Malignant Hyperthermia

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Malignant Hyperthermia (MH)
- rare, potentially fatal pharmacogenetic disorder
- autosomal dominant inheritance
- develop a hypermetabolic crisis of skeletal muscle when exposed to halogenated inhalation agents or succinylcholine

Anesthesiology 2009; 110: 84-89

History of MH
- 1960 → 1st case report published in Lancet
- 1970 → correlations to Porcine Stress Syndrome
- 1970s → muscle biopsy testing begins
- 1979 → FDA approves dantrolene for use
- 1985 → dantrolene shown to reverse intracellular hypercalcemia in skeletal muscle
- 2003 → genetic tests identified for diagnostic use

Anesthesiology. 2009; 110: 89-94
Anesthesiology. 2014; 120: 1333-8

Incidence of MH
- 500 to 800 suspected cases each year
- rare event → many cases are not found to be MH
- overall incidence in anesthesia: 1:3000 to 1:50,000
  - reported incidence has wide range in literature
- adult incidence: 1:50,000 anesthetics (1:100,000)
  - children: 1:5000 to 1:10,000 anesthetics (1:30,000)
    - peak mean age: 18.3 years of age
    - children under the age of 15 → account for 52.1% of all cases
    - earliest age report → 6 months old

Anesthesiology 2009; 110: 89-94
Anesthesiology 2014; 120: 1333-8
Incidence of MH

- males > females → ratio of 2:1
- inpatient surgery rate → 1:100,000
- ambulatory surgery rate
  - low incidence 0.31 per 100,000 cases
  - ASA Refresher Course 2011: at least 5 cases in ambulatory centers
- 30% patients won’t react until the third exposure to triggering agents

Mortality from MH

- 70 to 80% mortality during 1960s to 1980s
- 11.7% mortality rate reported in 2009
- < 5% rate in 2013 (as low as 1.4%)
  - due to widespread use of dantrolene in MH reactions
  - due to early perioperative recognition of rising end tidal CO₂ by capnography
  - halothane is not being used
  - decreased use of succinylcholine with inhalation agents
- rate increase to 9.5% in 2014

Muscle Contractions

- Ca²⁺ mediates skeletal muscle contractions
  - in resting state, Ca²⁺ is stored in the sarcoplasmic reticulum → not the muscle cytoplasm
- Acetylcholine binds to muscle receptors → get depolarization → Ca²⁺ released from SR → enters cytoplasm through RYR1 (ryanodine) receptor channels

Muscle Contraction

- Ca²⁺ binds to troponin
  - allows actin to bind to myosin to shorten the muscle fibers
  - muscle now contracts
- ATP in cytoplasm stops the actin-myosin reaction
  - also pumps excess Ca²⁺ back to sarcoplasmic reticulum
- ATP reaction is exothermic
Pathophysiology of MH

- RYR1 receptor channel remains open
  - also have a defect in the voltage regulator for the channel to help keep the RYR1 open

- Calcium continues to flow into the intracellular cytoplasm
  - develop hypercalcemia in the skeletal muscle

- Results in hypermetabolic reaction in muscle

Pathophysiology of MH

- RYR1 defect is primary mechanism in MH

- Secondary mechanism in MH
  - non selective cation channels in sarcoplasmic reticulum
    - they release Ca$^{++}$ into the cytoplasm during an MH reaction
    - they also release Ca$^{++}$ into the cytoplasm at rest as well
    - result is that MHS patients have higher than normal cytoplasmic Ca$^{++}$ levels

MHS is Malignant Hyperthermia Susceptible

Hypermetabolic State

- aerobic metabolism drives the events at first
  - oxygen consumption $V_{O2}$ is increased 3X normal
  - ATP stores are exhausted in attempt to stop contractions & pump Ca back into the SR

- ATP depletion causes exothermic reaction
  - heat production = hyperthermia of MH

- Anaerobic metabolism now takes over
  - develop metabolic acidosis

Anaerobic Metabolism

- acidosis develops → cells die → release K$^+$ into the circulation

  - hyperkalemia
    - monitor shows tall, peaked T waves
    - lactic acid levels are 15 to 20 times normal levels → metabolic acidosis

- muscle cell necrosis
  - myoglobin is released into the circulation
  - debris enters the circulation and ↑ blood viscosity
  - ↑ capillary obstruction
  - develop renal damage & coagulopathy
Death from MH

- hypoxia secondary to acidosis
- compromised blood flow to organs
  - especially kidneys = renal failure
- dyssrhythmias secondary to hyperkalemia

DIC develops especially if temperature is greater than 41.5°C
- rarely do patients survive if DIC develops
- 50 fold ↑ cardiac arrest  89 fold ↑ death

Malignant Hyperthermia  MH

- hypermetabolic response to potent, volatile inhalation agents
  - halothane (no longer in US) > isoflurane
  - sevoflurane > desflurane
  - less potent than halothane & isoflurane
  - desflurane is least potent MH trigger

- depolarizing muscle relaxant agents
  - succinylcholine
  - succ + volatile agents ---- see more intense reaction

- rarely seen: non anesthesia cases of heat & vigorous exercise

Malignant Hyperthermia  MH

- MH can occur on 1st exposure to a trigger
- 30% of cases take at least 3 exposures to trigger agents before MH is seen
  - reports exist where it took up to 10 anesthetic exposures before MH occurred
- Rare to see succinylcholine as a solo triggering agent: usually need volatile gas in addition
  - MH registry 6 out of 500+ cases only had succinylcholine as the trigger
  - all cases reported it took a dose of succ > 0.5 mg/kg
  - what is dose for laryngospasm?

Personal communication  MHAUS - Brandon

Case Reviews
2010 MH Case Reports

<table>
<thead>
<tr>
<th>Least likely cause</th>
<th>Agent</th>
<th>% of MH cases</th>
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<tbody>
<tr>
<td></td>
<td>Enflurane</td>
<td>2.8%</td>
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<tr>
<td></td>
<td>Desflurane</td>
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<tr>
<td></td>
<td>Halothane</td>
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<td>Sevoflurane</td>
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<td>Isoflurane</td>
<td>57.8%</td>
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<table>
<thead>
<tr>
<th>Most likely cause</th>
<th>Agents Used</th>
<th>% of MH Cases</th>
<th>Total Number</th>
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<tr>
<td></td>
<td>Volatile Gas Alone</td>
<td>45.1%</td>
<td>128 of 284 cases</td>
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<td>Gas + Succinylcholine</td>
<td>53.9%</td>
<td>153 of 284 cases</td>
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<tr>
<td></td>
<td>Succinylcholine Alone</td>
<td>0.7%</td>
<td>2 of 284 cases</td>
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7/10/2018

2014 MHAUS Registry Review

- 712 cases reported to MHAUS Registry 1987-2010
- 477 cases met criteria
  - 58.5% possible MH
  - 41.5% fulminant MH

**Results**
- Inhalation agent + succinylcholine: 53.9% cases
- Inhalation agents alone: 47.1% cases
- Succinylcholine alone: 2.9% cases
- No trigger agent used: 7 cases out of 477

394 Single Agent Cases

- **Volatile Agent without succinylcholine**
  - halothane had fastest onset → statistical difference among all 4 agents
- **Volatile Agent + succinylcholine**
  - onset was shorter in all agents used

<table>
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<tr>
<th>MH Onset Time in Presence or Absence of Succinylcholine</th>
<th>MH Onset Time ( minutes )</th>
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<tr>
<td>Agent</td>
<td>No Succinylcholine</td>
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<td>-------------------</td>
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<tr>
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<td>Desflurane</td>
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<td>Isoflurane</td>
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1 Unique First Sign of MH

- **Typical early signs of MH**
  - ↑ end tidal CO₂, muscle rigidity, sinus tachycardia, masseter muscle spasm (MMS)
- Can have a single unique 1st sign as well
  - 322 cases of 477 had a single 1st sign
    - hypercarbia 30.7% (illustrates the need for capnography)
    - masseter muscle spasm 24.8%
    - sinus tachycardia 21.1%

Masseter Muscle Spasm (MMS) is also known as Masseter Muscle Rigidity (MMR)
**MH Onset with Succinylcholine but no Inhaled Agents**

- 14 cases where succinylcholine was used but no inhaled agent (14 out of 477)
  - 11 of 14 (78.57%) had possible MH
  - 3 of 14 (21.42%) had fulminant MH
  - Dose was not defined → assume it was for intubation

- Most frequent initial signs
  - Masseter muscle spasm & sinus tachycardia (50%)
  - Hypercarbia (35.7%)
  - Elevated temperature (28.6%)

**MH Onset with Succinylcholine**

- Succinylcholine is used in only 5 to 10% of all general anesthetics
  - As solo agent → low risk of MH reaction
    - Canadian review: 20 out of 129 MH cases (~16% of cases)
      - Higher rate than other case reports
      - Dose range of 0.5 to 2.5 mg/kg
  - Succinylcholine + volatile gas: >50% of reported MH cases

**Summary from 2014 Report**

- Combination of inhaled anesthetics & succinylcholine has the fastest onset of MH
- MH onset time is very rapid when see MMS after use of succinylcholine
- Halothane has fastest onset compared to other gases
- Sevoflurane has faster onset than desflurane and isoflurane
- Since 1998 MH appears more so in 2nd or 3rd hour of anesthesia

**Delayed Onset of MH**

- Sevoflurane anesthesia
  - Median onset → 60 minutes
  - Range → 10 to 210 minutes
- Halothane anesthesia
  - Median onset → 20 minutes
  - Range → 5 to 45 minutes
- Use of non-depolarizing NMB agents
  - Delay the onset of MH and result in ↓ in CK levels

**Notes**

- Anesth Analg. 2014;118:388
- Br J Anesthesia. 2011;107:48-56
Clinical Manifestations of MH

- Early descriptions of MH reactions in literature
  - all patients have generalized muscle rigidity
  - high fevers & acidosis
  - high mortality rate

- Current descriptions in literature
  - muscle rigidity may or may not be present
  - temperature increase is a "late finding"
  - \( CO_2 \) increase is an early sign
  - occur at any time during anesthetic even post operatively
  - recrudescence may occur despite treatment with dantrolene

Classic Malignant Hyperthermia

- the \textit{sine qua non}, \( \uparrow \) in end tidal \( CO_2 \)
  - if you increase the minute ventilations, you will still see an \( \uparrow \) in end tidal \( CO_2 \) \( \rightarrow \) it just may be delayed
  - intubated patients end tidal levels of \( \geq 55 \text{mm} \) despite aggressive ventilation
  - \textit{has been described as the earliest & most sensitive sign of MH}
  - reinforces the need for capnography

- tachycardia & tachypnea
  - if open airway technique, you will see tachypnea

Classic Malignant Hyperthermia

- muscle rigidity in all of the extremities
  - may not always be present

- hypertension

- ventricular dysrhythmias secondary to hyperkalemia

- increase in temperature 1 to 2\( ^\circ \text{C} \) Q5mins
  - 2.9 fold \( \uparrow \) in complications for every 2\( ^\circ \text{C} \) \( \uparrow \) in temperature
  - temperatures \( \geq 41.5\text{\textdegree} \) lead to coagulopathies including DIC

- increase temperature in \( CO_2 \) absorbent canister
  - look for the "blue – purple" canister

- peripheral skin mottling, sweating, & cyanosis

- hyperkalemia & hypercalcemia

- cola colored urine = myoglobinuria

- acidosis as measured by blood gases

- increase in CK
  - \( \sum 20,000 \text{U in 1st 12 to 24 hours} \)
  - not always a consistent finding \( \rightarrow \) if present, most likely MH reaction

- DIC
  - PT, PTT, d-dimer

  - \( \uparrow \) in risk of death (89 fold increase)
  - \( \uparrow \) in risk of cardiac arrest (50 fold increase)

Anesthesiology 2009; 110: 89-94
Classic Malignant Hyperthermia

- Patients with increased muscle mass
  - ↑ in risk of death (14 fold increase)
  - ↑ in risk of cardiac arrest (19 fold increase)

- Longer it takes EtCO₂ to peak
  - greater the risk of death or cardiac arrest

Exceptions

- succinylcholine + inhalation agents
  - 1st sign is more likely to be muscle rigidity especially masseter muscle rigidity (MMR) (MMS)
  - ↑ in EtCO₂ will follow along with hyperthermia and tachycardia

- hyperthermia
  - typically not the first sign
  - “late sign” is relative term → it just follows the others but not by that much

MH in Children

- reported incidence depends upon study
  - Anest Analg. 2014; incidence of MH is 17%
  - #1 (0-24 months old) #2 (25 mo-12 yr) #3 (13-18 yr)

- most common findings in all 3 groups
  - tachycardia (73.1%)
  - hypercarbia (68.6%)
  - rapid temperature elevation (48.5%)
  - group 3 → more likely to develop these findings

- Group 3
  - took longer to get to maximum end tidal levels
  - had higher K⁺ levels, more rhabdomyolysis, higher CK levels

- Group 1
  - higher levels of metabolic acidosis

- Recrudescence rate 14.4% vs 20% in adults
**Post Operative MH**

- MH can occur any time perioperatively
- Post op MH
  - 1.9% of all cases in MH – N. America registry
  - maximum latency period is unknown
  - onset usually 0 to 40 mins post operative
  - *hyperthermia not a usual presenting sign*
  - most of these cases are atypical presentations
  - may only see rhabdomyolysis & cola-colored urine
    - *malignant hyperthermia → urine dip stick in office*

- Refer for MH testing to confirm
  - muscle biopsy and/or genetic testing

  Anesthesiology 2008; 109 (3)

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**Recrudescence of MH**

- recurrence of successfully treated MH crisis ≥ 2 hrs after initial reaction
- incidence in adults is **20%** (63 out of 308 cases)
  - 50% cases within 9 hrs
  - 80% cases within 16 hrs
- greater the intensity of the initial reaction
  - the more likely to see episode of recrudescence
- no correlation to dose of dantrolene used in initial reaction & risk of a recurrent reaction
- ↑ in muscle mass will double risk of recrudescence
- the longer it takes for the initial reaction to occur
  - get an ↑ in risk of recrudescence
  - greater exposure of muscle to trigger agents is a risk factor
- hyperthermia may be the only sign seen
- desflurane is weakest trigger → no cases reported

Anesthesiology 2007; 106(5): 902-906

Anesthesiology 2007; 106:903-904
### Trigger Agents
- halothane (no longer manufactured in US)
- isoflurane
- sevoflurane & desflurane
  - desflurane < sevoflurane < isoflurane < halothane as trigger
- succinylcholine
- older agents: ether, enflurane, & methoxyflurane
- question? Is it the agent itself or the dose of the agent that causes MH?

### Non Trigger Agents
- antibiotics & antihistamines
- local anesthetics & nitrous oxide
- barbiturates, propofol, & etomidate
- benzodiazepines, opioids, & ketamine
- droperidol & non depolarizing neuromuscular paralyzing agents

### Temperature Monitoring
- **MHAUS** → monitor temperature for all GA > 30 mins
- Core temperature is preferred method
  - tympanic membrane → soft probe touching membrane → difficult to insert
  - esophageal probe in an esophageal stethoscope
  - nasopharynx → less accurate in open airway breathing through nose
- urinary bladder & rectum are considered intermediate sites
  - temperature changes here lag behind changes in core temperature
- core temperatures are more accurate than peripheral temperatures

  Anesthesiology. 2008; 109:318-338

### Peripheral Temperature Monitors
- axilla → probe must be over the axillary artery with the arm covering it
  - underestimates the core temperature
- forehead liquid crystal skin strips
  - forehead skin subcutaneous insulation is minimal compared to other sites in body
  - sweating & shivering → little effect on readings
  - clinically accurate for anesthetic monitoring → remember the core temperature is 2° higher
- MHAUS → not acceptable for MH temperature monitoring
  - our setting is an office → we have limitations
- infrared tympanic → poor fit in ear canal
  - clinically inaccurate
Importance of Temperature Monitoring

- 30% mortality rate if temperature not monitored
- 21% mortality rate if relied on skin monitors
- 2% mortality rate if used core temperatures
- Skin temperature instead of core temperature
  - 50% increase in mortality
- No temperature vs core temperature
  - 2-fold increase in mortality
- Elevated temperature better identifies risk of death
  - Better than $K^+$, pH, arterial $CO_2$, or end tidal $CO_2$

Testing for Malignant Hyperthermia

Caffeine Halothane Contracture Test (CHCT)

- MHAUS → CHCT is gold standard at present
- Muscle biopsy under GA
  - Can not use local anesthesia - may alter test results
- Sensitivity = 97%  (false negatives rare)
- Specificity = 78%  (false positives rare)
- Need to wait for 3 to 6 months after suspect MH event or significant rhabdomyolysis to test

Malignant Hyperthermia (MH)

- Inherited as an autosomal dominant
- 3 genes linked to MHS
  - MHS 1 is the RYR1 gene
    - Genetic mutations account for 50% to 70% cases of MHS patients
  - MHS 5 is the CACNA1S gene
    - Mutations account for ~1% of MHS patients
  - STAC3 in native Americans in North Carolina
- Genetic testing identifies only 25 to 30% of patients with confirmed MHS
**RYR1 Gene**

- located on chromosome 19 (19q13.1-13.2)
- contains 106 exons of mRNA amino acid sequences
  - all capable of multiple mutations
    - as of 2018, ~50 are causative
- some patients may have > 1 mutation in RYR1
  - 2 or more mutations → compound heterozygous
  - greater incidence of MH 1:2000 to 1:8500

**Tiered Genetic Testing**

- Tier 1 testing → blood test
  - look at 3 “hot zones” on RYR1 known to have causative mutations
  - 17 exons examined
  - 23% sensitivity
- Tier 2 testing → blood test
  - looks at entire RYR1 gene
  - 70 to 80% sensitivity
  - very expensive compared to Tier 1
- Discordance Rate of 10%
  - muscle biopsy positive but negative genetics
  - unexplained at present

**Genetic Testing**

- not all MHS patients have known causative mutations
  - genetic testing can not replace muscle biopsy at present
- however, once a causative mutation is found in a family
  - family members can get the genetic test first
  - if the causative mutation is found in their test, they are MHS positive
  - there is no need for them to get a muscle biopsy

**Genetic Tests – Pros & Cons**

- **Pros**
  - less expensive than CHCT
  - far less invasive than CHCT
  - no need to travel
- **Cons**
  - discordance – CHCT results differ from genetic results
  - due to heterogeneity of MH, absence of causative mutation does not rule out MHS
  - still need a muscle biopsy
  - still expensive: $800 to $4000 for a partial to full gene scan

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Aunth Analg. 2014; 118: 375-380
Aunth Analg. 2014; 118: 397-406
Anesthesiology. 2006; 108: 208-215


MHAUS web site
Management of MH Crisis in the Office

Office Plan for MH Reaction
- need protocol in place
  - assigned doctor and staff duties
- transfer protocol to a specific hospital where MH can be treated
  - dantrolene, critical care units, & anesthesiologist on site
  - MHAUS hotline 1-800-644-9737
- transfer protocol with local EMS
  - 911 call → declare MH emergency with transfer to specific institution
  - EMS alerts hospital → have anesthesiologist in ER
  - do not delay transfer → you can give dantrolene in transit

Anesthesia Machine Preparation
- dedicated vapor free workstation
  - expensive & impractical
- intensive care ventilator
  - unit never exposed to volatile anesthetic agents
- unit that was treated with a “machine flush”
  - drain → disable → remove vaporizer from unit
  - flush with fresh gas 10 L/min for > 90 minutes
    - each manufacturer has specific guidelines
  - change anesthesia circuit, breathing bag, & CO₂ absorbent
  - keep gas flows at > 10 L/min to prevent rebound phenomenon
  - residual volatile gas diffuses out of plastic parts in unit
- charcoal filters

Vapor-Clean Charcoal Filters
- disposable filters
  - sterilization renders them useless
- can be used in an acute MH reaction
- can be used to prevent an MH reaction
- approved for isoflurane, sevoflurane, & desflurane
  - removes at least 99% of anesthetic vapors
- effective for 12 hours if not exposed to volatile agents
- will not capture or scavenge nitrous oxide

Anesth Analg. 2014; 119:67-75

www.dynasthetics.com
Vapor-Clean Filters
- turn off vaporizer
  - tape it shut so it can not be turned back on accidentally
- flush unit for 90 seconds at 10 L/min of fresh gas
- place filters on inspired and expired unit ports
- replace bag & circuit
- maintain fresh gas at > 10 L/min
- reduces volatile agent to < 5 ppm in < 2 minutes for 90 minutes
- no need to replace anesthesia machine

Vapor-Clean
- 8 filters (4 pair) retail $599.00

Office Equipment & Supplies
- monitors
  - capnograph
  - ECG, SpO₂, HR, BP, & temperature
- refrigerated IV solutions: NSS
  - 15 ml/kg/hr times 3 bags
  - no LR because of calcium & potassium in solution
- ice for axilla, groin, legs
  - reusable ice packs less mess
  - do not cool below 37.5 to 38°C → develop hypothermia
- 60 ml syringes (5) to mix & deliver dantrolene
- consider NG tube for cold lavage?

Medications
- dantrolene
  - 36 vials of 20 mg dantrolene or 3 vials of Ryanodex
- bacteriostatic free sterile water to dilute dantrolene
  - 60 ml needed to dilute → stock 100 ml vials
- ventricular dysrhythmias
  - 2% lidocaine pre filled syringes
  - amiodarone 300 mg vial
- sodium bicarbonate 8.4% 50 ml prefilled syringe
  - management of acidosis should be dictated by blood gases
- other advanced emergency medications
Dantrolene

- standard of care for MH reaction
  - only available treatment to reverse an MH episode
- acts within muscle cell to prevent Ca++ release from the sarcoplasmic reticulum (SR)
- it is a skeletal muscle relaxant
  - affects the contractile response of muscle
- MHAUS → must be available within 10 minutes of the decision to treat
  - previous 5 minute time impractical
  - 1.5 times ↑ in complications for each 30 min delay in giving drug

Dantrolene

- initial dose 2.5 mg/kg IV bolus
  - given based upon total body weight → not lean body weight
  - some sources say limit is 10 mg/kg → others disagree
  - additional doses based upon continuation of symptoms
    - continued ↑ in temperature, EtCO₂, acidosis, & tachycardia
    - therapeutic levels for 4 to 6 hours
- why is there mannitol in dantrolene??
  - diuresis of kidneys
  - dantrolene is insoluble
  - mannitol allows dantrolene to go into solution

Dantrolene

- If MH reaction returns → recrudescence
  - additional dose of dantrolene up to cumulative dose of 10 mg/kg
- all cases of MH → ICU admission for 36 hours
  - dantrolene 1 mg/kg IV Q 4 to 6 hours for next 24 hours
  - monitor coagulation
  - myoglobinuria → monitor with heme test strip
    - if positive → maintain urine output at 2 ml/kg/hr
  - monitor K⁺ and CK levels Q 8 h

Dantrolene Side Effects

- most common is muscle weakness
  - occurs in 25% of cases where dantrolene is used
  - dantrolene + non depolarizing NMB agents compound the weakness
    - make sure muscle strength has returned prior to extubation
- sterile phlebitis
  - ~ 11% of cases
  - treat with warm soaks and elevation of extremity
- in clinical doses for MH
  - rare to see myocardial contractility defects
- nausea & vomiting
Dantrolene Side Effect

- dantrolene & calcium channel blockers
  - dantrolene & calcium channel blockers
  - 2 common IV calcium channel blockers for emergency use
    - verapamil
    - diltiazem

- side effects of concern from the combination
  - hyperkalemia
  - myocardial depression

- no apparent, significant negative interactions with other medication

Dantrolene (Dantrium)

- Newer Brand Name Version
  - Reconstitute in 20 seconds

Dantrolene

- Generic version will take several minutes to reconstitute → delays treatment onset

Dantrolene (Revonto)

- generic version by US World Meds
  - www.usworldmeds.com
- reconstitutes in ≤ 20 secs with sterile water
- 36 vials is full dose
- can get it in packs of 6 vials
**Revonto**

- Reconstitute 20 mg vial with 60 ml sterile water
  - not bacteriostatic water
  - shake for 20 seconds until see clear liquid
  - use within 6 hours
- Each vial contains
  - 20 mg dantrolene
  - 3000 mg mannitol
  - sodium hydroxide to keep pH at 9.5 when mixed with water
  - need to supply 60 ml bacteriostatic free sterile water
- Shelf life → 36 months
  - store at 68-77°F and avoid light exposure

**Dantrolene (Ryanodex)**

- FDA approved in 2014
- Each vial has 250 mgs dantrolene
  - equivalent of 12.5 vials of other dantrolene preparations
  - total initial dose of dantrolene for a 100 kg patient
- Mix with 5 ml sterile water
  - reconstitutes in <1 minute → usually in 10 seconds
  - concentration is 50 mg/ml
  - opaque, bright orange color when mixed
- Must use it within 6 hours
- Shelf life of 24 months

**Revonto**

- Vial = 20 mg
- Cost = 6 vials for $473.95
- Minimum number of vials should stock
  - need 2.5 mg/kg to treat
  - 100 kg patient needs 250 mg for initial dose
- Need minimum of 12 vials = $950.00
- MHAUS will say 36 vials = $2844.00

**Ryanodex**

- Vial only has 125 mg of mannitol
  - subtherapeutic diuretic dose for protecting kidneys
  - other dantrolene products have 3000 mg of mannitol per vial
  - may need to address diuresis with other agents
- Use 99% less water with this product
  - some benefits → some disadvantages
  - sterile water without bacteriostatics
- MHAUS recommends minimum of 720 mg
  - 3 vials of Ryanodex
  - many MH reactions require median dose of 5.9 mg/kg which is more than the 3 vials
- Cost → $2300 per vial
Ryanodex

Malignant Hyperthermia Association of the United States (MH/USA) recommended loading dose is 2.5 mg/kg.

Comparisons

<table>
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<th>Manufacturer</th>
<th>US Pharmacists</th>
<th>Per Pharmacist</th>
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Costs: $3000.00 $3000.00 $6900.00

Management in Office

- activate 911 to initiate transfer
- turn off inhalation gases & stop succinylcholine
- switch to nontriggering TIVA anesthesia
- 100% O₂ flush for 90 seconds at 10 L/min
  - do not replace anesthesia machine → place Vapor-Clean filters → replace anesthesia circuit and breathing bag → keep gas flow > 10 L/min
- dantrolene 2.5 mg/kg IV bolus
  - many cases may respond to initial dose
  - EMS should be there by time dantrolene mixed and administered
- give chilled IV NSS → apply external ice packs

Office MH Reactions

- Primary goal in office
  - make the diagnosis
  - initiate transfer
  - get dantrolene into solution

- Takes 30 minutes on average to get to this point
  - EMS should be there by now
  - Do not delay transfer
  - Secondary management is very limited
Secondary Management

- Ventricular dysrhythmias
  - Most likely due to hyperkalemia
    - Do you stock CaCl₂, Ca-gluconate, or regular insulin-dextrose in your office?
    - Tall, peaked T waves or very wide QRS complexes may be hyperkalemia but you don’t know
    - Amiodarone: 150 mg for V-tach, 300 mg V-fib
    - 2% prefilled lidocaine 100 mg as alternative
- EMS still not there after dantrolene bolus given
  - Looking at 20 to 30 minutes by now
  - Metabolic acidosis: sodium bicarbonate
    - Consider 1 to 2 mEq/kg IV in office

Patient Transfer

- Do not advocate a “grab & go” from an office
  - Prepare dantrolene in office & support patient until EMS arrives
- Can not get laboratory values in office
  - Primary care is limited to
    - Stopping the trigger
    - 100% O₂
    - Dantrolene for bolus
    - Initial dysrhythmia management
    - Ice packs for cooling
  - Secondary care is working blindly without data & should not delay any transfer to a facility where comprehensive care can be delivered

Indicators of Stability

- EtCO₂ is declining or returns to normal
- Tachycardia is improving
- No ominous dysrhythmias
- Temperature is declining
- Generalized muscle rigidity is resolving
- IV dantrolene administration

Other Management Issues & Special Circumstances

...
**Hyperkalemia**

- **K+ levels > 5.9 or less if there are consistent ECG changes**
  - Tall peaked T waves or very wide QRS
- **insulin + glucose**
  - Insulin drives K+ back into cells → glucose prevents hypoglycemia
  - **Adults:** 10 U regular insulin + 50 mls of 50% dextrose IV
  - **Children:** 0.1 U/kg regular insulin + 1.0 mL/kg 50% dextrose
    - May need to dilute to 25% dextrose to decrease irritation to veins
    - Add albuterol by MDI or nebulizer to further drive K+ into cell

**MH presents with hypercalcemia**
- **no contraindication to using Ca to treat hyperkalemia**
- **Ca is used to stabilize myocardial cells to prevent dysrhythmias**
  - **CaCl2 → 10 mg/kg IV (max dose 2000 mg)**
    - More effective than Ca-gluconate
    - Central line preferred route
  - **Ca-gluconate → 30 mg/kg IV (max dose 3000 mg)**
    - Less irritation to veins
    - Can avoid central lines & use peripheral line
  - **Lasix 0.5 to 1.0 mg/kg IV (max 20 mg) 1 dose**

**Myoglobinuria**

- **assume myoglobinuria is present if**
  - Labs show ↑ in Creatine kinase (CK) and K+
- **need to alkalinize urine to prevent renal tubular necrosis**
  - Sodium bicarbonate 1 mEq/kg/hr
- **maintain urine output at > 1ml/kg/hr**
  - Mannitol in dantrolene will cause diuresis

**Masseter Muscle Rigidity MMR**

- **masseter muscle spasm after inject succinylcholine**
- **incidence 1: 12,000 GA**
- **more common in children & adolescents**
  - 1: 100 to 1:5000 general anesthetics using volatile gas + succinylcholine
- **it is associated with MHS**
  - Occurs in ~50% of MHS patients
- **most cases induced by volatile agent + succinylcholine**
  - TIVA cases + succinylcholine are less common
  - “tight jaw is not due to light anesthesia”

Masseter muscle rigidity (MMR) is same as Masseter Muscle Spasm (MMS)
Masseter Muscle Rigidity  MMR

- additional doses of succinylcholine or non depolarizing NMB agents
  - will not reverse the spasm if patient develops MH crisis

- 30% of MMR cases
  - immediate onset of MH crisis

- majority of cases of MH
  - occur in ~ 20 minutes post trigger exposure

Advice for Inpatient MMR

- elective surgery → stop the surgery & monitor for MH reaction over several hours

- emergency surgery → start MH protocol
  - stop triggering agents & switch to TIVA instead of volatile gas
  - flush volatile gas out for 90 secs at 10 L/min & place Vapor-Clean
  - maintain 100% O₂ at > 10 L/min
  - only proceed with surgery if dantrolene is on site
  - capnography is mandatory + monitor for other signs of MH
  - if MH reaction starts → stop surgery and treat MH
  - hospital case: keep for 12 to 24 hours
  - look for myoglobin in urine
  - follow CK levels → levels > 20,000 units  MH likely

Office MMR

- if seen in an office (especially child or teenager)
  - early transfer is far better than waiting for a fulminant reaction
  - succinylcholine was given → tight jaw is not due to light anesthesia

- start your office protocol
  - stop triggering agents → let the patient wake up
  - initiate transfer
  - 100% O₂ & prepare machine if volatile gases were used
  - get dantrolene & monitor for signs of MH

  be smart & transfer out

Myodystrophies & Anesthesia

- Duchenne Muscular Dystrophy

- Becker Dystrophy

- These patients develop cardiac arrest after succinylcholine or volatile anesthetic agents
  - due to release of potassium from muscle cells along with release of myoglobin

- Resembles a MH crisis
  - not felt to be true MH
Succinylcholine Induced Hyperkalemic Rhabdomyolysis & Cardiac Arrest

- Apparently healthy children with acute onset hyperkalemia & rhabdomyolysis within minutes of succinylcholine use
- Ventricular dysrhythmias & sudden cardiac arrest within mins of succinylcholine use
- Males, usually age 8 or younger
- On autopsy, muscular myopathy usually Duchenne’s

Succinylcholine Induced Hyperkalemic Rhabdomyolysis & Cardiac Arrest

- If you don’t suspect inadequate ventilation & hypoxia or anesthetic overdose as the cause
- Immediately start treatment for hyperkalemia
- Calcium, glucose + insulin, bicarb, & hyperventilate
- Resuscitation attempts are usually unsuccessful
- FDA placed black box warning
- Avoid succinylcholine in children and young adults for elective surgery
- Avoid succinylcholine in major burns, stroke, and spinal cord injuries

MH Associated Disease

- Central Core Disease (CCD)
  - Many case reports of MH in CCD patients
  - Gene mutations on RYR1 gene
- Myotonia
- King-Denborough Syndrome

Awake Malignant Hyperthermia

- Exertional heat related illness
  - Triggers: high environmental temperatures, high humidity, & strenuous physical activity
  - Symptoms
    - Confusion, dizziness, fatigue, HA, & syncope
    - Profuse sweating, hyperthermia, & tachycardia
    - Dark colored urine
      - Most likely dehydration so urine is concentrated
      - Or myoglobin in urine from rhabdomyolysis
    - May progress to heat stroke if left untreated
Awake Malignant Hyperthermia

- Heat stroke
  - usually seen in extremes of age: <4 or >65
  - men > women
  - often a progression of exertional heat exhaustion
  - symptoms
    - confusion, agitation, slurred speech, delirium, seizures, & coma
    - hyperthermia > 104°F or 40°C
    - skin
      - vasodilated
      - moist in exertion, dry in non-exertional heat stroke
    - tachycardia, N/V, & tachypnea
    - hyperkalemia, rhabdomyolysis, & multiple organ failure
  - untreated mortality 21%

Management of Heat Exhaustion & Stroke

- get out of sun into air conditioned room
- hydrate PO and IV & active cooling measures

Heat Stroke

- no association to MH at present

Exertional Heat Exhaustion

- 1% of MHS patients report history of heat related problems
- case reports of positive RYR1 MH mutation patients having “awake MH” reactions

MHAUS Guidelines

- Non-anesthetized MHS patient suffering sudden collapse, muscle rigidity, and hyperthermia
  - treat with dantrolene & active cooling
  - no succinylcholine if need to intubate

- MHS patient or relatives with no adverse effects from heat & exercise
  - no need to limit activity

- MHS patient or relatives with adverse effects from heat & exercise
  - should limit activity

Awake MH

- common findings
  - no succinylcholine or volatile gases
  - muscle rigidity, hyperthermia, CVS collapse, & positive MH RYR1 gene mutation

- 6 y.o. playing in splash pool on hot day
  - lower extremity rigidity, tachycardia, temperature 108.9°F
  - fulminant MH reaction transferred to IR
    - given succinylcholine to intubate & died
    - always defer succinylcholine for intubation in hyperthermic patient

Pediatric Anesthesia. 2013;23:842

Pediatric Anesthesia. 2013;23:851
**Case Presentation**

- **2 y.o. Female 12.7 kg for dental restorations**
  - MHS family history
  - TIVA GA + intubation
  - Propofol, MS, nitrous oxide, & glycopyrrolate
- **15 minutes post induction**
  - Hyperthermia → rapid rise temp to 41.6°C in 10 minutes
  - End tidal 52 mmHg despite increase in ventilation
- **28 minutes post induction**
  - Dantrolene 2.5 mg/kg IV + active cooling, fluids, & sodium bicarb
  - Temperature started to decrease in 5 minutes
  - Cancelled case, extubate, transfer to hospital, discharged next day

**Case Review**

- Machine was prepped overnight in standard fashion
- No infection
- Cause: **UNDETERMINED**

> "Until we understand the mechanism of human MH triggering, no anesthetic regimen can guarantee safety"

*Anesthesiology. 1981;54:1-2
Anesth Analg. 2012;111(3): 822*

**Mimics of MH**

- **Fever but no muscle rigidity**
  - Sepsis, thyrotoxicosis, pheochromocytoma, iatrogenic overheating during surgery, & *anticholinergic syndrome*
- **Fever along with muscle rigidity**
  - Serotonin syndrome
  - Neuroleptic malignant syndrome (NMS), cocaine, amphetamines, & ecstasy
- **Osteogenesis Imperfecta**

**MH Susceptible Employees**

- Are MHS employees at risk in your office?
  - In reviewing the literature, no reports were found documenting any risk to MHS staff participating in general anesthetics using volatile agents in the office
- Operatories should have proper scavenging
  - Volatile gases are heavier than air and fall to ground
  - Will keep gas levels to < 5 ppm
**MHS Patient Recovery Time**

- inpatient or ambulatory surgery
- general anesthesia without triggering agents
  - no adverse intraoperative event

**Recovery time**

- inpatient: PACU for at least 1 hour, may consider 2 hours
  - monitor vital signs Q 15 mins
- ambulatory surgery
  - PACU for 1 hour and monitor vital signs Q 15 mins
  - Phase 2 PACU/Step down for another 1 hour
  - consider use of chemstrip to document absence of myoglobin
  - vital signs: ECG, pulse oximetry, pulse, BP, temperature, & CO₂

**MHS Patients & Office Anesthesia**

- is it safe to do MHS patients in the office?
  - local anesthesia & nitrous oxide are not triggers
  - TIVA agents are not triggers
  - Yes, it should be safe

- Do I need to stock Dantrolene in the office?
  - Are there concerns?

**MH Concerns in the Office**

- emergency intubation for lost airway in offices without anesthesia machines & offices that just do moderate to deep sedation
  - incidence of this event → no data available
  - incidence of use of succinylcholine → no data available to assess risk
  - non depolarizing agents are an alternative

  **I Gel, LMA would be the most appropriate airway device**

**MH Concerns in the Office**

- Incidence of laryngospasm in children & adults?
  - Incidence of succinylcholine in these cases?
    - 7304 pediatric sedations by pediatric critical care specialists
      - 0.3% incidence of spasm
    - pediatric propofol anesthetics outside of OR by anesthesiologists
      - 0.2% incidence of spasm
    - 7581 dental pediatric anesthetics
      - 5 patients needed succinylcholine to manage spasm 0.065%
      - no current data on adults
    - Probability of needing succinylcholine for spasm is 0.03%
    - Recommendation from paper → stock dantrolene

_Anesth Analg. 2013;116:118_
MHS patients & Office Surgery

- If you use succinylcholine, do you need dantrolene?
- Dental literature
  - JOMS. 2006; 66: 1485-88… “until all trigger agents can be removed from an OMFS office, you need to stock 10 to 12 vials of dantrolene to give an initial dose to a 70 kg patient.”
  - OOO. 2011;112:e1-e7…. Stock 10 to 12 vials in office if you have triggering agents
- MHAUS site → stock 36 vials dantrolene or 3 vials of Ryanodex
  - remember: complications ↑ 1.6 times for every 30 minute delay from the 1st sign of MH and the use of dantrolene → 2.9 ↑ in complications for every 2°C rise in temperature

Alternatives to Succinylcholine

- Rocuronium
  - new onset laryngospasm → failed positive pressure → not “blue”
  - 0.6 mg/kg → full paralysis in ~2 minutes → cords sooner
  - laryngospasm → patient is “crashing”
    - 1.0 mg/kg → cord paralysis in ~1 minute
    - need to ventilate patient > 30 minutes
    - need reversal with neostigmine / glycopyrrolate before you discharge patient
- Sugammadex: encapsulates and inactivates rocuronium
  - 2-16 mg/kg: dose > 4 mg/kg reverses in < 3 minutes (1 to 2 min)
  - FDA approved in US

Alternatives to Succinylcholine

- Lidocaine 1%
  - positive pressure fails to relieve laryngospasm
  - inject 1 to 2 ml of 1% lidocaine through the cricothyroid membrane
  - 25 gauge needle
  - 1–2 ml of 1% lidocaine
  - causes an immediate cough to open cords
  - cords get anesthetized by lidocaine as it is coughed out of the airway
  - reduces risk of recurrent laryngospasm

Alternatives to Succinylcholine

- Propofol
  - study used low dose propofol for laryngospasm after LMA removal in children
  - 0.8 mg of Propofol IV
  - 752 LMA – General anesthetics
    - 20 pt had laryngospasm after LMA removed
    - all got positive pressure with 100% oxygen
    - 7 of 20 responded to positive pressure
    - 13 had desaturations to 85% → got Propofol
    - 10 patients responded
  - 3 got re-intubated after succinylcholine
  - proposed new study at 1 to 1.5 mg/kg in future


Paediatric Anesthesia 2002;12:625
MHS patients & Office Surgery

- MHAUS opinion if no triggers used in GA
  - no different than any ambulatory center
  - PACU for 1 hour and monitor vital signs Q 15 mins
  - Phase 2 PACU/Step down for another 1 hour
  - consider use of chemstrip to document absence of myoglobin
  - vital signs: ECG, pulse oximetry, pulse, BP, temperature, & CO₂

How long do you recovery your office anesthetics?

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