Background:
Timothy Syndrome is an autosomal dominant disorder described only in 2004, and characterized by prolonged QT interval, syndactyly, immune deficiency, and intermittent hypoglycemia. Neurological sequelae include mental retardation, hypotonia, seizures, and autism. All reported patients have presented in the newborn period, with no other affected family members. We present a case illustrating the challenges of providing anesthesia to a patient with Timothy Syndrome.

Case Report:
A 2-year old, 11.4 kg male with a new diagnosis of Timothy Syndrome presented for elective dental restoration. Medical history was significant for prolonged QT interval with a QTc of 535ms (Figure 1), second-degree heart block, moderate left ventricular hypertrophy, hypotonia, severe developmental delay, and a resistant seizure disorder characterized by apneic episodes. To decrease his seizures and prevent further prolongation of his QT interval he was on a strict ketogenic diet, and receiving clonazepam, diazepam, levetiracetam, and propranolol. Past surgical history included implantation of a permanent pacemaker and cardiac defibrillator, cardiac sympathectomy, lumbar puncture, flexible bronchoscopy, orchidopexy, and PEG tube insertion. According to his parents, previous anesthetics at an outside hospital led to post-operative ictal apneic episodes requiring airway management. Physical exam demonstrated severe hypotonia and marked developmental delay.

We ensured that all anti-epileptic medications were administered on the morning of surgery. On our cardiac electrophysiologists’ advice, the pacemaker was switched to AAI mode at a rate of 70/min with arrhythmia detection left functioning. Following inhalational induction with sevoflurane, and securing peripheral IV access, cisatracurium was administered and remifentanil infusion commenced at 0.1 mcg/kg/min. An endotracheal tube was placed via the nasal route. Sevoflurane anesthesia was maintained at 0.5 MAC. Vital signs remained stable without tachycardia or further prolongation of the QT interval over the 105-minute case. Sevoflurane and remifentanil were discontinued, the patient was extubated awake and transported to the Cardiac Intensive Care Unit.

Neuromuscular reversal agents were purposefully withheld due to their propensity to prolong the QT interval. There were no complications and the patient was discharged home one day later.

References:

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 (LQT8) results from a de novo missense mutation in the 1.2 L-type Ca2+ channel CACNA1C gene on chromosome 12p13.3. Average life expectancy is only 2.5 years with death most commonly due to lethal arrhythmias.

β-blockade decreases cardiac events and reduces mortality in LQT1, LQT2, and Timothy Syndrome, but is contraindicated in LQT3. ICDs are placed when β-blockade has failed to decrease syncopal events and cardiac arrest. Of note, 25% continue to suffer arrhythmias despite β-blockade and ICD placement. These are candidates for left cardiac sympathetic denervation to reduce arrhythmogenic potential. The primary anesthetic goal is limiting further QT prolongation. This includes avoidance of drugs which further prolong the QT interval by increasing transmural dispersion of repolarization (Table 1). Although volatile anesthetics prolong the QT interval in healthy individuals, they have been successfully used in β-blocked individuals with cLQTS. The ideal muscle relaxant should avoid bradycardia, vagal stimulation, and potassium shifts. It should cause little or no histamine release. Short duration of action obviates a need for reversal agents, which increase the QT interval. Succinylcholine also increases the QT interval. Pancuronium should be avoided due to its vagolytic properties. Vecuronium and cisatracurium show no effect on the QT interval.

Arrhythmias may be triggered by increased sympathetic nervous system output. It is vital to avoid abrupt and loud noises, light anesthesia, hypertension, bradycardia, tachycardia, hypoxemia, and hypercapnea, which affect repolarization of cardiac myocytes and augment sympathetic tone. Regional anesthesia may be beneficial. For this patient, we balanced volatile anesthesia with remifentanil to avoid sympathetic nervous system output and thus prevented further 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 that might further prolong the QT interval. Premedication with midazolam, a quiet operating room for induction, and a balanced anesthetic avoiding triggering agents, are appropriate.