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Malignant Hyperthermia: A Review

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Malignant hyperthermia is an uncommon, but potentially lethal condition that may be encountered during the perioperative period. There is wide variability in the manner in which malignant hyperthermia may manifest. For a patient to survive a malignant hyperthermia crisis, prompt recognition and treatment is of paramount importance. Perioperative nurses play a pivotal role in the successful management of malignant hyperthermia. The fictitious case study presented in this paper describes the identification, presentation, pathophysiology, and treatment of a general anesthesia patient with fulminant malignant hyperthermia.

Keywords: *malignant hyperthermia, ryanodine receptor, volatile anesthetics, succinylcholine.*
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OBJECTIVES–(1) DISCUSS the pathophysiology of malignant hyperthermia. (2) Identify the pharmacological triggers for malignant hyperthermia. (3) Identify the pharmacological antidote for malignant hyperthermia. (4) Describe the perioperative management of a malignant hyperthermia crisis.

Malignant hyperthermia (MH) is a genetic disorder most often associated with the administration of volatile general anesthetic agents and/or the muscle relaxant succinylcholine. First described in 1960, MH is an uncommon but potentially lethal condition that may be encountered during the perioperative period.[1,2] For a patient to survive an MH crisis, prompt recognition and treatment is of paramount importance. This article will present a fictitious case report of a surgical patient with MH. The incidence and etiology of MH will be described, and the evidence-based practice recommendations for the recognition

and treatment of MH in the perioperative setting will be reviewed.

Literature Review

MH is an uncommon pharmacogenic disorder that causes hypermetabolism by skeletal muscle in susceptible patients on exposure to volatile anesthetic gases such as desflurane, isoflurane, sevoflurane, halothane, and/or the depolarizing skeletal muscle relaxant succinylcholine.[2,3] Lidocaine and other local anesthetics are not MH-triggering agents.[4] Very rarely, nonpharmacogenetic triggers such as heat and rigorous exercise can precipitate MH.[5] The occurrence of MH is estimated to range from 1:5,000 to 1:50,000-100,000 anesthetics.[6] Children, less than age 15 years, encompass over half of the cases of MH (52%), with males at considerably higher risk than females (2:1).[6]

MH occurs because of a genetic autosomal dominant disorder involving a mutation on the ryanodine receptor (type 1: RyR1)[7] or dihydropyridine receptor.[8] These mutations cause an atypical increase in release of calcium from the sarcoplasmic reticulum of skeletal muscle cells.[7-9] Up to 1:3,000 individuals may be genetically susceptible to MH.[6] Although all ethnic groups are affected, the incidence of MH susceptibility may be significantly higher in the French, Scandinavian, and Japanese populations.[10] Due to pockets of genetically susceptible individuals, reports of MH cases in the United States appear to

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be clustered in Wisconsin, Nebraska, West Virginia, and Michigan.[2] Figure 1 illustrates the main ion channels involved in the initiation of a muscle contraction following neuromuscular impulse transmission. Figure 2 illustrates the ryanodine receptor and its associated proteins.

A molecular genetic blood test may identify MH-susceptible individuals; however, the caffeine-halothane muscle contracture test remains the gold standard for making that determination.[11] The caffeine-halothane muscle contracture test has been the standard diagnostic test for MH since the mid-1970s.[12] Test results depend on the in vitro muscle contracture response of biopsied muscle to graded concentrations of the calcium-releasing agents of caffeine and halothane.[12]

MH may present anytime during general anesthesia (GA) and the early postoperative phase.[13] The earliest signs of MH are tachycardia and an increase in the level of end-tidal carbon dioxide (ETCO$_2$), along with muscle rigidity.[13,14] Masseter spasm may occur, especially after succinylcholine administration.[6]

Unrestrained skeletal muscle hypermetabolism secondary to altered intracellular calcium homeo-stasis potentiates cellular hypoxia.[15] This is manifested by increasing acidosis that can lead to vital organ failure. If the acidosis is not corrected, ensuing myocyte death and rhabdomyolysis result in life-threatening hyperkalemia.[6]

Core body temperature may rise dramatically, but it is not always an early sign of MH.[16] When hyperthermia occurs, it is frequently marked by a rapid increase in temperature at the rate of 1 to 2°C every 5 minutes.[17] Severe hyperthermia leads to excessive oxygen consumption and a markedly increased production of carbon dioxide, which can ultimately result in fulminant uncompensated mixed respiratory and metabolic acidosis.[6]

Other signs of MH may include cardiac dysrhythmias, disseminated intravascular coagulation, hypocalcemia, hyperphosphatemia, mottled skin, and myoglobinuria.[10] However, it should be noted that the clinical presentation and initial signs of MH are greatly variable.[18] Some people may exhibit only one or just a few symptoms of variable intensity.[19] This can make it difficult to confidently diagnose MH.[20]

Treatment of MH should be initiated as soon as the disorder is suspected. Treatment comprises calling
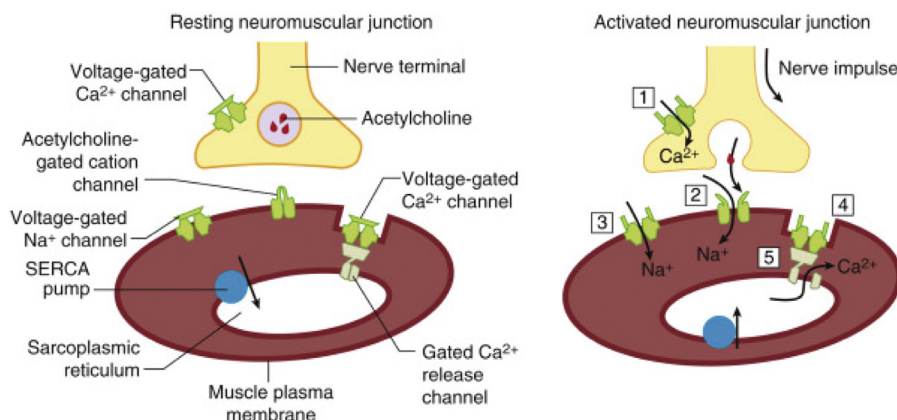

Figure 1.   Key ion channels involved in neuromuscular transmission and excitation-contraction coupling. Nerve impulses arriving at the nerve terminal activate voltage-gated Ca^{2+} channels (1). The resulting increase in cytoplasmic Ca^{2+} concentration triggers the exocytosis process of acetylcholine. Binding of acetylcholine to postsynaptic nicotinic acetylcholine receptors (nAChRs) activates an integral nonselective cation channel that depolarizes the sarcolemma (2). Depolarizing the sarcolemma to threshold activates voltage-gated Na$^+$ channels (3), which initiates action potential impulses that propagate deep into the muscle through the transverse tubule system. Within the transverse tubule system, L-type voltage-gated Ca^{2+} channels sense membrane depolarization and undergo a conformational change (4). A physical link between the α1 subunit (Ca$_V$ 1.1) of the dihydropyridine receptor (DHPR) and the ryanodine receptor (RyR1) is the means by which the electrical signal is transferred from the T tubule to Ca^{2+} release from the SR (5). Reprinted with permission from Elsevier. This figure is available in color online at www.jopan.org.
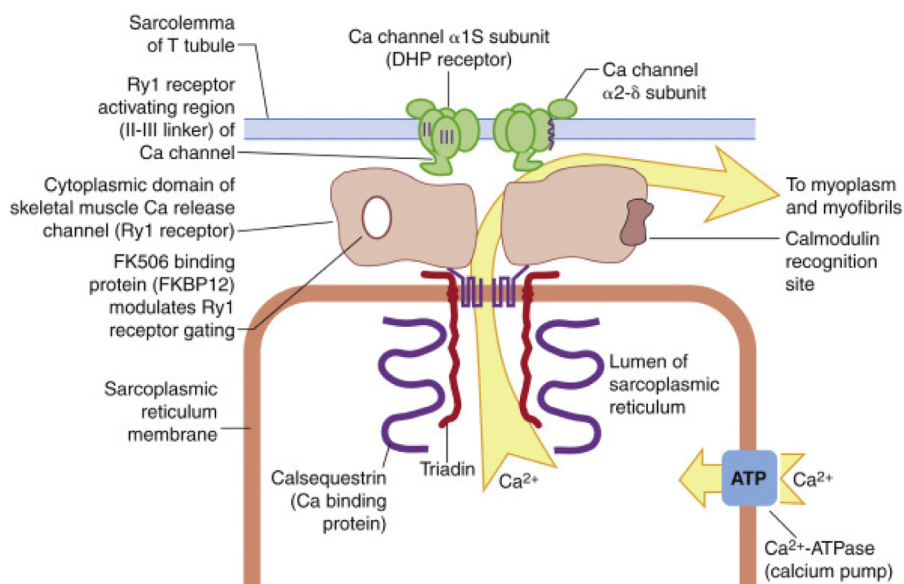
Figure 2. Schematic representation of the triadic junction of skeletal muscle shows the junctional foot protein (ryanodine [Ry1] receptor) and its associated proteins. In skeletal muscle, the α_{1S} subunit of the dihydropyridine receptor (DHPR) participate in the excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate the Ry1 receptor and release Ca^{2+} from the sarcoplasmic reticulum. Reprinted with permission from Elsevier. This figure is available in color online at www.jopan.org.

for help immediately, immediate discontinuation of MH-triggering agents, changing to a non–MH-triggering anesthetic, hyperventilation with 100% oxygen, and requesting the surgeon to abort the surgery.[13,14] Dantrolene sodium is the only pharmacologic antidote for MH. Dantrolene is given rapidly, preferably through a large bore intravenous (IV) line, at an initial dose of 2.5 up to 10 mg/kg.[13] In some circumstances, the recommended maximum dantrolene dose of 10 mg/kg will need to be increased until the respiratory and cardiac systems become stable and/or persistent muscle rigidity gets resolved.[14] Routine anesthetic monitoring should continue along with core temperature measurement. Symptomatic management of hyperthermia, hyperkalemia, acidosis, oliguria, and cardiac arrhythmias should be implemented per protocol.[13,14] Calcium channel blockers should be avoided for treatment of arrhythmias.[13]

Case Report

J. M., the 24-year-old dependent wife of an active-duty US Air Force captain, presented to the preoperative clinic of a 400-bed Air Force medical center in New York for preoperative evaluation by a certi-fied registered nurse anesthetist (CRNA) because she was scheduled for an elective bilateral breast reduction surgery on the following morning. During the preoperative visit, the CRNA conducted a physical examination and interview. The CRNA documented in the electronic health record that J. M. was a healthy, 60 kg woman with no past medical or surgical history; had no known drug allergies; and was not taking any prescribed or over-the-counter medications or herbal supplements. When the CRNA queried J. M. whether any of her close blood relatives had any history of anesthesia-related complications, she stated that she did not know because of her adopted status. This was noted by the CRNA in the electronic health record.

The next morning J. M. presented to the hospital for her elective surgical procedure. A preoperative registered nurse (RN) prepared J. M. for surgery. Afterward, a CRNA administered 2 mg of IV midazolam and subsequently transported her to the operating room (OR).

Once in the OR, standard anesthesia monitors were placed. Required continuous body

temperature monitoring was accomplished by application of a disposable thermometer to J. M.'s forehead. An oxygen mask was applied, and J. M. was preoxygenated with oxygen at 8 L per minute. Induction of anesthesia was performed using fentanyl, 100 mcg; propofol, 200 mg; and succinylcholine, 100 mg. Successful tracheal intubation with an endotracheal tube (ETT) was easily performed. Immediately after induction, J. M.'s vital signs were stable with a blood pressure of 112/68 mm Hg; heart rate 72 beats per minute; oxygen saturation (SaO$_2$) 100%; ETCO$_2$ 38 mm Hg; and skin temperature 36.9°C.

J. M. was mechanically ventilated with a fraction of inspired oxygen of 50%, respiratory rate of 10 breaths per minute (bpm), tidal volume of 500 mL, and positive end-expiratory pressure of 2.5 cm Hg. All IV fluids were warmed with a fluid warmer. A forced, warm air lower-body warming blanket was used at a temperature of 43°C. GA was maintained with desflurane, fentanyl, and vecuronium.

Twenty-five minutes after induction of anesthesia, J. M. exhibited masseter spasm and a bite block was inserted by the CRNA to prevent biting of the endotracheal tube. Simultaneously, J. M.'s heart rate increased to 112 bpm, her blood pressure increased to 172/102, and her ETCO$_2$ rose to 58 mm Hg. Subsequently, the surgeon noted increasing muscle rigidity and asked the CRNA to administer more muscle relaxing medication to facilitate the surgery. Formerly clear yellow urine in the urinary catheter changed to the color of cola in the catheter tubing. Although J. M.'s body temperature remained constant at 36.9°C on the forehead thermometer, the CRNA strongly suspected that these signs were indicative of the onset of MH.

The circulating nurse was asked by the CRNA to immediately summon additional manpower and the MH cart. After calling for help and the MH cart, the astute circulating RN called the Malignant Hyperthermia Association (MHAUS) of the United States' 24-hour MH hotline number at 800-644-9737 for telephone assistance in managing the suspected MH crisis. The anesthetic, desflurane, a known MH-triggering agent, was discontinued by the CRNA and the anesthesia circuit and machine were exchanged by an anes-

thesia technician. The CRNA hyperventilated J. M. with 100% oxygen to decrease hypercapnia. The anesthetic was converted to total IV anesthesia with propofol, a non–MH-triggering GA maintenance medication. The CRNA asked the surgeon to stop the surgery and close the incision. A full-spectrum laboratory panel (including a complete blood count, activated partial thromboplastin time, prothrombin time, creatinine, blood urea nitrogen, carbon dioxide, chloride, glucose, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, calcium, D-dimer, serum myoglobin, urine myoglobin, and a urinalysis) and an ABG (arterial blood gas) were subsequently ordered, drawn, and analyzed.

A second large bore IV line was started by one of the circulating RNs. Dantrolene sodium was reconstituted by three other OR nurses and administered at a loading dose of 2.5 mg/kg. An infusion of glucose, 25 mg with 10 units of insulin, was administered to treat hyperkalemia (serum potassium of 7.8 mEq/L). As recommended by MHAUS,[13] calcium gluconate at 30 mg/kg was also administered to treat J. M.'s hyperkalemia. Two ampoules of sodium bicarbonate (7.5%) were given to treat acidosis (ABG results revealed a pH of 7.2).

An esophageal stethoscope was inserted by the CRNA to monitor J. M.'s core body temperature; on initial placement it revealed a core body temperature of 40.0°C. The IV fluid warmer and forced warm air body warmer were discontinued. Cooling measures were instituted by the OR team, including administration of cold IV fluid, application of a cooling blanket, iced saline lavage via a nasogastric tube, room air conditioning, and ice packs applied bilaterally to the groin and armpits. These efforts to reduce J. M.'s core body temperature proved to be successful. Twenty minutes after initiation of the aggressive cooling measures, her core body temperature was reduced to 37.8°C. After a total dose of 10 mg/kg of dantrolene, J. M.'s vital signs stabilized. She was transferred to the surgical intensive care unit.

On postoperative day 4, J. M. continued to be in stable condition. She returned to the OR for completion of her bilateral breast reduction

surgical procedure, which had previously been aborted. To ensure prevention of another episode of MH, all MH-triggering agents were avoided. The anesthesia was delivered by total IV anesthesia with a continuous infusion of propofol. The surgery was successful, and J. M. was discharged to home in good condition on postoperative day one without sequelae from her episode of MH. On discharge, J. M. was educated by her nurses on the importance of reporting her personal history of MH to clinicians during any future medical encounters. The nurses also stressed that she should instruct her family members to report their family history of MH to their health care providers.

Discussion

Because MH is rare, most OR or postanesthesia care unit (PACU) personnel will never encounter an MH case during their career. The patient in the fictitious case report, J. M., was treated in a hospital in New York. Brady et al[10] conducted a retrospective study to determine the prevalence of MH due to anesthesia in the state of New York between the years of 2001 and 2005. They used New York hospital discharge data to identify patients who developed MH secondary to anesthesia during that time frame and found that 73 of 12,749,125 patients discharged from hospitals in New York State had a documented diagnosis of MH related to anesthesia.[10] Therefore, the occurrence of anesthesia-induced MH in hospitals in the state of New York is estimated to be rare at 1:100,000. This number is in accordance with the national average incidence of anesthesia-associated MH.

Because MH is exceedingly uncommon, it is important for anesthesia providers and perioperative clinicians to stay abreast of the signs, symptoms, and treatment of MH. Successful management of an MH crisis hinges on advanced preparation for an unexpected MH incident. Periodic MH crisis drills are one way to achieve this end.[21] A recommendation of this author is to conduct MH drills at a minimum of once annually. All facilities should test to ensure that telephones in the ORs, procedure rooms where GA is administered, and PACUs are programmed to allow outgoing long-distance calls.

The CRNA was astutely attentive to J. M.'s initial and continuing signs and symptoms of MH and acted accordingly. The circulating OR nurse swiftly retrieved the MH cart and recruited the help of other OR nurses to perform the essential and demanding job of reconstituting multiple vials of dantrolene. It is well established that early administration of dantrolene sodium during an MH crisis saves lives.[13] The circulating OR nurse wisely referred to the MHAUS emergency therapy poster on the MH cart and immediately called the MH hotline telephone number to procure expert consultation and support. Although no member of the surgical team had previously encountered a case of MH, all involved staff members were prepared and acted in unison to treat J. M. summarily and effectively. In the case of J. M., because of prompt recognition of the onset of MH by the CRNA and the concerted efforts of the entire OR team, she experienced a positive outcome.

Although not used in J. M.'s case, it is noteworthy that a new formulation of dantrolene sodium, known as Ryanodex (Eagle Pharmaceuticals, Woodcliff Lake, NJ), was approved by the US Food and Drug Administration in 2014.[22] Ryanodex is formulated to allow for more rapid reconstitution than standard vials of dantrolene sodium. This could prove beneficial in an MH crisis when rapid administration of dantrolene may be lifesaving. Perioperative nurses should be aware of the availability of the new dantrolene sodium formulation and should consider encouraging the acquisition of the product at the facilities where they are employed.

Larach et al[23] conducted a study to determine the effect of inadequate perioperative temperature monitoring on the risk of dying from MH. They hypothesized that the risk of fatal outcomes from MH is increased in patients whose body temperature is not adequately monitored during anesthesia. Because MH is rare, their study's sample size of 84 patients who developed MH after GA is relatively small. The findings indicated that of the 8 of 84 patients who died from MH, 30% died from MH when their temperature was not monitored. Twenty-one percent of subjects died when their temperature was monitored only by a skin probe, and only 2% (one patient) died when core body temperature was monitored. In J. M.'s case, her body temperature

was initially monitored by a disposable forehead skin temperature probe. Although her body temperature was within normal limits on the skin probe, when an esophageal stethoscope was inserted, it revealed that her core temperature was actually markedly increased at 40.0°C. Therefore, it may be prudent to consider core temperature monitoring, as opposed to skin temperature monitoring, during GA to ensure accuracy. MHAUS[13] recommends core temperature monitoring during GA. Therefore, OR nurses should consider educating perioperative staff on this topic at staff meetings and through in-service presentations.

Conclusions

There is wide variability in the manner in which MH may manifest. The clinical presentation of MH can range from mild symptoms to a fulminant MH crisis. Fulminant cases of MH, as experienced by J. M., are characterized by an amalgamation of swiftly developing signs of hypermetabolism (hyperthermia, tachycardia, hypertension, and hypercapnia); skeletal muscle symptoms (muscle rigidity and masseter spasm); and rhabdomyolysis. Rapid recognition and treatment of MH is vital to prevent MH fatalities.

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Malignant Hyperthermia: A Review

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1. Discuss the pathophysiology of malignant hyperthermia.
2. Identify the pharmacological triggers for malignant hyperthermia.
3. Identify the pharmacological antidote for malignant hyperthermia.
4. Describe the perioperative management of a malignant hyperthermia crisis.

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