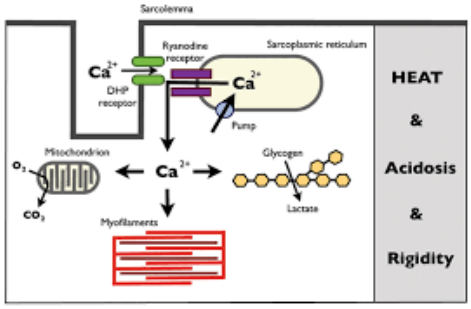
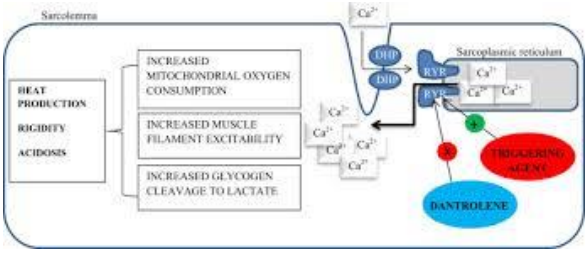
The Royal Melbourne Hospital

Perfusion Management of Malignant Hyperthermia





Heart lung machine preparation

- **Remove vapouriser from HLM. Replace all gas delivery tubing to the oxygenator with new. Flush with 10 L/min oxygen or medical air for at least 10 minutes through the circuit before connecting to the oxygenator.**

Monitoring

- During surgery monitor and record temperature.
- After surgery continue minimum mandatory monitoring.
- All patients should have a temperature recorded on arrival and on leaving.

Drugs that MUST be avoided with MHS patients

- Depolarising muscle relaxants (i.e. suxamethonium)
- ALL potent inhalational agents – including; desflurane, sevoflurane, isoflurane, enflurane, halothane, methoxyflurane

Drugs that can be used with MHS patients

All other pharmacological agents are safe including the following common drugs:

- Nitrous oxide (and xenon)
- Propofol and all intravenous induction agents including ketamine and benzodiazepines
- Non-depolarising muscle relaxants
- Local anaesthetics with or without adrenaline
- Opioids and other analgesics,
- Syntocinon, ergometrine, magnesium sulphate,
- Ephedrine, metaraminol, phenylephrine

Background information courtesy of ANZCA.

Definition

Malignant Hyperthermia (MH) is an acute pharmacogenetic (autosomal dominant) disorder, which develops during or immediately after the application of general anaesthesia involving volatile agents and/or depolarising muscle relaxants.

The disorder is as a result of a defect in calcium channel regulation in the muscle cell. Volatile anaesthetic agents and depolarising muscle relaxants interact with the calcium channel resulting in the clinical crisis.

The classic MH crisis is caused primarily by excess calcium availability in the skeletal muscle cytoplasm resulting in excessive muscle contraction and hypermetabolism.

This leads to massive CO2 production, skeletal muscle rigidity, tachyarrhythmias, unstable haemodynamics, respiratory acidosis, cyanosis, hyperkalaemia, lactic acidosis, fever, and eventually (if untreated) death. MH can present with a few or all of these features.

Overview

Malignant hyperthermia is a severe reaction to certain drugs used for anaesthesia. This severe reaction typically includes a dangerously high body temperature, rigid muscles or spasms, a rapid heart rate, and other symptoms. Without prompt treatment, the complications caused by malignant hyperthermia can be fatal. It may not present up to 40 minutes after induction.

In most cases, the defective gene that puts a patient at risk of malignant hyperthermia is inherited, though sometimes it's the result of a random genetic defect. Genetic testing can reveal whether they have an abnormal gene. This genetic disorder is called malignant hyperthermia susceptibility (MHS).

Treatments for malignant hyperthermia include the medication dantrolene (Dantrium, Ryanodex, Revonto), ice packs and other measures to cool body temperature, as well as supportive care.

History

Malignant hyperthermia was first described as genetically inherited entity in a letter to the editor of the Lancet in 1960 penned by Michael Denborough and Richard Lovell[1] and in a follow up article in 1962 in the British Journal of Anaesthesia[2].

The family described showed an autosomal dominant pattern of inheritance for this reaction to anaesthesia. The original letter called for others to share experiences with this type of reaction

and the term malignant (“deadly, tending to produce death”) hyperpyrexia (“an abnormally high fever”) was coined.

Preparing for the MHS patient

Patients with one of the following should be considered potentially susceptible:

1. Previous malignant hyperthermia reaction as yet untested
2. Positive in vitro contracture test (IVCT) on muscle biopsy
3. Positive DNA test for MH
4. Relative has positive IVCT and patient has not had an IVCT
5. Patient (with MHS relative) has negative DNA result
6. Relative with clinical MH reaction and patient has not had an IVCT

The proposed mechanism of MH

The normal process of calcium regulation in skeletal muscle

An action potential is generated at the motor end plate which electrically stimulates the L type calcium channel (DHPR). This induces a conformational change in the DHPR which in turn causes a conformational change in the skeletal muscle ryanodine receptor (RYR1) so that RYR1 is now more open and calcium is released into the cytoplasm. How much calcium is released in this process is a function of how “open” the RYR1 channel is. This open state is regulated by smaller related proteins at the junctional sarcoplasmic reticulum(SR) membrane (JP-45, calmodulin, FK506, junctin and triadin) and in the lumen of the SR (calsequestrin) as well as by Ca^{2+}, Mg^{2+} and ATP. Volatile agents may influence normal RYR1 to increase the probability of it being in the open state but the balance is maintained by compensation within the system.

The calcium concentration in the cell cytoplasm is now briefly but massively increased and calcium is available to bind troponin and thus displace tropomyosin to expose the cross bridge binding sites so actin and myosin can interact. Muscle contraction is the result.

Calcium levels in the cytoplasm are quickly restored by active reuptake of calcium into the sarcoplasmic reticulum via the Ca^{2+} ATPase pump (SERCA), where two Ca^{2+} are exchanged for every one ATP molecule. Calcium that is taken back into the SR is then buffered by calsequestrin to restore equilibrium. RYR1 channel opening is inhibited by high calcium concentrations both directly and via calmodulin.

The proposed MH process (what happens when it goes wrong)

Structural alterations in calcium regulating proteins upset the delicate balance between calcium release from and reuptake into the SR. In normal circumstances (without exposure to volatile

anaesthetic agents) in the vast majority of mutations, this balance is maintained. On exposure to volatile agents however, the system is overwhelmed and calcium continues to be released into the cytoplasm beyond the influence of the regulatory proteins.

Restoration of cytoplasmic calcium concentration is paramount to normal cellular function so the reuptake of calcium increases, and energy consumption rises dramatically (increased oxygen consumption and CO2 production, heat generation). Muscle gets no chance to relax because of continued calcium exposure (rigidity) and as energy consumption overwhelms oxidative capacity, muscle begins to source energy anaerobically. Lactic acid is produced and the toxic environment of low pH and high Ca^{2+} that has been created, results in cell breakdown and release of creatinine kinase.

We are not absolutely sure how volatiles affect RYR1 or indeed how they influence the entire calcium regulatory system in skeletal muscle. We do know the following:

1. Specific binding sites for halothane have been identified in RYR1 of the drosophila fly and it is possible that halothane (and by extrapolation any other volatile agent) binds directly to RYR1 and influences RYR1 to remain in its open state (4).

2. Halothane-induced RyR1-mediated SR Ca^{2+} release is enhanced by high ATP-low Mg^{2+}in the cytosol and by increased SR Ca^{2+} load. Thus, physiological or pathological processes that induce changes in cellular levels of these modulators could affect RyR1 sensitivity to halothane (5)

3. Mutated RYR1 are more sensitive (release more calcium) in response to halothane and increased temperature (6)

Differential diagnosis

This is one of the more challenging differential diagnoses because time to treat is critical.

If in doubt consider that:

- Dantrolene is a safe drug with the provision of appropriate ventilatory support
- Extreme hyperthermia can result in cell death and an unsalvageable situation
- Not all symptoms of MH need to be present to make the diagnosis
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If you have inappropriate tachycardia, elevated CO2 and hyper or hypotension, rapidly exclude:

- Insufficient anaesthesia
- Insufficient ventilation or gas flow

- Air/O2 Blender malfunction
- CO2 from chest insufflation
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If there is ongoing masseter spasm or rigidity and the situation is stable:

- It may be worth considering the response to the addition of non-depolarising muscle relaxant
- Masseter spasm and rigidity related to MH should **not** resolve with a non-depolarising muscle relaxant

Also consider the following differentials:

- Phaeochromocytoma – extreme fluctuations in arterial blood pressure, hyperthermia, sweating, usually no muscle involvement
- Infection, septicaemia – hyperthermia, usually no muscle involvement
- Thyroid Storm –hyperthermia, no rigidity but may have rhabdomyolysis
- Central anticholinergic syndrome – delayed emergence, hyperthermia and nystagmus, dilated pupils
- Serotonergic syndrome – Triggering agent (serotonergic, cocaine, MDMA, ketamine, methylene blue and SSRI), no nystagmus
- Neuroleptic malignant syndrome – slow onset hyperthermia (24-72 hours after withdrawal of dopamine agonist)
- Mismatched blood transfusion, blood in the fourth cerebral ventricle, drug toxicity and drug allergies may cause isolated hyperthermia

Masseter spasm

True masseter spasm can be the first and sometimes only sign of MH. True masseter spasm is a prolonged, palpable tightening of the masseter muscles that does not release gradually. The difficulty is distinguishing this from an inadequate dose of suxamethonium and the normal increased tone seen with suxamethonium in some patients.

There are two approaches to the patient with true masseter spasm

1. Discontinue volatile anaesthesia, continue the case with total intravenous anaesthesia and watch for signs of MH. Treat accordingly if signs develop. Refer to an MH diagnostic centre for follow up.
2. Abandon surgery and treat for MH if any other signs develop. Refer to an MH diagnostic centre for follow up.

The decision to take either of the above approaches may be influenced by the following:

- Testing for MH is not usually performed in patients who are less than 30kg or under ten years of age
- Testing will not be performed for at least three months after an episode of masseter spasm
- Patients need to travel to a testing centre for the biopsy

Disorders associated with MH

Patients with central core disease (CCD) and multiminicore disease (MMD) with gain of function *RYR1* defects are at risk of MH. While those with CCD and MMD and a loss of function *RYR1* defect should not be at risk of MH, this may not be clear based on symptomatology or genetic testing. The safest position is to treat all CCD and MMD patients as potentially MH susceptible unless they have had a negative IVCT. CCD and MMD are often asymptomatic in childhood.

King-Denborough syndrome is a myopathy with an *RYR1* defect and patients should be considered at risk for MH.

Patients who have a history of exertional heat illness (EHI) with no obvious predisposing factors may be at increased risk of MH. This is more likely of they have had repeated episodes in temperate climate and if there is a familial component to the EHI.

A myopathy caused by a defect in the *STAC3* gene manifest as muscle weakness with cleft palate also known as “Native American myopathy” has been associated with MH.

The in vitro contracture test (IVCT)

All current Australian and New Zealand laboratories follow the guidelines of the European Malignant Hyperthermia Group for In Vitro Contracture Testing.

The EMHG guidelines are summarised as follows:

Age and Weight

- The minimum patient age for the muscle biopsy is 4yr, but laboratories should not test children younger than 10yr of age without relevant control data. Laboratories may also set minimum body weight limits. *The minimum weight limit for Australian and New Zealand laboratories is 30kg and the minimum age for IVCT is 10 years.*

IVCT details

- The biopsy should be performed on the quadriceps muscle (either *vastus medialis* or *vastus lateralis*), using local (avoiding local anaesthetic infiltration of muscle tissue), regional, or trigger-free general anaesthetic techniques.
- The muscle samples can be dissected in vivo or removed as a block for dissection in the laboratory within 15 minutes.
- The time from biopsy to completion of the tests should not exceed 5 hours.
- Muscle specimens should measure 20-25mm in length and at least four tests should be performed each one using a fresh specimen.
- The tests should include a static cumulative caffeine test and a dynamic or static halothane test.
- The results should be reported as the threshold concentration, which is the lowest concentration of caffeine or halothane that produces a sustained increase of at least 2mN (0.2grams) in baseline force from the lowest force reached.

Laboratory diagnostic classification

- MHS_{hc}: a caffeine threshold of 2mmol/litre or less in at least one caffeine test and a halothane threshold concentration of 0.44 mmol/litre or less in at least one halothane test.
- MHS_{h}: a halothane threshold concentration of 0.44 mmol/litre or less in at least one halothane test and a caffeine threshold of 3mmol/litre or more in all caffeine tests.
- MHS_{c}: a caffeine threshold of 2mmol/litre or less in at least one caffeine test and a halothane threshold concentration above 0.44 mmol/litre in all halothane tests.
- MHN: a caffeine threshold at a caffeine concentration of 3mmol/litre or more in all caffeine tests and a halothane threshold concentration above 0.44 mmol/litre in all halothane tests.

MHS_{hc}, MSH_{h} and MHS_{c} are all considered to be susceptible to MH.

Laboratory MHN diagnosis is good evidence that the patient is not at risk of developing MH. An MHN-tested individual cannot transmit MH risk to their offspring.

Molecular genetic detection of susceptibility to malignant hyperthermia

All Australian and New Zealand laboratories follow the guidelines of the European Malignant Hyperthermia Group (EMHG) for molecular genetic testing.

The EMHG guidelines are summarised as follows:

Predictive testing based on a known familial mutation

- If an MH-associated *RYR1* (*or CACNA1s*) mutation has been identified in the index case, the RYR1 (or *CACNA1s*) mutation can be used for predictive testing of relatives.

- Persons carrying the familial mutation should be regarded as MH susceptible
- Persons who do not carry the familial mutation cannot be regarded as completely risk free (in about 5% of large pedigree studies there is discordance between IVCT results and genetic data) and should such persons seek maximal safety, an IVCT should be considered.

RYR1 mutation screening as a diagnostic test

- A clear clinical indication is a prerequisite for any genetic testing
- Genetic testing can be performed as a targeted analysis of known associated MH mutations or as screening of entire coding regions.
- If one of the known MH mutations is identified, the person should be considered at risk of MH
- As yet unclassified sequence variants will frequently be identified using entire coding region sequencing. The MH laboratory is responsible for checking the available published evidence and for applying prediction algorithms with the aim of eventually classifying the variant as neutral or potentially MH associated.
- For patient safety, individuals carrying a 'potentially MH-associated' *RYR1* variant should be regarded as at increased risk for MH until further diagnostic tests (i.e. an IVCT) have been performed

Clinical malignant hyperthermia

Signs of an MH Crisis

Early Signs

- Prolonged masseter muscle spasm after suxamethonium
- Inappropriately raised end tidal carbon dioxide during controlled ventilation or tachypnoea during spontaneous respiration
- Inappropriate tachycardia
- Cardiac arrhythmias; particularly ventricular ectopic beats

Developing signs

- Rapid rise in temperature (0.5°C per 15 minutes)
- Progressive metabolic and respiratory acidosis (ABG)
- Hyperkalaemia
- Profuse sweating
- Cardiovascular instability
- Decreased SpO2 or mottling of skin

- Generalised muscular rigidity

Later signs and symptoms

- 'Cola' coloured urine – due to myoglobinuria
- Generalised muscle ache
- Grossly raised serum CK
- Coagulopathy
- Cardiac arrest

In Brandom's 2010[4] paper which examined 268 AMRA (adverse metabolic and or musculoskeletal response to anaesthesia) reports the most frequent initial MH signs were hypercarbia, sinus tachycardia, or masseter spasm, however; temperature abnormalities were also a relatively early sign.

Treatment of an MH crisis

Immediate management with intravenous dantrolene is essential as is stopping the trigger agent. For cardiac patients, cardiopulmonary bypass can be used to manage the situation.

Therefore:

1. Give dantrolene as a priority
2. Turn off volatile agent and hyperventilate with very high flows (15L/min) of 100% O2. Do not waste time changing the circuit or the anaesthetic machine
3. Declare an emergency and where possible stop the surgery
4. Commence non-triggering anaesthesia (TIVA)

Dantrolene dose

Dantrolene 2.5mg/kg total body weight (not lean body weight) IV – initial push and repeat as necessary

- Dosing is the same per kg for paediatric patients
- Mobilise other sources of dantrolene (you may need at least 36 ampoules)
- Mix each ampoule with 60mls sterile water
- Dantrolene can be given peripherally or centrally

Simultaneously treat the life-threatening events:

Hyperkalaemia

- Hyperventilate and treat the acidosis
- CaCI2 10%(0.15ml/kg = 10mls = 7mmol in adults)
- Insulin 0.15u/kg + dextrose 50% 0.5ml/kg (10units insulin + 50ml dextrose 50% in adults)

Hyperthermia

- Cool the patient if T > 38.5°C
- IV normal saline at 4°C: surface cooling with ice
- Consider peritoneal lavage with normal saline at 4°C if the peritoneum is already accessed

Acidosis

- Hyperventilate to at least normocapnia
- Consider sodium bicarbonate 0.5 mmol/kg IV as necessary to maintain pH >7.2

Arrhythmias

- Lignocaine 1-2mg/kg
- Amiodarone 2-3mg/kg over 15 minutes
- Consider hyperkalaemia as a cause of rhythm disturbance

Additional Monitoring

- core temperature
- arterial blood pressure (arterial line)
- Urine output via catheter (aim for >2ml/kg/hr)
- Central venous access and monitoring

Pathology Tests

- Send urgent bloods and repeat frequently to monitor success of therapy
- ABG
- U+E
- FBC
- CK
- COAG
- Myoglobin (urine)

When the patient is stabilised:

- Admit for close monitoring in an intensive care environment
- Monitor the patient for at least 24hrs post reaction
- Recurrence may occur and large amounts of dantrolene may be needed in the first 24 hrs
- Consider mobilising additional sources of dantrolene
- Consider transferring patients with fulminant reactions to major centres after stabilisation

***Post-operative MH*[5]**

Postoperative MH is uncommon occurring in less than 2% of cases. All cases of post-operative MH (as reported in AMRA registry) occurred within 40 minutes of cessation of triggering agent.

Postoperative MH has been reported in the anaesthetic literature. A careful evaluation of these published cases reveals that they seem to follow one of four clinical patterns:

1. Classic acute MH occurring shortly after the completion of surgery and the general anaesthetic
2. Atypical MH manifesting as delayed rhabdomyolysis in patients subsequently identified as MH susceptible by contracture testing
3. Unsubstantiated reports made doubtful by the absence of positive contracture testing or unconvincing clinical characteristics
4. Cases in which the initial presenting signs of MH seemed to begin in the intraoperative period.

Classic MH with an initial presentation in the postoperative period is rarely reported; in addition to the cases found in the North American Malignant Hyperthermia Registry (NAMHR), only three additional published reports were identified.10–12 The clinical characteristics of these patients resembled the AMRA cohort of cases with regard to presenting signs and the short latency time of onset after the completion of the general anaesthetic. Of note, none of the published cases presented with hyperthermia without additional signs of acute MH.

Postoperative rhabdomyolysis in patients with proven MH susceptibility is more common. In all reported cases, the initial presentation was the onset of brownish discoloration of the urine, which then prompted further evaluation and discovery of rhabdomyolysis. Classic signs of MH such as generalized rigidity, tachypnoea, tachycardia, and hyperthermia were absent. It is presently unclear whether patients who present with post-operative rhabdomyolysis and subsequently demonstrate an abnormal caffeine–halothane contracture test result have an MH-causing mutation, or a subclinical muscle disease which results in a false-positive contracture test result.

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