

Malignant hyperthermia: considerations for the general surgeon

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Malignant hyperthermia is a potentially fatal genetic myopathy that presents when the patient is under anesthesia. It manifests as a hypermetabolic state involving tachycardia, hypercarbia, base deficit, rigidity and fever. Many of the hallmark traits of an acute malignant hyperthermic crisis overlap with signs and symptoms of an emergent abdominal condition. Historically, there has been a reluctance in local community hospitals to manage patients known to be susceptible to malignant hyperthermia, and this is a source of frustration for many families in which there is a history of this condition. This article outlines the diagnosis and management of an acute malignant hyperthermic crisis from the viewpoint of a community general surgeon and provides a review of the management of patients known to be susceptible to this condition in the surgeon's elective and emergent practice.

L'hyperthermie maligne est une myopathie d'origine génétique qui peut être mortelle et survient lorsque le patient est sous anesthésie. Cette myopathie se manifeste par un hypermétabolisme qui entraîne une tachycardie, une hypercarbie, un déficit de base, la rigidité et la fièvre. Beaucoup de caractéristiques d'une crise aiguë d'hyperthermie maligne ressemblent aux signes et aux symptômes d'un problème abdominal émergent. Les hôpitaux communautaires locaux ont toujours hésité à prendre en charge des patients dont la vulnérabilité à l'hyperthermie maligne est reconnue et il s'agit d'une source de frustration pour beaucoup de familles qui ont des antécédents à cet égard. Cet article décrit le diagnostic et la prise en charge d'une crise aiguë d'hyperthermie maligne du point de vue du chirurgien général communautaire et présente une revue de la prise en charge, dans la pratique élective et émergente du chirurgien, des patients dont la vulnérabilité à ce problème est reconnue.

Malignant hyperthermia is a potentially fatal genetic myopathy with autosomal dominant inheritance. It is asymptomatic until triggered by either a non-depolarizing muscle relaxant or potent inhalational vapours used in anesthesia. The incidence of a malignant hyperthermic reaction varies from 1 in 6 000 to 1 in 40 000 anesthetics. This variation in rate is influenced by the increasing availability of anesthetic agents that are safe for use in malignant hyperthermia, and the varying populations across the world. In the past, a fulminant malignant hyperthermic crisis was almost always fatal;

however, mortality is now less than 5%. This decrease is a result of improved education of patients and operating room personnel, improvements in anesthetic monitoring and the availability of dantrolene. Unfortunately for the general surgeon, many of the patients present with an abdominal condition requiring surgical exploration and indications of sepsis, which may cloud the diagnosis of malignant hyperthermia.

Much progress has been made in molecular genetics in regard to malignant hyperthermia. The discovery of the ryanodine receptor gene (*RYR1*) on chromosome 19 is in

close proximity to genetic markers that have been shown to map near the malignant hyperthermia susceptibility locus in humans. Many of the malignant hyperthermia diagnostic centres in North America and in Europe are working in close association with geneticists. There is hope that a blood test or needle biopsy will be developed that will replace the ffeine halothane contracture test, which involves an excisional muscle biopsy.

Pathophysiology

A malignant hyperthermic crisis results from the massive release of cal-

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Accepted for publication Oct. 17, 2001.

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cium from the sarcoplasmic reticulum into the skeletal muscle cell. This is triggered by the muscle relaxant succinylcholine or the use of potent inhalational vapours. Succinylcholine, a depolarizing muscle relaxant, is a favourite induction agent used for patients having a full stomach or an emergent abdominal condition. Succinylcholine is also used when paralysis is needed for inducing anesthesia but the patient will breathe spontaneously on inhalational vapour for the rest of the procedure (e.g., in tonsillectomy). Potent inhalational vapours are used in all anesthetic departments. There are cases in which patients have been referred to our clinic with suspected malignant hyperthermia in the absence of succinylcholine and inhalational vapours, yet the patient was receiving high doses of catecholamines for either cardiogenic or septic shock. Unfortunately, many general surgical patients have fever, tachycardia and base deficits before the induction of anesthesia. Rhabdomyolysis is one of the objective criteria of a malignant hyperthermic crisis; however, it can also occur in septic shock and ethanol intoxication. There may be a significant delay between exposure to the triggering agent and the onset of the crisis. Most cases present intraoperatively, although many cases in patients who are referred for diagnostic testing are diagnosed and the condition treated postoperatively in either the recovery room or the intensive care unit.

Malignant hyperthermia is a hypermetabolic state that is characterized by the following:

- Muscle rigidity
- Tachycardia
- Rising end tidal carbon dioxide
- Hypoxemia
- Hyperkalemia
- Fever
- Evidence of rhabdomyolysis with elevated serum creatine kinase and myoglobinuria
- Arrhythmias

One of the first clues may be muscular rigidity, which may manifest as

tightening of the abdominal wall unresponsive to non-depolarizing skeletal muscle relaxants. The mechanism of action for non-depolarizing muscle relaxants (e.g., pancuronium) is at the neuromuscular junction, whereas the metabolic defect in malignant hyperthermia is an intracellular problem at the sarcoplasmic reticulum. Persistent acidosis and an elevated partial pressure of carbon dioxide despite adequate ventilation should arouse suspicion. Fever is usually a late sign and often unreliable for patients who present with an infectious or inflammatory process.

Masseter muscle rigidity

Masseter muscle rigidity (MMR) is associated with inhalational induction followed by succinylcholine. There are several reviews in the literature on MMR, largely retrospective, in which the occurrence rate ranges between 0.3% and more than 1% in children receiving succinylcholine. It has been suggested that patients with MMR are at increased risk of malignant hyperthermia, and numbers as high as 50% have been quoted. The true incidence is much less than that; however, the degree of risk remains controversial. Patients who have experienced an episode of MMR should be alerted as to the possibility that they are at increased risk of malignant hyperthermia and should be referred to a diagnostic testing centre for further counselling.

Elective management of susceptible patients

The most common presentation of a patient susceptible to malignant hyperthermia is a family history of this disease (Table 1). There are several diagnostic test centres for malignant hyperthermia in North America and Europe that provide the caffeine halothane contracture test. This test involves an excisional muscle biopsy done under regional anesthesia. The fresh muscle fibres are exposed to predetermined concentrations of caf-

feine and halothane. The contracture is measured and compared to an internationally agreed upon standard. The majority of patients with a family history have not undergone formal investigation. The absence of a malignant hyperthermic crisis in the patient's past anesthetic exposures does not imply a nonsusceptible state. Some patients have 2 or 3 anesthetics before their first reaction.

Malignant hyperthermia is an autosomal dominant disorder with variable penetrance. Many patients may have the affected gene but have failed to manifest symptoms under anesthesia. If there is a family history of malignant hyperthermia, the patient should attend a preoperative anesthesia consultation either in an ambulatory or inpatient setting. It is frequently advisable for the surgeons to make a notation "malignant hyperthermia susceptible" on the operating room booking sheet so that ancillary personnel will be able to prepare the operating room for such a patient.

All departments of anesthesia, as well as nursing, should have a policy and procedures manual for the management of malignant hyperthermia, both elective and emergent. It is advisable to have a yearly inservice with operating room nurses to discuss the management of a patient with malignant hyperthermia in an elective setting, as well as resuscitation of an acute malignant hyperthermic crisis.

Preoperative management

Premedication is optional. Preop-

Table 1
Family History and Susceptibility to Malignant Hyperthermia (MH)

Degree of relative	Relationship	Chance of MH susceptibility, %
1st	Parent, sibling, child	50
2nd	Aunt, uncle, niece, nephew	25
3rd	Cousin	12.5

erative administration of dantrolene is rarely needed and is not given at our institution. Select indications for dantrolene preoperatively include patients with a previous life-threatening reaction or rhabdomyolysis requiring dialysis. A baseline serum creatine kinase measurement is helpful. Many patients with malignant hyperthermia have an elevated resting serum creatine kinase level, and this may be confused as evidence of a crisis or perioperative myocardial infarction postoperatively.

If a dedicated apparatus for delivering anesthesia to patients with malignant hyperthermia is not available, use vapour-free tubing, bellows and soda lime. Flush the machine with high gas (oxygen or air) flows for at least 20 minutes before use. The likelihood of a crisis occurring during the use of a trigger-free technique is virtually zero. There are reports in the literature that will describe "stress reactions" in the presence of a trigger-free technique. These reports do not bear close scrutiny and often lack objective measures or documentation of the signs of malignant hyperthermia. The benefits of having patients who are susceptible to malignant hyperthermia managed effectively in their local community far outweighs the theoretic risk of a malignant hyperthermic reaction occurring in the presence of trigger-free anesthetic management. Dantrolene should be immediately available regardless of the choice of anesthetic technique in all patients susceptible to malignant hyperthermia.

Intraoperative management

Monitor temperature continuously in both the axilla and nasopharynx. Avoid succinylcholine and potent inhalational vapours. In the past there has been discussion of stress- or catecholamine-induced malignant hyperthermic reactions. Vasopressors cause hypermetabolism in a pig model. We are aware of rhabdomyolysis occurring in susceptible patients after car-

diac arrest and several rounds of adrenaline. For the general surgeon whose patients may have septic shock and require vasopressors, we advise that patients with septic or cardiogenic shock and a known risk of malignant hyperthermia be managed with vasopressors, being mindful of clinical and laboratory evidence of malignant hyperthermia.

Postoperative management

Monitoring of vital signs, including temperature, should be continuous for at least 4 hours. For the general surgical patient who has had an uncomplicated trigger-free experience, postoperative fever should be reviewed by both the attending physician and the consultant anesthesiologist. It is our standard that for any patient with a temperature greater than 38.5°C, the anesthesiologist on call be informed and review the patient. Once again, the likelihood of a postoperative fever being caused by malignant hyperthermia following a trigger-free protocol is almost zero, but nevertheless the patient should be assessed for symptoms or biochemical evidence of rhabdomyolysis.

Managing an acute crisis

Once a malignant hyperthermic episode is suspected, the anesthesiologist or intensive care unit physician should call for assistance and dantrolene. Surgery, if appropriate, should be abandoned or expediently finished. Assistance can be obtained from intensive care unit or other ancillary hospital personnel. Prompt treatment is necessary to prevent morbidity as follows:

- Discontinue all volatile inhalational agents. Hyperventilate with 100% oxygen at gas flows of at least 10 L/min. If possible use a clean circuit but do not delay other treatments to change circuits.
- Delegate an assistant to mix the dantrolene. Rapidly administer dantrolene, an initial dose of 2 to

3 mg/kg with supplemental increments up to 10 mg/kg. Use a central venous line because dantrolene may cause venous thrombosis. Absence of a central line should not delay therapy; administer the drug peripherally until a central line is obtained. Each bottle of dantrolene contains 20 mg of dantrolene and 3 g of mannitol and reconstitutes with 60 mL of sterile water. Continue to administer dantrolene until signs of malignant hyperthermia (hypercarbia, rigidity, tachycardia and fever) are controlled. Doses in excess of 10 mg/kg have been used. Dantrolene can cause profound weakness and will delay the patient's time to extubation.

- Administer bicarbonate to correct the metabolic acidosis as guided by blood gas analysis.
- Treat hyperkalemia with correction of the acidosis as well as insulin with dextrose and hyperventilation.
- Arrhythmias, usually ventricular, result from hyperkalemia with acidosis. The arrhythmias will resolve if the hyperkalemia is controlled. If they persist, despite correction of the underlying cause treat with anti-arrhythmic agents that are appropriate for the abnormal rhythm. Calcium channel blockers are contraindicated in the presence of dantrolene, as they will cause a synergistic negative inotropic effect.
- Anticipate renal failure secondary to rhabdomyolysis. Maintain an hourly diuresis of greater than 2 ml/kg. This is facilitated by the mannitol in the dantrolene vial; additional administration of furosemide may be desirable.

Although the patient is having a potentially fatal reaction to anesthesia, you will still have to maintain anesthesia with intravenous techniques, which may include the administration of propofol, benzodiazepines and narcotics.

Postcrisis management

Keep the patient in the intensive care unit for at least another 24 to 48 hours. Recrudescence of a malignant hyperthermic crisis can occur and should be treated as follows:

- Administer boluses of dantrolene 1 mg/kg intravenously every 6 hours for 48 hours. Use dantrolene orally in extubated patients.

Perform serial arterial blood gas determinations and measure serum electrolytes, creatine kinase and urine myoglobin levels. We measure the serum creatine kinase level every 4 to 6 hours and check urine for myoglobin daily.

The differential diagnosis of ma-

lignant hyperthermia includes sepsis, thyroid storm and catecholamine secreting tumours. Once the patient is admitted to the intensive care unit draw samples for culture and test for endocrinopathies. Occasionally patients labelled as having a malignant hyperthermic crisis have been found to have a pheochromocytoma or a positive blood culture.

Family counselling should be carried out through the department of anesthesia or regional malignant hyperthermia diagnostic centre. Both the Malignant Hyperthermia Association of Canada and the Malignant Hyperthermia Association of the United States provide educational literature on the management of patients with this disease.

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REVISED:

- Guideline 5: The management of ductal carcinoma in situ (DCIS) [Oct. 2, 2001]
- Guideline 7: Adjuvant systemic therapy for women with node-negative breast cancer [Jan. 23, 2001]
- Guideline 8: Adjuvant systemic therapy for women with node-positive breast cancer [Mar. 6, 2001]
- Guideline 10: The management of chronic pain in patients with breast cancer [Oct. 30, 2001]

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- Guideline 11: Lymphedema [Jan. 23, 2001]
- Guideline 12: Chemoprevention of breast cancer [June 12, 2001]
- Guideline 13: Sentinel lymph node biopsy [July 24, 2001]
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