Malignant Hyperthermia
Updates in Pathophysiology and Treatment
Michael Boada, DO & Caroline So, DO

Objectives

- MH Pathophysiology
- MH Triggers/associated conditions
- MH Epidemiology
- MH Diagnosis
- MH Clinical presentation & Differential Diagnosis
- MH treatment
- Post-MH crisis care
- Caring for the MH Susceptible Patient
- MH Diagnosis and Treatment in the Cardiac Surgery Patient
- MHAUS

MH: Pathophysiology

- Malignant hyperthermia (MH) is a pharmacogenetic disease characterized by extreme hypermetabolism when a genetically susceptible individual is exposed to a triggering agent.

MH: Pathophysiology

Increased intracellular ionized calcium → increased ATP demand → increased metabolism → ATP depletion

MH: Associated Triggers

- Potent Volatile Anesthetics
  - Isoflurane
  - Sevoflurane
  - Desflurane
  - Halothane
- Succinylcholine

MH: Associated Conditions and Risk Factors

Risk Factors
- Family History
- Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility. Canadian Journal of Anesthesia: January 2017; Volume 64; p 396
- Exertional heat illness/unexplained rhabdomyolysis

Associated Conditions
- Central Core Disease
- Multiminicore Disease
- King-Denborough Syndrome
- Native American Myopathy
Epidemiology

- MHAUS.org 2010:
  - Frequency of 1 in 5,000 to 1 in 100,000 anesthetics
  - About 400 cases per year in the US

- Malignant Hyperthermia Deaths Related to Inadequate Temperature Monitoring

  Of 84 MH patients, there were 7 cardiac arrests during the initial MH event and 8 (9.5%) deaths before discharge from the hospital.
  Higher risk of death with no temperature monitoring
  Higher risk of death with longer anesthetic exposure before dantrolene
  Other studies have shown higher mortality with fulminant MH episodes in the ambulatory vs. hospital setting

MH: Diagnosis

Caffeine Halothane Contracture Test

- https://youtu.be/H6Q286CF728
  - Gold Standard
  - Sensitivity close to 100%
  - Specificity of approximately 80%
  - Drawbacks:
    - Costly
    - Requires travel to diagnostic center
Genetic Testing

- RYR1 (ryanodine receptor), CACNA1S (dihydropyridine receptor), STAC3 (protein required for colocalization of dihydropyridine and ryanodine receptors)

  - 35 RYR1 variants and 2 CACNA1S variants are sufficiently characterized for use in diagnostic genetic testing
  - cost-effectiveness makes it a viable first-line test for certain patients
  - sensitivity and specificity is varied

- MHAUS.org: “At this time, genetic testing is recommended as a confirmatory diagnostic measure for individuals known to be at high risk for an MH event, as determined by their own or a first-degree (sibling, parent, offspring) family member’s clinical episode of MH or positive muscle contracture test (caffeine-halothane contracture test).”

European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility
British Journal of Anaesthesia: July 2015 - Volume 115 - Issue 4 - p 531-9

- MH Diagnosis: Genetics vs. CHCT
Clinical Signs of MH

**Early signs:**
- Increase ETCO$_2$
- Tachycardia
- Hypoxia
- Muscle rigidity
- Abrupt rise in ETCO$_2$ following succinylcholine
- Masseter Spasm
- Hyperthermia (controversial)

**Non-specific signs:**
- Tachycardia
- Tachypnea
- Acidosis
- Metabolic vs. Respiratory
- Hyperkalemia

**Late signs:**
- Hyperthermia
- Rhabdomyolysis
- AKI
- Atelectasis
- Hypertension
- Circulatory collapse

Clinical Presentation, Treatment, and Complications of Malignant Hyperthermia in North America from 1987 to 2006

- Anesthesia & Analgesia: February 2010 - Volume 110 - Issue 2 - p 498-507
- 286 cases were included (112 graded very likely MH and 174 graded almost certain MH)
- First clinical sign:
  - Hypercarbia (38%)
  - Sinus Tachycardia (31%)
  - Masseter Spasm (20.8%)
Masseter Spasm

• Typically follows succinylcholine administration
• Precedes MH in 20-30% of cases
• Elevations in creatinine kinase are common
• CK levels greater than 20,000 are indicative of MH vs. Masseter spasm

Clinical Presentations

• Highly variable ranging from mild/moderate to fulminate MH crises
• ABG analysis demonstrates combined metabolic and respiratory acidosis, negative base excess, lactemia, hypercapnia, and hypoxemia
• Fulminant MH crisis will present with PaCO₂ >60mmHg and base excess of >8mEq/L
• Rhabdomyolysis leads to hyperkalemia, increased creatinine kinase, and myoglobinuria leading to acute renal failure
• Fulminant MH crisis is characterized by multisystem organ failure and circulatory collapse

Differential Diagnosis

• Malignant Hyperthermia
• Overheating
• Insufficient anesthesia/awareness
• Pain
• Insufficient Ventilation
• Anesthesia Machine Malfunction (i.e. I/E Valves)
• Anaphylaxis
• Sepsis
• Thyrotoxicosis
• Neuroleptic Malignant Syndrome
• Serotonin Syndrome
• Transfusion reaction (i.e. ABO incompatibility)
• Drug abuse (Cocaine, MDMA, Methamphetamines)
• Alcohol withdrawal
• Duchenne MD associated hyperkalemic arrest
Treatment

• Initiate MH Protocol
• Discontinue volatile inhalational agents and succinylcholine
• Initiate non-triggering anesthetic
• Call for help
• Alert surgeon and abort case if able
• Call MH Hotline: 1-800-MH-HYPER
• Hyperventilate with 100% O2
• Dantrolene 2.5mg/kg bolus, repeat 1mg/kg every 5 min until cardiac and respiratory systems have normalized
• If giving large doses (> 10 mg/kg) without symptom resolution, consider alternative diagnoses

• Ensure adequate IV access
• Cool the patient via lavage, fluids, skin with goal temperature <38°C
• Sodium Bicarbonate, 1-2 meq/kg, for base deficit greater than 8
• ABGs, monitor electrolytes and coagulation
• Monitor and treat hyperkalemia (Calcium, bicarbonate, and insulin/glucose)
• Monitor/treat for cardiac arrhythmia per ACLS
• Avoid Calcium Channel Blockers

Post Crisis Management

• Continue dantrolene 1mg/kg q4-6 hrs for 24-48 hrs; until arterial blood gases have normalized
• Trend electrolytes (i.e. hyperkalemia)
• Serial ABGs
• Monitor creatine kinase and signs of rhabdomyolysis
• Monitor urine output (goal 3ml/kg/hr), renal function, and myoglobinuria
• Continue hydration
• Continue studying (PT, PTT, INR, Fibrin split products, Fibrinogen)
• Monitor for signs of DIC

• Transferred to intensive care unit and monitored for 24 hrs following resolution of MH signs
• Goal temperature <38°C
• Monitor for signs of MH recrudescence which occurs in 25% of patients following initial treatment
• Counsel the patient on obtaining definitive testing for MH susceptibility for themselves and family members
Dantrolene
• Introduced in 1975
• Hydantoin derivative
• MOA: Specific ryanodine receptor antagonist
• Decreases release of calcium from the sarcoplasmic reticulum
• Reduced the 70-80% mortality rate of MH to 5%
• Metabolism: Liver
• Excretion: GI and Urine
• Side effects: Muscle weakness, tissues necrosis following extravasal injection, nausea, vomiting, dizziness

DANTRIUM™/REVONTO™
• Available in 20 mg vials
• Each vial should be reconstituted with 60 ml of sterile water for injection, USP (without a bacteriostatic agent) and the vial shaken until the solution is clear

RYANODEX™
• Dantrolene formulation made available in 2014
• Available in 250 mg vials
• Reconstituted with 5 ml of sterile water for injection, USP (without a bacteriostatic agent) and shaken to ensure an orange-colored uniform, opaque suspension
Preventing MH in a MH Susceptible Patient

- Identify those with MH history/confirmatory diagnosis, strong FH consistent with MH, and those with neuromuscular disorders who are MH susceptible
- MHAUS recommends:
  - Flush and prepare the anesthesia workstation according to manufacturer guidelines
  - Use of activated charcoal filters on inspiratory and expiratory ports
  - Remove vaporizers and succinylcholine from the anesthesia workstation
  - Replace the CO₂ absorbent
  - Continuous temperature (esophageal/bladder/PA) and end tidal CO₂ monitoring
  - Close availability of Dantrolene and a stocked MH cart with drugs and equipment to manage MH close to any location where triggering agents are used
  - Prophylactic dantrolene is not recommended
  - A MH designated machine is not necessary
  - Provide a safe non-triggering anesthetic
  - Discharge following 1.5 hours in PACU with all vital signs stable

Vapor Clean-Activated Charcoal Filters

Anesthetic Types

- MH Triggers
  - Halogenated hydrocarbon volatile Anesthetics (eg. Sevoflurane, isoflurane, desflurane)
  - Succinylcholine
- Safe Anesthetics in MH patients
  - IV anesthetics (eg. Propofol, etomidate, ketamine)
  - Opioids (eg. Fentanyl, remifentanil, sufentanil)
  - Non-depolarizing NMBs
  - Nitrous Oxide
  - Benzodiazepines
  - Local Anesthetics
The use of a checklist improves anaesthesiologists' technical and non-technical performance for simulated malignant hyperthermia management

• Jean-Baptiste Hardy *, Antoine Gouin, Cédric Damm, Vincent Comperre, Benoît Veber, Bertrand Dureuil


• Conclusion: Registered anaesthesiologists' use of the MH checklist during a simulation session widely improved their adherence to guidelines and non-technical skills.

• This study strongly suggests the benefit of checklist tools for emergency management.

Malignant Hyperthermia: Review of Diagnosis and Treatment during Cardiac Surgery with Cardiopulmonary Bypass

• Brian Butala, DO, Michael Busada, DO, Daniel Cormican, MD

• JCVA (2018), https://doi.org/10.1053/j.jvca.2018.03.029

• Diagnosis of patients on CPB may be more challenging given the alterations in physiology associated with CPB.

• Reviewed 30 cases of newly diagnosed MH during cardiac surgery and MH susceptible patients undergoing cardiac surgery from 1982-2016

Malignant Hyperthermia: Review of Diagnosis and Treatment during Cardiac Surgery with Cardiopulmonary Bypass

• Classic signs of MH include: tachycardia, increased ETCO₂, muscle rigidity, increased O₂ consumption, hyperthermia, hyperkalemia, rhabdomyolysis, and myoglobinuria

• Tachycardia and cardiac dysrhythmias are common in these patients

• Hypovolemia

• Pain

• Vasoactive medications (e.g. Epinephrine/Dopamine)

• Hyperthermia can be masked by active cooling during CPB
Malignant Hyperthermia: Review of Diagnosis and Treatment during Cardiac Surgery with Cardiopulmonary Bypass

- 17 cases of newly/presumed diagnosed MH and 13 cases of known MH susceptible patients undergoing cardiac surgery
- 9/17 described a clear MH triggering agent, rewarming during CPB presumed to be a trigger itself
- Most common and reliable sign of MH in these patients is elevation in end tidal CO₂
- The sweep of CPB is very efficient, so rise in end tidal CO₂ with other associated symptoms of MH should prompt investigation

MH Diagnosis Algorithm for the Cardiac Surgical Patient

- Identify signs and symptoms of MH
- Perform diagnostic testing
- Confirm diagnosis

MH Treatment Algorithm for the Cardiac Surgical Patient

1. Notify surgeon and halt procedure ASAP
   - If surgery needs to resume, administer reversal agents with IV nontriggering anesthesia (e.g., IV anesthesia, intubation, atropine and non-narcotic anesthetic drugs)
2. Discontinue volatile agents and avoid induction
   - If CPB is not yet initiated, discontinue volatile agents and provide IV reversal anesthetic agents
3. Call for help
MH Treatment Algorithm for the Cardiac Surgical Patient

1. Hypercarbia with 100% oxygen will not ease flows. Add activated charcoal filter to ventilation circuit if available. 
   a. If on CPB, ask perfusion to ensure 100% EUG and increase sweep gas flow to increase 
      ventilation. Determine CO2 level.
   b. If on CPB, consider adjunct ventilation for CPB to assist in improving blood 
      gas exchange and CO2 elimination.

2. Give IV methylprednisolone 2.5 mg/kg through large bore IV or drip pump.
   a. Monitor in frequency as indicated until patient responds with a decrease in 
      

3. Maintain adequate urine output (50-100 mg/kg/hour) with NaCl and fluid. 

4. If patient shows signs of hypotension, consider increasing IV fluids or 
   

5. Adjust ventilation to maintain adequacy. If urine output is less than 
   

6. If patient shows signs of hypotension, consider increasing IV fluids or 
   

7. If patient shows signs of hypotension, consider increasing IV fluids or 
   

8. If patient shows signs of hypotension, consider increasing IV fluids or 
   

9. If patient shows signs of hypotension, consider increasing IV fluids or 
   

10. If renal potassium >5.9 mEq/L, consider treatment:
    a. Calcium chloride IV 10 mg/kg, maximum dose 2,000 mg
    b. Sodium bicarbonate IV 1.2 mEq/kg
    c. 10 ml regular insulin IV and 50 ml 30% dextrose IV
    d. Check hourly glucose levels
    e. For refractory hyperkalemia, consider albumin, furosamide, heparin or 
       sodium polyprenylsuccinate. PD or PR dialysis, emergent initiation of CPB or 
       ECMO if patient is in cardiac arrest.
References


QUESTIONS?

Thank you!