Adverse Effects of Heat and Exercise in Relation to MH Susceptibility

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Recommendations
1. Any MHS (MH-susceptible) patient who experiences sudden collapse in association with muscle rigidity and hyperthermia should be immediately treated for MH. This includes immediate cooling measures, and transport to the nearest medical facility in order to treat with the drug dantrolene. Succinylcholine should be avoided during resuscitation and management.

2. MHS patients or their relatives who have not experienced adverse effects of heat and exercise should not restrict their activity. They should carry identification of their susceptibility and inform those responsible for their care of their MH status.

3. MHS patients who have experienced adverse effects of heat or exercise should restrict their activity based on their own experience.

4. Patients who develop documented recurrent rhabdomyolysis after exercise or with heat stroke should be referred to a neuromuscular specialist for evaluation. Malignant Hyperthermia Susceptibility should be considered as part of the evaluation.

Literature review:
All articles that discussed the association of heat/exercise and MH as identified in a literature search through PubMed were reviewed.

Background:
Although it is clear that some patients who experience heat and exercise related rhabdomyolysis and/or outright heat stroke are MH susceptible (MHS), it is not possible at present to prospectively identify those MH susceptibles who will develop signs of MH with exercise and/or heat exposure. A direct causal relationship has not been proven between adverse effects in MHS patients and exposure to heat and exercise, but there is supporting evidence to support an association.

Supporting Evidence:
Significant evidence exists that swine carrying (skeletal muscle ryanodine receptor gene) RYR1 mutations that are causal for MH develop signs of MH upon exposure to heat and with exercise or stress (Aberle et al, 1974). Similarly, genetically engineered mice that display one or more RYR1 mutations will develop signs of MH with heat exposure (Durham et al, 2008).

The evidence for the deleterious effects of heat and/or exercise in humans is based on multiple individual cases reports. In many cases, particularly prior to 2000, supporting evidence derives from muscle contracture testing (IVCT or CHCT) or where the patient derived from a family with MH (Ryan and Tedeschi, 1997).

For example, a French study of 45 subjects with exertional heat stroke evaluated MH susceptibility and other adverse effects in these subjects, using IVCTs performed at least 3 months after the exertional heat stroke episode (Figarella-Branger et al., 1993). This study revealed 11 MHS, 8MHE subjects and 26 MHN. In both groups, whatever the IVCT results, pathological findings were heterogeneous and revealed various changes: rhabdomyolysis, mitochondrial myopathy, denervation, type II atrophy, AMPase deficiency, non-specific findings or normal features.
In 2001, Tobin and colleagues reported a 12-year old patient with a clinical history of MH who developed signs of MH after soccer practice and died shortly thereafter. He and his family were found to have an MH-related RYR1 mutation (Tobin et al., 2001).

Wappler and colleagues (2001) described 12 healthy young men who developed exercise-induced rhabdomyolysis. Ten were MH positive on contracture test and three manifested RYR1 mutations.

Muldoon’s group reported (in an abstract) studies of 15 men who developed exercise-induced rhabdomyolysis, 6 had positive CHCT and three displayed RYR1 causal mutations (Capacchione et al., 2009).

Davis et al (2002) reported on two patients with exercise-induced rhabdomyolysis who also displayed a positive contracture test and RYR1 mutations suspected to be causal. Both patients came from families with MH susceptibility in other members.

Groom et al (2011) reported on two cases of ‘awake’ MH. In one case a nine year old male patient experienced anesthesia induced MH related to ptosis surgery and then experienced multiple episodes of high fever and rigidity possibly related to environmental factors. The child died following one of the episodes at age nine. The other case was a six year old girl who died suddenly after experiencing high body temperature and rigidity. A previous episode had been corrected with cooling only. The mutation in the RYR1 gene, although novel, effected intracellular calcium flux similar to causal mutations.

Capacchione et al (2011) reported on a six year old boy who developed high body temperature and muscle rigidity after playing in a splash pool. He and his father had marked hyperlordosis. The father’s muscle biopsy was positive for MH and displayed changes of CCD. A novel RYR1 variant was detected in the propositus and the father and a sibling with hyperlordosis. The variant was different from the ones reported by Groom et al (2011) for the nine year old boy and the six year old girl and by Tobin et al (2001) for the 12 year old boy.

Capacchione and colleagues (2010) also reported on a 30 year old patient with exercise induced rhabdomyolysis, positive CHCT and mutations in the RYR1 gene, the DHPR (dihydropyridine receptor) gene and the calsequestrin1 (CSQ1) gene. The RYR1 variant was in a different locus from the previous cases mentioned above.

One study of five MH susceptible and five non-susceptibles in an exercise laboratory at room temperature, showed that with vigorous exercise MH subjects developed higher core temperature than non MH subjects (Campbell et al., 1983). In the early stages of exercise a higher lactate level was noted in the MH subjects. However, there were no other signs of MH.

There has not been a large scale prospective study of MH susceptibility either by contracture testing or genetic testing of patients with either heat stroke or heat related problems with or without exercise induced rhabdomyolysis.

Finally, the importance of body temperature in the triggering of MH was demonstrated most clearly in studies of MHS swine who did not develop MH when hypothermic despite anesthesia with MH trigger agents, but did when body temperature was raised to normal levels (Iaizzo, 1996).

**Author Commentary**

The evidence supporting a relationship between heat, exercise and MH susceptibility is mostly level 4 as per AHRQ criteria, i.e., observational studies and expert opinion. Nevertheless in my opinion, there is a convincing case for associating problems related to heat and exercise with MH susceptibility because high quality data supporting this contention has been derived from genetically engineered animal models of MH as well as from calcium flux changes in response to SR (sarcoplasmic reticulum) calcium releasing agents in cells transfected with mutations from patients who experienced awake MH.

Hence it is prudent to follow the recommendations described above with emphasis on the importance of cooling during such an episode.

**References**

2. Campbell IT, Ellis FR, Evans RT, Mortimer MG. Studies of body temperatures, blood lactate, cortisol, and free fatty acid levels during exercise in human subjects susceptible to malignant hyperpyrexia.


Other references:

2. MacLennan DH, Zvaritch E: Response to “Malignant Hyperthermia – human stress triggering” in reference to original article “Mechanistic models for muscle diseases and disorders originating in the sarcoplasmic reticulum” http://dx.doi.org/10.1016/j.bbamcr.2010.11.009. Biochimica et Biophysica Acta 2011; 1813:2193-2194 (Recent comments on a review article concerning MH pointing out several instances of awake MH.)

3. Watson DB, Gray GW, Doucet JJ. Exercise rhabdomyolysis in military aircrew: two cases and a review of aeromedical disposition. Aviat Space Environ Med 2000; 71:1137-41. (One patient was shown to be MHS on contracture testing.)