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CASE REPORT

ADVANCED

CLINICAL CASE

# Mitral Annular Disjunction Associated With Fatal Ventricular Arrhythmia in an Adolescent With Marfan Syndrome

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## ABSTRACT

We discuss an adolescent with Marfan syndrome and a previous aortic valve-sparing root replacement who was found to have mitral annular disjunction on surveillance cardiac imaging in the setting of recurrent palpitations. Ambulatory heart rate monitoring incidentally captured a fatal ventricular arrhythmia, a well-recognized but underappreciated cause of sudden cardiac death in patients with Marfan syndrome. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1551–1556) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## HISTORY OF PRESENTATION

We report the case of a 19-year-old male patient with Marfan syndrome (MFS) type I that was caused by a de novo c.3302A>G mutation in fibrillin-1 exon 26 resulting in a tyrosine-to-cysteine conversion. He had moderate mitral regurgitation manifesting with recurrent palpitations. Cardiac examination revealed a midsystolic click and a 2/6 holosystolic murmur over the apex, consistent with known mitral valve prolapse (MVP) and mitral valve regurgitation.

## LEARNING OBJECTIVES

- To recognize MAD and associated findings on cardiac imaging.
- To understand the prevalence of MAD in adult patients with MVP and recognize the phenomenon in young patients with MFS.
- To identify the increased risk for malignant arrhythmias and SCD with MAD.

## PAST MEDICAL HISTORY

Valve-sparing aortic root and hemiarch replacement had been performed 4 years previously for an aortic root measurement of 5.3 cm by cardiac magnetic resonance (CMR). Mild to moderate mitral regurgitation, bileaflet MVP, and mitral annular disjunction (MAD) were demonstrated by transthoracic echocardiography (TTE), CMR (Video 1), and transesophageal echocardiography (TEE) at time of aortic root surgery (**Figures 1A to 1D**), comparable to initial TTE findings in our laboratory 1 year previously. Repeat CMR (Video 2) 2 months before palpitations demonstrated stable, moderate left ventricular dilatation, an end-diastolic volume of 144 mL/m$^2$, and an ejection fraction of 66%, comparable to the preoperative CMR.

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**ABBREVIATIONS AND ACRONYMS**

**AHRM** = ambulatory heart rate monitor

**CMR** = cardiac magnetic resonance

**CT** = computed tomography

**MAD** = mitral annular disjunction

**MFS** = Marfan syndrome

**MRA** = magnetic resonance angiography

**MVP** = mitral valve prolapse

**SCD** = sudden cardiac death

**TEE** = transesophageal echocardiography

**TTE** = transthoracic echocardiography

Mitral regurgitation had progressed from mild (regurgitant fraction, 20%) to moderate to severe (30%-35%) by ventricular stroke volume discrepancy on function analysis. Bileaflet MVP and MAD were again demonstrated. In both studies, there was only trivial aortic regurgitation and no area of myocardial fibrosis after gadolinium-based contrast enhancement.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis included anxiety-related palpitations, malignant arrhythmia, and aortic dissection.

## INVESTIGATIONS

A 7-day ambulatory heart rate monitor (AHRM) captured 2 untriggered 4-beat runs of ventricular tachycardia, with a maximum rate of 193 beats/min, and a ventricular extrasystole burden of <1%. Discussions were initiated regarding possible mitral valve intervention to address the increasing regurgitation. The patient continued taking atenolol 100 mg and losartan 50 mg daily for aortic aneurysm prophylaxis as his only medications, and his blood pressures were in the normal range for his age. Three months later, he presented to the emergency department with worsening palpitations at rest, dizziness, and shortness of breath in the setting of an acute febrile illness. There were no associated symptoms or evidence of myocarditis. A computed tomography (CT) scan was recommended for elevated D-dimer, but no imaging was performed because magnetic resonance angiography (MRA) and an echocardiogram had been performed 4 months earlier.

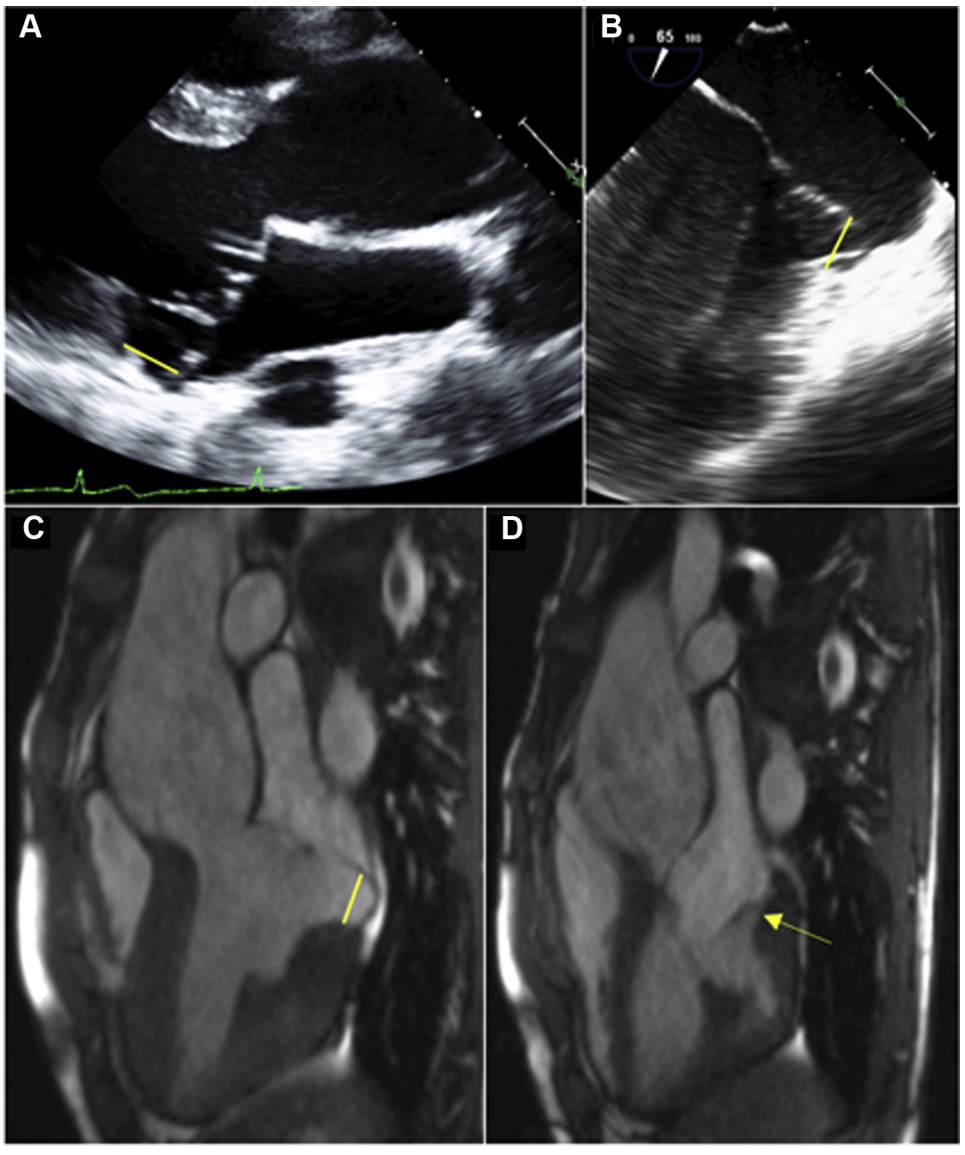
## MANAGEMENT

Palpitations persisted, and a repeat AHRM was ordered 1 month later. Thereafter, the patient was found in his bed, deceased. The AHRM had been active 6 days and 18 hours, recording rare ventricular premature beats, couplets, and triplets, a ventricular extrasystole burden of <1% (250 beats), and the terminal event (**Figures 2A to 2D**).

## DISCUSSION

Ventricular arrhythmias occur in as many as 33% of children with MFS (1). The rate of fatal arrythmias from presumed arrhythmogenic death in 1 large series of young patients with MFS was 4% (2), and it was 12% to 18% after aortic root replacement (3). Risk factors associated with malignant arrhythmias include palpitations, certain causative fibrillin-1 mutations, MVP, left ventricular dilation, dysfunction, and repolarization abnormalities (2-5). MAD has hitherto not been described in pediatric patients, but growing evidence suggests a relationship between MAD and ventricular arrhythmias and sudden cardiac death (SCD) (6,7). MAD is abnormal atrial displacement of the mitral hinge point, and it usually, albeit not always, appears with concomitant mitral valve disease, including MVP and myxomatous (or Barlow's) mitral valve, both of which are common in patients with MFS. Initially described on autopsy 40 years ago (8), MAD is readily diagnosed by echocardiography, CMR, or CT. During systole, separation between the mitral annular insertion and the adjacent basal left ventricular wall is appreciated (**Figures 1A to 1D**). The distance ranges from a few millimeters to >10 mm, with longer MAD distance and papillary muscle fibrosis seen on CMR more strongly associated with serious arrhythmic events (9). Not surprisingly, no cases of pediatric MAD have been reported because it has only recently received increasing interest in the adult literature as a result of the newly appreciated arrhythmogenic implications. A recent review suggests that one-third of patients with MVP may have MAD (6), although it is also described in patients without any mitral disease (9). The natural history of MAD is unknown, and in fact younger age may be a marker of more severe arrhythmias (9). It is likely that MAD is underappreciated in pediatric patients with MFS, who frequently manifest MVP at an early age, because of lack of awareness. The posterior annulus is more commonly affected (6), and CMR more reliably demonstrates MAD in patients with MVP (10). Serial MRA is already performed in routine follow-up of MFS-related aortic disease; however, TTE parasternal long-axis imaging and TEE can also reliably demonstrate MAD (**Figures 1A to 1D**). Our patient had several risk factors associated with malignant arrhythmia and SCD, including severe bileaflet MVP with moderate regurgitation, MAD, causative fibrillin-1 gene mutation, and previous aortic root replacement. Left ventricular dilatation, an additional risk factor for SCD in MFS, may be out of proportion to the degree of mitral regurgitation (3), as in our patient. Mitral valve repair may reduce the burden of ventricular arrhythmias in patients with

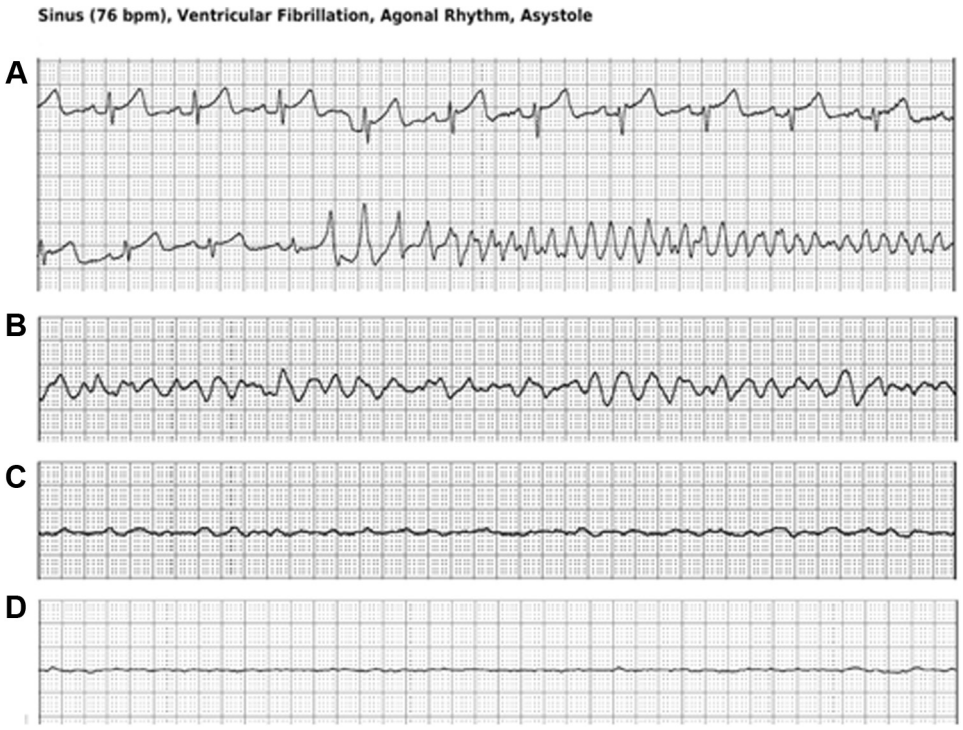
**FIGURE 1 MAD on Multimodality Imaging**




**(A)** Transthoracic echocardiography, parasternal long-axis view, mitral annular disjunction (MAD) **(line)** distance 16 mm. **(B)** Transesophageal echocardiography, midesophageal mitral commissural view, mitral annular disjunction **(line)** distance 12 mm. **(C)** Cardiac magnetic resonance left ventricular inflow-outflow view with mitral annular disjunction **(line)** distance 16 mm. **(D)** The largest mitral annular disjunction distance, typically at the posterior aspect of the annulus, is shown in end-systole rather than in diastole **(arrow)**.

MVP with mitral regurgitation (5), and it has been reported to improve arrhythmia burden in at least 1 patient with MAD after mitral clip (11). In patients with MFS, AHRM may help risk stratify palpitations, which are associated with malignant arrhythmia (1,3), but many of these patients are already taking β-blockers for aortic dilatation prophylaxis and do not otherwise meet criteria for implantable defibrillators. Additional findings of MAD >8.5 mm or left ventricular fibrosis seen on CMR may be useful in identifying a higher-risk cohort requiring more aggressive therapy (6).

**FIGURE 2 Terminal Event**




Ambulatory heart rate monitoring during the terminal event. **(A)** Sinus rhythm degenerating to ventricular tachycardia after very early-onset ventricular extrasystole caused by R-on-T phenomenon. Subsequent strips, at 10-minute intervals, showing **(B)** ventricular fibrillation, **(C)** minimal electrical activity, and **(D)** asystole.

## FOLLOW-UP

The coroner declined autopsy, and the patient's parents declined private autopsy. Previous 12-lead electrocardiograms had been unremarkable (Figures 3A and 3B).

## CONCLUSIONS

MAD, commonly seen in patients with MVP, is increasingly identified as a risk factor for malignant arrhythmia and SCD in adults. Ventricular arrhythmias, seen in patients with MFS, may be an underappreciated cause of SCD in younger patients. It is likely that MAD is also underappreciated in young patients with MFS. We propose that all patients with MFS should undergo evaluation for the presence and degree of MAD at the time of surveillance cardiac imaging because MAD may be yet another marker of risk for arrhythmogenic SCD in young patients with MFS.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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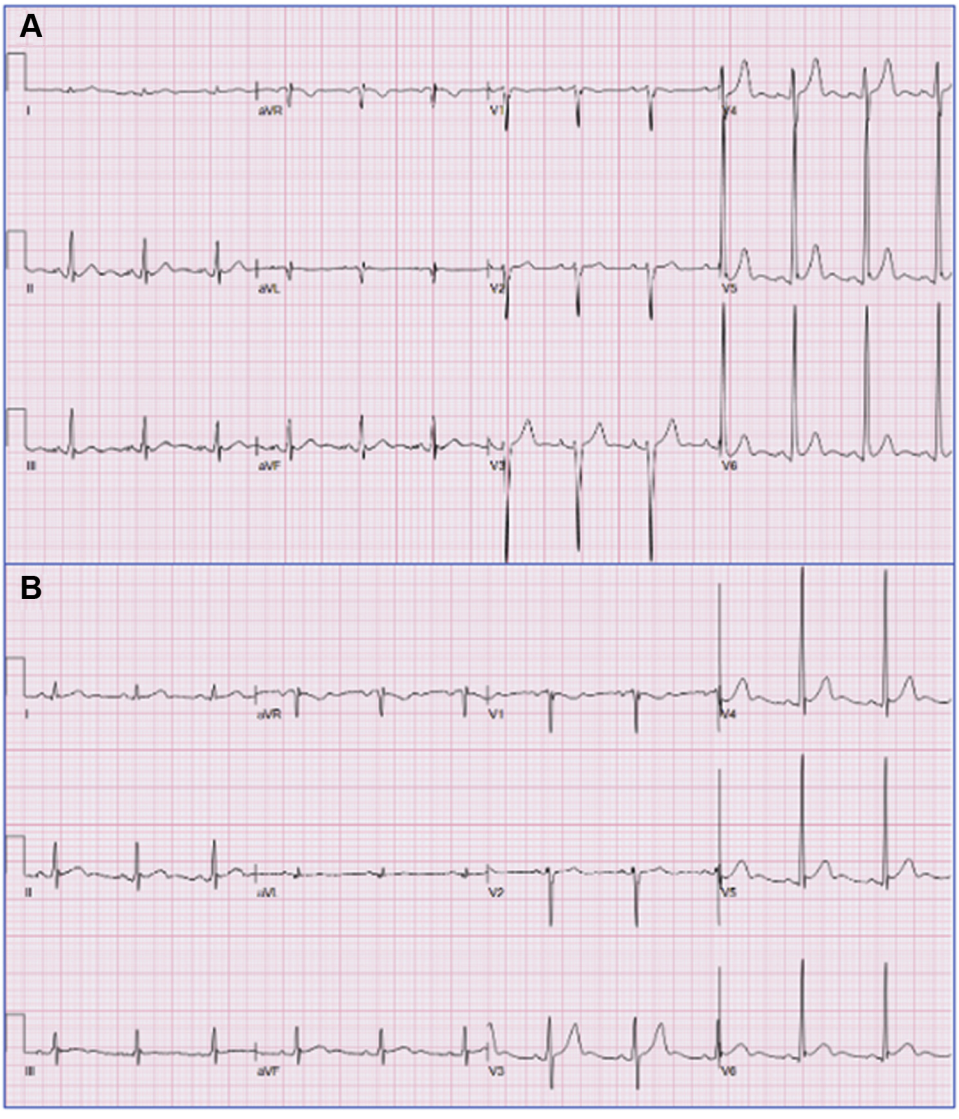
**FIGURE 3** **Serial Electrocardiograms**




**(A)** Preoperative electrocardiogram, 5 years earlier; QTc 420 ms. **(B)** Repeat electrocardiogram 6 months before the terminal arrhythmic event; QTc unchanged, normal ventricular forces. Benign early repolarization with J-point elevation was present on both electrocardiograms.

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**KEY WORDS** arrhythmia, connective tissue disorder, Marfan, mitral annular disjunction, sudden cardiac death

**APPENDIX** For supplemental videos, please see the online version of this paper.