

Atrial standstill in a pediatric patient with associated caveolin-3 mutation

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Introduction

Atrial standstill (AS), a rare arrhythmogenic condition, is defined by (1) the absence of P waves in surface and intracavitary electrocardiograms (ECGs), (2) the absence of A waves in jugular venous pulse and right atrial pressure tracings, (3) the presence of a supraventricular type QRS complex, (4) the immobility of the atria on fluoroscopy, and (5) the inability to stimulate the atria electrically.¹ Several etiologies have been identified including metabolic derangements, ischemia, drug intoxication, amyloidosis, and muscular dystrophies.¹ The discovery of familial AS leads to the identification of channelopathies involved, particularly *SCN5A* mutations leading to Nav1.5 sodium channel dysfunction.¹ AS is rarely reported in pediatric patients. An 11-year-old with permanent AS was found to have an *SCN5A* mutation; a 3-year-old developed AS transiently after dexmedetomidine infusion; and systemic illness was implicated in an 8-year-old with thiamine-responsive megaloblastic anemia.^{1–3} Here we present a unique case of AS, possibly due to novel caveolin-3 (*CAV3*) mutation, in a pediatric patient whose clinical presentation and progression were unusual.

Case report

An African American male patient presented with palpitations and syncope at the age of 12 years. His ECG initially revealed accelerated junctional rhythm with intermittent isolated ventricular ectopy (Figure 1A). With metoprolol, he had improved ectopy but Holter monitoring and subsequent ECG showed continued junctional rhythm and episodes of nonsustained atrial tachycardia alternating with junctional bradycardia with 3-second pauses (Figure 1B). Further evaluation with echocardiography

showed normal biatrial size with no atrial contraction (Figure 2). Cardiac magnetic resonance imaging showed normal morphology, function, and no delayed myocardial enhancement. Subsequent exercise testing revealed no sinus node activity and no sinus P waves. The rhythm was predominantly junctional with a maximum rate of 184 and episodes of nonsustained atrial tachycardia during exercise and recovery. He also had a 3-second pause during exercise with associated dizziness. Because of these findings and history of fatigue and frequent presyncopal episodes, he was taken off metoprolol, causing improvement in his symptomatic bradycardia but worsening of symptomatic tachyarrhythmia.

An electrophysiology study showed inducible left anterior mitral valve annulus atrial tachycardia, which was successfully ablated (Figure 3A). The left atrium appeared healthy without evidence of electrical scar. The right atrium showed small to no atrial activity with no atrial capture at high outputs. Voltage mapping showed significant right atrial scar (Figure 3B). After ablation, his symptomatic atrial tachycardia resolved but he remained in junctional rhythm with worsened fatigue and exercise intolerance. A repeat ECG showed marked junctional bradycardia without evidence of atrial activity (Figure 1C). Repeat Holter monitoring showed junctional bradycardia with more frequent and longer pauses, up to 5.1 seconds, and episodes of junctional tachycardia.

He underwent a second electrophysiology study 4 months after the initial procedure during planned implantation for a dual-chamber pacemaker. This study showed progressive right atrial disease (Figure 3C) and lack of right atrial sensing or capture with transvenous atrial lead placement attempts, so a single-chamber ventricular pacemaker was placed. This clinical course and findings were consistent with AS.

Since device placement, serial ECGs over 2 years continue to show junctional rhythm and follow-up device checks show chronic ventricular pacing with increasing dependence at 69% with heart rate set at 50 beats/min suggesting disease progression (Figure 1D). His family history is reassuring, but his asymptomatic parents refuse evaluation including ECGs and genetic testing. Because of his unusual course, he underwent genetic testing with comprehensive

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KEY TEACHING POINTS

- Atrial standstill is a rare arrhythmogenic disorder that has previously been associated with systemic disease and specific channelopathies, particularly *SCN5A* mutations.
- Reports of atrial standstill are rare in the pediatric literature and are most commonly associated with structural heart disease.
- Caveolin-3 mutations have been previously associated with systemic diseases but have not been previously reported in association with atrial standstill.
- Caveolin-3 mutation is possibly responsible for atrial standstill in the patient reported here.

arrhythmia panel through GeneDx (Gaithersburg, MD), which analyzed 30 genes known to cause arrhythmia syndromes. Of those 30 genes, 2 have been associated with AS—*RYR2* and *SCN5A*. Our patient's testing was negative for *RYR2* and *SCN5A* but did reveal mutation in *CAV3*. His mutation p.Leu84Pro (L84P) is a semiconservative amino acid substitution. It was initially classified as a likely pathogenic mutation, but given that there are no published reports on this variant, no functional studies, and no segregation data, it was reclassified as a variant of unknown significance. This mutation has not been reported as a benign polymorphism and was not observed in 6500 individuals in the NHLBI GO Exome Sequencing Project.

Discussion

AS with associated tachyarrhythmia and a progressive course is an unusual presentation. Many reports of AS in the literature are in patients with structurally abnormal hearts. In the adult literature, there are reports of structural abnormality related to cardiomyopathies secondary to systemic illnesses as well as related to muscular dystrophies.¹ In the pediatric literature, reports typically describe children with congenital heart disease including atrial septal defects, tetralogy of Fallot, and Ebstein anomaly.^{1–3} In contrast, our patient had no structural abnormalities. To date, only one other pediatric case of AS without structural abnormalities has been reported in a patient with *SCN5A* mutation.¹

Prior cases of AS have been reported in the adult literature with tachyarrhythmias in Brugada syndrome due to *SCN5A* mutation and catecholaminergic polymorphic ventricular tachycardia associated with *RYR2* mutation.^{4,5} Jorat et al⁶ reported a case of isolated right AS with left atrial tachycardia in a 32-year-old female patient. Like our patient, she presented with chronic fatigue and dyspnea suggestive of bradycardia and a progressive course. She was diagnosed with AS, but no genetic testing was performed. This case,

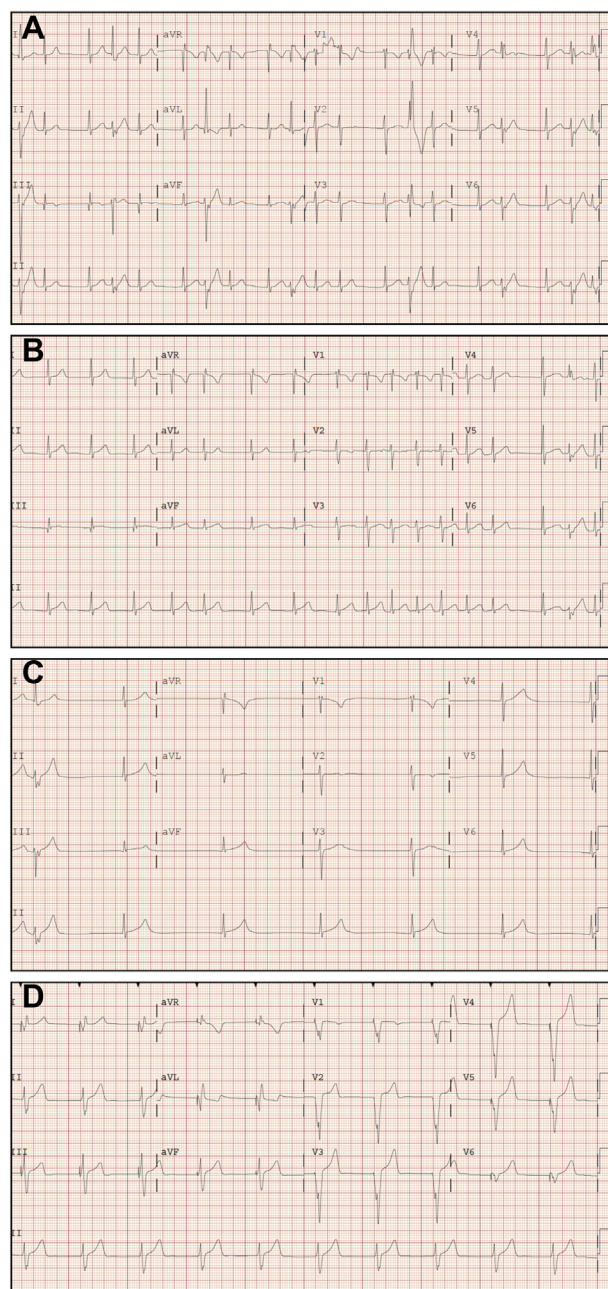


Figure 1 Progressive electrocardiograms (ECGs) demonstrating rhythm over time. **A:** Initial ECG showing junctional rhythm with isolated ectopic beats. **B:** ECG from presentation showing junctional rhythm with episodes of nonsustained atrial tachycardia. **C:** ECG after ablation showing junctional bradycardia and no evidence of atrial activity approximately 2 weeks after the first ECG. **D:** Last available ECG obtained 5 months after ablation with no evidence of atrial activity.

and ours, differs from those in the pediatric literature because of the associated atrial tachycardia and rapidly progressive clinical course.

Cardiac channelopathies have also been implicated as a cause of AS. *SCN5A* have been identified for some time as causing AS, among other rhythm issues.^{1,7} More recently, familial *RYR2* has been associated with AS.⁴ Bhuiyan et al⁴ described 2 unrelated family pedigrees with *RYR2* mutations.

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