



Malignant Hyperthermia

Definition

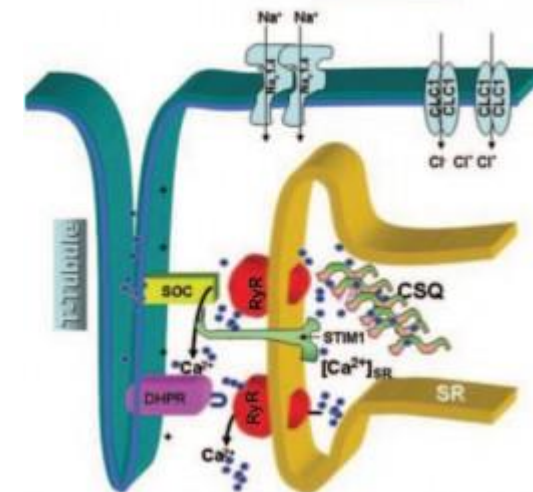
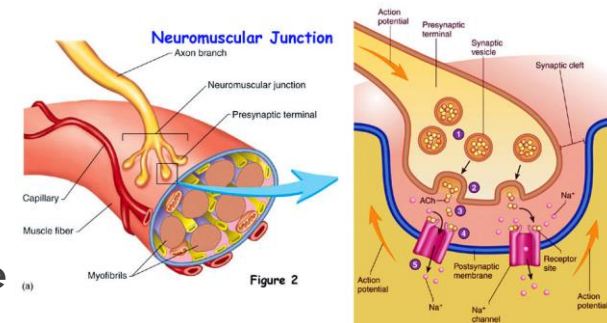
- ▶ ***Inherited disorder of skeletal muscle***
- ▶ **Mutations** in the gene encoding the skeletal muscle **Ryanodine Receptor 1 (RYR1)**
- ▶ Triggered in genetically susceptible individuals by **volatile inhalational anaesthetic agents** (eg: halothane, isoflurane, sevoflurane, desflurane) or **depolarizing muscle relaxants** (eg: succinylcholine)
- ▶ **Pharmacogenetic: Drugs + Genetics**
- ▶ **Characterised by:**
 - ▶ Hypermetabolism
 - ▶ Skeletal muscle damage
 - ▶ Hyperthermia
 - ▶ Death (if left untreated)

Epidemiology

- ▶ Clinical incidence: 1 in 10,000 to 50,000 anaesthetics
- ▶ Varies according to:
 - ▶ Age (more common in paediatrics – children < 19 yrs: 45-52% of reported events)
 - ▶ Sex (2:1 male : female ratio)
 - ▶ Concomitant drug administration
- ▶ Initially mortality ~70%; now with earlier diagnosis & use of dantrolene mortality ~5%

Pathophysiology

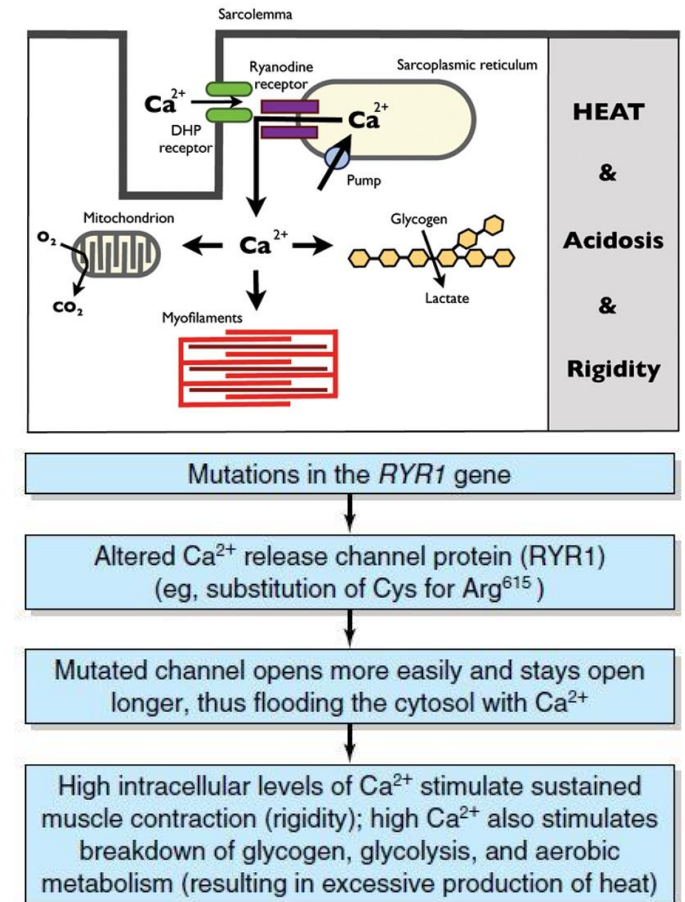
- ▶ Normal muscle contraction is initiated at the NMJ. The nerve cell signals to the muscle cell to contract.
- ▶ ACh is released from the terminals of motor neurons & diffuses to the postsynaptic membrane, where binding to nicotinic ACh receptors triggers a wave of depolarization (after Na^+ is pulled into cell) referred to as an Excitatory PostSynaptic Potential (EPSP) that leads to action potentials that propagate to T tubules.
- ▶ The T Tubules act as conduits to bring APs deep within the myofibrils, where the excitatory signal is transduced to the **SARCOPLASMIC RETICULUM** via the **dihydropyridine receptors (DHPR)** [located within the t tubule membrane] & **ryanodine receptors (RyR)** [located in the wall of the SR].
- ▶ This causes release of stored Ca^{2+} through a channel in the RyR into the interior of the cell.
- ▶ Ca^{2+} combines with troponin to crosslink actin & myosin → resulting in **muscle cell contraction**.
- ▶ The **influx of Ca^{2+}** also signals the mitochondria to produce **more ATP**.
- ▶ After the muscle cell contracts, the Ca^{2+} is taken back up into the SR & the muscle cell relaxes.



Malignant Hyperthermia – Dysregulation in calcium homeostasis due to mutation in RYR1 gene

INCREASE IN INTRACELLULAR Ca^{2+}

- ▶ Ca^{2+} is released from the SR in higher quantities
- ▶ Actin-myosin continuously contract (\rightarrow contracture \rightarrow Rigidity)
- ▶ Heat
- ▶ Excess lactate
- ▶ O_2 consumption
- ▶ \uparrow CO_2 production
- ▶ \uparrow cell metabolism \rightarrow cell runs out of energy \rightarrow cell breakdown \rightarrow release of intracellular contents \rightarrow downstream effects



Timing

- ▶ ONSET: intraoperatively or shortly afterwards (in recovery)
- ▶ RATE OF ONSET:
 - ▶ Fulminant: onset of full blown syndrome within *minutes* of induction of GA
 - ▶ More indolent: a few hours post exposure

Clinical features – Early Signs

- ▶ *Not all need to be present to initiate treatment*

EARLY SIGNS:

- ▶ **Rigidity** – Generalised or isolated
(**Prolonged masseter spasm** after suxamethonium - specific sign)
- ▶ Inappropriately **↑ end tidal CO₂ (ETCO₂)** (sensitive sign) or tachypnoea during spontaneous respiration
- ▶ Inappropriate **tachycardia**
- ▶ **Cardiac arrhythmias**, esp. VEBs

Clinical Features – Developing Signs

DEVELOPING SIGNS:

- ▶ **Rapid rise in temperature** (0.5°C per 15 min)
- ▶ Progressive respiratory & later metabolic acidosis
- ▶ Hyperkalaemia
- ▶ Profuse sweating
- ▶ Cardiovascular instability
- ▶ ↓ SpO₂ or mottling of skin
- ▶ Generalised **muscle rigidity**



Clinical Features – Late Signs

LATE SIGNS:

- ▶ “Cola” coloured urine – due to myoglobinuria from **rhabdomyolysis**
- ▶ Generalised muscle ache (in an awake patient)
- ▶ Grossly ↑ serum **CK**
- ▶ Coagulopathy (**DIC**)
- ▶ Cardiac arrest



Investigations

- ▶ An **ABG** is the single most useful investigation to perform
 - ▶ Mixed respiratory acidosis & metabolic (lactic) acidosis
- ▶ **Bloods:** FBC, EUC, CMP, CK, Coags, Myoglobin
 - ▶ Hyperkalaemia ($\uparrow \text{K}^+$)
 - ▶ Raised **CK**
- ▶ \uparrow serum & urine **myoglobin**
- ▶ **Coagulopathy** consistent with DIC (low fibrinogen; prolonged APTT, PT; thrombocytopenia, schistocytes)

Differential Diagnosis

- ▶ Inadequate anaesthesia/machine malfunction
- ▶ Sepsis or infection
- ▶ “Thyroid storm”
- ▶ Ecstasy or other recreational drugs
- ▶ Pheochromocytoma
- ▶ *Neuroleptic malignant syndrome* (hyperthermia, severe muscle rigidity, bradykinesia, autonomic dysfunction); Serotonin syndrome
- ▶ Intracerebral infection or haemorrhage

Crisis Management

- ▶ **Call for help** – MET Call
- ▶ **Turn off triggering anaesthetics** (inhalational agents, suxamethonium)
- ▶ Alert surgeons & nurses
- ▶ Check vaporizer removed from machine
- ▶ Check **fresh gas flow > 15L/min** (to avoid accumulation of small quantities of volatile agent)
- ▶ **Hyperventilate with 100% O₂**
- ▶ **DANTROLENE**
- ▶ **Cool**

Crisis Management – Team-member roles

1. **Anaesthetist 1: Resuscitation** (Coordinator in most cases)
 - ❖ Dantrolene 2.5mg/kg every 10-15 mins (DO NOT delay dantrolene to insert central venous line)
 - ❖ Total iv anaesthesia (TIVA) – avoiding inhalational agents
 - ❖ Hyperkalaemia management
 - ❖ Arrhythmia management
2. **Anaesthesia Assistant (nurse/JMO)** - Collect MH Box; Line set-up
3. **Nurses: responsible for Dantrolene**
4. **Anaesthetist/Dr 2: Lines & Investigations**
5. **Nurses/JMOs: assist with Cooling** – collect ice, collect refrigerated IVF & insulin, collect defibrillator, cover all exposed parts with ice
6. **Dr 3/NUM**: Logistics – call for additional Anaesthetists, additional dantrolene, arrange transfer to ICU
7. **Surgical Team** – complete/abandon surgery, insert IDC, expose pt to aid cooling

(1) Anaesthetist 1: Resuscitation

- ▶ **DANTROLENE:** 2.5 mg/kg every 10 -15 minutes IV until signs of hypermetabolism (acidosis, pyrexia, muscle rigidity) are resolving: • DO NOT delay dantrolene to insert central venous line
- ▶ NB that dantrolene can interact with CCBs (eg. verapamil) and precipitate profound hypotension (contraindicated)
- ▶ **Maintenance of Anaesthesia:** Choices include: • Propofol 1% (30-50ml/hr or TCI 4mcg/ml) • Midazolam 2.5-5mg IV PRN
- ▶ **Hyperkalaemia Management:** • Hyperventilation • Insulin 0.15U/kg + 0.5ml/kg 50% dextrose as rapid IV infusion (10U insulin in 50 ml 50% dextrose in adults) • CaCl₂ (10%) - 0.1ml /kg OR Ca gluconate (10%) 0.3ml/kg
- ▶ **Arrhythmia Management:** • Amiodarone: 3mg /kg slowly IV • Lignocaine: 1mg/kg IV • Procainamide: 300mg over 15 minutes, if available (ADULTS ONLY) • Metoprolol: 1-2mg IV prn • Hyperkalaemia management as above
- ▶ **Acidosis Management:** • Dantrolene (treats primary cause) • Hyperventilation • Consider 0.5-1 mmol/kg sodium bicarbonate - for pH < 7.2 (8.4% is 1mmol/ml)
- ▶ **Renal Protection:** • Maintain UO ≥ 2 ml/kg/hr by o maintaining intravascular volume – normal saline o mannitol - there is 3g mannitol / vial of dantrolene
- ▶ **Inotropic Support:** • Adrenaline / Noradrenaline prn

(2) Anaesthetic Assistant

- ▶ Once the MH Box and Refrigerated Supplies are in OT:
 1. Lay out contents on trolley
 2. Prepare arterial line equipment & assist Anaesthetist to insert art line
 3. Assist with Dantrolene mixing
 4. Ensure adequate stocks of resuscitation & TIVA drugs are maintained
 5. Set up central venous line equipment & assist Anaesthetist to insert central line

Ensure volatile agent has been removed from OT

Change sodalime when required

MH Box

- ▶ **Dantrolene**
 - ▶ 24 x 20mg vials of Dantrolene
 - ▶ Sterile water for injection
 - ▶ Drawing up needles & syringes
- ▶ **Drugs**
 - ▶ 8.4% sodium bicarbonate; 50% dextrose 50mL; Lignocaine 1%; Amiodarone 300mg
- ▶ **Cold Box in Fridge**
 - ▶ 2L N/Saline for IVF
 - ▶ Actrapid insulin
- ▶ **Blood tubes**
- ▶ **Urinary catheter**
- ▶ **Monitoring equipment**
 - ▶ Arterial and central line equipment

(3) Nurses: DANTROLENE

- ▶ Dantrolene works by an unknown mechanism to reduce release of Ca²⁺ from the sarcoplasmic reticulum
- ▶ Must be given ASAP – dantrolene reconstitution (*highest priority*)
- ▶ Mixing dantrolene can be time consuming – use as many people as are available
- ▶ Initial dose **2.5mg/kg**
- ▶ **20mg/vial**
- ▶ Mix with 60mL **STERILE WATER**
- ▶ **12 AMPOULES** will be required for each dose in a 100kg patient up to **every 10-15 minutes**
- ▶ Admin via large bore peripheral IVC/central line (but don't wait for insertion of CVC)



(4) Anaesthetist 2: Lines & Investigations

- ▶ Ensure temperature probe inserted
- ▶ Insert arterial line
- ▶ Send laboratory bloods
- ▶ Insert central venous line when appropriate
- ▶ Urine – when IDC inserted, send sample for myoglobin; maintain UO \geq 2mL/kg/hr
- ▶ Anaesthetic record

(5) Cooling

- ▶ **Ambient temperature**: turn down OT room temperature
- ▶ Uncover patient
- ▶ **Cool IV Fluids**
 - ▶ Collect 2L Normal Saline (for IV infusion) & Actrapid Insulin from refrigerator
- ▶ **ICE** packs to neck, groin, axilla (bring buckets of ice from ice machine)
- ▶ ± Gastric lavage
- ▶ **Defibrillator** to be collected
- ▶ **DON'T OVERCOOL** – Tissue destruction will occur at 41.5°C.
BUT do not overcool – cease active cooling at 38°C

(6) Logistics – Usually the OT Coordinator

- ▶ Call for additional Anaesthetic support (minimum of 2 Anaesthetists)
- ▶ Call Senior Surgeon
- ▶ Mobilise off-site dantrolene
- ▶ ICU bed/transfer
 - ▶ Up to 25% of patients relapse in the 1st 24 hours
- ▶ Assist with Dantrolene mixing

(7) Surgical Team

- ▶ Surgery – complete/abandon surgery ASAP
- ▶ Help cool patient
- ▶ Urinary catheter
- ▶ Assist with Dantrolene mixing

Prevention

▶ Drugs that **must be avoided** with MHS patients:

1. Depolarising muscle relaxants (i.e. **suxamethonium**)
2. ALL potent **inhalational agents** – incl. desflurane, sevoflurane, isoflurane, enflurane, halothane, methoxyflurane

▶ Drugs that **can be used** with MHS patients:

1. ALL other pharmacological agents are safe incl. the following common drugs
 - nitrous oxide
 - propofol & all other IV induction agents incl. ketamine, benzodiazepines, local anaesthetics, opioids...

Patients susceptible to MH

Who is treated as susceptible?

▶ **Patients with ≥ 1 of the following:**

1. Previous MH reaction
2. Positive In Vitro Contracture Test (IVCT) on muscle biopsy
3. Positive DNA test for MH
4. If an IVCT has not been done:
 - i. Relative with a +ve IVCT
 - ii. Pt (with MH relative) has negative DNA result
 - iii. Relative with clinical MH reaction

Guidelines for managing patient who is susceptible for MH

- ▶ Preparation of a Boyles anaesthesia machine
 - ▶ Remove vaporizer, replace sodalime with fresh sodalime
 - ▶ [**Soda lime** is a mixture of chemicals, used in granular form in closed breathing environments, such as GA, to remove CO₂ from breathing gases to prevent CO₂ retention and CO₂ poisoning.]
 - ▶ Replace hoses & rebreathing bags with new hoses & bags
 - ▶ Flush with 10L/min oxygen or medical air for ~20mins through the circuit
- ▶ Anaesthesia Workstation preparation
- ▶ Monitoring – temp, RR, ETCO₂