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ANESTHETIC IMPLICATIONS FOR PATIENTS WITH FRIEDREICH'S ATAXIA

By

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Bachelor of Science in Nursing, South Dakota State University, 2016

An Independent Study

Submitted to the Graduate Faculty

Of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

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## PERMISSION

Title           Anesthetic Implications for Patients with Friedreich's Ataxia  
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### Abstract

Title: Anesthetic Implications for Patients with Friedreich's Ataxia

Background: A 30-year-old male patient presented for posterior spinal fusion and instrumentation of thoracic 2 through lumbar 4 with thoracic osteotomies for alleviation of chronic pain. The patient had a history of Friedreich's Ataxia. Friedreich's Ataxia is a progressive, autosomal recessive neurodegenerative ataxic disorder, with the majority of cases being homozygous, caused by a GAA trinucleotide repeat defect.

Purpose: The purpose of this Independent Project is to provide a comprehensive and detailed review of Friedreich's Ataxia, along with common coexisting comorbidities, and recommendations regarding the delivery of anesthesia.

Process: A literature review was conducted and accessed through the University of North Dakota's Harley E. French Library of Health Sciences. Databases utilized included PubMed, CINAHL, and SCOPUS. Search limitations included peer reviewed, publications dates within the past 10 years, human controls, and English language. The search of reference lists of relevant literature were also used to discover additional articles. Information was analyzed to summarize current implications and recommendations for the delivery of anesthetics to patients diagnosed with Friedreich's ataxia.

Results: Friedreich's ataxia, along with the coexisting morbidities, encompass multiple risk factors which have not been studied extensively in terms of anesthetic management. Several recent case reports, and a limited number of studies, have demonstrated anesthetic techniques that have been shown to be both effective and without complications for Friedreich's ataxia patients. Recent data, in regards to pathophysiology, coexisting comorbidities, and similarly linked disease processes, allow for a better understanding of anesthetic management in this population.

Implications: Friedreich's ataxia is a complex disease process and anesthesia providers must be cognizant of potential anesthetic implications. A complete history and preoperative assessment are essential in anticipating concerns regarding this patient populations specific comorbidities. Perioperative care should encompass patient specific comorbidities, with special considerations to neurogenerative qualities, cardiac function, respiratory status, and endocrine manifestations. Postoperative implications include potential risk of respiratory failure.

Keywords: Friedreich's ataxia, FRDA, anesthetic management, frataxin

## Background

Friedreich's ataxia (FRDA) is an autosomal recessive inherited neurodegenerative ataxic condition that is often accompanied with scoliosis, cardiac myopathies, diabetes mellitus, abnormal reflexes, and dysarthria (St John Sutton et al., 2013). Nikolaus Friedreich, a German pathologist, was the first person to detail the characteristics of FRDA in 1863 (Schulz & Pandolfo, 2013). The majority of FRDA cases are caused by a defect in the GAA triplet repeat expansion in the frataxin (FXN) gene found on chromosome 9 (Azar, Beatly, & Canale, 2017).

Prevalence of FRDA in the United States of America is unknown but, according to Vankan (2013) it is predicted to be 1 in 80,667. Countries with the highest prevalence of FRDA include: northern Spain with 1 in 20,000, Ireland 1 in 23,000, France 1 in 43,000, and Germany 1 in 47,000. FRDA is very uncommon in individuals of Sub-Saharan and Far East descent, occurring primarily in those of Caucasian descent (Vankan, 2013). FRDA presents equally in males and females on average between the ages of 10 to 15, however, late onset can be seen after the age of 25 (Koeppen, 2011; Selvadurai, Harding, Corben, & Georgiou-Karistianis, 2018).

The diagnosis of FRDA at this time is incurable and is associated with a decreased life expectancy of 35 to 40 years (Selvadurai et al., 2018). The main causes of mortality in FRDA is related to cardiac dysfunction; congestive heart failure and arrhythmias being the leading causes, followed by stroke, ischemic heart disease, and pneumonia (Cook & Giunti, 2017).

The multisystem effects of FRDA can make the delivery of anesthesia a challenging task to the provider in regards to the pharmacologic, physiologic, and pathologic effects that occur with this disorder. Specific concerns to anesthesia include cardiac abnormalities, pulmonary function, neurodegenerative effects, and endocrine dysfunction. The current recommendations for administration of anesthesia for FRDA patients is to treat in similar regards as to patients

diagnosed with amyotrophic lateral sclerosis (ALS) (Hines & Marschall, 2018). Other diseases that are similarly related via mitochondrial dysfunction include Parkinson's disease, Huntington's disease, and Charcot-Marie-Tooth (DiMauro & Schon, 2008; Tatsuta & Langer 2008; as cited in González-Cabo & Palau, 2013, p. 54). Recent research is focused on genetics, supportive treatment, medication trials, cardiac dysfunction, cardiac transplant, cerebral studies, prosthetics, and surgical correction of kyphosis (Cook & Giunti, 2017; Hanson, Shaledon, Pacheco, Alkubeysi, & Raizada, 2019; Selvadurai et al., 2018)

### Case Report

A 30-year-old, 71 cm, 70 kg Caucasian male patient presented for a posterior spinal fusion and instrumentation of thoracic (T) 2 through lumbar (L) 4 with thoracic osteotomies. His past medical history included Friedreich's ataxia, scoliosis, bilateral upper extremity ataxia, wheel chair bound related to loss of bilateral lower motor reflexes, mild tricuspid regurgitation, moderate concentric hypertrophy, cardiac defibrillator, dysarthria, chronic pain, methicillin-resistant *Staphylococcus aureus* (MRSA), and daily tetrahydrocannabinol (THC) use. Allergies included codeine, cats, and dogs. His home medications included ferrous sulfate 325mg, acetaminophen 500mg, and sildenafil 20mg. His surgical history included cardiac defibrillator placement and teeth extraction.

A thorough preoperative history and assessment was obtained. His preoperative vital signs included the following: blood pressure 95/59, heart rate 88, respiratory rate 18, room air oxygen saturation of 96%, and temperature of 98.6 °F. Preoperative laboratory testing consisted of the following data: hemoglobin 12.3 g/dL, hematocrit 37.9%, platelet count of 196 K/uL, sodium 141 mEq/L, potassium 3.9 mEq/L, chloride 107 mEq/L, bicarbonate 26 mEq/L, glucose 97 mg/dL, blood urea nitrogen 14mEq/L, and creatinine 0.79mg/dL. A type and crossmatch was

collected and patient's blood type resulted as B-negative. Thoracic x-ray exhibited a 27 degree convex left curve of T6 through T11 and chronic wedging of right T8 and T9 with osteophytes. Evaluation of the airway revealed a Mallampati score of II, mouth opening greater than three fingerbreadths, thyromental distance greater than three fingerbreadths, and full cervical range of motion. A preoperative 12-lead electrocardiogram (ECG) was performed and interpreted by a cardiologist as sinus rhythm with ST and T wave abnormalities. The most recent echocardiogram demonstrated preserved left ventricular functions with an ejection fraction of 59% in addition to concentric hypertrophy, mild tricuspid regurgitation. The patient also had an AICD. The patient was classified as an American Society of Anesthesiologist class III.

Preoperatively, a 20-gauge IV was placed in the dorsum of the patient's left hand, a Lactated Ringers infusion was initiated, and 2 mg of IV midazolam was given prior to transport to the operating room. Upon entering the operating room, standard noninvasive monitors were attached to the patient while still on transfer cart and preoxygenation via a simple mask was initiated at 10 L/min. The patient's left radial pulse was palpated, a 2% lidocaine wheal was placed, skin was cleansed with an antiseptic swab, and a 20-gauge arrow catheter was utilized to place a radial arterial line under sterile conditions. An additional 18-gauge IV was started on the patient's right dorsal forearm and was connected to blood tubing primed with 0.9% normal saline. Preoxygenation was continued via facemask with 100% oxygen. An intravenous induction was performed with fentanyl 100 mcg, lidocaine 100 mg, propofol 200 mg, rocuronium 30 mg, and phenylephrine 100 mcg. An elective C-MAC video laryngoscope was used with a D-blade, a grade I Cormack-Lehane view was visualized, and a cuffed 8.0 mm oral endotracheal tube was placed. Endotracheal tube placement was confirmed via video visualization of tube passing through the vocal cords, presence of end-tidal carbon dioxide, and

positive bilateral breath sounds. After confirmation of endotracheal tube placement, an esophageal temperature probe and Foley catheter were placed. The patient was then placed in the prone position, with arms in the surrender position and head in neutral alignment in the prone view. Bilateral lung sounds were reconfirmed posteriorly. In addition, an upper Bair Hugger was applied. The patient was then placed on mechanical ventilation with the following settings: volume control with a tidal volume of 600 mL, respiratory rate of 10 breaths per minute, and positive end-expiratory pressure (PEEP) of 5. Neuromonitoring leads were placed by the technician for the purpose of somatosensory and motor evoked potentials.

Anesthesia maintenance was maintained with 0.5 minimum alveolar concentration of sevoflurane, propofol infusion of 75 mcg/kg/min, and remifentanyl infusion of 0.2-0.3 mcg/kg/min. Prior to surgical incision, cefazolin 2 g and vancomycin 1 g were given, as well as a 1 g tranexamic acid bolus, followed by 2 mg/kg/hr infusion of the tranexamic acid. A low dose phenylephrine infusion was used to maintain a mean arterial pressure greater than 65 mmHg. Antiemetics included 5 mg of dexamethasone after induction and 4 mg of ondansetron prior to extubation. Per surgeon request, every 3 hours either 1 g of ofirmev or 30 mg of ketorolac were to be given. During the 1<sup>st</sup> hour, 1 g of IV ofirmev was administered, followed by 30 mg of ketorolac during the 3<sup>rd</sup> hour, and an additional 1 g of ofirmev in the 6<sup>th</sup> hour. Fluids were restricted given the patient's prone position and length of surgery. The patient's deficit was determined to be 1,320 mL, in which 600 mL was replaced in the first hour, along with a maintenance rate of 110 mL/hr of Lactated Ringers. During the 3<sup>rd</sup> hour of surgery, 250 mL of 5% albumin was administered, followed by an additional 500 mL of 5% albumin in the 4<sup>th</sup> hour of surgery. Total amount of blood able to be returned via the cell saver at the end of the case was 500 mL. The total amount of fluids given included 1,500 mL of Lactated Ringers, 200 mL of

0.9% normal saline, 750 mL of 5% albumin, and 500 mL of cell saver blood products. The estimated blood loss totaled 700 mL.

During closing of the surgical site, the remifentanyl, propofol, and subsequently the phenylephrine infusions were discontinued. The patient did not require reversal of paralytic, as he did not receive any additional paralytic after induction. Train of four monitoring produced 4/4 twitches, sustained tetany, and adequate tidal volumes were observed prior to extubation. Total procedure duration was 9 hours and 25 minutes. The patient was extubated awake and transferred to the post-anesthesia care unit (PACU) on 10 L/minute of oxygen via a simple mask. The patient was discharge from the PACU in satisfactory condition, however, the patient's hospital stay was complicated by pain issues along with substance abuse withdrawal issues.

## Discussion

### Pathophysiology

FRDA is the most prevalent ataxic disorder of hereditary via an autosomal recessive disorder where both the mother and father are carriers of the mutated gene. Two types of FRDA exist, with the most predominant form (96 - 98%) being a homozygous GAA trinucleotide repeat expansion in the first intron of the FXN gene on the long arm of chromosome 9q21.11 and the least predominant form (2 - 4%) being heterozygous, characterized by a point mutation or exonic deletion (Arbustini et al., 2018; Selvadurai et al., 2017). Normal chromosomes in patients unaffected by FRDA have repeat GAA trinucleotide expansions containing typically less than 12 repeats, with 60 being the upper limit of normal. Those affected with FRDA have repeat trinucleotide expansions on average between 600 to 900, however, they can range from 6 to 1,500 repeats (Cook & Giunti, 2017; Arbustini, 2018). Thus, the greater proportion of GAA

repeats is linked to decreased measures of the frataxin protein, which accelerates the disease process at an earlier age and determines the severity of the disease (Selvadurai et al., 2017).

The significance of the FXN mutation at the cellular level is a reduction in the formation of the frataxin protein, which is a mitochondrial protein associated with iron homeostasis (Selvadurai et al., 2017). The complete role of frataxin is unclear, but it is a 210-small amino acid which is the precursor of protein 23kDa and can be found in all eukaryotic organisms (Gomes & Santos, 2013; González-Cabo & Palau, 2013). Frataxin can be found in cells throughout the body, predominant locations include the central nervous system, myocardium, skeletal muscle, and pancreas (Dantham, Srivastava, Gulati, & Rajeswari, 2018; Gomes & Santos, 2013). The repercussions of low levels of frataxin and its relationship with iron regulation leads to dysfunction of subunits comprising the iron-sulfur clusters (ISC) in the mitochondrial respiratory chain complexes I, II, III, oxidative stress, decline in mitochondrial adenosine triphosphate (ATP) production, and iron accumulation in the mitochondria (Cook & Giunti, 2017; Abeti et al, 2016; Schulz & Pandolfo, 2013). The accumulation of increased levels of free iron may escalate the generation of reactive oxygen species, causing elevated oxidative stress (Cook & Giunti, 2017).

### **Signs and Symptoms**

Clinical characteristics of FRDA which usually first present in the first or second decade of life includes gait ataxia that progresses to truncal ataxia and paraplegia, eventually causing the majority of patients to be wheelchair dependent by the third decade of life. The diagnosis of FRDA can encompass a variety of different phenotypic features, however, the following characteristics are found to be consistent in all FRDA diagnoses: ataxia of the extremities, gait unbalance, absence of lower extremity reflexes, and dysarthria. Common co-morbidities that

FRDA patients can also present with include cardiomyopathies, such as concentric cardiac hypertrophy and supraventricular arrhythmias, scoliosis, diabetes mellitus, dysphagia, nystagmus, optic neuropathy, reduced proprioception, and cognitive deficits (Cook & Giunti, 2017).

**Central and peripheral nervous system manifestations.** The central nervous system manifestations are the primary features associated with FRDA. According to Gomes and Santo (2013), the dorsal root ganglia is one of the earliest tissues to be susceptible to the FRDA mutation, with somatic instability occurring during embryonic development, and continuing throughout the duration of the patient's life span. A study, conducted by Rezende et al. (2017), utilizing high-resolution magnetic resonance imaging (MRI) on a 3T Achieva scanner compared pediatric and adult individuals with FRDA to controls and found abnormalities in the cervical spinal cord, medulla oblongata, inferior cerebellar peduncle, red nuclei, with additional cortical thinning and supratentorial damage in the adult population. Spinal cord abnormalities encompass developmental and neurodegenerative qualities, as the cord expansion area reaches its maximum by the age of 10, with subsequent atrophy occurring with maturation (Rezende et al., 2018).

Ataxia, as the diagnosis of FRDA suggests, is a definitive feature of the disease process. Recent research of microRNAs has isolated three protein molecules that are regulated by microRNAs: Brain-Derived Neurotrophic Factor (BDNF), dihydrofolate reductase (DHFR), and glucose-6-phosphate translocase (G6PT), which are linked to FRDA. MicroRNAs are a category of small noncoding RNA molecules which are associated with a regulatory role of gene expression. The central and peripheral nervous systems are affected by their affiliation with BDNF, which is of the neurotrophin family of growth factors, which are related to canonical nerve growth factor. A reduction in levels of these factors are linked to dysfunction of Purkinje

cells and ataxic disorders. Abnormal DHFR expression in FRDA is associated with progressive increases in neurodegeneration and may be associated with cardiac dysfunction. The ineffective functionality of G6PT with hexose-6-phosphate dehydrogenase is associated with dysfunction of the cortisol and corticosterone pathway, and the development of type 2 diabetes mellitus (Dantham et al., 2018).

Peripheral nervous system manifestations often present as Schwann cells and nerve axons damage occurs, which is related to decreased amounts of frataxin (Selvadurai et al., 2018). Within the peripheral nervous system, Schwann cells, which are a type of glial cell, are essential for the myelination of axons. The signaling that occurs among Schwann cells and neurons is crucial for Schwann cells establishment, proliferation, longevity, and myelination (Gomes & Santos, 2013). Sensory neuropathy may be attributed to the aberrant transmission between the Schwann cells and axons, along with axonal degeneration, as seen with the neurodegeneration of the sural nerve in FRDA patients (González-Cabo & Palau, 2013). Koeppen's (2011) autopsy reports of sural nerve specimens in individuals with FRDA exhibited an inadequacy or absence of myelin sheaths, particularly in larger diameter and that axons remained abundant but, decreased in size when compared to normal individuals.

**Cardiac manifestations.** Cardiac manifestations are prevalent among FRDA patients, with cardiomyopathies being the leading cause of death. The degree of left ventricular wall thickness is associated with the length of the repeat triplet expansion in the FXN gene (Vanlander & VanCoster, 2018). According to Vanlander and VanCoster (2018), "In accordance with the early involvement of the frataxin protein in ISC biosynthesis pathway, deficiencies of aconitase and of the OXPHOS (oxidative phosphorylation system) complexes I, II, and III have been reported in subject's cardiomyocytes" (p. 498). These deficiencies cause the inability to

remove excess iron from the myocytes, which can lead to chronic inflammation, scarring, fibrosis, and myocardial necrosis and apoptosis (Hanson, et al., 2019). Studies have estimated that 80% of FRDA patients have some degree of left ventricular irregularity. In most cases, left ventricular concentric remodeling occurs in the beginning of the disease process, with subsequent concentric hypertrophy developing in advanced stages of the disease, and a small percent of patients develop eccentric hypertrophy. Systolic function is unimpaired in most FRDA patients, as a reduction in ejection fraction is typically not seen until end stage cardiomyopathy develops (Weidemann et al., 2013).

Cardiac involvement of FRDA is identified with electrocardiogram and echocardiogram. ECG traits that are most prevalent in FRDA patients include a normal QRS duration and QT interval, with T-wave abnormalities such as flattening or inversion of the waves often seen in the inferior and lateral leads (Hanson et al., 2019; Weidemann et al., 2013). Bundle branch blocks have been reported in 15% of FRDA patients. Atrioventricular conduction blocks, atrial, and ventricular arrhythmias likely occur in relation to the pathological changes seen with scarring and fibrotic changes. Infrequently, atrial flutter or fibrillation can present, and to an even lesser degree ventricular arrhythmias (Hanson et al., 2019). Typical echocardiogram characteristics include concentric left ventricular hypertrophy, preserved left ventricle ejection fraction, decreased peak longitudinal strain, and sparkling texture (St John Sutton et al, 2013; Weidemann et al., 2013).

**Musculoskeletal manifestations.** Scoliosis is a common feature in patients presenting with FRDA and has a prevalence rate of 63 to 100% (Tsirikos & Smith, 2012). In a study conducted by Tsirikos and Smith (2012) that looked at 31 patients with FRDA and scoliosis, the average age at presentation was 15.5 years, with an average curvature of 51 degrees and types of

curves found included thoracic, thoracolumbar, and double major (thoracic/lumbar) curves. Curvatures of the spine greater than 40 degrees are considered severe and are linked to cardiac and pulmonary dysfunction (Hines & Marschall, 2018).

Cavovarus foot deformities often progress with age, caused by an overreactive plantar reflex causing the feet and toes to plantar flex with standing, resulting in an equinovarus from the pulling of the posterior tibial tendon (Azar et al., 2017). Progression of the disease causes most individuals with FRDA to become paraplegic and wheelchair bound, typically within 10 to 15 years after presenting symptoms (Hoffman-Zacharska et al., 2016; Selvadurai et al., 2018).

Dysphagia commonly occurs in a vast majority of FRDA patients related to delayed pharyngeal swallowing reflex and lingual dysfunction. It is thought that dysphagia is associated with cerebellar degeneration and is worsened by coexisting spasticity and weakness. Corticobulbar and corticopontine degeneration effects may be associated with deficits seen during the oral voluntary phase of swallowing. Aspiration, as well as the risk of silent aspiration is prevalent, and 10% of deaths in individuals with FRDA is caused by pneumonia (Keage, Delatycki, Gupta, Corben, & Vogel, 2017).

**Pulmonary manifestations.** Scoliotic changes found in FRDA can cause varying degrees of pulmonary dysfunction. The curvature of the spine can result in the lungs becoming constricted in the chest cavity, which decreases the individual's vital capacity and increases work of breathing, airway resistance, and dyspnea (Hines & Marschall, 2018). According to Azar et al. (2017), a 5% decrease in predicted vital capacity and 3% decrease in peak flow occurs with each 10 degree increase in the spines Cobb angle.

Increased risk of obstructive sleep apnea has been associated with FRDA, which increases with severity of the disease (Cook & Giunti, 2017). Patients with neuromuscular

disorders have increased risk of nocturnal hypoxemia and hypercapnia and subsequent development of cor pulmonale. Individuals with neuromuscular disorders are also at increased risk of restrictive lung processes from muscle weakness, causing a decreased ability to perform normal inspiration, exhalation, and a reduced ability to generate adequate expiratory airflow velocity required to produce forceful coughs (Hines & Marschall, 2018).

**Endocrine manifestations.** Patients with FRDA are at an increased risk for the development of diabetes mellitus. Prevalence rates of diabetes mellitus are varied among sources, however, the range average is 5 to 40% of patients presenting with FRDA (Greeley, Regner, Willi, & Lynch, 2014; McCormick et al., 2017). The exact mechanisms that contribute to development of insulin resistance, glucose intolerance, and diabetes mellitus are not entirely clear, but the greater number of GAA repeats, age, body habitus, and ambulatory status all can be contributive factors (Greeley et al., 2014). The role of frataxin in mitochondria function likely has a role in beta cell dysfunction and beta cell apoptosis, which impedes normal regulation of insulin production and secretion (Cnop, Mulder, & Igoillo-Esteve, 2013; Pappa et al., 2018). Insulin resistance may develop whether it is directly or indirectly related to mitochondrial dysfunction in the liver, adipose tissue, and muscle (Cnop et al., 2013). A study conducted by Pappa et al. (2018) found that FRDA patients with diabetes mellitus phenotype had mixed characteristics of both type 1 and type 2 diabetes. Onset is often acute or patients presenting with ketoacidosis, blood glucose levels that resembled type 1 diabetes, compounded by beta cell dysfunction, metabolic disturbances, and some cases presenting positive for beta cell antibodies (Pappa et al., 2018).

**Autonomic nervous system manifestations.** Urinary dysfunction can occur and may be related to pyramidal involvement, causing over active bladder symptoms, which can comprise of

incomplete bladder emptying, urgency, and frequency. Gastrointestinal symptoms can comprise of constipation, ileus formation, and incontinence, which is thought to be caused by a combination of decreased mobility and corticospinal involvement. Impaired thermoregulation may be present with cold sensitivity and hyperhidrosis. Erectile dysfunction has been reported in male patients (Cook & Giunti, 2017; Indelicato et al., 2018).

### **Diagnosis**

Diagnosis of FRDA usually begins with a thorough history and examination of the patient and based on clinical presentation. Azar et al. (2017) stated that a suggestive clinical diagnosis can be based on a “triad of ataxia, areflexia, and positive Babinski reflex” (p. 1417). Patellar and Achilles reflexes are often diminished or lost early in the disease process (Azar et al., 2017). Somatosensory evoked potentials (SEPs) are almost always absent related to the neurodegenerative affects at the dorsal root ganglia (Tsirikos & Smith, 2012).

Lab abnormalities indicative of FRDA can be seen in blood, urine, and tissue samples. Endocrine dysfunction manifestations can present with abnormal blood glucose, pH, and urine ketones (Paapa et al., 2018). Positive high-sensitivity troponin-T levels obtained in FRDA patients have been indicative of tachyarrhythmias and can reveal asymptomatic heart failure (Arbustini et al, 2018; Weidemann et al., 2013). Lateral flow immunoassay and Luminex xMAP-based immunoassay of whole blood and buccal cells, have been studied and show high positive predicative values to identify individuals with FRDA and those who are carriers (Deutsch, Oglesbee, Greeley, & Lynch, 2014).

MRI of the brain and spinal column exhibit atrophy of gray and white matter within portions of the cerebellum, brainstem, cerebellar peduncles, and motor cortex, as well as a volumetric reduction of the spinal cord (Martinez et al., 2018). Functional MRI of the cerebral

cortex differs among FRDA patients and control patients in regard to cerebral activation during motor and cognitive tasks, especially within the ventral networks (Selvadurai et al., 2018).

Cardiac MRI has exhibited a correlation between the left ventricle mass dimensions and greater number of GAA repeats (Rajagoplan et al., 2010, as cited in Weidemann et al., 2013).

Genetic molecular analysis tests can be performed to support a suspected clinical diagnosis of FRDA or to identify carriers of the FXN mutation gene. The first intron of the FXN gene are the target of molecular tests to determine the number of GAA repeats. The number of repeats are then used to classify if the FXN gene repeat is normal, intermediate, or pathogenic. Polymerase chain reaction (PCR) testing is used to analyze DNA that is isolated from leucocytes collected via peripheral blood draw. The PCR analysis for FRDA typically consists of two steps, the long – range PCR to verify if the allele(s) are or are not pathogenic and the triplet repeat primed PCR which is able to identify individuals with expanded alleles in both homozygous and heterozygous genotypes (Hoffman-Zacharka et al., 2016).

### **Treatment**

FRDA is a progressive disorder, which at this time has no cure. Management of FRDA encompasses a collaborative approach of holistic care, medical specialist, and monitoring. Holistic care should include physiotherapy, occupational, and speech therapists, as well as palliative care. Specialties that should be included in care include neurology, cardiology, orthopedics, geneticist, psychiatry, dietetics, ophthalmology, audiology, and endocrinology. Clinical monitoring should consist of neurological, musculoskeletal, cardiac, pulmonary, endocrine, visual, auditory, and behavioral (Cook & Giunti, 2017).

Holistic care integrated into the FRDAs patient care routine is important to promote independence and improved quality of life. Muscle stretching and strengthening, along with

aerobic exercise with the aid of a physiotherapist helps preserve balance, flexibility, and may reduce instability and fatigue. Occupational therapy is essential to assess and provide interventions as necessary to improve independence and functionality in a variety of aspects in life including home, professional, and academic settings with equipment and rehabilitation. Speech therapy is significant, as a prominent feature of FRDA is dysarthria and dysphagia (Cook & Giunti, 2017). In FRDA patients, dysarthria can cause communication barriers, ataxic limb movements may cause a nutritional impediment, and dysphagia may limit food choices and increase the risk of aspiration (Keage et al., 2017).

Surgical interventions typically include spinal, orthopedic, and cardiac procedures. Spinal surgeries are typically reserved for FRDA individuals with scoliotic curvature greater than 60 degrees, curves of 40 to 60 degrees in early onset patients, and based on severity of associated symptoms. Bracing with thoracolumbosacral orthosis has marginal benefits in the majority of individuals with FRDA, as the scoliosis progresses even with the orthosis in place (Tsirikos & Smith, 2012). Cavovarus foot deformities, causing an equinovarus, are often corrected with tenotomies or primary triple arthrodesis (Azar et al., 2017). Prophylactic automated implantable cardioverter-defibrillators are inserted for treatment of ventricular tachyarrhythmias and individuals at increased risk of sudden cardiac death. Heart transplantation may be an option for individuals with life threatening cardiomyopathies and may improve survival rates and provide an improved quality of life (McCormick et al., 2017b).

Clinical monitoring is essential once a diagnosis of FRDA has been made and throughout the progression of the disease process. Cardiac involvement remains the leading causing of death of FRDA, thus special attention should be placed on cardiac function with ECG and echocardiography studies. Auditory assessments should be conducted at diagnosis and on an

annual basis as sensorineural hearing loss can occur (Cook & Giunti, 2017; Vanlander & Coster, 2018). Visual screening should be conducted as progression of the disease may cause visual disturbances related to optic nerve atrophy and disruption of the cerebral pathways (Selvadurai et al., 2018). Blood glucose levels should be measured annually and HbA1c monitoring in those who are insulin dependent. Disorders of behavior should also be evaluated, as the multi-system effects of FRDA and volumetric reduction in the area of the frontal grey matter increase the risk of depression and anxiety (Cook & Giunti, 2017; Paapa et al, 2018).

Pharmacological therapy consists of strategies aimed at muscle relaxation, antioxidant supplementation, cardiac, and endocrine involvement. Treatment for tightness or stiffness from spasticity can include oral medications such as baclofen, tizanidine, gabapentin, and benzodiazepines or implantable intrathecal baclofen pumps. Eye movement such as square wave jerks or ocular flutter may be treated with memantine, acetazolamide, or clonazepam. Antioxidant supplementation such as idebenone, coenzyme Q10, vitamin E, creatine and iron chelation agents such as deferiprone, have been studied for the reduction of oxidative stress and iron accumulation, however, efficacy is inconclusive (Cook & Giunti, 2017, p. 24-27). Common cardiac management strategies may encompass calcium channel blockers for supraventricular tachycardias, angiotensin-converting inhibitors or angiotensin II receptor blockers for reduction in afterload, and loop diuretics for fluid overload (Cook & Giunti, 2017; Weidemann et al., 2013). Diabetes management often includes oral medications such as metformin or thiazolidinediones and subcutaneous insulin injections. Recent research has indicated that incretin analogs such as Glucagon-like peptide-1 agonists may provide neuroprotective effects in FRDA patients (McCormick et al., 2017a; Pappa et al., 2018).

### Anesthesia Considerations

**Preoperative and intraoperative considerations.** Prior to any procedure involving anesthetics, a thorough preoperative history and assessment should be completed. FRDA is progressive and severity varies from patient to patient. It is important to evaluate the extent of the disease progress and gather appropriate testing (Romero & Joshi, 2013). Baseline vital signs should be collected and recorded. Pertinent laboratory values for individuals with neuromuscular disorders should include a basic metabolic panel, creatinine kinase, myoglobin, complete blood count, and type and cross if blood loss is expected to be significant (Katz & Murphy, 2017). A neurologic evaluation should be completed in order to assess both sensory and motor baseline function.

Pulmonary function studies should be assessed, including vital capacity and expiratory volume. Individuals have increased pulmonary function risks when vital capacities are less than 30% of predicted normal values and may require respiratory support or prolonged continuous mechanical ventilation postoperatively (Azar et al., 2017). Preoperative chest x-ray should also be considered, as this population is at increased risk for aspiration-related pneumonia (Keage et al., 2017). Mechanical ventilation considerations should include settings appropriate for restrictive lung disease processes and avoidance of left ventricular outflow tract obstruction (LVOT), such as decreased tidal volumes and increased respiratory rate (Hines & Marschall, 2018). In a study of 102 patients conducted by Gurajala, Ramachandra, Lyengar, and Durga (2018), scoliotic fusions of more than eight vertebrae significantly increases the risk of post-operative ventilation requirements.

Cardiac function and workup should be considered for all FRDA patients undergoing surgical procedures. A 12-lead ECG should be obtained to assess for rhythm abnormalities and a

5 lead to monitor intraoperative cardiac function. Echocardiogram studies should be assessed for degree of cardiac dysfunction, left ventricular hypertrophy and mitral regurgitation can be common. Left ventricular ejection fraction is typically preserved, until end stage cardiac disease (Sutton et al., 2013). Patients with implantable cardioverter-defibrillators should be assessed to determine the type of device, degree of dependence, if a recent interrogation has taken place, and if a magnet will need to be utilized (Hines & Marschall, 2018).

Hypertrophic cardiomyopathies are prevalent among FRDA patients and LVOT obstruction should be avoided. Preoperatively, replacement of fluid deficit should be considered in an effort to replenish intravascular volume and decrease the risk of LVOT obstruction. During induction, sympathetic stimulation should ideally be avoided with direct laryngoscopy, premedication with a beta blocker or volatile anesthetic can be considered to blunt this response. Caution should be used when selecting an inhalation agent, as desflurane can result in sympathetic nervous system stimulation, causing tachycardia. Alpha-adrenergic agonists should be used to treat decreases in preload or afterload caused by hypotension, whereas beta-adrenergic agonists should be avoided related in increase in inotrophy and chronotrophy. Normal sinus rhythm should be maintained and therefore beta blockers such as esmolol and metoprolol can be considered to reduce tachycardia. Additionally, a cardioverter-defibrillator should be present within the operating room, in the event the patient develops supraventricular tachydysrhythmia (Hines & Marschall, 2018).

A case report by Kamata et al. (2014) demonstrated the preoperative care and management of a 14-year-old female weighing 37.3 kg with FRDA and hypertrophic cardiomyopathy undergoing posterior spinal fusion with spinal monitoring. The patient's echocardiogram revealed moderate to severe concentric left ventricular hypertrophy, mild mitral

insufficiency, and a preserved systolic function. Medications included 0.05 mg/kg of midazolam as a premedication, and for induction 0.25 mg/kg of etomidate, 1 mg/kg of lidocaine, 3  $\mu$ /kg of fentanyl, and rocuronium 0.5 mg/kg. Esmolol 0.25 mg/kg was used prior to and during induction to maintain a heart between 60 to 70 beats/min, patient was reported to have max heart rate of 110 beats/min during induction, an esmolol infusion was then started at the end of the case at 75  $\mu$ /kg/min to maintain heart rate between 60 to 80. Anesthesia was maintained with sevoflurane (end-tidal concentration of 2 to 3%), 0.05 to 0.3  $\mu$ /kg/min remifentanyl infusion, 0.2 to 0.5  $\mu$ /kg/min phenylephrine infusion to maintain a mean arterial pressure of 55 to 65, and 0.4  $\mu$ /kg/hr dexmedetomidine infusion without a loading dose. Additional aspects include placement of an arterial line, central line, bispectral index (BIS), and near infrared spectroscopy (NIRS) monitoring. Fluid management included 2,100 mL of isotonic fluids, 1000 mL of 5% albumin, and 225 mL of intraoperative cell salvage. Total procedure length was 360 minutes, there was no mention of neuromuscular blocker reversal, esmolol and dexmedetomidine infusions were continued until postoperative day one, and her hospital stay was noted as uncomplicated (Kamata et al., 2014).

Neuromuscular blocking agents for induction and maintenance should take into account the FRDA patient's neurologic deficits. The use of succinylcholine should be avoided, as FRDA is a neurodegenerative disease and anesthetic management should be treated in a similar fashion to ALS patients. The patient may be at risk for a hyperkalemic episode after administration of succinylcholine, thus a nondepolarizing neuromuscular blocker should be considered (Hines & Marschall, 2018). Furthermore, according to Katz and Murphy (2017), the administration of succinylcholine to any patients with muscular dystrophies, motor neuron diseases, and intrinsic

muscle disease should be avoided related to an increased risk of malignant hyperthermia, rhabdomyolysis, and cardiac arrest.

Nondepolarizing muscle blockade can be administered, however, a reduced dose should be considered, as patient's response can be variable (Romero & Joshi, 2013). Nondepolarizing muscle relaxants have not been reported to interfere with mitochondrial function and are considered safe when a secured airway is present (Niezgoda & Morgan, 2013). The patient's home medications and co-administered medications should also be monitored when administering nondepolarizing muscle blockers as corticosteroids, aminoglycosides, vancomycin, quinidines, ester-type local anesthetics, furosemide, calcium channel blockers, and beta-blockers can cause a prolonged block (Romero & Joshi, 2013). Information on the use of neostigmine for reversal of neuromuscular blockade in FRDA patients was not found, however, Romero and Joshi (2013) stated residual blockade from neuromuscular blockers in ALS patients could be reversed with neostigmine.

A case report by Guclu et al. (2014) reported the use of sugammadex (2 mg/kg) after the administration of rocuronium for an appendectomy in a 17-year-old FRDA patient. The patient had return of spontaneous respirations after 1 hour following administration of rocuronium, the patient was reversed with sugammadex, and total procedure time was noted as 1 hour and 15 minutes. Prior to extubation, Guclu et al. (2014) stated adequate tidal volumes were observed, extubation was uneventful, and patient was able to be transferred to the pediatric ward 10 minutes after the administration of the sugammadex. Additionally, Katz and Murphy (2017) reported in their research that sugammadex has safely been used in patients with other types of neuromuscular disorders, such as Duchenne muscular dystrophy, Becker's muscular dystrophy, and myasthenia gravis.

Mitochondrial deficits in individual with FRDA, specifically respiratory chain complexes I, II, and III, pose an uncertain risk for administration of volatile anesthetic agents. According to Niezgoda and Morgan (2013), those with respiratory chain complexes I defects are especially sensitive to volatile anesthetics, complexes II and III, however, are resistant to inhibition of volatile anesthetics. The selection of which inhalational agent will be based on the clinical picture and effects of each agent. Patients with mitochondrial deficits may be more sensitive to sevoflurane than other agents, however, if muscle relaxation is needed, sevoflurane or desflurane would be the ideal choice. Isoflurane or desflurane may be advantageous if cardiac output needs to be preserved, though caution should be exercised with use of desflurane, related to the risk of tachycardia. The use and consideration of BIS monitoring should be considered in order to administer the minimum amount of anesthetic needed for the proposed procedure. Lastly, inhalation agents may be safer than intravenous sedation, as volatile anesthetics are able to be exhaled and do not require extensive metabolism (Niezgoda & Morgan, 2013).

Intravenous anesthetic agents known to inhibit mitochondrial function of complex I include etomidate, ketamine, and barbiturates (Niezgoda & Morgan, 2013). Niezgoda and Morgan (2013) stated that propofol and thiopental have been given in bolus doses with minimal negative consequences, however, long-term infusions may have an increased risk of propofol infusion syndrome related to inhibition of mitochondrial function of complex's I, IV, and indirectly complex II. The use of propofol for induction and intraoperative infusions for maintenance of anesthesia have been documented without adverse effects in several case reports. Narcotics have not been reported to interfere mitochondrial function, however, the use of morphine though should be omitted, as it may cause some degree of mitochondrial dysfunction (Niezgoda & Morgan, 2013).

The selection of intravenous fluid selection should be patient and procedure specific. The administration of lactate containing fluids should be omitted in patients with mitochondrial deficits (Romero & Joshi, 2013). Vanlander and VanCoster's (2018) research found that the genetics of multiple defective ISC related diseases have increased lactate production in body fluids. Hypovolemia, from fluid deficit and blood loss, should be avoided to decrease the risk of LVOT obstruction (Hines & Marschall, 2018).

Intraoperative blood loss that is anticipated to be significant, should be managed using various approaches. Antifibrinolytics, such as a tranexamic acid bolus and continuous infusion can be considered to reduce bleeding. Blood salvaging systems, such as a cell saver, allows for autologous blood to be returned to the patient. Preoperative autologous blood donation may be collected in patients in both stable condition and that have laboratory values within normal limits (Azar et al., 2017). Allogenic blood transfusion can increase risk of transfusion related acute lung injury, ventilator associated pneumonia, and disease transmission. Measures to prevent hypothermia should also be considered, such as warm fluids and a forced air warming device, to reduce bleeding and coagulation dysfunction (Gurajala et al., 2013). Controlled hypotension may be requested by the surgeon, however, caution should be advised for those patients in the prone position, as they are at an increased risk of potential optic neuropathy and spinal cord ischemia (Hines & Marschall, 2018).

**Local anesthetic considerations.** No contraindications were found for neuraxial anesthesia in FRDA patients, however, it may present a challenge related to the presence of scoliotic changes. Respiratory status should be monitored in neuraxial blocks higher than the level of T10, as respiratory muscle involvement may become compromised (Hines & Marschall, 2018). Several successful case reports were found for spinal and combined spinal/epidural

anesthetics in patients with FRDA. Huercio, Guasch, Brogly, and Gilsanz (2014) reported the use of a combined spinal/epidural neuraxial technique for right cavus foot correction in a 35-year-old female patient. Her clinical presentation included thoracic scoliosis, pes cavus, ocular ataxia, cerebellar syndrome, and an ECG which showed a right bundle branch block. Her echocardiogram and cardiac MRI were normal, and pulmonary test which identified mild restrictive processes. The patient was placed in the sitting position and an 18-gauge Tuohy needle was introduced into the epidural space at the lumbar 4-5 interspace. A 27-gauge Whitacre spinal needle was then introduced through the Tuohy needle and 13 mg of hyperbaric bupivacaine and 10 mcg of fentanyl were injected intrathecally. After removal of the spinal needle, a 21-gauge epidural catheter was introduced into the epidural space. The spinal anesthetic was reported to reach the level of T8 and lasted 90 minutes. An epidural infusion of 5 mL/hr of 0.125% levobupivacaine was started postoperatively for pain control and discontinued 3 days later, prior to discharge (Huercio et al., 2014).

A report by Barbary, Remérand, Brillhault, Laffon, and Fusciardi (2012) demonstrated the successful use of bilateral popliteal fossa blocks in a 34-year old male patient with FRDA for bilateral tenotomies. Ultrasound guidance was used and 1.5% mepivacaine was infiltrated around the peroneal nerves (6 mL) and tibial nerves (13 mL) and duration of the blocks was reported to be 240 minutes. Barbary et al. (2012) choice of nerve blocks, as an alternative to general anesthesia or neuraxial technique, were related to the patient's sleep apnea, restrictive respiratory disease, and severe dysphagia. They avoided neuraxial technique related to severe kyphoscoliosis. The patient was reassessed one month later, and no neurological injury was observed. Azar et al. (2017) also stated, when general anesthesia is contraindicated in FRDA patients, local anesthetic infiltration is successful for equinovarus correction via tenotomies of

the Achilles tendon, posterior tibial tendon at the ankle, and toe flexors on the plantar side of the metatarsophalangeal joints.

A case report by Ganesan (2011) demonstrated the use of an LMA and field block for a 42-year old male with FRDA undergoing wide local excision of squamous cell carcinoma over the scrotum. The patient had symptoms of FRDA presenting at the age of 10 and was positive for diabetes, dysarthria, nystagmus, areflexia, absent plantar reflex, impaired position and vibration senses, and mild left ventricular hypertrophy. Premedication included diazepam 5 mg orally, and after 5 minutes of 100% preoxygenation, intravenous induction was performed with 2  $\mu$ g/kg of fentanyl and 2.5 mg/kg of propofol, a size 4 LMA was placed, and anesthesia maintenance was maintained with isoflurane. A scrotal field block was completed with 7 mL of 1% lignocaine and 13 mL of 0.25% bupivacaine. The LMA was removed once patient was awake, they were transferred to PACU, and discharge one week later (Ganesan, 2011).

**Evoked Potentials.** Motor evoked potentials (MEPs) and SEPs information is limited in patients with FRDA. Tsirikos and Smith (2012) found that MEPs and SEPs are usually significantly reduced or absent. Another study by Sival et al. (2009) researched whether idebenone treatment was effective in preserving neurologic function in 6 children diagnosed with FRDA and found that median nerve SEPs were absent in all participants and discernable sural nerve action potentials were observed in 50% of children at start of study, but absent after 2 years. Milbrandt, Kunes, and Karol's (2008) research found monitoring of SEPs to be ineffective and wake-up tests should be planned if necessary. If SEPs/MEPs monitoring is planned, low dose inhalation agents combined with intravenous agents should be utilized in addition to the avoidance of long acting neuromuscular blockers. If a wake-up test is planned, neuromuscular blockade should be avoided or reversed (Hines & Marschall, 2018).

### Recommendations

In retrospect, the case was planned and managed similar to that of an ALS patient and with what available literature on FRDA was able to be obtained prior to the case. Appropriate cardiac studies, thoracic x-ray, and labs were obtained preoperatively. The use of a depolarizing muscle relaxant was avoided, given the patient had a neurodegenerative disorder, and a reduced amount of a non-depolarizing agent, rocuronium, was administered. The patient remained hemodynamically stable during the procedure, with minimal use of phenylephrine, and heart rate was observed to be maintained between 50 to 70 bpm intraoperatively without intervention. For fluid management, isotonic fluids were minimized related to the prone positioning and to reduce the risk of respiratory compromise, and instead supplemental colloids for intravascular volume expansion were given. Blood loss was managed with a tranexamic acid bolus and infusion, intra-operative hemoglobin and hematocrit monitoring, and utilization of the cell saver to return salvaged autologous blood. For the purpose of intra-operative neuromonitoring, the combined administration of 0.5 MAC of sevoflurane, propofol, and remifentanyl infusions allowed for acceptable neuromonitoring conditions. However, according to the monitor technician, neuromonitoring of SEPs/MEPs were observed to be severely deranged or absent, related to the patient's disease process. Reversal from rocuronium was not required, as 4/4 twitches returned via train of four within 45 minutes after induction and the patient met extubation criteria prior to the removal of the endotracheal tube.

A few factors could have been improved upon after an in-depth literature search. Pulmonary function testing and results should have been obtained prior to the operation, to determine the level of pulmonary compromise. After placement of the radial arterial line, the collection of arterial blood gases with lactic acid would have been beneficial to assess the

patient's status. Given the mitochondrial effects of propofol, dexmedetomidine may have been a more prudent choice of anesthetic, with the benefit of alpha 2-adrenoceptor agonist effects of analgesia, reduction in heart rate, and minimal respiratory depression. The addition of BIS monitoring should have been considered to titrate and guide anesthetics agents in this population.

### **Conclusion**

Despite its rare occurrence, FRDA is the most prevalent ataxic hereditary disorder that necessitates comprehension of the disease process and the multisystem effects that can be compromised under anesthesia. Thorough preoperative monitoring, testing, evaluation, and planning should occur prior to any surgical procedure, as the perioperative period can pose considerable risks. Awareness of potential complications associated with FRDA enables the anesthesia provider the ability to administer an anesthetic in accordance with the patient's disease process and react appropriately to obstacles that may present.

The anesthesia provider should tailor an appropriate anesthetic plan that encompasses the multisystem effects of FRDA, the patient, and the proposed surgical procedure. Various approaches to anesthesia techniques have been demonstrated successfully through case reports. When appropriate, regional and neuraxial anesthesia techniques should be considered to reduce pulmonary and cardiac compromise. General anesthesia, which is often required in this population for spinal procedures, can be administered with the vigilant selection of medications and monitoring for the proposed procedure.

A collaborative approach should take place between the care team and providers in the preoperative, perioperative, and postoperative stages to maximize optimal surgical and patient outcomes. Multiple body systems have to be considered, including respiratory, cardiac, endocrine, neurologic, and musculoskeletal derangements, which can all be comprised by

mismanagement of FRDA patients. Comprehension of potential complications and management of this population improves patient safety and outcomes.

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## Anesthetic Implications for Patients with Friedreich's Ataxia

Clara Hoss, SRNA



## Introduction

- First introduced in 1863 by Nikolaus Friedreich, a German pathologist
- **Friedreich's ataxia (FRDA) is an inherited autosomal recessive neurodegenerative ataxic disorder**
- Most common ataxic disorder of hereditary

[Schulz & Pandolfo, 2013; St John Sutton et al., 2013]



## Pathophysiology

- Two types of FRDA exist:
  1. 96% being homozygous caused by a defect in the GAA trinucleotide repeat expansion in the first intron of the frataxin (FXN) gene on the long arm of chromosome 9q21.11
    - Patients unaffected by FRDA have typically less than 12 repeats, but can have up to 60.
    - FRDA patients have on average repeats of 600 to 900, however can range to over 1,500.
  2. 4% being heterozygous causes by a point mutation or exonic deletion
    - Display some atypical clinical features, less severe dysarthria but increased incidence of optic nerve atrophy

[Arbustini et al., 2019; Koennen, 2011; Selvadurai et al., 2017]



## Pathophysiology

- The FXN mutation causes a reduction in the mitochondrial frataxin protein that is associated with iron homeostasis
  - Frataxin is found throughout the body, but predominantly in the central nervous system, myocardium, skeletal muscle, and pancreas
- **Low levels of frataxin and defective iron regulation causes dysfunction of:**
  - **iron-sulfur clusters in mitochondrial respiratory chain complexes I, II, & III**
  - **oxidative stress**
  - **reduced mitochondrial ATP production**
  - **iron accumulation in the mitochondria**

[Cook & Giunti, 2017; Dantham et al., 2018]



## Prevalence of FRDA

- Prevalence rate in the United states is predicted to be 1 in 80,667
  - Increased prevalence rates in European countries
  - Mainly affects the Caucasian population
  - Rare in the Sub-Saharan African & Far East populations
- Affects males and females equally

[Vankar, 2013]



## Case Information

- **Surgical Procedure**
  - Posterior spinal fusion and instrumentation of thoracic 2 through lumbar 4 with thoracic osteotomies
- **Pertinent patient information**
  - 30 year old male
  - 70kg, 71cm
  - ASA 3
  - Allergies: codeine, cats, and dogs
  - Home medications: acetaminophen 500mg, ferrous sulfate 325mg, sildenafil 20mg



### Pre-operative Evaluation

- Past Medical History
  - FRDA, chronic pain, MRSA, daily THC use
- Surgical History
  - Cardiac defibrillator placement
  - Teeth extraction
- Pre-op VS
  - BP 95/59, HR 88, RR 18, RA O2 sat of 96%, temp 98.6
- Pertinent labs/ EKG/chest X-ray, etc.
  - H:H 12.3/37.9%, K+ 3.9, glucose 97, creatinine 0.79, all other labs WNL
  - Thoracic x-ray exhibited a 27 degree convex left curve of T6 through T11 and chronic wedging of right T8 and T9 with osteophytes
  - 12-lead ECG – sinus rhythm with ST and T wave abnormalities
  - Echo – EF of 59% with concentric hypertrophy and mild tricuspid regurgitation
- Airway evaluation
  - Mallampati II, full ROM of neck, mouth opening and thyromental distance > 3 fingerbreadths

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### Anesthetic Course

- Premedication
  - Midazolam 2mg
- Induction
  - Fentanyl 100mcg
  - Lidocaine 100mg
  - Propofol 200mg
  - Rocuronium 30mg
- Technique
  - Easy BMV, elective video C-MAC with D-Blade and 8.0 ETT
  - Video visualization, +BBS, chest rise, +EtCo2
- Ventilator settings
  - Volume control
  - Tidal volume : 600mL
  - Respiratory rate: 10bpm
  - PEEP: 5
- Maintenance
  - Sevoflurane 0.5 MAC
  - Propofol 75mcg/kg/min
  - Remifentanyl 0.2-0.3mcg/kg/min
  - Phenylephrine gtt
- Additional medications
  - TXA 1g bolus, followed by 2mg/kg/hr gtt
  - ofirmev 1g, x2
  - ketorolac 30mg
  - Dexamethasone 5mg
  - Ondansetron 4mg
- Reversal
  - None

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### Intraoperative Issues

- Surgical course was uneventful
  - Vital signs stable with minimal use of phenylephrine gtt
  - SSEPs/MEPs severely deranged r/t FRDA
- Total anesthesia time
  - 9 hours and 25 minutes
- Fluids
  - Crystalloids 1,700mL
  - Colloids 750mL
  - Cell saver 500mL
- Estimated blood loss
  - 700mL

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### PACU

- Awake extubation was preformed in the operating room
- Placed on simple mask with 10L/min of oxygen
- Transferred to inpatient room after 1 hour in PACU
- Inpatient stay was complicated by pain and substance abuse withdrawal issues

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### Presentation of FRDA

- Typically between the ages of 10-15
  - Late onset can occur after age 25
- **Initial symptoms**
  - Gait imbalance
  - Ataxia in extremities
  - Areflexia
  - + Babinski reflex
- **Progressive symptoms**
  - Truncal ataxia
  - Paraplegia
  - Dysarthria
  - Dysphagia
  - Nystagmus
  - Optic Neuropathy
  - Hearing loss
  - Reduced proprioception
  - Cognitive deficits

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(Asar et al., 2017; Cook & Giunti, 2017)

### Common Comorbidities

- Cardiomyopathies
  - 80% of patients
  - LV concentric remodeling
  - Leading cause of death
- Diabetes mellitus
  - 5-40% of patients
- Pulmonary
  - Decreased vital capacity, & increased airway resistance, & dyspnea r/t scoliosis
  - Increased risk of OSA
- Scoliosis
  - 63-100% of patients
  - Thoracic, thoracolumbar, & double major curves

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(Greenley et al., 2014; Weidemann et al., 2013; Trifiro & Smith, 2012)

### Diagnosis

- Diagnosis of FRDA is based on clinical presentation along with the following:
  - Genetic molecular analysis
  - Lateral flow immunoassay & Luminex xMAP immunoassay
  - MRI
    - Brain & spinal column
    - Cardiac
  - EKG
  - Echocardiogram
  - Evoked Potentials

(Deutsch et al., 2014; Hanson et al., 2019; Hoffman-Zacharka et al., 2016; Martinez et al., 2018; Tsirikos & Smith, 2012)

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### Treatment options

- **No cure for FRDA**
- Management of symptoms
- Holistic care
  - OT, PT, ST, psychiatry
- Surgical
  - Spinal, orthopedic, and cardiac
- Pharmacological
  - Muscle relaxation, antioxidant supplementation, cardiac, & endocrine
- Clinical monitoring
  - EKG, echo, hearing & visual screening, HbA1c

(Cook & Glunt, 2017; Keage et al., 2017; Tsirikos & Smith, 2012)

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### Preoperative Considerations

- Comprehensive assessment
  - Multi-system disease process with various comorbidities
- Laboratory analysis
  - BMP, CBC, consider creatinine kinase, myoglobin
  - Lactic acid, ABGs
- Neurologic exam
  - Sensory & motor
- Cardiac
  - 12 – lead EKG
  - Echocardiogram
  - Presence of cardioverter-defibrillator
- Pulmonary Function
  - Chest X-ray
  - Pulmonary function tests

(Azar et al., 2017; Hines & Marshchall, 2018; Katz & Murphy, 2017; Sutton et al., 2013)

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### Intraoperative Considerations

|  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Goals                             <ul style="list-style-type: none"> <li>• Maintain cardiovascular function</li> <li>• Respiratory function</li> <li>• Euvolemia</li> <li>• Normothermia</li> <li>• Glycemic control</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Monitoring                             <ul style="list-style-type: none"> <li>• Standard noninvasive</li> <li>• Arterial line</li> <li>• Labs                                     <ul style="list-style-type: none"> <li>• H:H, electrolytes, ABGs, lactate</li> </ul> </li> <li>• Neuromuscular</li> <li>• Bispectral index</li> </ul> </li> </ul> |
|--|--|

(Azar et al., 2017; Gurajala et al., 2013; Hines & Marshchall, 2018)

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### Neuromuscular Blockers

- FRDA is a neurodegenerative disease
  - Avoidance of depolarizing neuromuscular blockers
  - **Risk of hyperkalemic episode if administered**
- Response to Nondepolarizers may be varied
  - May have **increased sensitivity to NDMB**
  - Consider a reduce amount
  - Be cognizant of co-administered medications and the potential to potentiate block
- Reversal
  - Case report by Guclu et al. (2014) reported use of sugammadex with no adverse effects in FRDA patient
  - Sugammadex safely used in other neuromuscular disorders
  - Did not find data on neostigmine, however it has been safely used in ALS patients

(Glick et al., 2014; Katz & Murphy, 2017; Nierwoda & Morgan, 2013; Romero & Joshi, 2018)

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### Anesthesia

- Volatile agents
  - May have increased sensitivity
  - Caution with selection if LVOT is present
- IV agents
  - Propofol & thiopental induction doses are considered safe
  - Long term used of propofol may increase risk of propofol infusion syndrome
- Narcotics
  - Considered safe, however avoid morphine
  - Consider respiratory status
- Fluids
  - Normal saline
  - Colloids
  - Blood loss – transfusions, antifibrinolytics, cell saver

(Nierwoda & Morgan, 2013; Romero & Joshi, 2013; Vanlander & VanCoster, 2018)

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### Local Anesthetics

- **Regional/neuraxial may be safest route if available for proposed surgery**
  - Avoids risk of possible ventilator dependence postoperatively
- May be technically difficult related to scoliotic changes
- Consider respiratory status
  - Blocks higher than T10 can compromised respiratory muscle involvement
  - May reduce narcotic consumption when combined with a general anesthetic
- Multiple cases reports have reported successful and safe use of regional/neuraxial blocks
  - Barbary et al. (2012): bilateral popliteal fossa blocks
  - Ganesan (2011): scrotal field block
  - Huercio (2014): combined spinal/epidural

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(Barbary et al., 2012; Ganesan, 2011; Hines & Marschall, 2018; Huercio, 2014)

### Evoked Potentials

- Tsirikos & Smith (2012) found that **MEPs and SEPs are usually significantly reduced or absent in FRDA patients**
- Autopsy reports by Koeppen (2011) found that FRDA patients sural nerves had **inadequate or absence of myelin sheaths & abundant axons** but small in size
- A study by Sival et al. (2009) found that **median nerve SEPs were absent in all participants** and discernable sural nerve action potentials were observed in 50% of children at start of study, but absent after 2 years
- Milbrandt et al. (2008) **found the SEPs monitoring is ineffective** and if neurological compromise is anticipated, wake-up tests should be planned

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(Koeppen, 2011; Milbrandt et al., 2008; Sival et al., 2009; Tsirikos & Smith, 2012)

### Conclusion

- FRDA can present with a variety of presentations that requires a thorough history and assessment by the CRNA to tailor a patient specific anesthetic plan
- Awareness of disease process & potential complications allows anesthesia providers to react appropriately
- Provider must be cognizant when selecting an anesthetic route, with diligent monitoring when using neuromuscular blockers, volatile agents, & neuraxial anesthesia
- Avoid factors that may increase risk of neurological damage, LVOT, and respiratory insufficiency
- Monitor closely postoperatively
  - may require cardiac & respiratory support
  - pain and endocrine control
  - May require admission to critical care for observation

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Thank You

Are There Any Questions?

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