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Review Article

The current status of malignant hyperthermia

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Abstract

Malignant hyperthermia (MH) is a rare and life-threatening pharmacogenetic disorder triggered by volatile anesthetics, the depolarizing muscle relaxant succinylcholine, and rarely by strenuous exercise or environmental heat. The exact prevalence of MH is unknown, and it varies from 1:16 000 in Denmark to 1:100 000 in New York State. The underlying mechanism of MH is excessive calcium release from the sarcoplasmic reticulum (SR), leading to uncontrolled skeletal muscle hyper-metabolism. Genetic mutations in ryanodine receptor type 1 (*RYR1*) and *CACNA1S* have been identified in approximately 50% to 86% and 1% of MH-susceptible (MHS) individuals, respectively. Classic clinical symptoms of MH include hypercarbia, sinus tachycardia, masseter spasm, hyperthermia, acidosis, muscle rigidity, hyperkalemia, myoglobinuria, and *etc.* There are two types of testing for MH: a genetic test and a contracture test. Contracture testing is still being considered as the gold standard for MH diagnosis. Dantrolene is the only available drug approved for the treatment of MH through suppressing the calcium release from SR. Since clinical symptoms of MH are highly variable, it can be difficult to establish a diagnosis of MH. Nevertheless, prompt diagnosis and treatments are crucial to avoid a fatal outcome. Therefore, it is very important for anesthesiologists to raise awareness and understand the characteristics of MH. This review summarizes epidemiology, clinical symptoms, diagnosis and treatments of MH and any new developments.

Keywords: malignant hyperthermia, general anesthesia, dantrolene, ryanodine receptor

Introduction

Malignant hyperthermia (MH) is a rare and life-threatening pharmacogenetic disorder of skeletal muscle. MH is triggered by volatile anesthetics and succinylcholine. In addition, MH can be triggered by strenuous exercise, high temperature and even emotional stress[1–8]. The underlying mechanism of MH is excessive calcium release from the sarcoplasmic reticulum (SR) which lead to disturbance of intracellular calcium ion (Ca^{2+}) homeostasis and uncontrolled skeletal muscle hypermetabolism. This hypermetabolic state generates heat and leads to hypercarbia, hypoxemia, acidosis, arrhythmias,

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rhabdomyolysis, renal and circulatory failure, and fatal outcome. Dantrolene is the only disease-specific drug available for MH. The clinical effect of dantrolene therapy in MH is dramatic. It was reported the case fatality rate of MH was 70% in the 1970s[9]. This number had dropped to 9.5% according to a report from the Malignant Hyperthermia Association of the United States (MHAUS)[10]. Nevertheless, MH is still a fatal medical emergency in the operating room and this review aims to provide a more comprehensive knowledge including the epidemiology, molecular mechanism, clinical presentations, diagnosis and treatment of MH to anesthesiologists. Furthermore, every anesthesiologist needs to raise the awareness and recognize the characteristics of a fulminant MH and begins appropriate management without any delay.

Epidemiology

MH may occur in any race and the exact prevalence of MH is unknown. The anesthesia related MH varies from 1 per 16 000 in Denmark to 1 per 100 000 in the New York State of the USA[11–12]. A recent study containing a total of 9 745 539 inpatient discharge records showed the overall prevalence of 1.68 per 100 000 inpatient discharges and 2.37 per 100 000 surgical inpatient discharges[13]. A higher MH prevalence was seen in surgical inpatient discharges. The fatality rate was 11% of 164 patients with MH diagnosis in this study[13]. Another study of 1 238 171 patients undergoing general anesthesia and showed a prevalence of 1.37 per 100 000, and the fatality rate was 6%[14]. The prevalence of MH was more than doubled in male patients than in female patients[11,13,15–17]. It was reported that the muscular body build in males is likely to develop MH[16]. No more data explains the prevalence in children, but in a multi-center study including seven Europe MH units, 50% out of 200 patients were younger than 12 years old with a history of a clinical MH episode[17]. The prevalence of MH-susceptible (MHS) is much higher, because most people with a genetic mutation that predispose to a MH episode are never exposed to anesthetics. While the exact prevalence of MHS individuals is unknown, experts believe that approximately 1:2 000 individuals may be affected[18]. However, another study reported the prevalence of the genetic mutations may be as great as 1:400 individuals[19]. MH also exhibits variable penetrance in humans. Not all susceptible individuals have events upon exposure to triggering agents. This explains the discrepancy between reported clinical incidence and genetic prevalence.

Molecular mechanism

Experimental evidences such as cells, animals, and humans, have clearly explained MH is due to abnormal intracellular calcium homeostasis within the skeletal muscle[20–22]. When an action potentially spreads across the sarcolemmal membrane into the transverse tubule in a muscle cell, it activates a specific type of the voltage-gated Ca^{2+} channels, termed sarcolemmal L-type Ca^{2+} channel, or dihydropyridine receptor (DHPR). Activated DHPR produces conformational changes and physically interacts with the ryanodine receptor type 1 (RyR1), a Ca^{2+} channel located in the membrane of the SR. When RyR1 is activated and opened, Ca^{2+} release from the SR into the cytoplasm leads to muscular contraction (***Fig. 1***). This is the fundamental excitation-contraction coupling needed for normal skeletal muscle contraction.

RyR1 is the largest known Ca^{2+} channel capable of creating a rapid increase in cytosolic Ca^{2+}

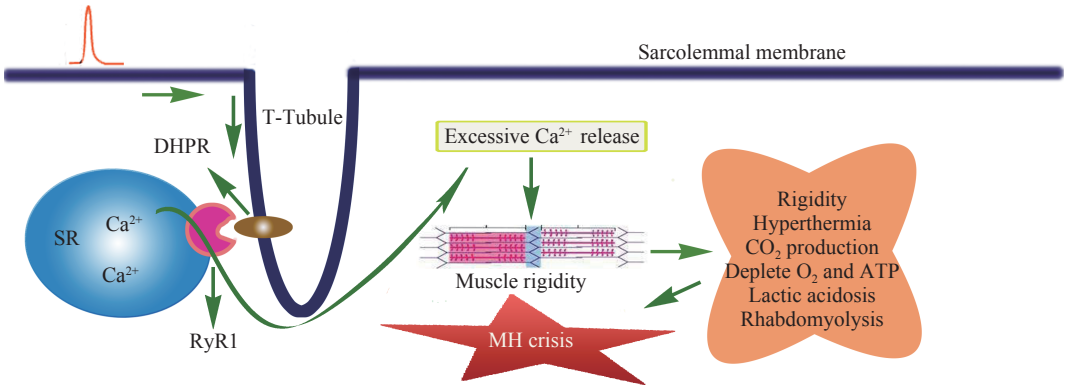

Fig. 1 **The proposed mechanisms of malignant hyperthermia (MH).** SR: sarcoplasmic reticulum; Ca^{2+}: calcium ion; DHPR: dihydropyridine receptor; RyR1: ryanodine receptor type 1; T-Tubule: transverse tubule; CO_2: carbon dioxide; ATP: adenosine triphosphate.

concentration[23]. Out of three known mammalian RYR isoforms, RyR1, RyR2, and RyR3, the RyR1 is predominantly expressed in skeletal muscle[24]. Genetic mutations in *RYR1* can lead to excessive Ca^{2+} release[25]. An abnormal increase in the intracellular Ca^{2+} may reach the threshold for myofibrillar contraction and muscular rigidity, subsequently develops a MH crisis. Muscular rigidity results in the rise of oxygen consumption and carbon dioxide production. Heat is generated and the body temperature rapidly rises following the increase of the lactic acid level. When adenosine triphosphate (ATP) stores become exhausted, the membrane integrity of the skeletal muscle cells is compromised and leads to rhabdomyolysis and the leakage of muscle cell contents, such as electrolytes, myoglobin and various other sarcoplasmic proteins, such as creatine kinase (CK) into the blood circulation, with potential consequences for renal failure.

The first causative genetic mutation associated with MH was identified in 1990[26–27]. The gene locus was mapped to chromosome 19q12-13.2, which is the position encoding the RyR1[26]. Since then, other mutations of *RYR1* associated with MH were also identified. Up to 430 mutations have been reported[28]. However, genetic mutations in the *RYR1* only induce 50%–86% of individuals associated with MH[29–37]. Roux and colleagues reported that *RYR1* mutation was identified in 13% of positive *in vitro* contracture test exertional heat stroke cohort, which was higher than expected for *RYR1* variants in the general population (6%) suggested that MH and exertional heat stroke may share the same mechanisms on *RYR1* genetic mutations[38].

Several mutations were also identified to be responsible for MH in the *CACNA1S* gene, which encodes the alpha1 subunit of the DHPR[39–43]. DHPR interacts with the RyR1 channel to control the Ca^{2+} release from SR. One study identified the *CACNA1S* gene on chromosome 1q as a new MHS locus in a large French family[39]. Stewart and colleagues also found the p.Arg1086His mutation in *CACNA1S* in a North American family was associated with MH[40]. However, mutations in the *CACNA1S*-associated MH only represent a very small proportion of MHS in North America (1%)[40]. *CACNA1s* variants were found in only 1.7% of UK MH patients with about 42% also had *RYR1* mutations[44].

The calsequestrin 1 encoded by the *CASQ1* gene is the major luminal Ca^{2+} binding/buffering protein of the SR. The *CASQ1* gene could be a new candidate gene for MH based on its function. The *Casq1* knock-out mice have the characteristics of human MHS, such as halothane-induced MH-like episodes which can be blocked by dantrolene[45]. However, other study suggested a low level of protein coding sequence variability within the human *CASQ1* gene indicating that it is not a major MHS locus, at least in the North American population[46]. Mestre and colleagues found a novel mutation in the *KCNA1* encoding the voltage-gated potassium channel in a family member with episodic ataxia, myokymia, and MHS[47]. The authors did not find mutations in the known MH genes *RYR1* and *CACNA1S*. Currently, *RYR1* and *CACNA1S* are the only known genes harboring causative mutations of MHS.

Clinical presentations

Clinical symptoms of MH vary greatly, range from masseter spasm, tachycardia, hypercarbia to fulminant MH crisis with severe rhabdomyolysis, cola-color urine, ventricular fibrillation, excessive bleeding and acute renal and circulatory failure. Larach and colleagues analyzed 255 cases of MH reported to the MHAUS from 1987 to 2006 and found the first appeared clinical symptoms were hypercarbia (38.0%), sinus tachycardia (31.0%), or masseter spasm (20.8%)[48]. In this study, the first clinical symptom was hypercarbia followed by sinus tachycardia, rapidly increasing temperature and elevated temperature. The order and percentage of appearance of the clinical symptoms during 255 MH events are listed in ***Table 1***. Similar to the above study, Nelson's study also showed sinus tachycardia, hypercarbia, and rapid temperature increase were the most common signs of MH crisis seen in 73.1%, 68.6%, and 48.5%, respectively[49]. Nelson and colleagues also demonstrated that the youngest patients (0–2 years old) were more likely to develop muscle rigidity and severe metabolic acidosis and the older children present with higher body temperature and higher potassium level.

MH can occur at any time during anesthesia. The interval between induction of anesthesia and the first symptom ranged from 0 minutes (MH occurred immediately on induction) to 168 minutes[48]. MH can also occur in the postoperative period[28,50–52]. In one study, postoperative MH occurred in 1.9% reported to the MHAUS, the latency period between the anesthesia finish time and the onset of MH ranged from 0 to 40 minutes[51]. An increasing number of cases has been reported that MH may occur one hour after the end of anesthesia[28,50,53], MH even occurred 10 hours after anesthesia[50]. Importantly, MH diagnosed postoperatively almost always exhibited

Table 1 **Order and percentage of appearance of the clinical symptoms during 255 malignant hyperthermia (MH) events**

Clinical symptom	Median of appearance number	Range of appearance number	Percentage of patients (%)
Masseter spasm	1.00	1.00–4.00	26.7
Hypercarbia	2.00	1.00–8.00	92.2
Sinus tachycardia	2.00	1.00–7.00	72.9
Generalized muscle rigidity	2.00	1.00–6.00	40.8
Tachypnea	2.00	1.00–6.00	27.1
Cyanosis	2.00	1.00–7.00	9.4
Skin mottling	2.00	1.00–7.00	6.3
Rapidly increasing temperature	3.00	1.00–7.00	64.7
Elevated temperature	3.00	1.00–8.00	52.2
Sweating	4.00	1.00–8.00	17.6
Ventricular tachycardia	4.00	1.00–7.00	3.5
Cola-colored urine	5.00	2.00–9.00	13.7
Ventricular fibrillation	5.50	1.00–8.00	2.4
Excessive bleeding	6.00	4.00–8.00	2.7

Clinical symptoms were listed in order of appearance. Appearance number was the numerical order in which a clinical symptom appeared such as the first clinical symptom that appeared during MH event would be marked 1. If the median of appearance number was same, the order of appearance depended on the percentage of MH patients.

signs of hypermetabolism alongside hyperthermia. Isolated temperature elevations are unlikely to be MH[51].

The current MH presentations are often more insidious. It is believed that this was most likely due to the lower triggering potency of modern volatile anesthetics, the alleviative effects of several intravenous drugs (such as non-depolarizing muscular relaxants, alpha 2 adrenergic receptor agonists, beta adrenergic blockade), techniques (neuro-axial anesthesia), the routine monitoring of end-tidal CO_2 ($ETCO_2$) and early withdrawal of triggering agents[54]. It is very important for anesthesiologists to know these changes in clinical presentation of MH since the early clinical diagnosis and fast appropriate management are critical for MH patient survival. Data clearly showed delays between diagnosis and initiation of dantrolene therapy increased the risk of complications[48].

Diagnosis

Like most other diagnoses, the diagnosis of MH is based on clinical symptoms and laboratory testing. The main clinical presentations of MH are unexplained increased $ETCO_2$ concentration, tachycardia, muscular rigidity, combined metabolic and respiratory acidosis, hyperthermia, cardiac arrhythmia and renal failure. An increasing $ETCO_2$ concentration may be an early warning sign of an impending MH[55], and unexplained tachycardia, muscular rigidity, acidosis and hyperkalemia are further key signs of a fulminant MH. Initial clinical features can be the elevated $ETCO_2$ followed by the body temperature rapidly exceeding 38.8 °C. However, the elevated temperature often occurs at a later time[48,51]. In some cases, there is no significant increase in body temperature[48,56]. Therefore, the diagnosis should not be delayed and early diagnosis and prompt treatment are quite crucial. Larach and colleagues developed an internationally clinical grading scale to assess the qualitative likelihood of a MH event using the Delphi method and an international panel of eleven experts on MH[57]. This MH clinical grading scale (***Table 2***) can be used to qualitatively estimate the likelihood of a MH event and MHS. MH is likely to occur when the score goes in excess of 20, while MH may almost be clinically diagnosed when the score goes in excess of 50. Successful treatment of the MH crisis requires early recognition and rapid intervention[58–59].

For about 30 years, the gold standard for diagnosing MHS individuals have been the *in vitro* measurement of contracture response of biopsied muscle to graded concentrations of caffeine and the anesthetic halothane. Two protocols of this test have been used currently, one is the caffeine/halothane contracture test (CHCT) established by the MHAUS, and the other is *in vitro* contracture test (IVCT) established by the European Malignant Hyperthermia Group (EMHG)[60–62]. For IVCT, it includes four laboratory diagnostic groups: MHS_{hc}, MHS_h, MHS_c, and MHN. Patients with positive responses to both halothane and caffeine are classified as MHS_{hc}, patients with normal responses to both halothane and caffeine are classified as MHN (MH normal), patients with positive responses only to halothane are classified as MHS_h, and patients with positive responses only to caffeine are classified as MHS_c[61]. Differences between CHCT and IVCT include halothane and caffeine concentration, the number of muscle fiber bundles, the time of exposure and the thresholds for a positive response[63–64]. A sensitivity of 99.0% and a specificity of 93.6% were reported in IVCT, while a sensitivity of 97% and a specificity of 78% in CHCT[65–66]. It has been demonstrated that these two protocols can reach similar diagnoses[63]. Although they are regarded as the gold standard for the diagnosis of MHS, CHCT/IVCT are invasive, expensive, restricted to a

Table 2 **Clinical grading scale for malignant hyperthermia**

Process	Indicator	Score
Ⅰ. Rigidity	·Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately following emergence from inhalational anesthesia)	15
	·Masseter spasm shortly following succinylcholine administration	15
Ⅱ. Muscle breakdown	·Elevated creatine kinase >20 000 IU after anesthetic that included succinylcholine	15
	·Elevated creatine kinase >10 000 IU after anesthetic without succinylcholine	15
	·Cola colored urine in perioperative period	10
	·Myoglobin in urine >60 μg/L	5
	·Myoglobin in serum >170 μg/L	5
	·Blood/plasma/serum K^+ >6 mEq/L (in absence of renal failure)	3
Ⅲ. Respiratory acidosis	·$PETCO_2$ >55 mmHg with appropriately controlled ventilation	15
	·Arterial $PaCO_2$ >60 mmHg with appropriately controlled ventilation	15
	·$PETCO_2$ >60 mmHg with spontaneous ventilation	15
	·Arterial $PaCO_2$ >65 mmHg with spontaneous ventilation	15
	·Inappropriate hypercarbia (in anesthesiologist's judgment)	15
	·Inappropriate tachypnea	10
Ⅳ. Temperature increase	·Inappropriately rapid increase in temperature	15
	·Inappropriately increased temperature >38.8 °C (101.8 °F) in the perioperative period	10
Ⅴ. Cardiac involvement	·Inappropriate sinus tachycardia	3
	·Ventricular tachycardia or ventricular fibrillation	3
Ⅵ: Family history (used for MH susceptible)	·Positive MH family history in relative of first degree#	15
	·Positive MH family history in relative not of first degree#	5
Ⅶ. Other indicators that are not part of a single process	·Arterial base excess more negative than −8 mEq/L	10
	·Arterial pH <7.25	10
	·Rapid reversal of MH signs of metabolic and/or respiratory acidosis with intravenous dantrolene	5
	·Positive MH family history together with another indicator from the patient's own anesthetic experience other than elevated resting serum creatine kinase#	10
	·Resting elevated serum creatine kinase in patient with a family history of MH#	10

#These indicators should be used only for determining malignant hyperthermia (MH) susceptible.

few specialized centers and need a surgical procedure under anesthesia to take a muscle biopsy specimen.

Genetic testing requiring only a blood sample and it has become an attractive alternative to the invasive muscle biopsy[26–27]. As of June 2017, 430 mutations in the *RYR1* and *CACNA1S* gene associated with MHS were identified[28]. As an alternative to CHCT/IVCT, genetic testing has been more and more widely used in last decade, especially in patients with a family history of MH[33,41,43,67–69]. However, genetic mutations in the *RYR1* only account for approximately 50%–86% of individuals affected with MH[29–37]. Discordance between MH diagnosed by the presence of causative mutations and skeletal muscle contracture tests has been reported[70]. CHCT/IVCT is still required to confirm or exclude MHS if genetic testing is negative. So, CHCT/IVCT still cannot be replaced. In 2000, molecular diagnosis for MH was introduced in Europe. There were 15 mutations in the *RYR1* was recommended by the EMHG for molecular genetic testing, while 17 mutations in the *RYR1* gene were recommended by the MHAUS[71–73] at that time. Currently, 50 genetic mutations, 48 in *RYR1* and 2 in *CACNA1S*, are accepted[74]. The diagnostic pathway for MHS from the EMHG are showed in ***Fig. 2***[61].

Emerging diagnostic methods

Since MH is a clinical syndrome of skeletal muscle hypermetabolic crisis caused by excessive calcium release from the SR, researchers hope to find a less invasive diagnostic method for diagnosing MHS through measuring the local metabolic change after intramuscular injection of low doses of MH triggered agents. Schuster and colleagues found that local lactate and PCO_2 level in MHS individuals increased significantly after intramuscular caffeine and halothane injection[75–78]. However, a relevant increase was also observed in some non-MHS individuals[78]. Johannsen and colleagues reported this minimally invasive test for diagnosing MHS through using a micro-dialysis technique to measure local lactate

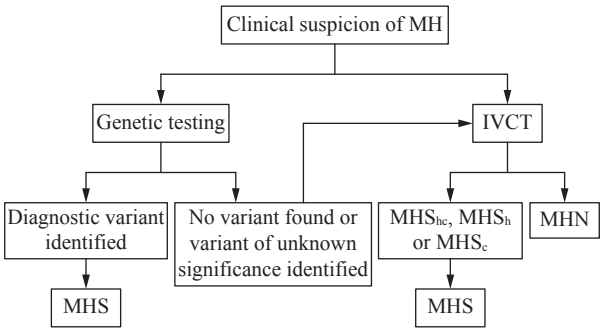

Fig. 2 **The diagnostic pathway for malignant hyperthermia susceptible (MHS) from European Malignant Hyperthermia Group.** IVCT: *in vitro* contraction test; MHS$_{hc}$: patients with positive responses to both halothane and caffeine; MHN: patients with normal responses to both halothane and caffeine; MHS$_h$: patients only with positive responses to halothane; MHS$_c$: patients only with positive responses to caffeine.

levels was not influenced by pre-existing hyper CK emia[79]. These studies showed evidence that local metabolic changes after intramuscular injection with MH triggered agents may afford a minimally invasive diagnostic method for diagnosing MHS. More experiments are needed to confirm the validity and diagnostic thresholds, and to determine whether negative test results need to be verified by CHCT/IVCT as required after genetic testing.

While CHCT/IVCT is the gold standard for MHS diagnosis, we are still exploring the less or non-invasive testing techniques. Although genetic testing has some limitations, because genetic mutations in *RYR1* and *CACNA1S* account for approximately 50% to 86% of individuals affected with MH[29–37], great progress has been made. There were only 15 causative mutations in *RYR1* were selected for initial gene test 17 years ago, it has increased to 44 now, including 42 in *RYR1* and 2 in *CACNA1S*. Among the approximately 20 000 in the human genome, candidate gene explored for further screening still remains a major obstacle in searching the new MHS-associated genes. However, the development of next generation sequencing technologies provides another powerful method for MHS.

As the RyR1 is also expressed in human B-lymphocytes[80], it was expected that the evidence of MHS might be found in human B-lymphocytes. Several studies had showed that intracellular Ca^{2+} concentration significantly increased in B-lymphocytes in MHS individuals compared with that in B-lymphocytes from MHN individuals after B-lymphocytes were exposed to RyR1-stimulating agents[81–82]. These results suggested that B-lymphocytes and skeletal muscles shared a common mechanism of Ca^{2+} release. Therefore, Ca^{2+} signaling phenotype of B-lymphocytes may be useful to diagnose MHS. Binap and colleagues reported a new and relatively simple method to test adenosine levels in B-lymphocytes from the blood of MHS and MHN using high performance liquid chromatography for distinguishing between MHN and MHS[83–84]. They demonstrated that the adenosine level of B-lymphocytes stimulated with a specific RyR1 agonist 4-CmC was significantly higher in the MHS group than in the MHN group. Hoppe and colleagues demonstrated the acidification rate, an indicator of metabolic activity, was significantly higher in B-lymphocytes from MHS patients after using a potent activator of RyR1 to challenge native B-lymphocytes[85]. Zullo and colleagues also demonstrated that the increased acidification rate of immortalized B-lymphocytes in response to 4-CmC is mostly due to *RYR1* mutation[86]. Thus, these tests potentially can be used for screening and diagnosing the MHS test in the future.

Olqin and colleagues[87] used 31-phosphorus nuclear magnetic resonance spectroscopy (^{31}P NMRS) to compare the nuclear magnetic resonance (NMR) spectra of the flexor muscles of the forearm *in vivo* from 13 humans defined as MHS on the basis of IVCT and 25 normal controls. They found that the levels of phosphocreatine and inorganic phosphate at rest were significantly higher and a slower post-exercise recovery in the MHS group. The authors estimated the sensitivity and specificity of this NMR test was 98.8% and 95.3%, respectively and suggested that this non-invasive technique may be used to diagnose MHS[88–89]. It has also been suggested that the early change of $ETCO_2$ could be used for early diagnosing MH events[90–93]. Ganesan and colleagues used a computer-based design of a micro-analysis system for MH diagnosis through $ETCO_2$ assessment[94]. But the increase of $ETCO_2$ is only one symptom of MH, and it occurs in many scenarios during anesthesia and post-anesthesia care including inadequate ventilation, rebreathing in a faulty breathing circuit, fever, systemic absorption during laparoscopic procedure, MH, and thyroid storm *etc*. It is impossible to diagnose MH solely based on the increased $ETCO_2$. Although the above mentioned less invasive MHS diagnostic tests using micro-dialysis, B-lymphocytes metabolic assay, and ^{31}P NMRS have been promising, none of these techniques have progressed beyond the experimental stage so far.

Treatment

The prognosis of a MH crisis depends on how soon

MH is suspected and how fast treatment is initiated. The treatment includes two steps, the immediate treatment is to interrupt the MH episode, while the symptomatic treatment is to prevent the subsequent complications. According to the guideline from the MHAUS and the EMHG, the specific treatments of MH are listed in ***Table 3***. After immediate treatment, appropriate monitoring should be used. Except continuing the routine anesthetic monitoring, core temperature should be measured at once. An arterial line should be considered to facilitate the amount of arterial blood gas measurements, and a urinary catheter should be placed to assess urine color. Repeated arterial blood gas analysis and monitoring of serum electrolyte, CK, myoglobin, and lactate levels are very important for determining the success of therapy. Renal and hepatic function, coagulation, and signs of compartment syndrome should be closely monitored. When stable, the patient should be transferred to the ICU to be monitored for a minimum of 24 hours.

Some cases may only need treatment with one dose of dantrolene which is a postsynaptic muscle relaxant that lessens ECC in muscle cells. It achieves this by inhibiting Ca^{2+} release from sarcoplasmic reticulum stores by antagonizing ryanodine receptors[92]. It is the primary drug used for the treatment and prevention of malignant hyperthermia. However, redosing should occur with any sign of recrudescence (increased rigidity, acidosis, temperature elevation, hypercarbia). Subsequent doses should be 1 mg/kg every six hours, although fulminant cases may require continuous infusions to maintain stability. Since 80% of recrudescence events occurred within 16 hours[95] of the initial MH treatment, it seems reasonable to suggest that if a patient receiving dantrolene is metabolically stable for 24 hours after initial therapy, dantrolene could be stopped.

Telephone hotlines for MH counselling and management guidelines have been established in many countries. A smart phone application (MHApp) issued by EMHG in cooperation with MHAUS can also provide direction to MH management. However, the best treatment is to prevent a MH crisis from happening. Recently, Litman and colleagues have presented a guideline to determine what types of patients should be considered MHS and should not

Table 3 **Malignant hyperthermia treatments according to the guideline**

Immediate treatment		Discontinue all trigger agents; Stop surgery. If surgery must be continued, maintain anesthesia with intravenous (IV) non-trigger anesthetics; Hyperventilate (use a minute volume 2–3 times normal) with 100% oxygen at flows of 10 L/minute; Call for help; Give IV dantrolene 2.5 mg/kg rapidly. Repeat as frequently as needed until the patient responds with a decrease in ETCO2, muscle rigidity, and/or heart rate; Remove the vaporizer and replace the soda lime.
Symptomatic treatment	Treat hyperthermia (temperature >39 °C or less if rapidly rising)	2 000 mL of cold crystalloid solutions (4 °C) IV infusion; Body surface cooling with ice packs and 75% medical alcohol wiped on body surface; Other cooling procedures available; Stop cooling when the temperature has decreased to <38 °C.
	Treat hyperkalemia (K^+ > 5.9 or less with ECG changes)	Calcium chloride 10 mg/kg or calcium gluconate 30 mg/kg; Sodium bicarbonate: 1–2 mEq/kg IV; Glucose/insulin: For pediatric patients: 0.1 units of regular insulin/kg IV and 0.5 g/kg dextrose; For adult patients: 10 units of regular insulin IV and 50 mL 50% glucose. For refractory hyperkalemia, dialysis, or ECMO if patient is in cardiac arrest may be required.
	Treat acidosis	Sodium bicarbonate: 1–2 mEq/kg IV;
	Treat arrhythmias	Amiodarone: 3 mg/kg IV (300 mg for an adult); β-blockers if tachycardia persists; Avoid calcium channel blockers which may cause hyperkalemia or cardiac arrest while using dontrolene; Treat acidosis and hyperkalemia if present (see above).
	Maintain urinary output	Furosemide 0.5–1 mg/kg and/or mannitol 1 g/kg IV to maintain urine output > 1 mL/(kg·hour); Crystalloids solutions IV; If creatine kinase or K^+ rise, assume myoglobinuria and give bicarbonate infusion of 1 mEq/(kg·hour) to alkalinize urine.

receive anesthetic triggering agents[58].

Conclusion

MH is a rare and life-threatening anesthesia complication. It is caused by Ca^{2+} release from the SR leading to uncontrolled skeletal muscle hypermetabolism. Genetic mutations in *RYR1* and *CACNA1S* have been identified to be causative of MH. Up to now, there are 430 genetic variants associated with MHS, but only 50 genetic mutations, 48 in *RYR1* and 2 in *CACNA1S*, are accepted as diagnostic genetic testing for MHS, and they only account for approximately 50%–86% of individuals affected with MH. The MH clinical presentations various greatly so it is difficult to diagnose all MH in its early phase. The current diagnostic methods of MHS used clinically are IVCT and genetic testing. Both diagnostic methods require specialized testing center, while IVCT is an invasive test and genetic testing has a low sensitivity. Though a few tests have focused on the less invasive diagnostic procedures for determining MHS, none of them have progressed beyond the experimental stage up to now.

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