DES MOINES UNIVERSITY

COLLEGE OF OSTEOPATHIC MEDICINE

# Case Presentation

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(DMU alumnus)
&
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Grand Rounds April 2, 2015

**HPI:**

37 year old **G7P0141** female at 38w5d who had SROM clear fluid at 1500 today. Onset contractions around 1800 today. GBS negative. Good FM. A2GODM. Takes Glyburide 5 mg QAM and 6 mg at suppertime. FSBS at time of admission was 87.

**MEDICATIONS:**

- Prenatal vitamins; Glyburide 5 mg PO BID; Advair Diskus; Albuterol nebulizer.

**ALLERGIES:**

No known drug allergies.

# 5/19/2014

**PAST MEDICAL HISTORY:**

- Repetitive pregnancy loss
- Abnormal Pap smear: Cervical cancer, per patient
- GODM
- Rh incompatibility
- Asthma- during pregnancy
- Postpartum depression (1998)
- Pregnancy Induced Hypertension (1998)

**PAST SURGICAL HISTORY:**

- Four suction D and Cs.
- Tonsils and adenoids (1995)

**SOCIAL HISTORY:**

- She denies tobacco, alcohol, or illicit drug use. She works at Vision 4 Less.

**PHYSICAL EXAMINATION:**

- VITAL SIGNS: Afebrile, Blood pressure is 138/90 and 126/80 on recheck. Weight 225 pounds.
- GENERAL: She appears comfortable.
- HEENT: Oropharynx is clear.
- NECK: Supple without thyromegaly
- CARDIOVASCULAR: Regular rate and rhythm.
- RESPIRATORY: Clear to auscultation in all lung fields.
- ABDOMEN: Gravid with estimated fetal weight of 3600 g.
- PELVIC: Leaking of fluid, 2 cm dilated with a thick, soft cervix. Pelvis is clinically adequate for estimated fetal weight.
- EXTREMITIES: There is 2+ tibial edema. Normal reflexes

# The Next Morning

- Non-reassuring fetal heart tones and evidence for chorioamnionitis.

- Taken to the operating theater for caesarean section
  - Pre-op metoclopramide
  - Bolus of epidural anesthetic

# Post Op

- The patient tolerated the procedure well and went to the recovery room in stable condition.
- Postop: delivery of viable female
  - Apgars of 7 of 1 at 8 and 5 minutes.

- Called to the bedside for a change in the patient's vital.
- Pt is tachypneic, tachycardiac and hypertensive.
  - Vitals: temperature of 37 C (98.6 F) , blood pressure is 147/106, pulse 172, respirations ~ 60 per min.
- Pt cannot respond, although makes eye contact, partially coherent

# 1 hour later

# Action Taken

- ABG
- Chest x-ray
- CBC
- ECG
- CMP Coag studies.
- Immediate consult with internal medicine.

# Timeline May 20 , 2015

- **0855** Tachycardia and tachypnea recognized
  - O2 per nasal cannula at 4 liters started.
- **0856** Call to Dr. DeJong to come to room and assess patient
- **0900** Dr. DeJong arrives to room, assesses patient, orders received
- **0905** Elevated temperature to 106 F reported by nursing
- **0916** OB alert call (anesthesia: Dr. DeWild arrives to bedside)
- **0920** Ice packs to patient
- **0921-1000** Dantrolene continuously given IV
- **0928** Art line placed
- **0930** Tympanic temp taken: 106.7 F
- **0933** IV start Left Antecube
- **0935** Axillary Temp 99.1 F
- **0936** Oral Temp 102.2 F
- **0937** Opposite Tympanic Temp 105.5 F
- **0941** Rectal probe in at 40.0 C (104 F)

- **0943** IV fluids/ Amp 2g IVPB
- **0954** Bicarb given IV; Gentamycin IVP
- **1005** Portable Chest x-ray
- **1013** NICU notified
- **1020** Chaplain at bedside
- **1021** NICU RN at bedside
- **1022** Clindamycin IVP
- **1026** Pt's family at bedside
- **1030** Rectal prob temp 38.6 C (101.5 F)
- **1033** 900 ml urine out
- **1045** Dantrolene drip
- **1053** Pt transferred to ICU
- **1100** Pt in ICU, Ice off, rectal probe temp 38.1 C

# Timeline May 20 , 2015

| | 05/20 0701 - 05/21 0700 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time: | 0939 | 1011 | 1052 | 1200 | 1557 | 2130 | 0005 | 0301 | 0624 |
| **Blood Gases** | | | | | | | | | |
| pH (arterial) | | | | 7.42 | 7.43 | 7.43 | 7.47 | 7.45 | 7.44 |
| pCO2 | | | | 34 | 36 | 38 | 33 | 35 | 36 |
| pO2 | | | | 113 | 144 | 98 | 78 | 116 | 105 |
| BE | | | | SEE. | SEE. | 0.4 | 0.7 | 0.1 | 0.5 |
| BD | | | | 1.8 | 0.4 | SEE. | SEE. | SEE. | SEE. |
| O2 Sat | 100 | 100 | 100 | 98.5 | 99.3 | 97.8 | 96.3 | 98.7 | 98.3 |

# Serial Blood Gases

| CHEM PROFILE | Serial Lab-work | (Q8H) 5/20/15 | | 5/21/2015 | | 5/22/2015 |
|---|---|---|---|---|---|---|
| Sodium | 136 | 137 | 138 | 135 | | 138 |
| Na I-Stat | 137 | | | | | |
| Potassium | 4.2 | 4.3 | 4.9 | 4.2 | | 4.4 |
| K I-Stat | 5.0 | | | | | |
| Chloride | 104 | 106 | 106 | 104 | | 105 |
| CO2 | 23 | 24 | 25 | 22 | | 22 |
| Anion Gap | 13 | 11 | 12 | 13 | | 15 |
| Glucose | 104 | 113 | 100 | 108 | | 133 |
| BUN, Blood | 8 | 5 | 8 | 9 | | 21 |
| Creatinine, Serum | 1.00 | 0.88 | 0.89 | 0.84 | | 1.54 |
| Calcium | 7.4 | 7.8 | 7.8 | 7.6 | | 7.3 |
| Total Protein | 3.9 | | | | | 4.6 |
| Albumin | 1.6 | | | | | 1.6 |
| Total Bilirubin | 0.6 | | | | | 0.5 |
| Alkaline Phosphatase | 84 | | | | | 76 |
| AST | 38 | | | | | 25 |
| ALT | 17 | | | | | 15 |
| BUN/Creatinine Ratio | 8.0 | 5.7 | 9.0 | 10.7 | | 13.6 |
| GFR Estimate | SEE N... | SEE NO... | SEE N... | SEE NO... | | SEE N... |
| Bilirubin, Direct | 0.1 | | | | | |
| ION CALCIUM-ISTAT | 0.99 | | | | | |
| Magnesium | | | 1.3 | | | |
| Phosphorus | | | 5.7 | | | |
| **CARDIAC PROFILE** | | | | | | |
| Total CK | 882 | 1218 | 770 | | | 228 |
| Myoglobin | | 642.0 | | | | 129.7 |
| **CBC** | | | | | | |
| WBC | 9.98 | 15.23 | 24.01 | 24.55 | | 21.62 |
| RBC | 3.92 | 3.70 | 3.27 | 3.15 | | 3.31 |
| Hemoglobin | 10.5 | 9.8 | 8.9 | 8.3 | | 8.9 |
| Hemoglobin IST | 9.5 | | | | | |
| Hematocrit | 32.3 | 30.1 | 26.9 | 25.7 | | 28.0 |

- 24 hours following MH event (POD #1 C/s under epidural anesthesia).
  - Rectal T 36.8 C (98.2 F), HR 97, RR 22 and BP 140/60.
- CPK peaked at 1200, continued to trend down.
- No rhabdomyolysis
- Chorioamnionitis- Abx (Zosyn 3.375 g Q6H)
- Mild AKI from dehydration
- Pt is stable and is transferred back to OB for post-op OB care.

# 5/21/2014 1:23 PM

# Outcome

- *Thanks especially to Methodist OB Nursing staff*, both mother and baby were discharged from the hospital with no signs of complication
- Both in stable and healthy condition
- Follow-up in clinic was uneventful, no deleterious developmental outcome has been observed over the course of the last year
- After more thorough investigation:
  - Distant relative (cousin) found to have a “bad reaction to anesthesia”
- Entire OB team honored with Unity Point ACE Award (Always Committed to Excellence)

# Discussion

- Post-op Malignant Hyperthermia crisis
  (volatile gases in Oxygen tubing?)
  vs
- Neuroleptic Malignant Syndrome crisis
  (pre-op IV metoclopramide?)

# Thank You

Now for the pathophys...

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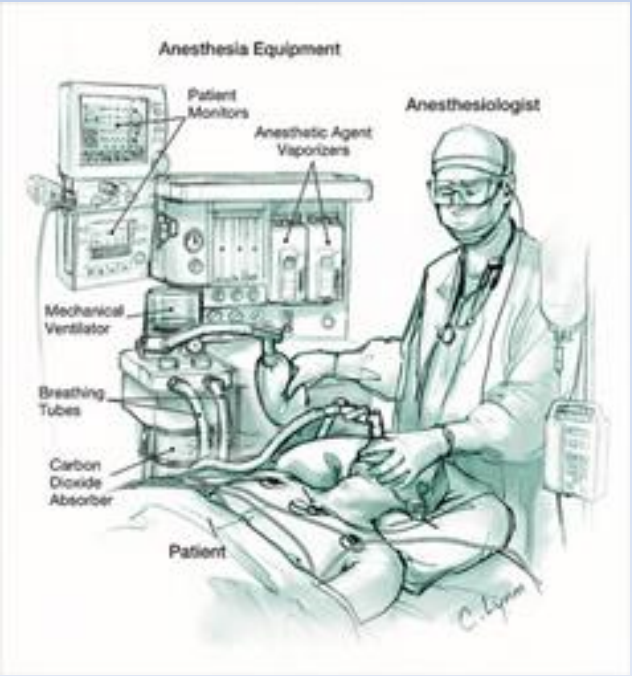
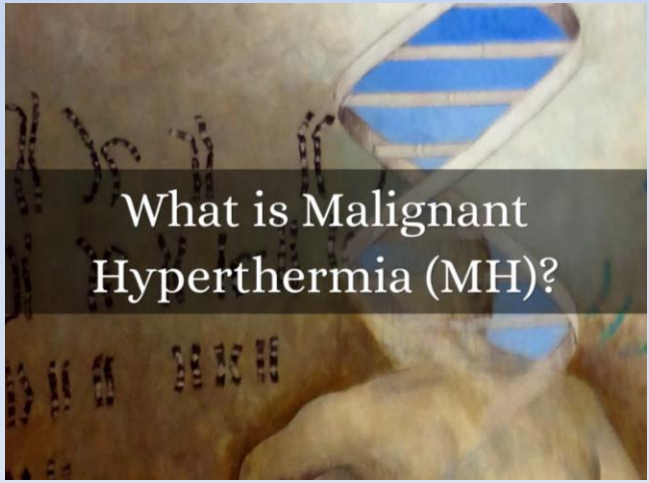
# Malignant Hyperthermia




Grand Rounds

Kevin Carnevale

4-2-15



# Malignant Hyperthermia

- Malignant hyperthermia occurs in 1 in 5,000 to 50,000 instances in which people are given anesthetic and/or muscle relaxants.
- Malignant hyperthermia is a severe reaction to particular drugs (particularly some anesthetic gases [halothane, sevoflurane, desflurane, isoflurane, enflurane]and muscle relaxant [suxamethonium and decamethonium]) used during surgery and other invasive procedures.
- Specifically, this reaction occurs in response to some anesthetic gases, which are used to block the sensation of pain, and with a muscle relaxant that is used to temporarily paralyze a person during a surgical procedure.

# Malignant Hyperthermia

- The disorder is due to an acceleration of metabolism in skeletal muscle (hypermetabolism).
- The underlying defect is abnormally increased levels of cell calcium in the skeletal muscle.
- The signs of MH include muscle rigidity, rapid heart rate, high body temperature, muscle breakdown (rhabdomyolysis), a high fever and acidosis.

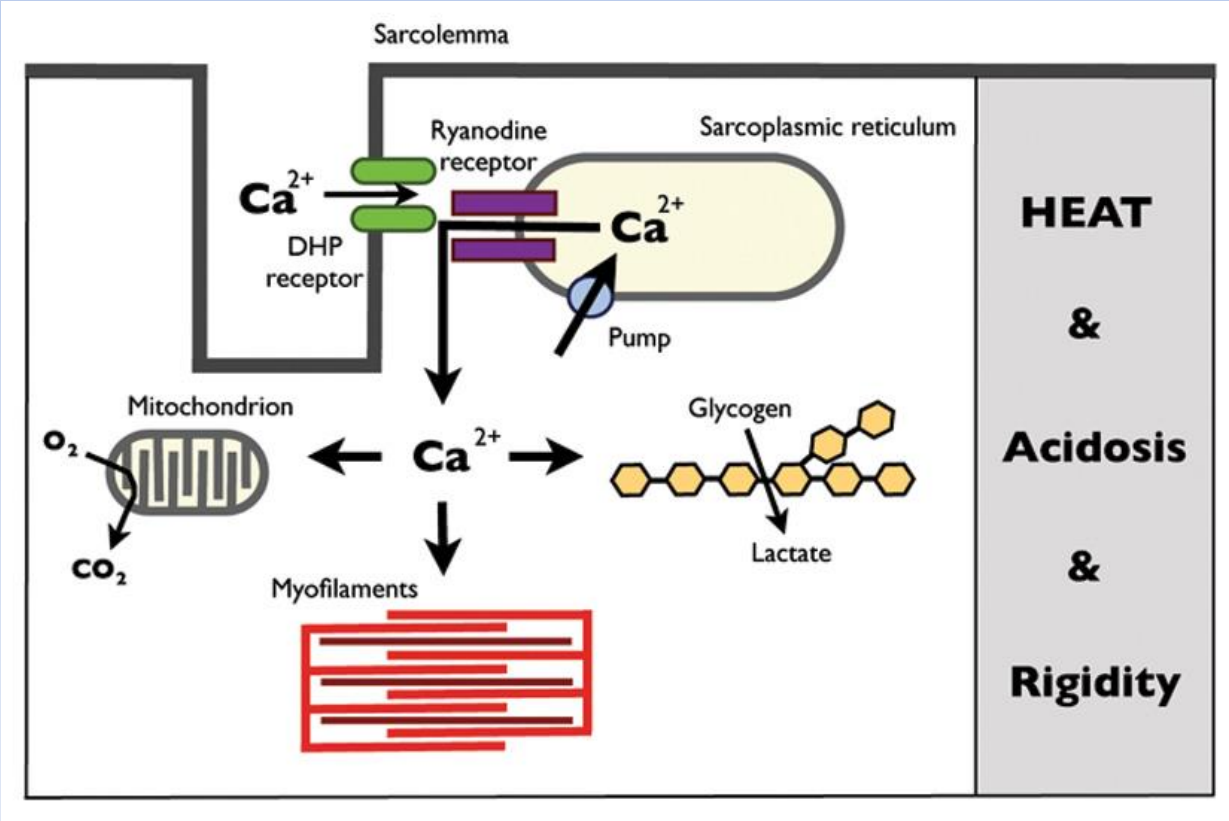
# MH - Pathophysiology

- Large amounts of calcium ions are released from the sarcoplasmic reticulum within muscle cells.
- This causes skeletal muscles to contract abnormally, glycogenolysis, and increased cellular metabolism which leads to muscle rigidity in people with malignant hyperthermia.
- An increase in calcium ion concentration within muscle cells also activates processes that generate heat (leading to increased body temperature) and produce excess acid (leading to acidosis).

# MH - Pathophysiology

Inherited Autosomal Dominant pharmacogenetic disorder with reduced penetrance and variable expression. Final common pathway is uncontrolled release and regulation of calcium.

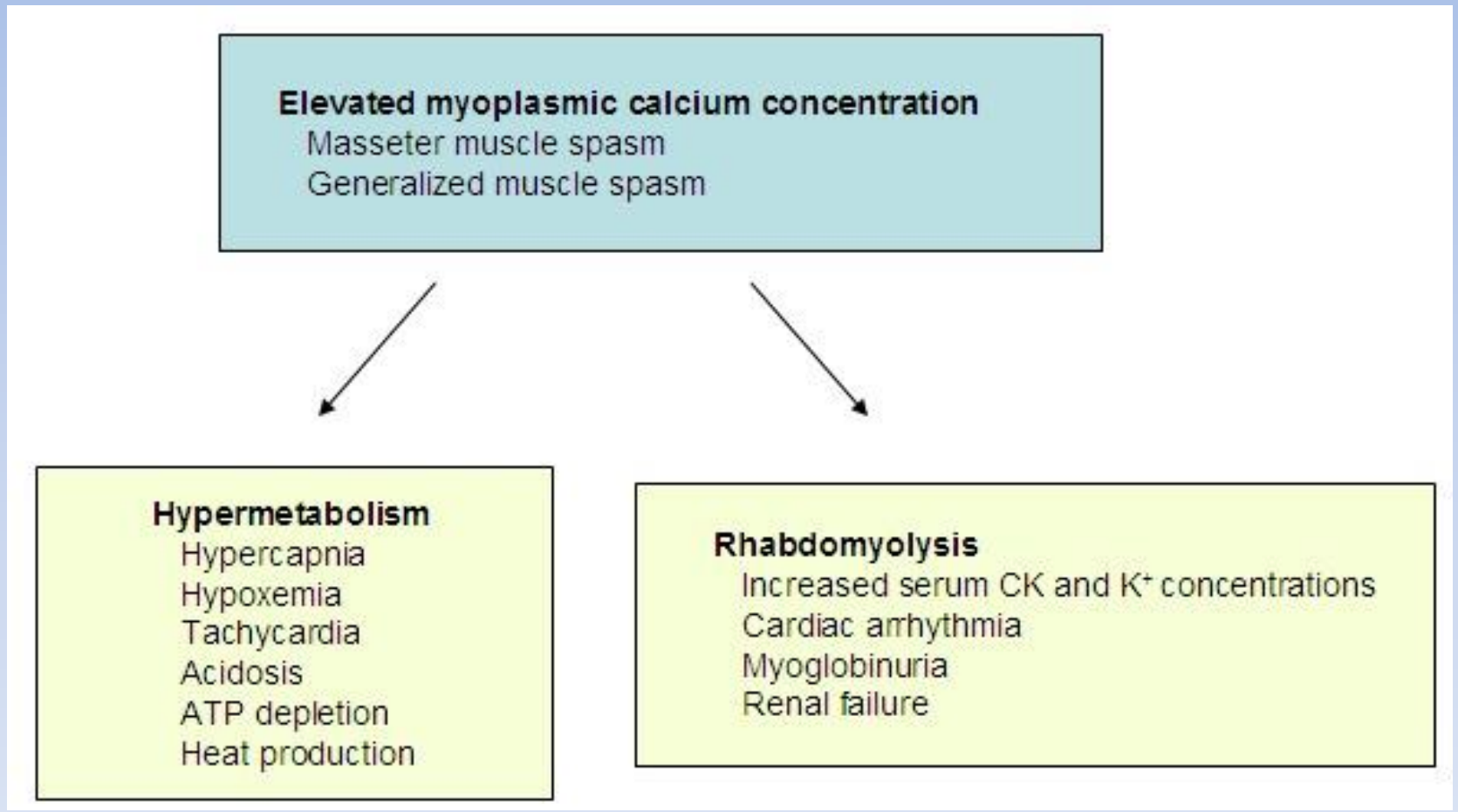
Persistent increase in intracellular $Ca^{2+}$ . The increased activity of pumps and exchangers trying to correct the increase in $Ca^{2+}$ causes the need for ATP, which in turn produces heat (the end result is hyperthermia).



# MH – Patient may develop

- Acidosis, hypercapnia, tachycardia, hyperthermia, muscle rigidity, compartment syndrome, rhabdomyolysis with subsequent increase in serum creatine kinase (CK) concentration, hyperkalemia with a risk for cardiac arrhythmia or even arrest, and myoglobinuria with a risk for renal failure.
- In nearly all cases, the first manifestations of MH (tachycardia and tachypnea) occur in the operating room; however, MH may also occur in the early postoperative period.

# Malignant Hyperthermia



Criteria Used in the Clinical Grading Scale for Malignant Hyperthermia

| Clinical Finding (Maximum Score) [1] | Manifestation [2] |
|---|---|
| Respiratory acidosis (15) | End-tidal $CO_2$ >55 mmHg, $PaCO_2$ >60 mmHg |
| Cardiac involvement (3) | Unexplained sinus tachycardia, ventricular tachycardia, or ventricular fibrillation |
| Metabolic acidosis (10) | Base deficit >8 mEq/L, pH <7.25 |
| Muscle rigidity (15) | Generalized rigidity, severe masseter muscle rigidity |
| Muscle breakdown (15) | Serum creatine kinase concentration >20,000/L units, cola-colored urine, excess myoglobin in urine or serum, plasma [K+] >6 mEq/L |
| Temperature increase (15) | Rapidly increasing temperature, T >38.8° C |
| Other | Rapid reversal of MH signs with dantrolene (score=5), elevated resting serum creatine kinase concentration (score=10) |
| Family history (15) | Consistent with autosomal dominant inheritance |

Larach et al. Anesthesiology. 1994;80:771–9.
Rosenberg et al. Anesthesiology. 2002;96:232–7.

Points are summed to produce a raw score, which translates to a likelihood score, range from 1 (raw score 0: “almost never/very unlikely”) to 6 (raw score ≥50: “almost certain”). The more criteria an individual fulfills, the more likely that a malignant hyperthermia (MH) episode has occurred.

# Malignant Hyperthermia

- HR, core temperature, $ETCO_2$, minute ventilation, blood gases, $K^+$, CK, urine myoglobin and coagulation studies (possibility of DIC) as warranted by the clinical severity of the patient.
- When stable, transfer to post anesthesia care unit or intensive care unit for at least 24 hours. Key indicators of stability include:
  - $ETCO_2$ is declining or normal
  - Heart rate is stable or decreasing with no signs of ominous dysrhythmias
  - Hyperthermia is resolving
  - If present, generalized muscular rigidity has resolved

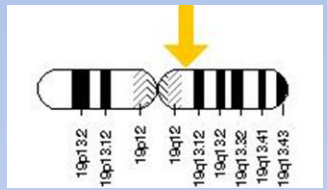
# Malignant Hyperthermia

- There are two types of testing for Malignant Hyperthermia: genetic testing and muscle biopsy.
- **Molecular Genetic Testing -** Variations of the RYR1 and CACNA1S genes. 3 centers in US.
- **Muscle Biopsy Testing – Fresh unfixed tissue only.** Caffeine Halothane Contracture Test (CHCT). 5 centers that do the test in US. Under anesthesia fresh muscle from the thigh 8 cm (3-4 inches) placed in physiologic buffer and sent to lab.

# MH - Genes

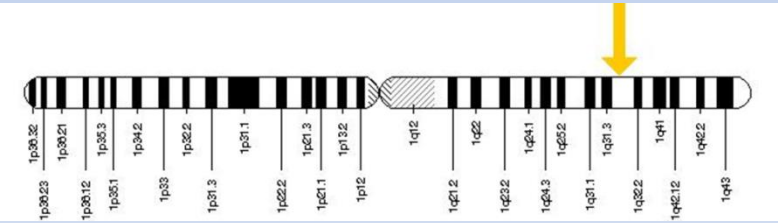
Inherited Autosomal Dominant pharmacogenetic disorder with reduced penetrance and variable expression.

- RYR 1 (MHS1 locus, 19q13.1) encodes the type 1 ryanodine receptor of skeletal muscle. Molecular genetic testing indicates that mutations in RYR1 are identified in up to 70%-80% of individuals with confirmed MHS.




(19q13.1)

- CACNA1S (MHS5 locus, 1q32) encodes the α1-subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel. Mutations in CACNA1S account for 1% of all MHS.




(1q32)

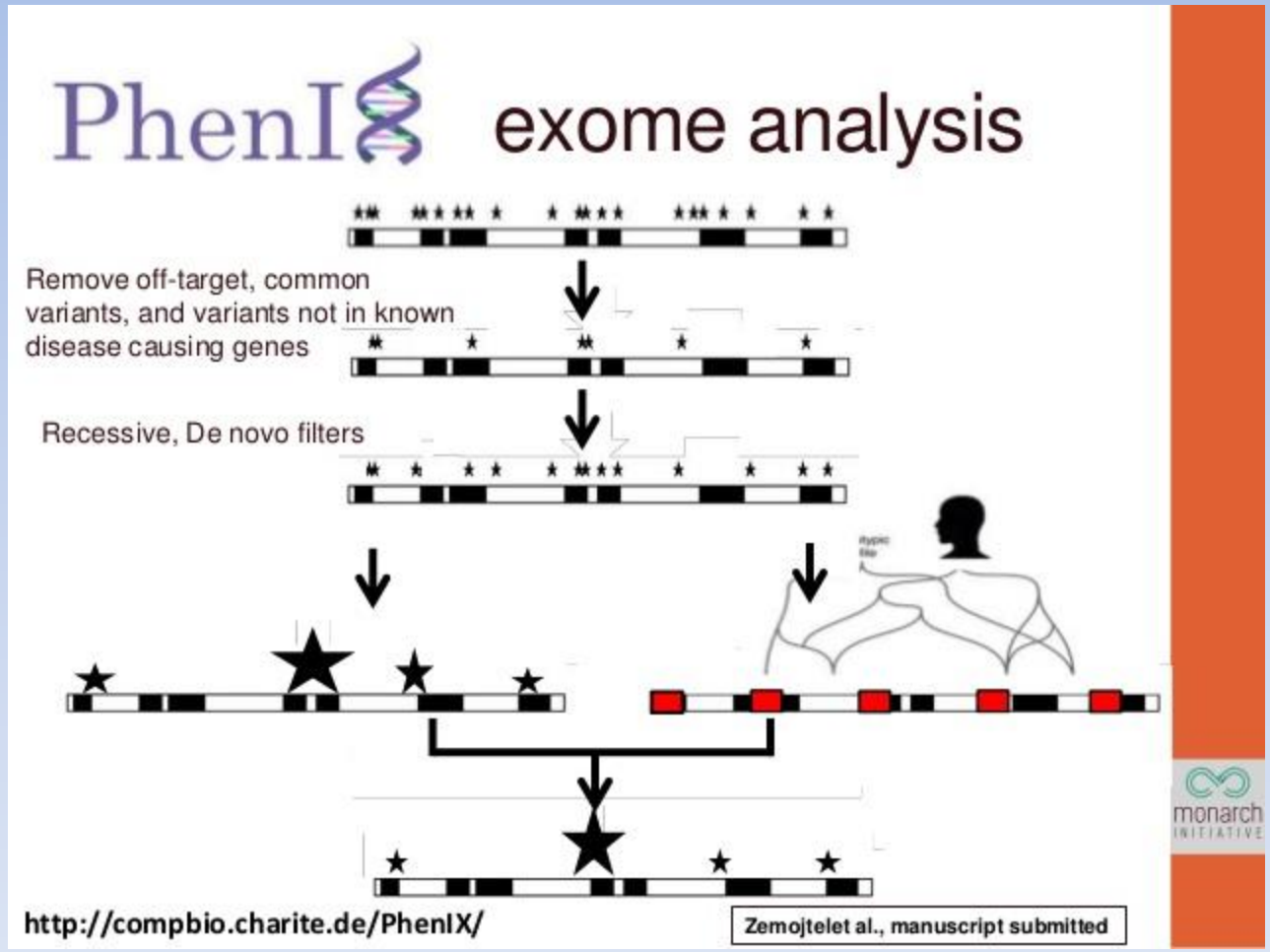
- Evidence for further locus heterogeneity. Four additional loci have been mapped; the genes have not been identified:
  - MHS2 (linked to chromosomal locus 17q11.2-q24)
  - MHS4 (3q13)
  - MHS6 (5p)
  - MHS3 (7q21-q22)

Summary of Molecular Genetic Testing Used in Malignant Hyperthermia Susceptibility

| Gene [1] / Locus Name | Proportion of MHS Attributed to Mutations in This Gene | Test Method | Mutations Detected [2] |
|---|---|---|---|
| *RYR1* / MHS1 | 70%-80% | Targeted mutation analysis | Mutation panel [3] |
| | | Sequence analysis [4] / mutation scanning of all exons and flanking intronic regions [5, 6] | Sequence variants |
| | | Sequence analysis [4] / mutation scanning of select exons & flanking intronic regions [5, 6] | Sequence variants |
| | Unknown | Deletion / duplication analysis | Unknown; none reported |
| | Unknown | Linkage analysis [7] | NA |
| *CACNA1S* / MHS5 | 1% [8] | Targeted mutation analysis | p.Arg1086His |
| | | Sequence analysis [4] / mutation scanning [5] | Sequence variants |
| | | Sequence analysis of select exons [4] | Sequence variants [9] |
| | Unknown | Linkage analysis [7] | NA |
| Unknown / MHS2 | Unknown | Linkage analysis [7] | NA |
| Unknown / MHS3 | Unknown | Linkage analysis [7] | NA |
| Unknown / MHS4 | Unknown | Linkage analysis [7] | NA |

Rosenberg et al. GeneReview [Online ]: Malignant Hyperthermia Susceptibility, 2013.

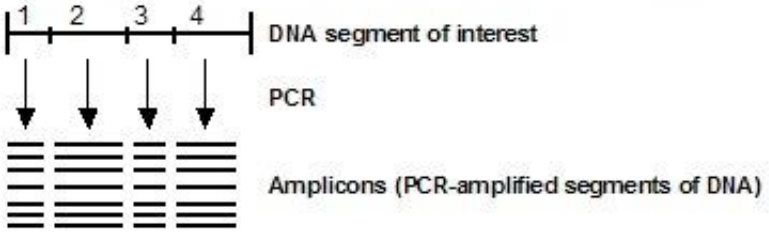
# Target Mutation Analysis



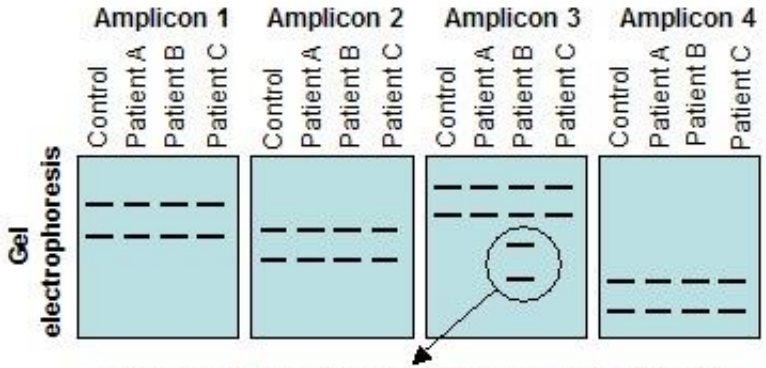
# Mutation Scanning

**Step 1: Scanning.**

**A.** PCR amplification of the DNA segment(s) of interest to create enough DNA for analysis



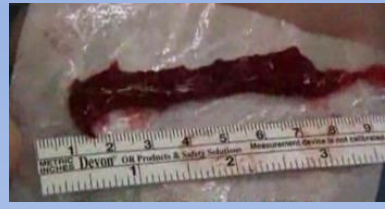

**B. Visualization and comparison.** Patient and control amplicons are compared using one of several different scanning methods (e.g., SSCP, CSGE, DGGE, DHPLC). In the SSCP example below, gel electrophoresis separates amplicons by mobility.




**Interpretation:** The additional bands and an abnormal migration pattern indicate that a DNA sequence alteration is present in amplicon 3 of Patient B.

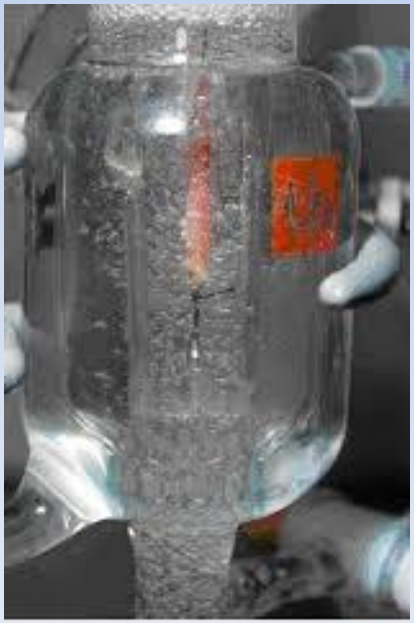
**Step 2:** In mutation scanning, variant DNA segments (e.g., segments with altered mobility in the SSCP example) may be subjected to further testing, such as sequence analysis, to identify the sequence alteration (mutation).

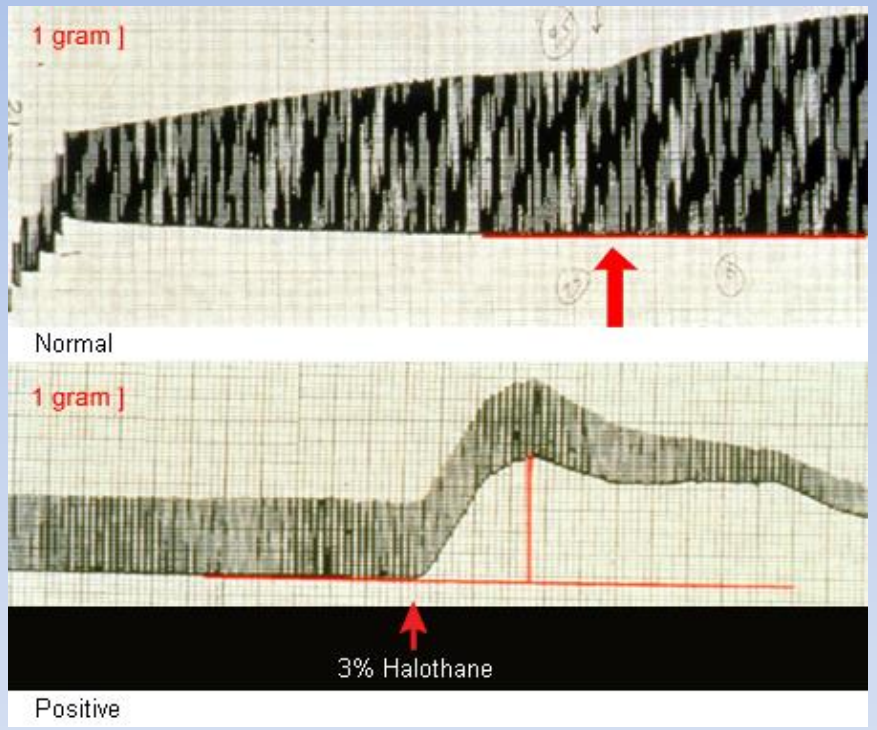
# MH- Muscle Biopsy test Physiologic test



- Fresh muscle biopsy done in OR and sent to the lab immediately in physiologic buffer for immediate testing.
- Muscle dissected into multiple separate strips tied and anchored at each end.
- Exposed to oxygenated buffer 37 °C until testing
- Electrically stimulated until twitch/contraction and recorded.
- Halothane (3%) put into bath and recorded. Muscle will produce very little tension when exposed to halothane normally but will have large contraction if MH.
- Caffeine is added to test contraction. Low doses of Caffeine (2mM) found in MH where 8mM needed for normal muscle to contract.

# MH- Muscle Biopsy test
# Physiologic test



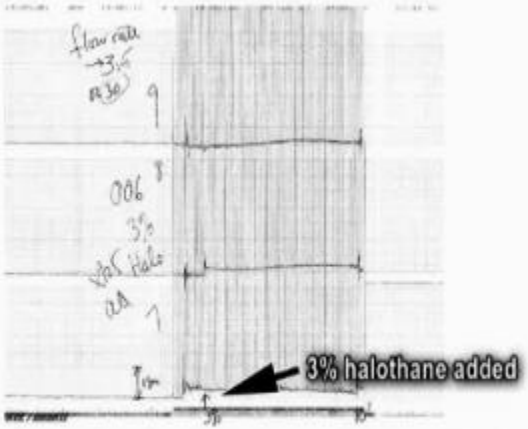


# MH-Physiologic test

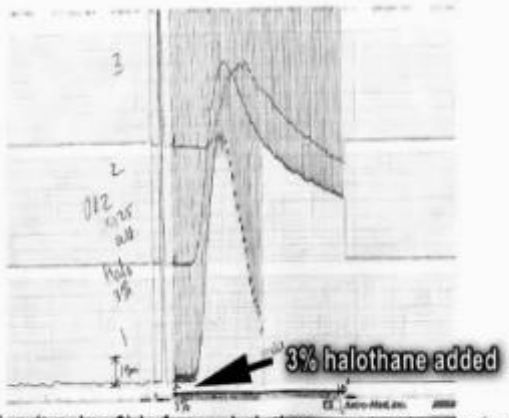
**Normal Muscle**

**Patient with MH**

**Halothane**

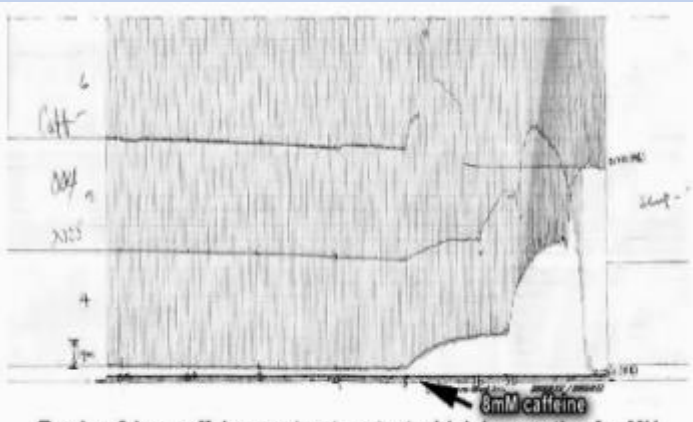



Tracing 1 is a halothane contracture test which is negative for MH susceptibility. The muscle develops very little tension upon exposure to halothane

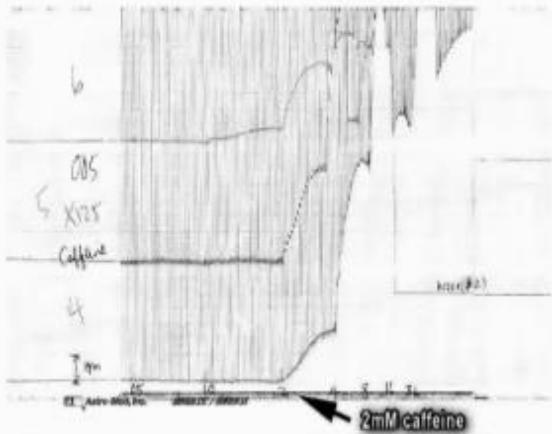



This tracing (tracing 2) is from a halothane contracture test which is positive for MH with severe tension developed by the muscle upon exposure to 3% halothane

**Caffeine**




Tracing 3 is a caffeine contracture test which is negative for MH susceptibility. (Contracture did not begin until 8mM caffeine)




Tracing 4 is a caffeine contracture test which is positive for MH susceptibility. (Contracture began at 2mM caffeine and developed large tension)

These tests are done on living tissue and can only be performed at specialized centers where the tissue can be immediately prepared for testing while it is still living.

# MH - Muscle Biopsy test

Testing Protocols for Malignant Hyperthermia

| Designation [1] | North American Protocol | European Protocol |
|---|---|---|
| MHS | Contracture of >0.7 g to 3% halothane<br>OR<br>Contracture of >0.3 g to 2.0 mmol/L caffeine | Contracture of ≥0.2 g to ≤2% halothane<br>AND<br>Contracture of ≥0.2 g to ≤2.0 mmol/L caffeine |
| MHE [2] | Contracture of 0.5-0.7 g to 3% halothane | Contracture to halothane only or caffeine only |
| MHN | No contracture<br>OR<br>Contracture of <0.5 g to halothane<br>OR<br>Contracture of <0.3 g to 2.0 mmol/L caffeine | No significant contractures to either agent |

MHS = malignant hyperthermia susceptible;
MHE = malignant hyperthermia equivocal;
MHN = malignant hyperthermia negative

the sensitivity is 97% and the specificity 78%

Litman & Rosenberg. JAMA. 2005;293:2918–24.
Urwyler et al. Brit J Anaesth. 2001;86:283–7.

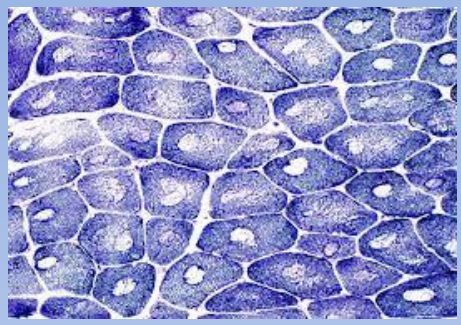
# Less Invasive Muscle Testing

Intramuscular injection of halothane 6 vol% has been shown to result in higher than normal increases in local pCO2 among patients with known malignant hyperthermia susceptibility. The sensitivity was 100% and specificity was 75%. This method may provide a suitable alternative to more invasive techniques.

# MH – Treatment Aim

- Discontinuation of potent inhalation agents and succinylcholine.
- Administration of dantrolene sodium intravenously.
- Surface, intravenous and body cavity cooling with cold solutions for hyperthermic individuals.
- Treatment of metabolic abnormalities.

# Differential Diagnosis



- **Central core disease – AD,** most cases have demonstrable mutations in the ryanodine receptor type 1 (RYR1) gene. Congenital myopathy resulting in muscle weakness (hypotonia) that ranges from almost unnoticeable to very severe. Patients at risk for malignant hyperthermia (MH) when receiving general anesthesia.
- **Multiminicore disease -** muscle weakness beginning in infancy or early childhood. This weakness is most noticeable in muscles of the trunk and neck (axial muscles) and is less severe in the arm and leg muscles. Mutations in the RYR1 and SEPN1 genes cause multiminicore disease.