Evidence-Based Patient Safety Advisory: Malignant Hyperthermia

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Summary: As more and more routine plastic surgery procedures move from the hospital to outpatient surgery facilities, plastic surgeons must be aware of the risk factors for life-threatening events that might occur in this setting. This awareness includes recognition of the signs and symptoms and the management of a rare but life-threatening condition, malignant hyperthermia. This article reviews the current understanding of the concepts pertinent to malignant hyperthermia diagnosis and treatment in the outpatient setting and current standards and recommendations for physicians and support personnel regarding malignant hyperthermia preparedness in office-based surgery and anesthesia. (*Plast. Reconstr. Surg.* 124 (Suppl.): 68S, 2009.)

As more and more routine plastic surgery procedures move from the hospital to outpatient surgery facilities, plastic surgeons must be aware of the signs and symptoms and the management of a rare life-threatening condition, malignant hyperthermia. Although the abrupt, unpredicted death of a healthy individual undergoing surgery in any setting is extremely unusual, when it occurs in an outpatient facility, it will always be questioned whether this person should have had their procedure performed instead as an inpatient. It is imperative then that all surgeons using general anesthesia understand what malignant hyperthermia risks are for their patients, and what to do if confronted by it.

Malignant hyperthermia is an inherited myopathy that presents as a hypermetabolic reaction to potent volatile anesthetic gases, such as halothane, enflurane, isoflurane, sevoflurane, and desflurane, and the depolarizing muscle relaxant succinylcholine. Critical worldwide insight into malignant hyperthermia began in 1960, when Denborough and Lovell described a series of anesthetic deaths in a family.[1] Since that time, awareness of malignant hyperthermia has reached critical mass where, through widely disseminated information and improvements in medication, successful treatment has become the norm rather than the exception. The incidence of malignant hyperthermia episodes during anesthesia is thought to be between one in 5000 and one in 50,000 to 100,000 anesthetic encounters, but because of accurate diagnosis, timely recognition, and appropriate treatment, mortality rates have fallen from 70 percent when the first cases came to light to less than 5 percent over 30 years later.

This article reviews the current concepts pertinent to malignant hyperthermia in the outpatient setting, with particular emphasis on presurgical evaluation, identification of susceptible individuals and selection of the appropriate setting for these patients, appropriate anesthetic agents for susceptible patients, early diagnosis and management of acute malignant hyperthermia, and postoperative vigilance and care. Also discussed are current standards/guidelines and recommendations for physicians and support personnel regarding facility and equipment requirements and malignant hyperthermia preparedness in office-based surgery and anesthesia.

This patient safety advisory was developed through a comprehensive review of the scientific literature and a consensus of the Patient Safety Committee. The supporting literature was critically appraised for study quality according to criteria referenced in key publications on evidence-

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based medicine.[2–6] Depending on study design and quality, each reference was assigned a corresponding level of evidence (I through V) with the American Society of Plastic Surgeons (ASPS) Evidence Rating Scales (Table 1),[7] and the evidence was synthesized into practice recommendations. The recommendations were then graded (A through D) with the ASPS Grades of Recommendation Scale (Table 2)[8]; grades correspond to the levels of evidence provided by the supporting literature for that recommendation. Practice recommendations are discussed throughout this document, and graded recommendations are summarized in Appendix A.

DISCLAIMER

Practice advisories are strategies for patient management, developed to assist physicians in clinical decision-making. This practice advisory, based on a thorough evaluation of the present scientific literature and relevant clinical experience, describes a range of generally acceptable approaches to diagnosis, management, or prevention of specific diseases or conditions. This practice advisory attempts to define principles of practice that should generally meet the needs of most patients in most circumstances. However, this practice advisory should not be construed as a rule, nor should it be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the appropriate results. It is anticipated that it will be necessary to approach some patients' needs in different ways. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of all the circumstances presented by the patient, the diagnostic and treatment options available, and available resources.

This practice advisory is not intended to define or serve as the standard of medical care. Standards of medical care are determined on the basis of all the facts or circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance, and as practice patterns evolve. This practice advisory reflects the state of knowledge current at the time of publication. Given the inevitable changes in the state of scientific information and technology, periodic review and revision will be necessary.

Table 1. Evidence Rating Scale for Studies Reviewed

Level of Evidence	Qualifying Studies
I	High-quality, multicentered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser quality, randomized controlled trial; prospective cohort study; or systematic review of these studies
III	Retrospective comparative study; case-control study; or systematic review of these studies
IV	Case series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research, or "first principles"

TRIGGERING OF MALIGNANT HYPERTHERMIA

Anesthetic drugs that trigger malignant hyperthermia include halothane, enflurane, isoflurane, desflurane, sevoflurane, and succinylcholine (Table 3).[9] Desflurane and sevoflurane are less potent triggers, producing a more gradual onset of malignant hyperthermia.[10,11] The onset may be explosive if succinylcholine is used.[12]

Volatile anesthetics and succinylcholine represent a stress for skeletal muscle because they perturb membranes and disturb Ca^{2+} homeostasis. In general, normal muscle can withstand and compensate for these stresses. In susceptible muscle, however, these membrane changes induced by halothane (or depolarization induced by succinylcholine) may cause an earlier calcium release that strikingly stimulates a calcium cascade.[13] When these abnormal amounts of Ca^{2+} build up in the myoplasm, the muscle remains in a contracted state, producing abnormal amounts of lactic acid, carbon dioxide, phosphate, and heat. This will result in metabolic acidosis, hypercapnia, hyperphosphatemia, and fever in the patient with a malignant hyperthermia crisis. As myoplasmic Ca^{2+} remains elevated, it will prevent the myosin and actin fibrils in the muscle from detaching and sliding back to their relaxed position. When myoplasmic Ca^{2+} levels increase further, mitochondria are uncoupled and adenosine triphosphate production decreases, whereas the consumption of both adenosine triphosphate and oxygen increases. As adenosine triphosphate becomes scarce, the function of ion transport systems of the sarcolemmal membrane ceases. Ions such as potassium, phosphate, and magnesium, and myoglobin, begin to leak across the sarcolemma into the extracellular fluid, causing a rise in serum levels (Fig. 1).[14]

GENETICS OF MALIGNANT HYPERTHERMIA

Malignant hyperthermia is an inherited skeletal muscle disorder. Genetic evaluation is consistent with autosomal dominant inheritance

Table 2. Scale for Grading Recommendations

Grade	Descriptor	Qualifying Evidence	Implications for Practice
A	Strong recommendation	Level I evidence or consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
B	Recommendation	Levels II, III, or IV evidence and findings are generally consistent	Generally, clinicians should follow a recommendation but should remain alert to new information and sensitive to patient preferences.
C	Option	Levels II, III, or IV evidence, but findings are inconsistent	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
D	Option	Level V: Little or no systematic empirical evidence	Clinicians should consider all options in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

Table 3. Safety of Agents in Malignant Hyperthermia–Susceptible Individuals*

Agents
Malignant hyperthermia–triggering agents
• Halothane (most potent), isoflurane, desflurane, enflurane, sevoflurane (volatile agents)
• Succinylcholine
• *d*-Tubocurarine
• Ether derivatives and chloroform
• Phosphodiesterase inhibitors (enoximone/methylxanthines in supertherapeutic doses)
• Rapid intravenous potassium
• Theophylline and aminophylline (supertherapeutic doses)
Safe drugs
• Anticholinergics
• Anticholinesterases
• Barbiturates (e.g., thiopental)
• Benzodiazepines
• Droperidol
• Etomidate
• Ketamine
• Local anesthetics (both ester and amide type)
• Narcotics
• Nitrous oxide
• Nondepolarizing muscle relaxants (e.g., vecuronium, rocuronium, pancuronium, atracurium, mivacurium, cisatracurium)
• Nonsteroidal antiinflammatory drugs
• Propofol
Use with care
• Catecholamines†
• Haloperidol
• Phenothiazines‡ (e.g., chlorpromazine, prochlorperazine)

*Adapted from Adamson PA, Dahiya R, Litner J, Vosu H. Malignant hyperthermia: Successful management in a private surgery centre. *J Otolaryngol.* 2006;35:186–189.
†May cause secondary sympathetic response, though it is not a trigger.
‡May cause neuroleptic malignant syndrome and often is confused with malignant hyperthermia.

with variable penetrance. It has been linked to the ryanodine receptor type 1 gene (*RYR1*), in which over 100 mutations associated with malignant hyperthermia have been identified.[14] Studies suggest that mutations cluster largely within three regions of *RYR1*; however, complete screening of the entire coding regions of *RYR1* has shown that mutations can occur in almost all regions of the gene.[15–17] *RYR1* mutations occur in at least 50 percent of malignant hyperthermia-susceptible patients and almost all families with central core disease.

Another mode of malignant hyperthermia inheritance is the gene that codes for the **ex**$_{1S}$ subunit of the dihydropyridine receptor. Two causative mutations in this gene are linked to less than 1 percent of malignant hyperthermia–susceptible families worldwide.[17,18]

PATIENT SELECTION

Patients known to be susceptible to malignant hyperthermia may actually undergo anesthesia several times before a clinical episode occurs.[19] Therefore, the population at risk may be considerably higher than believed. Thus, it is critical that awareness and prevention of the condition play significant roles in the management of malignant hyperthermia.

Because of the autosomal dominant inheritance pattern, the medical history should include questions regarding a family history of adverse outcomes after general anesthesia. The preoperative history and physical examination form (see Haeck et al., "Evidence-Based Patient Safety Advisory: Patient Selection and Procedures in Ambulatory Surgery," in this issue) can be expanded to include family and personal history of malignant hyperthermia.

The medical history should also inquire about other conditions that may predispose patients to true malignant hyperthermia, such as Evans myopathy, King-Denborough syndrome, and central core disease.[1,20,21] Patients with Duchenne muscular dystrophy are at risk of life-threatening hyperkalemia on administration of succinylcholine. However, anesthetic-related complications in these patients do not exhibit classic signs of malignant hyperthermia. Patients with any form of myotonia should not receive succinylcholine. Patients with hypokalemic periodic paralysis, central core disease,[21] multi-minicore disease (*RYR1*-related forms),[22] Duchenne or Becker muscular dystrophy, paramyotonia, or myotonia fluctuans should not receive triggering agents.[23]

The U.S. Food and Drug Administration's black box warning for succinylcholine was issued subsequent to its association with rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death in children with undiagnosed skeletal muscle myopathy. Its use in children should be reserved for emergency intubation, where securing the airway is necessary.

Patients who report a malignant hyperthermia crisis/susceptibility in their first-degree relatives must be considered malignant hyperthermia susceptible until proven otherwise and must not receive triggering agents. They therefore should be counseled and referred to the Malignant Hyperthermia Association of the United States for further investigation. Any susceptible individual should be encouraged to wear a "medical alert" bracelet notifying emergency personnel of this diagnosis.

Malignant hyperthermia–susceptible patients can undergo minor procedures, such as simple excisional surgery, under topical or local anesthesia (i.e., level I office procedures) in the office or ambulatory surgical center because there is no evidence that local anesthetics, vasoconstrictors, or patient anxiety increase the chance of a malignant hyperthermia reaction in this setting.[24–26] Malignant hyperthermia–susceptible patients undergoing complex procedures that require minimal or moderate intravenous or intramuscular sedation/analgesia, general anesthesia, or major conduction blockade (i.e., level II and III office procedures) should be referred to an accredited ambulatory surgical center or hospital for surgery (Fig. 2).

Although hypermetabolic responses in swine have been documented after exposure to heat, exercise, anoxia, and excitement,[27] the role of stress in triggering malignant hyperthermia in humans is controversial. There is some evidence in the literature that patients who have experienced heat stress in the past are more likely to have malignant hyperthermia–positive in vitro contracture tests.[28–30] However, stress has not been shown to directly precipitate malignant hyperthermia in humans.[12,14,24] Studies in mouse models suggest similarities between exertional or environmental heat stroke and malignant hyperthermia.[31] Clinical studies have shown no clear evidence of association between duration or type of surgery and risk of an episode for malignant hyperthermia–susceptible patients.[32] Nevertheless, susceptible patients should be counseled about their decision to have elective surgery and their increased risk of life-threatening complications associated with anesthesia.

DETERMINATION OF MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

Caffeine-Halothane Contracture Test

When the diagnosis of malignant hyperthermia susceptibility is in question, the standard means for determining susceptibility is the caffeine-halothane contracture test.[33–36] Two commonly used forms of this test have been developed, one by the European Malignant Hyperthermia Group (the in vitro contracture test) and the other by the North American Malignant Hyperthermia Group (the caffeine-halothane contracture test). The test consists of excising a piece of skeletal muscle from the patient's thigh and determining its contractile properties when exposed to the ryanodine receptor agonist halothane and/or caffeine. An abnormal level of contractile activity is indicative of susceptibility.

Using the in vitro contracture test, an individual is considered to be susceptible when both the caffeine and halothane test results are positive. A negative diagnosis is made when both tests are negative. A third possible result, known as malignant hyperthermia equivocal, is obtained when only one of the halothane or caffeine tests is positive. When the caffeine-halothane contracture test is used, an individual is diagnosed as susceptible if either halothane or caffeine test result is positive. A negative diagnosis is obtained when both are negative.[33,37,38] The in vitro contracture test may reduce the possibility of false-positive and false-negative results compared with the caffeine-halothane contracture test but, overall, similar results are obtained.

Genetic Testing: *RYR1* Screening for Malignant Hyperthermia Susceptibility

There are a limited number of biopsy test centers available for caffeine-halothane contracture testing, eight in the United States and two in Canada. To ensure accurate results, the patient must travel to the test center for surgical biopsy,[39] thus

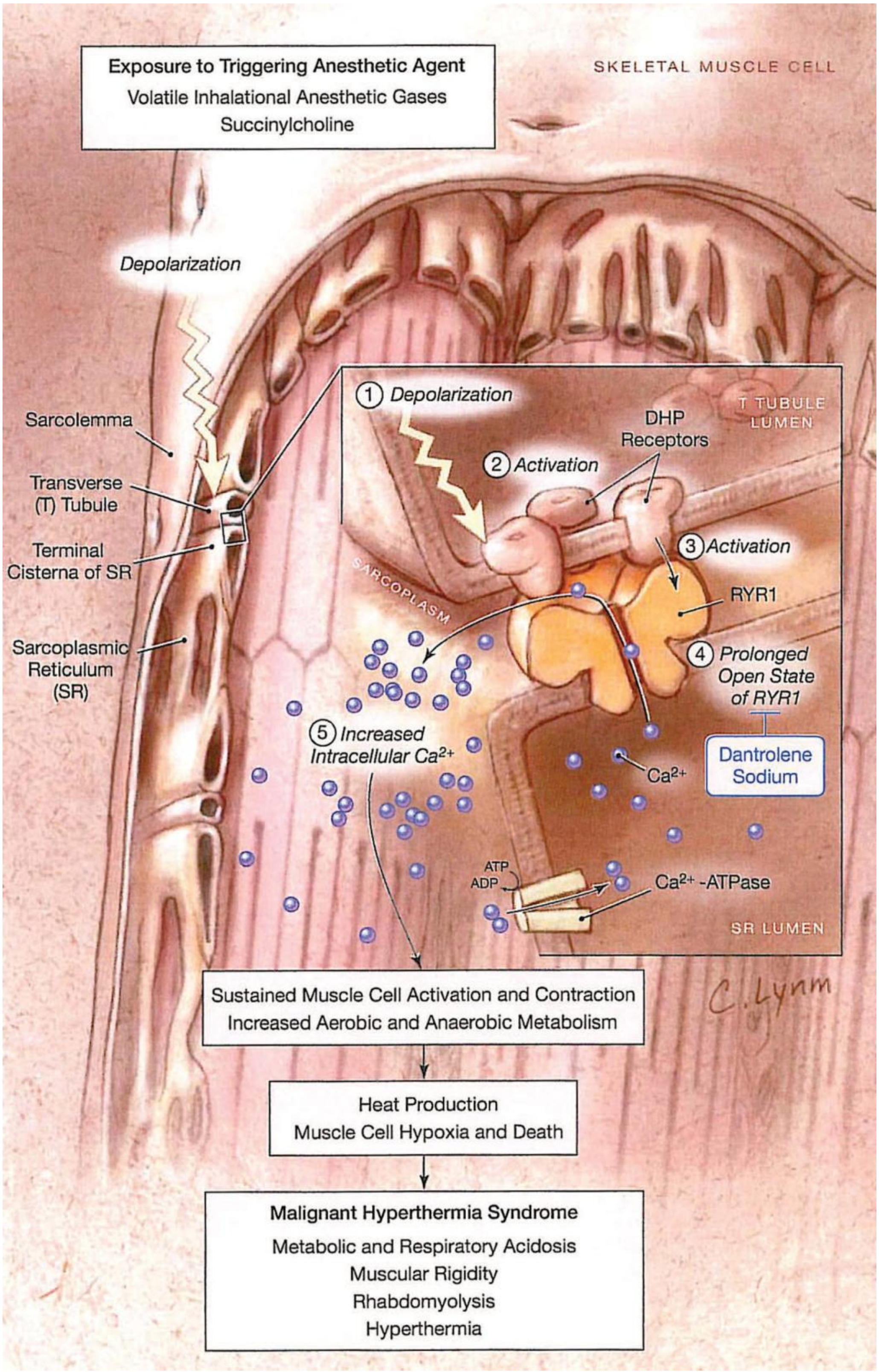

Fig. 1. Pathophysiology of malignant hyperthermia. In normal muscle, an electric impulse from the nerve terminals produces a wave of depolarization of the sarcolemma and transverse tubules. This leads to a conformational change in voltage-gated L-type Ca^{2+} channels, known as dihydropyridine (*DHP*) receptors located in the sarcolemma of the transverse tubule. One of the dihydropyridine receptor subunits

prompting some patients to initially elect mutation screening, which simply involves blood testing. However, because of its low sensitivity, a negative mutation screen does not rule out malignant hyperthermia susceptibility, and the caffeine-halothane contracture test is then recommended for definitive diagnosis. The North American mutation analysis protocol currently screens for 17 of the most common *RYR1* mutations and has a detection rate of 25 percent.[40] The genetic test is very specific; patients with a positive test are virtually assured of being at risk of malignant hyperthermia.

DNA testing is confounded by the genetic heterogeneity of the disorder[33,41,42]; thus, it should only be used in selected cases and within the European Malignant Hyperthermia Group or North American Malignant Hyperthermia Group guidelines for DNA testing.[43,44] At present, there are two laboratories in the United States that perform molecular genetic testing for malignant hyperthermia.[45]

Interpreting Risk for Family Members

An affected patient will have inherited malignant hyperthermia sensitivity from one of the parents. The risks to the siblings of that patient depend on the genetic status of the parents. If a parent is identified as malignant hyperthermia susceptible, each of the patient's siblings have a 50 percent chance of also being susceptible. If both parents receive a malignant hyperthermia normal result on in vitro contracture testing and *RYR1* analysis, the patient's siblings are at no greater risk than the general population. In addition, each offspring of an individual with proven susceptibility has a 50 percent chance of being susceptible. The patient's grandchildren would be considered to be at 25 percent risk until their parents' genetic status is known.[33]

Fig. 1. (Continued) (α_{1S} subunit) provides physical links between dihydropyridine receptors within transverse tubules and Ca^{2+} release channels within junctional sarcoplasmic reticulum. Those calcium channels are known as ryanodine receptors. Then, the free Ca^{2+} stored within the sarcoplasmic reticulum terminal cisternae is released to the cytoplasm of the muscle fibers. The increase in Ca^{2+} removes the troponin inhibition from the contractile proteins, resulting in muscle contraction. Sarcoplasmic/endoplasmic reticulum Ca^{2+}–adenosine triphosphatase (*ATPase*) rapidly reaccumulate Ca^{2+} back into the sarcoplasmic reticulum, and relaxation occurs. Exposure of a susceptible individual to a triggering agent results in an abnormal amount of Ca^{2+} in the myoplasm; the muscle remains in a contracted state; and abnormal amounts of lactic acid, carbon dioxide, phosphate, and heat are produced. This is the source of the metabolic acidosis, hypercapnia, hyperphosphatemia, and fever in the patient with a malignant hyperthermia crisis. Mitochondria are uncoupled and adenosine triphosphate (*ATP*) production decreases, whereas the consumption of both adenosine triphosphate and oxygen increases. The function of ion transport systems of the sarcolemmal membrane ceases. Ions such as potassium, phosphate, and magnesium, in addition to myoglobin, begin to leak across the sarcolemma into the extracellular fluid and their serum levels rise. (Reproduced with permission from Litman RS, Rosenberg H. Malignant hyperthermia: Update on susceptibility testing. *JAMA*. 2005;293:2918-2924. Copyright 2005, American Medical Association. All rights reserved.)

FACILITY REQUIREMENTS

It is recommended that plastic surgeons use guidelines and recommendations for safe office-based anesthesia and surgery published by the American Society of Anesthesiologists, the American College of Surgeons, the ASPS, and the American Society for Aesthetic Plastic Surgery.[46–54] Both the American Society for Aesthetic Plastic Surgery and the ASPS require that their members operate only in an accredited or licensed facility for all procedures that essentially involve anesthesia greater than just local.

All office surgical suites where general anesthesia is used should be equipped to manage a malignant hyperthermia emergency. Surgeons should be encouraged to review their state and national guidelines, because several state medical boards have established regulations concerning availability of dantrolene in the office. For instance, the Massachusetts Medical Board developed office-based surgical guidelines and recommended that the office have at least 20 ampules of dantrolene for level II and III procedures. The Mississippi Medical Board and Florida Medical Board passed regulations requiring at least 12 and 36 ampules of dantrolene in a level II and III office, respectively. In those guidelines, it is recommended that the office-based surgery suite must have sufficient equipment (i.e., pulse oximetry, capnography, temperature monitoring equipment, continuous electrocardiography, emergency resuscitative equipment), supplies [i.e., sterile water sufficient to dilute Dantrium (JHP Pharmaceuticals, Parsippany, N.J.)], D50, antiarrhythmics, calcium chloride, sodium bicarbonate, insulin, furosemide, and adequate ice), trained personnel, transfer and emergency protocols, and facility accreditation to treat a malignant hyperthermia emergency (Fig. 3).[48] Although having the necessary medication and equipment

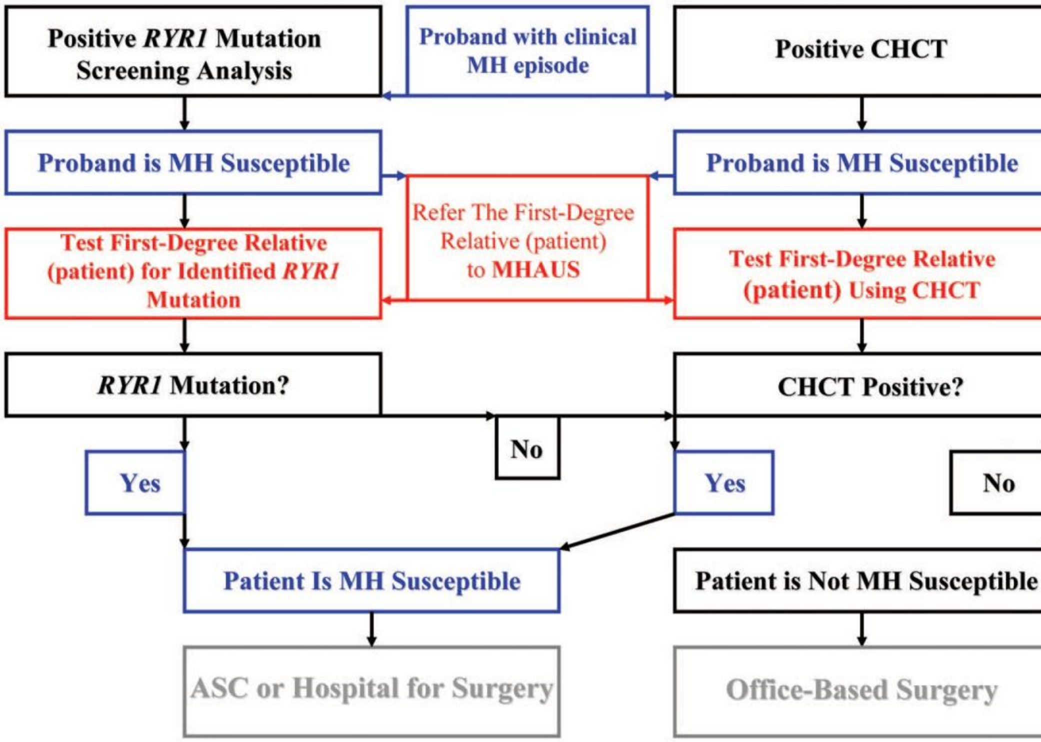

Fig. 2. An algorithm for the surgeon to work up a patient with a family history of malignant hyperthermia (*MH*). A first-degree relative (the surgical candidate or the patient) of a proband who has been determined to be susceptible to malignant hyperthermia by a clinical episode plus either a positive caffeine-halothane contracture test (*CHCT*) result or a mutation analysis should be counseled and referred to the Malignant Hyperthermia Association of the United States (*MHAUS*) for susceptibility testing. Biopsy test centers and mutation analysis laboratories are provided by the Malignant Hyperthermia Association of the United States at http://www.mhaus.org. If testing cannot be performed, a first-degree relative (the patient) should be considered malignant hyperthermia susceptible and referred to an ambulatory surgical center (*ASC*) or hospital for surgery. (Adapted from Litman RS, Rosenberg H. Malignant hyperthermia: Update on susceptibility testing. *JAMA*. 2005;293:2918-2924.)

to treat a malignant hyperthermia reaction is essential, more importantly, it should be the goal of managing the rare reaction in the office to quickly stabilize the patient and transfer them to an acute care facility where extensive personnel, laboratory resources (e.g., blood gases, electrolytes), and critical care staff are suited to manage this life-threatening situation.

MANAGEMENT

Pretreatment of susceptible patients with dantrolene is no longer recommended to prevent triggering of malignant hyperthermia with general anesthesia.[55–57] Instead, nontriggering agents must be used in all susceptible and suspect patients, and these procedures should be performed in a facility fully equipped to treat malignant hyperthermia. Nitrous oxide is safe to use, provided that the anesthesia machine is "vapor-free" and contains no traces of volatile gas. This can be ensured by selectively using a vaporizer-free anesthesia machine or by changing circuits, disabling or removing the vaporizers, and flushing the machine at a rate of 10 liters/minute for 20 minutes.[58]

Malignant hyperthermia can also be triggered by nontriggering agents in less than 1 percent of susceptible patients.[59,60] Therefore, continued and reasonable use of general anesthesia, especially with triggering agents, in office settings and ambulatory surgical centers mandates active malignant hyperthermia protocols. Practice drills should be considered if triggering agents, including succinylcholine, are used in the facility. Printed protocols on management of malignant hyperthermia are available through the Malignant Hyperthermia Association of the United States.[58,61]

Fig. 3. A malignant hyperthermia cart and close-up view of malignant hyperthermia drugs. Dantrolene sodium (Dantrium) is stocked on the hyperthermia cart. Unreconstituted product is stored at controlled room temperature (59° to 86°F or 15° to 30°C), and prolonged exposure to light should be avoided. The contents of the vial must be protected from direct light and used within 6 hours after reconstitution. Reconstituted solutions are stored at controlled room temperature (59° to 86°F or 15° to 30°C). The shelf life of dantrolene is 3 years and it costs $69 per bottle. The open drawer in this malignant hyperthermia cart can keep 36 bottles of dantrolene. Boxes contain six vials each.

Whenever possible, nontriggering agents should be considered for outpatient procedures to help avoid or minimize malignant hyperthermia cases. For instance, one study[62] used only the nontriggering agents propofol and vecuronium (nondepolarizing muscle relaxant), and reported no malignant hyperthermia in 23,000 office-based plastic surgery procedures performed under general anesthesia. In addition, multiple studies have demonstrated the safety of intravenous conscious sedation.

Diagnosis and Treatment of Malignant Hyperthermia

The onset of malignant hyperthermia signs may vary in order and time, often making clinical diagnosis rather difficult. Furthermore, a variety of unusual conditions that include sepsis, thyroid storm, pheochromocytoma, and iatrogenic overheating may resemble malignant hyperthermia during anesthesia. An impending episode is heralded by a rising end tidal carbon dioxide level in the anesthetized patient.[63] However, the differential diagnosis of unexplained end tidal carbon dioxide should include hyperthermia secondary to sepsis, iatrogenic warming, rebreathing, machine valve dysfunction, or equipment malfunction.[33] Skeletal muscle (particularly masseter muscle) spasm, tachycardia, acidosis, hyperthermia, and hyperkalemia are other signs. Trismus, with or without generalized muscle rigidity, can also occur; Figure 4 provides an algorithm for its management.

The treatment of malignant hyperthermia in the acute phases involves discontinuation of volatile agents and succinylcholine, and simultaneous mobilization of all available personnel. A call to a 911 operator should be made to prepare for patient transfer to an acute care hospital. At the same time, the medical staff should continue to administer dantrolene; attempt to cool the patient; and correct any dysrhythmias, hyperkalemia, and metabolic acidosis.[61]

Dantrolene sodium, a hydantoin derivative, is the drug of choice for preventing and reversing the symptoms of malignant hyperthermia.[64,65] It appears that dantrolene acts to stabilize domain interactions within the ryanodine receptor,[66–70] which in turn reduces calcium efflux from the sarcoplasmic reticulum (Fig. 1).

In an acute episode, rapid dantrolene resuscitation is of the highest priority; therefore, it is imperative that all perioperative staff have knowledge about the pathophysiology and treatment of malignant hyperthermia. Thus, it is recommended that all staff frequently review protocols for recognizing and treating malignant hyperthermia.

When preparing dantrolene for injection, each 20-mg vial of dantrolene should be dissolved with at least 60 ml of sterile, preservative-free wa-

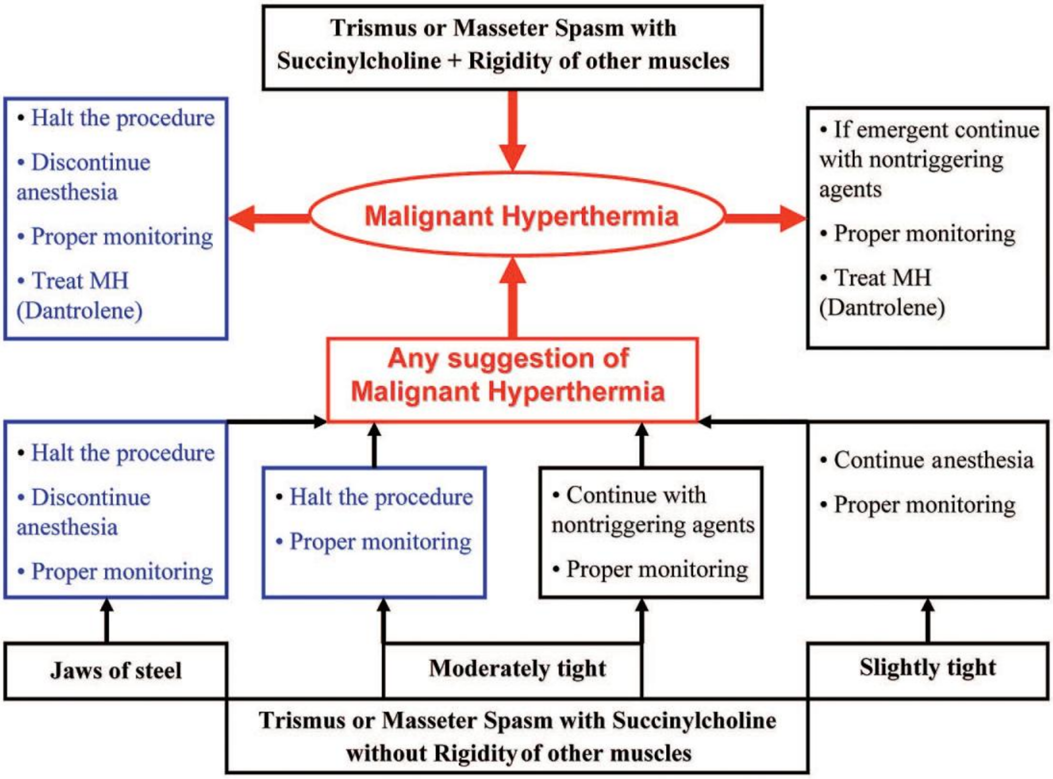

Fig. 4. An algorithm for the management of masseter muscle spasm associated with or without generalized muscle rigidity in an anesthetized patient. *MH*, malignant hyperthermia.

ter. Prewarming (not to exceed 39°C) the sterile water may expedite dissolving of dantrolene. The vial should be shaken until the solution is clear. The contents of the vial must be protected from direct light and used within 6 hours after reconstitution. Reconstituted solutions are stored at controlled room temperature (59° to 86°F or 15° to 30°C).[61]

In acute malignant hyperthermia, therapy should be started by administering 2.5 mg/kg of dantrolene as a rapid bolus through a large-bore intravenous line, repeating this administration at 5-minute intervals until signs of an episode are reversed. Once the patient has been stabilized, continuous intravenous infusion of dantrolene at 10 mg/kg/day (or even up to 30 mg/kg) should be given for at least 24 hours after the initial successful therapy, and the patient should be admitted to the hospital and observed in the intensive care unit for at least 24 hours, because of the risk of recrudescence.[61] Oral dantrolene capsules can be administered following a malignant hyperthermia crisis to prevent recurrence. Postoperative monitoring should be performed according to American Society of Anesthesiologists guidelines.

CONCLUSIONS

Both level II and level III office procedures, whether with deep sedation, general anesthesia (with or without triggering agents), or major conduction blockade, require malignant hyperthermia preparedness with immediate availability of dantrolene, as recommended by some medical boards and accreditation agencies. In addition to proper patient selection, safe anesthesia protocols, adequate equipment, appropriate monitoring, availability of trained personnel, and appropriate accreditation of the facility, a malignant hyperthermia protocol should be considered as an integral part of safe office-based surgery and anesthesia, regardless of a patient's susceptibility status. All office surgical suites should be ready and able to handle a malignant hyperthermia emergency. Unless procedures involve the use of topical or local anesthetics, susceptible individuals are not candidates for office-based surgery, and anyone identified for susceptibility to triggering agents should be referred to an accredited ambulatory surgical center or hospital for surgery.

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REFERENCES

1. Denborough MA, Lovell RRH. Anesthetic deaths in a family. *Lancet* 1960;2:45.
2. Greenhalgh T. *How to Read a Paper: The Basics of Evidence-Based Medicine*. 3rd ed. Oxford: Blackwell Publishing; 2006.
3. Lang TA, Secic M. *How to Report Statistics in Medicine*. 2nd ed. Philadelphia: American College of Physicians; 2006.
4. Straus SE, Richardson WS, Glasziou P, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*. 3rd ed. Philadelphia: Elsevier Churchill Livingstone; 2005.
5. Evidence-Based Medicine Working Group. *Users' Guides to the Medical Literature: Essentials of Evidence-Based Clinical Practice.* Chicago: American Medical Association; 2002.
6. Center for Evidence Based Medicine. Levels of evidence and grades of recommendations. Available at: http://www.cebm.net/levels_of_evidence.asp#levels. Accessed April 30, 2007.
7. American Society of Plastic Surgeons. Scales for rating levels of evidence. Available at: http://www.plasticsurgery.org/Medical_Professionals/Health_Policy_and_Advocacy/Health_Policy_Resources/Evidence-based_GuidelinesPractice_Parameters/Description_and_Development_of_Evidence-based_Practice_Guidelines/ASPS_Evidence_Rating_Scales.html. Accessed February 4, 2009.
8. American Society of Plastic Surgeons. Scale for grading practice recommendations. Available at: http://www.plasticsurgery.org/Medical_Professionals/Health_Policy_and_Advocacy/Health_Policy_Resources/Evidence-based_GuidelinesPractice_Parameters/Description_and_Development_of_Evidence-based_Practice_Guidelines/ASPS_Grade_Recommendation_Scale.html. Accessed February 4, 2009.
9. Adamson PA, Dahiya R, Litner J, Vosu H. Malignant hyperthermia: Successful management in a private surgery centre. *J Otolaryngol.* 2006;35:186–189.
10. Allen GC, Brubaker CL. Human malignant hyperthermia associated with desflurane anesthesia. *Anesth Analg.* 1998;86:1328–1331.
11. Shulman M, Braverman B, Ivankovich A, Gronert G. Sevoflurane triggers malignant hyperthermia in swine. *Anesthesiology* 1981;54:259–260.
12. Gronert GA. Malignant hyperthermia. *Anesthesiology* 1980;53:395–423.
13. Gallant EM, Gronert GA, Taylor SR. Cellular membrane potentials and contractile threshold in mammalian skeletal muscle susceptible to malignant hyperthermia. *Neurosci Lett.* 1982;28:181–186.
14. Gronert GA, Pessah IN, Muldoon SM, Tautz TJ. Malignant hyperthermia. In: Miller RD, ed. *Miller's Anesthesia*. Vol. 1, 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2008:1169–1190.
15. McCarthy TV, Quane KA, Lynch PJ. Ryanodine receptor mutations in malignant hyperthermia and central core disease. *Hum Mutat.* 2000;15:410–417.
16. Ibarra MC, Wu S, Murayama K, et al. Malignant hyperthermia in Japan: Mutation screening of the entire ryanodine receptor type 1 gene coding region by direct sequencing. *Anesthesiology* 2006;104:1146–1154.

17. Robinson RL, Brooks C, Brown S, et al. RYR1 mutations causing central core disease are associated with more severe malignant hyperthermia in vitro contracture test phenotypes. *Hum Mutat.* 2002;20:88–97.
18. Monnier N, Procaccio V, Stieglitz P, Lunardi J. 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;60:1316–1325.
19. Monaghan A, Hindle I. Malignant hyperpyrexia in oral surgery: Case report and literature review. *Br J Oral Maxillofac Surg.* 1994;32:190–193.
20. King JO, Denborough MA, Zapf PW. Inheritance of malignant hyperpyrexia. *Lancet* 1972;1:365–370.
21. Jungbluth H. Central core disease. *Orphanet J Rare Dis.* 2007; 2:25.
22. Jungbluth H. Multi-minicore Disease. *Orphanet J Rare Dis.* 2007;2:31.
23. Larach MG, Rosenberg H, Gronert G, Allen GC. Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. *Clin Pediatr (Phila.)* 1997;36:9–16.
24. Murray C, Sasaki SS, Berg D. Local anesthesia and malignant hyperthermia: Review of the literature and recommendations for the dermatologic surgeon. *Dermatol Surg.* 1999;25: 626–630.
25. Haas DA, Young ER, Harper DG. Malignant hyperthermia and the general dentist: current recommendations. *J Can Dent Assoc.* 1992;58:28–33.
26. Chang CY, Scher RL. Malignant hyperthermia and the otolaryngologist. *Ear Nose Throat J.* 2003;82:433–436.
27. Topel DG, Bicknell EJ, Preston KS, Christian LL, Matsushima CY. Porcine stress syndrome. *Mod Vet Pract* 1968;49:40–60.
28. Bendahan D, Kozak-Ribbens G, Confort-Gouny S, et al. A noninvasive investigation of muscle energetics supports similarities between exertional heat stroke and malignant hyperthermia. *Anesth Analg.* 2001;93:683–689.
29. Hackl W, Winkler M, Mauritz W, Sporn P, Steinbereithner K. Muscle biopsy for diagnosis of malignant hyperthermia susceptibility in two patients with severe exercise-induced myolysis. *Br J Anaesth.* 1991;66:138–140.
30. Hopkins PM. Malignant hyperthermia: Advances in clinical management and diagnosis. *Br J Anaesth.* 2000;85:118–128.
31. Durham WJ, Racena-Parks P, Long C, et al. RyR1 S-nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knockin mice. *Cell* 2008;133:53–65.
32. Bryson GL, Chung F, Cox R, et al. Patient selection in ambulatory anesthesia: An evidence-based review. Part II. *Can J Anaesth.* 2004;51:782–794.
33. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet J Rare Dis.* 2007;2:21.
34. Larach MG. Standardization of the caffeine halothane muscle contracture test. North American Malignant Hyperthermia Group. *Anesth Analg.* 1989;69:511–515.
35. Litman RS, Rosenberg H. Malignant hyperthermia: Update on susceptibility testing. *JAMA.* 2005;293:2918–2924.
36. Rosenberg H, Antognini JF, Muldoon S. Testing for malignant hyperthermia. *Anesthesiology* 2002;96:232–237.
37. 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;41:955–966.
38. 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;88:579–588.
39. Malignant Hyperthermia Association of the United States. MH muscle biopsy test centers page. Available at: http://www.mhaus.org/index.cfm/fuseaction/Content.Display/PagePK/BiopsyTestCenter.cfm. Accessed May 24, 2008.
40. Sei Y, Sambuughin NN, Davis E, et al. Malignant hyperthermia in North America: genetic screening of the three hot spots in the type I ryanodine receptor gene. *Anesthesiology* 2004;101:824–830.
41. Robinson R, Hopkins P, Carsana A, et al. Several interacting genes influence the malignant hyperthermia phenotype. *Hum Genet.* 2003;112:217–218.
42. Robinson RL, Anetseder MJ, Brancadoro V, et al. Recent advances in the diagnosis of malignant hyperthermia susceptibility: How confident can we be of genetic testing? *Eur J Hum Genet.* 2003;11:342–348.
43. Urwyler A, Deufel T, McCarthy T, West S; European Malignant Hyperthermia Group. Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. *Br J Anaesth.* 2001;86:283–287.
44. Girard T, Treves S, Voronkov E, Siegemund M, Urwyler A. Molecular genetic testing for malignant hyperthermia susceptibility. *Anesthesiology* 2004;100:1076–1080.
45. Malignant Hyperthermia Association of the United States. Molecular genetics test. Available at: http://www.patients.mhaus.org/index.cfm/fuseaction/Content.Display/PagePK/MolGenTestSites.cfm. Accessed June 3, 2008.
46. American Society of Anesthesiologists. Office-based anesthesia guidelines. Available at: http://www.asahq.org/Washington/oba.htm. Accessed June 3, 2008.
47. Rohrich RJ, White PF. Safety of outpatient surgery: Is mandatory accreditation of outpatient surgery centers enough? *Plast Reconstr Surg.* 2001;107:189–192.
48. American Society of Anesthesiologists. Office-based anesthesia: State statutes, regulations and guidelines. Available at: http://www.asahq.org/Washington/rulesregs.htm. Accessed-June 3, 2008.
49. Rohrich RJ. Patient safety first in plastic surgery. *Plast Reconstr Surg.* 2004;114:201–203.
50. Iverson RE; ASPS Task Force on Patient Safety in Office-Based Surgery Facilities . Patient safety in office-based surgery facilities: I. Procedures in the office-based surgery setting. *Plast Reconstr Surg.* 2002;110:1337–1342; discussion 1343–1346.
51. Iverson RE, Lynch DJ. Patient safety in office-based surgery facilities: II. Patient selection. *Plast Reconstr Surg.* 2002;110: 1785–1790; discussion 1791–1792.
52. Horton JB, Reece EM, Broughton G II, Janis JE, Thornton JF, Rohrich RJ. Patient safety in the office-based setting. *Plast Reconstr Surg.* 2006;117:61e–80e.
53. Byrd HS, Barton FE, Orenstein H, et al. Safety and efficacy in an accredited outpatient plastic surgery facility: A review of 5316 consecutive cases. *Plast Reconstr Surg.* 2003;112:636–641; discussion 642–646.
54. American Society of Anesthesiologists. AMA core principles for office-based surgery. Available at: http://www.asahq.org/Washington/coreprinciples.htm. Accessed June 3, 2008.
55. Krause T, Gerbershagen MU, Fiege M, Weisshorn R, Wappler F. Dantrolene: A review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004;59:364–373.
56. Wackym PA, Dubrow TJ, Abdul-Rasool I, Lesavoy MA. Malignant hyperthermia in plastic surgery. *Plast Reconstr Surg.* 1988;82:878–882.
57. Wedel DJ, Quinlan JG, Iaizzo PA. Clinical effects of intravenously administered dantrolene. *Mayo Clin Proc.* 1995;70:241–246.

58. Malignant Hyperthermia Association of the United States. The ABC's of managing malignant hyperthermia. Available at: http://www.mhaus.org/index.cfm/fuseaction/OnlineBrochures.Display/BrochurePK/BCD9151D-3048-709E-5A445BC0808B4767.cfm. Accessed November 5, 2008.
59. Carr AS, Lerman J, Cunliffe M, McLead ME, Britt BA. Incidence of malignant hyperthermia reactions in 2,214 patients undergoing muscle biopsy. *Can J Anaesth.* 1995;42:281–286.
60. Hackl W, Mauritz W, Winkler M, Sporn P, Steinbereithner K. Anaesthesia in malignant hyperthermia-susceptible patients without dantrolene prophylaxis: A report of 30 cases. *Acta Anaesthesiol Scand.* 1990;34:534–537.
61. Malignant Hyperthermia Association of the United States. Emergency therapy for malignant hyperthermia. Available at: http://medical.mhaus.org/PubData/PDFs/treatmentposter.pdf. Accessed May 24, 2008.
62. Hoefflin SM, Bornstein JB, Gordon M. General anesthesia in an office-based plastic surgical facility: A report on more than 23,000 consecutive office-based procedures under general anesthesia with no significant anesthetic complications. *Plast Reconstr Surg.* 2001;107:243–251; discussion 252–257.
63. Baudendistel L, Goudsouzian N, Cote' C, Strafford M. End-tidal CO2 monitoring: Its use in the diagnosis and management of malignant hyperthermia. *Anaesthesia* 1984;39:1000–1003.
64. Harrison GG. Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. 1975. *Br J Anaesth.* 1998;81:626–629; discussion 625.
65. Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. *Anesthesiology* 1982;56:254–262.
66. Paul-Pletzer K, Yamamoto T, Bhat M, et al. Identification of a dantrolene-binding sequence on the skeletal muscle ryanodine receptor. *J Biol Chem.* 2002;277:34918–34923.
67. Ikemoto N, Yamamoto T. Postulated role of inter-domain interaction within the ryanodine receptor in Ca(2+) channel regulation. *Trends Cardiovasc Med.* 2000;10:310–316.
68. Yamamoto T, Ikemoto N. Spectroscopic monitoring of local conformational changes during the intramolecular domain-domain interaction of the ryanodine receptor. *Biochemistry* 2002;41:1492–1501.
69. Kobayashi S, Bannister ML, Gangopadhyay J, Hamada T, Parness J, Ikemoto N. Dantrolene stabilizes domain interactions within the ryanodine receptor. *J Biol Chem.* 2005;280:6580–6587.
70. Murayama T, Oba T, Kobayashi S, Ikemoto N, Ogawa I. Postulated role of interdomain interactions within the type 1 ryanodine receptor in the low gain of Ca2+-induced Ca2+ release activity of mammalian skeletal muscle sarcoplasmic reticulum. *Am J Physiol.* 2005;288:C1222–C1230.
71. Larach MG, Localio AR, Allen G, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994;80:771–779.
72. Sambuughin N, Sei Y, Gallagher K, et al. North American malignant hyperthermia population: Screening of the ryanodine receptor gene and identification of novel mutations. *Anesthesiology* 2001;95:594–599.
73. Anderson AA, Brown RL, Polster B, Pollock N, Stowell KM. Identification and biochemical characterization of a novel ryanodine receptor gene mutation associated with malignant hyperthermia. *Anesthesiology* 2008;108:208–215.
74. Britt BA, Endrenyi L, Frodis W, Scott E, Kalow W. Comparison of effects of several inhalation anaesthetics on caffeine-induced contractures of normal and malignant hyperthermic skeletal muscle. *Can Anaesth Soc J.* 1980;27:12–15.
75. Reed SB, Strobel GE Jr. An in-vitro model of malignant hyperthermia: Differential effects of inhalation anesthetics on caffeine-induced muscle contractures. *Anesthesiology* 1978;48:254–259.
76. Flewellen EH, Nelson TE. Masseter spasm induced by succinylcholine in children: Contracture testing for malignant hyperthermia. Report of six cases. *Can Anaesth Soc J.* 1982;29:42–49.
77. Snoeck MM, Gielen MJ, Tangerman A, van Egmond J, Dirksen R. Contractures in skeletal muscle of malignant hyperthermia susceptible patients after in vitro exposure to sevoflurane. *Acta Anaesthesiol Scand.* 2000;44:334–337.
78. Gallant EM, Godt RE, Gronert GA. Mechanical properties of normal and malignant hyperthermia susceptible porcine muscle: Effects of halothane and other drugs. *J Pharmacol Exp Ther.* 1980;213:91–96.
79. Louis CF, Zualkernan K, Roghair T, Mickelson JR. The effects of volatile anesthetics on calcium regulation by malignant hyperthermia-susceptible sarcoplasmic reticulum. *Anesthesiology* 1992;77:114–125.
80. Nelson TE, Flewellen EH. Rationale for dantrolene vs. procainamide for treatment of malignant hyperthermia. *Anesthesiology* 1979;50:118–122.

Appendix A. Summary of Recommendations

Recommendations	Supporting Evidence	Grade
PATIENT SELECTION		
• During patient assessment, patients should be asked about personal and family history of:	58, 61, 71	D
– MH		
– Adverse anesthesia reactions (unexplained fever or death during anesthesia)		
• Patients with suspected MH should be referred for appropriate diagnostic testing:	37, 38	B
– CHCT or in vitro contracture test is the standard.		
– Genetic testing for mutations in the *RYR1* gene may be considered; however, it typically cannot replace contracture tests, as it has low sensitivity. Results do not always correlate with a positive contracture test, which suggests that there may be other loci involved with MH.	16, 72, 73	B

(*Continued*)

Appendix A. ***(Continued)***

Recommendations	Supporting Evidence	Grade
• Patients susceptible to MH may undergo outpatient surgery, provided that nontriggering anesthetics are used. All office surgical suites should be equipped to manage an MH emergency. However, anyone identified with MH susceptibility should be referred to an accredited ambulatory surgical center or hospital for surgery.	58, 61	D
PREOPERATIVE MANAGEMENT		
• In patients susceptible to MH, *do not use* the following MH-triggering drugs: Inhaled general anesthetics: – Desflurane – Enflurane – Halothane – Isoflurane – Sevoflurane Depolarizing muscle relaxants: – Succinylcholine	74–79	B
• The surgical suite should be equipped to manage malignant hyperthermia. Drugs and supplies should include: – Dantrolene sodium IV (36 vials) – Sterile water for dantrolene reconstitution – Sodium bicarbonate – Furosemide – Dextrose – Calcium chloride – Regular insulin (refrigerated) – Antiarrhythmics – A protocol for treating MH crisis. For additional information on how to treat a malignant hyperthermia crisis, consult the MHAUS documents, *Emergency Therapy for Malignant Hyperthermia* or *The ABC's of MH Management*, both found on the MHAUS web site: http://medical.mhaus.org/.	58, 61	D
ANESTHESIA		
• Local or regional anesthesia and monitored anesthesia care are considered to be safe for individuals susceptible to MH; this includes spinal, epidural, and nerve block anesthesia using local anesthetics (e.g., lidocaine, bupivacaine).	58, 61	D
• General anesthesia can be performed with alternative anesthetic regimens, including barbiturates (e.g., thiopental), propofol, nondepolarizing paralytic agents (e.g., vecuronium) and their reversal agents, nitrous oxide, and opioids (e.g., fentanyl) (anesthesia machine preparation: change circuits, disable or remove the vaporizers, flush the machine at a rate of 10 liters/min for 20 min).	58, 61	D
• If general anesthesia will be used, patients should undergo body temperature and capnographic monitoring.	58, 61	D
INTRAOPERATIVE MANAGEMENT		
• Monitor for clinical signs of MH: – Signs of respiratory acidosis: $ETCO_2$ >55 mmHg, $PaCO_2$ >60 mmHg (with appropriately controlled ventilation); $ETCO_2$ >60 mmHg, $PaCO_2$ >65 mmHg (with spontaneous ventilation); inappropriate hypercarbia and/or tachypnea – Trunk or total body rigidity – Masseter muscle spasm or trismus – Sinus tachycardia; ventricular tachycardia; ventricular fibrillation – Rapidly increasing temperature, or inappropriately increased temperature (>38.8°C); may be a late sign – Signs of muscle breakdown: elevated serum creatine kinase after anesthetics that included succinylcholine (>20,000 IU) or anesthetics without succinylcholine (>10,000 IU); cola-colored urine; excess myoglobin in urine (>60 μg/liter) and serum (>170 μg/liter); blood/plasma/serum K^+ >6 mEq/liter (in absence of renal failure) – Other: arterial base excess <–8 mEq/liter; arterial pH <7.25; rapid reversal of MH signs of respiratory and/or metabolic acidosis with IV administration of dantrolene	58, 61, 71	D

(*Continued*)

Appendix A. (***Continued***)

Recommendations	Supporting Evidence	Grade
• Treatment of MH crisis:		
– Call for help; summon emergency medical service.		
– Patient should be transferred to an acute care facility as soon as possible.		
– Administer dantrolene.	65, 80	B
– Hyperventilate with 100% oxygen.	58, 61	D
– Cool the patient.		
– Check electrolytes, especially potassium.		
– For specific treatment recommendations, consult the MHAUS documents, *Emergency Therapy for Malignant Hyperthermia* or *The ABC's of MH Management*, both found on the MHAUS web site: http://medical.mhaus.org/.		

MH, malignant hyperthermia; CHCT, caffeine-halothane contracture test; IVCT, in vitro contracture test; IV, intravenously; MHAUS, Malignant Hyperthermia Association of the United States; $ETCO_2$, end tidal carbon dioxide; $PaCO_2$, partial pressure of carbon dioxide.