Malignant Hyperthermia

29

Henry Rosenberg, Dorothea Hall, and Harvey Rosenbaum

Contents

H. Rosenberg (✉)
Department of Medical Education and Clinical Research, Saint Barnabas Medical Center, Livingston, NJ, USA
e-mail: henryrosenberg@yahoo.com

D. Hall • H. Rosenbaum
Department of Anesthesiology and Perioperative Medicine, UCLA, David Geffen School of Medicine, Los Angeles, CA, USA
e-mail: dhall@mednet.ucla.edu; hkrosenbaum@mednet.ucla.edu

J. Brent et al. (eds.), *Critical Care Toxicology*,
DOI 10.1007/978-3-319-17900-1_64

Malignant hyperthermia (MH) syndrome is an unusual disorder. Much like an individual who has an allergy, the MH-susceptible patient is often unaware of his or her problem unless there is a family history of anesthesia-related problems that suggest MH or until exposed to the "triggering" agent. MH syndrome may not develop on all exposures. The resemblance to an allergy breaks down, however, on further analysis. MH is an inherited disorder [1]. Patients develop a hypermetabolic condition on exposure to drugs that are generally used to produce general anesthesia such as isoflurane, halothane, desflurane, and sevoflurane or skeletal muscle paralysis, namely, succinylcholine [2]. The pathophysiologic change in MH relates to an uncontrolled increase of intracellular calcium in skeletal muscle that leads to hypermetabolism, depletion of energy sources, acidosis, and membrane breakdown [1–3]. Untreated, MH syndrome is fatal in most cases. With prompt discontinuation of trigger agents and administration of the drug dantrolene [4], mortality may be close to zero [5]. This chapter discusses clinical presentation, pathophysiology, molecular genetics, diagnosis, treatment, and sources of information for this unusual cause of anesthetic morbidity and mortality.

History

MH was recognized in the early 1960s by clinical anesthesiologists and a clinical geneticist in Melbourne, Australia [6]. The event that attracted

their attention related to surgery for a young man who sustained a motor vehicle injury. The patient expressed great concern because many members of his family had died unexpectedly while under anesthesia. The anesthesiologists administered halothane anesthesia, and, warned by the patient's concern, stopped the anesthetic and the procedure when the patient developed hypertension, then hypotension, tachycardia, and sweating. Michael Denborough, a consultant internist with an interest in inherited diseases, was called to investigate. He then described many salient features of the syndrome.

After Denborough and Lovell [6] described the syndrome, many others described similar cases throughout the world. By the end of the 1960s, the syndrome was called *malignant hyperthermia* or *malignant hyperpyrexia*. The reason for the appellation was the mortality of greater than 80% and the strikingly elevated body temperature that accompanied the disorder. Other peculiar features that were described included muscle rigidity, rhabdomyolysis, and in some cases, rigidity limited to the jaw muscles after the muscle relaxant succinylcholine was administered.

At the first international workshop on MH, held in 1971 in Toronto, Canada, clinicians and basic researchers began to exchange information about MH. Veterinarians and pig breeders reported that certain breeds of pigs developed what seemed to be MH on a regular basis when stressed [7]. The breeds were known for their muscle mass and included Pietrain, Poland China, and others.

Although there was great concern initially that MH-susceptible humans would develop the syndrome with stress, that has not been shown to be the case [2, 3]. However, some MH susceptibles may develop the signs of MH with vigorous exercise and exposure to heat [9]. There are many other differences between human and swine MH. The inheritance of the syndrome is autosomal recessive in pigs but autosomal dominant in humans. Nevertheless, the pig develops typical signs of MH on exposure to anesthetics that trigger MH. The pig has served as a useful model, however, for understanding the pathophysiology of MH, determining which drugs precipitate the syndrome, and determining the effective treatment of MH.

Table 1 Landmarks in malignant hyperthermia

Demonstration that biopsied muscle responds with abnormal contractures to halothane and to caffeine [8, 10]
Recognition that all potent volatile anesthetic gases are triggers for MH, as is the depolarizing relaxant succinylcholine [2, 3]
Demonstration that local anesthetics and intravenous anesthetics are not triggers of MH [2, 3]
The finding, in 1975, that dantrolene sodium is a specific treatment for MH and the introduction in clinical use in 1979 in the USA [4, 11]
The routine use of capnography in anesthesia and the recognition that elevated end-tidal carbon dioxide is an early sensitive and specific sign of MH [2, 3]
The creation of patient advocacy groups, registries, and hotlines throughout the world to assist anesthesia providers and others to recognize MH and guide treatment
Demonstration that mutations in a specific gene that elaborates a calcium channel in muscle, the ryanodine receptor, are responsible for almost all cases of pig MH and perhaps 50% of human MH [1]
Development of a "knock-in" mouse model of MH incorporating mutations that predispose to MH [13]
Introduction of molecular genetic testing for MH diagnosis in limited circumstances
Demonstration that time from diagnosis to treatment is crucial in enhancing survival [14]
Demonstration that early detection and mitigation of hyperthermia reduces mortality [67]
Cataloging of over 300 DNA variants associated with MH in the RYR 1 gene. Demonstration that the CACNA1S gene is associated with MH in some cases
Demonstration of prevalence of RYR 1 variants associated with MH in 1 in 2000 people
Association of MH susceptibility with several myopathies such as central core disease, multiminicore disease, nemaline myopathy, and others

MH malignant hyperthermia

Since the early 1970s, there has been an enormous growth in knowledge and awareness of how to diagnose and treat MH syndrome. Landmark advances are outlined in Table 1. All of these findings and many others have led to the reduction of mortality from MH to less than 7% in developed countries [5, 12].

In a sense, the term *malignant hyperthermia* has become a misnomer. Hyperthermia often follows other metabolic signs of MH and is often not manifest when the diagnosis is made.

Furthermore, with prompt recognition and treatment, the fatality rate of MH is low. The syndrome includes *anesthesia-induced myodystrophy* and *rhabdomyolysis of anesthesia*.

Incidence

MH, being an inherited myopathy, should be amenable to epidemiologic investigation of incidence, prevalence, and perhaps penetrance. However, the data have been difficult to gather. The reason is that MH patients in general have no specific phenotype, other than when exposed to anesthetic drugs or in special environmental stressors; the signs of MH during anesthesia may be nonspecific and mimicked by other processes, such as rapid absorption of carbon dioxide during laparoscopic surgery, fever, iatrogenic overheating, and myotonia. In addition, until the late 1998, there was no specific ICD-9 (*International Classification of Diseases – ninth revision*) code for MH, and the syndrome did not appear in the diagnostic databases of diseases.

The prevalence of MH is approximately 1 in 100,000 instances of exposure to general anesthesia, and the incidence of clinical signs that resemble MH but for which the diagnosis is not certain is 1 in 5000 instances of exposure to anesthesia [15]. In one small study, 25% of MH diagnoses based on ICD 9 or ICD codes represented an incident case of MH [16]. Overall, approximately 1000 cases of MH are diagnosed each year in the USA. In addition, the incidence of MH in children is about three times higher than in adults [17]. The incidence of clinical MH depends primarily on the use of the trigger agents for MH and the gene prevalence in the population. In the USA and Canada, a higher incidence of MH is found in Ontario, Wisconsin, and various locales where there are families who harbor the genetic change causal for MH. MH has been identified in every country and ethnic group where it has been looked for [12].

One study has determined that the incidence of susceptibility to MH in one province of Quebec is about 1 in 200 individuals [18]. That study was performed because many patients in the province had been tested for MH susceptibility with biopsy (see under Diagnostic Testing). The province was settled by a small number of families in the nineteenth century, and there had not been a large admixture of other families in the province. A few families with MH accounted for most of the cases.

A study examining surgical discharge diagnoses in NY state found that MH was recorded in one in 100,000 discharges [19].

Recent studies have examined the prevalence of DNA variants of the principle gene that is causal for MH, the ryanodine receptor gene (RYR1). Studies in France and Japan and one in Germany described a prevalence of MH-causative mutations of one in about 2000 people [20], while a study of patients in the Baltimore/Washington area directly measured a prevalence of pathologic DNA changes in one in 400 people [21].

The understanding of the very low penetrance of the syndrome is a crucial question in managing patients and their families. A great deal of further investigation is needed to determine the epidemiologic characteristics of the disorder with accuracy. To the best of our knowledge, there are fewer than five deaths from MH among the approximately thousand MH episodes each year in the USA.

Pathophysiology

Malignant hyperthermia is a disorder of skeletal muscle biochemistry and physiology, yet in the absence of triggering agents, there are no identifiable signs or symptoms. No muscle abnormalities are consistently observed in MH-susceptible people. Only small subsets of subjects with MH, identified either by clinical presentation or diagnostic testing, show evidence of muscle disorders. These include patients with central core disease, multiminicore disease, King-Denborough syndrome, Native American myopathy, and late-onset myopathies [23–26]. It is doubtful that other tissues are primarily responsible for the clinical manifestations of MH. Based on the

recognition that muscle rigidity was a dramatic manifestation of most cases of MH, Kalow and colleagues tested muscle biopsy specimens from susceptible pigs and humans for their response to caffeine, the agent known to produce muscle contracture secondary to calcium release from the sarcoplasmic reticulum [8]. They found that the response to biopsied skeletal muscle to caffeine, in vitro, was clearly abnormal. Contractures developed in muscle tissue of MH-susceptible subjects with concentrations as low as 0.5 mM, not observed in normal muscle. MH muscle also showed significant (>0.5 g) contractures on exposure to clinical concentrations of halothane [27–29]. The same findings were not found in the examination of smooth or cardiac muscle (Figures 3 and 4).

Further refinement of understanding of the pathophysiology of MH has focused on the mechanisms responsible for calcium control in muscle. Several proteins mediate calcium release and control intracellular calcium levels. Most attention has been focused on the ryanodine receptor, a calcium channel which mediates excitation-contraction coupling in skeletal muscle (Fig. 2) [1, 22, 23]. Excitation-contraction coupling occurs when an action potential along the muscle cell's T-tubule membrane is converted into an intracellular chemical signal, via Ca^{2+} ion flow, which drives muscle contraction. Specifically, a conformational change occurs in the voltage-dependent L-type calcium channel, which in turn triggers activation of the ryanodine 1 (RYR1) Ca^{2+} release channel in the terminal cisternae of the sarcoplasmic reticulum. Most attention has been focused on the ryanodine receptor; however, alterations in several other calcium signaling mechanisms and at least six other genes have been implicated in MH [30–33]. Specific MH-associated mutations have been identified in only three genes to date: RYR1, CACNA1S, which encodes the alpha-1S subunit of the voltage gated L-type calcium channel of the T-tubule, and the STAC3 gene associated with Native American myopathy [85].

Further investigations using calcium-sensitive dyes and calcium ion electrodes showed markedly increased levels of intracellular calcium in whole muscle or cultured muscle from MH-affected animals and humans on exposure to potent inhalational anesthetics [34–36]. The purported primary defect in MH is related to enhanced release and/or leak of calcium from the terminal cisternae of the sarcoplasmic reticulum (Fig. 1) [22]. Increased resting myoplasmic Ca^{2+} has been measured in several MH-causative RYR1 mutations; exposure of MH myotubes to ryanodine, which blocks *open* RYR1 channels, is without effect. In this model increased resting myoplasmic calcium is therefore not due to increased RYR1 calcium release but most likely to a mechanism called store-operated extracellular calcium entry (SOCE) [37]. Reuptake does not seem to be at fault in these tissues [38]. The consequence of enhanced release/leak of calcium is prolonged muscle contraction resulting from release of inhibition of actin-myosin interaction. Adenosine triphosphate (ATP) levels decline as a result of activation of processes to sequester calcium, leading to anaerobic metabolism and acidosis. Declining levels of ATP lead to breakdown of membrane integrity and release of intracellular enzymes, such as creatine kinase (CK), along with myoglobin, potassium, and hydrogen ions.

Recent research focus has been placed on a mechanism termed store-overload-induced calcium release (SOICR) as a possible etiology for MH. In this condition RYR1 spontaneously releases Ca^{2+} from the sarcoplasmic reticulum once luminal Ca^{2+} concentrations reach a critical concentration. New evidence suggests that mutations in RYR1 may lower the threshold for SOICR, thus causing spontaneous release or leak of Ca^{2+} [39]. A similar mechanism could be demonstrated in the RYR2-mediated, stress-triggered condition of catecholaminergic polymorphic ventricular tachycardia (CPVT). CPVT leads to bidirectional ventricular tachycardia and sudden cardiac death. Parallels can be drawn between the RYR1-mediated mechanism in MH and the RYR2-associated mechanisms in CPVT, in that they both reduce the threshold for store-overload-induced calcium release [40].

Another mechanism of RYR1 regulation via $Ca_v1.1$, a pore forming subunit of the L-type Ca^{2+} channel encoded by CACNA1S, has recently

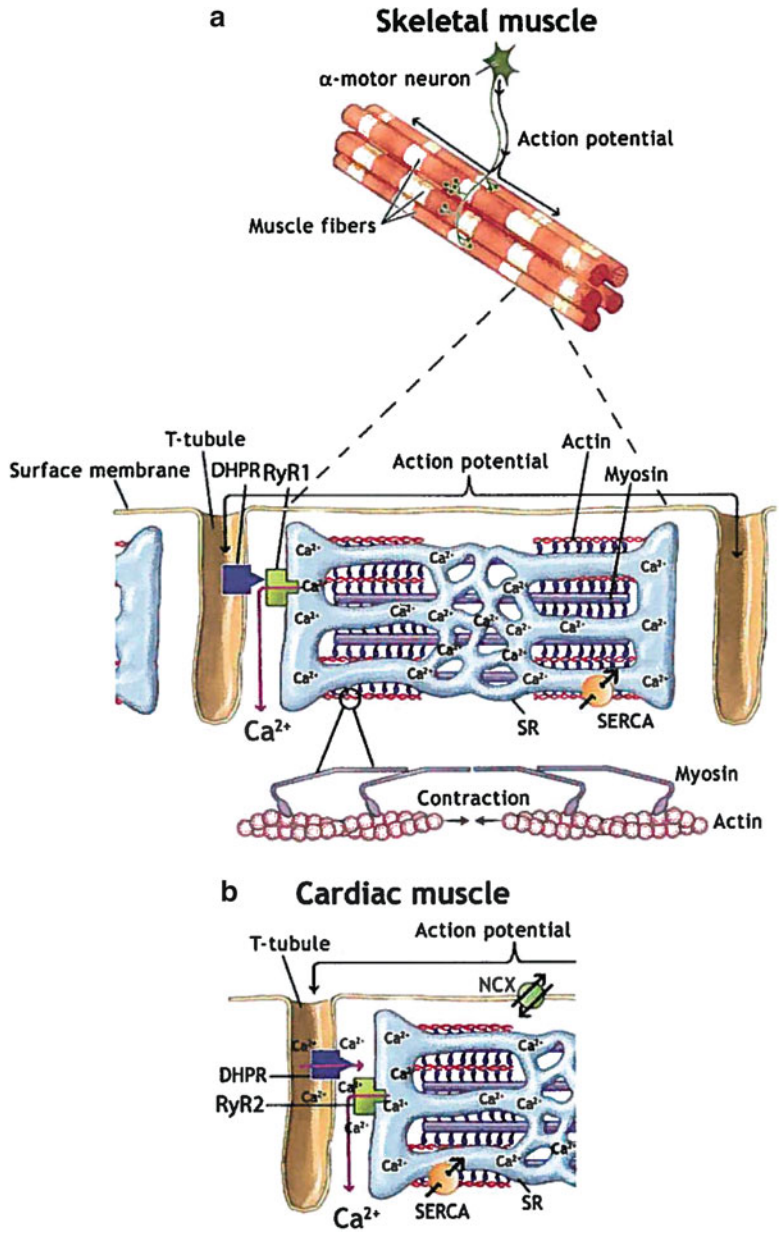

Fig. 1 Activation of the contractile machinery in skeletal and cardiac muscles. (**a**) An action potential travels along an α-motor neuron to a group of skeletal muscle fibers and triggers an action potential in each of the muscle fibers. The action potential in turn activated voltage-sensitive dihydropyridine receptors (*DHPR*). The DHPR opens ryanodine receptors (*RyR*) by mechanical interaction, resulting in release of CA^{2+} from SR and a transient increase in myoplasmic Ca^{2+}, which enables actin and myosin interaction and force development. SR (sarcoplasmic reticulum) Ca^{2+} -ATPase (*SERCA*) pumps Ca^{2+} back into SR and myoplasmic Ca^{2+} returns to resting levels and the contraction ceases. (**b**) The activation of the Ca^{2+}-dependent contractile machinery is almost identical in cardiac muscle, with the exception of the Ca^{2+} release process. The cardiac action potentials last longer compared to skeletal muscle, which results in Ca^{2+} influx through DHPRs, and these Ca^{2+} ions induce opening the RyR and Ca^{2+} release from SR. The increase in myoplasmic Ca^{2+} enables actin and myosin interaction. Myoplasmic Ca^{2+} return to resting levels by SERCA-mediated pumping of Ca^{2+} into SR and extrusion of Ca^{2+} via the Na^{+}-Ca^{2+} exchanger (*NCX*) (From *Calcium Signaling*, Islam MS ed, Springer 2012)

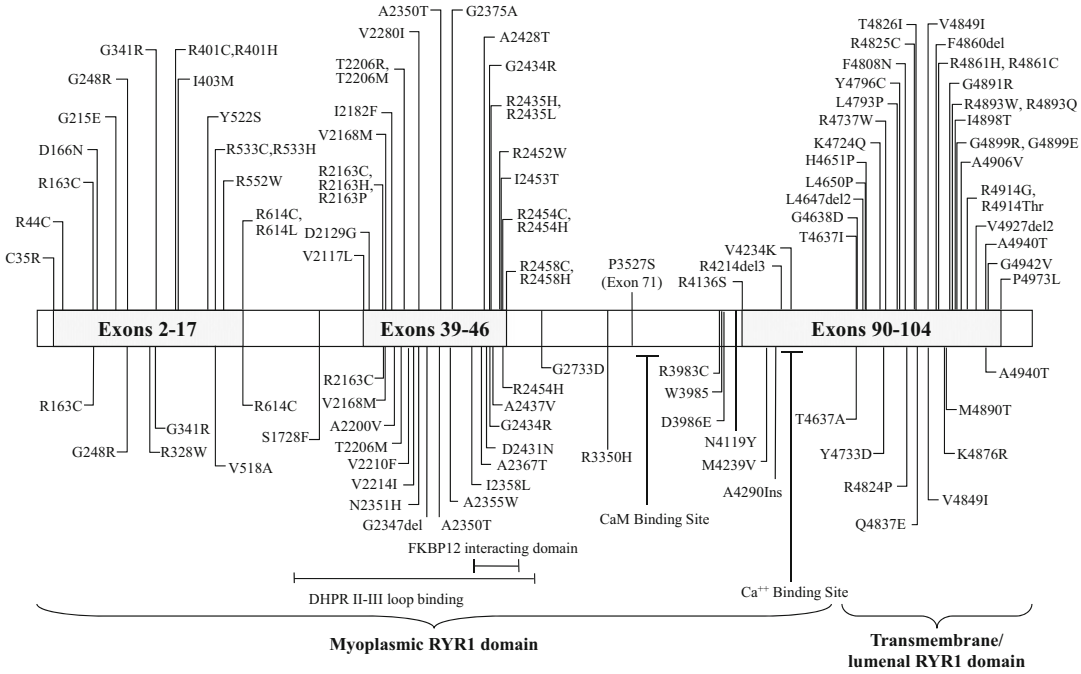

Fig. 2 Location of ryanodine receptor type 1 (*RVR 1*) mutations associated with malignant hyperthermia susceptibility and central core disease. Mutations found in European and Australian malignant hyperthermia-susceptible/central core disease families are shown at the top; mutations in North American malignant hyperthermia-susceptible/central core disease families are shown at the bottom of the diagram. The mutations reported only in North American MHS families and *RYR 1* variants identified in North American MHS subjects are shown in bold. The three mutational hot spot areas are shadowed. CaM, calmodulin; DHPR, dihydropyridine receptor; FKBP 12, FK 506 binding protein 12. Diagram courtesy of Dr. N. Sambuughin. (Reprinted, with permission, from Anesthesiology, second edition. Longnecker DE et al., eds. McGraw-Hill, New York, 2012)

been elucidated. $Ca_v1.1$ activates RYR1 during excitation-contraction coupling, but it also suppresses the leak of Ca^{2+} ions from the sarcoplasmic reticulum when RYR1 channels are at rest. Disruption of this inhibitory regulation may explain increased sensitization of muscle cells to MH triggers [41].

Recent work by Eltit et al. [42] demonstrated that nonspecific sarcolemmal cation channels can cause Ca^{2+} and Na^{+} overload both at rest and during an MH crisis [42]. Utilizing a knock-in mouse model, the study showed an overexpression of nonspecific sarcolemmal cation channels associated with influx of extracellular calcium and elevated resting intracellular calcium and sodium in the MH group. Halothane resulted in further increases in myoplasmic sodium and calcium in the MH animals.

Evidence of abnormal calcium control in MH-susceptible patients, even without exposure to anesthetic agents, is suggested by nuclear magnetic resonance studies in exercising human muscle in vivo [43–47]. These studies show greater inorganic phosphate levels at rest and with exercise, exercise-induced acidosis, and slower recovery of ATP levels in MH-susceptible patients. These changes do not lead to clinical signs of MH.

Although mutations in the ryanodine receptor appear to be an important factor in the pathophysiology of MH, only about 50–70% of MH-susceptible families have been linked to ryanodine mutations [1, 48] The presence of a mutation also does not explain the interindividual and intraindividual variability in the clinical expression of MH syndrome. In several families, there has been discordance between the MH

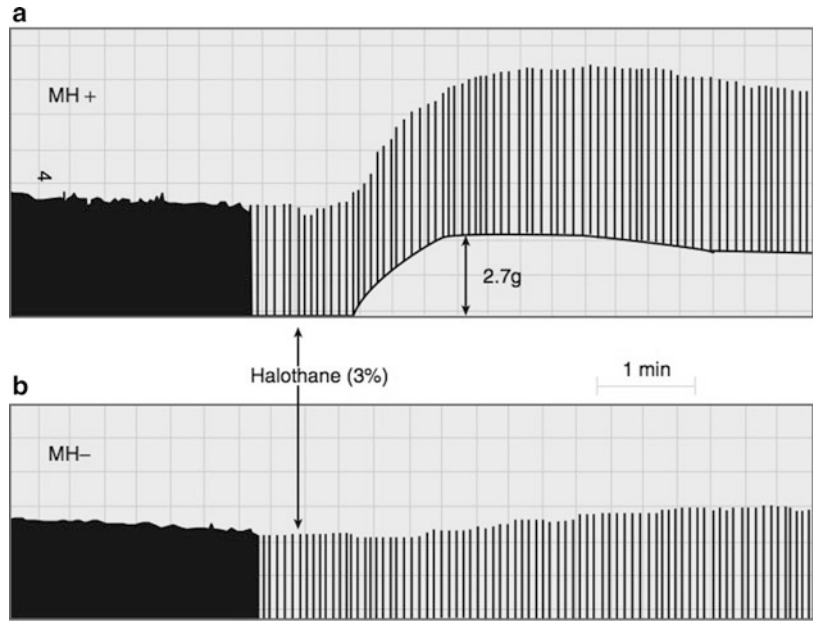

Fig. 3 In vitro contracture response. Cut muscle bundles from the vastus muscle weighing approximately 150 mg are mounted in a temperature-controlled bath. The muscle is stimulated at 0.1 Hz with a supramaximal stimulus. Halothane 3% in 95% oxygen and 5% carbon dioxide are introduced into the bath. (**a**) 3 g contracture typical of malignant hyperthermia susceptibility. (**b**) Normal response to halothane

ryanodine genotype and phenotype as determined by the in vitro caffeine halothane contracture test (IVCT) [49–53].

Central core disease, a dominantly inherited neuromuscular weakness, is one of the myopathies strongly associated with MH, and mutations in the ryanodine receptor have been shown to be the most common cause for central core disease [54, 55]. Hypokalemic periodic paralysis is another myopathy that has been associated with mutations in the dihydropyridine receptor in the same region as mutations related to MH [56]. Some patients with these disorders have displayed clinical MH reactions, whereas others have not.

The fine details of calcium control and its alteration in MH patients require further study and examination to better characterize the clinical presentations of MH. As the field of molecular genetics is rapidly advancing, we can anticipate identification of new MH-causative genes and greater sensitivity and efficiency of genetic testing. Continued growth of genetic databases will be of great use for better understanding of the genotype/phenotype relationships in MH. There is a lot more to be learned about the exact mechanisms of MH. Nevertheless, the basic finding that MH results from a hypermetabolic response to increased levels of intracellular calcium in skeletal muscle in genetically predisposed patients exposed to potent inhalational agents and/or succinylcholine remains an essential tenet of the pathophysiology of the disorder.

Diagnostic Testing

After the demonstration that biopsied skeletal muscle behaved abnormally on exposure to caffeine and to halothane [27, 28] in vitro, a standardized testing protocol to diagnose MH was developed. There are three major testing protocols in common use throughout the world [12]. The protocols in Europe [27] and North America [28] are similar [29]. The one in Japan is different [60].

In protocols using muscle bundles (Europe and North America) weighing about 100 mg, the tissue is tested on the same day as harvest. The muscle tested is either the vastus lateralis or the vastus medialis. Tests are conducted in duplicate or triplicate. The muscle is electrically stimulated to produce contractions of at least 0.5 g. Exposure to caffeine and to halothane results in contracture development (Figs. 3 and 4) in MH-susceptible individuals.

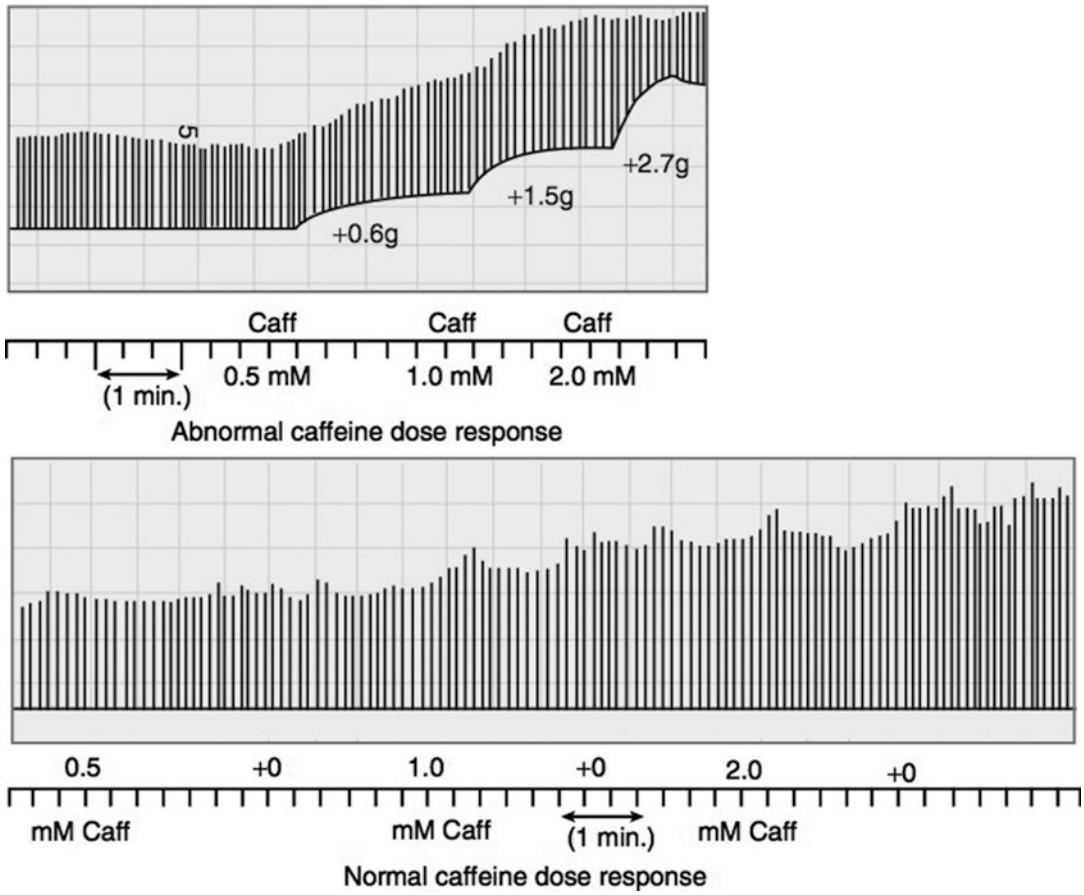

Fig. 4 Responses to caffeine in vitro. Same preparation with different muscle bundles as in Fig. 3 except the muscle bundle is exposed to incremental concentrations of caffeine for 4 min each. A positive response indicating malignant hyperthermia susceptibility is a contracture of 0.3 g or more to 2 mM of caffeine

In the European protocol [58], exposure to halothane is done in increments of 0.5%, 1%, and 2%. A positive response is a contracture of at least 0.2 g on exposure to 2% or less of halothane (see Fig. 3). Other strips are exposed to incremental doses of caffeine (0.25, 0.5, 1, 1.5, 2, 3, and 4 mM), and a positive response is 0.2-g contracture to 2 mM of caffeine or less (see Fig. 2). If the response to both agents is positive, the patient is considered *MH susceptible*. If the test is positive to only one agent, the patient is designated as *MH equivocal* but for clinical purposes is considered as MH susceptible.

In the North American protocol [59], the exposure is to 3% halothane, and a contracture of 0.5 g or greater is considered positive. Exposure to caffeine is essentially similar to that in Europe except that the concentrations are 0.5, 1, 2, 4, 8, and 32 mM. A contracture of greater than or equal to 0.3 g at 2 mM of caffeine is considered positive. Patients are considered MH susceptible if the response to one of the agents is abnormal.

Multicenter studies have shown a sensitivity of close to 100% [27, 28] but a specificity of about 82–93% in Europe [16, 28] and 78% in North America. In both tests, considerable interlaboratory variability is noted – not surprising, given that these are biologic tests. Because 5–15% of responses are considered equivocal by the European test, alternative agents have been

Table 2 Biopsy centers in the USA and Canada[a]

The USA	
Bethesda, MD	Uniformed Services University of the Health Sciences (military only)
Winston-Salem, NC	Bowman Gray School of Medicine
Minneapolis, MN	University of Minnesota
Sacramento, CA	University of California, Davis
Canada	
Toronto, Ontario	Toronto General Hospital

[a]Further information may be obtained from the Malignant Hyperthermia Association of the United States (MHAUS) at 1-607-674-7901 or www.mhaus.org

used. Responses to ryanodine [29, 57] and to chlorocresol [61] have been shown to be abnormal in MH muscle.

There are five biopsy centers for MH in North America (Table 2) and more than 20 in Europe. Other biopsy centers exist in other countries, including Australia, New Zealand, Brazil, and Israel. The test is time-consuming and expensive to perform. Despite the promise of other testing procedures, such as determination of high-energy phosphate depletion with exercise in vivo as measured by nuclear magnetic resonance spectroscopy [43–47], the biopsy response to caffeine and halothane remains the gold standard diagnostic test.

In Japan, the diagnostic test also uses skeletal muscle, but muscle in which the sarcolemma has been chemically removed [60]. Such skinned muscle showed accentuated responses to calcium and to caffeine. However, comparison between the skinned muscle test and IVCT test using whole muscle bundles showed a discordance between the two tests. As a result, biopsy centers in Europe and North America have decided not to employ this test [62].

Histologic examination of the biopsied muscle usually reveals nonspecific findings, such as type 1 atrophy, internal nuclei, and variation of fiber size. A few patients show changes consistent with central core or minicore disease, however [63]. Aside from this occasional finding, there is no distinctive pathologic change in MH muscle [64]. For diagnostic purposes, the patient must be sent to a biopsy center for testing.

With the demonstration of the association between *RYR1* mutations and MH susceptibility in certain families [1, 29], many believe that routine testing for ryanodine mutations has become essential [65]. Some investigators believe that if a known mutation in *RYR1* is found in a family member, other family members showing that mutation may be confirmed as MH susceptible. Further investigation is needed to rule out susceptibility if the mutation is not found in a family member. This is a promising and exciting prospect for simplified diagnosis of MH [27]. In Germany and in Australia, where several families have been identified and screened for *RYR1* mutations, 25% of families can be characterized by a *RYR1* mutation [66]. Family members may be evaluated by DNA testing for susceptibility to MH.

The virtue of molecular genetic testing is the high specificity and the fact that DNA may be harvested from white blood cells or buccal cells. Many other less invasive tests are in development. These include measurement of carbon dioxide production after microinjection of caffeine into muscle [67] and calcium release measurement on exposure of cultured muscle cells to halothane. B lymphocytes also manifest activity of the ryanodine receptor, and the calcium flux changes that are found in muscle may be shown in isolated B lymphocytes. Another study has demonstrated enhanced release of adenosine in B lymphocytes from MH susceptibles [68].

Consultation with an MH biopsy center director, a member of the professional advisory council of MHAUS and/or genetic counselor is adviseable prior to referral for diagnostic testing.

Clinical Presentation

The clinical diagnosis of MH may be easy and straightforward or challenging. MH may be precipitated during surgery on exposure to the potent inhalational anesthetic agents and/or succinylcholine only. Other drugs used in anesthesia to produce insensibility or muscle paralysis are not triggers for MH (Table 3).

Table 3 Safe and unsafe pharmacologic agents in malignant hyperthermia

Malignant Hyperthermia Triggers
Succinylcholine
All potent inhalational anesthetics
Halothane
Desflurane
Sevoflurane
Isoflurane
Enflurane
Methoxyflurane
Ethers
Agents that do not trigger malignant hyperthermia
Nitrous oxide
All local anesthetics
Intravenous anesthetics (e.g., thiopental, etomidate, propofol, ketamine, dexmedetomidine)
Nondepolarizing muscle relaxants (e.g., curare, rocuronium, vecuronium, atracurium, cisatracurium, mivacurium, pancuronium)
Opioids (e.g., morphine, fentanyl, sufentanil)
Anxiolytics and benzodiazepines
Reversal agents (e.g., naloxone, flumazenil, anticholinesterases, anticholinergics)
Mixed opioid agonists/antagonists (e.g., nalbuphine, butorphanol)
Droperidol/haloperidol

In the past, MH most often occurred shortly after induction of anesthesia and was marked by a paradoxical rigid response to succinylcholine, with tachycardia, hypertension, increase in end-tidal carbon dioxide, and fever [1–3]. Although this scenario still occurs, as anesthetic practice has evolved and succinylcholine use has declined, the manifestations of MH have also changed. MH now occurs later in the course of anesthesia and even in the recovery room [69].

The earliest, most sensitive, and specific sign of MH is an increase in end-tidal carbon dioxide that requires large minute ventilation to control. Patients who require two or more times predicted minute ventilation to maintain normocarbia are hypermetabolic. End-tidal carbon dioxide may increase to 50 or 100 mmHg during MH episodes. Besides MH, other causes of hypermetabolism include sepsis, iatrogenic overheating, faulty monitor function, and rarely thyrotoxicosis or pheochromocytoma (see later discussion of differential diagnosis of MH). Tachycardia is also an early sign of MH, but the differential diagnosis of tachycardia is extensive.

Hyperthermia is often considered a late sign of MH, but recent studies demonstrate that this is not the case. It is one of the three most common early signs of MH [70]. If the patient's body temperature has increased to 40 °C (104 °F), early signs of MH have been missed. If core temperature exceeds 42 °C, disseminated intravascular coagulation almost always supervenes, leading to a high fatality rate. It is vital to monitor a patient's core temperature during all general anesthesia exposures lasting longer than about 20 min. Hyperthermia is sometimes an important tip-off to the diagnosis of MH. A recent study demonstrated that the mortality from MH is increased 13-fold when core temperature is not monitored [70]. All patients undergoing general anesthesia lasting for 30 min or more should have core temperature monitored (esophageal, tympanic, bladder, pulmonary arterial or nasopharyngeal). Other sites of temperature monitoring are not as indicative of core temperature.

Muscle rigidity during anesthesia exposure is another important, specific sign for MH [71]. One of the common forms of muscle rigidity that has been noted in MH is masseter muscle rigidity after the use of succinylcholine. Of children anesthetized with an inhalational agent followed by administered succinylcholine, 1% develop masseter muscle rigidity [72–74]. Clinical MH follows in about 20% of cases, but the onset may be delayed. It is not clear why some patients who are not MH susceptible also develop succinylcholine-induced muscle rigidity. When there is generalized muscle rigidity, MH is almost certain. Masseter rigidity along with generalized rigidity is virtually pathognomonic for MH [75].

Rhabdomyolysis is another characteristic feature of MH [76]. CK elevation may be dramatic and extreme, whereas myoglobinuria may occur soon after the onset of the MH episode.

Myoglobinuria and CK elevation peak at about 14 h after the episode, however, and repeated determinations of CK are needed to diagnose MH or confirm the suspicion of MH. An easy screening test for myoglobin is urine dipstick for blood in the absence of red blood cells. In some cases where MH is detected early and treatment begun promptly, elevation of CK may be minimal.

Hyperkalemia and hypocalcemia are the typical electrolyte changes during an MH episode. Hyperkalemia may lead to arrhythmias. Hyperkalemia sufficient to cause ventricular fibrillation or asystole has been reported after the use of trigger agents in patients with a wide variety of myopathies, especially central core disease, muscular dystrophy, and various forms of myotonia.

Nonspecific signs of MH include tachycardia, tachyarrhythmias, tachypnea, sweating, hypertension, and hypotension. Coagulation abnormalities are more common in patients experiencing marked hyperthermia. Arterial blood gas analysis is essential in confirming the diagnosis of MH in many cases. Typically, respiratory and metabolic acidosis are found. Hypoxemia is not common during MH. Venous blood gas is a good substitute for arterial sampling. Elevation of venous carbon dioxide tension and marked acidosis are seen during MH crisis.

The presentation of MH may consist of a mixture of all of the abovementioned signs or may be limited to only a few, making the diagnosis challenging. When MH is suspected but not easily confirmed, it is advisable to treat with dantrolene, control the metabolic signs, and investigate the patient later. Table 4 lists common signs of MH and their incidence.

Table 4 Signs of malignant hyperthermia

Signs	Incidence (first 30 min) (%)
Tachycardia	90
Hypercarbia	80
Rigidity	80
Hypertension	75
Hyperthermia	70

Time of Onset

Most episodes of MH occur in the early part of the anesthesia exposure, certainly within the first few hours. Late-onset postoperative rhabdomyolysis is unlikely to be MH, but frequently there are not enough data to allow a true differential diagnosis. Perioperative rhabdomyolysis or myoglobinuria may occur in patients who are not susceptible to MH [77].

Normal patients who are not susceptible to MH may experience tenfold to 100-fold increases in serum myoglobin [78] after succinylcholine; repeated administration (i.e., intermittent intravenous bolus) is associated with more prominent increases in myoglobin level. Other causes of perioperative rhabdomyolysis include (1) pressure-induced muscle ischemia from prolonged surgical positioning [79], (2) muscle ischemia from prolonged tourniquet inflation [80], (3) extensive soft tissue trauma, (4) electrical injury, and (5) underlying myopathy enzymopathy (such as CPT2 deficiency) [81] or metabolic disorder, rendering muscle more susceptible to injury from ischemia, fever, or fasting. It is difficult to exclude MH from consideration with confidence unless the medical record clearly shows absence of hypermetabolism during anesthesia and in the early postoperative period. If the patient later undergoes a biopsy and is found to be MH susceptible by the caffeine halothane contracture test, there is a tendency to assume the episode was MH related. For example, if a patient develops flank pain and rhabdomyolysis starting more than 24 h after an uneventful 8-h anesthetic, and the subsequent caffeine halothane contracture test is positive for MH, it is possible that the patient is not truly MH susceptible [82]. It may be more likely that rhabdomyolysis was caused by skeletal muscle ischemia asssociated with intraoperative positioning, a previously subclinical metabolic myopathy, or morbid obesity. Whether this was an MH event is highly debatable, although based on contracture test results, the patient should be considered as MH susceptible. In the absence of other specific causes of rhabdomyolysis, such as

sepsis, the patient should be referred for neurologic evaluatiion for the presence of an occult myopathy or enzymopathy.

Malignant Hyperthermia-Like Conditions

Sudden Cardiac Arrest and Myopathies

In the early 1990s, a series of young, mostly male patients developed unexpected cardiac arrest soon after the induction of anesthesia or in the recovery room, and their cases were reported to the MH hotline [83]. Further investigations of these cases revealed that the patients were harboring myopathies that had not produced clinical signs and symptoms prior to the administration of anesthetic agents. The cardiac arrest in these cases was related to hyperkalemia, whereas hyperthermia, tachycardia, and muscle rigidity were not constant features in all of them. Rhabdomyolysis was, however, common.

After analysis of those events, the younger patients were identified as having classic Duchenne muscular dystrophy, whereas the older patients were found to have Becker's muscular dystrophy [83].

Since then RYR1 mutations have been implicated in a variety of inherited myopathies, and it has been increasingly important as well as difficult to delineate whether and to what extent these myopathies can predispose patients to an MH episode.

Increasing numbers of RYR1-related myopathies are being defined and added to the expanding spectrum of congenital myopathies. Along with the dominantly inherited core myopathies (e.g., central core disease and multiminicore disease), a growing collection of recessive noncore myopathies, with varying mutations along the RYR1 gene, are being investigated [84]. Mutations in RYR1 are considered the most common cause for inherited neuromuscular disease and are associated with a wide range of clinical symptoms from MH susceptibility to clinically recognized congenital myopathies.

Other, non-RYR1 related core myopathies are under investigation. Among them is a rare myopathy associated with dysmorphic features and MH susceptibility found among patients of Native American heritage. A recessive mutation on the STAC3 gene, which is a component of the excitation-contraction coupling machinery, was isolated in these patients [85]. This myopathy has also been found in individuals who are not Native Americans (Jerome Parness, M.D., Ph.D., Dept. of Anesthesiology, University of Pittsburgh School of Medicine, "personal communication").

Most pediatric anesthesiologists have phased out the routine use of succinylcholine after a black box warning issued by the US Food and Drug Administration ordered a change in the package insert stating that it should be administered in children and young adults only in situations where the patient has a full stomach or a difficult airway. Rapid-onset nondepolarizing agents have largely replaced succinylcholine in the operating room and should be considered for routine use for intubation in the emergency department as well as intensive care units.

Awake Malignant Hyperthermia

MH in the awake state is much harder to diagnose than MH in the operating room. A large increase in the production of carbon dioxide in an immobile and anesthetized patient is unusual. The cold operating room, depression of thermoregulation, and frequent use of neuromuscular blockade make the classic signs and symptoms unusual except in an MH episode. Even patients who are febrile from bacteremia usually lose heat and reduce metabolic rate under anesthesia. Therefore clinical signs frequently suggest the diagnosis of MH early in the disease process in the operating room. The diagnosis can then be confirmed with laboratory tests and subsequent muscle biopsy for IVCT.

Increasing numbers of non-anesthetic-related or awake MH cases have been reported in the last decade. Some of these are related to extreme exertion during sport or exercise [86–88], heat stress [89–91], and sudden death [92]. As we gain more insight into RYR1-mutation-related conditions, it is becoming apparent that sequelae seen with MH can often be seen without the traditional triggering agents. For example,

a recent case report of recurrent fever-induced rhabdomyolysis in a patient who had never been exposed to anesthesia, but was subsequently found to have a novel mutation in the RYR1 gene, highlights this overlap [93]. A study of 39 families with cases of rhabdomyolysis and/or exertional myalgia found nine heterozygous RYR1 mutations in 14 families, further strengthening our understanding of the link between inherited neuromuscular disease and the possibility for malignant hyperthermia susceptibility [94].

Conditions that overlap in their presentation and/or genetic mutations will be discussed in greater detail in the following paragraphs. Suffice it to say here that they may not represent MH in many instances, and they are harder to recognize, diagnose, classify, and sometimes treat than a true "classic" MH case. Even the postoperative patient, who awakens from anesthesia shivering, who may or may not have been febrile preoperatively, is much more difficult to evaluate for MH susceptibility. Although most patients awaken with little to suggest hypermetabolism, many who are hypothermic in the operating room shiver on awakening. This shivering may be confused with evidence of MH [95], even though shivering or rigors are not signs of MH; shivering is frequently treated with low-dose meperidine or acetaminophen. MH is ruled out if this treatment results in lysis of fever. Some patients emerge from anesthesia with excitement and agitation and may need physical restraint. As a result there may be abnormal laboratory results such as lactic acidosis or elevated CK levels. This response, although uncommon, is still more frequent than the incidence of MH in the population (1 in 10,000). Most such patients are not MH susceptible [96, 97] based on IVCTs.

Non-anesthetic Drugs and Circumstances

While MH is often not recognized right away in the operating room, it is even harder to diagnose in the patient who has not had an anesthetic at all or who is more than 24 h postanesthetic; confirmed postanesthetic MH episodes present within 1 h after discontinuation of anesthesia. In many instances MH is not immediately considered, especially if there is no personal or family history of MH. Aside from cases related to exertion and heat stress, non-anesthetic drugs and consumption of illicit substances have been implicated in triggering MH-like episodes.

Not everyone agrees that these cases are truly MH. Even with a positive IVCT, given its 10–20% false positive rate, a definitive MH diagnosis is uncertain. The more we understand the molecular genetic components and the biochemical mechanisms behind MH, as well as the mechanisms behind uncontrolled temperature elevation and rhabdomyolysis, the more we begin to see a multiplicity of subtypes and possible cumulative stressors and situations capable of triggering an MH-like episode.

Cocaine, for example, does not cause in vitro contracture of MH-susceptible muscle, and it does not change the response to low concentrations of halothane [98]. Intrinsic myotoxicity or direct stimulation of muscle metabolism also does not seem to be a factor. But in vivo, cocaine may potentiate triggering agents via its many effects on catecholamines, central excitation, and temperature regulation.

Because MH-susceptible muscle is known to be more sensitive to caffeine in vitro, one concern often raised is whether patients who are MH susceptible should avoid caffeine or the other methylxanthines such as theophylline. Sufficient evidence seems to have accumulated to indicate that both are safe at doses that are not toxic in normal individuals. Based on in vitro studies, it is possible that triggering agents will be more likely to cause an MH episode in patients who exhibit high levels of these agents [99].

Amide local anesthetics were previously thought to be harmful, because lidocaine may enhance in vitro contracture by inhibition of calcium sequestration into the sarcoplasmic reticulum. Reexamination has shown that lidocaine does not trigger MH in susceptible swine, even when given in doses above the convulsive threshold [100]. All local anesthetics, including the amides, are currently considered acceptable for anesthetic purposes [101, 102].

Other drugs and compounds have been suggested as triggers of MH or MH-like effects. A link between statin myopathies and MH is currently under investigation, since mutations in muscle disease genes, including RYR1, have been shown to exist in patients with statin induced myopathy [103]. It is still unclear whether statins pose a risk for MH during anesthesia in MH-susceptible patients. It appears reasonable to either avoid statins altogether in patients with MH susceptibility or, at the very least, be watchful for symptoms of rhabdomyolysis when statins are initiated in such patients.

Chlorocresol, a preservative in many drugs, is a potent, specific trigger in the IVCT [104] and is a trigger in vivo in susceptible pigs. However, large doses need to be given over a short period of time to see in vivo triggering. Since such high blood levels are close to the toxic dose in all animals, it is not likely that enough preservative to trigger an MH episode will ever be present in the blood stream [105]. For example, greater than 100 units *per kilogram* of insulin would contain the threshold dose of preservative to trigger MH.

Centrally acting agents, such as serotonin agonists and neuroleptic drugs, may produce a syndrome comprised of fever, acidosis, and rhabdomyolysis that resembles MH. Caroff and associates reported a high incidence of positive response to the IVCT in seven patients with previous NMS [106]. In contrast, Bello and coworkers reported normal IVCTs in 29 of 32 patients with previous NMS [107]. One should therefore not automatically assume that patients with NMS are MH susceptible, and to do so could put them at risk. Patients with severe NMS may benefit from electroconvulsive therapy, and the optimal anesthetic technique for this procedure includes the triggering agent succinylcholine. The rare possibility of an MH episode does not warrant prohibition of the use of succinylcholine in patients with acute NMS unless they are already exhibiting signs of rhabdomyolysis. Even though the pathophysiology of NMS is distinct from MH, dantrolene may benefit patients via reduction or abolition of muscle rigidity, temperature reduction, and attenuation of rhabdomyolysis [108].

A mention of methylene blue and its ability to act as an MAOI inhibitor is warranted in this section. The use of methylene blue in conjunction with a selective serotonin reuptake inhibitor has led to fatal toxicity in the postoperative setting, in part because the general anesthesia may have delayed or attenuated the typical presentation of serotonin syndrome and led to a protracted course [109], This drug's association with serotonin syndrome and its relative frequent intraoperative use should put anesthesiologists on high alert for MH-like signs. Methylene blue should be avoided in patients currently taking an SSRI.

Infection

Infection as a trigger for MH has been studied in susceptible pigs. Endotoxin injection, and the febrile state that follows, does not lead to MH. The outcome of septic, MH-susceptible pigs was worse, however, when they were also given a triggering agent. This finding is not surprising, because both stressors are potentially lethal [110]. In humans, a study of patients and their families after a suspected MH episode associated with appendicitis showed that only one of 13 were MH susceptible, but three other patients died and were assumed to be MH susceptible [111]. Death occurred in two patients despite the administration of dantrolene. No criteria could distinguish the septic patients from the patients who were MH susceptible. One study did not find any MH susceptibility by IVCT in a group of patients who developed postoperative fever [96].

Exercise and Heat Stress

Rhabdomyolysis has a multitude of etiologies and is characterized by muscle breakdown and elevation of creatine kinase. Commonly seen in cases of MH, it can also be triggered by intense exercise or heat in certain patients. Exertional heat stroke may be associated with MH, but it is not identical [90, 112]. Whether MH-susceptible patients are at increased risk of exertional heat stroke remains a

topic of controversy. Exercise-related problems are infrequently reported in MH-susceptible patients; however, a 2001 case report of exercise-related death raised cause for concern [113]. In this case a patient with a history of anesthetic-induced MH developed muscle rigidity after football practice and subsequently developed elevation in CK and lethal ventricular fibrillation. The patient, his father, and other family members were identified as harboring a typical MH-causative mutation. Although frequently associated with heat stress, several deaths have been attributed to MH after or during exercise. Underlying cardiac arrhythmias were frequently found, and these deaths could therefore be easily dismissed as related to cardiac arrhythmias. Furthermore, many patients who have a diagnosis of MH susceptibility have undergone strenuous exercise with little evidence for an unusual response. While some patients have been exposed to exercise in a controlled environment and shown no adverse effects [114], many suspicious cases have been reported [87, 88, 115]. In a study of 12 young men who developed rhabdomyolysis after exertion, nine were positive on the halothane-caffeine contracture test, and three of those displayed one of the typical MH-causative mutations [116].

In a knock-in mouse model with human RYR1 malignant hyperthermia mutations, exercise alone did not show increased rhabdomyolysis, but with an increase in ambient temperature, animals died of malignant hyperthermia [117, 118]. In a model in which homozygotes were viable, it could be shown that gene dose (homozygous vs. heterozygous), male gender, and elevated environmental temperatures increased the risk of death in MH-susceptible animals [118]. These studies further support the apparent multifactorial etiology for triggering an MH-like episode. While exercise alone could bring on rhabdomyolysis in a recent family cohort study, it was most often only triggered by a combination of stimuli, such as heat, exercise, and alcohol [94].

Since rhabdomyolysis, acidosis, and hyperthermia may be attributed to exercise or resuscitation alone, muscle rigidity and postmortem fever seem to be the major diagnostic criteria for malignant hyperthermia-related rhabdomyolysis [119]. Muscle biopsy for caffeine halothane contracture testing should not be ordered until the patients have recovered from rhabdomyolysis ($\geq$6 months), because damaged muscle may give rise to abnormal IVCTs. One may, however, send muscle tissue for molecular genetic testing.

Differential Diagnosis

Given that the signs of MH consist of tachycardia, acidosis, hypercarbia, fever, and muscle destruction, either together or in various combinations, it is not surprising that other syndromes may resemble MH (Table 5). Sepsis probably is confused most often with MH. Patients undergoing urinary tract surgery; ear, nose, and throat surgery; or appendectomy for appendicitis develop fever and sometimes acidosis. Elevated CK also may occur during episodes of sepsis. In contrast to MH, muscle rigidity is uncommon, although rigors may be mistaken for rigidity. In addition, signs of sepsis are treated effectively with nonsteroidal anti-inflammatory drugs and antibiotics. MH does not respond to such nonspecific therapy. Dantrolene often may be associated with acute reduction of fever. This finding is also nonspecific, however. Differentiating sepsis from MH is often not possible clinically.

Brain injury from a variety of causes has also been mistaken for MH [120, 121]. Patients may

Table 5 Differential diagnosis of malignant hyperthermia

Amphetamine toxicity	Intracranial bleed
Anticholinergic syndrome	Lethal catatonia
Brain injury	Meningitis
Cocaine toxicity	Neuroleptic malignant syndrome
Contrast-induced neurotoxicity	Pheochromocytoma
Drug/alcohol withdrawal	Salicylate toxicity
Extrapyramidal syndrome	Sepsis
Heatstroke	Serotonin syndrome
Hypoxic encephalopathy	Sympathomimetic toxicity
Iatrogenic overheating	Thyrotoxicosis

become febrile from hypothalamic damage or hemorrhage into the cerebral ventricles and may appear rigid due to posturing. If adequate ventilation is not provided, they may become hypercapnic. Ongoing muscle destruction is often associated with high temperatures (≥42 °C [107.6 °F]) Seizures can also produce an image of muscle rigidity. In contrast to MH, treatment with neuromuscular blocking agents will relax muscles and prevent acidosis, though true seizure activity requires treatment with anticonvulsants to prevent brain injury.

Endocrine disorders, such as pheochromocytoma and thyrotoxicosis, may produce increased oxygen consumption, tachycardia, hypertension, fever, and cardiovascular collapse. They have occasionally been misdiagnosed as MH. Pheochromocytoma is particularly difficult to diagnose, since patients often do not report a history suggestive of episodes of hypertension [122].

Iatrogenic overheating has been misdiagnosed as MH. In these situations, the patient is usually completely draped, the patient is externally warmed, and the procedure is lengthy. The patient develops fever, hypercarbia, tachycardia, and tachypnea if unparalyzed. Simple undraping leads to lysis of the fever, especially in an unanesthetized patient.

NMS is an idiosyncratic adverse drug reaction to neuroleptic drugs as well as to the newer atypical neuroleptics such as olanzapine and clozapine. There is no pathognomonic feature, nor are there diagnostic tests available for this syndrome. In contrast to the typically rapid onset of MH, NMS usually develops over days to weeks after initiation of the neuroleptic drug. NMS patients typically present with fever, extrapyramidal symptoms (e.g., rigidity, shuffling gate, resting tremors, dyskinesia, elevated CK), altered consciousness, and autonomic instability. In NMS, temperature is infrequently greater than 39 °C. MH-susceptible individuals tolerate neuroleptics, and individuals with NMS have tolerated general anesthetics and succinylcholine. Nondepolarizing paralytics (e.g., vecuronium or cisatracurium) cause muscle flaccidity in patients with NMS but do *not* resolve the rigidity of MH. Although NMS is rare in the perioperative setting, a thorough medication history is essential in making a diagnosis. Dantrolene has been shown to be beneficial in treating NMS [108] (see ▶ Chap. 31, "Neuroleptic Malignant Syndrome").

Many other drugs have been implicated in creating an MH-like presentation. Exposure to any drugs that greatly increase dopaminergic, serotonergic, or catecholaminergic function, or produce central anticholinergic syndrome, can produce signs similar to those of malignant hyperthermia. In contrast to the hypercarbia of an MH episode, respiratory alkalosis, complicated by metabolic acidosis in severe cases, would be the norm with poisoning from sympathomimetics or amphetamines.

A well-studied example is serotonin toxicity, leading to serotonin syndrome. This is yet another drug-induced hyperthermia syndrome, in this case due to greatly increased central nervous system serotonin. Serotonin syndrome is classically produced by the combination of an SSRI with a monoamine oxidase type A inhibitor. For example, antidepressants with or without opioid analgesics, such as meperidine, dextromethorphan, or fentanyl, lithium, or drugs of abuse such as lysergic acid diethylamide or methylenedioxymethamphetamine (MDMA) have been implicated. Methylene blue has also recently been shown to induce serotonin toxicity in combination with drugs having SSRI activity due to its potent monoamine oxidase inhibitor activity [123]. Serotonin syndrome is characterized by a constellation of neuromuscular, autonomic, and central nervous system manifestations and can superficially resemble both MH and NMS. The onset is typically fast (≤24 h) after introduction of the offending drug dose or combination, and it typically resolves within 24–36 h. The severity of muscle rigidity, rhabdomyolysis, and hyperthermia is typically less than that seen in MH or NMS but can be life threatening nonetheless. A comprehensive medical history helps establish the diagnosis. Most cases of serotonin syndrome are self limited with discontinuation of the offending drug or drug combination and administration of sedation and cooling measures, but central serotonin antagonism with cyproheptadine or olanzapine has been successfully used in

severe cases The role of dantrolene in life-threatening serotonin toxicity in unclear, with no reduction of mortality in an animal model [124]. Dantrolene, as an adjunct to supportive therapy including cooling measures, has been associated with good outcomes in cases of MDMA intoxication complicated by hyperthermia and rhabdomyolysis (see ▶ Chap. 24, "Serotonin Syndrome").

Other causes of misdiagnosis of MH include faulty temperature monitoring devices, faulty calibration of capnograph, absorption of carbon dioxide during laparoscopic procedures, underventilation of a septic patient, and a variety of causes of fever.

Although the only way to diagnose MH definitively is by means of the CHCT (caffeine halothane contracture testing) or the IVCT, the constellation of clinical signs may be helpful in determining the likelihood that a clinical event was related to MH. The clinical grading scale employs a point system based on the presence of signs of MH to score an episode. The details of the scoring system may be found elsewhere [125]. The utility of the scoring system depends on the completeness of data that are collected in a given patient. At present, the scoring system is used as a research tool only.

Management of Patients with Known Malignant Hyperthermia Susceptibility

Patients with MH susceptibility should have a preanesthetic evaluation. Safe anesthesia consists of either regional anesthesia with local anesthesia (all local anesthetics are safe) or general anesthesia using nitrous oxide and/or intravenous agents such as propofol, barbiturates, benzodiazepines, opioids, or ketamine. Intravenous sedation may be appropriate depending on the procedure and other patient comorbidities. All nondepolarizing neuromuscular blocking agents are safe. All potent inhalational agents and succinylcholine are MH triggers and must be avoided. Currently used potent inhalational anesthetics include desflurane, sevoflurane, and isoflurane. Halothane, enflurane, methoxyflurane, cyclopropane, and ether are no longer available for clinical use in humans in the USA. Dantrolene pretreatment is *not* necessary.

Preparation of older-generation anesthesia machines ("workstations") consisted of removing, closing, or disabling gas vaporizers, flowing 10 L/min of oxygen or air through the machine for at least 20 min, and changing the carbon dioxide absorbent. If a ventilator is to be used, the rebreathing bag should be affixed to the Y-piece and the ventilator cycled at 5–8/min during the 20 min flushing. The goal of these measures is to reduce the residual level of volatile anesthetic to <5 ppm, which is very unlikely to trigger an acute MH episode in a susceptible individual [127] and far below the concentration that can be detected by conventional anesthetic gas analyzers.

Current generation anesthetic workstations, using the method described above, require far longer times (e.g., >1 h) to achieve <5 ppm residual anesthetic [127]. The insertion of an activated charcoal filter (e.g., Vapor-Clean®) into the inspiratory limb of the breathing circuit results in prompt (e.g., <2 min) reduction of residual volatile anesthetic levels to <5 ppm; the filter is inserted following a brief (<2 min) flush of the breathing circuit with at least 10 L/min fresh oxygen flow. Because of the potential of users to unintentionally insert the filter in the expiratory limb, the manufactured product includes two filters for placement on both limbs of the breathing circuit. The manufacturer also recommends that high fresh gas flow be maintained during delivery of trigger-free general anesthesia [128–130] (link: http://www.dynasthetics.com/Vapor-Clean/Vapor-Clean-IFU.pdf).

Treatment

The success in controlling deaths from MH is due to early recognition of the acute syndrome and prompt treatment with dantrolene sodium intravenously (level of evidence [LoE] II-3). Dantrolene is a hydantoin derivative that inhibits calcium leak or release from the sarcoplasmic reticulum. Additional studies suggest significant inhibition of RyR1-dependent calcium influx via store-operated calcium entry, though this

inhibition does not involve a direct inhibition of store-operated calcium entry channels. It has no effect on excitation-contraction coupling in cardiac or smooth muscle. In an animal model of ventricular fibrillation, dantrolene was shown to facilitate successful defibrillation and return of spontaneous circulation; this was associated with a significant reduction of fibrillation-induced diastolic calcium leak/elevation [131]. Toxicity is limited when given over only a few days. Long-term administration may be associated with hepatotoxicity. The elimination half-life is 7–12 h.

Traditional preparations of dantrolene are poorly soluble in water – an initial treatment dose of 200 mg (=10 bottles) in a 80 kg patient requires 600 mL sterile water for injection to dissolve. Dantrolene is supplied as a lyophilized powder with 3 g of mannitol and sodium hydroxide to maintain pH of 9–10. Dantrium® or Revonto® must be mixed with 60 mL of *sterile water* and shaken vigorously. Each vial contains 20 mg of dantrolene.

In 2014, the FDA approved Ryanodex® (Eagle Pharmaceuticals), a nanocrystalline formulation of dantrolene sodium, for clinical use. Ryanodex® is

Table 6 Malignant hyperthermia treatment protocol

When MH is identified, notify surgeon/proceduralist and call for help; if in a freestanding surgery center or office, call 911. Immediately discontinue volatile anesthetic. If surgery must proceed, maintain anesthesia with intravenous agents and nondepolarizing muscle relaxants as needed. High oxygen flow should be employed to hasten reduction of inhalational agent level in the breathing circuit. If available, insert Vapor-Clean® filters into the breathing circuit to more rapidly reduce inhalational anesthetic levels
Hyperventilation: increase minute ventilation to ≥200 mL/kg/min, e.g., 20–25 breaths/min × 8–10 mL/kg tidal volume). Mechanical ventilation is recommended because simulation has shown that switching to manual ventilation usually results in significantly decreased minute ventilation [138] (LoE III)
Dantrolene should be mixed and a dose of 2.5 mg/kg injected rapidly
Repeat as frequently as needed until the patient responds with a decrease in $ETCO_2$, decreased muscle rigidity, and/or lowered heart rate. While the crisis is usually controlled with doses <10 mg/kg, large doses (>10 mg/kg) may be required for patients with persistent contractures or rigidity. If giving large doses (>10 mg/kg) without symptom resolution, consider alternative diagnoses. During this time, if the patient is decompensating or if blood gas shows base excess ≥ −8, bicarbonate should be given, 1–2 mEq/kg
If temperature ≥39 °C or rapidly rising, cooling should begin using cold intravenous isotonic crystalloid, surface cooling, or intraperitoneal lavage with cool isotonic solution as appropriate [139] (LoE II-3). Stop cooling when temperature is ≤38 °C In the case of cardiac arrest, potassium levels should be obtained immediately. If elevated or if hyperkalemia is suspected but quick lab results are unavailable, treatment should begin with calcium chloride, glucose, and insulin along with hyperventilation and sodium bicarbonate. Epinephrine and other β_2-agonists may be lifesaving Treatment of metabolic acidosis includes dantrolene and sodium bicarbonate as needed. Minute ventilation may need to be further increased to compensate for additional CO_2 released by any administered sodium bicarbonate (500 mL CO_2 gas is produced with administration of 25 mL intravenous sodium bicarbonate)
Arrhythmias should be treated with antiarrhythmics, with the exception of verapamil or diltiazem, because they may produce hyperkalemia or myocardial depression in the presence of dantrolene [140]. If a patient already taking oral verapamil or diltiazem is suspected of having an acute MH crisis, one should not hesitate to give dantrolene and should not reduce the initial treatment dose or avoid giving additional dantrolene if there are persistent signs of hypermetabolism or rigidity. One should exercise caution in the treatment of wide QRS complex rhythms with lidocaine or procainamide, as this may be a sign of hyperkalemia, and treatment with class 1 antiarrhythmics may result in asystole [141]
Arterial blood gases, electrolytes, creatine kinase, and coagulation studies should be obtained
When the initial crisis is under control, the patient should receive 1 mg/kg of dantrolene every 4–6 h or an infusion of 0.25 mg/kg/h for at least 24 h. Signs of recrudescence such as recurrent hypercarbia (not due to fighting the ventilator), rigidity not resolving with sedation, or recurrent myoglobinuria mandate re-bolusing with dantrolene in order to rapidly control hypermetabolism and prevent deterioration. Creatine kinase should be assessed every 12–24 h until stable
If myoglobinuria occurs, vigorous diuresis should be instituted with fluid administration and alkalinization. Each vial of Dantrium® or Revonto® contains 3 g of mannitol; 2.5 mg/kg of these dantrolene preparations gives the patient 0.4 g/kg of mannitol. One should carefully and frequently assess volume status in order to avoid either hypovolemia with impaired organ perfusion or fluid overload

vastly more water soluble – 250 mg of Ryanodex powder (1 bottle) is dissolved in 5 mL sterile water. Preclinical study in MH-susceptible swine demonstrated efficacy in treating acute MH triggered by halothane [126] Ryanodex® contains very little mannitol. It is recommended that at least 10 mg/kg of dantrolene for treatment of an MH crisis in a 70 kg patient be immediately available wherever general anesthesia with potent agents or succinylcholine is used. While the great majority of anesthesia-induced MH episodes are associated with potent inhalational anesthetics, there are a small number of documented cases where succinylcholine alone was administered [133, 134]. Short-term side effects of dantrolene include muscle weakness, phlebitis, nausea, and vomiting [135]. The drug does not impair respiration except in patients with underlying muscle disease.

Any facility where general anesthesia is administered should be prepared to treat MH. Ambulatory surgery centers or offices that use MH-triggering agents must have a plan in place for transfer of care to an emergency room that focuses on clear communication and ongoing urgent treatment of the MH crisis [137]; interruption or delay of treatment with dantrolene may result in death or severe complications from fulminant MH. A treatment protocol should be readily available, such as the one available from the MHAUS (Table 6). It is beneficial to refer to a cognitive aid, be it the MHAUS treatment protocol, an available iPhone app (link: http://www.mhaus.org/healthcare-professionals/managing-a-crisis/iphone-app), or the Stanford Emergency Manual (link: http://emergencymanual.stanford.edu) [137]. Table 7 lists suggested items to be kept in a treatment cart.

Help in diagnosing and managing clinical cases of MH is available through a hotline service offered by the Malignant Hyperthermia Association of the United States (MHAUS) at no cost. Experts in MH share responsibility in answering questions regarding MH and its treatment 7 days a week, 24 h per day. The hotline number is 1-800-MH-HYPER (1-800-644-9737). Outside the USA the number is 0011-315-464-7079. Further details about MHAUS are given subsequently. More than 1500 calls are handled by the hotline each year; only about 300 are related to actual MH cases.

Table 7 Treatment cart for care of malignant hyperthermia: suggested supplies and equipment (link: http://www.mhaus.org/faqs/stocking-an-mh-cart)

Dantrolene, 20 mg/vial, 36 vials or Ryanodex®, 250 mg/vial, 3 vials
Sterile water for injection USP in 50 or 100 mL vials for mixing Dantrium® or Revonto® Refrigerated 0.9% Sodium Chloride or Plasma-Lyte-A, 2–3 l
Sodium bicarbonate, 8.4%, 50 mL ampules x 5
Glucose 50%, 50 mL ampules × 2
Furosemide, 10 mg/mL, 2 vials
Calcium chloride 10%, 10 mL vials × 2
Lidocaine 1%, 10 mL, 2 vials Amiodarone HCl intravenous, 450 mg
Regular insulin, 100 U/mL × 1
Syringes (3 mL) for blood gas and electrolyte analysis or ABG kits × 6 for point-of-care monitors. Blood collection tubes for CK, PT, PTT, fibrin-split products, electrolytes, platelets
Arterial and central venous pressure kits
Plastic bags for ice
Mini-Spike or similar transfer pin to mix water with dantrolene
Urinary dipstick for hemoglobin (for detection of myoglobin)
Esophageal or nasopharyngeal temperature probes
Rectal or bladder temperature probes

CK creatine kinase, *PT* prothrombin time, *PTT* partial thromboplastin time

Sources of Information Concerning Malignant Hyperthermia

Updated information may be obtained from the MHAUS (www.mhaus.org; PO Box 1069, Sherburne, NY 13460, USA), a not-for-profit patient advocacy organization. Formed in 1981 to provide information to practitioners and patients regarding MH, MHAUS sponsors a hotline and the North American MH Registry and produces pamphlets, a newsletter, a fax-on-demand service, and a website (www.mhaus.org), among other services. The phone number is 1-607-674-7901. The board of directors of MHAUS consists of laypersons and professionals. Support for MHAUS is from a variety of sources, but mostly from voluntary contributions. In addition, MHAUS sponsors and supports the

Neuroleptic Malignant Syndrome Information Service (www.nmsis.org) with goals similar to the goals described previously. Another useful resource is GeneTests (www.genetests.org).

References

1. MacLennan DH, Phillips MS. Malignant hyperthermia. Science. 1992;256:789–94.
2. Rosenberg H, Dirksen R, Sambuughin NK. Malignant hyperthermia susceptibility in: GeneReviews at gene tests: medical genetics information resource [database online]. http://www.genetests.org (2013). Revised and updated 2013.
3. Jurkat-Rott K, McCarthy T, Lehmann-Horn F. Genetics and pathogenesis of malignant hyperthermia. Muscle Nerve. 2000;23(1):4–17.
4. Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. Anesthesiology. 1982; 56:254–62.
5. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. Anesthesiology. 2008;108(4):603–11.
6. Denborough MA, Lovell RRH. Anaesthetic deaths in a family. Lancet. 1960;2:45.
7. Harrison GG. Pale, soft exudative pork, porcine stress syndrome and malignant hyperpyrexia – an identity? J S Afr Vet Assoc. 1972;43:57–63.
8. Kalow W, Britt BA, Terreau ME, et al. Metabolic error of muscle metabolism after recovery from malignant hyperthermia. Lancet. 1970;2:895–8.
9. Groom L, Muldoon SM, Tang ZZ, Brandom BW, Bayarsaikhan M, Bina S, Lee HS, Qiu X, Sambuughin N, Dirksen RT. Identical de novo mutation in the type 1 ryanodine receptor gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. Anesthesiology. 2011;115(5):938–45.
10. Ellis FR, Harriman DG, Keaney NP, et al. Halothane-induced muscle contracture as a cause of hyperpyrexia. Br J Anaesth. 1971;43:721–2.
11. Harrison GG. Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. Br J Anaesth. 1975;47:62–5.
12. Rosenberg H, Fletcher JE. Report of a scientific meeting. International malignant hyperthermia workshop and symposium. Hiroshima, Japan, July 16–19, 1944. Anesthesiology. 1995;82:803–5.
13. Chelu MG, Goonasekera SA, Durham WJ, Tang W, Lueck JD, Riehl J, Pessah IN, Zhang P, Bhattacharjee MB, Dirksen RT, Hamilton SL. Heat- and anesthesia-induced malignant hyperthermia in an RYR1 knock-in mouse. FASEB J. 2006;20:329–30.
14. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from, 1987 to 2006. Anesth Analg. 2010;110(2):498–507.
15. Ording H. Incidence of malignant hyperthermia in Denmark. Anesth Analg. 1985;64:700–4.
16. Pinyavat T, Rosenberg H, Lang BH, Wong CA, Riazi S, Brady JE, Sun LS, Li G. Accuracy of malignant hyperthermia diagnosis in hospital records. Anesthesiology. 2015;122(1):55–63.
17. Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. Anesthesiology. 2009;110:89–94.
18. Bachand M, Vachon N, Boisvert M, et al. Clinical reassessment of malignant hyperthermia in Abitibi-Temiscamingue. Can J Anaesth. 1997;44:696–701.
19. Brady J, Sun L, Rosenberg H, Li G. Prevalence of malignant hyperthermia in New York state, 2001–2005. Anesth Analg. 2009;109:1162–6.
20. Monnier N, Krivosic-Horber R, Payen J-F, et al. Presence of two different genetic traits in malignant hyperthermia families: Implication for genetic analysis, diagnosis, and incidence of malignant hyperthermia susceptibility. Anesthesiology. 2002;97:1067–74.
21. Gonsalves SG, Ng D, Johnston JJ, Teer JK, Stenson PD, Cooper DN, Mullikin JC, Biesecker LG. NISC comparative sequencing program. Using exome data to identify malignant hyperthermia susceptibility mutations. Anesthesiology. 2013;119(5): 1043–53.
22. Mickelson JR, Louis CF. Malignant hyperthermia: excitation-contraction coupling, Ca^{2+}release channel, and cell Ca^{2+} regulation defects. Physiol Rev. 1996;76:537–92.
23. Rosenberg H, Brandom BW, Sambughin N. Malignant hyperthermia and other inherited disorders. In: Barash PG, Cullen BF, Stoelting RK, Cahalan M, Stock MC, editors. Clinical anesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2009.
24. Dowling JJ, Lillis S, Amburgey K, et al. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromucul Disord. 2011;21(6):420–7.
25. Duarte ST, Oliveira J, Santos R, et al. Dominant and recessive RYR1 mutations in adults with core lesions and mild muscle symptoms. Muscle Nerve. 2011; 44(1):102–8.
26. Loseth S, Voermans NC, Torbergsen T, et al. A novel late-onset axial myopathy associated with mutations in the skeletal muscle ryanodine receptor (RYR1) gene. J Neurol. 2013;260(6):1504–10.
27. Ording H, Brancadoro V, Cozzolino S, et al. In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: results of testing patients surviving fulminant

MH and unrelated low-risk subjects. The European Malignant Hyperthermia Group. Acta Anaesthesiol Scand. 1997;41:955–66.
28. Allen GC, Larach MG, Kunselman AR. The sensitivity and specificity of the caffeine-halothane contracture test: a report from the North American Malignant Hyperthermia Registry. The North American Malignant Hyperthermia Registry of MHAUS. Anesthesiology. 1998;88:579–88.
29. Fletcher JE, Rosenberg H, Aggarwal M. Comparison of European and North American malignant hyperthermia diagnostic protocol outcomes for use in genetic studies. Anesthesiology. 1999;90:654–61.
30. Robinson RL, Monnier N, Wolz W, et al. A genome wide search for susceptibility loci in three European malignant hyperthermia pedigrees. Hum Mol Genet. 1997;6:953–61.
31. Sudbrak R, Procaccioo V, Klausnitzer M, et al. Mapping of a further malignant hyperthermia susceptibility locus to chromosome 3q13.1. Am J HumGenet. 1995;56:684–91.
32. Iles DE, Lehmann-Horn F, Scherer SW, et al. Localization of the gene encoding the alpha2/delta-subunits of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families. Hum Mol Genet. 1994;3:969–75.
33. Levitt RC, Olckers A, Meyers S, et al. Evidence for the localization of a malignant hyperthermia susceptibility locus (MHS2) to human chromosome 17q. Genomics. 1992;14:562–6.
34. Iaizzo PA, Klein W, Lehmann-Horn F. Fura-2 detected myoplasmic calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. Pflugers Arch. 1988;411:648–53.
35. Lopez JR, Allen PD, Alamo L, et al. Myoplasmic free [Ca^{2+}] during a malignant hyperthermia episode in swine. Muscle Nerve. 1988;11:82–8.
36. Censier K, Urwyler A, Zorzato F, et al. Intercellular calcium homeostasis in human primary muscle cells from malignant hyperthermia-susceptible and normal individuals. Effect of overexpression of recombinant wild-type and Arg163Cys mutated ryanodine receptors. J Clin Invest. 1998;101:1233–42.
37. Yang T, Esteve E, Pessah IN, et al. Elevated resting [Ca^{2+}] (i) in myotubes expressing malignant hyperthermia RYR1 cDNA is partially restored by modulation of passive calcium leak from the SR. Am J Physiol Cell Physiol. 2007;292(5):1591–8.
38. Louis CF, Zualkernan K, Roghair T, et al. The effects of volatile anesthetics on calcium regulation by malignant hyperthermia-susceptible sarcoplasmic reticulum. Anesthesiology. 1992;77:114–25.
39. MacLennan DH, Chen SR. Store –overload induced Ca^{2+} release as a triggering mechanism for CPVT and MH episodes caused by mutations in RYR and CASQ genes. J Physiol. 2009;587:3113–5.
40. Riazi S, Kraeva N, Muldoon SM, Dowling J, Ho C, Petre MA, Parness J, Dirksen RT, Rosenberg H. Malignant Hyperthermia and the clinical significance of type-1 ryanodine receptor gene (RYR1) variants: proceedings of the MHAUS Scientific Conference. Can J of Anesth. 2014;61(11):1040–9.
41. Eltit JM, Bannister R, Moua O, et al. Malignant hyperthermia susceptibility arising from altered resting coupling between the skeletal muscle L-type Ca^{2+} channel and the type 1 ryanodine receptor. Proc Natl Acad Sci U S A. 2012;109:79023–8.
42. Eltit JM, Ding X, Pessah IN, Allen PD, Lopez JR. Nonspecific sarcolemmal cation channels are critical for the pathogenesis of malignant hyperthermia. FASEB J. 2013;27(3):991–1000.
43. Olgin J, Argov Z, Rosenberg H, et al. Non-invasive evaluation of malignant hyperthermia susceptibility with phosphorus nuclear magnetic resonance spectroscopy. Anesthesiology. 1988;68:507–13.
44. Webster DW, Thompson RT, Gravelle DR, et al. Metabolic response to exercise in malignant hyperthermia-sensitive patients measured by 31P magnetic resonance spectroscopy. Magn Reson Med. 1990;15:81–9.
45. Olgin J, Rosenberg H, Allen G, et al. A blinded comparison of noninvasive, in vivo phosphorus nuclear magnetic resonance spectroscopy and the in vitro halothane/caffeine contracture test in the evaluation of malignant hyperthermia susceptibility. Anesth Analg. 1991;72:36–47.
46. Payen JF, Fouilhe N, Sam-Lai E, et al. In vitro 31P-magnetic resonance spectroscopy of muscle extracts in malignant hyperthermia-susceptible patients. Anesthesiology. 1996;84:1077–82.
47. Bendahan D, Kozak-Ribbens G, Rodet L, et al. ^{31}Phosphorus magnetic resonance spectroscopy characterization of muscular metabolic anomalies in patients with malignant hyperthermia: application to diagnosis. Anesthesiology. 1998;88:96–107.
48. Brandt A, Schleithoff L, Jurkat-Rott K, et al. Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: novel mutations and concordance with the in vitro contracture test. Hum Mol Genet. 1999;8:2055–62.
49. Deufel T, Sudbrak R, Feist Y, et al. Discordance, in a malignant hyperthermia pedigree, between in vitro contracture-test phenotypes and haplotypes for the MHS1 region on chromosome 19q12–13.2, comprising the C1840T transition in the RYR1 gene. Am J Hum Genet. 1995;56:1334–42.
50. MacLennan DH. Discordance between phenotype and genotype in malignant hyperthermia. Curr Opin Neurol. 1995;8:397–401.
51. Serfas KD, Bose D, Patel L, et al. Comparison of the segregation of the RYR1 C1840T mutation with segregation of the caffeine/halothane contracture test results for malignant hyperthermia susceptibility in a large Manitoba Mennonite family. Anesthesiology. 1996;84:322–9.

52. Fagerlund TH, Ording H, Bendixen D, et al. Discordance between malignant hyperthermia susceptibility and RYR1 mutation C1840T in two Scandinavian MH families exhibiting this mutation. Clin Genet. 1997;52:416–21.
53. Fortunato G, Carsana A, Tinto N, et al. A case of discordance between genotype and phenotype in a malignant hyperthermia family. Eur J Hum Genet. 1999;7:415–20.
54. Quane KA, Healy JM, Keating KE, et al. Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia. Nat Genet. 1993; 5:51–5.
55. Zhang Y, Chen HS, Khanna VK, et al. A mutation in the human ryanodine receptor gene associated with central core disease. Nat Genet. 1993;5:46–50.
56. Monnier N, Procaccio V, Stieglitz P, et al. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium channel receptor in skeletal muscle. Am J Hum Genet. 1997;60:1316–25.
57. Hopkins PMRH, Snoeck MM, Girar T, Glahn KPE, Ellis FR, Muller CR, et al. The European Malignant Hyperthermia Group Guidelines for the investigation of malignant hyperthermia susceptibility. Br J Anaesth. 2015;115(4):531–9.
58. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia. Br J Anaesth. 1984;56:1267–9.
59. Larach MG, for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. Anesth Analg. 1989;69:511–5.
60. Maehara Y, Mukaida K, Hiyama E, et al. Genetic analysis with calcium-induced calcium release test in Japanese malignant hyperthermia susceptible (MHS) families. Hiroshima J Med Sci. 1999; 48:9–15.
61. Ording H, Glahn K, Gardi T, et al. 4-Chloro-m-cresol test – a possible supplementary test for diagnosis of malignant hyperthermia susceptibility. Acta Anaesthesiol Scand. 1997;41:967–72.
62. Adnet P, Bortlein ML, Tavernier B, et al. Caffeine skinned fiber tension test: application to the diagnosis of susceptibility to malignant hyperthermia. Ann Fr Anesth Reanim. 1999;18:624–30.
63. De Cauwer H, Heytens L, Lubke U, et al. Discordant light microscopic, electron microscopic, and in vitro contracture study findings in a family with central core disease. Clin Neuropathol. 1997;16:237–42.
64. Mezin P, Payen JF, Bosson JL, et al. Histological support for the difference between malignant hyperthermia susceptible (MHS), equivocal (MHE) and negative (MHN) muscle biopsies. Br J Anaesth. 1997;79:327–31.
65. Sambuughin N, Holley H, Muldoon S, Brandom BW, de Bantel AM, Tobin JR, Nelson TE, Goldfarb LG. Screening of the entire ryanodine receptor type 1 coding region for sequence variants associated with malignant hyperthermia susceptibility in the North American population. Anesthesiology. 2005;102(3):515–21.
66. Gillies RL, Bjorksten AR, Du Sart D, Hockey BM. Analysis of the entire ryanodine receptor type 1 and alpha 1 subunit of the dihydropyridine receptor (CACNA1S) coding regions for variants associated with malignant hyperthermia in Australian families. Anaesth Intensive Care. 2015;43(2):157–66.
67. Anetseder M, Hager M, Muller CR, et al. Diagnosis of susceptibility to malignant hyperthermia by use of a metabolic test. Lancet. 2002;359:1579–80.
68. Bina S, Capacchione J, Munkhuu B, Muldoon S, Buenger R. Is lymphocyte adenosine a diagnostic marker of clinical malignant hyperthermia? A pilot study. Crit Care Med. 2015;43(3):584–93.
69. Litman RS, Flood CD, Kaplan RF, Kim YL, Tobin JR. Postoperative malignant hyperthermia: an analysis of cases from the North American Malignant Hyperthermia Registry. Anesthesiology. 2008;109(5):825–9.
70. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007–2012: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. Anesth Analg. 2014; 119(6):1359–66.
71. Relton JE, Creighton RE, Conn AW, et al. Generalized muscular hypertonicity associated with general anaesthesia: a suggested anaesthetic management. Can Anaesth Soc J. 1967;14:22–5.
72. Donlon JV, Newfield P, Sreter F, et al. Implications of masseter spasm after succinylcholine. Anesthesiology. 1978;49:298–301.
73. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. Anesthesiology. 1984;61:772–5.
74. Lazzell VA, Carr AS, Lerman J, et al. The incidence of masseter muscle rigidity after succinylcholine in infants and children. Can J Anaesth. 1994;41:475–9.
75. Rosenberg H. Succinylcholine and trismus. Anesthesiology. 1989;70:162–163.
76. Litman RS, Rosenberg H. Malignant hyperthermia. Update on susceptibility testing. JAMA. 2005;239:2918–24.
77. Ryan JF, Kagen LJ, Hyman AI. Myoglobinemia after a single dose of succinylcholine. N Engl J Med. 1971;285(15):824–827.
78. Airaksinen MM, Tammisto T. Myoglobinuria after intermittent administration of succinylcholine during halothane anesthesia. Clin Pharmacol Ther. 1966;7:583–7.
79. Ziser A, Friedhoff RJ, Rose SH. Prone position: visceral hypoperfusion and rhabdomyolysis. Anesth Analg. 1996;82:412–5.
80. Alterman I, Sidi A, Azamfirei L, Copotoiu S, Ezri T. Rhabdomyolysis: another complication after prolonged surgery. J Clin Anesth. 2007;19(1):64–6.

81. Joshi PR, Deschauer M, Zierz S. Carnitine palmitoyltransferase II (CPT II) deficiency: genotype-phenotype analysis of 50 patients. J Neurol Sci. 2014;338(1–2):107–11.
82. Harwood TN, Nelson TE. Massive postoperative rhabdomyolysis after uneventful surgery: a case report of subclinical malignant hyperthermia. Anesthesiology. 1998;88:265–8.
83. Larach MG, Rosenberg H, Gronert GA, et al. Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. Clin Pediatr (Phila). 1997;36:9–16.
84. Amburgey K, Beiley A, Hwang JH, et al. Genotype-phenotype correlations in recessive RYR1-related myopathies. Orphanet J Rare Dis. 2013;8:117.
85. Horstick EJ, Linsley JW, Dowling JJ, et al. Stac3 is a component of the excitation-contraction coupling machinery and mutated in native American myopathy. Nat Commun. 2013;4:1952.
86. Ogletree JW, Antognini JF, Gronert GA. Postexercise muscle cramping associated with positive malignant hyperthermia contracture testing. Am J Sports Med. 1996;24:49–51.
87. Gronert GA, Thompson RL, Onofrio BM. Human malignant hyperthermia: awake episodes and correction by dantrolene. Anesth Analg. 1980;59:377–8.
88. Hunter SL, Rosenberg H, Tuttle GH, et al. Malignant hyperthermia in a college football player. Phys Sportsmed. 1987;15:77–84.
89. Denborough MA. Heat stroke and malignant hyperpyrexia. Med J Aust. 1982;1:204–5.
90. Hopkins PM, Ellis FR, Halsall PJ. Evidence for related myopathies in exertional heat stroke and malignant hyperthermia. Lancet. 1991;338:1491–2.
91. Kochling A, Wappler F, Winkler G, et al. Rhabdomyolysis following severe physical exercise in a patient with predisposition to malignant hyperthermia. Anaesth Intensive Care. 1998;26:315–8.
92. Britt BA. Combined anesthetic- and stress-induced malignant hyperthermia in two offspring of malignant hyperthermic-susceptible parents. Anesth Analg. 1988;67:393–9.
93. Molenaar JP, et al. Fever-induced recurrent rhabdomyolysis due to a novel mutation in the ryanodine receptor type 1 gene. Intern Med J. 2014.
94. Dlamini N, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. Neuromuscul Disord. 2013;23:540–8.
95. Ciofolo MJ, Clergue F, Devilliers C, et al. Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. Anesthesiology. 1989;70:737–41.
96. Halsall PJ, Ellis FR. Does postoperative pyrexia indicate malignant hyperthermia susceptibility? Br J Anaesth. 1992;68:209–10.
97. Christiaens F, Gepts E, D'Haese J, et al. Malignant hyperthermia suggestive hypermetabolic syndrome at emergence from anesthesia. Acta Anaesthesiol Belg. 1995;46:93–7.
98. Sato N, Brum JM, Mitsumoto H, et al. Effect of cocaine on the contracture response to 1% halothane in patients undergoing diagnostic muscle biopsy for malignant hyperthermia. Can J Anaesth. 1995;42:158–62.
99. Flewellen EH, Nelson TE. Is theophylline, aminophylline, or caffeine (methylxanthines) contraindicated in malignant hyperthermia susceptible patients? Anesth Analg. 1983;62:115–8.
100. Wingard DW, Bobko S. Failure of lidocaine to trigger porcine malignant hyperthermia. Anesth Analg. 1979;58:99–103.
101. Brownell AKW. Counseling of malignant hyperthermia susceptible individuals. In: Britt BA, editor. Malignant hyperthermia. Boston: Martinus Nijhoff; 1987. p. 309–23.
102. Berkowitz A, Rosenberg H. Femoral block with mepivacaine for muscle biopsy in malignant hyperthermia patients. Anesthesiology. 1985;62:651–2.
103. Vladutiu G, Isackson P, Kaufman K, et al. Genetic risk for malignant hyperthermia in non-anesthesia-induced myopathies. Mol Genet Metab. 2011;104:167–73.
104. Wappler F, Scholz J, Fiege M, et al. 4-chloro-m-cresol is a trigger of malignant hyperthermia in susceptible swine. Anesthesiology. 1999;90:1733–40.
105. Iaizzo PA, Johnson BA, Nagao K, et al. 4-chloro-m-cresol triggers malignant hyperthermia in susceptible swine at doses greatly exceeding those found in drug preparations. Anesthesiology. 1999;90:1723–32.
106. Caroff SN, Rosenberg H, Fletcher JE, et al. Malignant hyperthermia susceptibility in neuroleptic malignant syndrome. Anesthesiology. 1987;67:20–5.
107. Bello N, Adnet P, Saulnier F, et al. Lack of sensitivity to per-anesthetic malignant hyperthermia in 32 patients who developed neuroleptic malignant syndrome. Ann Fr Anesth Reanim. 1994;13:663–8.
108. Pawar S, Rosenberg H, Adamson R, Chamberlain R. Dantrolene for the treatment of malignant hyperthermia and other malignant hyperthermia-like syndromes: a multicenter 5 year cohort study. American Society of Anesthesiologists Annual Meeting; San Francisco, October, 2013.
109. Top WMC, Gillman PK, et al. Fatal methylene blue associated serotonin toxicity. Neth J Med. 2014;72:179–81.
110. Musley SK, Beebe DS, Komanduri V, et al. Hemodynamic and metabolic manifestations of acute endotoxin infusion in pigs with and without the malignant hyperthermia mutation. Anesthesiology. 1999;91:833–8.
111. Strecker G, Adnet P, Forget AP, et al. Malignant hyperthermia and appendicular sepsis: can they be differentiated during surgical procedure? Ann Fr Anesth Reanim. 1997;16:234–8.
112. Bendahan D, Kozak-Ribbens G, Confort-Gouny S. A noninvasive investigation of muscle energetics supports similarities between exertional heat stroke and

malignant hyperthermia. Anesth Analg. 2001; 93(3):683–9.
113. Tobin JR, Jason DR, Nelson TE, et al. Malignant hyperthermia and apparent heat stroke. JAMA. 2001;286(2):168–9.
114. Green JH, Ellis FR, Halsall PJ, et al. Thermoregulation, plasma catecholamine and metabolite levels during submaximal work in individuals susceptible to malignant hyperpyrexia. Acta Anaesthesiol Scand. 1987;31:122–6.
115. Hackl W, Winkler M, Mauritz W, et al. Muscle biopsy for diagnosis of malignant hyperthermia susceptibility in two patients with severe exercise-induced myolysis. Br J Anaesth. 1991;66:138–40.
116. Wappler F, Feige M, Steinfath M, et al. Evidence for susceptibility to malignant hyperthermia in patients with stress-induced rhabdomyolysis. Anesthesiology. 2001;94:95–100.
117. Corona BT, et al. Eccentric contractions do not induce rhabdomyolysis in malignant hyperthermia susceptible mice. J Appl Physiol. 2008;105(5):1542–53.
118. Yuen B, et al. Mice expressing T4826I-RYR1 are viable but exhibit sex and genotype dependent susceptibility to malignant hyperthermia and muscle damage. FASEB J. 2012;26(3):1311–22.
119. Ryan JF, Tedeschi LG. Sudden unexplained death in a patient with a family history of malignant hyperthermia. J Clin Anesth. 1997;9:66–8.
120. Francoise M, Francois C, Sandre D, et al. Hemorrhagic shock with encephalopathy syndrome or major hyperthermia syndrome? Pediatrie. 1993;48:792–5.
121. Itaya K, Takahata O, Mamiya K, et al. Anesthetic management of two patients with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Masui. 1995;44:710–2.
122. Allen GC, Rosenberg H. Phaeochromocytoma presenting as acute malignant hyperthermia – a diagnostic challenge. Can J Anaesth. 1990;37:593–5.
123. Gillman PK. CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity. J Psychopharmacol. 2010;25:1–8.
124. Nisijima K, et al. Potent serotonin (5-HT)2A receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome. Brain Res. 2001;890:23–31.
125. Larach MG, Localio AR, Allen GC, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology. 1994;80:771–9.
126. Schuette JK, Becker S, Burmester S, et al. Comparison of the therapeutic effectiveness of a dantrolene sodium solution and a novel nanocrystalline suspension of dantrolene sodium in malignant hyperthermia normal and susceptible pigs. Eur J Anaesthesiol. 2011;28(4):256–64.
127. Kim TW, Nemergut ME. Preparation of modern anesthesia workstations for malignant hyperthermia-susceptible patients. Anesthesiology. 2011;114: 205–12.
128. Birgenheier N, Orr J, Westenskow D. Activated charcoal effectively removes inhaled anesthetics from modern anesthesia machines. Anesth Analg. 2011;112:1363–70.
129. Bilmen JG, Gillies RI. Clarifying the role of activated charcoal filters in preparing an anaesthetic workstation for malignant hyperthermia-susceptible patients. Anaesth Intensive Care. 2014;42:51–8.
130. Orr J, Sakata D. Manufacturer's response to Bilmen and Gillies' manuscript entitled "clarifying the role of activated charcoal filters in preparing an anaesthetic workstation for malignant hyperthermia-susceptible patients". Anaesth Intensive Care. 2014;42(6):801–2.
131. Roden DM, Knollmann BC. Dantrolene: from better bacon to a treatment for ventricular fibrillation. Circulation. 2014;129(8):834–6.
132. Schütte JK, Becker S, Burmester S, et al. Comparison of the therapeutic effectiveness of a dantrolene sodium solution and a novel nanocrystalline suspension of dantrolene sodium in malignant hyperthermia normal and susceptible pigs. Eur J Anaesthesiol. 2011;28(4):256–64.
133. Riazi S, Green Larach M, Hu C, et al. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. Anesth Analg. 2014;118:381–7.
134. Visoiu M, Young MC, Wieland K, et al. Anesthetic drugs and onset of malignant hyperthermia. Anesth Analg. 2014;118:388–96.
135. Brandom BW, Larach MG, Chen MS, et al. Complications associated with the administration of dantrolene 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. Anesth Analg. 2011;112(5):1115–23.
136. Larach MG, Dirksen SJ, Belani KG, et al. Special article: creation of a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. Anesth Analg. 2012;114(1):94–100.
137. Ranganathan P, Phillips JH, Attaallah AF, et al. The use of cognitive aid checklist leading to successful treatment of malignant hyperthermia in an infant undergoing cranioplasty. Anesth Analg. 2014;118(6):1387.
138. Gardi T, Christensen UC, Jacobsen J, et al. How do anaesthesiologists treat malignant hyperthermia in a full-scale anaesthesia simulator? Acta Anaesthesiol Scand. 2001;45(8):1032–5.
139. De Waard MC, Biermann H, Brinckman SL, et al. Automated peritoneal lavage: an extremely rapid and safe way to induce hypothermia in post-resuscitation patients. Crit Care. 2013;17(1):R31.
140. Yoganathan T, Casthely PA, Lamprou M. Dantrolene-induced hyperkalemia in a patient treated with diltiazem and metoprolol. J Cardiothorac Anesth. 1988; 2(3):363–4.
141. McLean SA, Paul ID, Spector PS. Lidocaine-induced conduction disturbance in patients with systemic hyperkalemia. Ann Emerg Med. 2000;36(6):615–8.