Fall 2014

Malignant Hyperthermia

Chase Contri
Otterbein University, chase.contri@otterbein.edu

Malignant Hyperthermia

Chase Contri SRNA

Otterbein University, Westerville, Ohio

Introduction

Although very rare, occurring one out of every 100,000 anesthesia cases, malignant hyperthermia is a hypermetabolic disorder that anesthesia providers screen and interrogate patients prior to every case they are administering anesthesia. Many research studies about anesthesia induced malignant hyperthermia have explored new methods of testing for the genetic susceptibility for malignant hyperthermia and into hospital based protocols when a patient starts to show the signs and symptoms of the metabolic disorder. This new knowledge and understanding has decreased patient mortality of anesthesia induced malignant hyperthermia from eighty percent to five percent over the past three decades (Rosenberg et al, 2007).

PATHOPHYSIOLOGY

Malignant hyperthermia is a hypermetabolic disorder caused by mutation of the ryanodine receptor. More specifically it deals with the ryanodine receptor located on the major regulatory calcium release channel of the sarcoplasmic reticulum of skeletal muscle, known as the RYR1 receptor (Hines & Marschall, 2012). This mutation causes an excessive release of calcium from the sarcoplasmic reticulum when triggered that leads to sustained muscle contraction. The release of calcium is much more abundant compared to the body's abilities to remove the calcium from the muscles myoplasm. This causes an increased metabolic state that increases oxygen consumption, increases carbon dioxide production, increases heat production, increases anaerobic metabolism, and decreases ATP stores. Calcium is removed and pumped back into the sarcoplasmic reticulum by ATP. ATP stores are depleted due to exhaustion of attempting to replace the abundance of calcium back into the sarcoplasmic reticulum and the binding of calcium to muscle's troponin to elicit contraction. When ATP stores are depleted and oxygen can no longer be utilized, anaerobic metabolism takes place leading an acidotic and potentially fatal state.

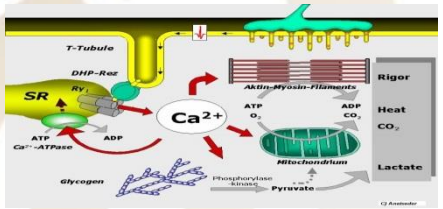

Figure 1. Mutation of RY1 receptor causes abundant release of calcium from sarcoplasmic reticulum that leads to a hypermetabolic state.

Preoperative Evaluation

Providers need to determine who is susceptible to this disorder in order to prevent malignant from occurring to begin with. Malignant hyperthermia is an inherited genetic disorder and is considered an autosomal dominant trait. Being autosomal dominant means that only one parent can carry the gene and still pass it along to their offspring. Incidence of this gene is 1/10,000 (Anderson-Pompa et al, 2008).

A detailed pre-operative assessment could possibly reveal a family history of the disorder which would warrant further pre-operative evaluation and susceptibility to malignant hyperthermia. To determine susceptibility, a patient could have genome testing done to see if they have the trait or undergo a caffeine-halothane contracture test (CHCT).

Caffeine Halothane Contracture Test

- CHCT have been shown to be 97%-99% sensitive for malignant hyperthermia (Rosenberg, Antognini, & Muldoon, 2002). The CHCT disadvantages include a small outpatient surgery required for a muscle biopsy, only six locations are present in the United States that provides the test, and it is expensive.

Genome Testing

- Genome testing is considered less invasive and more convenient but only detects thirty percent of people at risk (Anderson-Pompa et al, 2008).

Signs and Symptoms

Table 1

Clinical Presentation of Malignant Hyperthermia

Early Signs and Symptoms	Late Signs and Symptoms
Increased $ETCO^2$	Cutaneous changes
Tachypnea	Mottled skin
Muscle rigidity	Cyanosis
Masseter muscle spasms	Pyrexia
Generalized rigidity	Disseminated intravascular coagulation
Cardiac	Rhabdomyolysis
Tachycardia	Myoglobinemia/myoglobinuria
Arrhythmias	Renal failure
Cutaneous changes	Left ventricular failure
Generalized erythematous flush	Pulmonary edema
Electrolyte imbalance	Frothy sputum
Hyperkalemia	Metabolic acidosis
Hyperphosphatemia	Respiratory acidosis
Hypocalcemia	Hyperkalemia
	Hyper/hypocalcemia

Abbreviation: $ETCO^2$, end tidal carbon dioxide.

Table 1. Early and Late S/S of Malignant Hyperthermia

Malignant hyperthermia can be a difficult disorder to diagnosis while a patient is in the anesthetized state. An anesthetist must be knowledgeable of the early and late signs and symptoms of malignant hyperthermia. Early signs and symptoms can be vague and subtle at first and resemble side effects of the rapid and increased calcium release. The first sign of early progression of malignant hyperthermia is hypercarbia. Hypercarbia can be defined as carbon dioxide level above 45 mmHg. This can be measured by an arterial blood gas analysis or through Capnography. The increase in carbon dioxide is secondary to increase in oxygen consumption. When the hypercarbia is present, a patient will become tachypneic to compensate for the increase in carbon dioxide. Tachypnea will not be present with a patient who is in a paralytic state as during some surgical cases. In this case carbon dioxide monitoring will be crucial. Tachycardia is another early sign of malignant hyperthermia. Tachycardia is present due to the increasing hypoxia, hypercarbia, sympathetic stimulation, and catecholamine release that occur during this hypermetabolic state. Muscle rigidity can also be used as an early sign and symptom of malignant hyperthermia due to the sustained muscle contraction from the release of calcium. Masseter and extremity muscles are the most common sites for increased rigidity during progressing malignant hyperthermia. Muscle rigidity will still occur in these locations even if a patient has received neuromuscular blocking drugs (Glahn et al, 2010).

Late signs and symptoms can be more detrimental to the patient as it reflects anaerobic metabolism and deterioration. A patient can become extremely acidotic during a malignant hypertension crisis. Metabolic acidosis can ensue due to an over production of lactic acidosis due to anaerobic metabolism and cellular hypoxia. Systemic pH can drop dramatically due to a combination of hypercarbia and lactic acid production. Serial arterial blood gasses need to be analyzed during a malignant hyperthermia crisis to monitor the disease state. As the patient becomes increasingly acidotic, cells will try to regulate the abundance of hydrogen ions through the exchange of potassium. As a result a patient will become hyperkalemic causing cardiac arrhythmias. Hyperthermia typically is one of the latest symptoms that develop during a malignant hyperthermia episode. Hyperthermia occurs due to a significant amount of heat production during sustained muscle contraction and increased ATP phosphorylation. During a malignant hyperthermia crisis, temperatures can rise 1 degree Celsius every five minutes and can exceed 43 degrees Celsius (Nagelhout & Plaus, 2014).

If left untreated or identified too late, malignant hyperthermia can lead to overwhelming cell death, severe rhabdomyolysis, and life threatening disseminated intravascular coagulation (DIC). Rhabdomyolysis is caused by increase in muscle breakdown and death and the release of myoglobin into the bloodstream. The increase in free myoglobin can cause acute kidney injury or failure due to renal tubule blockage. DIC can occur in the late stages of a malignant hyperthermia crisis mainly due to profound hyperthermia. Hyperthermia causes DIC due to a destruction and instability of clotting proteins and when developed, leads to poor outcome for the patient. When DIC has develop during malignant hyperthermia, cardiac arrest is fifty times more prevalent and death is ninety times more likely to occur (Barash et al, 2013).

Anesthesia Triggers

Halogenated Agents

- Desflurane
- Sevoflurane
- Isoflurane
- Halothane
- Nitrous Oxide is NOT considered a triggereing agent and is safe to use for someone susceptible for malignant hyperthermia.

Depolarizing Muscle Relaxants

- Succinylcholine

Onset of malignant hyperthermia, after exposure to these agents, occurs commonly within sixty minutes. Some reports have shown a delay of six hours to the occurrence of malignant hyperthermia with the use of Desflurane and Sevoflurane (Hopkins, 2000).

When a patient has been determined to be at high risk for malignant hyperthermia either from pre-operative testing or previous malignant hyperthermia reaction, a safe and preventative anesthesia plan is developed by the anesthesia provider and nurse. Steps and interventions including in this plan include avoidance of the use of halogenated agents such as Desflurane, Isoflurane, Sevoflurane, and Halothane. Nitrous Oxide has been proven to not be a trigger for malignant hyperthermia and is considered safe. There must also be avoidance of the use of the depolarizing muscle relaxant Succinylcholine. The use of regional or total intravenous anesthesia (TIVA) is safe anesthetic plans for patients susceptible to malignant hyperthermia. Many institutions have anesthesia machines designated specifically for susceptible malignant hyperthermia patients that have not had any volatile agents that could trigger a malignant hyperthermia response. If an institution does not have such a machine, an anesthesia machine being used on a susceptible patient must have oxygen ran though it for a minimum of ten minutes at a rate of ten liters per minutes to ensure all volatile agents have been flushed out. Vigilant monitoring of these patients is imperative to ensure a reaction does not occur or if one does, it can be treated promptly (Butterworth, Mackey, & Wasnick, 2013).

Treatment

The first step is being able to recognize and determine that the patient is undergoing a reaction and to call for help to get the entire medical team present and aware of the situation. All potential triggers must be eliminated and removed from the patient. Dantrolene will be given to the patient to reverse the progression of malignant hyperthermia. Dantrolene is skeletal muscle relaxant by the mechanism of inhibiting calcium release from the sarcoplasmic reticulum. By inhibiting calcium release, the progression of malignant hyperthermia can be ceased. The use of Dantrolene for the treatment of malignant hyperthermia has decreased patient mortality from 70% to 5%. Dantrolene is given intravenously at a dose of 2.5mg/kg to a max dose of 10mg/kg until termination of malignant hyperthermia crisis. Redosing of dantrolene is done every six hours for 24 hours to prevent reoccurrence of the disease process at a dose of 1-2 mg/kg. Along with pharmacological intervention for reversing malignant hyperthermia process by decreasing calcium release, treatment and interventions can be done to help control the symptoms of malignant hyperthermia; hypercarbia, hyperthermia, acidosis, hyperkalemia, and arrhythmias. (Musselman and Saely, 2013).

Conclusion

Extensive and detailed pre-operative assessment must be obtained to determine a patient's susceptibility of the disease in order to determine a safe anesthetic plan to decrease or eliminate risk of malignant hyperthermia crisis. If a crisis does occur, the ability to recognize malignant hyperthermia will lead to faster treatment and intervention and decreased morbidity and mortality. The use and knowledge of different forms of treatment will aid and help provide the best possible outcome for the patient in the end.

References

Anderson-Pompa, K., Foster, A., Parker, L., Wilks, L., Cheek, D. (2008). Genetics and susceptibility to malignant hyperthermia. Critical Care Nurse, 28, 32-36. Retrieved from http://www.ccnline.org

Barash, P., Cullen, B., Stoelting, R., Cahalan, M., Stock, M., & Ortega, R. (2013). Clinical Anesthesia (7th Ed.). Philadelphia, PA: Lippincott, Williams, & Wilkins.

Butterworth, J., Mackey, D., Wasnick, J. (2013). Morgan & Mikhail's Clinical Anesthesiology (5th Ed.). New York, NY: McGraw Hill Education.

Glahn, K., Ellis, F., Halsall, P., Muller, C., Snoeck, M., Urwyler, A., & Wappler, F. (2010). Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. British Journal of Anaesthesia, 105(4), 417-420.

Hines, R., & Marschall, K. (2012). Stoelting's Anesthesia and Co-Existing Disease (6th Ed.). Philadelphia, PA. Elsevier Saunders.

Hopkins, P. M. (2000). Malignant hyperthermia, advances in clinical management and diagnosis. British Journal of Anaesthesia, 85(1), 118-128.

Malignant Hyperthermia Association of the United States. (2014). Health care professionals. Retrieved from: http://www.mhaus.org/

Nagelhout, J., & Plaus, K. (2014). Nurse Anesthesia (5th Ed.). St. Louis, MO: Elsevier Saunders.

Musselman, M. & Saely, S. (2013). Diagnosis and treatment of drug-induced hyperthermia. American Journal of Health-System Pharmacy, 70, 34-42.

Rosenberg, H., Antognini, J., Muldoon, S. (2002). Testing for malignant hyperthermia. Anesthesiology, 96(1), 232-237.

Rosenberg, H., Davis, M., James, D., Pollock, N., & Stowell, K. (2007). Malignant hyperthermia. Orphanet Journal of Rare Diseases, 2(21),. doi:10.1186/1750-1172-2-21.

OTTERBEIN UNIVERSITY