


Malignant Hyperthermia: A Literature Review

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ABSTRACT

Malignant hyperthermia (MH) is a life-threatening syndrome triggered by inhaled anesthetics and depolarizing muscle relaxants like succinylcholine, leading to uncontrolled skeletal muscle hypermetabolism. This condition is marked by massive calcium release from the endoplasmic reticulum, causing muscle rigidity, increased temperature, and metabolic disturbances. The genetic basis of MH is linked to mutations in the CACNA1S gene, which encodes a subunit of the dihydropyridine receptor (DHPR), which is essential to muscle calcium regulation. The condition is often triggered during surgeries requiring general or regional anesthesia, particularly in individuals with a family history of MH. Clinical manifestations may include hypercapnia, tachycardia, acidosis, rhabdomyolysis, and multi-organ dysfunction. Early diagnosis remains challenging because MH may resemble other hypermetabolic conditions and can progress rapidly if left untreated. Treatment involves the administration of dantrolene, a post-synaptic muscle relaxant that reduces excitation-contraction coupling (ECC) and mitigates hypermetabolism. Early recognition and prompt dantrolene administration are vital for successful management.

Keywords: Anaesthesia, dantrolene, dihydropyridine receptor, malignant hyperthermia.

ABSTRAK

Hipertermia maligna (HM) adalah sindrom yang dapat mengancam nyawa disebabkan oleh pemberian agen anestesi volatil dan relaksan otot depolarisasi seperti *succinylcholine*, berupa peningkatan metabolisme otot rangka yang tidak terkendali. Kondisi MH disertai pembukaan saluran kalsium pada membran retikulum sarkoplasma (SR), yang memicu kontraksi otot berlebihan, peningkatan suhu, dan gangguan metabolisme. Basis genetik MH dikaitkan dengan mutasi gen CACNA1S yang mengkode subunit reseptor *dihydropyridine* (DHPR), protein-protein penting untuk regulasi kalsium otot. Kondisi ini sering dipicu selama operasi yang membutuhkan anestesi umum atau regional, terutama pada individu yang memiliki riwayat keluarga MH. Manifestasi klinis dapat berupa hiperkapnia, takikardia, asidosis, rabdomiolisis, hingga disfungsi multiorgan. Diagnosis dini sering kali menjadi tantangan karena HM memiliki gejala yang menyerupai kondisi hipermetabolik lainnya dan dapat berkembang dengan cepat apabila tidak segera ditangani. Pengobatan meliputi pemberian *dantrolene*, yang berfungsi sebagai relaksan otot pasca-sinaptik untuk mengurangi *coupling* eksitasi-kontraksi (ECC) pada sel otot dan mengurangi hipermetabolisme. Pengenalan dini dan pemberian *dantrolene* segera sangat penting untuk keberhasilan penatalaksanaan. **Carla Oktaviani Pandrya , Kevin Anderson Surya. Hipertermia Maligna: Tinjauan Literatur.**

Kata Kunci: Anestesi, dantrolene, reseptor *dihydropyridine*, hipertermia maligna.

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INTRODUCTION

Malignant hyperthermia (MH) is an inherited skeletal muscle disorder that typically manifests as a hypermetabolic reaction to halogenated anaesthetic gases and/or the depolarizing muscle relaxant succinylcholine. It also relates to a massive calcium release from the endoplasmic reticulum, causing muscle rigidity, increased temperature, and metabolic disturbances.[1] The incidence of MH ranges from 1:35,000 to 1:68,000 in surgical patients, and globally, it was found in 200 million surgical cases, with 15% in China, it has a mortality rate as high as 73.5%.[2] The global population that is considered to be susceptible to MH can reach 1:2,000; this signifies that not only is this lethal, but it has a potentially high incidence rate.[3]

MH has been recorded since the 1980s by the Association of Anaesthetists, and a guideline was established in 2020 to provide a definitive approach for addressing this persistent issue.[4] A personal history of the anaesthetics of the patient and their family is important to identify potential risk of having MH during surgery and, therefore, to be able to mitigate or limit the potential risk of adverse events of MH.[4]

Most cases of MH are caused by the administration of a volatile anaesthetic agent with or without succinylcholine, and thus, should it be triggered, an administration of

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dantrolene is deemed suitable to handle this matter. Dantrolene is a post-synaptic muscle relaxant that lessens ECC in muscle cells, thus acting as a disease-specific drug for MH.[5,6]

This condition can also cause hypercarbia, hypoxemia, acidosis, arrhythmias, rhabdomyolysis, renal and circulatory failure and fatal outcomes such as death.[5] MH owes its high mortality rates due to false diagnosis and lack of targeted therapy due to its unpredictable nature. Thus, an increased education and awareness by the anaesthesiologist is needed.[7] This review aims to synthesize the current knowledge on malignant hyperthermia, focusing on its diagnosis and treatment.

DISCUSSION

Etiology

Despite its potentially life-threatening nature, MH in itself is a relatively uncommon problem, owing perhaps to its genetic predisposition, as some individuals are more susceptible to halogenated volatile anaesthetics, depolarizing muscle relaxants and succinylcholine. However, this condition can rarely occur due to physical exertion or heat stress.[8]

Genetics is shown to be the aetiology of MH. The primary genetic mutation associated with malignant hyperthermia occurs in the RYR1 gene, which encodes the ryanodine receptor, a critical calcium channel in skeletal muscle cells. Mutations in this gene lead to uncontrolled calcium release from the sarcoplasmic reticulum, resulting in sustained muscle contraction and increased metabolic activity. Other genes implicated include CACNA1S and STAC3, though these are less common.[1] Furthermore, RYR1 and CACNA1S are also well documented in cases of myopathies, thus highlighting the relationship between genetics and its effects on myopathy and, therefore, its potential to trigger MH.[5]

Further relations to systemic disease have also been observed, and variants classification of genetics involved has also been well catalogued.

Risk Factor

Patients at increased risk of developing MH when exposed to triggering agents include the following:[4]

- Individuals with a close relative confirmed to be susceptible to MH
- Personal or family history of suspected MH episodes during anaesthesia
- Individuals with a personal or family history of rhabdomyolysis, mainly triggered by exercise in extreme heat or humidity or by statin use
- Patients diagnosed with other genetic muscle disorders, such as Duchenne muscular dystrophy
- Those with idiopathic hyperCKemia
- Individuals with unexplained exertional heat illness

Patients found to be more susceptible to MH based on personal or family history can be confirmed through identification of pathogenic genetic variants to MH or thorough *in-vitro* muscle contracture tests; these procedures can be carried out pre-op to minimize the likelihood of MH.[9]

Pathophysiology

The pathophysiology of MH is linked to a defect in the ryanodine receptor (RYR1) located in the sarcoplasmic reticulum of skeletal muscle cells. This defect leads to an abnormal release of calcium ions when the muscle is exposed to triggering agents, resulting in prolonged muscle contraction and a significant increase in metabolic activity. The excessive calcium release also causes a cascade of events, including increased oxygen consumption, carbon dioxide production, and heat generation, which are hallmark symptoms of MH.[6]

The specific MH mechanism is closely linked to genetic factors, particularly mutations in genes such as CACNA1S. This gene encodes a subunit of the dihydropyridine receptor (DHPR), which plays a critical role in muscle cell excitation-contraction coupling. When motoneurons trigger action potentials in muscle cells, these electrical signals propagate along the T-tubular membrane, leading to its depolarization. This depolarization induces conformational changes in the DHPR, which in turn initiates a cascade of events resulting in the opening of calcium channels on the sarcoplasmic reticulum (SR) membrane. Through protein interactions, this process causes the release of calcium ions (Ca^{2+}) from the SR into the cytoplasm, ultimately triggering muscle contraction. In individuals with MH susceptibility, this pathway becomes dysregulated, leading to excessive calcium release and the characteristic symptoms of MH.[9]

In addition to genetic predispositions, several external factors can contribute to the onset or exacerbation of MH. These include viral infections, the use of statins, hyperglycemia, and underlying muscle metabolic dysfunctions. It has been confirmed that chronic viral infections can lead to muscle pathologies such as chronic inflammatory myopathy (CIM), myositis, and rhabdomyolysis. These conditions can increase the risk of developing MH by further compromising muscle function and exacerbating the hypermetabolic state triggered by anaesthetic agents. The interplay between these factors and the underlying genetic predispositions highlights the complexity of MH and underscores the need for vigilant monitoring and prompt intervention in susceptible individuals.[10-12]

Diagnosis

MH, also known as malignant hyperpyrexia, presents diagnostic challenges due to its similarity with other hypermetabolic conditions, notably Exertional Heat Stroke (EHS). Both MH and EHS are potentially life-threatening disorders characterized by a rapid and severe increase in metabolic activity, leading to hyperthermia, acidosis, and multi-organ dysfunction if not promptly treated. The shared feature of these conditions is their connection to calcium dysregulation within muscle cells, which is a critical factor in their pathophysiology.[13]

Despite these similarities, the underlying triggers and mechanisms for calcium dysregulation in MH and EHS are distinctly different. In the case of EHS, the condition arises from prolonged physical exertion combined with exposure to high environmental temperatures. This excessive heat load overwhelms the body's ability to dissipate heat, leading to an uncontrolled rise in body temperature and subsequent cellular stress. Excessive heat and exertion cause a breakdown in calcium homeostasis within muscle cells, resulting in hyperthermia and

the clinical manifestations of EHS.[13]

On the other hand, MH is a pharmacogenetic disorder triggered by the administration of specific anaesthetic agents, such as volatile inhalational anaesthetics (e.g., halothane, sevoflurane) and the depolarizing muscle relaxant succinylcholine. These agents cause a mutation-related malfunction in the ryanodine receptor (RYR1) or other proteins involved in calcium regulation within the sarcoplasmic reticulum of skeletal muscle cells. This malfunction leads to excessive calcium release into the cytoplasm, causing sustained muscle contractions, increased metabolic activity, and rapid onset of hyperthermia.[14]

A MH diagnosis is established based on clinical symptoms and laboratory findings. Key clinical signs of MH include unexplained elevations in ETCO2 levels, tachycardia, muscle rigidity, combined metabolic and respiratory acidosis, hyperthermia, cardiac arrhythmias, and renal failure. The international clinical grading scale, developed using the Delphi method, allows for the qualitative assessment of the likelihood of an MH episode by assigning scores to specific clinical indicators. The grading of MH risk is based on seven criteria, including:[5]

1. Rigidity, defined as muscle rigidity
2. Muscle breakdown, can be detected in an increased level of creatine kinase and the presence of myoglobin in urine
3. Respiratory acidosis, which is an increased presence of acid in the body's circulation, and furthermore, it can also cause hypercarbia and tachypnea
4. Temperature increase, this can be signified by a rapid increase
5. Cardiac involvement
6. Family history
7. Other indicators

Despite their differences, both MH and EHS highlight the importance of early recognition and prompt intervention to prevent fatal outcomes. The overlap in their clinical presentations, particularly in the early stages, underscores the need for careful assessment and differential diagnosis, particularly in situations where the trigger may not be immediately clear.[13-15]

Treatment

Given the distinct etiology of both MH and EHS conditions, their management strategies also differ significantly. Treatment of EHS focuses on immediate cooling to reduce core body temperature and supportive care to manage systemic complications. Rapid initiation of cooling measures is critical in reducing the risk of permanent organ damage and improving survival outcomes. In contrast, the treatment of MH involves the prompt administration of dantrolene, a specific antagonist that inhibits calcium release from the sarcoplasmic reticulum, thereby reversing the hypermetabolic state. Supportive care, including cooling measures, correction of acidosis, and management of electrolyte imbalances, is also essential in the management of MH.[15]

Most cases of MH are triggered by the administration of volatile anaesthetic agents, such as sevoflurane, isoflurane, and desflurane, either with or without the use of succinylcholine. These agents are commonly used in general anesthesia to induce and maintain unconsciousness during surgical procedures. In individuals with a genetic predisposition to MH, these anaesthetics can precipitate a life-threatening hypermetabolic reaction, characterized by a rapid increase in body temperature, severe muscle rigidity, acidosis, and hypercapnia, all of which can escalate rapidly if not promptly treated.[5] A workflow for anaesthesia in patients suspected of MH risk has been formulated **(Scheme)**.[9]

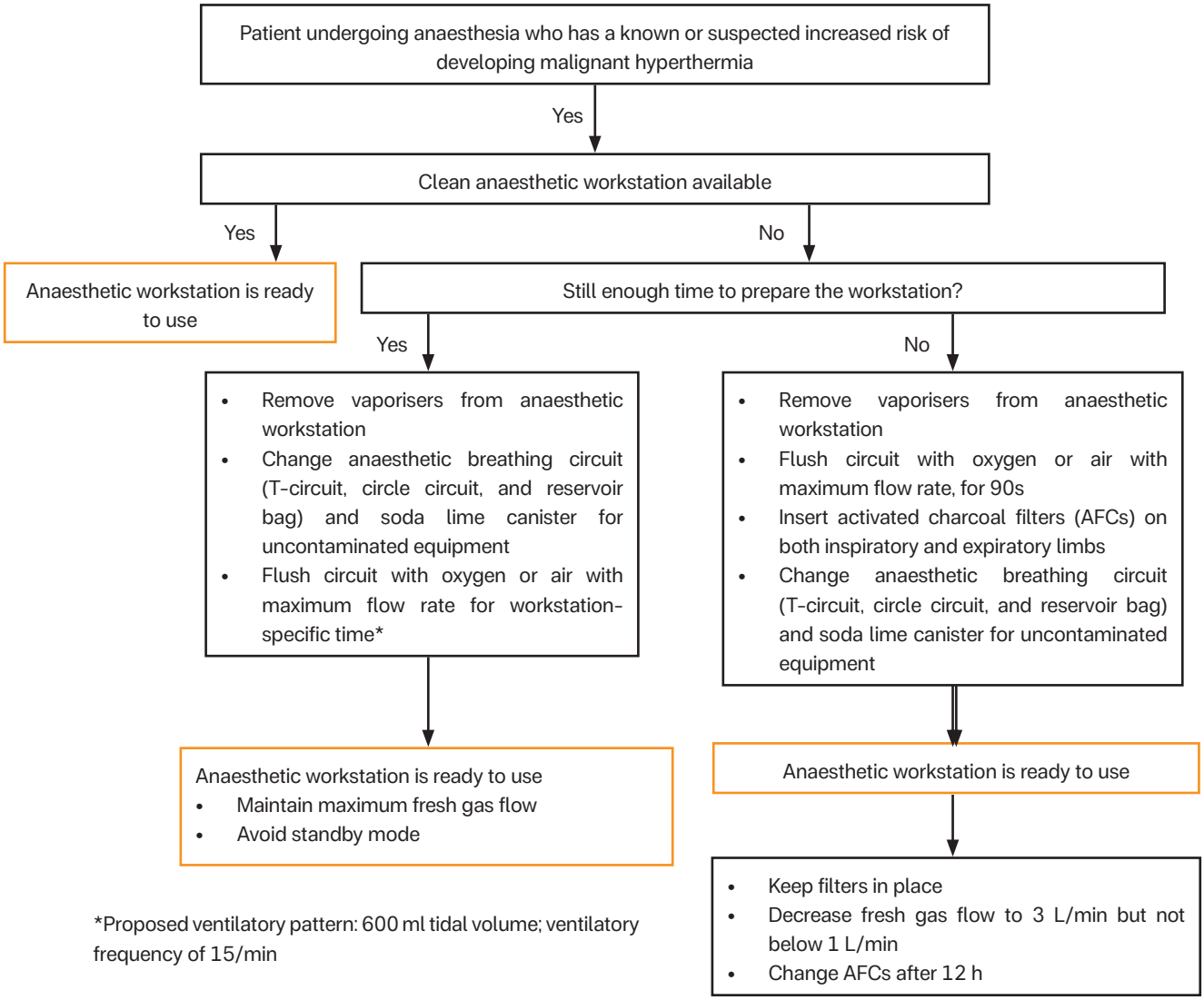
In the event of an MH crisis, the administration of dantrolene is deemed the most effective and specific treatment by inhibiting RyR1-mediated intracellular calcium release from the sarcoplasmic reticulum of skeletal muscle cells.[16] Dantrolene acts as a post-synaptic muscle relaxant by inhibiting excitation-contraction coupling (ECC) in muscle cells through binding to the ryanodine receptor, thereby reducing the release of calcium from the sarcoplasmic reticulum. By limiting calcium release, dantrolene helps to alleviate muscle rigidity and decrease the hypermetabolic state, effectively reversing the symptoms of MH.[16]

The role of dantrolene in the management of MH cannot be overstated. It is the only known antidote that directly addresses the underlying mechanism of the condition. Without timely administration of dantrolene, patients can rapidly progress to complications such as rhabdomyolysis, renal failure, disseminated intravascular coagulation, and even death. Therefore, the availability of dantrolene in any setting where volatile anaesthetics or succinylcholine are used is considered a critical safety measure.[16]

Dantrolene is the specific antidote for MH events. In addition to its acute therapeutic effects, dantrolene has been shown to improve survival rates and reduce the incidence of long-term complications associated with MH.[17,18] The drug's ability to specifically target the dysfunctional calcium channels in muscle cells makes it an essential component of the MH treatment protocol. Moreover, the use of dantrolene as a preventive measure in known MH-susceptible individuals undergoing surgery has also been explored, further highlighting its significance in the management of this condition.[16]

The administration of dantrolene involves titrating the dose to achieve the desired effect, starting with an initial dose of 2–3 mg/kg. As reconstitution takes time, each prepared syringe should be administered immediately. Additional doses of 1 mg/kg should be given as needed until the treatment goals are met. The treatment goals include achieving an ETCO2 level below 6 kPa, normal minute ventilation, and a core body temperature below 38.5°C. Once these goals are achieved, dantrolene administration can be paused; however, additional doses may be required if there is a rise in CO2 levels or body temperature.[4]

To support further management, essential routine monitoring should be enhanced with core temperature monitoring and direct arterial blood pressure measurement, facilitating regular blood sampling. A urinary catheter should be placed to monitor urine output and pH and detect myoglobinuria.[16] Laboratory analysis should include hemoglobin, coagulation panel, renal and hepatic function, creatine kinase, myoglobin, glucose, electrolytes, and arterial blood gases.[19,20]



Scheme. Schematic representations of the workflow for anaesthesia in patients suspected of MH (Adapted from Rüffert H, 2021).[9]

Post Malignant Hyperthermia Management

The ASA advises that the patient should remain sedated post-surgery until all metabolic abnormalities have been rectified.[4] Following the event, the patient should be gradually weaned from ventilatory support as per standard protocol.[21] The recurrence of malignant hyperthermia (MH) is widely documented; its probability and intensity correlate with the severity of the initial MH episode. If the reaction was managed in its initial phases, characterised by a response to the cessation of the triggering agents without requiring dantrolene, it is prudent to awaken the patient post-surgery and observe them for a minimum of one hour in the post-anesthesia care unit before transferring them to the postoperative ward. Discharging the patient from the hospital within 24 hours post-surgery, following a suspected MH reaction, would be imprudent. If dantrolene was necessary to counteract the initial malignant hyperthermia reaction, the patient must be observed and cared for in a high dependency unit or intensive care unit for a minimum of 24 hours post-event. The decision between high dependency and ICU management will be contingent upon the patient's state, the necessity for ongoing mechanical ventilation, and the requirement for invasive monitoring.[4]

Complications

Life-threatening complications caused by malignant hyperthermia include DIC, congestive heart failure, bowel ischemia, and compartment syndrome of the limbs secondary to profound muscle swelling, pulmonary edema, hepatic dysfunction, coma and renal failure from rhabdomyolysis. Indeed, when body temperature exceeds approximately 41°C, DIC is the usual cause of death.[22,23]

Prognosis

The prognosis of malignant hyperthermia depends on rapid recognition and early treatment of the crisis, and patients with high muscular mass are at higher risk for adverse outcomes.[19,20] When malignant hyperthermia was first recognized as a consequence of anesthesia, the mortality rate associated with MH was 70%–80%.[21] Currently, the mortality rate is estimated to be less than 5%, with early identification of malignant hyperthermia episodes using capnography, prompt use of the drug dantrolene, and the introduction of

diagnostic testing. Despite the low mortality rates associated with MH, a recent study by Larach et al. indicates that the morbidity rate is 34.8%.[22] The elevated morbidity rate underscores the necessity for ongoing education of anaesthesiologists regarding the most effective methods for diagnosing and treating MH.[23]

CONCLUSION

MH is a genetically predisposed and potentially fatal condition that may occur during procedures requiring general or regional anaesthesia that can be mitigated through very thorough anaesthesia usage and a family history of MH occurrence. Careful anesthetic assessment and detailed family history taking are essential to reduce the risk of MH occurrence. Early recognition and prompt intervention are essential to prevent fatal outcomes. An administration of dantrolene has been found to be sufficient to treat cases of MH during an ongoing surgery.

Acknowledgement

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Conflict of Interest

None.

REFERENCES

1. Watt S, McAllister RK. Malignant hyperthermia. StatPearls Publishing [Internet]. 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430828/.
2. Tan L, Teng Y, Yu H, Liu C, Xiao K, Yin J, et al. Clinical features of suspected malignant hyperthermia in China from 2015 to 2020: a retrospective study from China malignant hyperthermia emergency assistance group. J Multidisciplinary Healthcare. 2022;15:3005–13. doi: 10.2147/JMDH.S387208.
3. Rodrigues G, Andrade PV, Dos Santos JM, de Castro I, do Amaral JLG, da Silva HCA. Patient suspected susceptibility to malignant hyperthermia: impact of the disease. Braz J Anesthesiol. 2023;73(2):138–44. doi: 10.1016/j.bjane.2021.10.021.
4. Hopkins PM, Girard T, Dalay S, Jenkins B, Thacker A, Patteril M, et al. Malignant hyperthermia 2020: guideline from the Association of Anaesthetists. Anaesthesia. 2021;76(5):655–64. doi: 10.1111/anae.15317.
5. Yang L, Tautz T, Zhang S, Fomina A, Liu H. The current status of malignant hyperthermia. J Biomed Res. 2020;34:75–85. doi: 10.7555/JBR.33.20180089.
6. Litman RS, Smith VI, Larach MG, Mayes L, Shukry M, Theroux MC, et al. Consensus statement of the Malignant Hyperthermia Association of the United States on unresolved clinical questions concerning the management of patients with malignant hyperthermia. Anesth Analg. 2019;128(4):652–9. doi: 10.1213/ANE.0000000000004039.
7. Cieniewicz A, Trzebicki J, Mayzner-Zawadzka E, Kostera-Pruszczyk A, Owczuk R. Malignant hyperthermia - what do we know in 2019? Anaesthesiol Intensive Ther. 2019; 51:169–77. doi: 10.5114/ait.2019.87646.
8. Kim KSM, Kriss RS, Tautz TJ. Malignant hyperthermia: a clinical review. Adv Anesth. 2019;37:35–51. doi: 10.1016/j.aan.2019.08.003.
9. Ruffert H, Bastian B, Bendixen D, Girard T, Heiderich S, Hellblom A, et al. Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients from the European Malignant Hyperthermia Group. Br J Anaesth. 2021;126(1):120–30. doi: 10.1016/j.bja.2020.09.029.
10. Bin X, Wang B, Tang Z. Malignant hyperthermia: a killer if ignored. J Perianesth Nurs. 2022;37(4):435–44. doi: 10.1016/j.jopan.2021.08.018.
11. Van den Bersselaar LR, Hellblom A, Gashi M, Kamsteeg EJ, Voermans NC, Jungbluth H, et al. Referral indications for malignant hyperthermia susceptibility diagnostics in patients without adverse anaesthetic events in the era of next-generation sequencing. Anesthesiology. 2022;136(6):940–53. doi: 10.1097/ALN.0000000000004199.
12. Ortiz JF, Wirth M, Eskander N, Cozar JC, Fatade O, Rathod B. The genetic foundations of serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia: is there a genetic association between these disorders? Cureus. 2020;12(9):e10635. doi: 10.7759/cureus.10635.
13. Laitano O, Murray KO, Leon LR. Overlapping mechanisms of exertional heat stroke and malignant hyperthermia: evidence vs. conjecture. Sports Med. 2020;50:1581–92. doi: 10.1007/s40279-020-01318-4.
14. Glahn KPE, Bendixen D, Girard T, Hopkins PM, Johannsen S, Ruffert H, et al. Availability of dantrolene for the management of malignant hyperthermia crises: European Malignant Hyperthermia Group guidelines. Br J Anaesthesia. 2020;125(2):133–40. https://doi.org/10.1016/j.bja.2020.04.089.
15. Serano M, Pietrangelo L, Paolini C, Guarnier FA, Protasi F. Oxygen consumption and basal metabolic rate as markers of susceptibility to malignant hyperthermia and heat stroke. Cells. 2022;11(16):2468. doi: 10.3390/cells11162468.

16. Frassanito L, Sbaraglia F, Piersanti A, Vassalli F, Lucente M, Filetici N, et al. Real evidence and misconceptions about malignant hyperthermia in children: a narrative review. J Clin Med. 2023;12(12):3869. doi: 10.3390/jcm12123869.

17. 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(2):498–507. doi: 10.1213/ANE.0b013e3181c6b9b2.

18. Riazi S, Larach MG, Hu C, Wijeysundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia. Anesth Analg. 2014;118(2):381–7. doi: 10.1213/ANE.0b013e3182937d8b.

19. Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. Anesthesiology 2007;106(5): 901–6. doi: 10.1097/01.anes.0000265148.86566.68.

20. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. Orphanet J Rare Dis. 2007;2:21. doi: 10.1186/1750-1172-2-21.

21. Safety Committee of Japanese Society of Anesthesiologists. JSA guideline for the management of malignant hyperthermia crisis 2016. J Anesth. 2017;31:307–17. doi: 10.1007/s00540-016-2305-z.

22. Glahn KPE, Ellis FR, Halsall PJ, Muller CR, Snoeck MMJ, Urwyler A, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. Br J Anaesth. 2010;105(4):417–20. doi: 10.1093/bja/aeq243.

23. Kim DC. Malignant hyperthermia. Korean J Anesthesiol. 2012;63(5):391–401. doi: 10.4097/kjae.2012.63.5.391.