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Abstract

Premature ventricular complexes (PVC) are considered benign when they occur in patients without apparent structural heart disease. They usually originate from the right, or less commonly, left ventricular outflow tract. Their suppression was not beneficial in patients with heart disease like myocardial infarction and cardiomyopathies. Recently it has been shown that their suppression medically or by ablation, improved the left ventricular (LV) dysfunction. This led to the hypothesis that they may contribute to this LV dysfunction especially when they are particularly frequent (> 20000 per day). Because of some overlap with arrhythmogenic right ventricular dysplasia, the evaluation in patients without apparent heart disease should consider an magnetic resonance imaging if the echocardiography was not able to help in diagnosis especially when there is a suspicion.

Patients without structural heart disease and low-to modest PVC burdens do not always require treatment. When necessary, treatment for PVCs involves beta-blockers, calcium channel blockers, or other antiarrhythmic drugs and catheter ablation in selected cases. Catheter ablation can be curative, but it is typically reserved for drug-intolerant or medically refractory patients with a high PVC burden.

Introduction

Premature ventricular contractions (PVCs) are a frequent finding, occurring in one percent of adult population on standard ECG, 40-75% with ECG monitoring. PVCs >1/min occur in 1-4% of the general population¹⁻². Although often asymptomatic, PVC can manifest as palpitations, difficulty of breathing, chest pain, fatigue, and dizziness. They may be present in healthy subjects and in those with structural heart disease such as coronary artery disease, cardiomyopathy, arterial hypertension, myocarditis, and infiltrative disease.

Whereas, PVC's in patients with structural heart disease are a marker of risk of sudden cardiac death, it is admitted that the long-term prognosis in asymptomatic healthy subjects with frequent and complex ventricular ectopy is similar to that of the healthy U.S. population and suggests no increased risk of death³. Recently however, the concept of PVC-induced cardiomyopathy was proposed by Duffee et al in 1998 when pharmacological suppression of PVCs in patients with presumed idiopathic dilated cardiomyopathy subsequently improved left ventricular (LV) systolic dysfunction.⁴ Another point of concern is the possible association of these PVC's with subclinical arrhythmogenic right ventricular cardiomyopathy (ARVC) which is a leading cause of sudden cardiac death (SCD) in the Mediterranean region.⁵

This article will review the mechanism of PVCs, evaluation, and management in patients without apparent structural heart disease.

Electrophysiologic consideration

The most common sites of origin for ventricular ectopy in patients without structural heart disease are frequently the



Figure 1: The V2S/V3R index, defined as the S-wave amplitude in lead V2 divided by the R-wave amplitude in lead V3 during the outflow tract ventricular arrhythmias, was significantly smaller for LVOT origins than RVOT origins (10)



Figure 2: Epsilon wave

right outflow tracts, and less commonly the LV outflow tract and aortic sinuses; the typical corresponding ECG patterns are: 1) a left bundle branch block morphology with an inferior axis (positive R waves in limb leads II, III, and aVF) and typical precordial R-wave transition in V3 and V4; 2) a right bundle branch block with an inferior axis patter; and 3) a left bundle branch block pattern with early precordial R transition in V2 and V3, respectively.6-9

The V2S/V3R index, defined as the S-wave amplitude in lead V2 divided by the R-wave amplitude in lead V3 during the outflow tract ventricular arrhythmias, was significantly smaller for LVOT origins than RVOT origins (P < 0.001).¹⁰ figure 1



Figure 3: Regional wall motion abnormalities including dyskinetic or focal aneurysmal walls





Figure 4: Fibro-fatty infiltration of the LV wall

PVC's induced cardiomyopathy

Several studies have reported LV dysfunction in correlation with the presence of PVC's on Holter monitoring. The evidence of this relation was that ablation of PVC's improved the LV dysfunction¹¹⁻¹⁵. There has been an attempt to define the number of PVC's per 24h that constitutes such burden. The number varied from 10% to 25%.¹⁶; however, high PVC burden does not always result in LV dysfunction even after a long follow-up.¹⁵ The duration of the PVCs is thought to be a determinant of LV dysfunction. PVCs with longer QRS duration seem to be associated with worsening LV function and in these patients ablation leads to LV improvement (17). Mechanisms proposed for PVC-mediated LV dysfunction include alterations in calcium homeostasis, increased oxygen consumption, and ventricular dyssynchrony.¹⁸

Also, as PVC's and cardiomyopathy may co-exist in the same patient, it is difficult to determine prospectively which condition precedes the other.

Evaluation

The initial evaluation of frequent PVC's should consider the age at presentation. In adults, it is more likely associated to coronary heart disease and ischemia which should be ruled out by coronary angiography or stress testing. In young patients on the other hand, PVCs could be more likely related to an inherited channelopathies or cardiomyopathy such as arrhythmogenic right ventricular cardiomyopathy. Common tools for evaluation include resting ECG, 24 hour ambulatory monitoring, stress testing, and cardiac imaging.

A resting 12 channel ECG evaluates the presence of myocardial scar (Q-waves or fractionated QRS complexes), the QT interval, ventricular hypertrophy, and other evidence of structural heart disease. Special attention should be paid to the ECG patterns suggesting of a possible presence or ARVC such as negative T waves in V1-V3 or an epsilon pattern in V1-V2 (Figure 2).

The 24 h ambulatory monitoring is helpful to quantify the PVC's burden which is considered clinically significant when it exceeds 20000/24 hours.¹⁵ Also, ambulatory monitoring may detects asymptomatic non-sustained ventricular tachycardia that places the patient at higher risk of SCD and warrants further investigation.

Exercise treadmill stress testing is appropriate for patients who experience PVCs with exercise or for whom an evaluation for coronary artery disease is indicated. Exercise stress testing should be considered to determine whether PVCs are potentiated or suppressed by exercise, to assess whether longer duration ventricular arrhythmias are provoked. A negative exercise test can decrease the probability that catecholaminergic polymorphic ventricular tachycardia (CPVT) is the underlying cause. On the other hand, PVCs that worsen with exercise should prompt further investigation as these patients are more likely to require treatment.¹⁹

Table 1:

PVCs: markers of risk

- 1. Syncope or pre-syncope
- 2. Family history of sudden cardiac death
- 3. Short coupling R/T
- 4. Suspicion of ARVC on echo or MRI
- 5. LV dysfunction
- 6. Ventricular tachycardia
- 7. Coronary artery disease

Exercise testing can be combined with either echocardiographic or nuclear perfusion imaging to evaluate the possibility of myocardial ischemia. For patients unable to exercise, pharmacologic stress testing with dobutamine or a vasodilator agent can be performed.

Cardiac Imaging

Surface echocardiography will rule out overt structural heart disease such as abnormalities in cardiac chamber size, wall thickness, systolic function and valvular disease.

Cardiac magnetic resonance imaging

ARVC is one of the leading causes of SCD among athletes in the Mediterranean region, particularly in Italy, secondary to ventricular arrhythmia²⁰. It is characterized by areas of scarring and fibrosis, with or without fibro-fatty infiltration, in the right ventricular (RV) inflow, outflow tracts and/or apex. In addition, regional wall motion abnormalities including dyskinetic or focal aneurysmal walls occur (Figure 3), and that may progress to RV dilation and systolic dysfunction. The diagnosis of ARVC requires a combination of clinical suspicion, abnormal electrocardiogram, arrhythmia, and sometimes imaging confirmation. Echocardiography often misses subtle abnormalities of the RV wall motion particularly in the early stages of the disease. Cardiac magnetic resonance imaging (CMR) is recognized as an important imaging tool to aid in the diagnosis of the disease given its ability to visualize the RV walls, in multiple plans and three-dimensionally, without the limitations seen with echocardiography, and accurately quantify volumes and ejection fraction (with high reproducibility)²¹⁻²². The 2010 revised Task Force Criteria includes minor and major CMR parameters for regional RV dysfunction, volumes, and global systolic dysfunction with sensitivity and specificity of 79% and 85% in men, and 89% and 97% in women, respectively²³. Indeed, the 2010 updated Asian Society of Cardiac imaging²⁴ and the 2006 multi-society appropriateness guidelines²⁵⁻²⁶, consider CMR highly appropriate for the evaluation of patients with suspected ARVC (level of appropriateness A8-9).

Furthermore, the presence of late gadolinium enhancement is associated with high prevalence of appropriate ICD therapy and SCD reaching 48%²⁶⁻²⁷. In one study, the presence of scar was associated with inducible ventricular tachycardia in 75% of cases with a negative predictive value of 100%²⁸. While the Task force criteria focus predominately on RV involvement, recent studies and cases have shown subclinical left ventricular (LV) involvement with areas of fibro-fatty infiltration of the LV walls with or without scarring and late gadolinium enhancement ²⁹ (**Figure 4**). In a recent publication from our region, CMR has been shown to alter the diagnosis and impact clinical management in patients with clinical suspicion of disease, including those with suspected ARVC³⁰.

Treatment

Medical

Asymptomatic patients, with normal LV ejection fraction and after exclusion of risk factors (**Table I**), warrant no treatment. They represent the majority of the patients.¹⁵ Patients should be followed-up regularly by echocardiography and Holter monitoring especially when PVC's are > 15-2000/day. In symptomatic patients, beta-blockers or verapamil are indicated.

In patients with LV dysfunction, aggressive therapy is indicated.

Ablation

Consideration of Ablation

Ablation is indicated in patients with symptomatic PVCs when the use of antiarrhythmic medications is ineffective or unfavorable. Ablation is successful if the burden of PVCs, usually more than 10000/ 24 hours allows for meaningful mapping. Ablation usually targets the RVOT or less frequently the LVOT. With the advent of intracardiac echo and also contact force sensing catheters such ablations have become more successful and associated with less complications. In patients frequent PVCs with LV dysfunction, it is more common to encounter wider QRS PVCs which may originate from the LVOT, epicardial foci or the papillary muscles. In a recent study durable successful ablation was achieved in 66% of patients, with a significant improvement in LVEF from 33.7 \pm 8% to 43.8 \pm 9.4% and 45.8 \pm 10.9% at 6 and 12 months, respectively (p < 0.05) regardless of the etiology of heart disease.²⁹

Conclusion:

To answer the question: Yes PVCs in patients without apparent structural heart disease are safe once we rule out risk factors. Long QT, short QT, Brugada are easily recognized on a surface ECG. An echocardiography will determine the LV function, although determining which comes first PVCs or LV dysfunction is not always easy. The Holter monitoring is mandatory to quantify the PVC burden.

Patients without structural heart disease and with low-tomodest PVC burdens may not require specific treatment. PVCs at greater burdens, typically 15% to 20%, or with specific highrisk features carry a risk of tachycardia-related cardiomyopathy and may require treatment even if they are asymptomatic. Treatment involves medical therapy with a beta-blocker, a calcium channel blocker, or another antiarrhythmic drug, and catheter ablation in selected cases.

Catheter ablation can be curative but is typically reserved for drug-intolerant or medically refractory patients with a high PVC burden.

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