PBLD – Table #38: Sunday, March 9, 2014; 7:00-8:10 am

A patient with a prolonged QT interval and Timothy Syndrome

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Objectives:

- Review etiology, classification, associations and implications of long QT syndrome (LQTS) variants
- Plan anesthetic care of a child with complex medical needs including LQTS
- Understand perioperative management of a permanent pacemaker and implanted defibrillator
- Appreciate the role of regional anesthesia in LQTS patients

Case History:

A 2-year old, 11.4 kg male with a new diagnosis of Timothy Syndrome presents for elective dental restoration. Medical history includes prolonged QTc interval at 535 ms, second-degree heart block, hypertrophic cardiomyopathy, hypotonia, severe developmental delay, and a resistant seizure disorder characterized by apneic episodes.

Questions:

What is Timothy Syndrome? What are long QT syndromes? What types are there? How is the diagnosis made?

What are the anesthetic implications of the prolonged QT interval? What is the change in the electrophysiological status of the heart that it reflects? Which arrhythmias may occur? How should they be managed? Are there any other implications of Timothy Syndrome?

Case History and Physical Examination (continued):

The patient follows a strict ketogenic diet, and is receiving clonazepam, diazepam, levetiracetam, vigabatrin, and propranolol with the aim of decreasing his seizures and preventing further prolongation of his QT interval. He is also on taurine, calcium and vitamin D supplements, esomeprazole, furosemide (10 mg BD), plus acetaminophen and ibuprofen as required. Past surgical history includes implantation of a permanent pacemaker and cardiac defibrillator with cardiac sympathectomy and ligation of patent ductus arteriosus at one month of age. Lumbar puncture, flexible bronchoscopy, orchidopexy, and PEG tube insertion have

also been performed previously under general anesthesia. According to his parents, previous anesthetics led to post-operative ictal apneic episodes requiring airway management. The family stated that they did not want too much intraoperative fluid given, as the patient had required an extra dose of furosemide after his orchidopexy.

The patient has severe osteopenia. He was evaluated in the chronic pain clinic last month for recurrent episodes of crying, grimacing and screaming. No obvious cause was found, but poor dentition and multiple caries were noted.

Vital signs include a room air saturation of 99%, heart rate of 100/minute, respiratory rate of 24/minute, and blood pressure 114/88 mmHg.

On physical examination, the patient is resting comfortably without distress. There is a pectus excavatum deformity, a well-healed left lateral thoracotomy scar and a firm mass in the right subcostal position, consistent with a pacemaker/defibrillator generator. Cardiac exam is unremarkable, with no murmurs, gallop or rubs. Lungs are clear to auscultation. A gastrostomy tube is visible in the upper left quadrant of the abdomen. The patient is generally hypotonic but moves all extremities spontaneously. Marked developmental delay is evident: he makes occasional vocalizations but does not form words.

Questions:

Are there any anesthetic implications of the patient's ketogenic diet? Do the medications raise any concerns? What other questions would you like answered before taking this patient to the OR for anesthesia? What drugs affect the QT interval? What is your induction plan? What monitors do you require for this case? Will you take any special precautions? Are there any studies that you would like to see before proceeding?

Preoperative Studies:

The last echocardiogram, performed 7 months prior to surgery, shows mild asymmetric septal hypertrophy without obvious left ventricular outflow tract obstruction, systolic anterior motion of the mitral valve or left ventricular intracavitary gradient. Left ventricular systolic performance is qualitatively low normal. There is trivial tricuspid regurgitation producing a jet estimating a right ventricular pressure of 15 mmHg + central venous pressure. There is <50% collapse of the inferior vena cava with respiration. Tricuspid annular plane systolic excursion (TAPSE) is below normal limits at 1.01cm. Valve function is otherwise normal and there is no pericardial effusion. The findings are essentially stable since the previous echocardiogram of 6 months prior.

An electrolyte panel from 10 weeks ago is normal except for a K of 3.2 mmol/l (ref. 3.3-4.7), Cl of 90 mmol/l (ref. 98-107), creatinine of 0.08 mg/dl (ref. 0.17-0.35) and anion gap of 20 mmol/l (ref. 4-15).

At the same time, cholesterol was 432 mg/dl (ref. 37-178) and triglycerides 834 mg/dl (ref. 25-119). β-hydroxybutyrate was 94.1 mg/dl (ref. 0.0-3.0).

CBC, also performed 10 weeks prior, shows WBC 7.0, Hgb 12.8, Hct 35.9%, Plt 356.

Blood type is A, Rhesus D positive with negative antibody screen (last checked 2 years ago).

Questions:

Will you proceed without repeating labs? What is the relevance of the lipid panel and β-hydroxybutyrate results?

What is the significance of the echocardiographic findings, in particular the abnormal IVC collapse and TAPSE?

What will you do with the pacemaker? Does its defibrillator function make any difference to your plan?

Case Progression:

You ensure that all anti-epileptic medications are administered on the morning of surgery. The consulting cardiac electrophysiologist checks the pacemaker. Lead impedances and capture thresholds are stable. They advise switching to AAI mode at a rate of 70/min with arrhythmia detection left functioning.

You undertake an inhalational induction with sevoflurane, and secure peripheral IV access. You administer cisatracurium and commence remifentanil infusion at 0.1 mcg/kg/min. You place an endotracheal tube via the nasal route.

Questions:

What are your concerns for intraoperative management of a patient with a prolonged QT interval? What is your plan for maintenance of anesthesia? Is there a role for regional anesthetic techniques? What precautions are advisable to take in caring for this patient? Do you plan to extubate the patient at the end of the case? Do you think the patient should recover in the PACU and then the floor, or should he be directly transported to CICU for recovery and care?

Intra-operative Course:

Sevoflurane anesthesia is maintained at 0.5 MAC, along with remifentanil infusion at 0.1 mcg/kg/min. A full dental clearance is performed. A skin biopsy is taken for a research study. Vital signs remain stable without tachycardia or further prolongation of the QT interval over the 105-minute case.

The child's parents are adamant that local anesthetics must not be administered. Morphine and acetaminophen are given for pain relief.

At the end, sevoflurane and remifentanil are discontinued, and the patient is extubated awake. Neuromuscular reversal agents are purposefully withheld due to their propensity to prolong the QT interval; anti-emetic prophylaxis is likewise limited to dexamethasone. The patient is transported uneventfully to the Cardiac Intensive Care Unit where a safe-handoff is performed. Later in the afternoon the EP service reprograms the pacemaker back to VVI mode with a backup rate of 50/min. There are no complications and the patient is discharged home one day later.

Discussion:

Congenital long QT syndromes (cLQTS) are classified on a genetic basis. The most prevalent, LQT1 and LQT2, involve K^+ channels, and LQT3 affects Na^+ channels.

Timothy Syndrome (TS) has been classified as LQT8, and results from a de novo missense mutation in the 1.2 L-type Ca^{2+} channel *CACNA1C* gene on chromosome 12p13.3. Average life expectancy is only 2½ years with death most commonly due to lethal arrhythmias. (This patient unfortunately succumbed at 3¾ years of age.)

TS is an autosomal dominant disorder and was described only in 2004. It is characterized by prolonged QT interval, syndactyly, immune deficiency, and intermittent hypoglycemia. Typical facial features include low-set ears, flat nasal bridge, small upper jaw, and small abnormal teeth. Neurological sequela include mental retardation, hypotonia, seizures, and autism. Most reported patients have presented in the newborn period. Usually there are no other affected family members, but there has recently been reported a mosaic mother suffering from isolated syndactyly and carrying the mutation in just a proportion of her cells. TS is especially associated with malignant dysrhythmias under anesthesia.

β-blockade decreases cardiac events and reduces mortality in LQT1, LQT2, and TS, but is contraindicated in LQT3. ICDs are placed if β-blockade fails to decrease syncopal events and cardiac arrest events. Of note, 25% continue to suffer arrhythmias despite β-blockade and ICD placement. These patients are candidates for left cardiac sympathetic denervation to reduce arrhythmogenic potential.

The primary anesthetic goal is limiting further QT prolongation, though this is really only a surrogate measure for the dispersion of transmural repolarization, which represents the underlying substrate for arrhythmia in both congenital and acquired LQTS. It is important to avoid any drugs that prolong the QT interval (see examples in the Table below). Such drugs tend to prolong the rapidly activating delayed rectifier potassium current (I_{Kr}) of the cardiac action potential. In general, prescribed antiarrhythmics should be continued throughout the perioperative period.

Although volatile anesthetics prolong the QT interval in healthy individuals, they have been successfully used in β-blocked individuals with certain LQTS. Midazolam and ketamine do not cause QT prolongation. Propofol inhibits both potassium and calcium currents during the cardiac action potential, but appears not to prolong the QT interval at clinically appropriate doses. The ideal muscle relaxant should avoid

bradycardia, vagal stimulation, and potassium shifts. It should cause little or no histamine release. Short duration of neuromuscular blockade obviates a need for combination anticholinergic-anticholinesterase reversal agents, which are known to increase the QT interval. Succinylcholine also increases the QT interval. Pancuronium should be avoided due to its vagolytic properties and demonstrated effect on QT. Vecuronium and atracurium show no effect on the QT interval. Opioids can affect the QT interval, but fentanyl and morphine have been used safely in patients with pre-existing QT prolongation. Ondansetron, and other 5-HT_3 antagonist anti-emetics licensed for pediatric use, should be avoided. Dexamethasone and metoclopramide are probably safe.

Arrhythmias may be triggered by increased sympathetic nervous system output, especially in LQT1 and LQT2. By contrast, in LQT3, cardiac pauses during sleep or while resting are liable to trigger arrhythmias. Accordingly for LQT1/2 it is vital to avoid abrupt and loud noises, light anesthesia, hypertension, tachycardia, hypoxemia, and hypercapnea, which affect repolarization of cardiac myocytes and augment sympathetic tone. Bradycardia must be avoided in LQT3. Hypokalemia, hypomagnesemia, and hypocalcemia are all associated with prolongation of the QT interval. Hypothermia prolongs the recovery of inactivated sodium channels resulting in QT prolongation. Hypothyroidism has a similar effect. Adjuvants, such as epinephrine, which can themselves prolong the QT interval must however be avoided. Regional anesthesia may be beneficial. Successes with both spinal and epidural anesthesia in LQTS patients have been reported. For this case, we balanced volatile anesthesia with remifentanil to avoid sympathetic nervous system output and thus prevented further prolongation of the QT interval.

Torsades de pointe (TdP), a polymorphic ventricular tachycardia, is the arrhythmia classically associated with QT prolongation. If TdP is accompanied by cardiovascular collapse intraoperatively, immediate asynchronous cardioversion is indicated. TdP carries a substantial risk of degeneration into ventricular fibrillation. Hence even well-tolerated TdP warrants treatment. Magnesium sulfate is the drug of choice, administered as a 30 mg/kg bolus over 2-3 min followed by an infusion. This drug is indicated even if magnesium levels are within the normal range, as serum measurements are poorly reflective of intracellular levels. Standard ACLS protocols should be modified in TdP associated with LQTS to include early use of magnesium. Similarly, amiodarone is best avoided in such cases, due to its prolongation of the QT interval.

Timothy Syndrome is a rare condition mandating careful preparation and vigilance throughout the perioperative period. It is essential to avoid triggering agents and electrolyte imbalances that might further prolong the QT interval. Appropriate measures include premedication with midazolam, a quiet operating room for induction, and a balanced anesthetic avoiding triggering agents. In general, LQTS patients should be discussed on an individual basis with their cardiac electrophysiologist, in order that a tailored anesthetic plan can be devised, including an optimal strategy for managing arrhythmias that may occur during the case.

Table:

Drugs well documented to prolong the QT interval			
Cardiac: • amiodarone • bepridil • disopyramide • dofetilide • ibutilide • procainamide • quinidine • sotalol	Antimicrobials: • clarithromycin • erythromycin • grepafloxacin • pentamidine • sparfloxacin	Psychotropics: • chlorpromazine • haloperidol • mesoridazine • pimozide • thioridazine	Miscellaneous: • droperidol • haloperidol • methadone
Drugs with moderate association or case reports of QT prolongation			
Cardiac: • flecainide • moexipril • nicardipine • isradipine	Antimicrobials: • azithromycin • foscarnet • gatifloxacin • levofloxacin • moxifloxacin	Psychotropics: • lithium • quetiapine • risperidone • venlafaxine • ziprasidone	Miscellaneous: • amantadine • octrotide • ondansetron • salmeterol • dolasetron
Drugs with potential increased potential risk in LQTS patients			
Cardiac: • dobutamine • dopamine • ephedrine • epinephrine • isoproterenol • midodrine • norepinephrine • phenylephrine		Miscellaneous: • albuterol • levalbuterol • phenteramine • pseudoephedrine • ritodrine • terbutaline	

References:

Gillis J, Burashnikov E, Antzelevitch C, Blaser S, Gross G, Turner L, Babul-Hirji R, Chitayat D: Long QT, Syndactyly, joint contractures, stroke and novel CACNA1C mutation: Expanding the spectrum of Timothy Syndrome. *American Journal of Medical Genetics* 2012; **158A**: 182-187

Homme JH, White RD, Ackerman MJ: Management of ventricular fibrillation or unstable ventricular tachycardia in patients with congenital long-QT syndrome: A suggested modification to ACLS guidelines. *Resuscitation* 2003; **59**: 111–5

Kies SJ, Pabelick CM, Hurley HA, White RD, Ackerman MJ: Anesthesia for patients with congenital long QT syndrome. *Anesthesiology* 2005; **102**: 204-210

Nathan AT, Berkowitz DH, Montenegro LM, Nicolson SC, Vetter VL, Jobes DR: Implications of anesthesia in children with long QT syndrome. *Anesthesia and Analgesia* 2011; **112**: 163-8

Nathan AT, Antzelevitch C, Montenegro LM, Vetter VL: Case scenario: Anesthesia-related cardiac arrest in a child with Timothy Syndrome. *Anesthesiology* 2012; **117**: 1117-26

Navaratnam M, Dubin A: Pediatric pacemakers and ICDs: how to optimize perioperative care. *Paediatric Anaesthesia* 2011; **21**: 512-21

Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, Joseph RM, Condouris K, Tager-Flusberg H, Priori SG, Sanguinetti MC, Keating MT: Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004; **119**: 19-31

Staikou C, Chondrogiannis K, Mani A: Perioperative management of hereditary arrhythmogenic syndromes. *British Journal of Anesthesia* 2012; **108**: 730-44

Valencia I, Pfeifer H, Thiele EA: General anesthesia and the ketogenic diet: clinical experience in nine patients. *Epilepsia* 2002; **43**: 525-9

www.qtdrugs.org – A useful web-based reference for drugs known to prolong the QT interval