Heat Production and the Importance of Temperature Management in Malignant Hyperthermia

D. Freiermuth[1,*], O. Bandschapp[1] and P.A. Iaizzo[2]

[1]*Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland*

[2]*Departments of Surgery and Integrative Biology and Physiology, Institute for Engineering in Medicine, University of Minnesota, Minneapolis, USA*

Abstract: Malignant hyperthermia (MH) is a rare pharmacogenetic, subclinical disorder of the striated skeletal muscle. Acute episodes are usually triggered by exposure to halogenated volatile anesthetics and/or succinylcholine. During an MH episode, the patient's muscles go into a hypermetabolic state, which in turn causes variable clinical signs and symptoms: i.e., muscle rigidity, respiratory and metabolic acidosis, muscle breakdown, cardiac responses (tachycardia) and ultimately elevation of body temperature. At the cellular level, MH is the consequence of abnormally sustained high myoplasmic calcium concentrations, which causes dramatically elevated turnover of energy rich compounds (e.g., adenosine triphosphate (ATP)). Although often a late sign of MH, the production of heat can play an important role in the treatment and clinical consequences of an elicited episode. In other words, the production of heat thereby is not merely a simple consequence of MH, but a substrate of high relevance during an ongoing MH event: it has been suggested that heat itself may trigger MH in some genetic mutations. Since the introduction of dantrolene, which has provided a specific MH therapy by normalizing myoplasmic calcium levels, mortality of MH has decreased from 70% to 4%. Nevertheless, strong consideration for proper temperature management of the known or suspected MH patient, in all clinical areas (pre-, intra- and post-operative), is critical: as hyperthermia can cause multisystemic involvements, including the brain, the heart and the hemostatic system.

Keywords: Anesthesia, Malignant Hyperthermia, Ryanodine Recepetor Calcium Release.

1. INTRODUCTION

Already in 1912 a case of a perioperative "heat-stroke" was reported [1]. In 1960, Denborough and Lovell [2] then described a hyperthermia–disorder during anesthesia with several deaths in an Australian family. Because of the very high fatality rate (up to 70%) until the 1970s [3] and the steep increase in body temperature they named the disorder of unknown origin "malignant hyperpyrexia" or "malignant hyperthermia" (MH). They also recognized that this disorder was inherited in an autosomal dominant manner in humans.

In 1966, Hall and colleagues first described MH-like triggering in pigs [4]. This set the stage for numerous experimental investigations as to the identification of the pathophysiology associated with MH, including the description of heat generation during a triggered MH episode. More specifically, during such elicited MH events, an increase in body temperature as rapid as 1°C per 5 minutes, reaching more than 44°C in humans [5] and experimentally in pigs [6], was not unusual. Initially some uncertainty as to the primary source of this heat production existed. First, a centrally derived fever-like thermo upregulation was discussed [7]. Then the liver was suspected to be a major heat source during MH (internal cooling using peritoneal dialysis directly involving the hepatic surface was proposed as a possible means of rapid cooling in such cases [8]). Later on, pathological mitochondrial oxidative phosphorylation was thought to be a source of heat, but eventually ruled out, as studies in isolated skeletal mitochondria of MH susceptible subjects did not show abnormalities [7,9] . Briefly, the brown adipose tissue (BAT) was believed to play an important part in the heat generation during an MH event: in BAT the uncoupling protein one (UP1) leads to proton-influx into the inner site of mitochondria resulting in thermogenesis without synthesis of ATP [10]. This was considered especially important for newborns, where BAT represents an important source of heat generation. Recent work has shown that even in adult humans, BAT is present and measurable [11,12]. Yet, despite its presence, it is reported that BAT can only account for less than 21 kilo Joule (kJ) per day [13] (and therefore represents an improbable primary source for heat generation in cases of MH).

Since 1970, there has been the general consensus that the primary site of heat generation in MH is from within striated skeletal muscle; e.g., in accordance to the finding that femoral venous blood was up to 2°C warmer than femoral arterial blood in hyperthermic Poland China pigs [14]. Furthermore, the development

*Address correspondence to this author at the Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Spitalstrasse 21, 4031 Basel, Switzerland; Tel: +41 61 265 2525; Fax: +41 61 265 7320; E-mail: David.Freiermuth@usb.ch

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of in-vitro contracture tests (IVCT) for MH diagnosis, also emphasizes the primary phenotypic pathology associated with MH lies within the skeletal muscles, independent of its neural innervation or the use of a non-depolarizing muscle relaxant [15-17]. Importantly, obtained muscle biopsies from MH susceptible subjects will elicit abnormal contractures upon exposure to halothane and/or caffeine. These pharmacological tests were standardized and integrated into the MH diagnostic procedures of both the European and North American MH Groups in 1984 and 1989, respectively [18,19]. In-vitro contracture testing (IVCT) still represents the gold standard in the diagnosis of MH [20]. In 1990, the first MH causative gene mutation on chromosome 19 encoding the ryanodine receptor one (RyR1) was identified [21]. Since then, about 274 RyR1 variants have been described, 31 of which have been classified as MH causative by the European Malignant Hyperthermia Group (EMHG) (www.emhg.org).

2. NORMAL EXCITATION-CONTRACTION COUPLING AND THE PATHOPHYSIOLOGY OF MALIGNANT HYPERTHERMIA

Under physiologic conditions a muscle contraction is the result of an initial depolarization of a muscle cell. This is achieved by the release of the transmitter acetylcholine (ACh) from the presynaptic terminus of the motoneuron innervating the muscle fiber at the neuromuscular junction. ACh binds to the junctional receptors, which in turn opens non-specific cation channels, resulting in ion influxes into the skeletal muscle cell. If the excitatory postsynaptic potential reaches a critical threshold, depolarisation spreads along the muscle cell (as voltage-gated sodium channels get activated) and propagates along the surface membranes and inward *via* the transverse (t)-tubule system. Subsequently, this rapid spread of depolarization causes a conformational change of the L-type calcium channel located within the t-tubules, also called dihydropyridine receptors (DHPR), resulting in calcium influx from the outer membrane into the muscle cell. The DHPR is mechanically linked to RyR1 *via* its α1-subunit [22]. Therefore, the conformational change of DHPR is directly relayed to RyR1, which leads to activation and opening of the latter, independent of the calcium-current *via* DHPR [23]. Through activation of the RyR1, stored calcium is released from the sarcoplasmic reticulum into the cytoplasm. By binding of the released calcium with troponin-c tropomyosin complex, there is a conformational change within the contractile apparatus (binding site becomes available), allowing interaction of myosin and actin-filaments, ultimately resulting in muscle contraction (force production). The contractile activating effects of calcium are terminated as the pumping of the calcium either back into the sarcoplasmic reticulum *via* Sarcoplasmic/Endoplasmic Reticulum Calcium ATPases (SERCA1), or out of the cell *via* sodium-calcium exchangers, significantly lowers myoplasmic calcium concentrations (Figure **1**). Aberrations in the RyR1 and/or the DHPR (due to mutations in the respective genes) [24] have been associated with sustained elevations in intracellular calcium within skeletal muscle as is the case in MH. Of note, in the heart muscle cell the corresponding enzyme to RyR1 in skeletal muscle cell is the ryanodine receptor type 2 (RyR2). Interestingly, known mutations at the site of RyR2 were linked to severe cardiac pathologies (e.g., arrhythmogenic right ventricular dysplasia) [25].

3. HEAT GENERATION

In endothermic mammals including humans (also known as homeotherms), core temperature homeostasis is critical to keep multiple enzymes and thus the vital organs operational. Therefore, besides heat conserving /dissipating mechanisms (e.g. vasoconstriction, sweating), heat de novo production is essential [26]. As noted above, in newborns, the brown adipose tissue (BAT) is the major site of heat generation, whereas in adults this function is taken over primarily by skeletal muscle, which can account for about 30-50% of an individual's total body weight [27].

In addition to the significant heat production an individual will elicit *via* shivering, non-shivering muscular thermogenesis also plays a role and is also common in many animals. In one unique example of adaptation, the so-called heater organs found in swordfishes are modified muscle cells, which include numerous mitochondria, sarcoplasmic reticular (SR) and SERCA-pumps, but without contractile filaments. These modified muscle cells elevate the fish's brain temperature up to 14 degrees above ambient water temperature by cycling calcium [28]. Importantly, a similar but unregulated calcium cycling happens in skeletal muscle during MH. Calcium is continually released (leaks out) from the sarcoplasmic reticulum *via* the RyR1 and is pumped back into the SR *via* SERCA. Both the contractile activation and the SR sequestration (pumping) uses energy in the form of adenosine triphosphate (ATP): i.e., to move Ca^{2+}

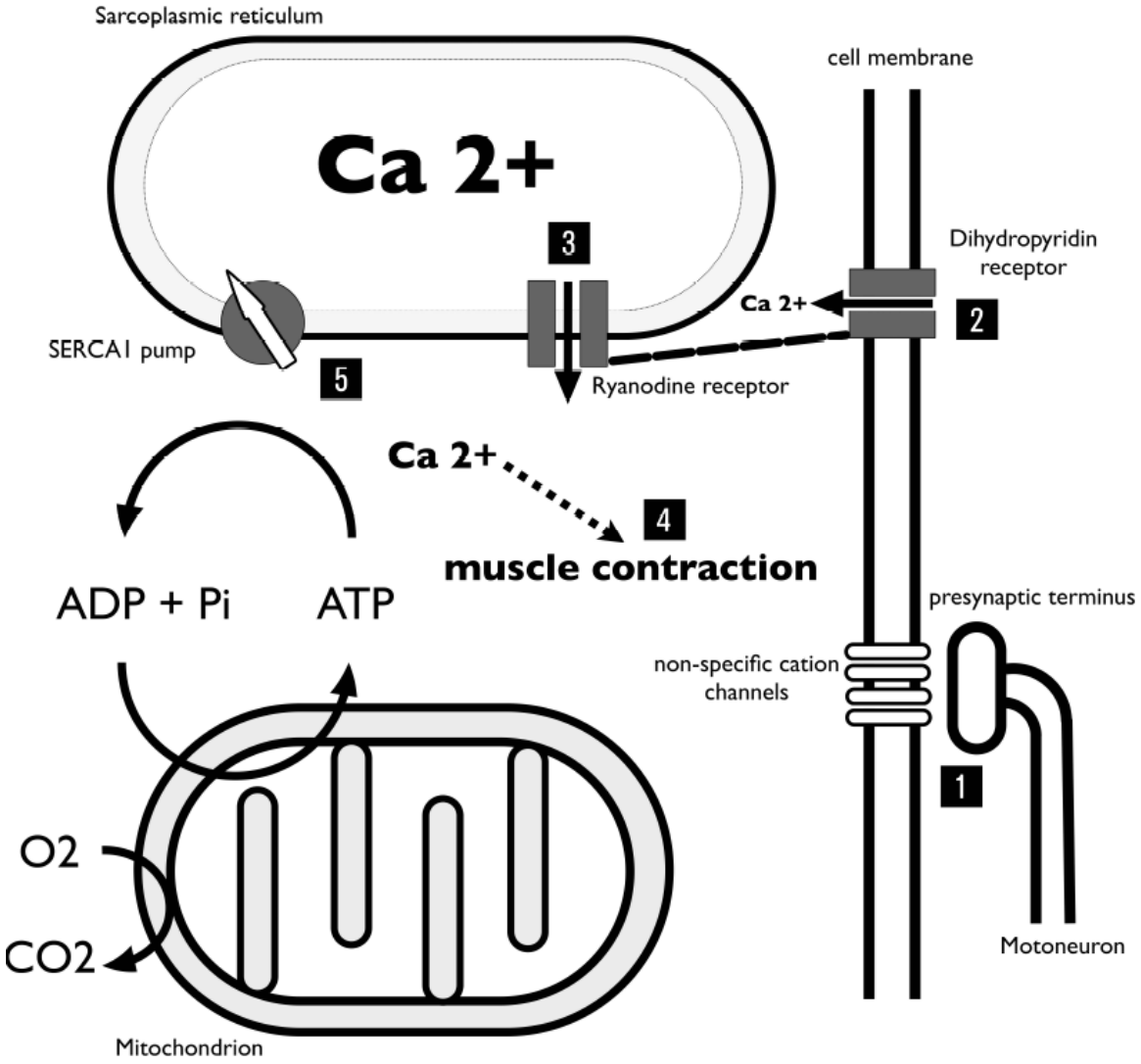

Figure 1: shows a schematic representation of calcium shifts during a "normal" excitation-contraction coupling. Acetylcholine release from the presynaptic terminus causes a depolarization of the muscle cell by opening non-specific cation channels (1). This depolarization propagates along the cell membrane, provokes a conformational change of L-type calcium channels called dihydropyridine receptors (DHPR) thus leading to an influx of calcium (2). The DHPR are mechanically linked to ryanodine receptors one (RyR1) located in the sarcoplasmic reticulum. Thus activation of DHPR provokes an opening of RyR1 and leakage of calcium out of the sarcoplasmic reticulum (3). By binding of the released calcium with troponin-c tropomyosin the contractile apparatus becomes activated and muscle fiber contraction takes place (4). The muscle contraction ends as the sarcoplasmic/endoplasmic reticulum ATPase one (SERCA1) reduces cytosolic calcium concentration by pumping calcium, against its gradient, back into the sarcoplasmic reticulum (5). The SERCA-pump is "powered" by cleaving adenosine triphosphate (ATP).

against its gradient back into the SR. It should be emphasized that while part of the energy generation *via* the ATP-hydrolysis (ATP -> ADP + Pi + energy) is used to pump calcium into the SR, a large percentage of the energy (almost half) is converted into heat (enthalpy ΔH^{cal} -10 to -12kcal/mol ATP) [29]. Theoretically, a maximum in heat production can be achieved when SERCA1 stops moving calcium and merely cleaves ATP (enthalpy ΔH^{cal} -20 to -24kcal/mol ATP) [29]. Recently, sarcolipin (Sln), a 3k Dalton membrane protein in the sarcoplasmic reticulum, was found to be an important regulator of muscle based thermogenesis [30]. In this study, Sln seemed to be able to uncouple the SERCA-pump, thereby releasing a maximum of heat by ATP hydrolysis. Yet currently, the role of Sln during an MH episode is unknown.

It is generally accepted that the patient's hyperthermia in MH is caused by a pathomechanism within the striated skeletal muscles themselves and develops independently of neural innervation (e.g., MH diagnostic procedure is done by IVCT with excised skeletal muscle bundles). On the other hand, this is not considered the case for the following diagnoses, which

may also elicit hyperthermic conditions: the malignant neuroleptic syndrome, serotoninergic syndrome, or Parkinson-hyperpyrexia syndrome [31,32]. These hyperthermic conditions are all primarily caused by 'upstream' autonomic dysfunction and/or dysinhibition of motoneurons, which then leads to an exaggerated contractile activation by neural induced excitation-contraction coupling.

From patient to patient or even for a given patient the heat generated during a triggered MH event can vary enormously: e.g., a fulminant increase in core body temperature of up to 1°C per 5 minutes, reaching up to more than 44°C, is possible [5]; on the other hand, only a modest temperature increase during a documented MH event has been observed as well [33]. Based on theoretical models, it was argued earlier that the heat production during an MH event was mostly of aerobic origin in metabolism [34]. Many years ago, in an animal experiment with Pietrain pigs, Hall *et al*. [14] compared oxygen consumption while measuring the resulting temperature. After inducing MH by the administration of halothane, body temperature increase (up to 40°C) was in line with the theoretically calculated body temperatures resulting by accelerated aerobic glucose metabolism. Above 40°C, however, oxygen consumption is considered to significantly decline, while body temperature can still be increasing; this being most probably due to anaerobic metabolism. Such reasoning was found to be in accordance with high levels of lactate being produced and measured within the dissected muscles of these animals.

Using temperature increase as the sole clinical sign of MH development could be highly problematic. Indeed, several points should be taken into account: first, a significant temperature increase may only appear late in the course of the disease [1]. Second, muscle-group involvement has been shown to be heterogenous within the human body; in one study it was shown that marked disparity of tissue temperatures within various organ systems and/or muscle groups can occur during a full-blown MH event triggered in susceptible swine [35]. Third, elevated catecholamine-levels during MH [6] can cause peripheral vasoconstriction and may therefore contribute to further elevations in core temperature by not allowing the skin to dissipate heat. Importantly, the monitoring of skin surface temperatures as a means to detect MH and/or the progression of such is not recommended to use as clinical guidance (in such cases it is considered to have a poor accordance to the core temperature changes).

4. THE IMPACT OF HEAT IN MALIGNANT HYPERTHERMIA

Heat itself is not merely a simple result (bystander) of MH, but rather an important substrate (actor) or an MH trigger. It was demonstrated that prior hypothermia attenuates both the initiation and progression of MH in susceptible swines [35]. Prior induced mild hypothermia (≈35°C core-temperature) protected 2 out of 6 animals from developing a full-blown MH event and in 1 of those 6 an MH episode subsided spontaneously. Furthermore, in animals that were rendered moderate hypothermic (≈33°C), this totally prevented MH development in all four animals exposed to both halothane and succinylcholine simultaneously. Yet, subsequently when rewarmed back to normal core temperatures (≈38°C), fulminant MH developed in each of them, following re-exposition to succinylcholine and halothane.

Besides genetic polymorphisms of proteins interacting with RyR1 molecules (Yasuda *et al*. [36]) or variable administration (in dosages) of triggering agents, one needs to consider that the aforementioned protection rendered by mild hypothermia may be a further explanation for the observed variance in MH penetration/presentation (e.g., affected patients undergo on average three anesthetic procedures before a first MH event [1]). Of note, Mitchell *et al*. previously measured that mild hypothermia preoperatively is a common occurrence [37].

On the other hand, it has been reported that the application of heat alone is able to trigger malignant hyperthermia: e.g., the "porcine stress syndrome" [38] is caused by a well-known autosomal recessive inherited mutation usually affecting the RyR1-gene. It was shown that both stress and environmental heat significantly affected those susceptible pigs when they were submitted to slaughter, resulting in unsellable "pale, soft, exudate pork" (PSE meat). In one study Denborough *et al*. [39] exposed such MH susceptible piglets to heat: seven out of eight piglets developed MH and died, while the same temperature was well tolerated by the control group of animals. Importantly, such heat-stress induced MH as observed in these animal experiments has also been reported in a selected subgroup of MH susceptible patients. For example, Lichtman and Oribabor [40] reported an MH event that developed in a 54 year old male only after rewarming from hypothermic cardiopulmonary bypass operation. In this specific case, all anesthetic procedures were done trigger-free as the patient had a

positive family history concerning MH. So, core rewarming *via* the cardiopulmonary bypass seemed to be the most reasonable trigger. Unfortunately, in this case, the patient refused any further genetic analysis. Nevertheless, some genetically verified, non-anesthetic "awake" MH episodes have been reported over the years [1,41,42]. Importantly, in these cases, the triggering of MH was merely associated with heat (core temperature rises), either resulting from exertion or fever during a viral infection. Yet it should also be considered that to date, only a small subgroup of MH patients seems to be MH susceptible in a way that elevated body temperature alone will suffice to trigger a fulminant MH episode. In other words, the majority of the identified genetic MH aberrations must be subclinical relative to such clinical/environmental circumstances.

5. HYPERTHERMIA WILL CAUSE BRAIN DAMAGE AND/OR LEADS TO MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

Hyperthermia independently of its origin can lead to cellular vulnerability, dysfunction or death. A fact that is therapeutically being used in certain anticancer therapies [43]. Yet, from a clinical perspective, one needs to be aware that the brain seems to exhibit a peculiar vulnerability to temperature elevations. For example, even a slight temperature elevation of 1°C (from 37°C to 38°C) resulted in significant worsening of neurological function and histopathologic findings in a canine model of complete cerebral ischemia [44].

The elicitation of hyperthermia related to a trigger MH event can be considered to share many features with the known "heatstroke". The latter is defined as core body hyperthermia >40°C with associated central nervous dysfunction [45] and usually occurs in young adults during extensive exercise (e.g., athletes). It may also be elicited in the elderly during hot summer periods as their thermoregulatory defenses become limited. Finally, rarely, the symptoms of heatstroke may be attributed to the aforementioned small subgroup of MH susceptible individuals.

Normally, during any exposure to a hyperthermic situation, one's brain temperature is maintained by various thermoregulatory processes, including the venous system removing the heat. Yet, when core temperature steadily increases, the arterial-brain temperature gradient becomes reduced, which results in elevated brain temperatures (heat levels being maintained within the cranium) [46]. This undesired clinical situation rapidly deteriorates, as heat also increases overall brain metabolism, thereby being a source of heat generation itself: thus inducing a vicious circle.

It is generally considered that two important factors occur during heat stroke that contribute to primary neuronal damage: endotoxaemia and focal heat per se [47,48]. Endotoxaemia is regarded as a result of critically lowered splanchnic perfusion with translocation of bacteria and its endotoxins. This in turn causes an inflammatory response syndrome, including hypotension and altered microcirculation. Importantly, heat per se denatures cellular proteins, causes mitochondrial damage and activates caspases, all which can contribute to apoptosis and ultimately neuronal death [49]. Caspases are aspartat-specific proteases. Once activated by heat, they can continue to cause neuronal apoptosis up to several days [50], even after reestablishing normothermia. Another key consequence among the deleterious effects of hyperthermia may lie in the excitatory toxicity. For example, it was shown that in patients with cerebrovascular stroke, heat seemed to promote an increase in excitatory neurotransmitter release (e.g. glutamate, glycine) leading to ATP depletion, intracellular acidosis and ultimately apoptosis [51].

In summary, many complications of hyperthermia caused by the elicitation of fulminant MH are similar to those described in heat stroke. This could imply that beyond the potential deleterious effect on the brain, other organ systems may be affected similarly. Note, that severe skeletal muscle contractures during an MH episode may not only dramatically elevate body temperature, but may also be associated with the release of large quantities of potassium and other undesired agents into the patient's circulation. In some patients, severe muscle damage may lead to permanent tissue damage. Therefore, whether pathomechanisms of heat induced complications in heat stroke differ relevantly from MH is unclear, but it is well accepted that untreated hyperthermia, irrespective of its cause, can have vast deleterious clinical consequences: activating different mechanistic cascades, often ending up in multiorgan dysfunction, including disseminated coagulopathy, renal failure, brain edema, acute respiratory failure and/or the breakdown of the cardiocirculatory system.

6. TEMPERATURE MONITORING DURING MALIGNANT HYPERTHERMIA

The Malignant Hyperthermia Association of the United States (www.mhaus.org) recommends

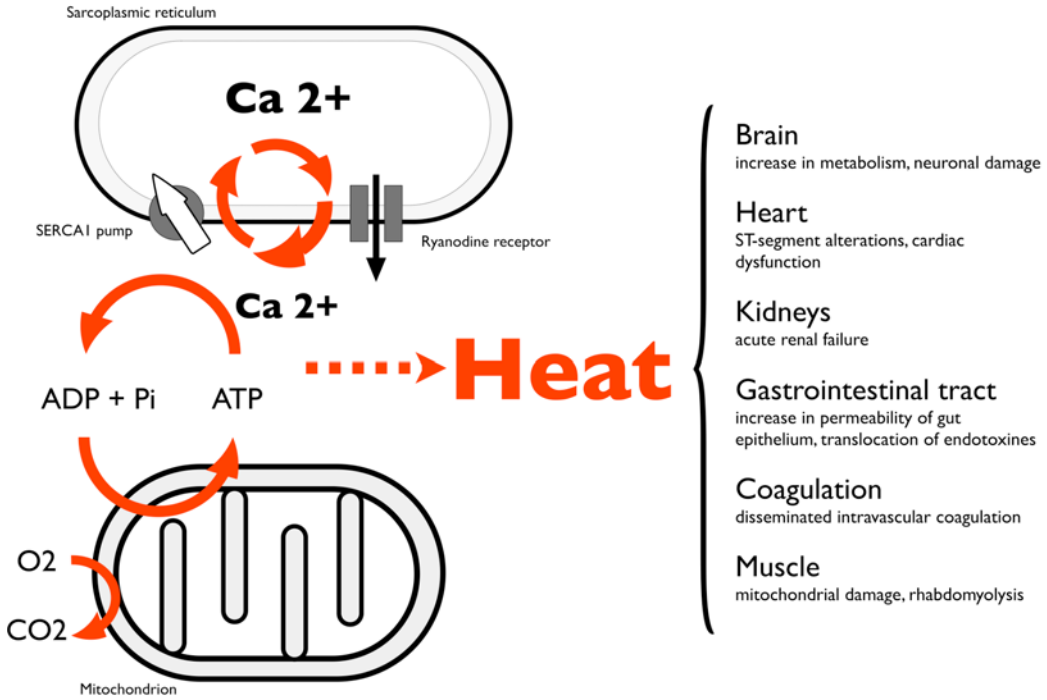

Figure 2: shows a schematic representation of uncontrolled heat production by calcium (Ca^{2+}) cycling in a skeletal muscle cell during an episode of malignant hyperthermia. Halogenated volatile anesthetics and/or succinylcholine induce a sustained opening of the ryanodine receptor. An increase in calcium concentration in the cytoplasm activates the ATP dependent calcium-pump SERCA1 (**s**arcoplasmic/**e**ndoplasmic **r**eticulum **c**alcium **A**TPase **1**). Despite a maximal activation of SERCA1 cytoplasmic calcium concentration rises further. To meet escalating demands of energy rich compounds, mitochondrial synthesis of ATP, mostly by aerobic glycolysis, is raised permanently. The energy of this uncontrolled hyper-metabolism is released in form of pure heat. Heat itself promotes damage in different organ systems.

temperature monitoring for all patients undergoing general anesthesia exceeding 30 minutes. An analysis by Larach *et al*. showed rapidly rising body temperature was the third most frequent clinical sign present during an MH event (65%), following hypercarbia (92%) and sinus tachycardia (73%) [52]. In this analysis elevated body temperature or its rapid increase was observed as one of the first three signs of an MH event, together with others like masseter spasm, hypercarbia, sinus tachycardia, muscular rigidity. Interestingly, 91% of the patients in the analysis of Larach *et al*. had a temperature monitoring, whereas a survey of 316 hospitals in Europe in 2007 found that only 25% of patients undergoing general anesthesia had a temperature monitoring at all [53]. Besides the invasive gold standard of core temperature measurement using a pulmonary artery catheter, multiple alternative temperature monitoring sites like tympanal, rectal, esophageal or urinary bladder seem to reproduce values that are in acceptable correlation to the “true” core temperature [54]. Of note, even after an MH event has been successfully treated with dantrolene, recrudescence of MH can occur (with a remarkable delay). MH recrudescence was reported in up to 20% after an initial MH event. 80% of these events occurred within 16 hours after the initial MH event [55]. So, continuous temperature monitoring may help to timely diagnose such second MH event.

7. EFFICACY OF COOLING MEASURES

The treatment of an MH episode according to the European Malignant Hyperthermia Group (EMHG) [56] should include the following clinical actions: immediately stopping the administration of any triggering agents; installing hyperventilation with 100% oxygen at high flows; calling for help and assistance; changing to non-trigger anesthesia when possible; administering as soon as possible dantrolene (intravenously, 2mg kg^{-1}, including repetition of dosage until cardiac and respiratory systems stabilize); continuous clinical monitoring; and active treatments for and/or preventing hyperthermia, hyperkalemia, acidosis and arrhythmias.

It has been shown that dantrolene can inhibit the ongoing excitation-contraction coupling in the skeletal muscle associated with MH, by depressing the calcium release from the SR. Dantrolene has been reported to bind directly to the RyR1 complex and thus stabilizes the closed state of this calcium release channel, which

in turn restores the inhibitory action of myoplasmic magnesium (Mg^{2+}) [57]. Thus, it ultimately rapidly stops calcium cycling, ATP turnover, elevated oxygen consumption as well as excessive heat production [58] (Figure **2**).

In the MH patient, rapid therapeutic thermoregulatory control is considered important due to the multiple negative effects of hyperthermia on the human body: as was outlined above. More specifically, according to the EMHG, patient cooling should consist of 2000-3000ml of chilled (4°C) 0.9% saline given intravenously together with surface cooling measures (cold sheets, ice packs placed in the axillae and groin) until a temperature of <38.5°C is reached and maintained.

From a therapeutic perspective, heat energy in a given patient can be estimated by assuming an average heat capacity of $3.475 kJ°C^{-1}kg^{-1} \approx 3.5\ kJ°C^{-1}kg^{-1}$ [59] and an equal distribution of heat and or using the Burton formula [60]: MBT= 0.64 T_{Core} + 0.36 T_{Skin} (MBT= Mean Body Temperature, T_{Core}= core-temperature, T_{Skin} = skin-temperature). Therefore, each 1000ml of chilled saline (4°C) applied intravenously will lower body temperature about -0.5°C in a 70-80kg adult and further cooling will likely be necessary. In a recently published study by our group [61] where the efficacy of different noninvasive cooling methods was compared, a temperature decrease of about 0.8°C per hour was observed by using topical cooling measures (with counterwarming of the face to increase shivering threshold [26,62]). Furthermore, Plattner *et al*. [63] compared different cooling modalities and calculated its efficacy in cooling healthy volunteers during general anesthesia: the most effective mechanism in their study was the immersion into slurry ice-water with a cooling effect of -9.7°C ± 4.4°C/hour. (It should be noted that the clinical application of gastric lavage is no longer in common clinical use because of induced adverse events (abdominal cramps, diarrhoea) and that bladder lavage did not provide a clinically relevant cooling benefit).

8. CONCLUSION

It was the aim of this review to emphasize the importance of heat during an ongoing MH event. Overproduction of heat plays a paramount role in pushing towards fatality in case of evolving MH: Hyperthermia is not merely a simple consequence (bystander) of MH, but rather a major factor in a severe or even fatal course of events itself. Hyperthermia, irrespective of its causative origin, can lead to multisystem organ dysfunctions and eventually failures, which includes the brain, the heart and the hemostatic systems. Thus, heat monitoring and active control of body temperature by the use of cooling measures are cornerstones in the treatment of an MH event, besides discontinuation of trigger substances and dantrolene medication.

REFERENCES

[1] Bandschapp O, Girard T. Malignant hyperthermia. Swiss Med Wkly 2012; 142: w13652.

[2] Denborough M, Lovell R. Anaesthetic deaths in a family (letter). Lancet 1960; 276: 45. http://dx.doi.org/10.1016/S0140-6736(60)92690-8

[3] Denborough M. Malignant hyperthermia. Lancet 1998; 352: 1131-36. http://dx.doi.org/10.1016/S0140-6736(98)03078-5

[4] Hall LW, Woolf N, Bradley JW, Jolly DW. Unusual reaction to suxamethonium chloride. Br Med J 1966; 2: 1305. http://dx.doi.org/10.1136/bmj.2.5525.1305

[5] Britt BA, Kalow W. Malignant hyperthermia: A statistical review. Can Anaesth Soc J 1970; 17: 293-15. http://dx.doi.org/10.1007/BF03004694

[6] Lucke JN, Hall GM, Lister D. Porcine malignant hyperthermia. I: Metabolic and physiological changes. Br J Anaesth 1976; 48: 297-304. http://dx.doi.org/10.1093/bja/48.4.297

[7] Nelson TE. Heat production during anesthetic-induced malignant hyperthermia. Biosci Rep 2001; 21: 169-79. http://dx.doi.org/10.1023/A:1013696124358

[8] Gjessing J, Barsa J, Tomlin PJ. A possible means of rapid cooling in the emergency treatment of malignant hyperpyrexia. Br J Anaesth 1976; 48: 469-73. http://dx.doi.org/10.1093/bja/48.5.469

[9] Ruitenbeek W, Verburg MP, Janssen AJ, Stadhouders AM, Sengers RC. In vivo induced malignant hyperthermia in pigs. Ii. Metabolism of skeletal muscle mitochondria. Acta Anaesthesiol Scand 1984; 28: 9-13. http://dx.doi.org/10.1111/j.1399-6576.1984.tb02002.x

[10] Foster DO, Frydman ML. Brown adipose tissue: The dominant site of nonshivering thermogenesis in the rat. Experientia Suppl 1978; 32: 147-51. http://dx.doi.org/10.1007/978-3-0348-5559-4_16

[11] Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, *et al.* Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009; 360: 1509-17. http://dx.doi.org/10.1056/NEJMoa0810780

[12] Richard D, Monge-Roffarello B, Chechi K, Labbe SM, Turcotte EE. Control and physiological determinants of sympathetically mediated brown adipose tissue thermogenesis. Front Endocrinol 2012; 3: 36. http://dx.doi.org/10.3389/fendo.2012.00036

[13] Muzik O, Mangner TJ, Granneman JG. Assessment of oxidative metabolism in brown fat using pet imaging. Front Endocrinol 2012; 3: 15. http://dx.doi.org/10.3389/fendo.2012.00015

[14] Hall GM, Bendall JR, Lucke JN, Lister D. Porcine malignant hyperthermia. Ii: Heat production. Br J Anaesth 1976; 48: 305-308. http://dx.doi.org/10.1093/bja/48.4.305

[15] Britt BA, Endrenyi L, Kalow W, Peters PL. The adenosine triphosphate (atp) depletion test: Comparison with the

caffeine contracture test as a method of diagnosing malignant hyperthermia susceptibility. Can Anaesth Soc J 1976; 23: 624-35.
http://dx.doi.org/10.1007/BF03006745

[16] Ellis FR, Harriman DG, Keaney NP, Kyei-Mensah K, Tyrrell JH. Halothane-induced muscle contracture as a cause of hyperpyrexia. Br J Anaesth 1971; 43: 721-22.

[17] Hall GM, Lucke JN, Lister D. Porcine malignant hyperthemia iv: Neuromuscular blockade. Br J Anaesth 1976; 48: 1135-41.
http://dx.doi.org/10.1093/bja/48.12.1135

[18] A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. The european malignant hyperpyrexia group. Br J Anaesth 1984; 56: 1267-69.
http://dx.doi.org/10.1093/bja/56.11.1267

[19] Larach MG. Standardization of the caffeine halothane muscle contracture test. North american malignant hyperthermia group. Anesth Analg 1989; 69: 511-15.
http://dx.doi.org/10.1213/00000539-198910000-00015

[20] Bandschapp O, Iaizzo P, Girard T. Malignant hyperthermia - update of diagnostics. Trends in Anaesthesia and Critical Care 2012; 2: 218-23.
http://dx.doi.org/10.1016/j.tacc.2012.08.001

[21] MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk RG, *et al*. Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature 1990; 343: 559-61.
http://dx.doi.org/10.1038/343559a0

[22] Toppin PJ, Chandy TT, Ghanekar A, Kraeva N, Beattie WS, Riazi S. A report of fulminant malignant hyperthermia in a patient with a novel mutation of the cacna1s gene. Can J Anaesth 2010; 57: 689-93.
http://dx.doi.org/10.1007/s12630-010-9314-4

[23] Eltit JM, Bannister RA, Moua O, Altamirano F, Hopkins PM, Pessah IN, *et al*. Malignant hyperthermia susceptibility arising from altered resting coupling between the skeletal muscle l-type ca2+ channel and the type 1 ryanodine receptor. Proc Natl Acad Sci USA 2012; 109: 7923-28.
http://dx.doi.org/10.1073/pnas.1119207109

[24] Kraeva N, Riazi S, Loke J, Frodis W, Crossan ML, Nolan K, Kraev A, Maclennan DH. Ryanodine receptor type 1 gene mutations found in the canadian malignant hyperthermia population. Can J Anaesth 2011; 58: 504-13.
http://dx.doi.org/10.1007/s12630-011-9494-6

[25] Dulhunty AF, Beard NA, Pouliquin P, Kimura T. Novel regulators of ryr Ca^{2+} release channels: Insight into molecular changes in genetically-linked myopathies. J Muscle Res Cell Motil 2006; 27: 351-65.
http://dx.doi.org/10.1007/s10974-006-9086-1

[26] Bandschapp O, Iaizzo PA. Induction of therapeutic hypothermia requires modulation of thermoregulatory defenses. Therapeutic Hypothermia and Temperature Management 2011; 1: 77-85.
http://dx.doi.org/10.1089/ther.2010.0010

[27] Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol 2000; 89: 81-88.

[28] Morrissette JM, Franck JP, Block BA. Characterization of ryanodine receptor and ca2+-atpase isoforms in the thermogenic heater organ of blue marlin (Makaira nigricans). J Exp Biol 2003; 206: 805-12.
http://dx.doi.org/10.1242/jeb.00158

[29] Arruda AP, Nigro M, Oliveira GM, de Meis L. Thermogenic activity of Ca^{2+}-atpase from skeletal muscle heavy sarcoplasmic reticulum: The role of ryanodine Ca^{2+} channel. Biochim Biophys Acta 2007; 1768: 1498-505.
http://dx.doi.org/10.1016/j.bbamem.2007.03.016

[30] Bal NC, Maurya SK, Sopariwala DH, Sahoo SK, Gupta SC, Shaikh SA, *et al*. Sarcolipin is a newly identified regulator of muscle-based thermogenesis in mammals. Nat Med 2012; 18: 1575-79.
http://dx.doi.org/10.1038/nm.2897

[31] Kim JH, Kwon TH, Koh SB, Park JY. Parkinsonism-hyperpyrexia syndrome after deep brain stimulation surgery: Case report. Neurosurgery 2010; 66: E1029.
http://dx.doi.org/10.1227/01.NEU.0000367799.38332.43

[32] Robottom BJ, Weiner WJ, Factor SA. Movement disorders emergencies. Part 1: Hypokinetic disorders. Arch Neurol 2011; 68: 567-72.
http://dx.doi.org/10.1001/archneurol.2011.84

[33] Allen GC, Brubaker CL. Human malignant hyperthermia associated with desflurane anesthesia. Anesth Analg 1998; 86: 1328-31.

[34] Gatz EE, Wingard DW. Malignant hyperthermia. Nebr Med J 1973; 58: 434-37.

[35] Iaizzo PA, Kehler CH, Carr RJ, Sessler DI, Belani KG. Prior hypothermia attenuates malignant hyperthermia in susceptible swine. Anesth Analg 1996; 82: 803-809.

[36] Yasuda T, Delbono O, Wang ZM, Messi ML, Girard T, Urwyler A, *et al*. Jp-45/jsrp1 variants affect skeletal muscle excitation-contraction coupling by decreasing the sensitivity of the dihydropyridine receptor. Hum Mutat 2013; 34(1): 184-90.
http://dx.doi.org/10.1002/humu.22209

[37] Mitchell AM, Kennedy RR. Preoperative core temperatures in elective surgical patients show an unexpected skewed distribution. Can J Anaesth 2001; 48: 850-53.
http://dx.doi.org/10.1007/BF03017348

[38] Nonneman DJ, Brown-Brandl T, Jones SA, Wiedmann RT, Rohrer GA. A defect in dystrophin causes a novel porcine stress syndrome. BMC Genomics 2012; 13: 233.
http://dx.doi.org/10.1186/1471-2164-13-233

[39] Denborough M, Hopkinson KC, O'Brien RO, Foster PS. Overheating alone can trigger malignant hyperthermia in piglets. Anaesth Intensive Care 1996; 24: 348-54.

[40] Lichtman AD, Oribabor C. Malignant hyperthermia following systemic rewarming after hypothermic cardiopulmonary bypass. Anesth Analg 2006; 102: 372-75.
http://dx.doi.org/10.1213/01.ane.0000189596.70694.36

[41] Groom L, Muldoon SM, Tang ZZ, Brandom BW, Bayarsaikhan M, Bina S, *et al*. Identical de novo mutation in the type 1 ryanodine receptor gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. Anesthesiology 2011; 115: 938-45.
http://dx.doi.org/10.1097/ALN.0b013e3182320068

[42] Capacchione JF, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. Anesth Analg 2009; 109: 1065-69.
http://dx.doi.org/10.1213/ane.0b013e3181a9d8d9

[43] Pandita TK, Pandita S, Bhaumik SR. Molecular parameters of hyperthermia for radiosensitization. Crit Rev Eukaryot Gene Expr 2009; 19: 235-51.
http://dx.doi.org/10.1615/CritRevEukarGeneExpr.v19.i3.50

[44] Wass CT, Lanier WL, Hofer RE, Scheithauer BW, Andrews AG. Temperature changes of > or = 1 degree c alter functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia. Anesthesiology 1995; 83: 325-35.
http://dx.doi.org/10.1097/00000542-199508000-00013

[45] Zeller L, Novack V, Barski L, Jotkowitz A, Almog Y. Exertional heatstroke: Clinical characteristics, diagnostic and therapeutic considerations. Eur J Intern Med 2011; 22: 296-99.
http://dx.doi.org/10.1016/j.ejim.2010.12.013

[46] Bertolizio G, Mason L, Bissonnette B. Brain temperature: Heat production, elimination and clinical relevance. Paediatr Anaesth 2011; 21: 347-58.
http://dx.doi.org/10.1111/j.1460-9592.2011.03542.x

[47] Lim CL, Mackinnon LT. The roles of exercise-induced immune system disturbances in the pathology of heat stroke: The dual pathway model of heat stroke. Sports Med 2006; 36: 39-64. http://dx.doi.org/10.2165/00007256-200636010-00004

[48] Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002; 346: 1978-88. http://dx.doi.org/10.1056/NEJMra011089

[49] White MG, Luca LE, Nonner D, Saleh O, Hu B, Barrett EF, Barrett JN. Cellular mechanisms of neuronal damage from hyperthermia. Prog Brain Res 2007; 162: 347-71. http://dx.doi.org/10.1016/S0079-6123(06)62017-7

[50] Burke S, Hanani M. The actions of hyperthermia on the autonomic nervous system: Central and peripheral mechanisms and clinical implications. Auton Neurosci 2012; 168: 4-13. http://dx.doi.org/10.1016/j.autneu.2012.02.003

[51] Castillo J, Davalos A, Noya M. Aggravation of acute ischemic stroke by hyperthermia is related to an excitotoxic mechanism. Cerebrovasc Dis 1999; 9: 22-27. http://dx.doi.org/10.1159/000015891

[52] Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in north america from 1987 to 2006. Anesth Analg 2010; 110: 498-507. http://dx.doi.org/10.1213/ANE.0b013e3181c6b9b2

[53] Torossian A. Survey on intraoperative temperature management in europe. Eur J Anaesthesiol 2007; 24: 668-75. http://dx.doi.org/10.1017/S0265021507000191

[54] Shin J, Kim J, Song K, Kwak Y. Core temperature measurement in therapeutic hypothermia according to different phases: Comparison of bladder, rectal, and tympanic versus pulmonary artery methods. Resuscitation 2013; 84: 810-17. http://dx.doi.org/10.1016/j.resuscitation.2012.12.023

[55] Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. Anesthesiology 2007; 106: 901-906; quiz 1077-1078. http://dx.doi.org/10.1097/01.anes.0000265148.86566.68

[56] Glahn KP, Ellis FR, Halsall PJ, Muller CR, Snoeck MM, Urwyler A, *et al*. Recognizing and managing a malignant hyperthermia crisis: Guidelines from the european malignant hyperthermia group. Br J Anaesth 2010; 105: 417-20. http://dx.doi.org/10.1093/bja/aeq243

[57] Kobayashi S, Bannister ML, Gangopadhyay JP, Hamada T, Parness J, Ikemoto N. Dantrolene stabilizes domain interactions within the ryanodine receptor. J Biol Chem 2005; 280: 6580-87. http://dx.doi.org/10.1074/jbc.M408375200

[58] Inan S, Wei H. The cytoprotective effects of dantrolene: A ryanodine receptor antagonist. Anesth Analg 2010; 111: 1400-10. http://dx.doi.org/10.1213/ANE.0b013e3181f7181c

[59] Burton A. Human calorimetry ii. The average temperature of the tissues of the body. J Nutr 1935; 9: 261-80.

[60] Lenhardt R, Sessler DI. Estimation of mean body temperature from mean skin and core temperature. Anesthesiology 2006; 105: 1117-21. http://dx.doi.org/10.1097/00000542-200612000-00011

[61] Bandschapp O, Sweney M, Miller J, Tahvildari S, Sigg D, Iaizzo P. Induction of mild hypothermia by non-invasive body cooling: Assessment on healthy, unanesthetized subjects. Therapeutic Hypothermia and Temperature Management 2011; 1: 193-98. http://dx.doi.org/10.1089/ther.2011.0006

[62] Iaizzo PA, Jeon YM, Sigg DC. Facial warming increases the threshold for shivering. J Neurosurg Anesthesiol 1999; 11: 231-39. http://dx.doi.org/10.1097/00008506-199910000-00002

[63] Plattner O, Kurz A, Sessler DI, Ikeda T, Christensen R, Marder D, *et al*. Efficacy of intraoperative cooling methods. Anesthesiology 1997; 87: 1089-95. http://dx.doi.org/10.1097/00000542-199711000-00013

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