Round Table on Malignant Hyperthermia in Physically Active Populations: Meeting Proceedings

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*****Note: Tables may be found at the end of this document.**

Abstract:

Context: Recent case reports on malignant hyperthermia (MH)-like syndrome in physically active populations indicate potential associations among MH, exertional heat stroke (EHS), and exertional rhabdomyolysis (ER). However, an expert consensus for clinicians working with these populations is lacking. **Objective:** To provide current expert consensus on the (1) definition of MH; (2) history, etiology, and pathophysiology of MH; (3) epidemiology of MH; (4) association of MH with EHS and ER; (5) identification of an MH-like syndrome; (6) recommendations for acute management of an MH-like syndrome; (7) special considerations for physically active populations; and (8) future directions for research. **Setting:** An interassociation task force was formed by experts in athletic training, exercise science, anesthesiology, and emergency medicine. The "Round Table on Malignant Hyperthermia in Physically Active Populations" was convened at the University of Connecticut, Storrs, September 17–18, 2015. **Conclusions:** Clinicians should consider an MH-like syndrome when a diagnosis of EHS or ER cannot be fully explained by clinical signs and symptoms presented by a patient or when recurrent episodes of EHS or ER (or both) are unexplained. Further research is required to elucidate the genetic and pathophysiological links among MH, EHS, and ER.

Keywords: exertional heat stroke | exertional rhabdomyolysis | ryanodine receptor 1

Article:

Recent advances in the understanding of malignant hyperthermia (MH) warrant that sports medicine professionals recognize the associations among the ryanodine receptor 1 (*RYR1*), exertional heat stroke (EHS), and exertional rhabdomyolysis (ER).[1–6] Although MH has been listed as one of the potential predisposing medical conditions for EHS in the National Athletic Trainers' Association (NATA) position statement on exertional heat illnesses,[7] currently no consensus has been published on the implications of MH in physically active populations.

OBJECTIVES

The "Round Table on Malignant Hyperthermia in Physically Active Populations" was convened by the Korey Stringer Institute at the University of Connecticut, Storrs, on September 17–18, 2015, to discuss MH and explore the potential associations among MH, EHS, and ER in physically active populations. Researchers, medical professionals, and members of the NATA were assembled at the meeting. The round-table agenda consisted of 4 major aims: (1) provide an overview of MH, (2) identify the epidemiology and diagnosis of MH, (3) discuss the management and potential outcomes of MH, and (4) evaluate the current evidence linking or distinguishing MH, EHS, and ER in physically active populations.

Definition of Malignant Hyperthermia

Malignant hyperthermia (MH) is an anesthetic-induced, autosomal-dominant, pharmacogenetic disorder of skeletal muscle, triggered by inhalation anesthetic agents or succinylcholine and resulting in hypermetabolism, skeletal muscle damage, hyperthermia, and if left untreated, death.

The *MH-like syndrome* is a nonanesthetic-induced, often exertion-related episode, presenting with 2 or more of the following signs and symptoms: markedly elevated body temperature, muscle pain with muscle breakdown, and muscle rigidity. This syndrome is often identified in the absence of another readily identifiable diagnosis; these patients require further evaluation to assess the cause of their signs and symptoms.

History, Cause, and Pathophysiology of MH

Michael Denborough, MD, and his colleagues first described MH in the early 1960s.[8] Later that decade, Beverly Britt, MD, conducted pioneering research on the occurrence and manifestations of MH.[9] This seminal work demonstrated that MH was precipitated by exposure to potent inhalational anesthetics and the paralyzing agent succinylcholine but not to other anesthetics. The MH syndrome was determined to be inherited in an autosomal-dominant manner and was independent of ethnicity.[10,11]

Skeletal muscle from MH-susceptible individuals displayed an accentuated muscle-contraction response when exposed to the anesthetic halothane and to calcium-releasing agents such as caffeine.[12] It became clear that MH was a muscle disorder caused by uncontrolled calcium release from the sarcoplasmic reticulum. In the 1990s, MH susceptibility was genetically linked to the skeletal muscle-specific calcium channel *RYR1*. Mutations of *RYR1* are found in approximately 70% of MH-susceptible patients.[13] Hundreds of DNA variants exist for the *RYR1* gene, but fewer than 40 have been definitively identified as causing

MH.[14] Additionally, although many proteins regulate calcium flux, another gene, calcium channel, voltage-dependent, L type, alpha 1S subunit (*CACNA1S*), has been associated with MH in fewer than 1% of cases.[15] It should be noted that genetic changes in the *RYR1* are also found in a variety of muscle disorders (eg, central core disease) that demonstrate abnormal histopathology and result in muscle weakness. The muscle weakness in these myopathies is caused by reductions in calcium release and muscle activation.[16]

The pathophysiology of MH is linked to the impairment of myoplasmic calcium homeostasis, which leads to increased muscle tension and metabolism. Malignant hyperthermia manifests as increased production of carbon dioxide and heart rate and is often accompanied by accentuated muscle rigidity, hyperkalemia, increased acid content in the blood, release of myoglobin into the urine, and release of the muscle enzyme creatine kinase.[1] Downstream metabolic effects include adenosine triphosphate breakdown and increased cell membrane leakage and acidosis. Hypermetabolism also results in hyperthermia that may reach fatal levels of greater than 40.5°C (105°F), which may lead to symptoms such as failure of the blood coagulation system.[17]

Through the 1970s, MH mortality was close to 80%.[9] When anesthesiologists were made aware of the signs of MH and the steps required to treat it, mortality rates declined.[18] However, a specific antidote, dantrolene sodium, was not approved by the Federal Drug Administration until 1979. The efficacy of dantrolene was demonstrated first in naturally occurring breeds of heavily muscled swine and then tested in humans.[19] With the widespread use of dantrolene sodium, mortality rates decreased to 15% or lower. Most developed countries now require dantrolene to be available in all operating rooms, yet in many parts of the world, this is not standard practice, despite the very high likelihood that a patient who develops MH will die without the administration of dantrolene.

Although early MH researchers discovered the syndrome in association with exposure to anesthetics, MH was also observed to develop in specific breeds of pigs exposed to nonpharmacologic stress, environmental heat stress, or exercise. Four decades ago, Wingard and Gatz[20] hypothesized that EHS and MH could be 2 phenotypes of a latent skeletal muscle disorder. This hypothesis was substantiated by later case reports suggesting that human patients may also present with an MH-like syndrome on exposure to exertion and environmental heat stress in the absence of anesthesia. Not all cases of EHS are due to the calcium-dependent pathophysiology of MH, but the relationship between MH-like syndromes and MH is under intensive study.[4]

Epidemiology of MH

Current Knowledge.

1. Episodes of MH occur predominantly in young, muscular males.[21,22] All ethnicities are affected. The estimated incidence of MH is 1 in 250 000 surgeries involving all types of anesthesia and 1 in 62 000 uses of potent inhalational anesthetics or succinylcholine.[23] In a study[21] of New York hospitals, the prevalence rate of MH was 0.96 per 100 000 surgical discharges.

2. Malignant hyperthermia has a variable presentation, ranging from a full metabolic crisis after induction of anesthesia to a slowly appearing reaction up to 1 hour after termination of anesthesia. The penetrance is also variable, meaning that MH-susceptible patients do not develop the syndrome with every exposure to triggering agents.[1,22]

3. The condition is a genetically heterogeneous disorder, with variants in the *RYR1* and *CACNA1S* genes responsible for 50% to 75% and 1% of MH cases, respectively.[24] The prevalence of genetic variants associated with MH susceptibility was estimated at 1 in 3000.[1,25] To date, 34 *RYR1* variants and 2 *CACNA1S* variants have been confirmed as causing MH and recommended for diagnostic genetic testing by the European Malignant Hyperthermia Group.[14]

4. Nonanesthesia-related MH-like syndromes may share a common pathogenic mechanism with MH. This possibility is based on similarities of the clinical signs (Table 1), the presence of an *RYR1* variant in 30% of patients, and a positive in vitro contracture test or caffeine halothane contracture rest test (CHCT) in 45% of this population.[2,4,26]

Gaps in Current Knowledge.

1. The true incidence of MH episodes remains unknown due to the variable genetic penetrance and presentation and the fact that most MH-susceptible patients are asymptomatic before an MH event. The functional consequences of hundreds of reported *RYR1* variants and the possible association with MH remain unknown. The risk of MH among EHS and ER patients and the risk of EHS and ER in MH-susceptible patients have not yet been ascertained.

2. To date, it is unclear if MH-susceptible patients should avoid performing strenuous exercise in hot or humid environments or if anesthetic triggers should be avoided in patients with a history of EHS. Because the in vitro contracture test and CHCT are designed for diagnosis in patients with a personal or family history of MH, the appropriateness of applying MH-diagnostic functional bioassays to all unexplained or recurrent cases of EHS and ER is debatable.

3. A small number of studies suggest the use of B cell bioassay as a possible alternative to the CHCT.[27]

4. The potential utility of dantrolene in the treatment of EHS and ER is controversial due to the lack of randomized controlled clinical studies in patients with these conditions.[28]

Association of MH with EHS and ER

Current Knowledge.

1. Multiple MH-like syndrome case reports and case series suggest similarities and associations among MH-susceptible, EHS, and ER patients (Table 2).[6,9–35]

2. Common signs and symptoms among the 3 conditions include hyperthermia, hypermetabolism, and muscle breakdown, resulting in death if untreated.

3. The MH-like syndrome, EHS, and ER are mechanistically similar in that they share triggers such as exercise, hot or humid environmental conditions, and recent illness.[31]

4. In unexplained or recurrent cases of EHS and ER, MH susceptibility has been reported, which suggests involvement of MH-related genetic mutations as some of the underlying risk factors for EHS and ER.[30,31]

5. Assessing an MH-like syndrome includes neuromuscular evaluation and, in the absence of a clinical diagnosis, muscle biopsy and CHCT or genetic screening. Ongoing research will define the relationship among MH-like syndromes, EHS, and ER.

Gaps in Current Knowledge.

1. Genetic susceptibility may partially define low exercise or heat tolerance in patients with MH-like syndrome, but much remains unknown.

2. Whether MH-susceptible individuals are at increased risk of developing EHS and ER is uncertain. Similarly, we do not know if patients with a history of EHS or ER are at increased risk of developing intraoperative MH.

Identification of MH-Like Syndrome

Current Knowledge.

1. The MH-like syndrome is challenging to identify in physically active individuals because it lacks consistent diagnostic genotypes or phenotypes. Care providers should be on the alert when the nonanesthetized patient presents with MH-like syndrome signs and symptoms after other differential diagnoses have been exhausted.

2. Diagnosis of an MH-like syndrome in the field without prior knowledge of an individual's susceptibility to the condition is not possible due to its nonspecific signs and symptoms. However, the condition should be considered in the differential diagnosis when other possibilities have been excluded (Table 1). Family members, if available, can provide useful information about a history of anesthesia intolerance, a personal or family history of MH, or concurrent medications or supplements that may be risk factors. If awake, the patient should be asked about any personal or familial history of adverse reactions to volatile anesthesia.

3. The MH-like syndrome is usually diagnosed retrospectively after a patient undergoes advanced medical testing at an MH referral center or when an MH episode occurs under anesthesia. The MH-like syndrome has also been associated with myopathies (eg, central core disease) and recent viral illness.[36]

4. Clinical signs at the time of presentation include an elevated end-tidal CO_2 (indicating a hypermetabolic state), muscle rigidity (particularly masseter muscle spasms), rapid heart rate, and high body temperature; the end result is muscle breakdown, myoglobinuria, an elevated creatine kinase level (>10 000 U/L), or a slow or inadequate response to cooling strategies (or a combination of these).

5. The most accurate way to diagnose MH susceptibility is by having a patient undergo an in vitro CHCT.[1] However, this is a costly and invasive test, which requires a muscle biopsy. The sensitivity of the test is greater than 95%, but the specificity is about 80%.[37] Patients with positive results to either caffeine or halothane or to both tests are classified as MH susceptible.[1]

6. Although functionally tested MH-causative *RYR1* and *CACNA1S* gene mutations have been identified, many novel variants of unknown significance have not been functionally characterized. Thus, the identification of novel variants of unknown significance cannot confirm the diagnosis of MH. Furthermore, the absence of *RYR1* and *CACNA1S* mutations or variants cannot rule out MH, as genes that have not yet been identified may also confer MH susceptibility.[1]

7. Determination of MH susceptibility requires expert advice concerning the choice of test and interpretation of the results.

Recommendations for Acute Management of MH-Like Syndrome

The Malignant Hyperthermia Association of the United States (MHAUS) is a valuable resource for information about MH and its treatment.[38] The MHAUS provides a hotline with direct access to providers for real-time management of patients with MH and MH-like syndrome.[1] Recommendations for acute care based on our knowledge to date using the Strength of Recommendation Taxonomy[39] are as follows:

1. Initial attention should focus on basic life support with rapid interventions for those who may require airway management or early chest compressions and defibrillation. *Evidence Category: C*

2. Clinicians must obtain a rectal temperature to confirm initial body temperature and any changes. Any patient with a rectal temperature greater than 40.5°C (105°F) with coexisting signs or symptoms of central nervous system dysfunction should be aggressively cooled before being transported to a hospital. Whole-body immersion in cold water is recommended until rectal temperature is reduced to 38.3°C to 38.9°C (101°F−102°F).[1,40,41] Other methods, such as wrapping in ice-chilled or filled towels or sheets or providing chilled intravenous fluids and ice packs are acceptable only during transport or when whole-body water immersion is not available.[42,43] *Evidence Category: C*

3. If an MH-like syndrome is suspected or known to be present, succinylcholine is contraindicated because it will exacerbate an MH crisis. Similarly, volatile anesthetics are

contraindicated in anyone suspected of having experienced an MH-like crisis. *Evidence Category: C*

4. If the clinician suspects an MH-like syndrome, the receiving hospital should be notified (ie, "code blue") to have an anesthesiologist or another provider with experience in MH available to prepare dantrolene. *Evidence Category: C*

5. When an MH-like syndrome is suspected, administration of intravenous dantrolene should be considered on the patient's arrival at the hospital.[1] The initial dose of dantrolene is 2.5 mg/kg intravenously, repeated as needed every 10 to 15 minutes to control signs of the crisis. Dantrolene is a relatively benign medication in the normal population but may induce some muscle weakness. Aggressive cooling is also warranted if the patient is hyperthermic. After initial treatment, the patient should be admitted to the intensive care unit for 24 to 36 hours to be monitored for recurrence of an MH-like syndrome.[36] *Evidence Category: C*

Special Considerations for Physically Active Populations

Given the potential associations among MH, EHS, and ER, clinicians who work with physically active populations may implement the following practices to prevent and mitigate the risk of potential MH events.

1. Team physicians should add questions regarding MH to the athlete's preparticipation examination (Table 3). If the evaluation identifies a risk (*yes* to a previous history of MH, complications with anesthesia, or recurrent EHS or ER), referral to a neuromuscular specialist is encouraged for electromyography and muscle histology testing is encouraged to investigate a differential diagnosis of myopathy. Genetic testing and counseling may also be required. Currently, 5 CHCT testing sites are available in North America (Uniformed Services University of the Health Sciences, University of California-Davis, University of Minnesota, University of Toronto, and Wake Forest University). A complete genetic workup may cost $3000 to $5000, and *RYR1* screening is approximately $1000. A commercial laboratory, PreventionGenetics (Marshfield, WI), offers genetic testing for MH and multiple other genetic disorders. The Robert Guthrie Biochemical & Molecular Genetics Laboratory at Buffalo General Hospital (Buffalo, NY) also offers genetic testing for MH and related disorders. *Evidence Category: C*

2. Create an MH-like syndrome-specific emergency action plan for acute referral of a patient from the field to the hospital. If an MH-like syndrome is suspected, the first responder (eg, athletic trainer, team physician) should notify emergency medical services and the receiving hospital about any previous history of adverse reactions to anesthesia and instruct them to avoid the use of succinylcholine and volatile anesthetics. Additionally, the first responder should prompt the hospital to prepare dantrolene in case of fulminant MH. It should be noted that the lack of a previous history of complications from anesthesia does not eliminate the risk or concern for MH or MH-like episodes. *Evidence Category: C*

3. Implement measures to address risk factors for EHS and ER. Probable risks for MH-like syndromes can be mitigated by optimizing hydration throughout exercise, providing athletes

with heat-acclimatization periods before exercising in the heat for the first time, selecting exercise intensities that are appropriate for each individual, and avoiding physical activities when ill.[40] *Evidence Category: C*

4. Return-to-play considerations after an MH-like syndrome. Currently, no evidence-based guidelines exist to direct return-to-play after an MH-like event. The athlete's condition should be discussed with an appropriate consultant to guide a prudent reintroduction to activity, with careful attention to both exercise and environmental acclimatization. The athlete should obtain a medical alert bracelet, and the athletic training staff should be well prepared to implement the emergency action plan. *Evidence Category: C*

5. Be aware of the potential risk during elective surgeries for injuries. If the family history suggests a risk of MH susceptibility, physicians should be notified to avoid the use of succinylcholine and volatile anesthetics. Severe cases of MH-like syndrome do not always occur at the patient's first exposure to these anesthetic triggers. A genetically susceptible patient may manifest clinical signs at any point in his or her life.[29] *Evidence Category: C*

6. Education for staff and athletes. If an athlete with known MH susceptibility is participating, the clinicians should develop an MH-specific emergency action plan and prepare an on-site cooling plan. Athletes with MH susceptibility should not exercise alone and should notify their medical providers (eg, athletic trainer, team physician) about the condition. Furthermore, clinicians should call the MHAUS 24-hour hotline at 800-644-9737 if they suspect a fulminant MH or MH-like syndrome. *Evidence Category: C*

Future Directions for Research

The clinical implications of MH in physically active populations constitute a critical gap in knowledge for researchers and medical professionals. We identify 3 main future areas of research to fill this gap: (1) evaluation of MH susceptibility in individuals with recurrent EHS or ER episodes of unknown cause, (2) tests to identify individuals with an MH-like syndrome, and (3) standard treatments of MH-like syndromes induced in an exercise-related setting.

SUMMARY

1. Researchers and clinicians should collaborate to expand databases on MH-susceptible patients to better identify links among MH, MH susceptibility, EHS, and ER.

2. A definitive diagnosis of MH or an MH-like syndrome is currently limited to a positive result on CHCT testing. Genetic testing for *RYR1* appears promising as a second diagnostic criterion. However, because not all genetic loci that are causal for MH have been identified, further refinement is necessary before large-scale testing is implemented.

3. The field requires additional research to identify best practices for likely cases of an MH-like syndrome, in addition to cooling and other basic life-support actions.

4. Research into the use of dantrolene for MH-like syndrome, EHS, and ER will determine its effectiveness in improving patient outcomes.

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Table 1. Suggested Similarities Between Malignant Hyperthermia-Like Syndrome and Other Medical Diagnoses Based on Current Supporting Evidence

	Predisposing Conditions								Signs and Symptoms						Treatment	
Medical Condition	Genetic Mutation or Variant	Positive Caffeine Halothane Contracture Test	Family History of Adverse Reaction to Volatile Anesthetics	Exposure to Anesthetic Agent	Recent Illness	Hot or Humid Environment	Strenuous Exercise	Low Exercise or Heat Tolerance	Hyperthermia > 40°C	Hypermetabolism	Central Nervous System Dysfunction	Increased Heart Rate	Muscle Rigidity	Flaccid Muscles	Dantrolene	Aggressive Cooling
Malignant hyperthermia-like syndrome	[a]	[a]	[b]	NA	[a]	[a]	[c]	[a]	[b]	[b]	[a]	[b]	[b]	NA	[b]	[b]
Malignant hyperthermia	[b]	[b]	[b]	[b]	NA	NA	NA	NA	[b]	[b]	*	[b]	[b]	NA	[b]	[b]
Exertional heat stroke	[a]	NA	NA	NA	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]	NA	[b]	[a]	[b]
Exertional rhabdomyolysis	[a]	NA	NA	NA	NA	NA	[b]	[a]	NA	NA	NA	[b]	NA	NA	[a]	[a]

Abbreviation: NA, not applicable according to the definition of the condition.

[a] Inconclusive evidence to suggest association or effectiveness and requires further research.

[b] Sufficient evidence to suggest a strong association or effectiveness.

[c] Sufficient evidence to suggest the criterion is not a required characteristic.

Table 2. Summary of Case Reports

Characteristics	Capacchione et al[33] (2010)	Lavezzi et al[35] (2013)	Potts et al[6] (2014)	
Patient information	African American male; 30 y old, 93 kg Physically fit Denied personal and family history of MH Denied heat intolerance	White male; 6 y old, 20 kg Personal and family history of lordosis Denied family history of MH or heat or exercise intolerance No recent illness Previous history of feeling overheated and stomach cramping while playing in the heat	African American male; 30 y old Identical twin History of recurrent rhabdomyolysis with and without exercise Underwent 2 uncomplicated surgical procedures with general anesthesia as a child Denied personal or family history of MH	African American male; 30 y old Identical twin; tested positive for MH susceptibility before elective surgery after twin brother tested positive on CHCT Oral dantrolene (100 mg tid) to treat muscle cramping and fatigue History of unexplained rhabdomyolysis History of cardiac arrest while under anesthesia
Clinical presentations and diagnoses	Initial: bilateral leg pain Secondary: rhabdomyolysis, bilateral compartment syndrome Tertiary: MH-like syndrome	Initial: generalized seizure Secondary: MH-like syndrome Tertiary: death due to cardiac arrest	Initial: chest pain Secondary: rhabdomyolysis Tertiary: exercise intolerance	Initial: muscle cramping and fatigue Second: recurrent rhabdomyolysis
Case description	Bilateral calf pain after 2.5-mi walk, advised to rest, and discharged with diazepam and oxycodone/acetaminophen; increased leg pain in ensuing wk and diagnosed with exertional rhabdomyolysis and bilateral compartment syndrome; bilateral fasciotomies conducted without adverse reaction to inhalational anesthetics Next visit: irrigation and debridement of fasciotomy wound under general anesthesia led to total body rigidity (maximum nasal	Lower extremity rigidity, trismus, and hyperthermia (40°C) after playing in splash pool for <10 min; unable to open mouth or speak clearly; generalized seizure with profuse sweating (rectal temperature = 42.7°C; heart rate = 190 bpm; cooling [IV, ice packs] ineffective); endotracheal tube placed using succinylcholine, but jaw did not relax, and cardiac arrest occurred	Chest pain after working outside on hot summer day Visited emergency room; diagnosed with rhabdomyolysis; discharged after IV hydration Persistent exercise intolerance, severe muscle cramps with only moderate exertion, jaw and face cramps at rest, and developed complete inability to exercise	Developed recurrent rhabdomyolysis with routine physical activity after discontinuing oral dantrolene Visited emergency room due to spontaneous muscle pain without exercise; discharged after IV hydration Revisited emergency room next day and referred to another hospital; stayed for 5 days and received IV hydration and opioid for pain control; no dantrolene administered and patient discharged home while still in pain

Characteristics	Capacchione et al[33] (2010)	Lavezzi et al[35] (2013)	Potts et al[6] (2014)	
	temperature = 38.5°C, end-tidal CO_2 = 70 mm Hg, HR = 128 bpm) Hyperthermia (oral = temperature 39.4°C) with tachycardia (HR = 110 bpm) observed postoperation; dantrolene (240 mg) administered but rectal temperature rose to 39.7°C; additional dantrolene (1 mg/kg) administered			Revisited emergency room 2 weeks later because muscle pain never resolved; dantrolene administered and patient discharged home with decreased pain and residual muscle weakness
Diagnostic testing	CHCT: positive for halothane, negative for caffeine Muscle histology: mild denervation atrophy Exercise-intolerance mutation panel test: negative	Autopsy: negative for gross pathologic findings and infection	CHCT: positive Muscle histology: normal	Not applicable
Genetic screening	*RYR1* variant Ser1342Gly in exon 28 *CACNA1S* variant in Leu1800Ser in exon 44 *CASQ1* variant His66Arg in exon 1	*RYR1* Gly4820Arg in exon 100	*RYR1* Arg2454Cys mutation	*RYR1* Arg2454Cys mutation
Prognosis and additional testing	No additional testing conducted	*RYR1* Gly4820Arg in exon 100 also found in decedent's father and 2 siblings, all with lordosis Father positive on CHCT and muscle histology revealed central core disease	Oral dantrolene (100 mg tid) to treat muscle cramping and fatigue Could not tolerate moderate exercise	Could not tolerate moderate exercise

Abbreviations: bpm, beats per minute; CHCT, caffeine halothane contracture test; HR, heart rate; IV, intravenous; MH, malignant hyperthermia; tid, 3 times per day

Table 3. Preparticipation Examination Questions Regarding Malignant Hyperthermia

1. Have you or has a family member been diagnosed with malignant hyperthermia? Have you ever been tested for malignant hyperthermia?
2. Have you had 1 or more surgeries under anesthesia?
    a. Did you have any adverse reactions to anesthesia (eg, succinylcholine) during the surgery?
    b. Has a family member experienced any adverse reactions to anesthesia during surgery?
3. Have you ever been diagnosed with exertional heat stroke?
4. Have you ever been diagnosed with exertional rhabdomyolysis?