THE UNIVERSITY OF RHODE ISLAND COLLEGE OF PHARMACY

Malignant Hyperthermia

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July, 2013

THINK BIG WE DO℠

Financial Disclosure

I have no financial obligations to disclose.

Outline

- Introduce malignant hyperthermia including its causes and implications
- Describe the underlying pathophysiology
- Detail the clinical presentation of MH
- Summarize the necessary pharmacological and non-pharmacological treatment of MH
- Highlight necessary considerations with the use of dantrolene
- Discuss recrudescence

Malignant Hyperthermia

- A life threatening reaction that is most often triggered by the use of inhalational anesthetics
- Estimated incidence of 1 in 5,000 to 1 in 100,000 anesthesia inductions
- Early recognition and treatment is essential in reducing morbidity and mortality
- Screening patients for past anesthesia history and family history, as well as conducting testing on at risk individuals is necessary to reduce MH occurrence

Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. Orphanet J Rare Dis. 2007 Apr 24;2:21. Review.

Drugs Triggering Malignant Hyperthermia

- Desflurane
- Enflurane
- Halothane
- Isoflurane
- Methoxyflurane
- Sevoflurane

- **Succinylcholine-** only non-inhalational anesthetic that triggers MH
- **Nitrous Oxide-** only inhalational anesthetic that does ***not*** cause MH

Hopkins PM. Malignant hyperthermia: pharmacology of triggering. Br J Anaesth. 2011 Jul;107(1):48-56. doi: 10.1093/bja/aer132. Epub 2011 May 30. Review.

Pathophysiology

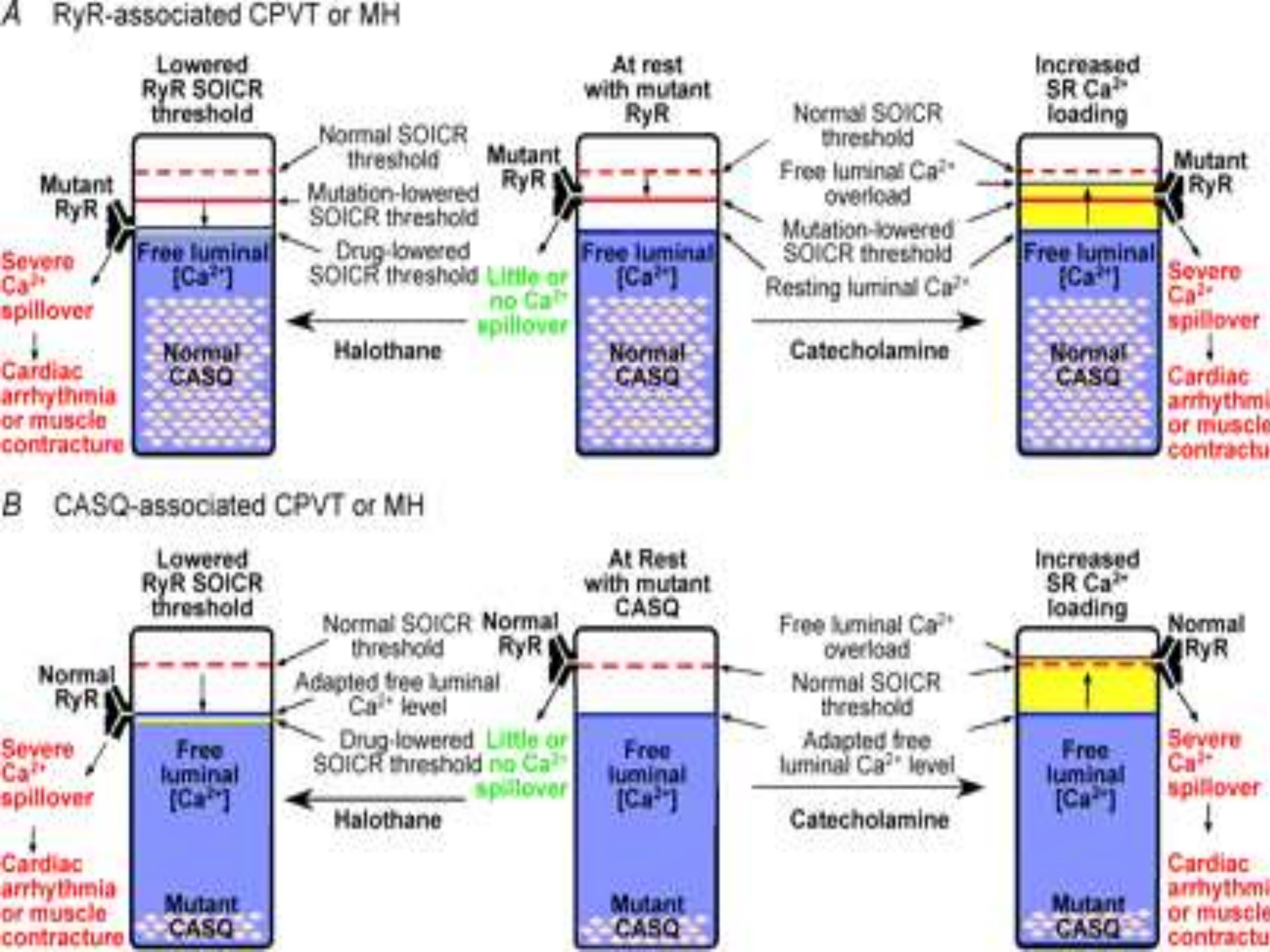
- MH partially attributed to a dominant mutation in the ryanodine receptror 1 (RYR1)
  - Ryanodine receptors are activated by elevated Ca^{2+} levels, known as store overload induced calcium release (SOICR)
  - Mutant receptors are activated by lower Ca^{2+} levels
  - Volatile anesthetics further lower the SOICR threshold

MacLennan DH, Chen SR. Store overload-induced Ca2mutations + release as a triggering mechanism for CPVT and MH episodes caused by in RYR and CASQ genes. J Physiol. 2009 Jul 1;587

Pathophysiology

- In MH, the Ca^{2+} level repeatedly exceeds the lowered SOICR threshold, increasing cytosol Ca^{2+} concentrations
  - Increased muscle contracture, hypermetabolism
  - ATP hydrolysis by myosin causes hyperthermia
- Dantrolene is a RYR1 receptor antagonist, inhibits SOICR

MacLennan DH, Chen SR. Store overload-induced Ca2mutations + release as a triggering mechanism for CPVT and MH episodes caused by in RYR and CASQ genes. J Physiol. 2009 Jul 1;587


A RyR-associated CPVT or MH
Lowered RyR SOICR threshold
Normal SOICR threshold
Mutation-lowered SOICR threshold
Drug-lowered SOICR threshold
Mutant RyR
Free luminal [Ca2+]
Normal CASQ
Severe Ca2+ spillover
Cardiac arrhythmia or muscle contracture
Halothane
At rest with mutant RyR
Mutant RyR
Free luminal [Ca2+]
Normal CASQ
Little or no Ca2+ spillover
Normal SOICR threshold
Free luminal Ca2+ overload
Mutation-lowered SOICR threshold
Resting luminal Ca2+
Catecholamine
Increased SR Ca2+ loading
Mutant RyR
Free luminal [Ca2+]
Normal CASQ
Severe Ca2+ spillover
Cardiac arrhythmia or muscle contracture
B CASQ-associated CPVT or MH
Lowered RyR SOICR threshold
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Severe Ca2+ spillover
Cardiac arrhythmia or muscle contracture

Testing for MH

Caffeine Halothane Contracture Test

- Gold standard
- Requires muscle biopsy, invasive
- False negatives extremely rare
- 80% specific, 20% false positives

RYR Genetic Testing

- At least 29 identified causative mutations in RYR
- Presence of any is diagnostic for MH
- Absence of mutation, must complete muscle biopsy

MHAUS Guidelines: Testing for Malignant Hyperthermia Susceptibility. *Malignant Hyperthermia Association of the United States*. Web. <MHAUS.org>.

Non-Trigger Anesthetic Agents

- Thiopental sodium
- Pancuronium
- Droperidol
- Benzodiazepines
- Ester-type local anesthetics
- Nitrous oxide, ketamine

- Prophylaxis with IV dantrolene is not necessary if these safe agents are used in patients with a history of MH

Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. Orphanet J Rare Dis. 2007 Apr 24;2:21. Review.

Malignant Hyperthermia: Clinical Presentation

Early Signs

Metabolic

- Tachypnea, elevated CO_2 production and increased O_2 consumption
- Combination metabolic and respiratory acidosis
- Profuse sweating and mottling of skin

Cardiovascular

- Tachycardia
- Arrythmias

Muscle

- Masseter spasm if succinylcholine has been given
- **Generalized muscle rigidity**

Later Signs

- **Rapid increase in core temperature** (1-2 degrees Celsius every 5 min)
- Rhabdomyolysis
- Grossly elevated blood CPK and myoglobin levels
- Darkly colored urine
- Hyperkalemia
- Severe cardiac arrythmias
- Disseminated intravascular coagulation

Glahn KP, Ellis FR, Halsall PJ, Müller CR, Snoeck MM, Urwyler A, Wappler F;European Malignant Hyperthermia Group. Recognizing and managing a malignanthyperthermia crisis: guidelines from the European Malignant Hyperthermia Group.Br J Anaesth. 2010 Oct;105(4):417-20.

Differential Diagnosis

- Insufficient anesthesia and/or analgesia
- Infection or septicemia
- Insufficient ventilation, anesthetic machine malfunction
- Anaphylactic reaction
- Pheochromocytoma
- Thyroid Crisis
- Cerebral Ischemia
- Neuromuscular disorders
- Elevated end tidal CO_2 due to laparoscopic surgery
- Use of drugs of abuse
- Malignant neuroleptic syndrome

Glahn KP, Ellis FR, Halsall PJ, Müller CR, Snoeck MM, Urwyler A, Wappler F;European Malignant Hyperthermia Group. Recognizing and managing a malignanthyperthermia crisis: guidelines from the European Malignant Hyperthermia Group.Br J Anaesth. 2010 Oct;105(4):417-20.

Variable Onset of Malignant Hyperthermia

- The inhalational anesthetics are capable of initiating a MH reaction within minutes of exposure to hours after the initial exposure

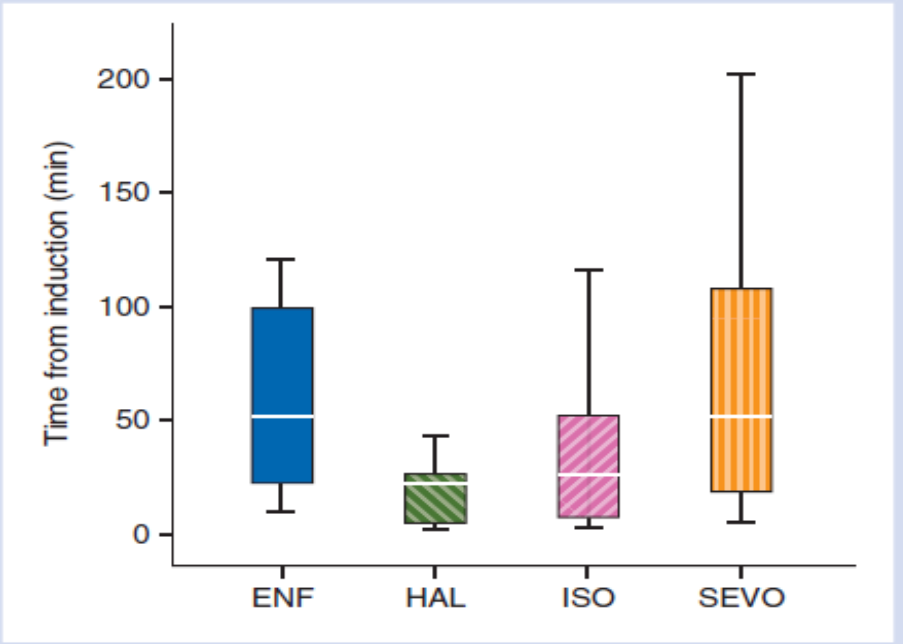

Fig 1 Box and whisker plot of the time from induction of anaesthesia to the onset of MH in 73 patients (eight received enflurane, 11 halothane, 42 isoflurane and 12 sevoflurane). The boxes delineate the inter-quartile range, the white horizontal line within the box is the median value, and the whiskers indicate the range. Using a general linear regression model, there was a statistically significant faster onset of the MH reaction with halothane *vs* enflurane and sevoflurane but not isoflurane.

Hopkins PM. Malignant hyperthermia: pharmacology of triggering. Br J Anaesth. 2011 Jul;107(1):48-56. doi: 10.1093/bja/aer132. Epub 2011 May 30. Review.

Post-Operative Malignant Hyperthermia

- Cases of MH can present in the postoperative period, but this is uncommon
- An analysis of the North American MH Registry detected 10 of 528 suspected cases occurring post-operatively
- Of these ten cases the longest latency time was 40 minutes from completion of surgery
- In all 10 cases hyperthermia was not the initial presenting sign

Litman RS, Flood CD, Kaplan RF, Kim YL, Tobin JR. Postoperative malignant hyperthermia: an analysis of cases from the North American Malignant Hyperthermia Registry. Anesthesiology. 2008 Nov;109

Treatment of Acute Malignant Hyperthermia

- Begin treatment as soon as a MH crisis is suspected
- Immediately stop administration of trigger agents and change to non-trigger anesthesia
- Inform surgeon and terminate/postpone surgery
- Hyperventilate with 100% O_2 using 2-3 times the normal minute volume
- **<u>Administer dantrolene</u>**

Malignant Hyperthermia Association of the United States: Emergency Therapy for Malignant Hyperthermia. Malignant Hyperthermia Association of the United States. Sherburne, NY. 2008.

Dantrolene: Dosing

- Dose of 2.5 mg/kg rapid IV push through large bore IV, no less than 1 mg/kg should be given
- Higher doses are often necessary and the initial dose should be repeated until signs of MH reversal
- The maximum dose is 10 mg/kg, although larger doses up to 30mg/kg may be needed
- No dosage adjustment in renal failure, caution in active hepatic disease

Malignant Hyperthermia Association of the United States: Emergency Therapy for Malignant Hyperthermia. Malignant Hyperthermia Association of the United States. Sherburne, NY. 2008.

Dantrolene: Preparation

- 20 mg vials, requiring dilution with at least 60 mLs of sterile preservative free water
- Incompatible with NS, D5W and other acidic solutions

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Revonto [Prescribing Information] Greenville, NC. DSM Pharmaceuticals; 2009.

Dantrolene: Considerations

- Protect from light
- Vesicant!!!
- Storage is room temperature
- 6 hours expiration, prepare immediately before use
- Do not prepare infusion in glass (precipitates), use sterile plastic bags
- Prepare using PF sterile water, may add multiple vials to bag if needed for infusion

Revonto [Prescribing Information] Greenville, NC. DSM Pharmaceuticals; 2009.

Treatment of Acute Malignant Hyperthermia

- Administer bicarbonate for metabolic acidosis, 1-2 mEq/kg if no blood gas values are available
- If temperature is >39 C, cool the patient applying ice to surface, lavage open cavities, infuse cold NS IV. Cease cooling once temperature is below 38 C
- Treat dysarrhythmias by addressing acidosis and hyperkalemia, use standard drug therapy except **do not use calcium channel blockers** in conjunction with dantrolene (cardiac arrest, hyperkalemia may ensue)

Malignant Hyperthermia Association of the United States: Emergency Therapy for Malignant Hyperthermia. Malignant Hyperthermia Association of the United States. Sherburne, NY. 2008.

Treatment of Acute Malignant Hyperthermia

- Monitor: ETCO2, electrolytes, blood gases, CK, core temperature, urine output and color, coagulation studies
- A rise in CPK and/or K^+ or a fall in urine output to less than 0.5 mL/kg/hr requires induction of diuresis at a rate > 1 ml/kg/hr
- Bicarbonate should also be given to alkalize the urine and prevent myoglobinuria induced renal failure

Malignant Hyperthermia Association of the United States: Emergency Therapy for Malignant Hyperthermia. Malignant Hyperthermia Association of the United States. Sherburne, NY. 2008.

Management of Post-Acute Phase of Malignant Hyperthermia

- Due to risk of recurrence, observe patient in ICU for at least 24 hours
- Give dantrolene 1 mg/kg q 4-6 hours, or 0.25 mg/kg/hr by infusion for at least 24 hours. Further doses may be indicated.
- Continue to hydrate, alkalinize and give diuretics to prevent myoglobin precipitation in the renal tubules

Malignant Hyperthermia Association of the United States: Emergency Therapy for Malignant Hyperthermia. Malignant Hyperthermia Association of the United States. Sherburne, NY. 2008.

Recrudescence of Malignant Hyperthermia

- The reoccurrence of signs and symptoms of MH after completion of the initial episode
- One study of 308 reports of MH found 20% of cases recrudesced
- Mean time to recrudescence found to be 13 hours, with a range of 2.5-72 hours
- 80% occurred within 16 hours

Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. Anesthesiology. 2007 May;106(5):901-6

Factors Associated with Recrudescence

Table 5. Clinical Variables Associated with Recrudescence

Factor	n	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Body type*					
Normal or lean	184	Reference		Reference	
Muscular	76	2.57 (1.37–4.82)	0.003	2.00 (1.04–3.86)	0.03
MH reaction after induction, min†	308	1.003 (1.001–1.004)	0.009	1.002 (1.000–1.004)	0.05
Temperature increase					
Absent	97	Reference		Reference	
Present	211	2.92 (1.41–6.02)	0.004	2.34 (1.01–5.41)	0.04
Sevoflurane					
Absent	257	Reference			
Present	51	0.47 (0.19–1.15)	0.099	NA	

Malignant Hyperthermia Association of the United States (MHAUS)

- The goal of MHAUS is to promote optimum care and scientific understanding of Malignant Hyperthemia and related disorders
- Hotline available 24/7 : 1 (800) 644-9737
- Office number for non-emergencies
  1-800-986-4287
- www.mhaus.org

"Contact - MHAUS." *MHAUS*. N.p., n.d. Web. 09 Jan. 2013.

THANK YOU,
QUESTIONS?