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Case Report

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Intraoperative Cardiac Arrest: Immediate Treatment and Diagnostic Evaluation

Nathan Fister[a, d], Ahsan Syed[b, c], Joseph D. Tobias[b, c]

Abstract

Although perioperative cardiac arrest during anesthetic care in infants and children is a rare event, its consequences can be devastating. Risk factors associated with perioperative cardiac arrest include cardiac surgery, younger age, presence of comorbid conditions and emergency surgery. Although medication-related etiologies formerly predominated, the elimination of halothane from anesthetic care has resulted in a shift in etiology to hemodynamic events related to blood loss or hyperkalemia associated with the rapid administration of blood products. Rarely, cardiac arrest can be sudden and unexpected without an obvious pre-existing etiology in an otherwise apparently healthy patient. We present a 16-month-old child who experienced a sudden cardiac arrest following anesthetic induction for a routine urologic procedure. The potential etiology of cardiac arrest during anesthesia is reviewed, keys to resuscitation discussed, and an outline for the investigative work-up presented.

Keywords: Cardiac arrest; Pediatric anesthesia; Cardiomyopathy

Introduction

Intraoperative cardiac arrest is a rare yet devastating complication of anesthesia in children with an estimated incidence of 2.9 per 10,000 cases in non-cardiac surgery [1]. The Perioperative Cardiac Arrest (POCA) Registry was formed in 1994 to study the causes and outcomes from perioperative cardiac arrest during anesthetic care [2]. Initially, medication-related cardiac arrests, particularly those due to the cardiovascular depressant effects of halothane, were most common. However, as halothane has been replaced in anesthetic practice by sevoflurane, the etiology of perioperative cardiac arrest has shifted to blood loss and hyperkalemia associated with the rapid administration of blood and blood products [3-5]. Rarely, cardiac arrest can be sudden and unexpected without an initially obvious etiology in an otherwise apparently healthy patient. We present a 16-month-old child who experienced a sudden cardiac arrest following anesthetic induction for a routine urologic procedure. The potential etiology of cardiac arrest during anesthesia is reviewed, keys to resuscitation discussed, and an outline for the investigative workup presented.

Case Report

Preparation of this case report followed the guidelines of the Institutional Review of Nationwide Children's Hospital (Columbus, OH). The patient was a 9.75 kg, 16-month-old male with bilateral cryptorchidism who presented for second stage orchidopexy. There were no perinatal concerns and the patient was born at 39 weeks via normal spontaneous vaginal delivery. The patient's past medical history was unremarkable with no previous hospitalizations. There were no acute or chronic medical conditions and he was not receiving any medications. The first stage of the orchidopexy was performed at 10 months of age with a combined spinal-caudal epidural anesthesia without issues [6]. The second stage orchiopexy was scheduled 6 months after the initial orchiopexy. The patient was held *nil per os* for 6 h and evaluated preoperatively by the attending anesthesiologist. The patient was transported to the operating room where routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced with the inhalational of incremental concentrations of sevoflurane in nitrous oxide and oxygen. After the induction of anesthesia, a peripheral intravenous cannula was placed, propofol (15 mg) administered, and a size 2 laryngeal mask airway (LMA) placed. The patient was then turned to the right lateral position for placement of a single shot, caudal epidural block to provide postoperative pain relief. Following positioning, a decrease in the blood pressure (BP) was noted from 66/47 to 41/32 mm Hg followed by a decrease in the heart rate (HR) from a baseline of 150 - 160 to 130 beats/min. This was followed by a change in the waveform and dampening of the pulse oximetry plethysmograph. At this time, sevoflurane and nitrous oxide were discontinued and the patient was ventilated with 100% oxygen. The pulse oximetry probe was moved to another site without success in an attempt

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[a]Heritage College of Osteopathic Medicine, Dublin, OH, USA
[b]Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, OH, USA
[c]Department of Anesthesiology and Pain Medicine, The Ohio State University College of Medicine, Columbus, OH, USA
[d]Corresponding Author: Nathan Fister, Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA. Email: nf365511@ohio.edu

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to obtain a better waveform. Lactated Ringers (50 mL) was administered as a bolus. As the HR continued to decrease from 80 to 40 beats/min, the oxygen saturation decreased to 10-20%, and peripheral pulses were not detectable. A diagnosis of pulseless electrical activity (PEA) was made and cardiopulmonary resuscitation (CPR) initiated with chest compressions and the administration of atropine (0.02 mg/kg) and epinephrine (10 µg/kg). The patient's trachea was intubated. Throughout the resuscitation, the end-tidal carbon dioxide (ETCO2) remained ≥ 20 mm Hg. Two subsequent doses of epinephrine (10 µg/kg) were administered at 3 min intervals and CPR was continued. Nine minutes after the initiation of CPR, there was return of spontaneous circulation (ROSC). A fluid bolus (30 mL/kg of isotonic fluid) was administered. After resuscitation and stabilization, the surgical procedure was cancelled and arrangements were made to transfer the patient to the pediatric intensive care unit (PICU).

Following admission to the PICU, the initial workup included an echocardiogram that revealed moderate depression of left ventricular systolic function, mild depression of the right ventricular systolic function, mild mitral regurgitation, a patent foramen ovale and a borderline concentric left ventricular hypertrophy. Given the findings on the echocardiogram, cardiology consultation was obtained. There was a concern for a pre-existing, subclinical cardiomyopathy and a suspected mitochondrial disorder. Additional evaluation revealed mildly elevated liver function tests with an aspartate aminotransferase (AST) 159 IU/L and alanine aminotransferase (ALT) 106 IU/L. An abdominal ultrasound revealed echogenic changes in the liver with hepatic steatosis and nodularity that were compatible with a mitochondrial disorder with hepatic involvement. Further workup including a muscle biopsy, liver biopsy, and mitochondrial DNA (mtDNA) were normal and therefore not suggestive of an underlying mitochondrial disorder. Subsequent workup including magnetic resonance imaging (MRI) of the brain showed Leigh-like heterogeneous white matter signals with diffuse changes in the white matter tracks. Additional workup included normal serum ammonia, serum amino acids, and urine organic acids. A Baylor whole exome sequencing (WES) test identified the presence of a paternally-inherited heterozygous pathogenic variant in the DNA polymerase subunit gamma (*POLG*) gene. The patient's PICU course was somewhat protracted with myocardial dysfunction requiring ongoing endotracheal intubation and the administration of epinephrine and milrinone. Following tracheal extubation, respiratory support was provided by bilevel positive airway pressure (BiPAP) for an additional 2 - 3 days. The vasoactive agents were slowly weaned off and the patient transitioned to oral enalapril.

At the time of hospital discharge and subsequent follow-up, his myocardial function remained stable with a recent echocardiogram showing low normal function, moderate hypertrophy without dilation of the left ventricle, and mild mitral valve regurgitation without pericardial effusion. The patient continues to have gastrointestinal symptoms including intermittent vomiting and mild gross motor function delay, which are being managed as an outpatient. He is gaining weight and reported to be doing well. His clinical features are thought to be most consistent with a disorder of mitochondrial oxidative phosphorylation with a presumptive clinical diagnosis of Leigh syndrome of unknown molecular etiology.

Discussion

The etiology of perioperative cardiac arrest in children has shifted from medication-related causes, primarily halothane, to etiologies related to the respiratory or cardiovascular system. Respiratory causes of cardiac arrest are primarily related to difficulties with airway management, failed endotracheal intubation, upper airway obstruction or other pathology that prevents effective airway management leading to inadequate oxygenation and ventilation. Cardiovascular causes of perioperative cardiac arrest are primarily related to hypovolemia due to blood loss and hyperkalemia related to the rapid administration of blood. These cardiovascular causes of perioperative arrest now predominate as the primary causes of perioperative cardiac arrest in infants and children [3-5].

The outcome following cardiac arrest in the pediatric population is related to a number of factors including the efficacy of the resuscitation, location of the arrest, comorbid conditions, and the age of the patient [7, 8]. In-hospital arrests are associated with the improved chances for survival due to a rapid response and a reduced time from the onset of the arrest to the initiation of effective CPR. An effective and immediate response to cardiac arrest is key in ensuring the best possible outcomes [9, 10].

Following cardiac arrest, effective resuscitation is dependent on various modifiable factors including early airway management, prompt administration of epinephrine, and effective CPR. The ultimate goal of CPR is to minimize the time during which there is inadequate blood flow and restore oxygen delivery to the brain and other vital organs. Even with CPR under ideal circumstances and high quality manual chest compressions, cardiac output is estimated to be 20-30% of normal, therefore making the prompt ROSC necessary to ensure optimal outcomes [11]. Indications for the initiation of CPR in the perioperative period include concerns regarding the adequacy of HR, BP or cardiac output as judged by clinical assessment and monitoring equipment including continuous electrocardiography, BP, ETCO2, and pulse oximetry [12]. The depth and rate of chest compressions should follow standard Pediatric Advanced Life Support (PALS) guidelines with a compression depth of 1.5 inches (4 cm) in infants and 2 inches in children from 1 year of age to adolescence at a rate of 100 - 120 per minute [12]. The efficacy of chest compressions and resuscitative efforts can be judged by monitoring ETCO2 and diastolic BP. Improved outcomes and ROSC have been shown to correlate with an ETCO2 ≥ 15 - 20 mm Hg and diastolic BP ≥ 25 mm Hg [13-15]. Failure to achieve these goals should result in an evaluation of the efficacy of chest compressions and the resuscitative efforts. Additionally, the use of new defibrillators with pads that guide the efficacy of chest compressions and provide instantaneous provider feedback may help ensure the adequacy of resuscitation.

During resuscitative efforts, unless emergent care is needed to reverse the cause of the arrest such as bleeding, surgical

intervention should be stopped. Anesthetic agents which may negatively impact myocardial function or resuscitative effects should be stopped and the patient ventilated with 100% oxygen unless there are specific concerns in patients with congenital heart disease in which 100% oxygen may negatively affect systemic cardiac output [16]. Rapid airway control with assisted or controlled ventilation is indicated to reverse or prevent hypoxemia and hypercarbia. Although this is generally best accomplished with endotracheal intubation as was the case with our patient, there are limited data to demonstrate differences in outcome based on the technique of airway management [17]. Ventilation is controlled to achieve normocarbia while excessive ventilation resulting in hypocarbia should avoided given its deleterious effects on cerebral perfusion [18].

The electrocardiogram (ECG) should be assessed and a shockable (ventricular tachycardia or fibrillation) differentiated from a non-shockable rhythm (PEA and asystole). A non-shockable rhythm indicates the need for prompt initiation or continuation of chest compressions along with the administration of epinephrine in a dose of 10 µg/kg. The early administration of epinephrine has been shown to directly correlate with ROSC [19]. If intravenous access is not readily available, an intraosseous (IO) needle should be placed and epinephrine administered via the IO route to avoid delays in resuscitation [20]. An ECG demonstrating a shockable rhythm requires the administration of a shock (2 - 4 J/kg) followed by immediate resumption of high quality chest compressions.

The current case highlights the potential for a previously undiagnosed genetic or metabolic condition to present as a sudden cardiac arrest as well as the need for a thorough evaluation to identify uncommon etiologies for the event. The *POLG* gene is located on the long arm of chromosome 15 at position 26.1. It codes the α subunit of polymerase γ (pol γ or POLG) which binds with two copies of the β subunit to form a DNA polymerase that functions primarily in the mitochondria. DNA polymerases play a key role in replicating cellular genetic material for repair of DNA. Each mitochondrion contains a small amount of DNA, known as mitochondrial DNA (mtDNA). Pol γ is the only DNA polymerase that is active in mitochondria, replicating and repairing mtDNA. Defects in the *POLG* gene can affect mitochondrial function with involvement of the central nervous system (CNS), liver, skeletal, and cardiac muscle [21-25]. Various disorders have been characterized related to mtDNA depletion in patients carrying *POLG* gene mutations. These disorders comprise a spectrum of overlapping clinical signs and symptoms, ranging from a rapidly fatal infantile cerebro-hepatic form to progressive external ophthalmoplegia that may not present until the fifth to sixth decade of life. The reader is referred to reference 23 for a more in-depth discussion of these novel disorders of the *POLG* gene, clinical presentation, and diagnostic workup [23].

Clinical features, some of which were noted preoperatively in our patient, that increase the suspicion of a *POLG* gene related disorder include hypotonia, developmental delay, seizures, movement disorders, myopathy, ataxia, peripheral neuropathy, psychiatric illness, and endocrinopathies. Abnormalities in hepatic function, especially following exposure to antiepileptic drugs may be associated with *POLG* gene related disorders. Cardiac involvement with arrhythmias or progressive myocardial dysfunction occurs in approximately 30% of patients with genetic disorders of mitochondrial function [26]. In our patient, the usually well tolerated effects of sevoflurane on myocardial contractility resulted in the cardiac arrest given the underlying baseline depression of myocardial function [27]. Given the intricacies involved with diagnosis and genetic testing, consultation with a pediatric genetics specialist is recommended [28].

In summary, we present an unexpected and sudden cardiac arrest related to a *POLG* gene depletion in a previously healthy 16-month-old toddler. The keys to successful resuscitation during intraoperative arrest include strict adherence to PALS guidelines including prompt airway management, the rapid administration of epinephrine, and high quality chest compressions. Following resuscitation, a thorough workup following may uncover previously undiagnosed and rare genetic or metabolic disorders.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Author Contributions

Nathan Fister: preparation of initial, subsequent, and final drafts. Ahsan Syed: review of final draft, perioperative care of patient. Joseph Tobias: concept, review of all drafts.

Abbreviations

POCA: perioperative cardiac arrest; BP: blood pressure; ROSC: return of spontaneous circulation; HR: heart rate; ETCO2: end-tidal carbon dioxide; CPR: cardiopulmonary re-

suscitation; ICU: intensive care unit

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