Malignant Hyperthermia

- An inherited (autosomal dominant trait) disorder of skeletal muscle
  - If you have MH you would have a 50% chance of passing it to your child
- Results in:
  - Hypermetabolism
  - Skeletal muscle damage
  - Hyperthermia
  - Death if untreated
- Underlying physiologic mechanism – abnormal handling of intracellular calcium levels

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Testing for MH

- Muscle Contracture Test: Caffeine Halothane Contracture Test (CHCT)
- **Gold Standard**
- Requires skeletal muscle biopsy from patient's thigh to assess muscle contractile properties upon exposure to ryanodine receptor agonists (eg. caffeine, halothane).
- **Must be performed at the MH Muscle Biopsy Center.**
- Abnormally high levels of contractile force indicate MH susceptibility.
- Sensitivity: close to 100% (false negatives are rare)
- Specificity: ~80% (~20% false positives)

- * Genetic testing is also available, but is not as definitive.
  - 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)

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How is MH Triggered

- Triggering Agents
  - Potent Volatile (inhaled)Anesthetics (eg. halothane, sevoflurane, desflurane)
  - Succinylcholine
- Non-triggering Agents
  - IV anesthetics (i.e. propofol, etomidate, ketamine)
  - Nitrous Oxide
  - Non-depolarizing muscle relaxants
  - Opioids
  - Benzodiazepines, dexmedetomidine
  - Local Anesthetics

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Clinical Presentation

- MH may occur at any time during anesthesia and in the early postoperative period.
- The principal diagnostic features:
  - Unexplained elevation of end-tidal carbon dioxide ($ETCO_2$) concentration, despite increased minute ventilation
  - Tachycardia
  - Muscle rigidity (masseter muscle is the classic sign, especially after succinylcholine administration)
  - Acidosis
  - Hyperthermia (often a late sign)
    - Increase in core temperature at a rate of 1–2°C every five minutes. Severe hyperthermia (core temperature greater than 44°C) may occur, and lead to a marked increase in oxygen consumption, carbon dioxide production, widespread vital organ dysfunction, and disseminated intravascular coagulation
  - Hyperkalemia
- Variability in the order and time of onset of signs often makes the clinical diagnosis rather difficult.

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Clinical Presentation Progression

- Uncontrolled hypermetabolism leads to cellular hypoxia that is manifested by a progressive and worsening metabolic acidosis.
- If untreated, continuing myocyte death and rhabdomyolysis result in life-threatening hyperkalemia
- Myoglobinuria may lead to acute renal failure.
- Additional life-threatening complications include DIC, congestive heart failure, bowel ischemia, and compartment syndrome of the limbs secondary to profound muscle swelling, and renal failure from rhabdomyolysis. Indeed, when body temperature exceeds approximately 41°C, DIC is the usual cause of death.

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Dantrium vs Ryanodex

- 12.5-36 vials
- 750-2160ml sterile water
- >15mins to reconstitute
- 1-3 staff members
- 20mg dantrolene per vial

- 1-3 vials
- 5-15ml sterile water
- Less than 1 min to reconstitute
- 1 staff member
- 250mg dantrolene per vial

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Treatment: Dantrolene

- Blocks the release of calcium from the sarcoplasmic reticulum
- Inhibits excitation-contraction coupling in the muscle fiber
- Reduces mortality from 75% to 5%
- Note the concentration difference between Dantrium and Ryanodex!
- 1 vial of RYANODEX® contains the same amount of dantrolene as 12.5 vials of other approved dantrolene sodium forms

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Crisis Management

- Discontinue inhalation agents, succinylcholine
  - Notify surgeon to halt the procedure; call for help
- Hyperventilate at high flows with 100% O_2
- Change soda lime and place charcoal filters
- Give IV dantrolene 2.5mg/kg (repeat until symptoms resolve -> i.e. EtCO2/muscle rigidity/HR decreases)
  - Typical max dose 10mg/kg but may continue if needed
- Check blood gas and consider sodium bicarbonate 1-2 mEq/kg dose
- Treat arrhythmias/hyperkalemia
  - Calcium, bicarb, insulin/glucose, albuterol
  - Avoid additional Ca+ channel blockers as this can cause hyperkalemia
- Nursing: cool patient and place foley catheter
  - Mix dantrolene prn
- Diurese to >1 ml/kg/hr urine output

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MH Treatment Rolls in the OR

Surgeon

- Halt procedure ASAP

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Disposition

- When stable, transfer to PACU or ICU for at least 24 hours
  - ETCO2 declining/normal
  - HR is stable/decreasing; no dysrhythmias
  - Hyperthermia resolving
  - Muscular rigidity resolved
- Give dantrolene 1 mg/kg every 4-6 hours for 24 – 48 hours
- Monitor for recrudescence – rate is 25%
- Follow electrolytes, blood gases, CK, core temperature, urine output and color, coagulation studies

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MH Like Syndromes

- Neuroleptic Malignant Syndrome (NMS)
  - CNS dopamine deficit
  - Neuroleptics like haloperidol and dopamine blocking antiemetics (metoclopramide and prochlorperazine)
  - Treatment: stop antipsychotic, treat hyperthermia, supportive care
    - Some role for dantrolene and dopamine agonists (i.e. bromocriptine/amantadine); benzos for agitation
- Parkinsonism/Hyperthermia Syndrome (PHS)
  - Parkinsonian dopaminergic withdrawal
    - Complete discontinuation of dopaminergic therapy in the perioperative period should be avoided
- Serotonin Syndrome (SS)
  - Treatment: supportive care and cyrpoheptadine (anti-histamine)
- Baclofen withdrawal
- Intoxication
  - Amphetamines, MDMA, cocaine, PCP, LSD

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Drug-Induced MH-like Syndromes in the Perioperative Period

Charles Watson, MD; Stanley N. Caroff, MD; Henry Rosenberg, MD

Syndrome Drug	Probable Cause	Implicated Drugs	Factors	Onset	Signs & Symptoms
NMS	CNS dopamine deficit	Neuroleptics like haloperidol. Dopamine blocking antiemetics like metoclopramide & prochlorperazine	Dehydration, overdose, increasing or mixed drug doses	1–2 weeks	Fever, hypermetabolism, rigidity, shivering, abnormal CNS, unstable BP, rising creatinine kinase, MOSF
PHS	Dopamine deficit	Parkinsonian dopaminergic withdrawal	Abrupt discontinuation, dehydration & stress	Hours to days	As above
SS	CNS & peripheral serotonin excess	SSRIs, SNRIs, triptans, MAOIs, TCAs, some anesthetic adjuvants, methylene blue, some OTC drugs like loperamide, dextromethorphan	Overdose or increasing doses, multidrug interactions	1–24 hours	Ac above & myoclonus, agitation, confusion, dilated pupils, GI symptoms, evolving MOSF
Baclofen	Withdrawal	Baclofen	Pump failure, prescription stop	Hours to days	Hypertension, rigidity, dysautonomia, depressed CNS, coagulopathy, & MOSF
Amphetamines & CNS stimulants	Direct CNS & peripheral effects	Amphetamines, dexamphetamine, MDMA, cocaine	Dehydration, stress, other illness	Hours	Hyperdynamic circulation, fever, sweating, pupillary dilatation, cardiorespiratory, & MOSF
PCP	Direct CNS & peripheral effects	PCP or "angel dust"	Dehydration, stress, other illness	Hours	Slurred speech, abnormal gait, rigidity, sweating, hypersalivation, convulsions, coma, MOSF
LSD	Direct CNS & peripheral effects	LSD & LSD preparations	Dehydration, major stress, intercurrent illness	Hours	Hallucinations, rigidity, psychosis, CNS depression, respiratory arrest, coagulopathy, MOSF

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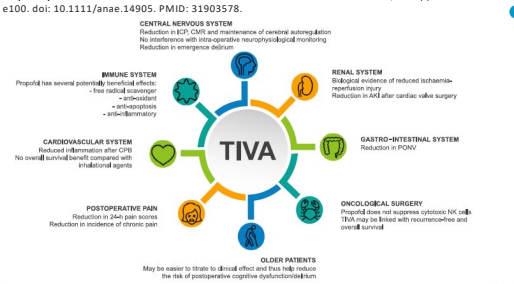
Irwin MG, Chung CKE, Ip KY, Wiles MD. **Influence of propofol-based total intravenous anaesthesia on peri-operative outcome measures: a narrative review**. Anaesthesia. 2020 Jan;75 Suppl 1:e90-e100. doi: 10.1111/anae.14905. PMID: 31903578.



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TIVA

Irwin MG, Chung CKE, Ip KY, Wiles MD. Influence of propofol-based total intravenous anaesthesia on peri-operative outcome measures: a narrative review. Anaesthesia. 2020 Jan;75 Suppl 1:e90-e100. doi: 10.1111/anae.14905. PMID: 31903578.

- **Propofol-based total intravenous anaesthesia is well known for its smooth, clear-headed recovery and antiemetic properties, but there are also many lesser known beneficial properties that can potentially influence surgical outcome.**
- Modern anaesthesia is still mostly administered by the inhalational route but there is increasing concern over their potential for pollution and other adverse effects.
- Exposure to halogenated hydrocarbons may cause reduction in antioxidant activity in plasma and erythrocytes, inhibition of neutrophil apoptosis, depression of central neurorespiratory activity, increased DNA breaks, effects on cerebral blood circulation and altered renal function.
- There are other disadvantages of inhalation drugs that can be avoided or reduced with propofol such as inhibition of hypoxic vasoconstriction, increased intracranial pressure, administration practicalities (laryngoscopy, bronchoscopy, jet ventilation), malignant hyperthermia and PONV.
- Propofol has anti-inflammation and powerful anti-oxidant properties which are organ protective and may contribute to the better analgesia seen after surgery compared with inhalation anaesthesia.
- Inhalational agents do have certain advantages in that administration is relatively simple, potency in terms of MAC is familiar and end-tidal concentrations can be measured in real time.

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Our patient

- Stabilized in OR after 2 doses of ryanodex (400mg); surgeon closed knee but had not replaced ACL
- Transferred ventilated and sedated to ICU at our institution as a direct admit with lifeguard transport
  - Anesthesiologist and ICU attending closed loop communication
- Patient extubated that evening and transferred to step-down the following day. Discharged POD # 2 with no sequelae/complications
  - Returned to OR 1 week later for ACL repair with a non-triggering anesthetic
- "Even though a MH crisis may develop at first exposure to anesthesia with those agents known to trigger an MH episode, on average, patients require three anesthetics before triggering"
  - Rosenberg, H., Davis, M., James, D. *et al.* Malignant hyperthermia. *Orphanet J Rare Dis* **2**, 21 (2007). https://doi.org/10.1186/1750-1172-2-21

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