AN INTRODUCTION TO MALIGNANT HYPERTHERMIA

by Kit (F)

ABSTRACT:

This report discusses malignant hyperthermia. It will detail the diseases pathophysiology, history, clinical manifestation, epidemiology as well as the genetic factors in being susceptible to malignant hyperpyrexia and its treatment during the perioperative period using dantrolene.

Introduction – What is MH?

Malignant Hyperthermia, Malignant Hyperpyrexia or MH, is a severe, potentially lethal reaction to volatile inhalation agents (particularly halothane) or depolarising muscle relaxants (such as succinylcholine) used in General Anaesthesia (Schuster, Roewer, Schneiderbanger and Johannsen, 2014). It is characterised by the disturbance of calcium homeostasis in skeletal muscle, which may lead to a fatal hypermetabolic state known as an MH crisis. Susceptibility to MH is determined by the inheritance of an autosomal dominant gene from one or both of a patient's parents. (Ibid, 2014)

HISTORY:

Mortality due to intraoperative hyperthermia has been documented since the early 1900s. However, Denborough et al (1960) was the first research team to propose that there was a genetic predisposition to mortality from general anaesthesia and hence defined MH as an independent condition.

In 1975, the drug dantrolene sodium ($C_{14}H_{10}N_4O_5$) was introduced and effective treatment became available. As a result, the mortality rate from an acute MH crisis fell from 70%-80% to around 5% (Britt and Kalow, 1970).

EPIDEMIOLOGY:

MH can be expressed in the phenotype of all races worldwide (Rosenberg et al., 2007). There is a significant majority of male patients that have the mutated gene that causes susceptibility to MH, and according to a study in New York State carried out in 2001-2005, the prevalence of MH in males is 2.5-4.5 times higher than in females (Brady, Sun, Rosenberg and Li, 2009). The genetic occurrence of MH is estimated to be 1/2,000, whilst the clinical incidence of fulminant MH episodes can vary widely depending on the region from 1/5,000 to 1/100,000 (Ibid, 2014) (Hopkins, 2000). However, abortive cases are predicted to occur more frequently, but the diagnosis is difficult as the symptoms are much milder than in fulminant cases (Ibid, 2014) (Schuster, Johannsen, Schneiderbanger and Roewer, 2013).

In the past few years, the risk of an acute MH crisis has fallen significantly. This is in part due to the ceased use of halothane, an MH triggering agent, in general anaesthesia (Ibid, 2014). The current, commonly used inhalation agents in western countries (sevoflurane, desflurane and isoflurane, among others) have a much longer onset of MH compared with halothane and as a result, MH cases are more likely to be abortive cases with attenuated symptoms (Ibid, 2014).

Furthermore, the muscle depolarising relaxant succinylcholine, which is another MH triggering agent, has had its use been gradually restricted by international anaesthesia societies (Ibid, 2014).

GENETIC FACTORS:

There are three known isoforms of the ryanodine receptor, they include RYR1, the dominant form of the receptor that is expressed in skeletal muscle; RYR2, the dominant form of the receptor expressed in cardiac muscle; and RYR3, found in the CNS, skeletal and smooth muscle (Hamilton, 2005). The mutated RYR1 gene (with the locus on chromosome 19) was the first gene to have been associated with the predisposition to MH

(McCarthy et al., 1990). However, a causal mutation in the RYR1 gene has only been found in 50% of MH patients (Broman et al., 2011). Therefore, it can be concluded that the mutated RYR1 gene is not solely responsible for the susceptibility of MH in patients. Another locus has been identified in MHS patients on chromosome 1, the CACNA1S gene, which encodes the α subunit of the 1,4-Dihydropyridine receptor present in calcium release channels. This mutated CACNA1S gene is responsible for less than 1% of all cases of MH susceptibility (Genetics Home Reference, 2020).

Both of these known mutations are inherited through an autosomal dominant inheritance pattern.

The different MH phenotypes are assessed and determined by the intervalence charge transfer (IVCT) when samples of skeletal muscles are exposed in vitro to increasing concentrations of trigger agents (namely halothane and caffeine). The contractile response of the muscle is measured, and the measurements are used to define the IVCT phenotypes. If a sample responds to both triggers then the sample is MH susceptible, or MHS. If the sample only responds to one trigger then it is described as MH equivocal, or MHE. If the sample does not respond to the trigger then the sample is described as MH normal, or MHN. The MHS and the MHE phenotypes are clinically considered to indicate a high risk of developing an MH crisis. (Robinson et al., 2009)

PATHOPHYSIOLOGY:

During an MH crisis, the triggering agent induces the opening of the mutated ryanodine receptors, causing an uncontrolled release of Ca^{2+} from the sarcoplasmic reticulum. This results in prolonged skeletal muscle activation, manifesting itself as rigidity

(Struk, Lehmann-Horn and Melzer, 1998). Furthermore, this constant muscle activation requires immense energy to maintain rigidity resulting in the use of both aerobic and anaerobic respiration pathways. This results in dramatically increased oxygen consumption, leading to hypoxia (oxygen deficiency in respiring tissues), progressive lactic acidosis, excessive production of CO_2 and increased body temperature as a result of catabolic reactions within the body (Ibid, 2014).

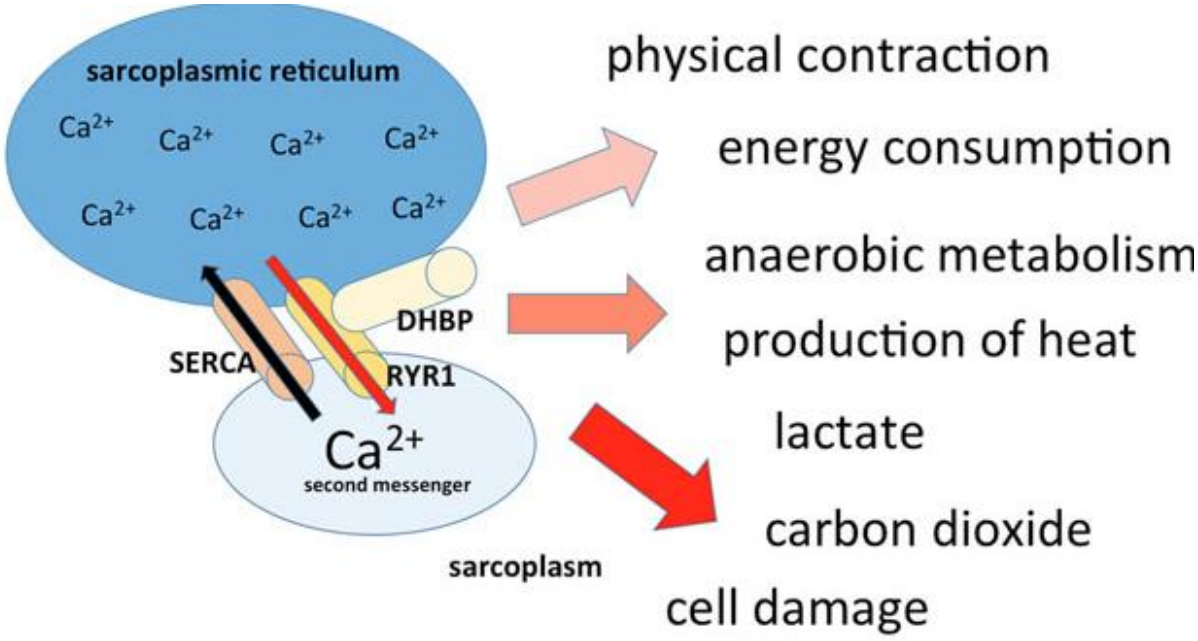


Fig. 1 Excitation contraction coupling of skeletal muscle and its (Broman, Islander and Müller, 2015)

These reactions and calcium reuptake into the sarcoplasmic reticulum are energy-intensive processes, thus consuming very large amounts of adenosine triphosphate (ATP). The depletion of cellular stores of ATP leads to extended muscle rigidity and eventually rhabdomyolysis, reducing the integrity of muscle cell plasma membranes and resulting in the release of cell contents and the destruction of cells (Ibid, 2014).

SYMPTOMS:

As MH case in patients can range from abortive cases with mild symptoms to fulminant crises, clinical symptoms can vary widely. The table below shows symptoms that may be seen during the perioperative period.

Table 1

Clinical signs of malignant hyperthermia

Early	Late
Masseter spasm	Hyperthermia
Generalized muscular rigidity (50%–80%)	Rhabdomyolysis
Tachycardia (>80%)	Acute renal failure
Hypercapnia	Cardiac arrhythmia
Hypoxia	Hypotension
Combined metabolic-respiratory acidosis	Circulatory failure

(Ibid, 2014)

An early sign of an imminent MH crisis is an increase of end-tidal CO2 concentration or hyperventilation, displaying increased CO2 production. As succinylcholine is a trigger agent for MH, an abrupt rise in tidal CO2 concentration may occur simultaneously with the administration of succinylcholine (Tautz, Urwyler and Antognini, 2010). Other early symptoms are shown in the table above.

Interestingly nonspecific sinus tachycardia may be interpreted as inadequate anaesthesia. This often delays the diagnosis of MH.

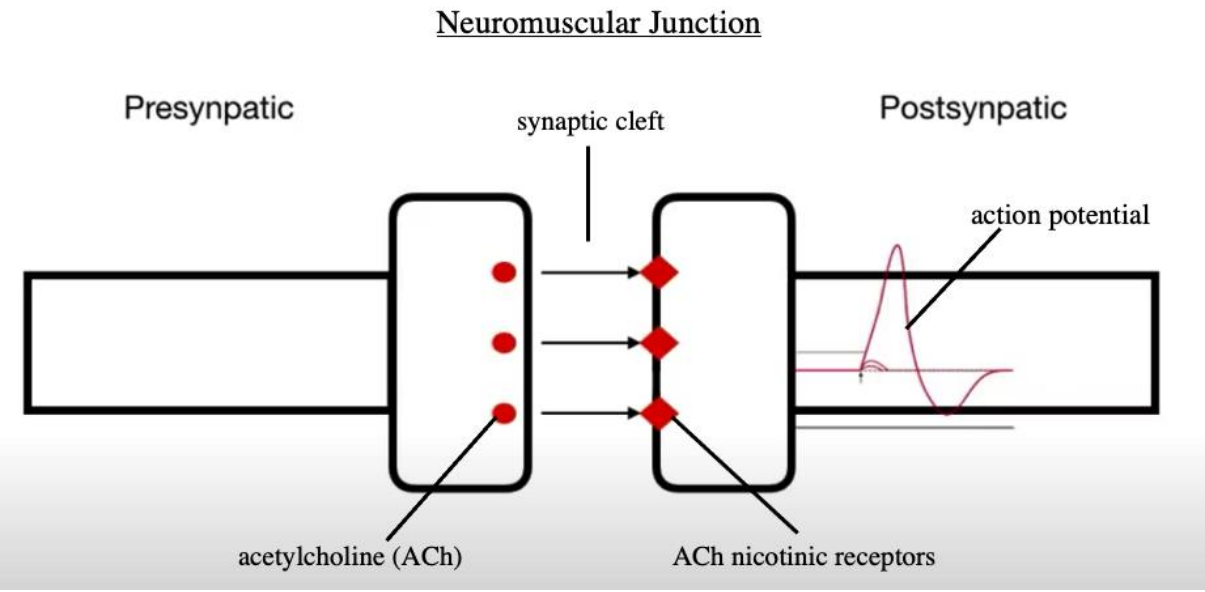
If treatment occurs early in the onset of MH, there may be no significant changes to body temperature (Glahn et al., 2010).

As fulminant MH cases can result in rhabdomyolysis, the expulsion of cell contents into the blood may lead to hyperkalemia (the increase of potassium concentration in the blood), increased creatine phosphokinase concentration in the blood and myoglobinuria. The increased concentration of these substances may result in renal failure and circulatory failure (Rosenberg et al., 2007).

The action of the MH Trigger Agent, succinylcholine:

To understand how succinylcholine can enhance an MH crisis and increase mortality rates from MH, one has to understand the action over a neuromuscular junction and how it is affected by different types of muscle relaxants. Under normal circumstances, voluntary muscle contract starts with the intention to move, which is generated in the motor cortical regions of the brain (Dubowitz and Everson Pearse, 1960). These cortical areas send electrical impulses to the spinal cord (Rios and Brum, 1987). The motor neurons process the signal in the CNS and their axons then leave the spinal cord forming motor nerves, which branch from the to the target muscle (Hernández-Ochoa, Pratt, Lovering and Schneider, 2016). The action potential reaches the neuromuscular junction where acetylcholine (ACh) is released from the presynaptic membrane, diffuses across the synaptic cleft and binds to postsynaptic ACh nicotinic receptors (Hernández-Ochoa, Pratt, Lovering and Schneider, 2016). Activation of ACh nicotinic receptors generates an

action potential in the muscle, coordinating muscular contraction and eventually causing movement. This process is called excitation-contraction coupling.



(Dirty Medicine, 2020)

Muscle relaxants can be split into two categories, depolarising and non-depolarising, and this denotes their action on the neuromuscular junction.

Non-depolarising muscle relaxants (-curiums) work in a similar way to competitive enzyme inhibitors as they bind to the ACh nicotinic receptors and block any ACh that is released by the presynaptic membrane from binding to their receptors. This causes a fade in muscular activity as less ACh can bind to their receptors and initiate an action potential until all of the receptors are blocked by the non-depolarising muscle relaxants (Dirty Medicine, 2020).

Depolarising muscle relaxants diffuse across the synaptic cleft and constantly stimulate the ACh nicotinic receptors. This causes action potentials to fire across the muscle constantly and as a result, this causes the membrane to depolarise and 'tire' as repolarisation is not allowed by succinylcholine, resulting in the deactivation of sodium channels and the characteristic two-step pathway to muscle relaxation: increase in muscle activity followed by fade-in muscle activity (Ibid, 2020).

Within muscles Ca^{2+} (which is released from the sarcoplasmic reticulum) plays an important role in muscle contraction by binding to actin filaments in the muscle, which in turn exposes the binding site for the myosin head to bind to, for muscle contraction to be stimulated. This occurs further along the process than where succinylcholine acts on the neuromuscular junction.

While succinylcholine is bound to the ACh nicotinic receptors and is producing the increase in muscle activity and Ca^{2+} is being moved out of cells by the ryanodine receptors, the Ca^{2+} cannot be moved back into the sarcoplasmic reticulum at a high enough rate to replenish their stores. Meaning, that in effect, there is a one-way pathway for the calcium ions and hence producing in a higher concentration of calcium ions outside the sarcoplasmic reticulum and eventually resulting in akinesia (Science Direct, 2020). In MHS patients the mutation in the RYR1 gene or the CACNA1S gene causes the ryanodine channel (encoded by the RYR1 gene) to open more

easily and to close more slowly. This results in the abnormal release of Ca^{2+} ions out of the muscle (Genetics Home Reference, 2020).

SUSCEPTIBILITY TESTING:

Susceptibility testing occurs or is recommended when a patient has risk factors for MH. There are two main methods to test for susceptibility to MH in patients. The first of which is Genetic testing:

A sample of blood is taken before the operation and is sent off to a lab for genetic testing. The test is used to determine whether the patient has the mutated RYR1 gene and hence whether they are clinically susceptible to the onset of MH (Mayo Clinic, 2020).

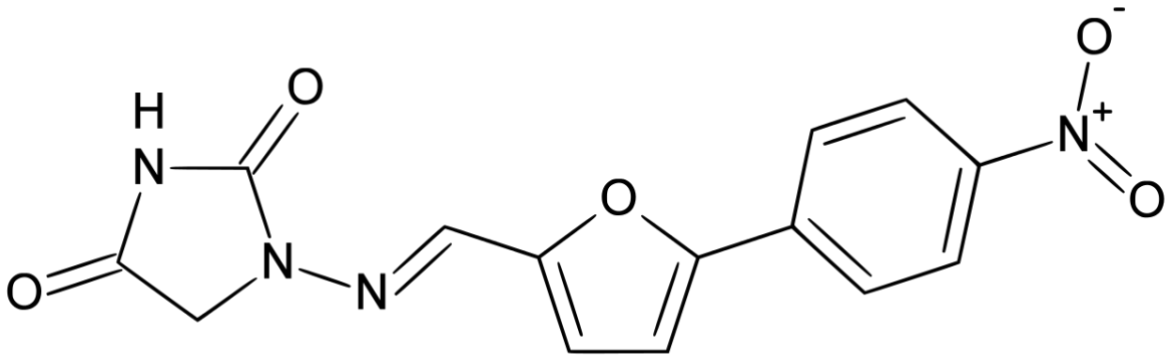
The second testing method is a contracture test of a muscle biopsy. In some cases, a contracture test may be recommended in the clinic. This involves the measurement of the aforementioned IVCT of a biopsy of skeletal muscle taken from the patient. In which the sample is exposed to MH trigger agents and the reaction of the muscle is measured (Agrawal, Suryakumar and Rathor, 2018).

If the patient's tests come back positive for MH susceptibility the anaesthetist may decide to change the method of which they induce and maintain a state of general anaesthesia, in order to avoid utilising potential trigger agents. The anaesthetist will also take extra care in monitoring the physiology of the patient whilst they are under GA.

Treatment and the Use of Dantrolene:

The first and most crucial step in the treatment of MH is the cessation of trigger agent administration (Harvard Health, 2020). Dantrolene is then administered intravenously.

Dantrolene is another skeletal muscle relaxant but acts differently to succinylcholine and can hence be used as an antidote.



(Dantrolene Structure, 2006)

Dantrolene inhibits the catch and release function of the RYR1 receptors on the sarcoplasmic reticulum (eGPAT, 2020). This means that the Ca^{2+} ions released as part of the first increased muscle action stage of succinylcholine's action are no longer released once dantrolene acts at the

site. Thus the provocation of muscle action triggered by Ca^{2+} is halted, slowing down respiration, heat and lactate production until they reach normal levels again and oxygen is able to diffuse into the skeletal muscle cells and can convert lactic acid back into carbon dioxide and water, reducing oxygen deficit at the site. (Ibid, 2020)

Dantrolene is hydrophobic and has low solubility in water, therefore when it is administered to patients it is combined with Mannitol (an alcohol) which increases dantrolene's solubility and allow it to be administered intravenously. NaOH is also added to the solution to change the pH to 9.5. An alkaline pH is required as it reduces irritation at the site of infection.

Dantrolene is a muscle relaxant therefore side effects include loss of grip strength and muscle weakness. Other symptoms can also include dizziness, drowsiness, phlebitis (inflammation of the veins at the sight of infusion) and tissue necrosis. Upon prolonged administration, dantrolene can produce hepatoxicity. (Ibid, 2020)

Conclusion:

Until the production of dantrolene in 1975 and the cessation of the use of halothane and succinylcholine, MH was a common and potentially lethal complication in anaesthesia. Although it may seem that it is no longer relevant to modern anaesthesia, it still occurs, and indeed there is only one general anaesthetic that is suspected not to be an MH trigger agent, and that is propofol. It is therefore clear that precautions have to be taken with any patient that is undergoing general anaesthesia, especially those who are deemed susceptible to an MH crisis.

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