

Chapter 29

MALIGNANT HYPERTHERMIA

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INTRODUCTION

Despite screening efforts to remove them from combat roles, soldiers who are susceptible to malignant hyperthermia will be deployed to the battlefield. A soldier may be unknowingly susceptible, or may have a first-degree relative who has been diagnosed since the soldier arrived in the combat theater. Rarely, the soldier may have concealed his or her susceptibility.

The diagnosis and treatment of malignant hyperthermia in the combat environment differs from that during peacetime. Peacetime care relies on heightened awareness, capnographic monitoring, and a readily available supply of dantrolene (the

specific agent for the prevention and treatment of malignant hyperthermia). This combination has reduced fatal outcomes to 2% to 3%.¹⁻⁴ The management of malignant hyperthermia in combat must rely on diagnosis and treatment in light of the available resources. Therefore, to approach this level of success on the battlefield, heightened awareness and increased vigilance, rather than the availability of advanced monitors, must be emphasized. Although all efforts will be made to provide the most advanced equipment available, this equipment may not always perform optimally in a hostile environment.

CLINICAL SYNDROME

Fulminant Malignant Hyperthermia

Malignant hyperthermia is a pharmacogenetic disorder of skeletal muscle metabolism that is expressed as a broad clinical spectrum. The term malignant hyperthermia is most commonly used to refer to a fulminant presentation that begins at the time of an anesthetic induction, but the spectrum also encompasses episodes that develop later in the anesthetic course and progress less rapidly.

Masseter muscle rigidity, which occasionally progresses to fulminant malignant hyperthermia, and less well-defined or documented entities (ie, stress or exercise-induced hyperthermic responses) are also included in the spectrum. When the susceptible patient is anesthetized with triggering agents, the fulminant episode presents as tachypnea and tachycardia that can rapidly progress to arrhythmias, muscle rigidity, and high fever. Rhabdomyolysis can lead to myoglobinuria, acute renal failure, and disseminated intravascular coagulation. Death results from arrhythmias, inability to ventilate, cardiovascular collapse, or brain damage.

A fulminant malignant hyperthermia episode can occur at induction, hours into a stable anesthetic, in the recovery room, or on the ward. The rate of progression varies from minutes to hours, and appears to be independent of the time of onset. The clinical signs reflect the body's inability to respond to an extraordinary increase in metabolic demand. When the demand can no longer be sustained, organ-system failure occurs and accelerates the syndrome. The ability to recognize the clinical syndrome is complicated by (a) its rare occurrence,

(b) the lack of a noninvasive screening test, and (c) the well-known fact that 50% of patients with fulminant episodes will have had at least one previous, uneventful exposure to triggering agents. Although contracture testing with halothane and caffeine has been useful in predicting malignant hyperthermia susceptibility in humans, this test is unacceptable for general screening due to (a) the complexity of the testing conditions and (b) its invasiveness (the testing requires a skeletal muscle biopsy). For the same reasons, contracture testing has no place in the management of an acute episode of malignant hyperthermia. In addition, like all other diagnostic tests, it is not 100% sensitive or specific. A detailed discussion of halothane and caffeine contracture testing follows later in this chapter.

Potent inhalational anesthetics and succinylcholine can initiate the malignant hyperthermia syndrome in susceptible individuals. Factors that may influence the onset include

- the patient's genetic predisposition,
- stress,
- trauma,
- the potency and dosage of the triggering agent, or
- the presence of nondepolarizing neuromuscular blocking agents or other nontriggering anesthetics in the anesthetic technique.

Although the exact site (or sites) for the initiation of the syndrome is still unknown, data on human subjects and swine document that aerobic and anaerobic metabolism in skeletal muscle increase

very early in the clinical syndrome.⁵ Elevations in carbon dioxide and lactic acid production in the muscle cause both a decrease in venous pH and an increase in venous carbon dioxide content.⁶ The sympathetic nervous system responds to this hypermetabolic state with a massive release of catecholamines, which increases minute ventilation and cardiac output. Tachycardia and blood pressure elevations appear early. Tachypnea is also an early sign in patients who are allowed to ventilate spontaneously; however, this sign is often masked in controlled ventilation with muscle relaxation (the current clinical practice). In this setting, elevation of the end-tidal carbon dioxide is the earliest clinically detectable sign of the syndrome.

Once metabolic demand exceeds the body's ability to compensate, core temperature begins to rise because the body is no longer able to dissipate the heat generated from the skeletal muscle. Temperature can increase more than 1°C every 15 minutes; however, this rate will vary depending on conditions such as the ambient temperature, site and size of the surgical incision, and measures of heat preservation employed for the patient.

In a review of cases published in 1970, (prior to the discovery of dantrolene therapy) muscle rigidity was found in 70% of the patients.⁷ The progression of muscle rigidity usually parallels the progression of the clinical syndrome and can interfere with perfusion and with ventilation. Less frequently, severe rigidity can occur immediately after the administration of succinylcholine, and has been associated with profound fasciculations. Alterations in skeletal muscle membrane permeability lead to elevations in serum potassium, sodium, calcium, phosphate, myoglobin, and creatine kinase (CK, formerly called creatine phosphokinase [CPK]).⁸

Ventricular arrhythmias result from hypoxia, hyperkalemia, severe acidosis, or increased catecholamine release. Although patients can appear cyanotic, mottled, or their blood can appear dark in the surgical field, arterial blood-gas analysis rarely identifies gross hypoxia. Peripheral vasoconstriction and decreasing cardiac function probably account for regional hypoperfusion, which compounds the metabolic disorder. Without prompt treatment, death is inevitable if the syndrome has progressed to this point. Even after treatment, the patient is at risk for recrudescence of the syndrome for up to 24 hours.⁹

Masseter Muscle Rigidity

Trismus, masseter muscle spasm, and masseter muscle rigidity all describe rigidity of the jaw

muscles after the administration of succinylcholine. This transient phenomenon occurs despite flaccid paralysis of the extremities. Tachycardia, ventricular arrhythmias, and elevations in end-tidal carbon dioxide are common. Discontinuing the triggering agents usually permits an uneventful recovery; however, progression to the fulminant episode can begin immediately. More commonly, progression to the fulminant episode develops 20 to 30 minutes after the resolution of masseter muscle rigidity. Therefore, monitoring for the syndrome should continue during this period. Serum creatine kinase levels, which peak 8 to 12 hours after induction, will be elevated (5,000–10,000 international units) and can be markedly elevated especially if a second dose of succinylcholine was administered. Patients should be monitored postoperatively for the resolution of rhabdomyolysis and myoglobinuria to decrease the risk of renal complications.

The incidence of masseter muscle rigidity progressing to the fulminant episode is unknown, and until this question is answered, induction techniques that are closely associated with the development of masseter muscle rigidity should be limited. The incidence of masseter muscle rigidity following an intravenous induction is greatly reduced compared to that seen with inhalational induction.¹⁰ Therefore, the use of intravenous succinylcholine following induction with a potent inhalational agent should be avoided.¹¹ If an inhalational induction is required, intubation can be accomplished with a short-acting, nondepolarizing muscle relaxant or by deepening the level of anesthesia. In situations when rapid airway control is mandatory, no other muscle relaxant can match succinylcholine's combination of rapid onset and short duration of action. The onset time of nondepolarizing muscle relaxants can be decreased by doubling or tripling the recommended dose for intubation, but this markedly prolongs the duration of action. Before nondepolarizing muscle relaxants are administered in this fashion, four factors must be considered:

1. the plan of action if ventilation is not improved following adequate muscle relaxation,
2. the resources available for mechanical ventilation in the postoperative period,
3. the number of soldiers requiring surgical procedures, and
4. the length of the anticipated surgical procedure.

Although masseter muscle rigidity was originally described as an early sign of malignant hyper-

thermia, the validity of this idea and the operating room management of this condition are being re-evaluated.¹²⁻¹⁴ The following facts have become accepted:

1. Although masseter muscle rigidity can follow both intravenous and inhalational inductions, it is far more likely in the latter (1:4,000 vs 1:100).^{10,15,16}
2. Most of the data concerning masseter muscle rigidity is in the pediatric population, presumably because inductions with inhalational anesthetics are more frequent in children.
3. In vitro halothane and caffeine contracture testing (discussed later in this chapter) is positive for malignant hyperthermia after clinical masseter muscle rigidity in approximately 50% of pediatric patients and 25% of adult patients.¹⁷⁻¹⁹
4. Succinylcholine transiently increases the basal tension of masseter muscles, possibly by a mechanism similar to its action on extraocular muscles. The relationship between this modest increase in tension and masseter muscle rigidity or malignant hyperthermia is unknown.^{20,21}

Why the incidence of masseter muscle rigidity is more common after an inhalational induction remains elusive. Because inductions with inhalational anesthetics are rare in adults, it is unknown if the incidence in this population is the same as in children, or if age is a factor. Reporting slight increases in masseter tension as actual instances of masseter muscle rigidity may account for some of the disparity; however, data from one hospital center that examined 42,000 children showed a 10-fold

increase in masseter muscle rigidity following induction with inhalational anesthetics (1:370) versus induction with intravenous agents (1:3,879).¹⁰ When the incidence of masseter muscle rigidity following induction with inhalational anesthetics is applied to halothane and caffeine contracture data, the incidence of masseter muscle rigidity continues to be markedly higher than the currently accepted incidence of malignant hyperthermia (1:370 • 50% = 1:740). Once the role that inhalational agents or endogenous catecholamines play in sensitizing the masseter muscles is determined, we may have a better understanding of the physiology of this phenomenon. Until then, patients with marked increases in jaw tension (ie, the anesthesia provider is unable to open the patient's mouth) should be identified and treated as susceptible to malignant hyperthermia.

Stress-Induced Malignant Hyperthermia

In susceptible swine breeds, the malignant hyperthermia syndrome can be triggered by environmental stresses that include heat, exercise, fear, and excitement. These stresses have occasionally been implicated in humans, but convincing and complete data are hard to obtain.²²⁻²⁵ Malignant hyperthermia triggered by combat stress has not been reported. Patients who are identified as susceptible to malignant hyperthermia—either by clinical episode or by contracture testing—but who have no history of an adverse reaction to stress are not likely to experience an adverse reaction to stress in the future. Activity need not be limited in this group, although patients must avoid the triggering anesthetics. If a susceptible patient has experienced a reaction to stress, that stress and similar stresses should be avoided or approached with caution.

BATTLEFIELD RESOURCES

Combat anesthesia depends on both the battlefield environment and the supply of anesthetic equipment on the battlefield. Sophisticated techniques can be performed even under austere conditions with a basic minimum of equipment (Exhibit 29-1).²⁶ As new advances in anesthetic management occur, the specific equipment will change; however, the principle of optimizing care with limited resources will not change. To achieve the goals of early diagnosis and treatment of malignant hyperthermia, the monitors that are available at each level will be evaluated. Achieving this goal will reduce the morbidity and mortality of

malignant hyperthermia patients and therefore will reduce the amount of resources devoted to their postoperative care. Clinical suspicion is the cornerstone for detecting malignant hyperthermia in any environment. This section will also include a discussion of the role of the clean anesthesia machine, the malignant hyperthermia cart, and laboratory testing.

Levels of Equipment Availability

The signs of malignant hyperthermia can present in almost any order or combination. However, the

EXHIBIT 29-1**LEVELS OF EQUIPMENT AVAILABILITY****Equipment Level 1**

Ohio 885A Field Anesthesia Machine
 Ohmeda Universal Vaporizer Portable Anesthesia System
 Pulse oximeter
 Basic blood pressure monitoring equipment
 Blood-warming and -delivery system
 Oxygen source
 Fundamental airway and ventilation equipment including suction
 Intravenous fluid administration equipment
 Intravenous and inhalation drugs

Equipment Level 2

All equipment included in equipment level 1, plus:
 Temperature-monitoring device
 Automatic pneumatic blood pressure device
 Electric or compressed gas-driven ventilator
 Blood autotransfusion equipment

Equipment Level 3

All equipment included in equipment levels 1 and 2, plus:
 Capnograph
 Invasive blood pressure monitor
 Electrocardiograph

Adapted from Condon BC, Temo JM, Crowl FD, et al. Anesthesia guidelines. In: Bellamy RF, ed. *Combat Casualty Care Guidelines: Operation Desert Storm*. Washington, DC: US Department of the Army, Office of The Surgeon General, and Borden Institute; 1991: 24.

progression of the syndrome usually follows a general pattern (Table 29-1). Because the scope and availability of laboratory facilities will vary, laboratory signs will be discussed later in this section. When only the first level of equipment is available, early diagnosis involves the recognition that non-specific signs (ie, an elevated heart rate and blood pressure) are out of proportion to the expected condition. If the patient is breathing spontaneously (mechanical ventilators are not included at this level), tachypnea will probably be the earliest sign. Rhythm irregularities can be detected by the pulse oximeter and confirmed with a finger on the pulse. Skeletal muscle rigidity may be detected by

- masseter muscle spasm at the time of intubation,
- increasing difficulty with ventilation, or
- the surgeon's complaint of inadequate muscle relaxation.

Late signs will include an elevated temperature detected by touch or by warm carbon dioxide-absorption canisters, the exhaustion of carbon dioxide canisters (indicating increased carbon dioxide production), or dark blood on the surgical field (indicating a relative hypoxia).

Additional equipment at the second level of availability includes automated blood pressure- and temperature-monitoring devices. Due to high levels of ambient battlefield noise (like those experienced during Operation Desert Storm), the automated blood pressure device may be the only reliable, noninvasive means for monitoring blood pressure. Although the temperature monitor provides objective data, its usefulness in diagnosing malignant hyperthermia is limited: elevated temperature is a *late* sign.

Additions at the third level of equipment availability include capnographic and electrocardiographic monitoring. The capnograph identifies one of the earliest signs of the syndrome and is easily applied to any anesthetic procedure. This combination makes it an ideal monitor for the detection of malignant hyperthermia. Changes in venous blood-gas analysis, serum lactate, oxygen consumption, and cardiac output also occur very early in the syndrome; but these changes cannot be detected, continuously monitored, or easily applied to the battlefield with current monitoring technology. Although pulse oximetry can alert the clinician to ongoing arrhythmias, electrocardiographic monitoring is needed for identifying and treating complex arrhythmias. Electrocardiography can also be useful in detecting changes in serum potassium levels.

The Clean Anesthesia Machine

A *clean* anesthesia machine is one that either (a) has never been used to administer a potent inhalational agent or (b) has been made safe for use with malignant hyperthermia-susceptible patients. This item may be taken for granted in most operating suites in the continental United States, but it is not included in the equipment provided at any of the three levels of equipment availability. Three steps are required to create a clean anesthesia machine from one that has already been exposed to potent

TABLE 29-1
DETECTING CLINICAL SIGNS OF MALIGNANT HYPERTHERMIA AT EACH LEVEL
OF EQUIPMENT AVAILABILITY

Signs of Malignant Hyperthermia in Common Order of Progression (top = early; bottom = late)	Equipment Level 1	Equipment Level 2*	Equipment Level 3†
Increased CO ₂ production and/or minute ventilation	Tachypnea Hot or expired CO ₂ canister		Capnograph
Increased O ₂ consumption	Dark blood on surgical field		
Increased cardiac output			
Increased pulse	Stethoscope Palpation Pulse oximeter		ECG
Increased blood pressure	Manual cuff	Automated cuff	Invasive monitoring
Arrhythmias	Palpation Pulse oximeter		ECG
Rigidity	Touch Ventilation difficulties		
Temperature elevation	Touch Hot CO ₂ canisters	Temperature monitor	

*Includes means available in Level 1

†Includes means available in Levels 1 and 2

inhalational anesthetics. First, because the rubber parts of anesthesia machines will retain potent inhalational anesthetics, the fresh gas hose, ventilator bellows, and circuit (if nondisposable) must be replaced with new or disposable parts. Second, the machine must be flushed with a high fresh gas flow (10 L/min) for 10 minutes. Finally, the vaporizers should be removed or drained to prevent any possibility that they will be turned on during the perioperative period. A nonrebreathing system (eg, the Mapleson or Jackson-Rees anesthesia breathing circuits) can also serve as a clean anesthesia machine when attached to an oxygen source with adequate fresh gas flow.

The Malignant Hyperthermia Cart

The rationale for a malignant hyperthermia cart is to have the supplies required for treatment of malignant hyperthermia assembled and ready so the response time for treatment of an episode can be

decreased (Table 29-2). Supplies and medications available for anesthetists are found in two medical material sets (MMSs, which are discussed in Chapter 6, Deployable Hospitals): MMS D301, Operating Room, and MMS D306, Pharmacy. Recommendations are under study to create a separate MMS for anesthesia equipment and medications. Currently, MMS D301 contains six vials of dantrolene (20 mg per vial), lidocaine, calcium chloride, epinephrine, and sodium bicarbonate. Because the average adult requires 160 to 200 mg of dantrolene at the beginning of treatment, coordination with the pharmacy will be necessary to ensure the smooth and rapid administration of the initial dose. An additional 30 vials of dantrolene are contained in MMS D306, along with procainamide, dextrose 50%, insulin, mannitol, furosemide, and sterile water. The current supply of sterile water is contained in 5-mL vials (60 mL of sterile water is required to dissolve each vial of dantrolene). Therefore, another recommendation has been made to include two 500-mL

TABLE 29-2
SUPPLIES FOR MALIGNANT HYPERTHERMIA CART

Supply	Quantity	Purpose
Dantrolene	At least 36 vials	—
Sterile water for injection	3 L	Reconstitution of dantrolene
50-mL syringes and large-gauge needles	12	Draw up dantrolene
Lidocaine	5 ampules	Bolus and continuous infusion
Procainamide	5 ampules	Bolus and continuous infusion
Dextrose 50%	4 ampules	Treatment of hypokalemia
Mannitol 25%	100 g (8 ampules)	Renal protection
Furosemide	200 mg	Renal protection
Sodium bicarbonate	50 meq (10 ampules)	Treatment of metabolic acidosis
Epinephrine	1 mg (4 ampules)	Treatment of hypotension
Calcium chloride 10%	4 ampules	Treatment of hyperkalemia
Normal saline (refrigerated)	6 L	For injection and irrigation

Also included on the cart: crushed ice or ice maker, irrigating Foley catheter, rectal tube, cooling blanket, central venous access kits, pulmonary artery catheter, new fresh gas hose, carbon dioxide-absorption canisters, anesthesia breathing circuit, ventilator bellows, blood-collection tubes, lab slips, labels

bags of sterile water to MMS D301 and four 500-mL bags of sterile water to MMS D306 for more-rapid mixing of dantrolene.

Laboratory Testing

Laboratory tests that aid in making the diagnosis include

- arterial and venous blood-gas analyses;
- serum potassium, glucose, sodium, and calcium;
- prothrombin and partial thromboplastin times;

- serum creatine kinase; and
- serum and urinary myoglobin.

Laboratory support will be crucial in confirming the diagnosis of malignant hyperthermia and in managing advanced cases. Severe metabolic and electrolyte disturbances require frequent laboratory analyses in both the initial treatment and the recovery phases. The most valuable tests of the initial treatment phase are the arterial blood-gas analyses and serum potassium levels, while serum creatine kinase and myoglobin levels are useful in preventing renal damage in the recovery phase.

BATTLEFIELD MANAGEMENT

Early recognition of the syndrome, discontinuation of the triggering agent or agents, rapid administration of dantrolene, and prompt initiation of supportive care are the four cornerstones of successful management. It is unlikely that the coordination of this complex process will progress smoothly unless a plan has already been discussed and implemented. Although the Malignant Hyperthermia Hotline [(800) 644-9737] is theoretically available for assistance in the management of suspected cases, communication linkage to this resource from the battlefield is doubtful. The management of the patient with a fulminant episode,

masseter muscle rigidity, and a history of malignant hyperthermia needs to be considered in light of these constraints.

A Fulminant Episode

Treatment of a fulminant malignant hyperthermia episode requires that two distinct approaches be initiated simultaneously: (1) preparation and administration of dantrolene sodium, and (2) initiation and maintenance of supportive care. Assistance from other medical personnel is essential if these tasks are to be completed rap-

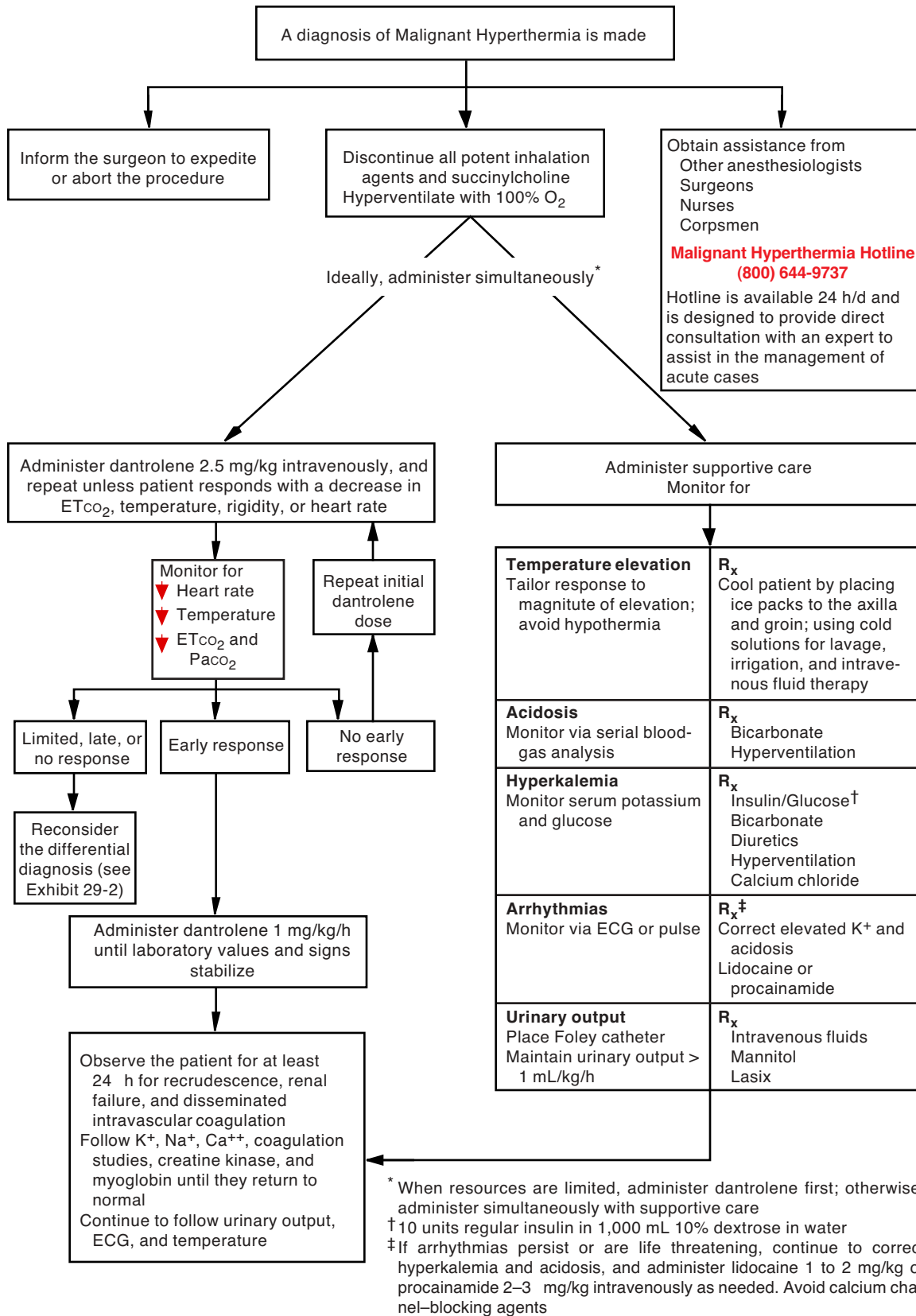


Fig 29-1. Management of a patient with fulminant malignant hyperthermia. The Malignant Hyperthermia Hotline should be contacted as soon as possible after the working diagnosis is made.

idly and with the recommended priority (Figure 29-1). If another anesthesia provider is unavailable, an operating room nurse or technician or a surgeon can assist.

Potent inhalational agents and succinylcholine infusions must be stopped and the patient hyperventilated with 100% oxygen at high rates of flow. These two actions will limit the patient's exposure to the triggering agents and enhance the elimination of the inhaled agents. Switching to a clean anesthesia machine will further enhance the elimination of inhaled agents; however, this task is usually difficult, time-consuming, and unnecessary. In less severe cases, or in brief exposures, these two actions may be adequate to stop the syndrome. In severe cases, even vigorous manual ventilation cannot return carbon dioxide levels to normal. Even if the syndrome is halted with supportive care alone, the administration of dantrolene is still recommended because resources for observation in an intensive care unit may be extremely limited.

Dantrolene Therapy

Intravenous administration of dantrolene (2.5 mg/kg) is recommended, as dantrolene not only reverses the episode but also decreases the postoperative complications. Myocardial depression or severe rigidity can lead to inadequate muscle perfusion and therefore limit the delivery of the drug to its site of action.²⁷ If the patient does not respond to the first bolus, additional doses should be administered until decreased carbon dioxide, temperature, rigidity, and heart rate have been achieved. Once the acute episode is controlled, dantrolene should be continued at 1 to 2 mg/kg/h for a minimum of 2 hours, or until the clinical and laboratory signs have returned to baseline (with the exception of creatine kinase and myoglobin).

Dantrolene is supplied in a lyophilized form and has a shelf life of 3 years. It is reconstituted with sterile water (50 mL for each 20-mg vial) due to its high osmotic content. Dantrolene is almost insoluble in water, but the manufacturer's addition of mannitol (3 g) and sodium hydroxide to each vial has rendered the drug soluble and therefore preparation time has been reduced to 2 to 3 minutes. The pH of the reconstituted solution is 9.5; therefore, dantrolene should be administered in a large vein to decrease the risks of thrombophlebitis and tissue necrosis from extravasation.

Dantrolene is the most effective treatment for both arrhythmias and elevated temperatures because it reverses the abnormal metabolic state.

Arrhythmias result from the combination of hypoxia, acidosis, hyperkalemia, hypercarbia, and elevated endogenous catecholamines. Lidocaine (1–2 mg/kg) or procainamide (2–3 mg/kg) should be administered as needed for persistent or life-threatening arrhythmias. If control of heart rate is necessary, short-acting β -adrenergic blocking agents should be used instead of calcium channel-blocking agents. (Hyperkalemic cardiovascular collapse has been reported with the combination of dantrolene and calcium channel-blocking agents.^{28,29})

Recrudescence

After an adequate clinical response, tachycardia may return as the patient emerges from the anesthetic. A titration of narcotics or benzodiazepines is useful in this situation. Recrudescence of the syndrome is managed with the same urgency as the original episode. Recrudescence has occurred up to 24 to 30 hours later; therefore, continued monitoring in the postoperative period is advocated.⁹ If the patient fails to respond or only partially responds to appropriate therapy, then treatment of malignant hyperthermia should continue but other diagnoses should be considered (Exhibit 29-2). Pheochromocytoma and thyroid storm mimic malignant hyperthermia and can be confused with malignant hyperthermia crises.

EXHIBIT 29-2

DIFFERENTIAL DIAGNOSIS OF MALIGNANT HYPERTHERMIA

Hypoxia
Hypercarbia
Sepsis
Light anesthesia
Thyroid storm
Pheochromocytoma
Drug reaction
Cocaine toxicity
Intracranial trauma
Neuroleptic malignant syndrome
Hypoxic encephalitis
Factitious malignant hyperthermia
Iatrogenic hyperthermia

Therapeutic Cooling

Lowering the patient's temperature reduces oxygen consumption and prevents brain injury. Core cooling, which is more effective than surface cooling, is accomplished by using refrigerated solutions for gastric and rectal lavage, wound irrigation, and intravenous infusion. Surface cooling is more effective when ice packs are placed in the groin and axilla. Drastic cooling of the room or placing the patient in an ice bath may actually be counterproductive, as they will induce shivering and vasoconstriction. Once the patient's temperature is controlled, continued monitoring is necessary to detect hypothermia or recrudescence of the syndrome.

Acid-Base Disturbances

Serial measurements of arterial blood gases are essential for assessing and correcting the metabolic and respiratory acidoses as well as in evaluating the effectiveness of therapy. Overaggressive bicarbonate therapy risks severe alkalosis and requires additional ventilation to eliminate the excess carbon dioxide produced. During rapid ventilation, a stable plateau phase may be impossible to obtain on the capnogram. Therefore, blood-gas analysis is necessary to validate the accuracy and trend of the capnograph. Finally, arterial blood-gas analyses can be used to determine oxygen consumption if cardiac output and mixed venous oxygen are known.

Hyperkalemia

The most life-threatening serum abnormality is hyperkalemia. It results from leakage out of damaged muscle cells and from acidosis when a hydrogen ion is exchanged for a potassium ion. This abnormality should be corrected with glucose, insulin, and bicarbonate therapy. Hypokalemia can follow the initial hyperkalemia; therefore, frequent measurements of serum potassium and glucose are required. Currently, calcium therapy is reserved for life-threatening arrhythmias or inotropic support, as it may increase intracellular calcium levels through calcium-induced calcium release. Hypocalcemia, which is common and detected on the electroencephalogram as a prolongation of the QT interval, is refractory to calcium therapy. Changes in phosphate, sodium, and chloride may also occur and usually correct with control of the syndrome.

Late Complications

Late complications include renal failure, disseminated intravascular coagulation, and neurological deficits. Reversal of these complications is difficult and frequently not possible; therefore, early diagnosis and treatment are essential to limit or prevent damage. Renal protection is achieved by maintaining urinary output at 1 to 2 mL/kg/h and should continue until urinary myoglobin has cleared and creatine kinase levels have peaked. Central venous pressure monitoring can be helpful in guiding this therapy. Creatine kinase and urinary myoglobin elevations usually peak 12 to 24 hours after the event, and should be followed every 8 hours until they approach baseline. They reflect the destruction of skeletal muscle and leakage of enzymes from intact skeletal muscle cells, possibly due to increased intracellular osmotic pressure.³⁰ Continued elevation of these parameters can indicate a partially treated case or recrudescence of the syndrome. Disseminated intravascular coagulation results from hemolysis, released tissue thromboplastin, and hypoperfused tissue. Serial laboratory evaluation of prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products will help to identify this complication before clinical signs appear. Treatment of disseminated intravascular coagulation in malignant hyperthermia is managed as it is from any other source. Neurological complications include delayed awakening (possibly due to cerebral edema) and permanent neurological deficit secondary to hypoxia or hypotension.

Masseter Muscle Rigidity

When an anesthetized patient is found to have masseter muscle rigidity, the anesthesia provider has three treatment options:

1. Cancel the operation.
2. Continue the operation but convert to a nontriggering anesthesia technique.
3. Continue the operation as planned.

The differential diagnosis of a "stiff jaw" must also be considered and ruled out (Exhibit 29-3). The status of the patient, the estimated length of the surgery, the resources available to initiate and sustain treatment of a fulminant episode, and the anesthesia provider's own familiarity with the treatment of malignant hyperthermia must all be considered. The conservative approach, option 1, is to stop the anesthetic, observe for signs of ma-

EXHIBIT 29-3**DIFFERENTIAL DIAGNOSIS OF MASSETER MUSCLE RIGIDITY**

Inadequate skeletal muscle relaxation
 Temporomandibular joint disease
 Myotonia congenita
 Abnormal physiological response to succinylcholine

lignant hyperthermia and renal dysfunction, identify the patient as susceptible to malignant hyperthermia, and return to the operating room another day with a nontriggering anesthetic.^{1,3} This approach is supported by the facts that (a) morbidity and mortality continue to be associated with malignant hyperthermia and (b) the anesthesia provider cannot predict the severity or progression of the syndrome once masseter muscle rigidity is identified. Discontinuing the anesthetic is the safest approach in the face of limited resources, but will not be possible when the surgery is life or limb saving. When surgery must be performed, convert to a nontriggering technique, administer dantrolene 2.5 mg/kg, maintain adequate urinary output, and proceed with the surgery with heightened vigilance.

In options 2 and 3, surgery is permitted to proceed even when it is not emergent. Clinical malignant hyperthermia only infrequently follows masseter muscle rigidity; therefore, the argument can be made that the operation can continue as long as the anesthesia provider is equipped to monitor for malignant hyperthermia and to treat it if the syndrome occurs. Supporters of option 2 believe that masseter muscle rigidity is part of the spectrum of malignant hyperthermia; therefore, they convert to a nontriggering technique to prevent further exposure.² The patient is (a) identified as susceptible to malignant hyperthermia and (b) administered only nontriggering anesthetics for future surgeries. Supporters of option 3 do not believe that masseter muscle rigidity is part of the spectrum of malignant hyperthermia.^{10,14} Following this reasoning, triggering agents are continued.

All three options have limited support in the literature, but more information is needed to determine the true relationship of masseter muscle rigidity and malignant hyperthermia. Until this question is answered adequately, the conservative

options, 1 and 2, appear better suited for the treatment of masseter muscle rigidity.

A History of Malignant Hyperthermia

Soldiers who are susceptible to malignant hyperthermia are not eligible for combat duty. Despite this policy, however, the situation will undoubtedly arise in which a wounded soldier reports with a questionable or even a documented history of malignant hyperthermia. In combat, there will be no practical means to document a questionable history; therefore, the management of such a casualty will not differ from that of a soldier with a documented history. Whenever possible, the casualty should be evacuated to a combat support hospital, where equipment and personnel are less limited. If evacuation is not possible, a safe anesthetic can be administered with additional preparation. The anesthetic technique will depend on both the casualty's condition and the proposed procedure, and may involve monitored care, regional anesthesia, or a nontriggering general anesthetic technique. Whichever technique is chosen, the anesthetic machine must be prepared, dantrolene must be on hand, and extra personnel should be alerted in anticipation of any signs of malignant hyperthermia. The rubber parts of the field machine will retain potent inhalational anesthetics and therefore must be replaced with new or disposable parts, and flushed clear with a high fresh gas flow.³¹ The vaporizer should be drained or removed.

When time is limited, an alternative to the field anesthesia machine is a clean Mapleson system with an oxygen source. If possible, use either the operating room with the best ventilation system or the one in which the lowest level of potent inhalational agents was used that day. If the operating rooms are designed to accommodate two separate anesthetizing locations in the same room, arrangements should be made so that a triggering anesthetic is not being administered at the second location. End-tidal carbon dioxide monitoring should be used whenever possible. Because nitrous oxide will probably not be available, nontriggering techniques that do not rely on this agent must be employed. Intravenous techniques include infusions of pentothal, ketamine, narcotics, or propofol; titrated combinations of benzodiazepines; ketamine and narcotics; or neuroleptic anesthesia. An extended observation period (4–6 h) is required, and the recovery personnel must be educated in the signs of malignant hyperthermia. Although most Malignant Hyperthermia Hotline consultants no

longer believe that pretreatment with dantrolene (2.4 mg/kg, administered intravenously) is required, the decision to pretreat with dantrolene is left to the individual anesthesia provider and circumstance. While preoperative administration of dantrolene will provide a measure of reassurance to the clinician in an emergent situation or when the certainty

of a clean environment is questionable, it may deplete a limited supply of the drug or cause postoperative weakness in the patient. Oral dantrolene premedication has no place in this setting. If dantrolene is administered, a Foley catheter is required because the mannitol in the intravenous formulation has a diuretic effect.

EPIDEMIOLOGICAL AND GENETIC FACTORS

Incidence

The prevalence of the malignant hyperthermia gene and the incidence of the syndrome remain unknown in the general population. Determinations of prevalence and incidence are complicated by the following factors:

- The human genetic defect or defects responsible for the malignant hyperthermia syndrome remain elusive.
- The presentation of the clinical syndrome is variable.
- Greater awareness of the disease has resulted in treatment of suspicious episodes before true diagnosis-confirming signs develop.
- A simple and accurate screening test is lacking.

In light of these difficulties, the incidence of malignant hyperthermia is estimated to be in the range of 1:4,200 to 1:250,000 anesthetics, depending on the patient population and criteria used in the analysis.^{7,32,33} It is impossible to predict (a) whether an episode of malignant hyperthermia will occur in the operating room during the next armed conflict or (b) if an individual soldier is susceptible to malignant hyperthermia. No acute episodes of malignant hyperthermia were reported during Operation Desert Storm. However, seven soldiers were identified as susceptible (via their family histories) and removed from the combat area for further evaluation. Susceptible soldiers probably will be deployed during future conflicts, but their number is likely to be small.

Although at this time it is impossible to influence the incidence of malignant hyperthermia in the military, proper planning and vigilance will limit the morbidity and mortality of this disease. Fatal outcomes continue to decline. Since 1970, mortality has fallen from 70% to 2% to 3%; this decline is a direct result of both widespread education of anesthesiologists concerning malignant hyperthermia and the availability of dantrolene therapy.^{4,7}

Genetics

An autosomal dominant pattern of inheritance was suggested in the first reported case of malignant hyperthermia.³⁴ Features of this mode of inheritance are that it (a) appears in every generation, (b) is transmitted to approximately one half the offspring of affected family members, (c) does not appear in the offspring of unaffected family members, and (d) is not influenced by the gender of the affected family member for transmission. However, as more families were investigated, the autosomal dominant pattern was not always evident. In 1982, the families of 93 malignant hyperthermia-susceptible patients were reviewed to determine their mode of inheritance.³⁵ Only 52% of the families were identified as clearly or possibly autosomal dominant (Table 29-3). The concept of multiple gene defects as an explanation for the apparent heterogeneity of the syndrome has several supporters.³⁵⁻³⁷ The inheritance of malignant hyperthermia will remain incompletely understood until the genetic defect or defects that give rise to malignant hyperthermia are identified.

TABLE 29-3
INHERITANCE PATTERN OF 93 FAMILIES WITH MALIGNANT HYPERTHERMIA

Genetic Pattern	Present in Families (%)
Clearly autosomal dominant	38
Possibly autosomal dominant	14
Associated with dominant myopathies	3
Isolated	17
Questionable recessive (isolated)	21
Insufficient information	7

Adapted with permission from McPherson EW, Taylor CA. The genetics of malignant hyperthermia: Evidence for heterogeneity. *Am J Med Genetics*. 1982;11:277.

PATHOPHYSIOLOGY

The clinical presentation of malignant hyperthermia is the result of abnormal calcium regulation in skeletal muscle following exposure to triggering anesthetic agents. Original theories postulating a central nervous system origin for malignant hyperthermia could not explain why the syndrome was initiated in a caudal animal preparation or following total spinal blockade.^{5,38} The sympathetic nervous system was ruled out as the initiating site for malignant hyperthermia when researchers studying swine found that metabolic changes preceded increases in sympathetic tone and temperature.³⁹ Data from the same study also showed that uncoupling of oxidative phosphorylation could not explain the heat production during a malignant hyperthermia episode. A distinctive myopathic defect is unlikely in malignant hyperthermia. Skeletal muscle from susceptible individuals usually exhibits no characteristic histological defect; however, variable nonspecific changes are seen. Conclusive evidence supporting skeletal muscle as the functional site of the defect has been found in both the swine model and in human data.^{40,41} These data include

1. the observation that during a fulminant episode, a patient experienced total-body rigidity, with the exception of the one extremity that was protected by a tourniquet;
2. the development of *in vitro* contractures to halothane in biopsied muscle samples from susceptible patients; and
3. elevated levels of creatine kinase and myoglobinemia following fulminant episodes.

The Excitation–Contraction Coupling Pathway

A brief review of the excitation–contraction coupling pathway will provide a framework to understand the current theories in the pathogenesis of malignant hyperthermia (Figure 29-2). Although normal excitation–contraction coupling is not completely understood, skeletal muscle contractions start with an action potential at the neuromuscular junction that rapidly spreads over the sarcolemma and into the transverse tubule (T) system (invagination of the sarcolemma).⁴² This electrical signal results in the rapid release of calcium from the terminal cisternae of the sarcoplasmic reticulum. It is yet to be discovered how the signal traverses from

the T system to the sarcoplasmic reticulum, but a calcium-release channel that forms a bridge between the two structures has been identified.⁴³ This channel is now known as the ryanodine receptor. Ryanodine, an alkaloid insecticide, binds to the channel with high affinity and specificity and causes skeletal muscle contraction. During normal skeletal muscle contraction and relaxation, the calcium-release channel will close shortly after activation. The myoplasmic calcium concentration reaches a plateau and therefore facilitates relaxation by allowing calcium uptake to exceed calcium release. Skeletal muscle relaxation is accomplished by the return of calcium to the sarcoplasmic reticulum. Calcium uptake into the sarcoplasmic reticulum is an active process performed by a calcium pump, the major portion of which is a 100-Kd (kilodalton) protein.

Early investigations noted that skeletal muscle from susceptible individuals developed contractures at lower caffeine concentrations than normal muscle.⁴⁴ This focused investigators' attention on the sarcoplasmic reticulum, because caffeine produces contractures in skeletal muscle at that site.⁴⁵ However, biochemical studies failed to reveal either the specific defect in sarcoplasmic reticulum or a site where anesthetic agents would increase the release of calcium. Because calcium regulation is the primary function of the sarcoplasmic reticulum in skeletal muscle, calcium regulation in the excitation–contraction coupling pathway was also investigated.

The identification of dantrolene's pharmacological site of action supported this approach, because its site of action is thought to be somewhere between the transverse tubule and the sarcoplasmic reticulum.²⁷ Direct evidence of defective intracellular calcium regulation was provided by two separate methods of measuring myoplasmic calcium concentrations. In one study⁴⁶ utilizing fura-2 (an intracellular calcium-selective dye), elevations in myoplasmic calcium were found to correlate with the force of *in vitro* contracture in susceptible swine muscle induced by halothane or caffeine. In the other study,⁴⁷ calcium-selective microelectrodes detected myoplasmic calcium concentrations that increased when the malignant hyperthermia syndrome was triggered in swine, and reversed following the administration of dantrolene. Prolonged elevation of myoplasmic calcium (*a*) produces muscle contracture and a sustained contraction and (*b*) appears to be the source of the metabolic disturbances during a malignant hyperthermia episode.

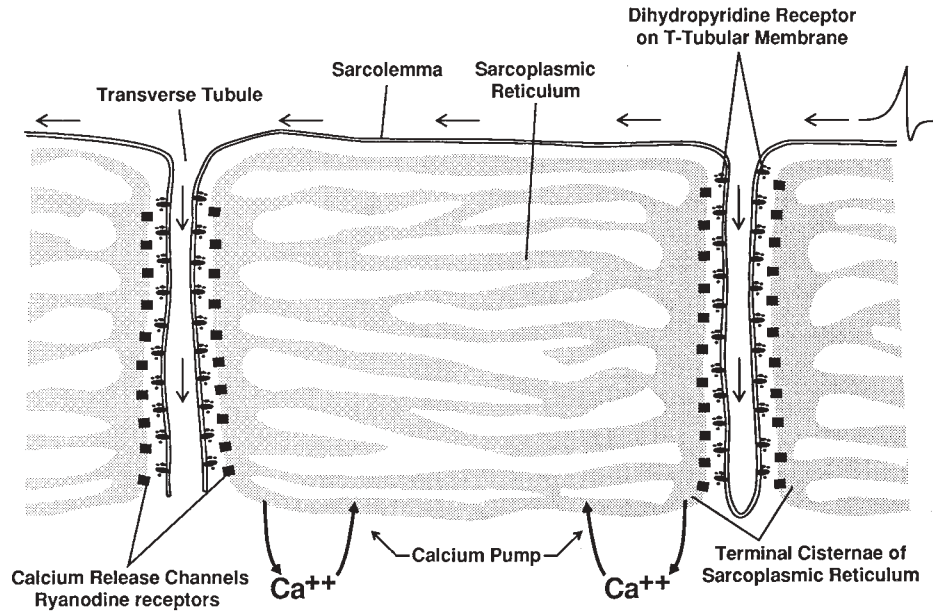


Fig. 29-2. This skeletal muscle transverse tubule–sarcoplasmic reticulum system illustrates the cellular components involved in excitation-contraction coupling. An action potential begins at the top right corner of the figure and traverses the sarcolemma and transverse tubules, as the arrows depict. This electrical activity is transformed into the release of calcium from the terminal cisternae of the sarcoplasmic reticulum. Although the exact mechanism is unclear, the dihydropyridine receptor on the T-tubular membrane and the nearby calcium-release channels and ryanodine receptors on the terminal cisternae appear to have major roles. During normal excitation–contracting coupling, calcium is released from the terminal cisternae through the open calcium-release channels. This increases the myoplasmic calcium concentration and initiates contraction. Closure of the calcium-release channels and uptake of the myoplasmic calcium by the calcium pumps have the net effect of decreasing the myoplasmic calcium concentration, thus limiting contraction. In malignant hyperthermia, calcium hemostasis is abnormal, as evidenced by elevated myoplasmic calcium concentrations. The elevated myoplasmic calcium concentrations may be the result of an abnormality of the dihydropyrimidine receptor, ryanodine receptor, or some modulator of these receptors. Adapted with permission from Muldoon SM, Karan SM. Hyperthermia and hypothermia. In: Rogers MC, Tinker JH, Covino BG, Longnecker DE, eds. *Principles and Practice of Anesthesiology*. St Louis, Mo: Mosby–Year Book; 1993: 2504.

Either alone or in combination, exaggerated calcium release or depressed calcium uptake can produce an elevation of the myoplasmic calcium concentration.

Because calcium uptake appears to be unaffected in susceptible muscle, recent investigation is focused on identifying defects in calcium release or regulation. This approach is supported by the facts that (1) dantrolene has no effect on calcium uptake in the sarcoplasmic reticulum and (2) dantrolene also reduces calcium release in the sarcoplasmic reticulum.²⁸ A mechanism for abnormal calcium release was first described in 1981, when a researcher postulated that calcium-induced calcium release was responsible for the abnormal contractures induced by caffeine or halothane in biopsied skeletal muscle from malignant hyperthermia–susceptible patients.⁴⁸ (The term calcium-induced calcium re-

lease describes the observation that skeletal muscle sarcoplasmic reticulum will release calcium when calcium is applied to its cytoplasmic surface.) Calcium-induced calcium release is activated by calcium, halothane, and caffeine, and is inhibited by high magnesium, calmodulin, tetracaine, and ruthenium red^{49,50}; it is also associated with the sarcoplasmic reticulum terminal cisternae, site of the ryanodine receptor, and may be activated or inhibited by ryanodine.⁵¹ Abnormal calcium-induced calcium release has also been reported in the swine model. While one researcher⁵² reports that susceptible swine have a lower calcium threshold to initiate calcium-induced calcium release, others⁵³ report that susceptible swine have a higher rate of calcium-induced calcium release. To date, biochemical evidence of a ryanodine receptor abnormality exists only in swine.⁵⁴ Other investigators suggest

that the calcium-release channel is normal but the structures that modulate its function are abnormal.^{55,56} Alternative theories to a defect in the ryanodine receptor include the dihydropyridine receptor,⁵⁵ hormone-sensitive lipase,⁵⁶ phospholipase A₂,⁵⁷ and inositol 1,4,5-triphosphate phosphatase⁵⁸ deficiency. In light of the broad spectrum of clinical presentation of malignant hyperthermia, more than one defect will probably be identified with the malignant hyperthermia syndrome. Advances in genetic analysis may provide some answers for this complex disease.

Defect Linked to Chromosome 19

The first major genetic breakthrough was the linkage of a possible malignant hyperthermia defect to chromosome 19q12-13.2 by two independent laboratories (Figure 29-3).^{59,60} Linkage is said to occur when two distinct genes on the same chromosome tend to be inherited together. The likelihood of linkage is increased as the distance between the genes is decreased. The *lod* score (logarithm of the odds) quantifies the likelihood of linkage. Linkage is considered proven when the lod score is 3 (1,000:1 in favor of linkage) and ruled out when the lod score

is -2 . With the knowledge that porcine malignant hyperthermia is genetically linked to the glucose phosphate isomerase (GPI) locus, a team of researchers examined three extended Irish families who expressed malignant hyperthermia susceptibility as an autosomal dominant trait for linkage to the human GPI locus.⁵⁹ Human GPI was previously mapped to chromosome 19q12-13.2, an area with several well-defined polymorphic loci from which lod scores could be determined. The lod score for linkage between malignant hyperthermia susceptibility and the genetic marker CYP2A was 5.65. The researchers concluded that in both humans and swine, malignant hyperthermia is probably due to mutations in homologous genes, and that the malignant hyperthermia defect in humans is probably located in the CYP2A area. Other research supports this conclusion by demonstrating a linkage (lod score 4.20) between the ryanodine receptor gene and malignant hyperthermia susceptibility in nine families with ryanodine gene polymorphisms (two or more expressions of the same gene).⁶⁰ Eleven families in the study did not exhibit polymorphism of the gene; this suggests another genetic site for the malignant hyperthermia defect.

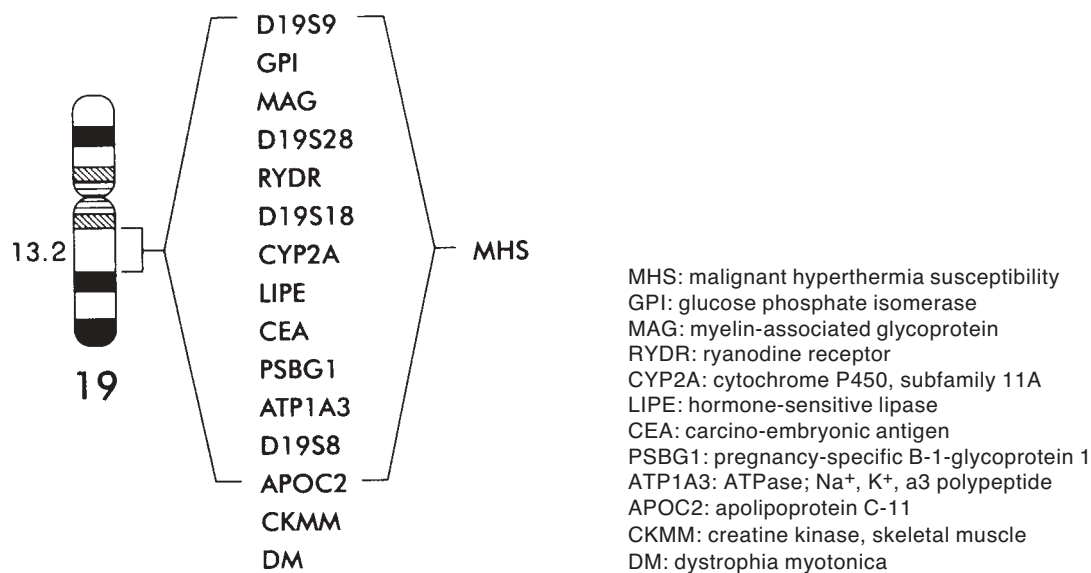


Fig. 29-3. Regional localization of gene and DNA-segment markers on chromosome 19. This type of genetic map only gives information as to the sequence of markers on a gene, but gives no information as to the size of the marker or the distance between markers. Using *lod* scores (logarithm of the odds), researchers have linked malignant hyperthermia susceptibility to chromosome 19 between markers D19S9 and APOC2. Genes located within this region are considered to be candidates for the elusive, defective "gene" for malignant hyperthermia. Markers identified with a D and followed by a sequence of numbers and letters have not yet been identified as part of a known gene sequence. Adapted with permission from Levitt RC, McKusick VA, Fletcher JE, Rosenberg H. *Nature*. 1990;345:298. Letter.

Single-Point Mutation of Ryanodine-Receptor Gene

The second breakthrough in the genetics of malignant hyperthermia was reported in 1991. This research identified a single-point mutation of the porcine ryanodine-receptor gene, which results in the substitution of a cysteine for an arginine at position 615 in the ryanodine receptor of susceptible swine.⁶¹ The mutation was present in five of six breeds and was present at the same frequency as porcine stress syndrome for that breed. In the sixth breed, Hampshire, porcine stress syndrome has not been reported.

Using this information, another team of researchers examined 35 families whose members are susceptible to malignant hyperthermia for the corresponding human ryanodine gene mutation.⁶² In one family, three members were identified as heterozygous for the substitution. Genetic identification of susceptibility was consistent with the results of prior halothane and caffeine contracture testing. This family was originally identified when the proband exhibited masseter muscle spasm after the administration of succinylcholine. Although the study identifies a common defect in porcine and human malignant hyperthermia, it also indirectly indicates genetic heterogeneity in human malignant hyperthermia.

The most convincing data supporting genetic heterogeneity in human malignant hyperthermia were provided in 1991.³⁷ In three susceptible families, linkage measurements were calculated for the ryanodine receptor gene, CYP2A, and several other markers in the area of 19q12-13.2. Malignant hyperthermia susceptibility did not cosegregate with any of the previously identified markers or genes. Although linkage for the human lipase gene was not calculated in this report, it can also be eliminated as a candidate gene in these families, because the human lipase gene is flanked on both sides by markers that were tested for linkage. Even though the data do not identify a new site for the malignant hyperthermia defect in these families, they support the evidence for at least one additional genetic locus for the syndrome.

Advances in the pathophysiology of malignant hyperthermia will continue to rely on the application of genetic analysis to families whose susceptibility has been delineated through halothane and caffeine contracture testing. Likewise, animal models will continue to be invaluable in the search for other causes of malignant hyperthermia. If porcine malignant hyperthermia proves to be a homogeneous defect, the model may only apply to a small percentage of humans susceptible to the syndrome. Perhaps other models (canine, equine, goat) will provide new clues to explain the clinical syndrome of human malignant hyperthermia.

EVALUATION OF SUSCEPTIBILITY

No simple screening test or minimally invasive diagnostic test exists to identify patients susceptible to malignant hyperthermia. Although physical examination can identify loosely associated abnormalities that are common in the general population, the syndrome lacks a distinct physical sign to identify susceptible patients. Numerous tests have tried to identify susceptible patients. These include serum creatine kinase, serum cholinesterase levels, chemiluminescence, human leukocyte antigen, platelet nucleotide depletion test, erythrocyte fragility, and the calcium uptake test in muscle. While some of these tests may be useful under restricted conditions, they have not been successful when applied to a larger population of patients. The only tests that reliably identify patients who have exhibited the clinical syndrome are the halothane and caffeine contracture tests.⁶³ However, these tests require not only a skeletal muscle biopsy, they also require the biopsy to be performed at a malignant hyperthermia diagnostic center be-

cause the muscle must remain viable throughout the testing period (tests must be completed within 5 h of the biopsy) and cannot be preserved or frozen. Only 12 medical centers in North America provide diagnostic contracture testing. Tests that show some promise for the future include genetic analysis⁶⁴ and phosphorus nuclear magnetic resonance spectroscopy.^{64,65} Although further development of these tests is necessary, they provide hope for a simpler and more accurate diagnostic test in the future.

Physical findings that have been associated with malignant hyperthermia include increased muscle bulk, hyperextensible joints, strabismus, and scoliosis. Rare diseases such as Duchenne and Becker type muscular dystrophies, myotonia congenita, central core disease, King-Denborough syndrome, Schwartz-Jampal syndrome and osteogenesis imperfecta have been linked to malignant hyperthermia, but these are highly unlikely to be seen on the battlefield. A history of muscle cramps

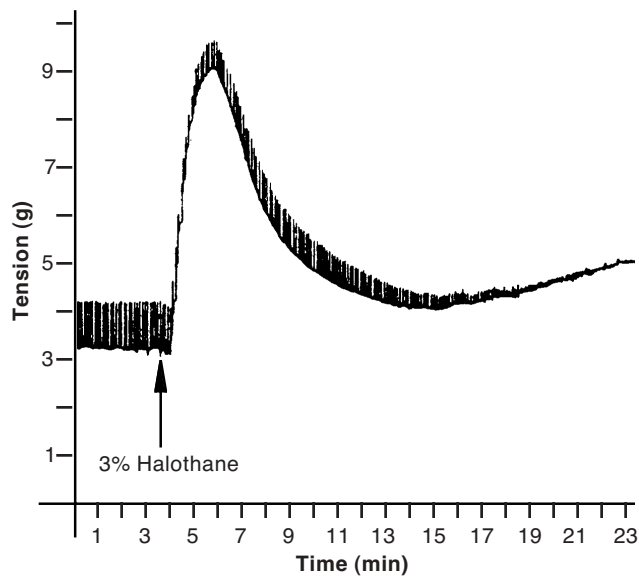


Fig. 29-4. This tracing illustrates an abnormal contracture response of human skeletal muscle to 3% halothane. A strip of muscle (2–3 cm, 100–200 mg) is tied with silk thread at both ends. One end is attached to a hook in the tissue bath, while the other is attached to a strain-gauge transducer. The muscle strip is submerged in Krebs solution and oxygenated via a sintered disk with a mixture of 95% oxygen and 5% carbon dioxide. Transmural electrical stimulation is applied to the muscle strip via platinum electrodes. The muscle is electrically stimulated for a minimum of 15 minutes, or until a stable baseline tension is obtained. A twitch height of greater than 0.5 g tension to the electrical stimulation is considered viable for testing. Halothane is delivered to the tissue bath by adding it to the mixture of oxygen and carbon dioxide. A response is considered positive when baseline tension increases by greater than 0.7 g within 10 minutes of exposure to 3% halothane. A normal skeletal muscle response to halothane is an increase in twitch tension height without an increase in baseline tension. Reprinted with permission from Muldoon SM, Karan SM. Hyperthermia and hypothermia. In: Rogers MC, Tinker JH, Covino BG, Longnecker DE, eds. *Principles and Practice of Anesthesiology*. St Louis, Mo: Mosby-Year Book; 1993: 2508.

or heat intolerance has no predictive value for the occurrence of malignant hyperthermia.

The halothane and caffeine contracture tests are the most widely accepted diagnostic tests for the identification or conformation of malignant hyperthermia susceptibility; however, due to the constraints already discussed, these tests will not be available on (or near) the battlefield. The response of skeletal muscle to halothane is the most specific test for malignant hyperthermia, but it is the least sensitive (Figure 29-4). Caffeine will produce a contracture in any skeletal muscle, but this response will occur at a lower dosage in susceptible individuals. Besides requiring a biopsy from the vastus lateralis muscle (3 cm • 1 cm), these contracture tests have other drawbacks:

- They require a significant amount of technical expertise to perform.
- They are performed at only 12 sites in North America.
- A diagnostic gray zone exists when the muscle responds to halothane or caffeine but not strongly enough to meet the positive requirements. By applying a wide spectrum of susceptibility, these patients are usually identified as positive at the lower end of the spectrum.
- At this time, false-positive results cannot be identified because these patients will

not be exposed to triggering agents.

- Although no false-negative results have been reported, few reports exist of patients with negative contracture results and subsequent exposure to triggering agents.⁶⁶

Any soldier who exhibits the clinical syndrome does not need contracture testing prior to future anesthetics, (eg, if further surgery were necessary before the soldier could be discharged from the military). Contracture testing is most useful in confirming suspicious episodes and in helping to identify susceptible family members. Soldiers who have not exhibited the clinical syndrome, but have been informed they may be susceptible, should be evaluated with contracture testing as soon as possible. Malignant hyperthermia diagnostic evaluations can be arranged for armed forces personnel or their dependents by contacting the following address or commercial telephone number:

Uniformed Services University of the Health Sciences
 Department of Anesthesiology
 Director, Malignant Hyperthermia Diagnostic Center
 4301 Jones Bridge Road
 Bethesda, Maryland 20814-4799
 Telephone: (301) 295-3140

SUMMARY

Malignant hyperthermia is a rare pharmacogenetic disease that can be expressed on exposure to triggering anesthetic agents. No simple, widely applied test exists to screen for susceptible individuals. The hypermetabolic syndrome is identified by increases in carbon dioxide production, lactic acid production, muscle rigidity, and sympathetic tone. Temperature elevation is a late

sign. Treatment consists of prompt recognition of the clinical syndrome, removal of the triggering agents, rapid administration of dantrolene, and supportive care. Successful management of malignant hyperthermia is possible, even in austere conditions, when treatment plans are formulated in advance and are tailored to the resources available.

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