ANESTHESIOLOGY NEWS

Commentary
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Anesthesiologists' Critical Role in Treating Malignant Hyperthermia

Henry Rosenberg, MD
President Emeritus
Malignant Hyperthermia Association of the United States

Chris Heine, MD
Associate Professor
Department of Anesthesiology
Medical University of South Carolina
Charleston
MH Hotline Consultant

Teeda Pinyavat, MD
Associate Professor of Anesthesiology
Division of Pediatric Anesthesiology
Columbia University Medical Center
New York City
MH Hotline Medical Director

Malignant hyperthermia (MH) is a pharmacogenetic disorder well known to anesthesiologists that results in a hypermetabolic response triggered most often by succinylcholine and the potent volatile anesthetics. There are also cases of non–anesthesia-associated MH, often triggered by heat alone.[1] MH is characterized by several symptoms, including sustained muscle contracture, mixed metabolic and respiratory acidosis, hypercarbia, hyperkalemia, hyperthermia, disseminated intravascular coagulation, and high likelihood of mortality if not treated. Beyond the acute phase of illness, we maintain that anesthesia providers should assume the responsibility of guiding MH-affected patients and others through diagnosis and care.



The established approach to managing MH is encapsulated in the four C's mnemonic: control, consult, confirm and communicate.

Step 1: Control

First, the anesthesiologist must control the episode, perhaps by using dantrolene, the only drug effective in treating MH. This drug was produced as a modification of macrodantin by Eaton Pharmaceuticals and quickly approved by the FDA in 1979. In countries lacking dantrolene, death caused by MH is over 50%, demonstrating the drug's importance and efficacy.[2]

Step 2: Consult

The second step in treatment for all cases of MH is consulting other specialties, specifically genetics and neurology. Geneticists can help identify the genetic variants associated with MH, confirming the diagnosis and assessing the risk for family members. Neurologists can assist in evaluating and managing any neuromuscular complications that may arise from MH or its treatment. Because these consultations ensure a comprehensive approach to patient care, addressing both the immediate and long-term implications of the disorder, anesthesiologists should play an active role in connecting patients with MH to these specialties.

Step 3: Confirm

Anesthesiologists should encourage MH diagnosis through genetic testing. Additionally, we believe that anesthesiologists should guide their patients and family members through diagnostic workups to confirm MH susceptibility (MHS) after the acute episode. One test to evaluate MHS is a specific muscle biopsy contracture test, the caffeine-halothane contracture test (known as the in vitro contracture test in Europe). This test is accurate in detecting MHS, but it requires special laboratory facilities and a surgical procedure to harvest muscle in the OR. It is expensive and rarely reimbursed by insurance, and limited availability is another obstacle. Thus, it is not commonly pursued following an MH event, ultimately leaving patients and family members with a critical unknown for any future anesthetics.

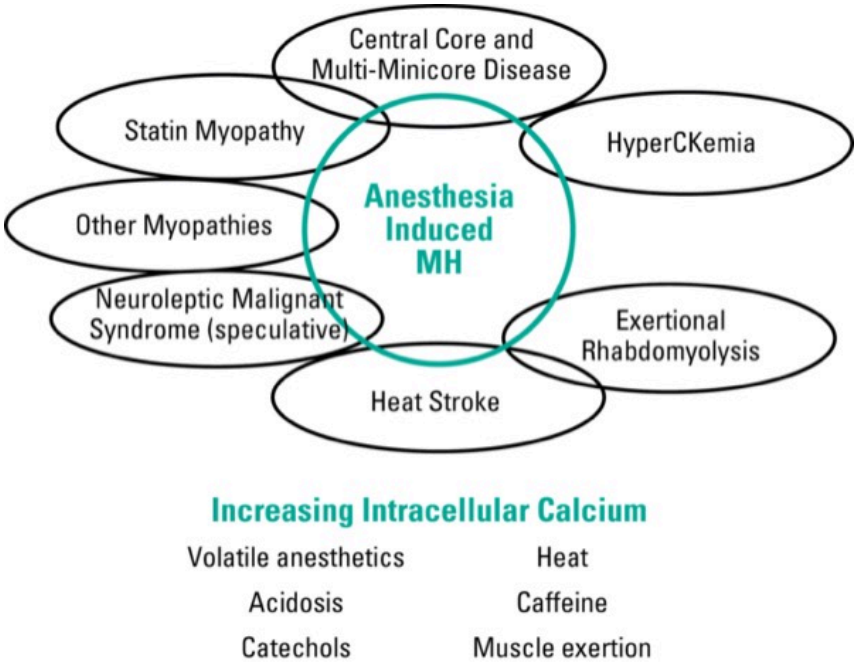


Figure 1. Venn diagram outlining disorders and pharmacologic agents associated with malignant hyperthermia.

With increased access to genetic testing, the contracture test has fallen out of favor. In fact, advances in genetic testing using next-generation sequencing have made genetic testing the first step in laboratory diagnosis for MH in most countries. Based on studies in MH-susceptible swine, many genetic variations predictive of MH were

identified starting in the 1980s. Currently, ClinVar, a National Institutes of Health–funded, publicly accessible database of genetic variants and associated phenotypes, has classified more than 60 DNA variants in three genes underlying MH susceptibility. Thirty variants are considered benign or likely benign, and 219 variants are of unknown significance. Although MH is not a common disorder, recent data show that more than 500,000 people in the United States are likely to be carriers of one of the causative DNA variants.[3] Manifestations of MH pathogenic DNA variants include myopathies, exertional rhabdomyolysis, statin-induced rhabdomyolysis and heat stroke; so, knowing if patients are MHS through genetic testing can help prevent these presentations.[4]

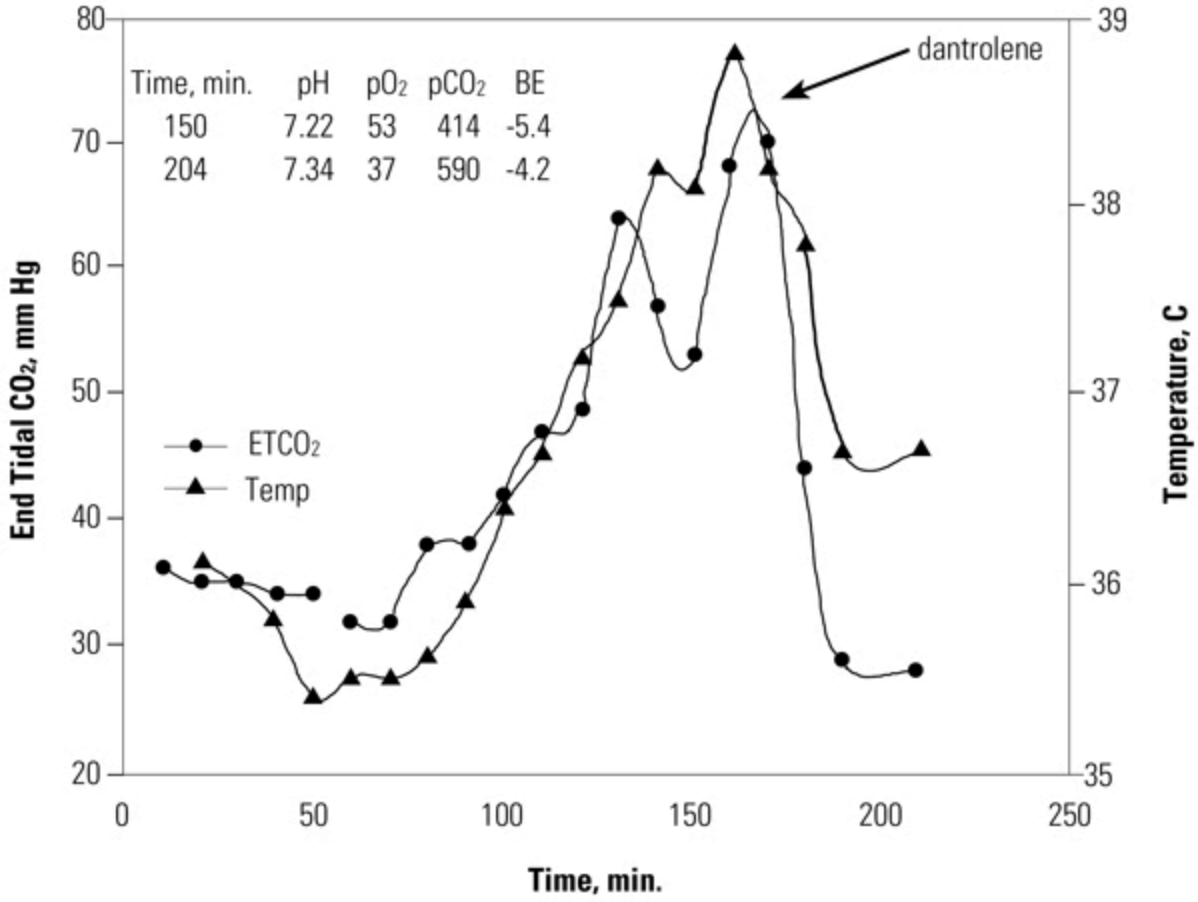


Figure 2. Outline of a malignant hyperthermia episode. Note that end tidal carbon dioxide elevation occurs before temperature elevation. Also note the delay in onset of MH and the prompt response to dantrolene.

Since many primary care physicians are unfamiliar with MH, anesthesia providers must play an active role in not only acute management of MH, but also guiding their patients through the diagnostic workup including genetic testing and follow-up with a geneticist and neurologist. Thus, it is critical for anesthesiologists to be familiar with MH genetic testing, which can be performed quickly, locally and without a surgical procedure, and can cost as little as $250. A list of commercial genetic testing facilities is available on the website of the Malignant Hyperthermia Association of the United States (mhaus.org) or through consultation with genetic counselors, geneticists and pathologists. Although failure to identify a causal variant does not necessarily imply that the patient is not MH-susceptible–as all pathogenic variants have not yet been identified–genetic testing remains an important tool for identifying known variants and guiding further diagnostic and management decisions. Several laboratories in the United States and Europe are working on identifying all pathogenic variants, meaning the accuracy of genetic testing in detecting MHS will improve more with time.

Step 4: Communicate

Information sharing involves anesthesiologists engaging with the patient, their family and other healthcare providers to ensure everyone is informed of the diagnosis and subsequent care plan to prevent future episodes. Communication is essential for patient safety, ongoing management and support. Anesthesiologists should play a key role in this process and provide resources to support the patient and their family, as well as facilitate coordination among the patient's medical team. It is also important for anesthesia providers to report cases to the North American MH Registry of MHAUS (NAMHR.org), a patient database assisting in understanding clinical and genetic presentations of MH. This will help build a comprehensive database that can improve the understanding of MH, facilitate research, and contribute to better clinical guidelines and management strategies.

As the key providers in the identification, treatment and management of MH in the OR and PACU, anesthesiologists must be actively involved in the diagnosis and treatment of MH through the four C's, guiding their patients through the diagnostic workup to include genetic testing and appropriate follow-up with a geneticist and neurologist. Additional resources for anesthesiologists for the clinical management of MH are available through the Malignant Hyperthermia Association website and hotline.

Heine and Rosenberg reported no relevant financial disclosures.

References

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4. RYR1 Foundation. RYR1.org