Malignant hyperthermia is a rare, life-threatening, autosomal-dominant, pharmacogenetic, anesthetic-related disorder that occurs in susceptible patients following the administration of a triggering agent, such as inhaled halogenated volatile anesthetics or depolarizing neuromuscular blocking agent. Once triggered, a rapidly progressive hypermetabolic reaction involving sustained muscle contraction occurs with catastrophic consequences. Recent advances in our understanding of malignant hyperthermia have decreased the fatality rate from >70% to <5% per episode.1,4 Malignant hyperthermia can occur at any time following administration of a triggering agent. Many triggers of malignant hyperthermia are used during the routine administration of general anesthesia. Pharmacologically, malignant hyperthermia triggers include the halogenated volatile anesthetics including halothane, isoflurane, desflurane, sevoflurane, and enflurane and the depolarizing neuromuscular blocking agent, succinylcholine.5,7

The reported incidence of malignant hyperthermia episodes ranges from 1 in 5000 anesthetics to 1 in 50,000 to 150,000 anesthetics.2,4,7 Malignant hyperthermia occurs more commonly in children and young adults, in men more frequently than women, and in all ethnicities in equal proportion. Additionally, many cases of malignant hyperthermia may go undetected because many susceptible patients are never anesthetized, have short durations of exposure, or have mild, uncomplicated presentations that are never diagnosed.8

Given the rarity and lethality of malignant hyperthermia, it is critical that all health care providers practicing in the perioperative setting have the ability to identify and institute timely life-saving therapy for this disorder. PATHOPHYSIOLOGY Malignant hyperthermia has been linked to mutations within the calcium channel receptor, known as the ryanodine receptor (RYR1), within the sarcoplasmic reticulum.9,10 To date, more than 40 different point mutations in the gene encoding RYR1 have been discovered.4 These mutations are translated into a dysfunctional receptor with resultant uncontrolled release of calcium from the sarcoplasmic reticulum that leads to a prolonged and sustained muscle fiber contraction.

The sustained muscle contraction produces a rapid depletion of adenosine triphosphate (ATP) with a concomitant increase in glucose metabolism, oxygen consumption, and heat production. Acidosis, hyperthermia, and ATP depletion lead to the destruction of the sarcolemma, cell death, and release of intracellular materials.1,8 This series of events...
leads to a hypermetabolic crisis, including electrolyte imbalances, cardiac arrhythmias, hyperthermia, acidosis, disseminated intravascular coagulopathy, and death.

**IDENTIFYING SUSCEPTIBILITY**

The gold standard test for identifying susceptibility to malignant hyperthermia is the skeletal muscle contracture test. This test, which uses a small piece of live muscle from biopsy, assesses the muscular contractility in response to halothane and caffeine exposure.

The strength of contractility is a function of free calcium in the myoplasm. Exposure to halothane and caffeine increases the skeletal muscle contractility in patients who are susceptible to malignant hyperthermia. The sensitivity of this test for predicting the development of malignant hyperthermia is approximately 97% and the specificity, 78%. This test is costly, is only performed in a limited number of specialized testing centers, and because it requires fresh muscle specimen, patients must travel to one of these specialized centers.

Genetic testing for the mutations that result in malignant hyperthermia is also available with advantages over the muscle contracture test that include reduced invasiveness and lower cost. The disadvantage of genetic testing is a substantially lower sensitivity with only a 30% detection rate for patients at risk for malignant hyperthermia.

**CLINICAL PRESENTATION**

Malignant hyperthermia symptoms can occur within a few minutes to a few hours of initial exposure to a triggering agent (Table 1). Early clinical signs of malignant hyperthermia include a steadily rising heart rate and end-tidal carbon dioxide (ETCO₂) concentration. Although frequently also cited as an initial sign of malignant hyperthermia, masseter muscle spasm may be seen following succinylcholine administration in patients who do and do not develop malignant hyperthermia.

Caffeine-halothane contracture testing of patients who developed these spasms found that only 28% to 50% of these patients were susceptible to malignant hyperthermia. Muscle rigidity is also prevalent in patients with malignant hyperthermia, especially in the jaw, chest, and extremities and is frequently refractory to neuromuscular blocking agents.

As the crisis progresses, late clinical signs such as cyanosis, cardiac arrhythmias, mixed respiratory and metabolic acidosis, and various electrolyte imbalances may arise.

Of note, rhabdomyolysis is another frequent feature of the disorder related to the destruction of skeletal muscle tissue. As a result, patients commonly develop myoglobinemia, myoglobinuria, hyperkalemia, hyperphosphatemia, and hypocalcemia. Acute renal failure requiring renal replacement therapy may occur due to myoglobin precipitation in the renal tubules and close observation and laboratory monitoring of urine for myoglobin should be instituted.

Although the initial descriptions of this syndrome are centered on the development of severe, rapidly developing hyperthermia, it is known that its occurrence is often late in the development of malignant hyperthermia. When it occurs, the temperature may rise as quickly as 1°C every 5 minutes.

Patients may progress to severe acidosis, shock, and ventricular fibrillation in as quickly as 20 minutes from the onset of hyperthermia. Oxygen stores are more rapidly depleted when the patient is hyperthermic with an increase in consumption to at least 2 to 3 times normal. Mixed venous oxygenation also decreases indicating increased oxygen extraction by the skeletal muscles. Disseminated intravascular coagulation is also associated with the elevated core body temperature. Patients may present with one or

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**Table 1**

**Clinical Presentation of Malignant Hyperthermia**

<table>
<thead>
<tr>
<th>Early Signs and Symptoms</th>
<th>Late Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased ETCO₂¹</td>
<td>Cutaneous changes</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Mottled skin</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Masseter muscle spasms</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Generalized rigidity</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Myoglobinemia/myoglobinuria</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Cutaneous changes</td>
<td>Left ventricular failure</td>
</tr>
<tr>
<td>Generalized erythematous flush</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>Frothy sputum</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Hyper/hypocalcemia</td>
</tr>
</tbody>
</table>

Abbreviation: ETCO₂, end tidal carbon dioxide.
any combination of the above mentioned clinical signs that may evolve into sudden, unexplained cardiac arrest.

Several disorders have a similar clinical presentation to malignant hyperthermia. Neuroleptic malignant syndrome is characterized by muscle rigidity, hyperthermia, hyperkalemia, acidosis, autonomic instability, and altered mental status most often occurring after the use of neuroleptic agents such as haloperidol, but it has also been implicated with the use of non-neuroleptic agents. Other disorders that resemble malignant hyperthermia include thyroid storm, pheochromocytoma, heat stroke, and cocaine/ecstasy overdose.4,15

TREATMENT

Treatment of malignant hyperthermia requires the rapid identification of symptoms, discontinuation of the triggering agent, institution of dantrolene therapy, and control of associated symptoms. After the triggering agent has been discontinued, if the surgical procedure must continue, a non-triggering anesthetic technique should be implemented. This may involve the use of opioids, sedatives, and non-depolarizing neuromuscular blockers as needed (Table 2).

Dantrolene therapy, a skeletal muscle relaxant that inhibits the excitation-contraction coupling in skeletal muscle without affecting neuromuscular transmission or the electrical properties of the muscle, should also be initiated as rapidly as possible to prevent the development of the rapidly deteriorating clinical course described above.4,16,17 Dantrolene preparation should begin as soon as possible as it entails a time-consuming reconstitution process and requires several people for its rapid preparation. The powdered drug dissolves slowly and requires 60 mL of sterile water for injection added to each 20-mg vial. After reconstitution, dantrolene 2.5 mg/kg/dose should be administered rapidly through a large-bore IV, if possible.14 Doses may be repeated every 5 minutes as needed for regulation of signs and symptoms. The typically described upper limit of dosing is 10 mg/kg cumulative dose; however, more may be used if clinically indicated.

After the acute crisis has been controlled, dantrolene 1 mg/kg every 4 to 6 hours or alternatively 0.25 mg/kg/hr continuous infusion for 24 hours is recommended.14 Following reconstitution, dantrolene is stable at room temperature for 6 hours when protected from light.18 Adverse effects associated with dantrolene include loss of grip strength, muscle weakness, drowsiness, dizziness, and injection site reactions, including pain, erythema, and swelling. Extravasation of dantrolene has been associated with tissue necrosis.

The mixed respiratory and metabolic acidosis should be treated with hyperventilation at 2 to 3 times the predicted minute ventilation with 100% oxygen and intravenous administration of sodium bicarbonate. Hyperkalemia may precipitate cardiac arrhythmias and therefore should be aggressively treated with insulin, dextrose, sodium bicarbonate, and calcium.

Initial management of cardiac arrhythmias includes treatment of the underlying acidosis and hyperkalemia. Cardiac arrhythmias should not be treated with calcium channel antagonists (eg, verapamil, diltiazem) due to a severe drug interaction with dantrolene resulting in hyperkalemia and cardiac arrest.19 Persistent arrhythmias may necessitate the use of standard antiarrhythmic medications such as amiodarone and lidocaine.14

Hyperthermia, a late clinical sign, should be treated with aggressive cooling measures. Core temperature must be monitored using appropriate monitoring sites including the pulmonary artery, distal esophagus, nasopharynx, tympanic membrane, rectum, bladder, or axilla. Cooling techniques include use of cold 0.9% sodium chloride intravenous fluids, lavage of the stomach, bladder, rectal, or open cavity, and placement of ice packs on the neck, axilla, and groin. Cooling techniques should be suspended when the core body temperature reaches 38°C.5,14

Acute rhabdomyolysis should be treated with adequate hydration, urine alkalinization, and diuretics to maintain a urine output of 2 mL/kg/hr.

Laboratory monitoring parameters include arterial and venous blood gases, electrolytes, coagulation parameters, myoglobinemia, myoglobinuria, and creatine kinase. These should be performed immediately at the onset of the reaction and periodically thereafter.4 The syndrome recurs in 25% of patients within 48 hours.
spinal, epidural, regional, or local anesthetic techniques including administration of susceptibility, alternative therapies had undergone a prior incident.2,15 The concentration of malignant hyperthermia has only been established in 3 disorders. They include Evans myopathy (named after the family in which malignant hyperthermia was first detected), central-core disease, and King-Denborough syndrome.3 Of note, susceptible patients who have undergone a previously uncomplicated general anesthetic with an inhaled volatile anesthetic or succinylcholine may develop malignant hyperthermia during a subsequent anesthetic. Population studies have determined that approximately 24% to 50% of patients with malignant hyperthermia had undergone a prior anesthetic procedure without incident.2,15 The concentration of anesthetic, duration of exposure to triggering agents, and degree of malignant hyperthermia susceptibility are thought to be significant factors in explaining this phenomenon.3

If patients are known to be susceptible or if there is suspicion of susceptibility, alternative anesthetic techniques including spinal, epidural, regional, or local anesthesia should be used. If a susceptible patient must undergo general anesthesia, the potent volatile anesthetics (halothane, isoflurane, desflurane, sevoflurane, enflurane) and succinylcholine must be avoided. This is accomplished through the use of an anesthetic machine that has been thoroughly cleansed of volatile anesthetic residue and an intravenous infusion of anesthetic, typically propofol. The use of dantrolene as prophylaxis prior to general anesthesia in malignant hyperthermia susceptible patients is no longer a recommended practice.5,6

CONCLUSION

Early recognition and prompt treatment of malignant hyperthermia have resulted in substantial reduction in morbidity and mortality. A thorough preoperative assessment, knowledgeable health care professionals, and interdisciplinary collaboration can significantly impact patient outcomes.14

REFERENCES


THE BOTTOM LINE

- Early identification of associated signs and symptoms is an essential component to improved patient survival. Once symptoms have been identified, discontinue all volatile agents and succinylcholine immediately.
- Prepare and administer dantrolene 2.5 mg/kg IV and repeat every 5 minutes until signs of malignant hyperthermia are reversed. Continue treatment with 1 mg/kg every 4 to 6 hours for 24 hours or alternatively 0.25 mg/kg/hr continuous infusion for 24 hours in the intensive care unit.
- For more information, visit http://www.mhaus.org.