Malignant Hyperthermia

First identified in the late 1960's, Malignant Hyperthermia is a rare, life-threatening complication that may be triggered by drugs commonly used in anesthesia. Malignant hyperthermia is inherited. Only one parent has to carry the disease for a child to inherit the condition. Malignant hyperthermia occurs in 1 in 5,000 to 50,000 instances in which people are given anesthetic gases. Inhalational anesthetics and succinylcholine are the most frequently implicated triggering agents. Trauma, strenuous exercise, or emotional stress also may induce Malignant Hyperthermia. It is multifactorial and genetically transmitted as an autosomal dominant trait with variable expression in affected individuals. The incidence of Malignant Hyperthermia is increased in patients with central core disease (a congenital myopathy) and some muscular dystrophies.

The syndrome begins with a hypermetabolic condition in skeletal muscle cells that involves altered mechanisms of calcium function at the cellular level. Characteristics include cellular hypermetabolism resulting in hypercarbia, tachypnea, tachycardia, hypoxia, metabolic and respiratory acidosis, cardiac dysrhythmias, and elevation of body temperature at a rate of 1-2 degree C every 5 minutes. Increase in body temperature is a late manifestation of MH. These signs may occur during induction or maintenance of anesthesia, although MH can occur postoperatively or even after repeated exposures to anesthesia. It is seen most frequently in children and adolescents. The signs and symptoms associated with MH are listed in table 1.1.

Table 1.1

Signs and Symptoms often seen with Malignant Hyperthermia

- Hypercarbia
- Tachycardia
- Tachypnea (may not be seen in a paralyzed patient)
- Muscle stiffness or rigidity
- Hypoxia and dark (desaturated) blood in operative field
- Unstable or elevated blood pressure
- Cardiac dysrhythmias
- Changes in CO2 absorbent (temperature, color)
- Metabolic and respiratory acidosis
- Peripheral mottling, cyanosis, or sweating
- Rising body temperature (1-2 degrees C every 5 minutes)
- Myoglobinuria
- Hyperkalemia, hypercalcemia, lactic academia
- Pronounced elevation in creatine kinase level

The earliest signs of MH are a rise in end-tidal carbon dioxide concentration (despite increased minute ventilation), tachycardia, and muscle rigidity. Despite the name, elevation of body temperature is often a late sign. Other signs may include acidosis, tachypnea (in a spontaneously breathing patient), and hyperkalemia. Core body temperature should be measured in any patient undergoing general anesthesia longer than 20 minutes.

It is important to remember that MH is a rare, multifaceted syndrome and can have variable clinical presentations. Many of the signs and symptoms associated with MH can have other causes. Other disorders,

such as neuroleptic malignant syndrome (NMS), may have similar presentations. NMS occurs after use of neuroleptic drugs, such as haloperidol, and is characterized by muscular rigidity, akinesia, hyperthermia, and autonomic dysfunction. As MH is such a life-threatening protocol when some of these early signs and symptoms occur that cannot otherwise be readily explained.

The main candidates for testing are those with a close relative who has suffered an episode of MH or has been shown to be susceptible. The standard procedure is the "caffeine-halothane contracture test", CHCT. A muscle biopsy is carried out at an approved research center, under local anesthesia. The fresh biopsy is bathed in solutions containing caffeine or halothane and observed for contractions; under good conditions, the sensitivity is 97% and the specificity 78%. Negative biopsies are not definitive, so any patient who is suspected of MH by their medical history or that of blood relatives is generally treated with nontriggering anesthetics, even if the biopsy was negative. Some researchers advocate the use of the "calcium-induced calcium release" test in addition to the CHCT to make the test more specific.

Less invasive diagnostic techniques have been proposed. Intramuscular injections of halothane 6 vol% have been shown to result in higher than normal increase in local pCO_2 among patients with known malignant hyperthermia susceptibility. The sensitivity was 100% and specificity was 75%. For patients at similar risk to those in this study, this leads to a positive predictive value of 80% and negative predictive value of 100%. This method may provide a suitable alternative to more invasive techniques. A 2009 study examined another possible metabolic test. In this test, intramuscular injection of caffeine was followed by local

measurement of the pCO2; those with known MH susceptibility had a significantly higher pCO2 (63 versus 44 mmHg).

Malignant hyperthermia is diagnosed on clinical grounds, but various investigations are generally performed. This includes blood tests, which may show a raised creatine level, elevated potassium, increased phosphate (leading to decreased calcium) and – if determined – raised myoglobin; this is the result of damage to muscle cells. Metabolic acidosis and respiratory acidosis (raised acidity of the blood) may both occur. Severe rhabdomyolysis may lead to acute renal failure, so kidney function is generally measured on a frequent basis. Patients may also get cardiac arrhythmias (PVCs) due to the increased levels of potassium released from the muscles during episodes.

Susceptibility to MH or malignant hyperpyrexia is often inherited as an autosomal dominant disorder, for which there are at least 6 genetic loci of interest, most prominently the ryanodine receptor gene (RYR1). MH susceptibility is phenotypically and genetically related to central core disease (CCD), an autosomal dominant disorder characterized both by MH symptoms and myopathy. Malignant hyperthermia's inheritance is autosomal dominant. The defect is typically located on the long arm of the nineteenth chromosome (19q13.1) involving the ryanodine receptor. More than 25 different mutations in this gene are linked with malignant hyperthermia. These mutations tend to cluster on one of three domains within the protein, designated MH1-3. MH1 and MH2 are located in the N-terminus of the protein, which interacts with L-type calcium channels and Ca2. MH3 is located in the transmembrane forming C-terminus. This region is important for allowing Ca2 passage through the protein following opening. **See table 1.2 for abnormalities in the Ryanodine receptor 1 gene**.

Table 1.2

ICD – 10	T88.3
ICD – 9	995.86
OMIM	145600 154275 600467 601887 601888
DiseasesDB	7776
MeSH	D008305

In a large population (50-70%) of cases, the propensity for malignant hyperthermia is due to a mutation of the ryanodine receptor (type 1); located on the sarcoplasmic reticulum (SR), the organelle within skeletal muscle cells that stores calcium. RYR1 opens in response to increases in intracellular Ca2 level mediated by L-type calcium channels, thereby resulting in a drastic increase in intracellular calcium levels and muscle contraction. RYR1 has two sites believed to be important for reacting to changing Ca2 concentrations: the A-site and the I-site. The A-site is a high affinity Ca2 binding site that mediates RYR1 opening. The I-site is a lower affinity site that mediates the protein's closing. Caffeine, halothane, and other triggering agents act by drastically increasing the affinity of the A-site for Ca2 and concomitantly decreasing the affinity of the I-site in mutual proteins. Mg2 also affect RYR1 activity, causing the protein to close by acting at either the A- or I- sites. In MH mutant proteins, the affinity for Mg2 at either one of these sites is greatly reduced. The end result of these alterations is greatly increased Ca2 released due to a lowered activation and heightened deactivation threshold.

The process of reabsorbing this excess Ca2 consumes large amounts of adenosine triphosphate (ATP), the main cellular energy carrier, and generates the excessive heat (hyperthermia) that is the hallmark of the disease. The muscle cell is damaged by the depletion of ATP and possibly the high temperature, and cellular constituents “leak” into the circulation, including potassium, myoglobin, creatine, phosphate and creatine kinase.

The other known causative gene for MH is CACNA1S, which encoded an L-type voltage-gated calcium channel subunit. There are two known mutations in this protein, both affecting the same residue, R1086. This residue is located in the large intracellular loop connecting domains 3 and 4, a domain possibly involved in negatively regulating RYR1ivity. When these mutant channels are expressed in human embryonic kidney (HEK 293) cells, the resulting channels are five times more sensitive to activation by caffeine (and presumably halothane) and activate at 5-10mV more hyperpolarized. Furthermore, cells expressing these channels have an increased basal cytosoloic Ca2 concentration. As these channels interact with and activate RYR1, these alterations result in a drastic increase of intracellular Ca2, and thereby, muscle excitability. Other mutations causing MH have been identified, although in most cases the relevant gene remains to be identified.

Research into malignant hyperthermia was limited until the discovery of “porcine stress syndrome” (PSS) in Danish Landrace and other pig breeds selected for muscling, a condition in which stressed pigs develop “pale, soft, exudative” flesh (a manifestation of the effects of malignant hyperthermia) rendering their meat less marketable at slaughter. This “awake triggering: was not observed

in humans, and initially cast doubts on the value of the animal model, but subsequently, susceptible humans were discovered to "awake trigger" (develop malignant hyperthermia) in stressful situations. This supported the use of the pig model for research. Pig farmers use halothane cones in swine yards to expose piglets to halothane. Those that die were MH-susceptible, thus saving the farmer the expense of raising a pig whose meat would not be able to be sold. This also reduced the use of breeding stock carrying the genes for PSS. The condition in swine is also due to a defect in ryanodine receptors. Gillard discovered the causative mutation in humans only after similar mutations had first been described in pigs. Horses also suffer from malignant hyperthermia. It is the Thoroughbred breed that was found to have susceptibility. It can be caused by overwork, anesthesia, or stress. An inheritable genetic mutation is found in susceptible animals. In dogs, its inheritance is autosomal recessive.

In the past, prophylactic use of dantrolene was recommended for MH susceptible patients undergoing general anesthesia. However, multiple retrospective studies have demonstrated the safety of trigger-free general anesthesia in these patients in the absence of prophylactic dantrolene administration. The largest of these studies looked at the charts of 2214 patients who underwent general or regional anesthesia for an elective muscle biopsy. About half (1082) of the patients were muscle biopsy positive for MH. Only five of those patients exhibited symptoms consistent with MH, four of which were treated successfully with parenteral dantrolene, and the remaining one recovered with only symptomatic therapy.

After weighing its questionable benefits against its possible adverse effects (including nausea, vomiting, muscle weakness and prolonged duration of action of nondepolarising neuromuscular blocking agents), as of 2010, experts no longer recommend the use of prophylactic dantrolene prior to trigger-free general anesthesia in MH susceptible patients.

Anesthesia for known MH susceptible patients requires avoidance of triggering agents (all volatile anesthetic agents and succinylcholine). See table 1.3 for the drugs that trigger malignant hyperthermia.

Table 1.3

What drugs trigger MH?

- Desflurane
- Enflurane
- Halothane
- Isoflurane
- Methoxyflurane
- Sevoflurane
- Succinylcholine

All other drugs are safe (including nitrous oxide), as are regional anesthetic techniques. Where general anesthesia is planned, it can be provided safely by removing vaporizers from the anesthesia machine, placing a new breathing circuit on the machine, flushing the machine and ventilator with 100% oxygen at maximal gas flows for 20-30 minutes, and inducing and maintaining anesthesia with nontriggering agents (e.g.: propofol). Modern anesthesia machines

have more rubber and plastic components which provide a reservoir for volatile anesthesia, and should be flushed for 60 minutes.

Time is crucial when MH is diagnosed. All OR and anesthesia personnel should be familiar with the protocol for its management. In the past, mortality ranged up to 80%, but the immediate infusion of dantrolene (Dantrium) and proper treatment have reduced the mortality to about 7%. Dantrolene is a hydantoin skeletal muscle relaxant that also has effects on vascular and heart muscle. In addition to dantrolene, the major modalities of treatment include cooling the patient with ice packs and cold IV solutions, administering diuretics, treating cardiac dysrhythmias, correcting acid-base and electrolyte imbalances, and monitoring fluid intake and output and the body temperature. Many hospitals maintain an emergency MH kit or cart that contains the drugs, laboratory tubes, other supplies, and instructions to treat MH in the OR area. The location of the iced or cold saline and other equipment also should be listed with the emergency kit. Chilled saline is often kept in the refrigeration unit for blood products. The Rapid Response Team box presents an outline for emergency treatment of MH. The Malignant Hyperthermia Association of the United States has names of on-call physicians available for consultation in MH emergencies.

The current treatment of choice is the intravenous administration of dantrolene, the only known antidote, discontinuation of triggering agents, and supportive therapy directed at correcting hyperthermia, acidosis, and organ dysfunction. As stated before, treatment must be instituted rapidly on clinical suspicion of the onset of malignant hyperthermia.

Dantrolene has been mentioned before, but what is it? Dantrolene is a muscle relaxant that appears to work directly on the ryanodine receptor to prevent the release of calcium. After the widespread introduction of treatment with dantrolene, the mortality of malignant hyperthermia fell from 80% in the 1960s to less than 10% in 2011. Dantrolene remains as the only drug known to be effective in the treatment of MH.

Its clinical use has been limited by its low water solubility, leading to requirements of large fluid volumes, which may complicate clinical management. Azumolene is a 30-fold more water – soluble analogue of dantrolene that also works to decrease the release of intracellular calcium by its action on the ryanodine receptor. In MH susceptible swine, azumolene was as potent as dantrolene. It has yet to be studied in vivo in humans, but may present a suitable alternative to dantrolene in the treatment of MH.

Care of the surgical patient is a cooperative effort, and perioperative personnel should function as a smooth, well-coordinated team. As part of conducting the preoperative patient assessment and developing the plan of care, the perioperative nurse participates with the anesthesia provider in the preoperative verification process. As part of this process, the nurse checks the chart to verify the patient's identity, the surgeon, and the scheduled procedure; confirms that the operative and anesthesia permits are properly signed; identifies and communicates any patient allergies; ensures that the surgical site is marked; and ensures that current reports of laboratory tests and diagnostic studies are complete and in the chart.

In many OR suites, a preoperative preparation or holding area is used for insertion of arterial, central venous, or pulmonary arterial nerve blocks. Nursing personnel from the OR, PACU , or anesthesia department may staff this area. The purpose of this area is to improve patient care delivery, optimize flow of patients, and provide supportive patient care.

A patient should never be left alone in the OR suite. When an anesthetized patient is in the OR, a perioperative nurse should always be immediately available to provide assistance if needed. During the insertion of IV, arterial, central venous, or pulmonary arterial catheters, the nurse assists as required.

During induction of anesthesia, particularly with urgent and emergency surgical procedures, the patient is presumed to have a "full stomach. " The perioperative nurse should be ready to apply cricoids pressure to prevent regurgitation of stomach contents and assist the anesthesia provider in visualizing the vocal cords. When cricoids pressure is used to prevent aspiration, it should not be released until the intubation is accomplished, the cuff of the ETT is inflated, and proper placement of the ETT has been verified. When two anesthesia providers are present, one of them usually provides this support.

OR personnel should never move an unconscious patient without first coordinating the positioning or move with the anesthesia provider. When the patient is positioned for surgery, the perioperative nurse collaborates with the anesthesia provider in checking the arms and legs to secure that no pressure points exist and that the extremities are appropriately positioned and padded

(See the course: Positioning by Cutting Edge). After positioning, prepping, and draping, the time-out is conducted and documented.

Before transporting the patient from the OR to the PACU, the circulating nurse, in most institutions, calls the PACE to give a preliminary status report of the patient's condition. This report includes the surgical procedure, type of anesthesia care provided, information specific to the patient's preoperative diagnosis and subsequent outcome related to intraoperative intervention, and any special equipment required.

The sudden unexpected death of a healthy individual undergoing elective surgery is a tragedy almost beyond comprehension in this day of modern medical miracles. Yet, this still happens to patients susceptible to malignant hyperthermia. It is our responsibility as qualified, competent health care providers to be familiar with malignant hyperthermia and know how to treat MH. I hope that this course has educated you on malignant hyperthermia to allow you to do what you do best….save a life!

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