Intermediate-coupled premature ventricular complexes and ventricular tachycardia during exercise recovery

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Introduction

Idiopathic ventricular tachycardias (VT) occur in the absence of structural heart disease, which includes previous myocardial infarction, cardiomyopathy, and congenital heart disease. They can originate from the conduction system or from other focal sources in the myocardium, most commonly the left ventricular outflow tract and the right ventricular outflow tract (RVOT).[1] Idiopathic VTs usually manifest between the third and fifth decades of life, and only a few small case series have reported the arrhythmia in the pediatric population, making it difficult to determine the true prevalence within this age group. The typical presentation of these arrhythmias is nonsustained, repetitive, monomorphic VT characterized by frequent isolated premature ventricular complexes (PVCs) and salvos of nonsustained VT.[1] These arrhythmias are generally considered benign and the vast majority of patients have an excellent outcome.[2]

The small minority of patients with poor outcomes may have subtle forms of structural heart disease or a more malignant form of idiopathic VT that can cause sudden cardiac death (SCD).

Idiopathic ventricular fibrillation (VF) describes the disease in which a patient experiences VF and cardiac arrest in the absence of any identifiable substrate for VF. Short-coupled variant torsades de pointes (SCTdP) and malignant RVOT tachycardia are 2 malignant arrhythmias with high mortality rate that fall under the umbrella of idiopathic VF.[3] These arrhythmias occur in the setting of normal QT

> **KEY TEACHING POINTS**
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> - Idiopathic ventricular fibrillation (VF) is a disease that causes cardiac arrest in the absence of any identifiable substrate for VF. Short-coupled variant torsades de pointes is a malignant arrhythmia that falls under the umbrella of idiopathic ventricular tachycardia (VT)/VF and is characterized by premature ventricular complex (PVC) coupling intervals of <300 ms, relatively short QRS durations, and normal QT intervals.
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> - Intermediate-coupled PVCs is characterized by PVC coupling intervals of <400 ms, normal QT intervals, negative genetic testing, and initiation of VT/VF in early recovery from exercise. This entity shares some similarities with short-coupled variant torsades de pointes and catecholaminergic polymorphic VT but does not satisfy diagnostic criteria for these syndromes. No previous pediatric studies have identified this phenomenon.
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> - In this preliminary series, this electrocardiography pattern is responsive to verapamil.

intervals and short-coupled PVCs with intervals less than 300 ms compared to the very long coupling intervals (600 to 800 ms) seen in classic TdP.[3]

We describe 3 unrelated cases of adolescent male patients with structurally normal hearts who were found to have VT in the recovery period following exercise stress testing. These cases are notable for their electrocardiogram (ECG) pattern leading up to and after peak exercise and their response to calcium channel blocker therapy. Review of current literature indicates that this phenomenon has not been previously described in this population.

Case report
Case 1

A 13-year-old previously healthy male patient was referred to pediatric cardiology for assessment of murmur on routine physical exam. The patient complained of an occasional chest fluttering sensation at rest and exercise, but denied ever having chest pain, dyspnea, or syncope. His mother had mitral valve prolapse discovered in her third decade of life, for which she underwent surgical repair. She also had a pacemaker implanted, though the exact indication was not available. There was no family history of SCD. The patient's baseline ECG was normal with a corrected QT interval of 400 ms (Supplemental Figure 1a). Exercise stress testing showed occasional monomorphic PVCs without ST segment shifts. Echocardiogram showed normal cardiac anatomy and function without evidence of mitral valve prolapse. The patient was seen again 3 years later for reassessment of his PVCs. Twenty-four-hour Holter monitor revealed monomorphic PVCs (6%). Repeat exercise stress testing showed PVCs during the late stages of exercise, and the test was stopped prematurely owing to a 4-beat run of VT. PVC couplets at a rate of 300 beats per minute were noted in recovery. Corrected QT intervals remained normal during rest, exercise, and recovery phases of the stress test. Exercise stress testing the following year showed frequent PVCs and short runs of nonsustained polymorphic VT at peak exercise (Supplemental Figure 1b). A single PVC with left bundle branch morphology is seen in Supplemental Figure 1b, the significance of which is unclear, though this patient did have another PVC during exercise testing with this morphology. The 12-lead ECG tracing in Supplemental Figure 1c shows PVCs with a right bundle branch morphology, suggesting a left ventricular origin for the VT. There were 4 episodes of 4–5 beats of nonsustained VT. There was an increase in PVC and nonsustained VT burden compared to initial stress testing. Echocardiography and cardiac magnetic resonance imaging (MRI) showed no evidence of cardiomyopathy; late gadolinium enhancement was not performed during the cardiac MRI. A comprehensive cardiac gene panel investigating 217 genes for arrhythmia and cardiomyopathy (including KCNQ1, PKP2, RyR2, and SCN5A) returned negative. On follow-up 1 year later, the patient reported intermittent chest tightening at rest and exercise. His exercise stress test revealed 35 PVCs in singlets, couplets, and triplets, which were principally noted both in the final stage of testing and, most prevalent, in immediate recovery. The patient was started on verapamil 240 mg twice daily and was asymptomatic with a benign stress test at 6-month follow-up on medication. To confirm the effect of verapamil, a repeat stress test during interruption of verapamil again showed more ventricular ectopy, and verapamil was therefore resumed.

Case 2

An 11-year-old previously healthy male patient was referred to pediatric cardiology for assessment of an irregular heartbeat that was incidentally found on routine physical examination. The patient regularly participated in physical activity and denied ever experiencing symptoms of chest pain, dyspnea, palpitations, or syncope. Family history was negative for SCD. Baseline ECG showed normal sinus rhythm with a normal corrected QT interval and ambient PVCs with morphology consistent with RVOT posteroseptal origin (Supplemental Figure 2a). Initial 24-hour Holter showed 3% monomorphic PVCs with periods of bigeminy that suppressed with physical activity. Echocardiography showed normal cardiac anatomy and function. Repeat Holter monitoring 1 year later showed 15% PVCs with periods of couplets and triplets, and then 7% the following year, with the majority of PVCs occurring during periods of increased heart rate. Wide-complex tachycardia runs with durations ranging from 800 to 1200 ms at heart rates of 230 to 250 beats per minute were also observed. The patient was asymptomatic on exercise stress testing and demonstrated persisting monomorphic PVCs of left bundle branch morphology with increasing heart rate. In recovery, he initially showed monomorphic PVCs and then 4 3-beat runs of wide-complex PVCs. Episodes of couplets and triplets were also seen (Supplemental Figure 2b). The patient returned to baseline with previously demonstrated PVCs at complete recovery. No other abnormalities, including myocardial ischemia, were present during the exercise stress test. Cardiac MRI showed a structurally normal heart. Late gadolinium enhancement was not performed during the cardiac MRI. A cardiac gene panel investigating 57 genes for arrhythmia and cardiomyopathy (including KCNQ1, PKP2, RyR2, and SCN5A) was negative. The patient was started on verapamil 120 mg twice daily. Repeat exercise stress test 1 month later continued to show monomorphic PVCs from RVOT origin and short periods of bigeminy during early activity with a fixed intermediate coupling interval. PVCs with unchanged morphology were again present at peak activity. In contrast to initial exercise stress testing and Holter monitoring before starting verapamil, no episodes of rapid VT were seen during the recovery phase (Supplemental Figure 2c). Verapamil was increased to 240 mg long acting once daily. The patient remains asymptomatic at 1-year follow-up.

Case 3

A 13-year-old male patient was referred to pediatric cardiology after experiencing 2 syncopal episodes in the context of exercise. The first episode occurred during a soccer tournament, where the patient briefly lost consciousness while running on the field. Recovery was immediate without a postictal state, and a subsequent ECG showed PVCs. The second episode happened 2 months later when running in gym class and presented in the same manner. In cardiology clinic, the resting ECG showed normal sinus rhythm with 2 monomorphic PVCs. Normal QT intervals were seen. Exercise stress test showed multiple wide complex monomorphic PVCs with right bundle branch morphology in lead V_1, suggesting left ventricular origin. Rapid PVC couplets were seen at peak exercise and the test was stopped when the patient reached volitional fatigue. In early recovery, the patient

went into sustained polymorphic VT (Supplemental Figure 3a) and lost consciousness. The patient was defibrillated twice and received chest compressions in between shocks before returning to normal sinus rhythm with bigeminy. He immediately recovered and felt alert and well afterwards without complaints.

Investigations showed normal cardiac structure on chest radiograph, cardiac MRI, and echocardiogram. Following this episode, the patient was given a provisional diagnosis of catecholaminergic polymorphic VT (CPVT). He was started on nadolol 40 mg daily and an implantable cardioverter-defibrillator (ICD) was placed. Limited genetic testing was unremarkable and there were no mutations in ryanodine or calsequestrin genes. At 6-month follow-up, there was 1 ICD shock associated with a missed dose of medication; at 12-month follow-up, there were 4 shocks, 2 of which resulted from nonsustained VT. The diagnosis was changed to short-coupled idiopathic polymorphic VT owing to the events that occurred in the recovery period of exercise testing. Nadolol was discontinued and replaced with verapamil 120 mg twice daily. The patient did not experience further ICD shocks after starting on verapamil. He was asymptomatic on subsequent follow-up appointments and eventually transitioned to adult cardiology care. A broader cardiac genetic panel was negative.

Discussion
The 3 presented cases show similarity across many electrophysiological characteristics, which are summarized in Supplemental Table 1. All clinical investigations revealed previously healthy, young adolescent male patients at baseline with no family history of SCD or inherited arrhythmia syndrome. Exercise stress testing showed PVCs with coupling intervals less than 400 ms that increased in frequency with activity and persisted into the recovery period, during which time nonsustained and sustained VT developed. The coupling interval ratios, defined as the PVC coupling interval divided by the preceding sinus cycle length, were greater than 50% (ranging from 54% to 73% in the patient group). The isolated PVCs in all 3 cases displayed the same characteristic morphology as those that initiated the nonsustained and sustained episodes of VT (Supplemental Figure 3b); that is, the first beat of the PVC or VT always occurred on the descending limb of the T wave of the last supraventricular QRS complex. Only case 3 demonstrated sustained polymorphic VT or VF following this pattern, which required defibrillation. Case 3 also experienced a resulting syncopal episode in the recovery period of the exercise stress test. This challenges the generally held belief that postexertional syncope is benign, distinct from exertional syncope, which is concerning for SCD risk.[4] To emphasize the rarity of this phenomenon, none of the 34 patients evaluated for idiopathic PVCs at the British Columbia Children's Hospital over the past 4 years displayed the malignant phenotype seen in case 3. Although these 3 cases share some similarities with CPVT, the arrhythmias in CPVT are progressive, with increasing workload. The differentiation from SCTdP is more nuanced, and these cases may represent a variant of SCTdP. The coupling intervals, ages, and exercise stress testing results differ between our cases and the published SCTdP cases (Supplemental Table 2); however, both phenomena are responsive to verapamil therapy. SCTdP may warrant a broader definition as the reported experience grows, or it may be that intermediate-coupled PVCs represents a novel ECG entity.

Short-coupled PVCs triggering polymorphic VT have been described as a rare cause of cardiac arrest in adult patients,[5–7] with early reports indicating a high mortality risk despite traditional medical treatment with beta blockers or calcium channel blockers.[8] Leenhardt and colleagues[5] were first to describe a series of patients with structurally normal hearts who developed potentially lethal polymorphic VT despite the presence of normal QT intervals. A minority (30%) of these cases also had a positive family history of SCD. A key characteristic of SCTdP is the unusually short coupling interval of less than 300 ms to the first beat of the isolated PVC or VT.[5] These patients develop polymorphic VT at rest or during exercise, unlike those in our study, who presented with VT only after exercise in the early recovery periods. The coupling intervals in our phenomenon measured in the range of 260–360 ms. We were unable to compare coupling interval ratios, as they were not readily calculable in other series. Verapamil is the only identified effective treatment for SCTdP and placement of an ICD is strongly recommended.[5,7,8] Catheter ablation of PVCs should also be strongly considered to reduce the incidence of polymorphic VT.[8] Notably, all 3 of our patients showed a positive response to treatment with verapamil and did not have recurring arrhythmia on repeat exercise stress testing.

Exercise-induced PVCs are a common finding in clinical practice,[9] and ambient PVCs that are suppressed with exercise in healthy patients are considered benign. PVCs with left ventricular origin that persist or increase in frequency during exercise and disappear or reduce with rest are a marker for elevated risk of underlying cardiac abnormalities that may predispose patients to SCD.[9] PVCs originating from the right ventricular apex, inflow tract, and outflow tract are associated with arrhythmogenic right ventricular cardiomyopathy (ARVC). Additionally, high PVC burden is a predictor of VT risk in those with structural heart disease such as ARVC.[10] A recent study found *PKP2*-dependent electropathy and subclinical forms of ARVC in patients with gene-negative, clinically diagnosed CPVT. These patients had exercise-associated arrhythmias or SCD independent of structural heart changes.[11] Although our 3 cases all had negative genetic test results, they each had relatively short follow-up durations of less than 10 years (Supplemental Table 1). A longer duration of follow-up is required to monitor for development of structural heart disease, which may not manifest clinically until later in time.

Genetic mutations leading to augmented intracellular calcium release may play a role in the pathophysiology of intermediate-coupled PVCs. Loss-of-function mutations in

ryanodine calcium channels (*RyR2*) can result in an SCTdP phenotype; similar mutations have also been described in CPVT.[12] High-density electrophysiological endocardial and epicardial mapping in conjunction with genetic testing results has also shown promise in confirming a definitive diagnosis for patients with idiopathic VT/VF.[13] This detailed investigation method phenotypically characterizes patients to identify microstructural cardiomyopathic areas and Purkinje system abnormalities that can act as substrate for re-entry, or trigger ectopy, respectively. Purkinje extrasystoles have also been identified as a trigger for VT in other inherited arrhythmia syndromes, including long QT syndrome and CPVT.[14]

Conclusion

Intermediate-coupled PVCs may represent a novel ECG entity within the spectrum of idiopathic VT/VF that can result in polymorphic VT in the absence of structural heart disease. There are no previous descriptions of this phenomenon in pediatric studies. Patients with intermediate-coupled PVCs have increasing burden of PVCs with exercise that persist into and initiate VT in the recovery period. This entity does not fully meet diagnostic criteria for SCTdP or inherited syndromes such as CPVT, though there are some overlapping characteristics; therefore, this ECG entity may also represent a variant of SCTdP that presents in pediatric patients. This ECG pattern is responsive to verapamil calcium channel blocker therapy. Reporting of more cases is required to determine the true incidence of this pattern, as coupling intervals in idiopathic PVCs are highly variable. The underlying pathophysiology potentially involves augmented intracellular calcium handling. It remains to be seen if this phenomenon affects other patient groups outside of the healthy adolescent male population.

Acknowledgments

Appendix
Supplementary data

Supplementary data associated with this article can be found in the online version at https://10.1016/j.hrcr.2020.11.001.

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