-density, voltage-gated L-type Ca^{2+} channels, historically labeled *dihydropyridine receptors* (DHPRs). The DHPR possesses an integral membrane voltage sensor whose function is to respond to T-tubule depolarization and initiate long-range conformational changes within the Ca^{2+} channel complex. Voltage-dependent activation of DHPR opens an integral Ca^{2+} -selective conductance path that permits entry of small amounts of Ca^{2+} into the muscle cell. The entry of Ca^{2+} into the skeletal myotube is not necessary for engaging skeletal-type EC coupling. Rather, one of the DHPR subunits (α_{1S} -subunit) provides physical links between DHPRs within T tubules and Ca^{2+} release channels within junctional SR. Skeletal muscle expresses a specific type of Ca^{2+} release channel called the *skeletal isoform*, or RYR1. Skeletal EC coupling is the result of physical coupling between α_{1S} -subunits and RYR1 at specialized "triadic" regions where the T-tubule membrane comes in close apposition to junctional SR and does not depend on the influx of Ca^{2+} . After EC coupling is initiated, the free, ionized, unbound intracellular Ca^{2+} concentration within the relaxed muscle cell increases from 10^{-7} M to about 5×10^{-5} M. The increase in Ca^{2+} removes the troponin inhibition from the contractile proteins, resulting in muscle contraction. Intracellular Ca^{2+} pumps (i.e., sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase [SERCA] pumps) rapidly reaccumulate Ca^{2+} back into the SR, and relaxation occurs when the concentration is restored to less than mechanical threshold. Contraction and relaxation require adenosine triphosphate (ATP); both are energy-related processes that consume ATP (Fig. 29-1).

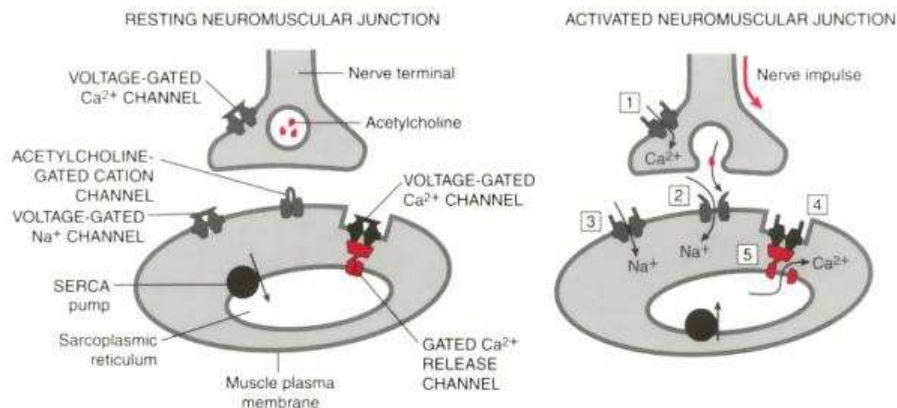


Figure 29-1 The key ion channels involved in neuromuscular transmission and excitation contraction coupling. Nerve impulses arriving at the nerve terminal activate voltage-gated Ca^{2+} channels (1). The resulting increase in cytoplasmic Ca^{2+} concentration is essential in exocytosis of acetylcholine. Binding of acetylcholine to postsynaptic nicotinic cholinergic receptors activates an integral nonselective cation channel, which depolarizes the sarcolemmal membrane (2). Depolarizing the sarcolemma to threshold activates voltage-gated Na^{+} channels (3), which propagate action potential impulses deep into the muscle through the transverse tubule system. Within the transverse tubule system, L-type voltage-gated Ca^{2+} channels sense membrane depolarization and undergo a conformational change (4). A physical link between the α_1 -subunit and the ryanodine receptor is thought to transfer the signal to sarcoplasmic reticulum to induce the release of stored Ca^{2+} (5). (Adapted from Alberts B, Bray D, Lewis J, et al: *Molecular Biology of the Cell*, 3rd ed. New York, Garland Press, 1994.)

Clinical and laboratory data for swine and humans indicate decreased control of intracellular Ca^{2+} , resulting in a release of free, unbound, ionized Ca^{2+} from storage sites that normally maintain muscle relaxation. Aerobic and anaerobic forms of metabolism increase to provide added ATP to drive the Ca^{2+} pumps that maintain Ca^{2+} homeostasis in SR and mitochondria and across the sarcolemma in extracellular fluid. Virtually all of these reactions are exothermic (i.e., they produce heat). Rigidity occurs when unbound myofibrillar Ca^{2+} approaches the contractile threshold. Dantrolene is therapeutic because it reduces Ca^{2+} release from the SR without altering Ca^{2+} reuptake.

Molecular Events in Excitation-Contraction Coupling

Understanding the mechanisms underlying MH requires a more detailed description of the process of EC coupling, the process by which skeletal muscle transforms a chemical signal in the form of a neurotransmitter at the surface of the fiber into muscle contraction. [\[17\]\[18\]\[19\]](#)

[Figure 29-1](#) depicts a neuromuscular junction in which an efferent motor neuron synapses with muscle fibers to form a motor end plate. Membrane depolarization at the nerve terminal activates voltage-dependent Ca^{2+} channels on the presynaptic membrane. Most members of the family of voltage-dependent Ca^{2+} channels are composed of five subunits: α_1 , α_2 , β , γ , and δ . Although subunits α_2 , β , γ , and δ contribute important membrane targeting and modulatory functions, it is the larger α_1 -subunit that performs essential functions of voltage sensing and conduction of Ca^{2+} . Specifically, it is the N-type channel (i.e., $\text{Ca}_v2.1$ in International Union of Pharmacology nomenclature, α_{1A} in alternate

nomenclature) that is primarily responsible for depolarized induced Ca^{2+} entry into motor nerve terminals. Rise of cytosolic Ca^{2+} concentrations within the nerve terminals initiates a process of vesicle migration and fusion that leads to exocytosis of acetylcholine stored within the synaptic vesicles. Simultaneous release of thousands of quanta of acetylcholine results in EPSPs. Acetylcholine binds to nicotinic acetylcholine receptors, which are nonselective cation channels, and activates inward current (primarily carried by sodium ions), thereby depolarizing the muscle cells. When EPSPs sum to threshold, action potentials are propagated from the sarcolemma to the T tubule. Acetylcholinesterase in the synaptic cleft catalyzes rapid breakdown of acetylcholine; rapid removal from the cleft enables the motor unit to be ready for another stimulus within a few milliseconds.

Within the T-tubule membrane of skeletal muscle, a highly homologous relative of the N-type channels, the L-type voltage-gated Ca^{2+} channel ($\text{Ca}_v1.1$ or α_{1S}), or DHPR, is enriched within the T-tubule membrane. Three chemical classes of drugs used for controlling cardiovascular function—dihydropyridines, phenylalkylamines, and benzothiazepines—are also capable of blocking DHPRs by direct interaction with α_1 -subunits. In skeletal muscle, it is α_{1S} -DHPR that participates in EC coupling. Unique to skeletal muscle is the highly ordered arrangement of α_{1S} -DHPRs into linear arrays of clustered tetrads. Electron microscopic and immunocytochemical analyses indicate that each α_{1S} -DHPR tetrad is close to (superimposed above) a single RYR1 within the junctional face of SR terminal cisternae (Fig. 29-2). Because each functional RYR1 channel is composed of a tetramer of four identical subunits, each α_{1S} -DHPR overlies a single RYR1 subunit. The relative restrictions imposed by the dimensions of α_{1S} -DHPR tetrads and RYR1 tetramers permit only alternate RYR1 channels to pair with α_{1S} -DHPR tetrads. In common with other voltage-gated ion channels, each α_{1S} -DHPR possesses a stretch of amphipathic amino acids within the fourth α -helix (S4) of each of four transmembrane domains that functions as a voltage sensor within the T-tubule membrane. Membrane depolarization induces a discrete movement of charge within the S4 segment of the α_{1S} -DHPR. A mechanical signal, thought to be in the form of a conformational transition, is transmitted to the cytoplasmic loop between repeats II and III of the α_{1S} -DHPR. Significant evidence exists for a direct physical coupling between the II-III loop of α_{1S} -DHPR and multiple noncontiguous regions within the large, hydrophilic cytoplasmic domain of RYR1. Such physical links transmit essential signals across the narrow gap of the triadic junction that activate RYR1 and release Ca^{2+} from SR. This conformational coupling model is consistent with the nature of skeletal muscle EC coupling, which is independent of extracellular Ca^{2+} . However, after the initial signal activates Ca^{2+} release from SR, Ca^{2+} -induced Ca^{2+} release appears to play a role in regulating the temporal and quantitative characteristics of RYR1 activation. RYR1 also sends a retrograde signal to α_{1S} -DHPR, enhancing its Ca^{2+} entry function. However, unlike Ca^{2+} entry mediated by α_{1S} -DHPR, which is essential for cardiac EC coupling, Ca^{2+} entry through α_{1S} -DHPR is neither essential nor needed for engaging skeletal type EC coupling. Bidirectional signaling between α_{1S} -DHPR and RYR1 in skeletal muscle appears to represent a fundamental mechanism involving conformational coupling between sarcoplasmic/endoplasmic reticulum Ca^{2+} release channels and voltage- or store-operated Ca^{2+} entry (SOC) channels within the surface membrane in a variety of mammalian cells.

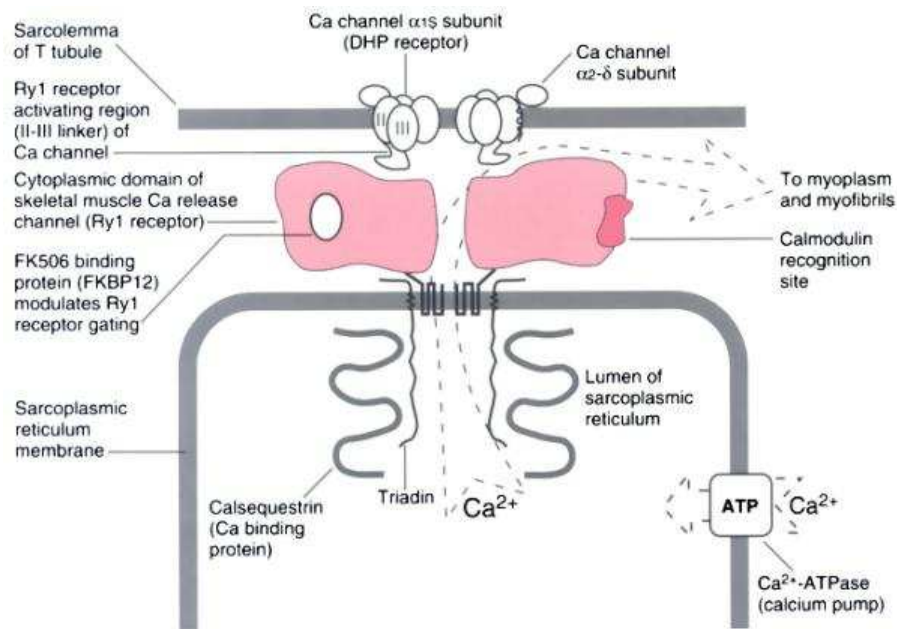


Figure 29-2 Schematic representation of the triad junction of skeletal muscle shows the junctional foot protein (ryanodine receptor [RyR1]) and its associated proteins. In skeletal muscle, the α_{1S} -subunit of the dihydropyridine receptor (DHPR) participates in excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate RyR1 and release Ca^{2+} from the sarcoplasmic reticulum. (Adapted from Pessah IN, Lynch C III, Gronert GA: *Complex pharmacology of malignant hyperthermia*. *Anesthesiology* 84:1275, 1996.)

After release into the sarcoplasm, Ca^{2+} is rapidly removed through active transport by SERCA pumps located on junctional and longitudinal SR. Calsequestrin inside the lumen of SR binds to Ca^{2+} and further enhances Ca^{2+} loading within SR. Cytosolic Ca^{2+} is typically brought back to basal nanomolar concentration within 30 msec of muscle contraction. The rapid removal of cytosolic Ca^{2+} is essential for normal muscle relaxation and requires rapid termination of Ca^{2+} efflux from SR. Aberrant termination of RYR1 activity has emerged as a key underlying mechanism in MH susceptibility.

Ryanodine Receptor

The toxic plant alkaloid ryanodine was first purified and characterized from the powdered stem wood and roots of *Ryania speciosa* Vahl by Rogers and coworkers in 1948. The alkaloid produces profound rigidity in skeletal muscle.^{[17][19][20]} Isolation of 9,21-dehydroryanodine from *Ryania* facilitated the synthesis of radiolabeled ryanodine ($[^3\text{H}]$ ryanodine) and permitted direct studies aimed at understanding the mechanism of this muscle poison. The availability of $[^3\text{H}]$ ryanodine led to identification of the RYR receptor, which is synonymous with the junctional foot protein and possesses Ca^{2+} -release channel activity. RYRs bind $[^3\text{H}]$ ryanodine with selectivity, and the high-affinity binding interaction

is sensitive to the conformational state of the channel (see [Fig. 29-2](#)). High-affinity and low-affinity ryanodine binding sites appear to be located within a 76-kd tryptic fragment from the carboxyl terminus of RYR1 of rabbit skeletal muscle ([Fig. 29-3](#)). MacLennan's group^[19] reports that the hydrophobic segments within residues 3985–4362 are thought to form the M₁ through M₄ transmembrane domains, enabling RYR1 to span the SR membrane four times. The M₁ through M₄ domains of RYR1 have high sequence homology to the analogous domains of inositol triphosphate receptors, suggesting a possible role in forming the sarcoplasmic/endoplasmic reticulum Ca²⁺ channel pore.

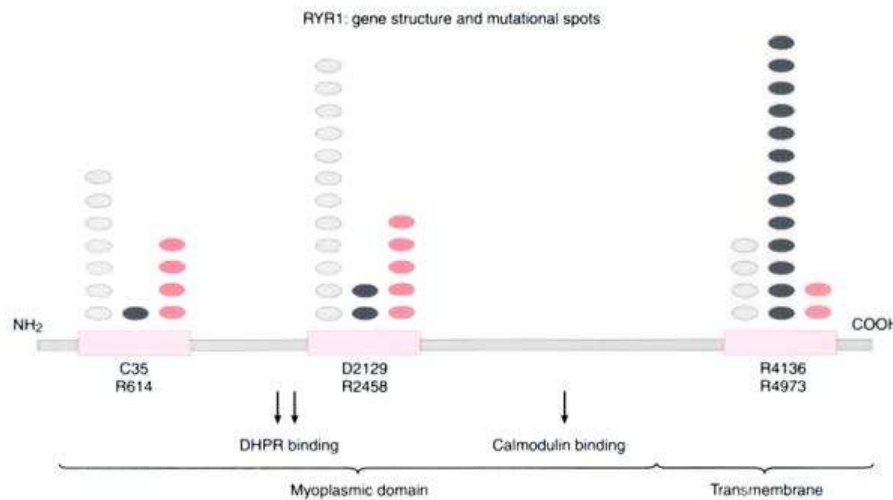


Figure 29-3 Ryanodine receptor 1 gene (*RYR1*) structure and mutational hot spots. Amino- and carboxyl-terminal domains are indicated as NH₂ and COOH, respectively. Myoplasmic and transmembrane domains are shown at the bottom and arrows indicate dihydropyridine receptor (DHPR) and calmodulin binding sites. Red boxes indicate mutational hot spots with amino acid numbers below. The ovals above represent mutations associated with malignant hyperthermia (gray), central core disease (black), or both (red). (Courtesy of N. Sambuughin, Barrow Neurological Institute, Phoenix, AZ.)

Skeletal (RYR1), cardiac (RYR2), and brain (RYR3) isoforms are encoded by three genes located on human chromosomes 19q13.1, 1q42.1-q43, and 15q14-q15, respectively. Based on sedimentation analysis and channel reconstitution studies in bilayer lipid membranes, each functional RYR consists of four identical subunits. Multiple isoforms of RYR are coexpressed in many cell types. Coexpression of different RYR isoforms in HEK293 cells has revealed that RYR2 is capable of physically interacting with RYR3 and RYR1, but that RYR1 does not interact with RYR3.^[20] Whether formation of mixed oligomeric RYRs extends beyond heterologous expression models such as HEK293 cells to mammalian tissue in situ has not been determined.

Complementary DNA (cDNA) sequence analysis reveals that each RYR protomer is composed of 5032 to 5037, 4968 to 4976, and 4872 amino residues with calculated molecular masses of 564 to 565, 565, and 552 kD for the RYR1, RYR2, and RYR3 isoforms, respectively. Typically, a sequence homology of 66% to 70% is observed between

any two conspecific isoforms. RYR receptors are also highly conserved in the same tissue among different species (>95% sequence homology of RYR1 found in mammalian skeletal muscle of human, pig, and rabbit). The tetrameric organization of the RYR1 from skeletal muscle has been corroborated by electron microscopy of cryosections of purified RYR1 protein. Three-dimensional reconstruction of RYR1 cryosections has revealed the quatrefoil appearance of each homo-oligomer, with four radial channels on the cytoplasmic face that may converge into a single, common transmembrane pore on the luminal face. Evidence of direct coupling of α_{1S} -DHPR and RYR1 has been demonstrated by expressing chimeric $\alpha_{1S/C}$ -DHPR cDNAs in dysgenic myotubes that lack constitutive expression of α_{1S} -DHPR. Such studies have provided compelling evidence that the cytoplasmic region between repeats II and III (i.e., cytosolic II-III loop) contains a stretch of 46 amino acids (L720 to Q765) that is essential for engaging bidirectional signaling with RYR1, even in the presence of drastic alterations of sequence surrounding residues L720 to L765. ^{[19][21][22]}

In addition to α_{1S} DHPR, RYR1 has been shown to interact with and be modulated by several intracellular accessory proteins. Calmodulin interacts directly with RYR1 of skeletal muscle, with a stoichiometry of two to three calmodulin molecules per subunit. The calmodulin sites with greatest affinity have been localized to the foot region of RYR1 (see [Fig 29-2](#)). Through a mechanism independent of kinase activity, calmodulin enhances channel activity at low cytoplasmic Ca^{2+} , whereas it inhibits channel activity at optimal Ca^{2+} (10 to 100 nM). Calsequestrin, the major Ca^{2+} binding protein within the SR lumen, links indirectly to a luminal domain of RYR1. The conformational change in RYR1 also conveys information to the SR lumen through calsequestrin and may be essential in regulating the Ca^{2+} release process. Functional interactions between RYR1 and calsequestrin may play an important role in regulating excitability of the Ca^{2+} channel in response to different filling states of SR. Triadin, a 95-kd, highly basic glycoprotein, was initially suggested to couple RYR1 and the α_1 -subunit of DHPR; however, amino acid analysis of triadin indicates only a single pass through the SR membrane, which contradicts its hypothesized role in coupling. The extremely high density of basic residues in the luminal terminus of triadin may be critical in interacting with the acidic moiety of RYR1. The linkage between RYR1 and triadin is thought to provide an anchorage site for calsequestrin within the SR lumen.

FKBP12, the major T-cell immunophilin, tightly associates with RYR1 in skeletal muscle with a stoichiometry of four molecules per channel oligomer. The site on RYR1 that recognizes FKBP12 is distinct from that which binds calmodulin (see [Fig. 29-2](#)). Binding of FKBP12 appears to stabilize the closed conformation of the Ca^{2+} channel complex and its full conductance transitions. The immunosuppressant FK506 promotes dissociation of FKBP12 from RYR1 by competing with a common binding site essential for protein-protein interaction of the heterocomplex. The resulting FKBP12-deficient channel conducts current with multiple subconductance states. In the presence of channel activators such as Ca^{2+} and caffeine, activity of the FKBP12-deficient channel is further enhanced by increasing the mean open time and open probability. Association of FKBP12 to RYR1 may promote cooperativity among subunits. Dissociation of FKBP12 with FK506 increases maximal binding capacity of [^3H]ryanodine with lowered binding affinity, suggesting loss of negative allosteric interaction between high-affinity and low-affinity [^3H]ryanodine binding sites. The association of FKBP12 with the RYR1 complex may be involved in promoting

cooperativity between neighboring channels. The "coupled gating" behavior of multiple channels has been reported in measurements with multiple channels reconstituted in membrane lipid bilayer by use of recombinant RYR1 (coexpressed with FKBP12) and native SR. Introduction of FK506 dissociates FKBP12 from the recombinant RYR1 complex and eliminates the coupled gating behavior of multiple channels. The cooperativity between neighboring RYR1 channels may contribute significantly to the robust release of Ca^{2+} from SR during EC coupling.

Homer proteins form an adapter system that regulates coupling of group 1 metabotropic glutamate receptors with intracellular inositol triphosphate receptors and is modified by neuronal activity. Homer proteins physically associate with RYR1 and regulate gating responses to Ca^{2+} , depolarization, and caffeine. The EVH1 domain appears to mediate the actions of Homer on RYR1 function.^[23] Dyspedic myotubes expressing RYR1 with a point mutation of a putative Homer-binding domain exhibit significantly reduced amplitude in their responses to potassium ion (K^+) depolarization compared with cells expressing wild-type protein. Homer therefore appears to be a direct modulator of increased Ca^{2+} release and EC coupling in skeletal myotubes.

Two novel proteins (60 kd and 90 kd), whose function is unknown, are also associated with the RYR1 complex. One possesses kinase activity, and the other is the substrate of this kinase. Another 150/160-kd protein also is associated with RYR1. Phosphorylation of the 150/160-kd protein by casein II kinase inhibits RYR1 channel activity.

Factors Other Than Ryanodine Receptor Abnormalities

Other cellular processes affect MH episodes. The pathophysiology of MH may be affected by various inherited abnormalities, especially in heterogeneic humans, or by secondary changes prompted by the altered RYR1. These processes include changes involving inositol triphosphate, lipase and fatty acids, and catecholamines; oxidation-reduction activity; ionic reactivity; and the mechanical threshold of muscle.

GENETICS

Mutations in *RYR1* occur in at least 50% of susceptible subjects and almost all families with central core disease (CCD). More than 30 missense mutations^[24] and one deletion^[25] have been associated with a positive contracture test (CHCT or IVCT) result or clinical MH, or both. Genetic heterogeneity in MH is documented by five other loci (17q21-24, 1q32, 3q13, 7q21-24, and 5 p), designated as malignant hyperthermia susceptibility (MHS) 2 through 6, respectively. The only known gene other than *RYR1* is the one coding for the α_{1S} -subunit of DHPR, *CACNL1A3*, in MHS3. Two causative mutations in this gene are linked to less than 1% of MHS families worldwide.^[26] For practical purposes, the *RYR1* gene remains the target for genetic analysis.

Distribution of *RYR1* Mutations

Multiple mutations that segregate with MHS are dispersed throughout the *RYR1* gene, and many silent polymorphisms are present in the coding region.^[27] Some of these have been found in patients with CCD, and in others, the *RYR1* mutation is associated with CCD and

MH phenotypes (Fig. 29-3). All reported mutations lead to an amino acid change or, in one case, a deletion, and all are putatively functional.^{[24][25]} Until recently, it was thought that most *RYR1* mutations were clustered between amino acid residues 35 and 614 (MH/CCD region 1) and amino acid residues 2163 and 2458 (MH/CCD region 2) in the myoplasmic foot region of the protein, but a third hotspot is in the carboxyl-terminal transmembrane loop of the receptor, where MHS/CCD region 3 mutations may cluster.^[28] The first mutation found in this region (Ile4898Thr) was identified in a large Mexican family with a severe and highly penetrant form of CCD, but no evidence of clinical MH was found despite exposure of 18 members to triggering anesthetics. Subsequently, 14 more mutations associated with CCD have been identified in this region, but many are private, found only in the index case and his or her family. However, mutations causing MH exist in this region. In one large Maori family, the mutation Thr4826Ile was found in five probands who experienced clinical episodes of MH and in 130 members diagnosed by IVCT.^[29]

Regional differences in the frequencies of common MHS mutations are observed across Europe. The G341R mutation (Table 29-1) is present in about 6% of Irish, English, and French families but is rare in Northern Europe. The Arg614Cys mutation is more common in German families but less frequent in other European families. G2434R, the most prevalent mutation in the United Kingdom, accounting for 17.5% of MHS families, has a low frequency in continental Europe.^[26] Frequencies of *RYR1* gene mutations detected in North Americans vary significantly from those found in Europe.^[25] The Arg614Cys and Val2168Met mutations, common in Germany and Switzerland, are rare in North America. Moreover, the G341Arg mutation, common in Ireland, England, and France, was not detected in the first 73 North American MH-susceptible patients screened for causative mutations. The mutation common to Europe and North America is G2434Arg, occurring in 4% to 7% of European and 5.5% of North American families. Overall, the mutations identified in North Americans accounted for 22% of the screened population, similar to studies in Germany and Italy.^[25] In Europe, IVCT data and *RYR1* mutations correlate well for the response to caffeine but not to halothane. In North America, all patients identified with a causative *RYR1* mutation were highly positive for the halothane response in the CHCT, but less so for caffeine. This variation may be caused by differences in the method of delivery and the concentration of halothane used in the IVCT and CHCT (see "Evaluation of Susceptibility"). Genetic screening in European and North American studies targeted only regions 1 and 2, the original two hot spots in the gene, accounting for about one fourth of the coding region of the *RYR1* gene. The absence of *RYR1* mutations in the rest of the screened population may be explained by mutations located outside these two regions or by involvement of other genes.

Table 29-1 -- Findings of the North American malignant hyperthermia mutation panel, 2002

Exon	Mutation*	<i>RYR1</i> Amino Acid Change	No. of Families in North America†	Estimated Incidence in Europe	Phenotype
6	C487T	R163C	2	2–7%	MHS, CCD

Exon	Mutation*	RYR1 Amino Acid Change	No. of Families in North America†	Estimated Incidence in Europe	Phenotype
9	G742A	G248R	2 (1+1)	2%	MHS
11	G1021A	G341R	1	6–17%	MHS
17	C1840T	R614C	6 (4+2)	4–45%	MHS
39	C6487T	R2163C	2	4%	MHS
39	G6488A	R2163H	0	1%	MHS, CCD
39	G6502A	V2168M	1	8%	MHS, CCD
40	C6617T	T2206M	2	One family	MHS
44	Deletion	ΔG2347	2	0%	MHS
44	G7048A	A2350T	1	0%	MHS
45	G7303A	G2434R	9 (5+4)	4–10%	MHS
45	G7307T	R2435H	1	2.5%	MHS, CCD
46	G7361A	R2454H	4	One family	MHS
46	C7372	R2458C	0	4%	MHS
46	G7373A	R2458H	0	4%	MHS
101	G14582A	A4861H	0	Multiple families	CCD
102	T14693C	I4898T	0	Multiple families	MHS, CCD

CCD, central core disease; MHS, malignant hyperthermia susceptibility.

* Criteria for the 17 mutations: (1) they occur in more than one family in North America or Europe, and (2) previously tested sequence variant shows that it is not a polymorphism.

† Data collaboration of the Uniformed Services University of the Health Sciences, Thomas Jefferson University, Wake Forest University, University of California, Davis, and Barrow Neurological Institute, + indicates those also found in Canada (e.g., for exon 45, four families with the mutation G2434R were found in Canada).

Inheritance and Penetrance of Malignant Hyperthermia

No longer can the inheritance of human MH be considered solely autosomal dominant with variable penetrance, because more than one genetic locus has been identified in some families. Six nonconsanguineous families harbor at least two genes causing MH.^[30] MHS homozygotes are common in affected pigs but rare in human populations. MHS homozygous humans appear clinically normal but exhibit stronger responses to IVCT and CHCT than do heterozygous individuals.^[31] They do not exhibit signs or symptoms of CCD.

Discordance in Malignant Hyperthermia Testing

Discordance has confounded linkage analysis worldwide. Examples include IVCT-tested normal (MHN) patients carrying an *RYR1* mutation or an IVCT-tested positive (MHS) patient who does not carry the familial *RYR1* mutation. Several explanations are possible: inexact thresholds for the IVCT or CHCT leading to errors in determining MHN or MHS; variable penetrance; and other unknown genes or modifier genes. Robinson and associates demonstrated by the transmission disequilibrium test (TDT) that loci on chromosomes 5 and 7 and, to a lesser extent, loci on chromosomes 1 and 7 influence susceptibility to MH.^[32] A number of families have two *RYR1* mutations on separate haplotypes.^[30] Because of discordance, it is not possible to exclude MH on the basis of genetic testing alone.^[33]

European Guidelines for Screening

In 2000, the European MH group^[33] formulated guidelines for *RYR1* mutation screening with linkage data to other loci for some MH families, but the investigators emphasized the vital role for the IVCT in the diagnosis of MH. These guidelines have reduced the number of relatives requiring contracture testing without increasing risk^{[26][34]} and include the following:

1. Confirmation of MHS in a family member (preferably a proband) by IVCT before genetic testing.
2. Use of 15 *RYR1* mutations characterized by in vitro functional assays for the genetic protocol.
3. If a causative mutation is detected in a first-degree relative, MHS is confirmed, and IVCT is omitted.
4. If a familial mutation is not detected, IVCT is necessary.

Future Genetic Testing in North America

In contrast to European genetic efforts, only a small number of MH susceptible families have been extensively investigated by North American phenotyping, linkage analysis, and screening of specific genes. Collaborative protocols over the past 5 years between MH biopsy centers and molecular biologists have screened 140–160 unrelated MHS subjects for mutations in the *RYR1* gene (see "Distribution of *RYR1* Mutations"). In September 2002, MHAUS sponsored a meeting of molecular geneticists and MH experts to examine expanded screening in North America. They achieved consensus on several points:

1. Genetic testing limitations include low sensitivity due to diversity of the mutations and genes.
2. The *RYR1* gene is the primary focus for genetic testing, but further studies are required for more complete understanding of the relationship between mutations and susceptibility.
3. Guidelines for referral and education are needed to establish clinical testing in a Clinical Laboratories Improvement Act (CLIA)-certified laboratory.

4. A North American MH *RYR1* Mutation Panel was established and agreed on a table of mutations (see [Table 29-1](#)).

Functional Changes in *RYR1* Associated with Malignant Hyperthermia Mutations

Altered SR Ca^{2+} channel gating kinetics appear to underlie the uncontrolled skeletal muscle metabolism associated with administration of halogenated anesthetics or depolarizing agents. The sustained elevation of the Ca^{2+} level in the sarcoplasm results in abusive stimulation of aerobic and glycolytic metabolism, which accounts for combined acidosis, rigidity, altered permeability, and hyperkalemia. Although studies using Ca^{2+} -selective microelectrodes have indicated that MH-affected muscle has a higher level of resting Ca^{2+} , the findings have not been confirmed by radiometric fluorescent Ca^{2+} dyes. Study of the chronologic relationship of the biochemical and clinical development of porcine MH demonstrates that the increase in intracellular Ca^{2+} concentration precedes the increase in expired carbon dioxide and the classic first sign, tachycardia.^[35]

Extensive study of the porcine model has defined the biochemical and functional changes in SR Ca^{2+} transport and RYR1 function underlying MH. The validity of the single-point porcine *RYR1* mutation^[36] for defining MH malfunction is affirmed by use of the fluorescent calcium indicator indo-1 to determine the concentration of Ca^{2+} in myoblastic cells transfected with wild-type or mutated *RYR1* complementary DNA. The cells expressing the porcine *RYR1* mutation showed higher sensitivity to caffeine. Clinical doses of halothane resulted in a rapid increase of intracellular Ca^{2+} concentration in cells expressing the mutated RYR1, whereas no changes in intracellular Ca^{2+} concentration were observed in cells expressing the wild-type receptor. These results provide definitive evidence that a single amino acid mutation, Arg615Cys, in RYR1 causes porcine MH.^{[17][18][19]}

Although active SR Ca^{2+} accumulation appears to be normal in MH-affected pig muscle, significant abnormalities in the process of Ca^{2+} release have been documented in several types of in vitro bioassays. In skinned muscle fiber preparations, the rate and the extent of Ca^{2+} release from SR were higher in fibers with MH abnormalities. These results in skinned fibers correlate well with those obtained from isolated SR membrane preparations enriched in RYR1 protein. Although initial studies revealed a difference in the Ca^{2+} threshold for activation for SR Ca^{2+} release, later studies using rapid-quench methods found no apparent difference in the sensitivity of SR Ca^{2+} release with respect to Ca^{2+} . O'Brien and Li^[37] developed a microassay that revealed functional differences in Ca^{2+} transport in SR membranes isolated from normal or from MHS pigs. They found that SR from MHS swine had normal maximal Ca^{2+} -ATPase pumping but that the activity of RYR1 after addition of a bolus of Ca^{2+} was 50% greater in heterozygotes and 100% greater in homozygotes for the mutation. Hypersensitivity to receptor agonists, such as caffeine, and an associated hyposensitivity to inhibition with magnesium (Mg^{2+}) was also demonstrated. There has been some controversy about whether changes exist in the sensitivity of MH-affected muscles to inhibition by Mg^{2+} compared with normal fibers. Owen and colleagues^[38] demonstrated that fibers from pigs heterozygous or homozygous for the *RYR1* MH allele needed only a smaller reduction in the free concentration of Mg^{2+} to induce Ca^{2+} release from SR. Dantrolene counteracted the effect of reduced Mg^{2+} inhibition in MH-affected

muscle. The abnormal responsiveness of MH-affected muscle to various stimuli may result from the reduced ability of myoplasmic Mg^{2+} to inhibit Ca^{2+} release from SR.

Reconstitution of channels isolated from MHS pigs studied in bilayer lipid membranes has revealed significantly reduced sensitivity to inactivating concentrations of Ca^{2+} , whereas the sensitivity of channels to activating Ca^{2+} remains unchanged. The Ca^{2+} channels from MHS pigs exhibit a significantly higher open probability compared with wild-type channels across a broad range of Ca^{2+} concentrations (7 μM to 10 μM) on the cytoplasmic face when measured at pH 6.8. Whether Ca^{2+} channels reconstituted in bilayer lipid membranes from pigs with MH susceptibility exhibit an altered response to inhibition by Mg^{2+} remains controversial. In porcine MH, Mg^{2+} inhibition of RYR1 channels was not altered, whereas there is a threefold lower potency for Mg^{2+} inhibition of MH-affected Ca^{2+} channels. Similar findings were seen in human MHS skinned fibers.^[39] The underlying cause of these various porcine experimental results is unclear, but the concentration of monovalent ions in measuring channel activity might have influenced the inhibitory potency of Mg^{2+} . Channels isolated from pigs heterozygous for the MH mutation suggest that the heterozygous porcine population of Ca^{2+} release channels contains heterotetramers with properties distinct from those of MH homozygote or normal channels. The data also imply that the population of Ca^{2+} release channels in humans with MHS who are heterozygous for a dominant mutation in this protein also contains heterotetrameric channels. In contrast to Ca^{2+} uptake and release studies with isolated SR, single-channel measurements have failed to reveal an altered sensitivity of channels to activation by caffeine.

Radioligand-receptor binding studies with nanomolar concentrations of [3H]ryanodine have determined differences between SR isolated from normal humans and pigs and those with MH susceptibility. [3H]Ryanodine binding assays represent a sensitive means of assessing functional anomalies regulating the channel pore by use of a simple tube assay. This is possible because [3H]ryanodine binds to a conformationally sensitive site within or near the channel pore. Mickelson and coworkers^[17] first demonstrated that the binding of [3H]ryanodine to MH homozygotic porcine heavy SR exhibited an altered Ca^{2+} dependence at the low-affinity (inhibitory) Ca^{2+} site and a lower affinity for ryanodine compared with normal porcine SR. However, the maximum capacity of SR to bind [3H]ryanodine was the same in both tissues, indicating an altered structure or function, or both, of the receptor rather than a change in expression associated with the disease. Studies performed with RYR1 isolated from human biopsies revealed a higher affinity for [3H]ryanodine and a higher sensitivity to activation by caffeine with MHS preparations. Surprisingly, it was the activation, not the inactivation, of the binding of [3H]ryanodine by Ca^{2+} that was abnormal in human MH SR.

DANTROLENE

Dantrolene is the drug of choice for preventing and reversing the symptoms of MH. Dantrolene sodium is a hydantoin derivative (1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]imino]-2,4-imidazolidinedione) that relaxes but does not totally paralyze skeletal muscle. These properties of dantrolene have been closely correlated with its ability to reduce Ca^{2+} efflux from SR in vitro. Dantrolene (20 μM) counteracts the effect of reduced Mg^{2+} inhibition in MH-affected muscle.^[38] Caffeine contractures induced after K^+

conditioning of porcine skeletal muscle were found to render muscles refractory to brief electrical stimulation, but there was still an enhancement of contracture tension elicited by subsequent direct caffeine stimulation of SR calcium release. This enhanced sensitivity to caffeine was inhibited by dantrolene (20 μM) and its water-soluble analog azumolene (150 μM).

Preparations of skeletal SR membrane vesicles have been used to examine the ability of dantrolene to alter Ca^{2+} fluxes. Dantrolene (10 to 90 μM) was shown to inhibit SR Ca^{2+} release, especially when assayed in the presence of caffeine and adenosine triphosphate. Later, depolarization-induced Ca^{2+} release, measured from triadic vesicles by use of a stopped-flow apparatus and fura-2, was shown to be inhibited by dantrolene.^[40] However, the exact mechanism by which dantrolene induces muscle relaxation is unclear, and some results have been conflicting. For example, halothane-activated RYR1 from frog skeletal muscle was unaffected by concentrations of dantrolene as high as 100 μM , whereas single-channel studies with porcine and human RYR1 revealed a biphasic action of dantrolene: channel activation at low (0.5 to 2 nM) concentrations and channel inhibition at a higher (5 μM) concentration. Species variability may in part account for this difference.

Experiments of radioligand-receptor binding performed with [^3H]ryanodine have shown that under certain assay conditions, micromolar concentrations of dantrolene or its water-soluble derivative azumolene could inhibit the binding of ryanodine to its conformationally sensitive site. In this respect, doxorubicin-stimulated binding was much more inhibited by dantrolene than by caffeine or Ca^{2+} -stimulated binding. These results are in agreement with Ca^{2+} transport studies with skeletal SR, in which azumolene was shown to block doxorubicin-induced Ca^{2+} release. However, a later investigation found little pharmacologic overlap between the modulation of [^3H]ryanodine and [^3H]dantrolene binding sites in porcine skeletal muscle. For example, the binding of [^3H]dantrolene was insensitive to ryanodine and Ca^{2+} and adenosine nucleotides. Experiments performed with [^3H]dantrolene have revealed that specific binding sites for the drug colocalize to junctional SR membranes with [^3H]ryanodine binding sites. [^3H]Dantrolene binding sites were not detected in T-tubule membranes or sarcolemmal membranes.

The idea that dantrolene suppresses SR Ca^{2+} release as a result of direct interactions with RYR1 has been somewhat controversial. Significant progress has been made to positively identify the location of dantrolene binding sites within the EC coupling machinery. Paul-Pletzer and associates^[41] demonstrated that [^3H]azidodantrolene, a pharmacologically active, photoaffinity analog of dantrolene, specifically labels the amino terminus of RYR1. The [^3H]azidodantrolene binding site was localized to the 1400-amino acid residue fragment of RYR1 cleaved by *n*-calpain, a tissue-specific isoform of this Ca^{2+} and thiol-activated protease. More detailed analysis further localized the [^3H]azidodantrolene binding site to a single domain containing the core sequence corresponding to amino acid residues 590 through 609 of RYR1.^[42] Evidence of the specificity of the [^3H]azidodantrolene photoaffinity-labeling procedure was provided based on the observation that a monoclonal antibody that recognizes the 172-kD, *n*-calpain-cleaved, amino-terminal fragment inhibited [^3H]azidodantrolene photolabeling of RYR1 in SR in a concentration-dependent manner. Ikemoto and coworkers^{[43][44]} proposed that this very region of the RYR1 structure (DP1 domain) participates in interdomain interactions that stabilize the closure of the Ca^{2+}

channel state. Based on this model, one possible mechanism by which dantrolene inhibits release of SR Ca^{2+} is by directly binding to the DP1 region and stabilizing the interdomain interaction of DP1.^[42] How dantrolene binding to the DP1 domain stabilizes rather than destabilizes interdomain interactions remains a mystery.

SPECIFIC ORGAN AND TISSUE ABNORMALITIES

Skeletal Muscle

Affected human muscle frequently has no histologic defect or else has protean nonspecific pathology so variable that none can be directly attributed to MH. These include central cores, internal nuclei, target fibers, supercontracted fibrils, and marked variation in fiber diameter.^[45]

Metabolism, Enzymatic Considerations, Heat Production, Contractures, and Fiber Type

Affected muscle is close to loss of control of intracellular Ca^{2+} . With that, aerobic (oxygen consumption [$\dot{V} \text{O}_2$]) and glycolytic metabolism increase dramatically. There is an approximately threefold increase in $\dot{V} \text{O}_2$ and a 15- to 20-fold increase in blood lactate level, with related acid-base imbalances. The earliest changes appear as an increase in muscle intracellular Ca^{2+} concentration^[35] and in the venous effluent from skeletal muscle, as decreases in pH or partial pressure of oxygen (PO_2), or as increases in PCO_2 , lactate, potassium, or temperature.^[46] These changes occur before the increases in heart rate, temperature, and circulating catecholamine levels. The most sensitive early sign during anesthesia is an increase in expired carbon dioxide (during constant ventilation), but it can be misleading (see "Diagnosis"). Heat production during acute MH derives from aerobic metabolism, glycolysis, neutralization of hydrogen ions, and hydrolysis of high-energy phosphate compounds involved in ion transport and in the contraction-relaxation process.^[47] Precise calculations of the expended energy are difficult because of unsteady metabolic and circulatory states, variable and uncontrolled heat loss, and production of heat by neutralization of acid.

Muscle rigidity in MH is a contracture, similar to a muscle cramp, that is nonpropagated, prolonged, and sometimes irreversible. Contractures are used in tissue baths in the laboratory to study various aspects of MH. The lack of consistent correlation of fiber type or fiber proteins with abnormal function underscores the difficulties in analyzing this disorder; stress is necessary to detect the abnormality. The altered RYR1 protein is expressed in fast and slow fibers.

Calcium

The SR is the intracellular organelle primarily responsible for control of intracellular Ca^{2+} transients, and mitochondria serve a secondary reserve function in binding Ca^{2+} . When intracellular Ca^{2+} levels increase beyond the capabilities of the SR, mitochondria aid in binding. The mitochondrion provides the greatest supply of ATP through aerobic metabolism; only secondarily does it bind and store Ca^{2+} . There is evidence of muscle mitochondrial binding and accumulation of Ca^{2+} during acute episodes of porcine MH.^[48] Mitochondrial deficiencies do not explain the diminished aerobic responses in MH. $\dot{V} \text{O}_2$ consistently increases about threefold during MH, in contrast to the 10-fold increase

possible during severe exercise. In view of the serious acid-base imbalances and depletion of muscle energy stores, this increase seems paradoxically low. Perhaps $\dot{V}O_2$ and ATP production by mitochondria is limited during MH by several factors, including ATP translocation, mitochondrial Ca^{2+} binding, intracellular acid-base status, and electrolyte aberrations.

Ca^{2+} antagonists are associated with hyperkalemia and potentially increased mortality in vivo when used in conjunction with dantrolene.^[49] They do not prevent or effectively treat MH in susceptible pigs.^{[50][51]} In addition to the risk of hyperkalemia with Ca^{2+} antagonists and dantrolene, there is the added hazard that the hyperkalemia could trigger MH in susceptible skeletal muscle.^[52]

Electrophysiologic Measurements

The Ca^{2+} -control abnormalities of MH are reflected in altered electrophysiology. Multiple-pulse stimulation of porcine muscle (i.e., six pulses with 5-msec spacing) demonstrated an increase in tension and an increased rate of rise of tension in susceptible pigs; this difference was accentuated after dantrolene was given, and the susceptible pig muscle recovered much more effectively from the effects of dantrolene than did that of the normal animals.^[53] This confirms abnormally increased Ca^{2+} transients through intracellular organelles. Similar differences in humans were inaccurate by MH testing,^[54] although one study suggests better precision.^[55] During slaughter, affected swine are found to have a lower (and rapidly declining) resting membrane potential than that of normal swine.^{[56][57]} This may contribute to the rapid decline of muscle pH and energy stores because this is prevented or attenuated by curarization and ventilation to maintain oxygenation.^[56] Halothane lowers mechanical threshold in susceptible and normal muscle, predisposing susceptible muscle toward the development of a contracture.^[58]

Channelopathies

One of the considerations regarding MH and disorders of EC coupling is the existence of channelopathies, disorders of the voltage-gated ion channels that control fluxes of ions across membranes.^[18] These channels are ion-conducting proteins with a membrane-spanning pore, gates, and voltage sensors, equipping them for passage of sodium, calcium, and chloride ions. Chloride channels provide 75% to 80% of membrane conductance at rest, contributing to the fast repolarization phase of the action potential. These channels are present in the surface and inner membranes of all excitable and most nonexcitable cells. There are naturally occurring mutations that alter their function with specific pathologic consequences. Abnormalities relating to skeletal muscle pathology include those of the sodium channel (i.e., hyperkalemic periodic paralysis, paramyotonia congenita, and some others, known collectively as potassium-aggravated myotonias), potassium channel (i.e., myokymias such as episodic ataxia), calcium channel (i.e., DHPR mutations causing hypokalemic periodic paralysis or dysgenic muscle in mice), and the chloride channel (i.e., myotonia congenita in humans, mice, and goats). The RYR1 is not a voltage-gated channel.

Implications of Findings in Skeletal Muscle

The single-point mutation of RYR1 in all susceptible swine is the major cause of porcine MH, ^[36] and other abnormalities are secondary or occur in parallel. Inositol trisphosphate is a major physiologic second messenger mobilizing Ca^{2+} from endoplasmic reticulum, but it does not seem to be involved in MH because it lacks the surface membrane interactions possessed by the RYR1 for SR. ^{[17][19][20]} Altered lipase, fatty acids, and triglycerides may play a more important role. ^[59] Free radical peroxidation probably occurs during porcine MH as an adaptive response to sustained stress that contributes to abnormal calcium homeostasis and fatty acid metabolism. ^[60] Volatile anesthetics and succinylcholine represent a stress for skeletal muscle because they perturb membranes and disturb Ca^{2+} homeostasis. In general, normal muscle can withstand and compensate for these stresses. In susceptible muscle, the membrane perturbation induced by halothane or the depolarization induced by succinylcholine may cause an earlier Ca^{2+} release that strikingly stimulates greater Ca^{2+} release. Coupled with the lower mechanical threshold, an early MH response may result. ^[58] Although MH-susceptible muscle may briefly tolerate these stresses, a cascading cycle of increasing metabolism, temperature, and acidosis eventually results. Skeletal muscle, about 40% of body weight, represents a sleeping giant in regard to metabolism, and once aroused, it dominates whole-body responses. MH-affected muscle may always be closer to loss of control than normal muscle. Normal muscle can respond abnormally with extremely prolonged effort, such as the overstraining disease or capture myopathy of wild animals after prolonged chase. ^[61]

Heart

Myocardial function is severely altered in human and porcine MH. Tachycardia and arrhythmias are followed by hypotension, decreased cardiac output, and eventual cardiac arrest. Porcine data suggest that these alterations are secondary; increased myocardial oxygen consumption during MH is related to β -agonist stimulation of sympathetic activation without the lactate production or potassium efflux that suggests a primary MH response. ^[62] Porcine MH myocardium does not respond abnormally to exaggerated concentrations of calcium, digoxin, potassium, or carbon dioxide. ^[52] Overall, the heart appears to be affected primarily by the tremendous, potentially ischemic demands placed on it by exaggerated whole-body metabolism. ^[63]

Central Nervous System

Central nervous system involvement during fulminant human MH appears to result from increased temperature, acidosis, hyperkalemia, hypoxia, and hypo-osmolality related to fluid shifts as factors in acute cerebral edema. The extreme picture includes coma, areflexia, and fixed, dilated pupils. Recovery varies and is related to the duration and severity of the MH episode. Severe fever (to 42.5°C [108.5°F]) may result in a virtually flat electroencephalogram and coma, but recovery is still possible. ^[64]

MH is not a central nervous system disorder, as demonstrated by the fact that a tourniquet-isolated limb remains flaccid during the whole-body rigidity of an acute episode. ^[65] Cerebral oxygen consumption and lactate production are not increased in swine during MH episodes. ^[66] Kochs and colleagues ^[67] observed early profound electroencephalographic depression during porcine MH and improvement with dantrolene, which they interpreted as

primary brain involvement. Hofer and coworkers^[68] contradicted this opinion by correlating alteration of electroencephalographic and cerebral metabolites with beginning whole-body MH episodes

Sympathetic Nervous System

Activation of the sympathetic nervous system occurs early during MH. Fight, fright, or flight can initiate an MH episode in susceptible swine without anesthetic agents.^[9] This is rarely observed in humans (see "Awake Triggering: Exercise and Heat Stroke"). During MH, circulating levels of epinephrine and norepinephrine increase markedly (e.g., from less than 1 ng/mL to 30 ng/mL). Sympathetic responses appear to be secondary in porcine MH, although the physiologic effects of sympathetic excitation can magnify the changes of an MH episode. For example, metabolic responses precede altered sympathetic activity^[46]; the MH response is unaltered despite acute sympathetic denervation (total spinal anesthesia)^[69]; infusion of norepinephrine to blood levels greater than those associated with MH does not trigger MH^{[70][71]}; and norepinephrine does not potentiate halothane-induced porcine MH, although triggering is delayed when blood flow to muscle is reduced.^[71] β -Agonist effects result in pronounced myocardial stimulation.^[62] Administration of α -agonists and β -agonists does not result in increased metabolism in susceptible porcine muscle.^{[70][72]}

Sympathetic antagonists may protect from or ameliorate episodes of MH by lowering body temperature and modifying acid-base changes.^[73] The β -antagonists appear to increase heat loss and potentially increase muscle perfusion. β -Antagonists attenuate metabolism and fever during MH but do not improve survival.^[73] They block myocardial stimulation of porcine MH, but this stimulation is secondary to β -agonist effects without evidence for myocardial MH.^[62] There is no direct evidence that the sympathetic nervous system initiates MH.^[46]

Miscellaneous Abnormalities

Disseminated intravascular coagulation is caused by the release of tissue thromboplastin during fever, acidosis, hypoxia, hypoperfusion, and gross alterations in membrane permeability.^[46] Porcine MH erythrocytes show greater fragility and peroxidation.^[74] Lymphocytes reflect MH mutations and constitute a means for MH testing.^{[75][76]} These findings directly support the alteration of porcine tissue other than skeletal muscle by MH.

Liver from normal swine transplanted into MH-susceptible swine remains normal, and liver from swine homozygous for MH that is transplanted into normal swine functions as normal.^[77] Pulmonary changes during MH appear to be secondary to systemic manifestations. These include tachypnea, hyperventilation, \dot{V} and \dot{Q} abnormalities, increased blood and expired carbon dioxide, decreased blood PO_2 , and ultimately, pulmonary edema. The increase in whole-body carbon dioxide stores during MH is better reflected by measurements of expired carbon dioxide or venous carbon dioxide than arterial measurements. Renal function during active MH is altered indirectly; oliguria and anuria result from shock, ischemia, cardiac failure, myoglobinuria, and myoglobinemia.

CLINICAL SYNDROMES

Fulminant MH is rare. The usually muted onset is quickly detected by increased levels of expired carbon dioxide, developing tachycardia, or muscle rigidity. Onset can be acute and rapid if anesthesia includes a potent inhaled anesthetic or succinylcholine. It can be delayed and may not be overt until the patient is in the recovery room. Once initiated, the course of MH can be rapid. When clinical signs, such as increased expired carbon dioxide, muscle rigidity, tachycardia, and fever, suggest MH, the association is not strong unless more than one abnormal sign is observed. A single adverse sign usually does not indicate MH.

Volatile anesthetics and succinylcholine cause affected subjects to undergo a striking increase in aerobic and anaerobic metabolism, resulting in intense production of heat, carbon dioxide, and lactate and an associated respiratory and metabolic acidosis. ^{[11][46]} These reactions markedly alter whole-body acid-base balance and temperature because of skeletal muscle bulk (40%) and are magnified as temperature increases. Whole-body rigidity occurs in almost all pigs and in most humans. Temperature may exceed 43°C (109.4°F), PaCO₂ may exceed 100 mm Hg, and pH_a may be less than 7.00. Associated with this increased permeability of muscle are increased serum levels of potassium, ionized calcium, CK (although MH-related changes do not differ overall from CK changes observed during surgery ^[78]), myoglobin, and serum sodium. ^[46] Later, serum potassium and calcium levels decrease; muscle edema may occur. Sympathetic hyperactivity (e.g., tachycardia, sweating, hypertension) occurs early as a sign of increased metabolism. With metabolic exhaustion, cellular permeability increases with whole-body edema, including acute cerebral edema. As MH progresses, disseminated intravascular coagulation and cardiac or renal failure may develop. MH is a disorder of increased metabolism; it need not involve increased temperature, for example, if heat loss is greater than production or if cardiac output plummets early. The clinical MH syndrome can occur as a final common pathway in situations that may not involve susceptibility to MH, as various disorders may mimic MH (Table 29-2). ^{[79][80][81][82][83][84]}

Table 29-2 -- Mimics of malignant hyperthermia

Disorder	Reference
Alcohol therapy for limb arteriovenous malformation	^[81]
Contrast dye	^[144]
Cystinosis	^[145]
Diabetic coma	^[80]
Drug toxicity or abuse	^[46]
Environmental heat gain more than loss	^[64]
Equipment malfunction, increased carbon dioxide	^[114]
Exercise hyperthermia	^{[106][107][108][109][110][111][146]}
Freeman-Sheldon syndrome	^[151]

Disorder	Reference
Heat stroke	[109] [110] [111] [112] [113]
Hyperthyroidism	[79]
Hypokalemic periodic paralysis	[83]
Intracranial free blood	[82]
Muscular dystrophies (Duchenne, Becker)	[84]
Myotonias	[18]
Neuroleptic malignant syndrome	[116]
Osteogenesis imperfecta	[147]
Pheochromocytoma	[148]
Prader-Willi syndrome	[149]
Rhabdomyolysis	[46] [90] [91] [92]
Sepsis	[46]
Ventilation problems	[114]
Wolf-Hirschhorn syndrome	[150]

Trismus-Masseter Spasm

Trismus-masseter spasm is defined as jaw muscle rigidity in association with limb muscle flaccidity after administration of succinylcholine. It is a unique property of jaw muscle in normal people. Masseter and lateral pterygoid muscles contain slow tonic fibers that can respond to depolarizers with a contracture.^{[\[85\]](#)[\[86\]](#)} This is manifested clinically on exposure to succinylcholine as an increase in jaw muscle tone, well defined by van der Spek and associates.^{[\[87\]](#)} When this increase in jaw muscle tone becomes exaggerated, prolonged, and tight ("jaws of steel"), the likelihood of MH increases greatly. There is a spectrum of normal responses: a tight jaw that becomes a rigid jaw and then a very rigid jaw ([Fig. 29-4](#)). Somewhere in the area of the declining curve is the boundary for the MH population; the difficulty is in defining it. Trismus may still occur after pretreatment with a defasciculating dose of a nondepolarizing relaxant. If there is rigidity of other muscles in addition to trismus, the association with MH is absolute; anesthesia should be halted as soon as possible and treatment of MH begun. The following discussion considers trismus without rigidity of other muscles.

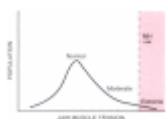


Figure 29-4 Succinylcholine usually increases jaw muscle tone slightly. In some patients, this increase is moderate, and in very few, the effect is extreme (i.e., "jaws of steel"). As much as 50% of this latter group may be susceptible to malignant hyperthermia (MH). Somewhere in the area of the declining curve is the boundary for the MH population.

After trismus occurs, proper monitoring should include end-expired carbon dioxide, examination for pigmenturia, and arterial or venous blood sampling for CK, acid-base status, and electrolyte levels, particularly potassium. The initial degree of tightness of the jaw and its duration suggest the gravity of the response. For patients with jaws of steel, the procedure should be halted, especially if the condition persists for more than several minutes. If the jaw is slightly resistant to opening, the anesthesiologist may continue anesthesia during proper monitoring. If the jaw is modestly tight and distinctly a problem, there are two choices: halt the procedure or continue with nontriggering agents. Any suggestion of MH should prompt MH therapy, including the use of dantrolene. The patient with a fever may have an exaggerated response to succinylcholine's effect in increasing jaw muscle tension. Patients who experience trismus should undergo testing for MH susceptibility. Trismus occurring after use of nondepolarizing muscle relaxants is not apparently related to MH or to hyperkalemia.^[88]

Sudden, Unexpected Pediatric Cardiac Arrest

MH rarely begins as an abrupt cardiac arrest after the use of succinylcholine. In the absence of upregulation of nicotinic skeletal muscle acetylcholine receptors,^[89] this reflects an occult myopathy that responds to succinylcholine with abrupt massive rhabdomyolysis and an associated acute rapid massive hyperkalemia.^{[90][91][92]} It is devastating to caregivers and family because an apparently healthy child can scarcely be resuscitated because of the difficulties in aiding redistribution of potassium to diminish hyperkalemic levels. Heroic efforts, including cardiopulmonary bypass, can be successful.^[93] These cases may respond acutely to calcium because it aids in counteracting hyperkalemia by reestablishing the ionic membrane balance in the heart and to dantrolene because of its effect in stabilizing muscle membrane permeability. Myopathic muscle continually suffers marked stress, and dantrolene may help to relieve that by attenuating calcium fluxes until more ATP is generated. Because of potential cerebral ischemia, glucose should be administered with caution. Succinylcholine continues to be valuable, because a nondepolarizing relaxant has not yet matched its advantages, but there should be precise indications for its use in young children.

Rhabdomyolysis

Rhabdomyolysis may occur during an MH episode or trismus, but milder forms occur more often than realized. In a study of 11 normal children, those given succinylcholine had a serum myoglobin level of 1187 ± 615 ng/mL, in contrast to 30 ± 9 ng/mL in those not given succinylcholine.^[94] Myoglobinuria with rhabdomyolysis can occur in various muscle disorders and without exposure to succinylcholine.^[92] Because of the virtual identity of myoglobin and hemoglobin, myoglobinuria can be misdiagnosed as hemolysis during MH. Any unusual anesthetic incident—muscle response, arrhythmia, trismus, or fever—should prompt examination of urine color and plasma electrolytes, especially potassium.

TRIGGERING OF MALIGNANT HYPERTHERMIA

Acute episodes of MH depend on three variables: a genetic (perhaps rarely acquired) predisposition, the absence of inhibiting factors, and the presence of a sufficiently potent anesthetic or nonanesthetic trigger.

Anesthetic Triggering

Anesthetic drugs that trigger MH include halothane, enflurane, isoflurane, desflurane, sevoflurane, and succinylcholine. Desflurane and sevoflurane are less potent triggers, producing a more gradual onset of MH.^{[95][96]} The onset may be explosive if succinylcholine is used.^[46] Inbred, susceptible swine are identified during an inhalation induction with a potent volatile anesthetic; they develop pronounced hind limb rigidity within 5 minutes.^[46] Prior exercise even an hour before induction of anesthesia increases the severity and hastens the onset of these attacks in swine.^[46] Mild hypothermia, depressants such as barbiturates and tranquilizers, and nondepolarizing relaxants delay the onset of MH.^{[15][97][98]}

Susceptible humans respond less predictably than swine to these triggers. Many affected humans have previously tolerated potent triggers without visible difficulty.^[14] This unpredictability may in part be related to the delaying effects described earlier, as well as to a brief anesthetic. Some patients have experienced MH episodes during anesthesia that did not involve recognized triggering agents; fortunately, all have responded appropriately to dantrolene. The mechanism of anesthetic triggering in humans is unsolved.

Succinylcholine has several variant responses that can occur singly or in combination. The first is a muscle contracture, also observed in muscle that is myotonic or denervated.^[89] The second is a change in muscle membrane permeability without contracture, resulting in the release of CK and myoglobin from muscle. Even in normal patients, succinylcholine releases CK and myoglobin from muscle in small amounts. This action is exaggerated in the presence of halothane and attenuated by curare^[46]; myoglobin release can be fairly marked even in the absence of obviously discolored urine.^[94] The third response is an increase in metabolism, as in MH, which is usually associated with muscle contracture and increased membrane permeability.^[46]

Nitrous oxide has been proposed as a weak trigger of human MH.^[46] This is most unlikely because it has been used repeatedly and safely as the basic anesthetic in MH-susceptible humans and swine. Hyperbaric nitrous oxide does not produce MH in susceptible swine, even in concentrations causing apnea.^[99]

Nondepolarizing muscle relaxants block the effects of succinylcholine in triggering MH. They attenuate the effects of volatile anesthetics.^{[15][97]} D-Tubocurarine has been incriminated as an MH trigger because it produced fever in two susceptible children.^[46] D-Tubocurarine results in greater lactate production in susceptible pigs exposed to environmental stress,^[46] but it has not been shown to be a trigger; it does produce a contracture in denervated muscle, suggesting that it may have a mild depolarizing action that is not generally apparent.^[100] Reversal of a nondepolarizing neuromuscular blockade does not trigger MH.

Episodes of MH have been reported during various operative procedures, with general or regional anesthesia, and in extremes of ages. Prior fever or succinylcholine-induced trismus should not be ignored, even if the patient survived without obvious mishap.^[101] The youngest probable case of MH involved succinylcholine-related muscle rigidity in utero just before birth.^[102] Presumably, the fetus inherited the paternal susceptibility that was triggered by maternal anesthesia.

Prolonged propofol infusions in pediatric intensive care are associated with complications that may mimic MH reactions.^{[103][104]} Propofol is not an MH trigger, and its effects on membranes of MH-affected skeletal muscle are stabilizing and opposite to those of volatile triggers.^[105]

Awake Triggering: Exercise and Heat Stroke

Porcine environmental stress such as exercise, heat stress, anoxia, apprehension, and excitement triggers MH (see "History").^{[46][72]} These responses are related to muscle movement or to increased temperature. Susceptible swine in vitro or in vivo react to carbachol or heat (41°C to 42°C) with abnormally increased oxygen consumption and lactate production, but not to α -sympathetic or β -sympathetic agonists, or both.^[72] Abnormal responses can be blocked or delayed by nondepolarizing relaxants.^{[15][46][56][97]} However, mechanisms in porcine awake MH may not relate to human awake MH.

Epidemiologic studies reveal that exercise-induced symptoms occur more frequently in MHS patients,^[106] including exercise-induced rhabdomyolysis.^{[107][108]} A novel mutation with an Arg401Cys substitution in the amino terminus occurred in three cases of exercise-induced rhabdomyolysis.^[108] There was a stress-induced hyperthermic death of a 12-year-old boy. He had an MH episode during sevoflurane anesthesia and was treated successfully with dantrolene.^[109] Eight months later, after a football game in the setting of an ambient temperature of 80°F (26.7°C), he complained of weakness, tingling in his extremities, and muscle stiffness. He was hot, diaphoretic, and hyperventilating. Seizures and respiratory arrest occurred; jaw rigidity prevented endotracheal intubation. Ventricular fibrillation occurred, and cardiopulmonary resuscitation was begun. In the hospital, his rectal temperature was 108°F (42.2°C), pH was 6.76, and potassium level was 8.8 mEq/L. Despite dantrolene, resuscitation was unsuccessful. Autopsy revealed normal cardiac anatomy and no explanatory pathology. Analysis of DNA in the boy (postmortem) and his father revealed an altered *RYR1* gene sequence of C487T, with a substitution of arginine for cysteine 163. Other reports relate heat stroke, sudden and unexpected death, unusual stress and fatigue, or myalgias to possible awake MH episodes.^{[110][111][112][113]} Stresses include exercise and environmental exposure to volatile vapors. Despite these rare exceptions, susceptible patients with no history of prior problems may live their everyday lives normally.

DIAGNOSIS

MH is a disorder of increased metabolism, and early signs may be subtle (see "Clinical Syndromes"). These must be distinguished from other disorders with similar signs (see [Table 29-2](#)). Postoperative fever alone seldom represents MH.

When the diagnosis is obvious (i.e., fulminant MH or succinylcholine-induced rigidity with rapid metabolic changes), there is marked hypermetabolism and heat production, and there may be little time left for specific therapy to prevent death or irreversible sequelae. If end-tidal carbon dioxide increases and ventilation is then increased to maintain normal end-tidal values, diagnosis of MH may be delayed.^[114] A clinical grading scale aids in establishing the likelihood of MH in specific problem cases. It is based on weighted scores for muscle tone, muscle breakdown, acid-base parameters, temperature, tachycardia or other arrhythmias, and response to dantrolene. This scale is hampered if clinical laboratory evaluation has been minimal.^[115]

In general, MH is not expected to occur when nontriggers are administered (see "Anesthesia for Susceptible Patients"). When volatile anesthetics or succinylcholine is used, MH should be suspected if there is increased end-expired carbon dioxide, undue tachycardia, tachypnea, arrhythmias, mottling of the skin, cyanosis, increased temperature, muscle rigidity, sweating, or unstable blood pressure. If any of these occur, signs of increased metabolism, acidosis, or hyperkalemia must be sought. Analysis of arterial blood gases demonstrates metabolic acidosis and may show respiratory acidosis if the patient is unable to increase ventilation as metabolism increases. Central venous oxygen and carbon dioxide levels change more markedly than do those in arterial blood; therefore, end-expired carbon dioxide or venous carbon dioxide levels more accurately reflect whole-body stores. Venous carbon dioxide, unless the blood drains an area of increased metabolic activity, should have PCO₂ levels only about 5 mm Hg greater than that of expected or measured PaCO₂. In small children, particularly without oral food or fluid for a prolonged period, base deficit may be 5 mEq/L because of their smaller energy stores. Any patient who is suspected of having an MH episode should be reported to the North American Registry using the rare disease protocol (AMRA) available from the MHAUS web site.

ASSOCIATION WITH OTHER DISORDERS

The King-Denborough syndrome, characterized by short stature, musculoskeletal abnormalities, and mental retardation, is associated with susceptibility to MH, as is CCD. CCD was present in the family of Denborough's original patient^[5] and discovered during later evaluations. Duchenne dystrophy is an X-linked myopathy; the associated deterioration of muscle membranes can result in a clinical MH episode on exposure to membrane perturbors such as MH triggers despite normal contracture testing results.^[84] Patients with Duchenne dystrophy can respond to anesthesia with sudden, acute, difficult-to-resuscitate cardiac arrest or sudden, acute rhabdomyolysis, even without the use of succinylcholine.^{[84][90][91][92]} Patients with any occult myopathy, even without exposure to succinylcholine, may experience these potentially and rapidly disastrous anesthetic events.^{[90][91][92]}

Neuroleptic malignant syndrome^[116] (NMS) is an uncommon condition caused by central effects of drugs with dopamine antagonist properties, including antipsychotics (e.g., haloperidol), and by drugs used for sedation or as antiemetics (e.g., Compazine, metoclopramide, droperidol). In affected patients, these drugs may cause a reaction involving a range of symptoms culminating in fulminant MH-like hypermetabolism. The onset ranges from hours to days after beginning drug treatment. There are three key clinical

components of NMS. First, the patient usually experiences an impairment of motor function with generalized rigidity, akinesia, or extrapyramidal disturbances, or some combination of these conditions. Second, deterioration in mental status occurs, producing coma, stupor, or delirium. Third, hyperpyrexia develops, with deterioration and lability of other "vegetative" functions, resulting in diaphoresis, dehydration, fluctuations in blood pressure and heart rate, and tachypnea. Duration averages 7 to 10 days, with gradual recovery that parallels the slow metabolism of the triggering drugs.

NMS patients may experience predictable complications of hypermetabolism, including rhabdomyolysis, renal failure, disseminated intravascular coagulation, thromboembolism, and sudden cardiac arrest. Treatment involves discontinuation of the drugs and symptomatic control of temperature, acid-base balance, intravenous fluid balance, and muscle tone. Specific pharmacotherapy is empirical. Clinical reports support consideration of benzodiazepines, dopamine agonists, and dantrolene. Dantrolene aids in therapy because it lowers muscle heat production and therefore body temperature, and it eases rigidity without the need for tracheal intubation. In refractory cases and patients with prominent catatonic features, electroconvulsive therapy has helped. Succinylcholine, usually part of such therapy, may risk hyperkalemia in patients with muscle necrosis. Although often similar in presentation, NMS and MH result from different pathophysiology. Unlike MH, dopamine antagonists trigger NMS in the brain; it may respond to centrally acting agents, electroconvulsive therapy, and neuromuscular blockers. MH triggers appear safe in NMS patients and their families. Some NMS patients have had positive MH muscle biopsy results, but their significance is unclear.

The relationship of isolated CK elevations and MH susceptibility remains unclear. Some have had positive contracture testing, and others with a long-standing benign course have received triggers uneventfully.^[117] Less convincing is a direct association of MH with other disorders: crib death, or sudden infant death syndrome; Smith-Lemli-Opitz syndrome^[118]; and Charcot-Marie-Tooth syndrome.^[119] Exercise and heat stroke are discussed under "Awake Triggering: Exercise and Heat Stroke." Succinylcholine induces contractures in myotonic muscle, which could be confused with MH. Myotonic goats develop brief rigidity after succinylcholine administration but, even with the concomitant use of halothane, show no evidence of MH. In myotonia, there appears to be rigidity in the absence of serious metabolic abnormalities; infrequent positive biopsy results appear to be related to non-MH factors.

TREATMENT

Discontinuation of the trigger may be adequate treatment for acute MH if the onset is slow or if exposure was brief. Dantrolene, the therapeutic mainstay, is packaged in 20-mg bottles with sodium hydroxide for a pH of 9 to 10 (otherwise it will not dissolve) and mannitol (converts the hypotonic solution to isotonic). Dantrolene must be dissolved in sterile water rather than solutions because the extra molecules lead to a salting-out effect and greater difficulty in dissolving it. It may be heated to hasten solution.^[120] In a large adult, as many as 10 bottles may be required. Dantrolene's cardiac effects are complex and include interactions with calcium antagonists (see "Calcium"). Dantrolene has a half-life of at least 10 hours in children and adults.^{[121][122]} It does not paralyze; peak effects include moderate

muscle weakness with adequate strength for deep breathing and coughing. Weakness is accentuated in myopathic patients. Aside from cholestasis during long-term (>3 weeks) therapy, dantrolene has no serious side effects.

Acute therapy for MH can be summarized as follows:

1. Discontinue all anesthetic agents and hyperventilate with 100% oxygen. Normal ventilation is that required to remove metabolic carbon dioxide. With increased aerobic metabolism, normal ventilation must increase. However, carbon dioxide production is also increased because of neutralization of fixed acid by bicarbonate; hyperventilation removes this additional carbon dioxide.
2. Repeat administration of dantrolene (2 mg/kg, every 5 minutes to a total dose of 10 mg/kg, if needed, although doses to 29 mg/kg have been used).^[123]
3. Administer bicarbonate (2 to 4 mEq/kg). Continued efflux of lactate from skeletal muscle may result in recurrent acidosis^[124] because lactate, being ionized, slowly crosses the muscle cell membrane to extracellular fluid.
4. Control fever by iced fluids, surface cooling, cooling of body cavities with sterile iced fluids, and a heat exchanger with a pump oxygenator.^[93] The clinician must not become so preoccupied with cooling and other busy work that he or she neglects the prime factor in therapy: intravenous administration of dantrolene. Cooling should be halted at 38°C to 39°C to prevent inadvertent hypothermia.
5. Monitor urinary output to prevent shock to kidneys or acute tubular necrosis and to examine for myoglobinuria.
6. Further therapy is guided by blood gases, electrolytes, temperature, arrhythmia, muscle tone, and urinary output.
7. Analyze electrolytes; CK concentrations; liver profile; levels of blood urea nitrogen, lactate, and glucose; coagulation studies (e.g., INR, platelet count, prothrombin time, fibrinogen, fibrin-split or degradation products); and serum hemoglobin and myoglobin and urine hemoglobin and myoglobin.

The clinical course determines further therapy and studies. Dantrolene should probably be repeated at least every 10 to 15 hours (its half-life) for several doses.^{[121][122]} Recrudescence of MH can approach 50%, usually within 6.5 hours.^[123] Treatment of hyperkalemia should be slow. The plasma K⁺ level must be serially monitored because it may be an important factor in treatment (e.g., persistently elevated K⁺ level may prevent defibrillation).^[93] The most effective way to lower serum potassium is reversal of MH by effective doses of dantrolene. Calcium administration is indicated only for related arrhythmias or for poor cardiac function. However, when indicated, calcium and cardiac glycosides may be safely used because their administration to the susceptible pig does not trigger MH.^[52] They can be lifesaving during persistent hyperkalemia.^{[90][91][92]}

Permanent neurologic sequelae, such as coma or paralysis, may occur in advanced cases, probably from inadequate cerebral oxygenation and perfusion for the increased metabolism and because of the fever, acidosis, hypo-osmolality with fluid shifts, and potassium release.

Even satisfactory care during anesthesia may not prevent neurologic complications. Measurements of intracranial pressure may help in the evaluation of cerebral edema. Disseminated intravascular coagulation or consumptive coagulopathy may be caused by hemolysis, release of tissue thromboplastins, overt tissue damage, or shock. The best treatment is adequate therapy for MH to prevent stagnation of peripheral blood flow and to lower temperature.

Among the ineffective therapeutic adjuncts are calcium antagonists and sympathetic antagonists. Calcium antagonists do not increase porcine survival.^{[50][51]} They may interact with dantrolene to produce hyperkalemia, which can result in retriggering MH^[52] or in myocardial depression.^[49] Magnesium reduces the increase in intracellular calcium during porcine MH but does not prevent the increase in metabolism. Although it may play a role in MH mechanisms (see "Pathophysiology and Molecular Biology"),^[38] its therapeutic value appears to be minimal.

Early diagnosis and treatment of MH are essential. Complications are difficult to treat and may lead to serious and permanent sequelae. Retriggering may occur as dantrolene is redistributed or metabolized. The physician should contact the MH Hotline to verify treatment and report the case using an AMRA form.

ANESTHESIA FOR SUSCEPTIBLE PATIENTS

Anesthesia should consist of nitrous oxide, barbiturates, etomidate, propofol, opiates, tranquilizers, or nondepolarizing muscle relaxants. Potent volatile agents and succinylcholine must be avoided, even in the presence of dantrolene. Some human patients have experienced a hypermetabolic state despite these precautions, but they have always responded favorably to intravenous dantrolene. Preoperative dantrolene is not needed because the use of nontriggering agents is almost always associated with uneventful anesthesia. If used, 1 to 2 mg/kg should be given intravenously just before induction to avoid the side effects of lengthy pretreatment. In obstetric cases, it is best given after the cord is clamped to avoid the problems of a floppy child, because cord blood levels may approach 65% of maternal levels.^[125] Regional anesthesia is safe and may be preferred. Amide anesthetics had been considered dangerous in susceptible patients because they induce or worsen contractures in vitro as a result of their effect in increasing calcium efflux from the SR. However, these effects require millimolar concentrations, far greater than plasma values achieved in clinical use. Porcine and human studies demonstrated the lack of danger of amide anesthetics. Intravenous lidocaine was used as long ago as 1970 to treat acute MH without harm and with apparently good results.^[6]

Anesthetic machines may be "cleansed" of potent volatile agents by removal or sealing of the vaporizers, change of soda lime, perhaps replacement of the fresh gas outlet hose, and use of a disposable circle with a flow of 10 L/min for 5 minutes. After flow is reduced, the volatile agent's concentration may again increase. A gas analyzer demonstrates a continuous volatile vapor concentration. This is important because some new machines require a constant high flow to minimize volatile agent concentrations.^[126]

The anesthesiologist should confidently discuss the anesthetic care with the patient, assuring him or her that all will be done to avoid difficulties with MH and that the appropriate drugs, knowledge, and skills are immediately at hand if any problems occur. Many of these patients have undergone procedures uneventfully, such as dental analgesia and obstetric anesthesia, before the diagnosis of susceptibility was made. The patient can enter the therapeutic environment in a reassured, relaxed, and comfortable state. Outpatient procedures are feasible in most environments; the time of discharge depends on usual outpatient criteria. Any facility using MH triggers on an inpatient or outpatient basis should have dantrolene immediately available.

Several species, such as pigs, dogs, cats, and horses, have suffered MH episodes.^[46] A canine colony inbred for MH has the canine *RYR1* gene.^[127] Cosgrove and colleagues^[128] examined contractures in greyhounds in conjunction with a triggering anesthetic challenge; all findings were normal. Continuing study of the capture myopathy of wild animals, more recently in feral deer, suggests that this is "overstraining" during the chase of normal animals rather than a genetic disorder similar to MH.^[129]

EVALUATION OF SUSCEPTIBILITY

Evaluation includes a history and physical examination for the detection of subclinical abnormality. A genealogy with specific information about anesthetic exposure and agents can estimate the likelihood of exposure to triggering agents. Blood CK values, when determined in a resting, fasting state without recent trauma, reflect muscle membrane stability. When CK level is elevated in a close relative of a person with known MH susceptibility, the relative may be considered to have MH susceptibility without contracture testing. If the CK level is normal on several occasions, there is no predictive value, and contracture studies are necessary. The patient must travel to the test center for surgical biopsy to ensure viability and accurate results.

Muscle biopsy contracture studies, performed at about 30 centers around the world, use exposures to halothane, caffeine, halothane plus caffeine, and ryanodine.^[33] 4-Chloro-*m*-cresol may add to precision.^[130] There is a crisis in the United States, with only six test centers (December 2003), in part because of medical care limitations. This is inappropriate considering geography and population. Contracture responses are sometimes positive in patients with myopathies that bear no direct relationship to MH and therefore may not indicate susceptibility. Dantrolene must be avoided before the biopsy, because it masks the response to contracture-producing drugs. After a patient is diagnosed with MHS, DNA testing for mutations should follow. When one is detected, other relatives with that mutation are considered to have MHS without the need for the invasive contracture test, and they need not travel to a testing center (see "Genetics").

For the student of anesthesia, susceptible individuals have a lower threshold to contracture-producing drugs. The muscle specimen must be viable (i.e., twitch when stimulated electrically) because the contracture threshold may vary if the fiber is deteriorating. Bath kinetics are stable with the use of experienced laboratories, and variations in temperature have less effect than anticipated on contracture thresholds.^[131]

Advice should be given to the susceptible patient. Precautions are necessary in regard to general anesthesia, and triggers include all potent volatile agents and succinylcholine. Awake episodes are uncommon, and if not experienced before the diagnosis, they are an unlikely problem. Military personnel may have restrictions because of the necessary avoidance of combat trauma and the possible mandatory use of triggers, and soldiers with MH susceptibility may be less desirable because some authorities believe that they may fatigue sooner with harsh military conditioning because of their subclinical myopathy.

The predictive value (i.e., percentage of positive results that are true positives) or efficiency (i.e., percentage of all results that are true, whether positive or negative) of contracture testing in determining susceptibility cannot be estimated. False-positive results resulting from cautious interpretation or decreased specificity are masked because the patient will never be exposed to triggering agents. European and North American contracture protocols have yielded sufficient multicenter data to confirm acceptable test results.^{[132][133]} Separation of control patients from MH patients was based on purely clinical information using the clinical grading scale.^[115] Both protocols have 97% to 99% sensitivity (i.e., frequency of positive results in the patients with clinically established MH) and acceptable (78% to 94%) specificity (i.e., frequency of negative results in low-risk controls). Threshold values attempt to provide 100% sensitivity to detect all MHS patients; this restriction limits specificity.

The North American testing protocol (CHCT) uses incremental caffeine concentrations of 0.5, 1, 2, 4, 8, and 32 mM and uses 3% halothane as a bolus application. It yields two diagnoses: normal (MHN) or abnormal (MHS). The European testing protocol (IVCT) uses additional steps in its increments: caffeine concentrations of 0.5, 1, 1.5, 2, 3, 4, and 32 mM, and halothane in concentrations of 0.5%, 1%, 2%, and sometimes 3%. Greater fractionation of caffeine and halothane increments in the European protocol results in lower diagnostic thresholds (i.e., 0.2 g for both drugs).^[132] The lesser fractionation of increments in the North American protocol leads to greater thresholds (0.3 g) for caffeine and a relatively large gray area for halothane of about 0.5 to 0.8 g.^[133] Interpretation of IVCT yields three diagnoses: MHS, for which halothane and caffeine results are abnormal; MHN, for which both results are normal; and equivocal (MHE), for which only one result is abnormal. Fewer MHE diagnoses and better genetic correlations exist when contractures are markedly abnormal instead of near threshold; this may lessen discordance.^{[134][135]}

What is needed in MH testing is an accurate, noninvasive or nondestructive measure of susceptibility that has no overlap between the ranges of normal and susceptible responses. A promising innovative in vivo human application involves physiologically based microdialysis infusion of caffeine or halothane into muscle of MH-susceptible patients, triggering exaggerated localized changes in acid-base balance.^{[136][137]} White blood cells express MH mutations and provide a substrate for genetic analysis.^{[75][76][138][139]} Nuclear magnetic resonance has promise,^[140] the difficulty is to standardize a stress, such as forearm ischemia, that can differentiate susceptible tissue from normal. Although early ultrasound results were encouraging, study results for skeletal muscle were inaccurate in humans with MH susceptibility.^[141] Adnet and coworkers^[142] examined masseter muscle in a skinned fiber in vitro preparation in attempts to explain its propensity for contracture. They observed greater sensitivity to Ca^{2+} and caffeine than that in quadriceps muscle. Their findings were

contradicted in a contracture study of masseter biopsy specimens taken during major craniofacial cancer surgery.^[143] These responded similarly to quadriceps.

SUMMARY

MH is a subclinical myopathy featuring an eerie and erratic metabolic mayhem that is unmasked on exposure to potent volatile anesthetics or succinylcholine. Skeletal muscle acutely and unexpectedly increases its oxygen consumption and lactate production, resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. MH-susceptible skeletal muscle differs from normal muscle in that it is always closer to loss of control of Ca^{2+} concentration within the muscle fiber, and it can involve a generalized alteration in cellular or subcellular membrane permeability. This is an EC coupling defect resulting from an alteration in the receptor encoded by *RYR1*. It is a homozygous, single-point mutation of *RYR1* in swine and a heterozygous disorder in humans, in whom there may also be a modification of RYR1 protein function by interacting structures, membranes, or enzymes; MH may occur as a final common path phenomenon. Diagnosis rests on extraordinary temperature, acid-base alterations, and muscle aberrations. Specific treatment is the action of dantrolene on muscle Ca^{2+} movements; symptomatic treatment is by reversal of acid-base and temperature changes. Evaluation of affected families is guided by measurements of circulating CK, analysis of drug-induced muscle contractures (by European IVCT and North American CHCT protocols), and genetic testing of DNA samples. General or regional anesthesia is safe for patients susceptible to MH, provided that care is taken to specially prepare the anesthesia machine and to avoid all potent volatile anesthetics and succinylcholine if a general technique is chosen.

Research on MH has yielded insights into the physiology of metabolism and into the molecular biology of genetic muscle disorders. Remaining challenges include identification of all genetic mutations responsible for human MH, elucidation of the mechanism that links exposure to the subsequent loss of Ca^{2+} control, development of noninvasive and nondestructive testing for susceptibility, and determination of the mode of action of dantrolene.

KEY POINTS

1. MH is an anesthetic-related disorder of increased metabolism of skeletal muscle. It is an inherited condition and occurs in swine and humans.
2. Skeletal muscle accounts for approximately 40% of body weight; its increased metabolism therefore has a profound effect on whole-body metabolism.
3. Signs of MH, including tachycardia, increased expired carbon dioxide, muscle rigidity, and increased temperature, are related to increased metabolism.
4. Function of the ryanodine receptor of skeletal muscle is abnormal in MH, causing barely controlled calcium concentration within the cell.
5. Added loss of control of intracellular calcium leads to marked metabolic stimulation within the cell to provide extra ATP to drive the calcium pumps that restore calcium to its reservoirs (e.g., SR, mitochondrion, extracellular fluid).

6. Dantrolene markedly attenuates loss of calcium from SR, restoring metabolism to normal, with reversal of the signs of metabolic stimulation.
7. MH is inherited; one mutation accounts for all porcine MH, and more than 30 mutations account for human MH.
8. Evaluation of persons susceptible to MH includes contracture of a skeletal muscle biopsy specimen with halothane or caffeine, estimation of muscle permeability by measurement of plasma CK level, and evaluation of DNA to identify mutations. Only DNA testing is needed to evaluate swine MH.
9. Future MH goals include advancement of genetic evaluations in North American and European medical programs and finances that are stronger for supporting genetic studies, identification of the mode of action of dantrolene, determination of the immediate cause of MH triggering, and development of effective, nondestructive tests for MH susceptibility.

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