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Premature Ventricular Contractions from Benign to Seriousness - A Narrative Updating Review

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Abstract

***Background:** Premature ventricular contractions are the most frequent cardiac arrhythmia with or without structural heart diseases. These common type of arrhythmia possess both benign and serious outcome. Premature ventricular contraction may be an independent predictor for either sudden or non-sudden death.*

***Objective:** An exploring the clinical significance, type verification, recent management, and outcome of premature ventricular contraction in the patients were the purpose of this study.*

***Method of study:** A narrative updating review was the study method in the current research.*

Conclusions: Premature ventricular contraction may be benign and may be a serious arrhythmia. Early and rapid verification of premature ventricular contractions hurry avoidance of the serious outcome. Recent efficient use of nitroglycerin in many types of premature ventricular contractions make it for in front of future selection as an antiarrhythmic drug.

Keywords: *Premature Ventricular Contraction, From Benign to Seriousness, PVC, Ectopics, Extraststole.*

Abbreviations

AADs: Antiarrhythmic drugs

AMI: Acute myocardial infarction

ARVC: Arrhythmogenic right ventricular cardiomyopathy

BB: Beta-blocker

CCB: Calcium channel blocker

CHF: Congestive heart failure

CMR: Cardiac magnetic resonance imaging

CPVT: Catecholaminergic polymorphic ventricular tachycardia

DCM; Dilated cardiomyopathy

ECG: Electrocardiogram

EF; Ejection fraction

EPS: Electrophysiological study

HCM: Hypertrophic cardiomyopathy

HF: Heart failure

HFrEF: Heart failure with a reduced ejection fraction

HTN: Hypertension

ICD: Implantable cardioverter-defibrillator

IHD: Ischemic heart disease

ICM: Ischemic cardiomyopathy

LBB: Left bundle branch

LBBB: Left bundle branch block

LV: Left ventricle

LVD: Left ventricular dysfunction

LVEF: Left ventricular ejection fraction

LVOT: Left ventricular outflow tract

MRI: Magnetic resonance imaging

NSVT: Non-sustained ventricular tachycardia

PVC: Premature ventricular contraction

PVCi-CMP: Premature ventricular contraction-induced cardiomyopathy

RBBB: Right bundle branch block

RVOT: Right ventricular outflow tract

SAECG: Signal-averaged ECG

SCD: Sudden cardiac death

SHD: Structural heart diseases

VF: Ventricular fibrillation

VHD: Valvular heart disease

VT: Ventricular tachycardia

Introduction

Historical Bit

Historically, premature ventricular contractions (PVCs) were considered precursors of sudden cardiac death (SCD)[1]. For many years, the traditional studies evaluating acute myocardial infarction (AMI) outcome showed that PVCs were independent predictors of sudden and non-sudden death[2]. The concept that ventricular fibrillation (VF) and ventricular tachycardia (VT) are preceded by PVCs arose when coronary care units were created to treat the complications of AMI[1]. Studies in the post-thrombolytic era concluded that PVCs was associated with poor outcome[3]. For many years, their mere presence was taken as an indication for prescribing antiarrhythmic agents[1]. Lastly, studies in PVCs with ischemic heart disease showed suppression with antiarrhythmic agents coming at the expense of greater all-cause mortality[4]. Subsequent studies using amiodarone in ischemic heart disease, as the EMIAT or the CAMIAT trials, failed to demonstrate any benefit with this drug[5,6]. But, until 2015, no new agents were developed in this field and the treatment of premature ventricular contractions with drugs has remained as something trivial for the past 20 years[1]. Recently, nitroglycerin was introduced by the author as a newer antiarrhythmic agent in two case reports. The first reported case (2017)[7] was a case of ischemic PVCs-bigeminy had shown a dramatic response to a trace dose of intravenous nitroglycerin infusion. The second reported case (2019)[8] was another case of ischemic PVCs-quadrigeminy had shown a dramatic response to a trace dose of intravenous nitroglycerin infusion.

Scoping, Epidemiology and Statistics

Generally, PVCs are the most common cardiac arrhythmia in patients with or without structural heart diseases (SHD)[9-13]. The prevalence of PVCs depends on the co-morbidities of the patients being screened and the duration of monitoring[14]. They are more prevalent with increasing age[11]. The estimated prevalence of PVCs on standard 12-lead electrocardiography (ECG) was >1 PVCs /min occurs in 1% to 4% of adult in the general population and 40% to 75% in 75% of healthy persons using on 24- to 48-hour Holter monitoring[10,15-18].

Pathophysiology and Electrophysiological Study (EPS)

Premature ventricular contractions are early depolarization of the myocardium originating in the ventricle[19] caused by an electrical impulse or ectopic rhythm from any part of the ventricles, including the ventricular septum before the sinoatrial impulse has reached the ventricles[20]. PVC is a common arrhythmia triggered by impulses arising outside the normal conduction pathway of the heart occurs even in people with no underlying heart disease[21]. PVCs often arise from a pre-excitation, mostly in the right ventricle[9]. A PVC is a sign of decreased oxygenation to the myocardium but is also found in healthy heart[22]. In most cases, premature ventricular contractions have a focal origin[1]. This means that an abnormal automatism, triggered activity or reentrant mechanism have an electric impulse of focal origin. This site of the impulse propagates centrifugally to the rest of the ventricles resulting in after depolarizations[11,23]. Endocardial mapping of the electrical activity with electrode catheters can show the activation pattern and the earliest electrogram or signal during PVCs and, thus, their site of origin[24]. The patient must have a significant number of PVCs during the procedure. Once the target has been identified, radiofrequency energy can be applied during the same procedure with an ablation catheter to eliminate the tissue and suppress PVCs[25]. Most PVCs originate from the right ventricular outflow tract (RVOT), followed by the left ventricular outflow tract (LVOT) including the sinuses of Valsalva and less common sites of origin are the left bundle branch (LBB) fascicles, the RV moderator band and the left ventricular (LV) epicardium[25]. Ventricular arrhythmias originating from the RV present late

precordial transition (V4 lead) while those with LV origin present lead V1/V2 transition[25-27]. So, it is important to be taking the ECG, tracings to record PVCs in all the leads[1]. Currently, catheter ablation can cure 70-90% of patients[25,28]. Recently, catheter ablation using 3-D navigation systems is a feasible approach to eliminate PVCs in symptomatic patients[24].

Classification Patterns

There are numerous interesting classifications for the premature ventricular contractions. Premature ventricular contractions are classified: 1. according to the number of normal sinus beats for each PVC into bigeminy, trigeminy, quadrigeminy, pentageminy, and hexageminy,.. etc. (**Figure 1**)

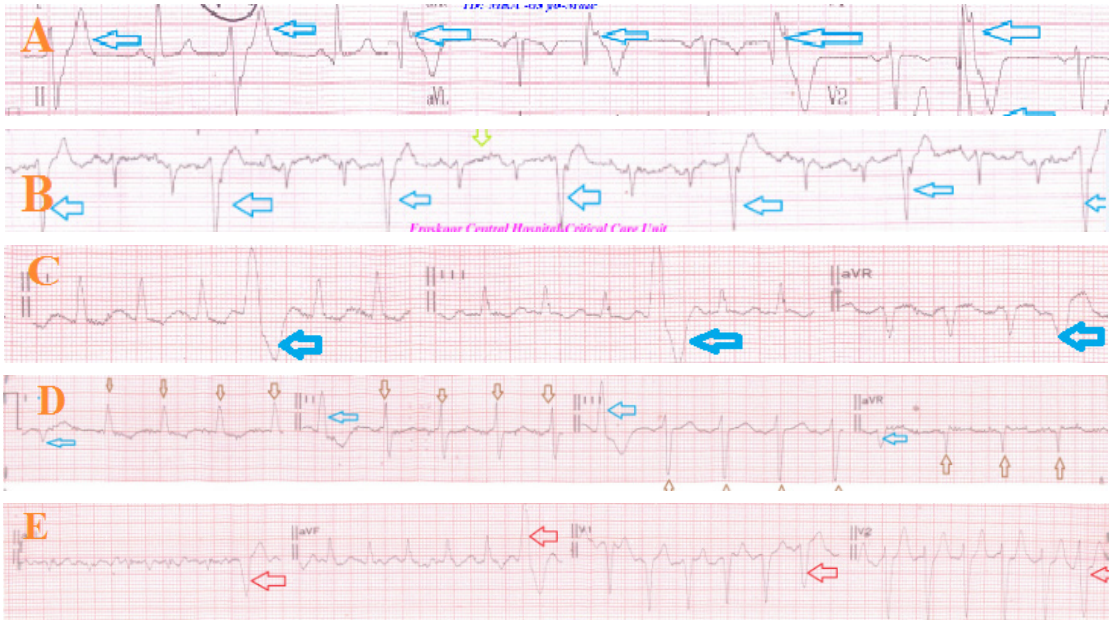

Figure 1. *ECG tracing A showing bigeminy. ECG tracing B showing trigeminy. ECG tracing C showing quadrigimeny. ECG tracing D showing pentageminy. ECG tracing E showing hexageminy.*

2. according to the number of consequent PVCs into couplet, triplet, salvos, and ventricular tachycardia. 3. according to the origin of PVCs into unifocal and multifocal. (**Figure 2**)

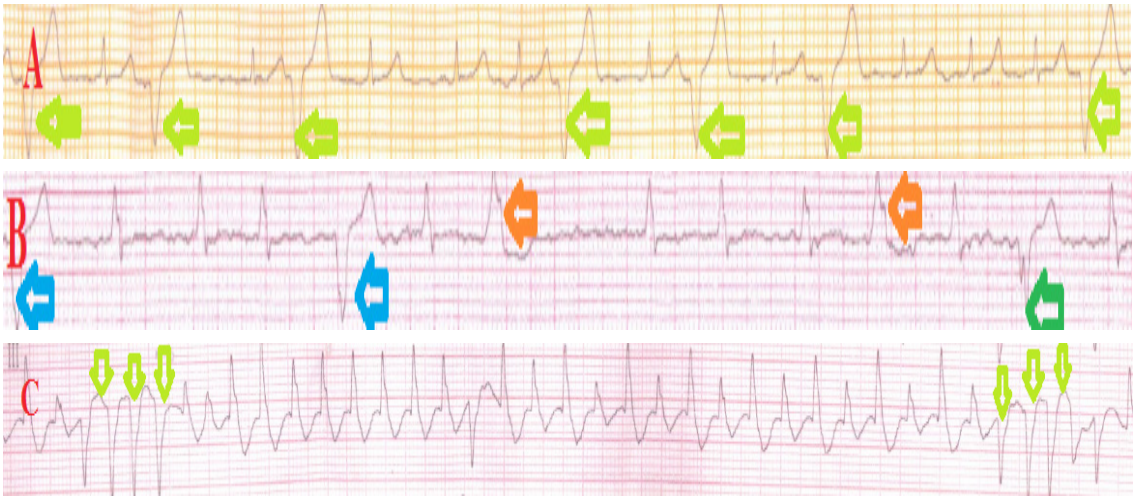

Figure 2. *ECG tracing A showing Unifocal PVCs. ECG tracing B showing multifocal PVCs. ECG tracing C showing runs of ventricular tachycardia (non-sustained ventricular tachycardia).*

4. according to the morphology of PVCs into multiform and R on T phenomenon. 5. according to the etiology and frequency of PVCs per minute into sporadic, frequent (sustained), and idiopathic. 6. according to the seriousness of PVCs into benign and malignant. (**Table 1**)

Table 1. *Classification patterns and definitions for variable premature ventricular contractions*

Classification type	Patterns	Definitions
• According to the number of normal sinus beats for each PVC[11,93,139,140]	• Bigeminy	• One normal QRS followed by PVC or a PVC follows every atrial beat
	• Trigeminy	• 2 Sinus QRS followed by PVC or a PVC occurs every 3rd beat
	• Quadrigeminy	• 3 sinus QRS followed by PVC
• According to the number of consequent PVCs[11,93,139,140]		
	• Couplet	• 2 consecutive PVCs or 2 PVCs occur in a row
		• 3 consecutive PVCs
	• Triplet	• 3 or more occur in a row
	• Salvos (brief VT)	• ≥ 3 successive beats
	• Ventricular tachycardia (VT)	
• According to the origin of PVCs[11,93,139,140]		
	• Unifocal	• All PVCs look the same
	• Multifocal	• PVCs have more than one morphology or PVCs have different sites of origin. PVCs have more than one morphology or PVCs have different sites of origin. PVCs have different coupling intervals
• According to the morphology of PVCs[11,93,139,140]		
	• Multiform	• PVCs usually have the same coupling intervals but their conduction through the ventricles differ. PVCs have the same coupling intervals. common in digitalis intoxication.
	• R on T phenomenon	• The R wave of the PVC is so close to the previous beat that it has a chance to fall on the T wave of that previous beat. PVCs may occur early in the cycle (R-on-T phenomenon), after the T wave, or late in the cycle; often fusing with the next QRS (fusion beat). R-on-T PVCs are more vulnerable to ventricular tachycardia or fibrillation esp. in IHD.
• According to the etiology and frequency of PVCs per minute[29,86,141,142]		• <6 PVCs/min, which can occur in healthy people
		• >6 PVCs/minor PVCs as >10 per hour(AHA/ESC), can occur in patients with structural heart disease. Frequent PVCs is a risk factor that leads to ventricular tachycardia
		• PVCs in which there is no structural heart disease. PVCs have a benign prognosis
	• Sporadic	
	• Frequent (sustained)	• PVCs occur in patients without apparent structural heart disease (SHD)
		• Frequent PVCs originating from a focal source in triggering idiopathic VF. PVCs originating from the RVOT
	• Idiopathic	
• According to the seriousness of PVCs[29,30,50]		
	• Benign	
	• Malignant	

Prognosis and Mortality

Premature Ventricular Contractions with or Without Structural Heart Diseases (SHD)

Most patients of PVCs are considered benign when the patients have no SHD[29,30]. PVCs in absent SHD is safe once the risk factors excluded[29]. PVC's with SHD is considered a hallmark to SCD[29, 31]. Cohort studies showed that PVCs are associated with increased ischemic heart disease (IHD) events and death[32]. Because PVCs with established IHD may be viewed as a marker of disease severity or as an endpoint in the natural history of the disease process[33]. The presence of PVCs in patients of CAD is associated with a poor prognosis[34,35]. Asymptomatic frequent or complex PVCs have good prognosis[15,16,30]. PVCs may have some risk for ischemic stroke[32]. Patients with PVCs are strongly more likely to develop subsequent IHD events and mortality in comparison to the patients without PVCs[33]. However, PVCs-associated risk may be found among apparently healthy patients without IHD[19]. The incidence, frequency, and complexity of ventricular arrhythmias were greater in the presence of SHD[19]. Incidental PVCs are harmless in less than 1% of heartbeats[9]. Indeed, PVCs are accidentally diagnosed on a routine examination may have favorable outcome[1]. The long-term prognosis in asymptomatic healthy patients with frequent and complex PVCs have no increased risk of SCD[15]. The increased all-cause mortality in elderly patients linked

to the history of IHD, left ventricular dysfunction (LVD), hypertension (HTN), and valvular heart disease (VHD)[36]. The association of PVCs with sub-clinical arrhythmogenic right ventricular cardiomyopathy (ARVC) is a leading cause of SCD in the Mediterranean area[37]. PVC with LBBB morphology increased the risk of SCD from IHD[21]. Population-based studies have shown a link between PVC's and cardiovascular risk[33,38-40]. In a study of patients with congestive heart failure with reduced ejection fraction (HFrEF) less than 35%, PVC frequency did not predict the risk of SCD or prognosis[41].

Prognosis and Frequency of PVCs

The high frequent PVCs can vary from 10,000 to 20,000 PVCs/day according to relevant studies[31]. Frequent PVCs are associated with AMI and SCD in patients without known CAD[36]. Some studies carry a significant risk of AMI and SCD if there are >30 PVCs per hour[36,42,43]. Reports have suggested that frequent PVCs increase the risk of SCD, cardiovascular events, and LVD[44]. Multiform PVCs are associated with an adverse prognosis in the general population[45]. PVCs and runs of non-sustained ventricular tachycardia (NSVT) in subjects with SHD contribute to increased mortality risk, the magnitude of nature, and extent of the underlying SHD[19]. Frequent PVCs post-recovery from exercise stress testing is also associated with increased mortality[36]. But, frequent PVCs arising during exercise stress testing were not accompanied to increased risk[46]. The initial evaluation of frequent PVC's should consider the age at presentation[29]. There are red flags and risk markers for premature ventricular contractions with a higher risk for SCD **(Table 2).**

Table 2. *Red flags and risk markers for PVC's with a higher risk for sudden cardiac death*

Items	Red flags
• History[29,36,86,141]	• Syncope or pre-syncope related to palpitations • Palpitations on activity or exertion • Known significant heart disease e.g. congenital heart disease • History of cardiac surgery • Family history of premature, unexplained, sudden cardiac death especially in a first-degree relative.
• On physical examination[86]	• Significant murmurs • Abnormal S3 or S4 • Displaced and diffuse point of maximal impulse or precordial heave • Signs of right or left heart failure, or both, eg, peripheral edema, elevation of jugular venous pulse, rales, S3, S4.
• After enough monitoring[36,86,141]	• Multifocal PVCs or nonsustained ventricular tachycardia • Polymorphic nonsustained ventricular tachycardia • Sustained ventricular tachycardia; this still may be idiopathic and have a benign prognosis but generally should prompt referral.
• On ECG[29,36,86,141]	• Short coupling R/T • Pathologic Q-waves • Coronary artery disease • Ventricular fibrillation • >10 PVCs per hour • Long QT-interval • Ventricular tachycardia • ST-segment elevation in leads V1and V2 consistent with a Brugada pattern • Epsilon-waves (in right ventricular arrhythmogenic cardiomyopathy)
• On Echo or MRI[29]	• LV dysfunction • Suspicion of ARVC on echo or MRI
• For cardiomyopathy[86]	• Multifocal PVCs, or non-sustained ventricular tachycardia on monitoring • Syncope on active exercise • Abnormal imaging findings that are consistent with arrhythmogenic right ventricular cardiomyopathy, cardiac sarcoidosis, or amyloidosis.

ARVC: Arrhythmogenic right ventricular cardiomyopathy, MRI: magnetic resonance imaging

PVCs as a Precursor for Ventricular Tachycardia and Ventricular Fibrillations

PVCs have also been shown to trigger malignant ventricular arrhythmias in certain patients with idiopathic ventricular fibrillation and other syndromes[30]. Ventricular tachycardia (VT) is the myocardial arrhythmias under His bundle branch and myocardial conduction fiber[20]. Wellens[47] defined VT as more than 100 beats/min, and three or more consecutive spontaneous PVCs. Six or more rapid PVCs (frequency>100/min) are considered as persistent VT (longer than 30 seconds), while less than 6 beats as non-persistent VT (episodes less than 30 seconds)[20]. Persistent VT is very dangerous, as it can trigger ventricular fibrillations (VF) and SCD[20]. Patients with PVC couplets are more inducer for VT than with single PVC[48]. A higher PVC burden (> 26 %/day) is associated with LVD, especially, in patients without SHD[13,49]. Although, univariate regression

analysis revealed that PVC couplets, multifocal PVCs, and polymorphic PVCs might be the predictors of VT, in opposite the multivariate analysis demonstrated that only PVC couplets were an independent predictor for VT, but not multifocal PVCs or polymorphic PVCs. Besides, PVC burden was also an independent predictor for VT. The results of multivariate analysis further indicated that depressed left ventricular ejection fraction (LVEF), extensive PVC burden and PVC couplets are the risk factors for the risk of VT and that PVC couplets were the factor with the highest risk for VT occurrence[20]. PVCs arising from the RVOT mostly accompanied to malignant ventricular arrhythmias. The ability of frequent PVCs originating from a focal source in triggering idiopathic VF in seemingly normal hearts was first reported by Haissaguerre et al.[50]. Analogous triggers have been shown in a few patients with long QT and Brugada syndromes, thereby reporting successful elimination of PVCs with catheter ablation[51]. Few studies regard PVCs as a trigger for VF were reported[52]. Regards MADIT (Multicenter Automatic Defibrillator Implantation Trial) type-II patients, a study of primary prevention of CAD and LVD. In this study revealed that PVCs triggered 77% of VF attacks[53]., Kakishita et al[54] described PVC-triggered VF. Sánchez et al[52] found the same consistency in VF-inducing PVC characteristics in their study in patients with Brugada syndrome. The PVCs were mapped to sites at the RVOT and also along with the distal Purkinje system in both left and right ventricles. Catheter ablation is effective in acutely aborting PVCs and decreasing the incidence of later VF recurrence[55]. (**Figure** 3)

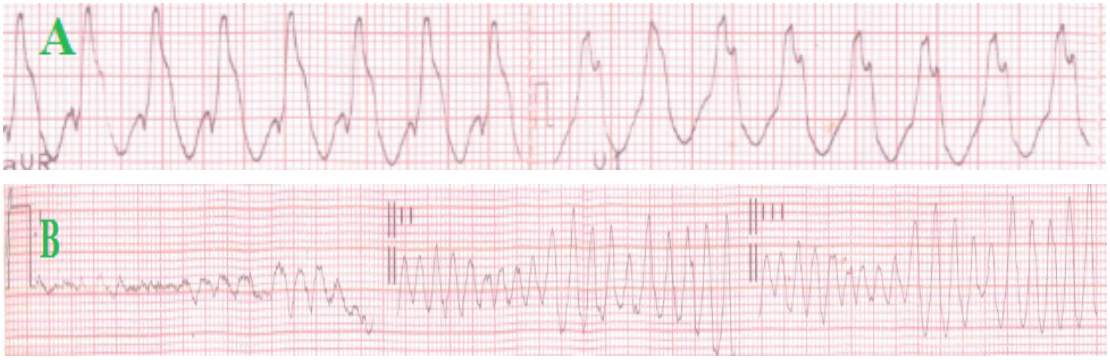

Figure 3. *ECG tracing A showing ventricular tachycardia (sustained ventricular tachycardia).ECG tracing B showing ventricular fibrillation*

PVCs-Induced Ventricular Dysfunction and Heart Failure

Historically

Indeed, in the last three decades, the concept of premature ventricular contraction-induced cardiomyopathy (PVCi-CMP) arised[56-59]. However, the concept of PVCi-CMP was proposed by Duffee et al. (1998) [60] when pharmacological suppression of PVCs in patients with presumed idiopathic dilated cardiomyopathy subsequently improved left ventricular(LV) systolic dysfunction.

Prevalence, Significance, Pathogenesis, Prognosis and Risk Factors

Indeed, about 50% of cases of congestive heart failure (CHF) are labeled as idiopathic, yet many may be secondary to excessive ventricular ectopic activity[61]. The prevalence of PVCi-CMP is estimated as only 5% to 7% among patients with a PVC burden >10%[62,63]. Most patients presenting with frequent PVC will not develop any PVCi-CMP at all[62,63]. An only small prospective study reported on the risk of subsequent development of PVCi-CMP [56,64]. Indeed, frequent PVCs are linked to the presence of subsequent development of progressive LV dilatation and dysfunction[13,65,66]. Arrhythmias maybe contribute to the development of CHF[66]. The presence of PVC has been linked with incidental HF[67]. Numerous studies have reported LV dysfunction in correlation with the presence of PVC's on Holter monitoring[13]. In the ARIC study, Agarwal et al.,[68] found that participants, who at baseline had no CHF or IHD, had an increased risk of incidental HF if PVC were present on baseline ECG. Further work by Agarwal et al.[69] demonstrated that the presence of PVC was associated with nearly a two-fold risk of systolic HF. There is evidence that left ventricular dilatation and dysfunction may be normalized and improved after successful catheter ablation of the PVCs[13, 62,70,71,72,73]. In 2000, a publication reported the first case of dilated

cardiomyopathy (DCM) with a high density of PVCs where radiofrequency catheter ablation resulted in complete recovery of ventricular function[74]. The mechanism responsible for PVCs-mediated LVD remains unclear[13]. Mechanisms and risk factors for PVCi-CMP remain largely debated[59]. The suggested mechanisms for PVC-mediated LV dysfunction include alterations in calcium homeostasis, increased oxygen consumption, and ventricular dyssynchrony[13]. Recurrent ventricular arrhythmias are responsible for significant mortality and morbidity in patients with CHF secondary to reduced ejection fraction (EF)[75]. The number of PVCs/24 h that is related to LV dysfunction has mostly been reported at burdens above 15–25% of the total cardiac beats, though this may be as low as 10%[30]. A significant number of PVCs is necessary to produce a deleterious effect[76]. This PVC burden is better expressed as PVC percentage over the total number of beats in 24-hour Holter monitoring. The critical value seems to be >20%; yet, some authors propose lower values, about 10% to 13%[77]. The number may be varied from 10% to 25%[76]. The duration of the PVCs is also a determinant factor for LVD[78]. PVCs with longer QRS-duration seem to be linked to LV function worsening[78]. A higher PVC burden is independently associated with PVC mediated LV dysfunction[13]. The cut-off PVC burden related to LVD was 26%/day, with a sensitivity of 70% and specificity of 78%[13]. The presence of retrograde P waves is independently liked to PVC-mediated LVD[13]. A retrograde contraction of the atrium following a PVC may cause abnormal atrioventricular contractility and transient LVD[13].

The Association Between PVCs and Cardiomyopathy

Indeed, there is a vicious cycle between PVCs and cardiomyopathy. However, since PVCs may be the result of underlying cardiomyopathy. It is difficult to accurately determine which of any of both was a sequence for the other[79]. So, PVC's and cardiomyopathy may co-exist in the same patient, it is difficult to determine prospectively which condition precedes the other[29]. Several studies have demonstrated an association between frequent PVCs and potentially reversible cardiomyopathy, which in selected patients resolves after catheter ablation[13,71,72,78,80,81]. PVC-induced cardiomyopathy" which consists of presumed idiopathic LVD with frequent PVCs, which after radiofrequency catheter ablation significantly improves ventricular function parameters[25,70]. Different meta-analyses of patients with apparently idiopathic cardiomyopathy confirm that ventricular function recovers with the improvement of ventricular volumes after catheter ablation of PVCs[28]. Probably, magnetic resonance imaging (MRI) can determine LVD recover after ablation depending on the magnitude of fibrosis detected by late gadolinium enhancement[1]. Radiofrequency catheter ablation of PVCs in patients can be simultaneously used with the indications of an implantable cardioverter-defibrillator (ICD) for primary prevention due to severe LVD. In the patients with very frequent PVCs, ejection fraction improves in a high proportion of patients and the indication of ICD could be withheld[82-84].

Arrhythmogenic Right Ventricular Cardiomyopathy is not Benign

Arrhythmogenic right ventricular cardiomyopathy (ARVC) may give rise to PVCs or non-sustained ventricular tachycardia with morphologies similar to those of RVOT PVCs and VT. The VT complicating ARVC is, like PVCs arising from the RVOT, commonly associated with exercise or activity. Unlike RVOT tachycardia, VT related to arrhythmogenic cardiomyopathy is not benign[85]. Distinguishing RVOT tachycardia from tachycardia secondary to arrhythmogenic cardiomyopathy is therefore critical[86]. Recently, MRI has been used most for infiltrative diseases as the imaging modality of choice due to its superior tissue characterization and noninvasive morphological and functional evaluation. MRI findings in patients with arrhythmogenic cardiomyopathy well linked with those of endomyocardial biopsy, angiography, and echocardiography and have been associated with incremental arrhythmic risk in the setting of electrical abnormalities[86].

Etiology and Risk Factors

Generally

Premature ventricular complexes are common both in patients with and without SHD[30]. Psychiatric; e.g. anxiety disorders, drug-induced; e.g. beta-agonists, abuse substance;e e.g. alcohol, electrolytes and metabolic disturbance; e.g. hypokalemia, endocrinal; e.g. thyroid function disorders, cardiovascular; e.g. myocardial ischemia, and miscellaneous causes; e.g. dental surgery. (**Table 3)**

The physician should be checked the following items in cases with frequent or symptomatic PVCs risk

factors: age and a family history of (sudden) heart disease, unrelated aspects: tobacco or coffee use[10,63]. African American ethnicity, male sex, lower educational attainment, and lower serum magnesium or potassium levels are directly related to PVC prevalence[87]. PVCs can be observed in both healthy people and patients with or without structural cardiomyopathy[44,88]. PVC couplets is the only highest risk factor for the development of VT in the patients with frequent PVCs[20]. PVCs in patients without apparent SHD are safe once we rule out risk factors[29]. There is evidence that patients with HTN and left ventricular hypertrophy are more likely to have PVCs[87].

Table 3. *Etiology and risk factors for premature ventricular contractions*[9,11,87,93,143-145]

Category	Aetiology
• Psychiatric	• Anxiety disorders
• Drug-induced	• Sympathomimetics Beta-agonists • Anti-arrhythmics • Digoxin toxicity
• Abuse substance	• Alcohol • Tobacco • Excess caffeine • Halothane
• Electrolytes and metabolic disturbance	• Hypokalemia • Hypomagnesaemia
• Endocrinal	• Hypercarbia
• Cardiovascular	• Thyroid function disorders
	• Myocardial ischemia • Myocardial infarction • Hypertension • Congestive heart failure (CHF) • Valvular heart disease • Idiopathic cardiomyopathy
• Miscellaneous	• Myocardial trauma • Dental surgery • Anal stretch • Light depth of anaesthesia

Ethnicity

There is a direct relationship between African American ethnicity and PVC prevalence[87]. There is a probable association of these PVC's with subclinical ARVC which is a leading cause of SCD in the Mediterranean region[37].

Aging and Infancy

The initial evaluation of frequent PVC's should consider the age at presentation[29]. The incidence and frequency of PVCs increase with age[51, 89,90]. In the age group of 45- 65 years prevalence, is roughly 6%[51, 89,90]. But the studies had failed to establish a sharp link between PVCs and SCD in older persons[51, 90]. Epidemiologically, PVCs are extremely rare in infants[93].

Diagnosis and Clinical

Medical history is essential that is including HTN, IHD, DCM, ischemic cardiomyopathy (ICM), smoking, and alcohol drinking[29]. Patients with frequent PVCs are often symptomatic[18, 91]. PVCs may be asymptomatic even for patients with a high frequency of these beats[30]. Patients may complain from an irregular heartbeat, missed beats or abnormally strong beats (due to the increased output of the post-ectopic sinus beat[91]. Although PVCs are often asymptomatic, PVC can manifest as palpitations, the difficulty of breathing, chest pain, fatigue, and dizziness[29]. The presence of PVCs such as in a bigeminal rhythm can significantly lower the effective heart rate, resulting in a low cardiac output state. In such instances, symptoms might include dizziness, near syncope, and syncope. Reduced stroke volume, may occasionally cause fatigue, exertional intolerance, dyspnea, and lightheadedness[92]. In more frequent PVCs (>10% heartbeats) fatigue and exertional dyspnoea may occur. When > 20% of heartbeats are PVCs, patients may develop cardiomyopathy and CHF[9].

Pvcs Workup

Resting12-Lead ECG

The ECG has been widely used to diagnose PVC[22]. Today, the ECG remains the simplest and cost-effective

non-invasive diagnostic method for determining PVCs arrhythmias[11]. They are recognized on the ECG by their wide (generally >120 msec) and bizarre QRS morphology, which occurs independently of atrial activation P waves[91,93]. ECG is very useful in the evaluation of myocardial scar (Q-waves or fractionated QRS-complexes), the QT interval, ventricular hypertrophy, and other evidence of SHD[30]. The electrical events of the heart detected with the ECG allow the PVC to be easily distinguished from a normal heart beat[20]. PVCs are usually have the following characteristics; the duration of more than 120 msec, bizarre-morphology that different than the usual aberrations (i.e. a typical RBBB or LBBB), T-wave in the opposite direction from the main QRS vector, and a fully compensatory pause[11]. The morphological features of the PVCs are the key for the presence or absence of SHD[94]. Scherf and Schott[95] recognized that PVCs with exceptionally wide QRS-complexes frequently occurred in SHD. Soloff [11] found that PVCs with a bizarre and distorted configuration was highly suggestive of underlying myocardial disease versus those with the "classic" smooth pattern. Morphology is important in localization the site of origin of PVCs before the ablation therapy that may potentially improve ablation outcomes[96].

The ECG May Point to the Origin of the PVCs

PVCs may originate from various foci[26]. If PVC focus is in the right ventricle, it would appear as LBBB and if it is in LV, it would appear as RBBB because in this state LV would depolarize earlier[26,86]. In general, there are three common regions are defined for PVC foci: RVOT, LVOT, and aortic cusp (AC)[26]. Roughly 60% to 80% of idiopathic PVCs originates from the right ventricle, in particular, the RVOT[97]. Outflow tract PVCs often occur only, or at much greater frequency, within a range of heart rates[98]. A PVC arising on the right side of the heart will activate the right ventricle first and then the left ventricle. This is analogous to the sequence of ventricular activation in a patient with LBBB. The right-sided PVCs look similar to the QRS complex seen in LBBB similar, but not identical. When describing PVCs or the morphology of non-sustained VT, the terms "LBBB-pattern" and "RBBB- pattern" refer to lead V1. If the PVC is negative (or mostly negative) in V1, the PVC has LBBB-pattern. A PVC that is positive in V1 is said to have RBBB-pattern and by implication arises from the left side of the heart. A PVC originating from the top of the heart will move from top to bottom. The electrical axis of the PVC will be directed inferiorly. This means the PVC will be strongly positive in the inferior leads, ie, II, aVF, and III[86]. If the PVC arises from the LVOT, the axis will still be inferiorly directed. However, the further to the left the origin of the PVC, the earlier the precordial transition will occur (the point at which the PVC is more positive than negative in the precordial leads). A PVC origin far enough to the left will result in RBBB-pattern PVC[86]. Not all idiopathic PVCs arise from the outflow tracts[86]. PVCs may arise from both the tricuspid and mitral valve annuli, the left ventricular fascicles, or from the epicardium[86]. RBBB-pattern PVC does not imply the presence of underlying SHD[86].

Ambulatory Monitoring (Holter Monitor and Event Recorder)

The type of monitoring to order depends on the frequency of the palpitations. If the patient reports several episodes per day, then a 24- or 48-hour Holter monitor should both allow for a diagnosis and document the PVC burden (i.e., the percent of the patient's heartbeats that are PVCs), or the burden of whatever is the cause of the patient's palpitations. If the palpitations are less frequent, a 14-to-30-day monitor should be considered. A standard event recorder can confirm that the palpitations are due to PVCs but do not tell you the PVC burden[86]. A Holter monitor or other monitoring system is useful in determining whether the PVCs are **unifocal** (all look the same) or **multifocal** (have more than one morphology) and whether, in addition to PVCs, the patient has nonsustained ventricular tachycardia or sustained ventricular tachycardia (by definition lasting longer than 30 seconds or associated with symptoms of hemodynamic compromise such as near-syncope)[86]. The load of PVCs can be detected by both Holter and event recording[9]. The ambulatory monitoring may detect asymptomatic **non-sustained-VT** that places the patient at higher risk of SCD and warrants further investigation[29]. The presence of at least some PVCs during 24-hour ambulatory monitoring is extremely common and may be considered normal[30]. The 24-hour Holter monitoring is essential for quantifying the PVCs burden[29] which is considered clinically significant when it exceeds 20000/24 hours[62]. Patients should be followed-up regularly by Holter monitoring especially when PVC's are > 15-2000/day[29]. Because the finding of PVCs during 24-hour ambulatory monitoring is very likely, any conclusion that they are related to symptoms requires careful correlation[30].

Echocardiography

Transthoracic echocardiography will rule out overt SHD such as assessment of RV and LV structure and function abnormalities, valvular disease, and pulmonary artery systolic pressure[29,30]. It is indicated for patients with symptomatic PVCs, a high frequency of PVCs (10% burden), or when the presence of SHD is suspected[30]. Patients should be followed-up regularly by echocardiography especially when PVC's are > 15-2000/day[29].

Exercise Testing and Premature Ventricular Complexes

For selected patients with symptoms associated with exercise, 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[29, 30,99]. Exercise treadmill stress testing is recommended for symptomatic PVCs with exercise or for whom an evaluation for IHD is indicated[29]. A negative exercise test can decrease the probability that catecholaminergic polymorphic ventricular tachycardia (CPVT) is the underlying cause. PVCs that worsens with exercise should prompt further investigation as these patients are more likely to require treatment[30,99]. If the patients are unable to exercise, pharmacologic stress testing with dobutamine or a vasodilator agent will be indicated [29].

Cardiac Magnetic Resonance Imaging (MRI)

The management of several forms of SHD with PVCs may be guided by MRI, including DCM, hypertrophic cardiomyopathy (HCM), sarcoidosis, amyloidosis, and ARVC[100-102]. ARVC is one of the important leading causes of SCD among athletes secondary to ventricular arrhythmias[103]. Indeed, 2010 updated Asian Society of Cardiac imaging[104] and the 2006 multi-society appropriateness guidelines[105,106], consider cardiac magnetic resonance imaging (CMR) highly appropriate for the evaluation of patients with suspected ARVC[29]. CMR has sensitivity and specificity of 79% and 85% in men, and 89% and 97% in women, respectively[107]. It is characterized by areas of scarring and fibrosis, with or without fatty infiltration, in the RV inflow, outflow tracts and/or apex. Besides, regional wall motion abnormalities including dyskinetic or focal aneurysmal walls occur, and that may progress to RV dilation and systolic dysfunction[29]. CMR is recognized as an important imaging tool to aid in the diagnosis of the ARVC 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) [108,109]. The 2010 revised Task Force Criteria includes minor and major CMR parameters for regional RV dysfunction, volumes, and global systolic dysfunction[107].

Signal-Averaged ECG

The detection of PVCs by means of Signal-averaged ECG (SAECG) is an important for the prediction of possible HF[110]. In suspected cases of ARVC, the SAECG may provide useful idea about a minor diagnostic criterion for this disorder[30].

Management

Treatment the Underlying Causes and Risk Factors

The management of PVCs should be initially focused on the correction of obvious causes and risk factors[111](**Table**). Aggressive management of cardiovascular risk factors, especially hypertension, would seem to be a prudent clinical response to a finding of PVCs on electrocardiography[33]. Asymptomatic patients, with normal LV ejection fraction and after exclusion of risk factors, warrant no treatment. They represent the majority of the patients[62].

Indications for the Treatment in Patients without Structural Heart Disease (SHD)

The following are indications for the treatment of PVCs in patients without SHD:

1. The most common indication for treating PVCs in the absence of SHD is the presence of symptoms that are not improved by reassurance[29,30,86]. 2. Frequent asymptomatic PVCs with longitudinal imaging surveillance shows an interval decrease in LV systolic function or an increase in chamber volume[30]. **3.** Patients with 10000 PVCs/24 hours on follow-up with repeated echocardiography and Holter monitoring[30].

Indications for the Treatment in Patients with Structural Heart Disease

When considering the need for further intervention and planning treatment for patients with PVCs, it is important to consider: (1) whether there is SHD; (2) the frequency of the PVCs and if VT has been documented; and (3) the frequency and severity of symptoms[10].

The following are indications for the treatment of PVCs in patients without SHD: 1. Presence of symptoms in patients with SHD is considering primary indication. 2. High burden PVCs (10%) in patients with impaired LV function can be associated with significant improvement of LV function[71,72], even when significant scarring is present[82,112]. 3. Patients with a very high burden (> 20%) are at high risk of arrhythmia-induced cardiomyopathy. In these patients, a referral is prudent, as some patients may opt for more aggressive treatment of their PVCs[86]. Patients who have a high PVC burden (> 10% of total heartbeats, though this is a subject of debate) should have an evaluation of their systolic function[86].

Reassurance

For patients without structural heart disease and mild symptoms, the first step in the treatment of patients with PVCs is reassurance[30].

Antiarrhythmic Drugs (AADs)

No drugs are approved by the US Food and Drug Administration for treating PVCs or **non-sustained VT**[86].AADs should be considered in case of frequent PVCs[9]. Treatment with a type Ic drugs (propafenone and flecainide) or a type III drug (sotalol, amiodarone, and dofetilide) was studied vs catheter ablation. Treatment with class I or class III AADs always entails a small risk of proarrhythmia. The choice of drug therapy or ablation therapy is highly individualized[86]. Patients with known IHD should be on beta-blockers (BBs) therapy due to the proven benefits on cardiovascular morbidity and mortality: this may also help suppress PVCs[51]. BBs may be used to control symptoms from **multifocal PVCs**. It should also be considered in patients along with aldosterone antagonists with impaired ventricular function and/or heart failure[51]. No large-scale randomized trials of drug treatment for PVCs in the absence of SHD have been performed[113]. For patients whose symptoms are not effectively managed in this manner, a trial of BBs or non-dihydropyridine calcium channel blockers (CCBs) may be considered although the efficacy of these agents is quite limited with only10–15% of patients achieving 90% PVC suppression[114], similar to placebo[113]. The data supporting the use of CCB are less than for BBs and that these agents may themselves produce significant symptoms. While membrane-active AADs are more effective to suppress PVCs, the risk-benefit ratio has not been carefully evaluated in patients without SHD. Nevertheless, these agents are highly effective and may significantly improve symptoms in markedly symptomatic patients. Because these agents may increase the risk of mortality in patients with significant SHD, perhaps with the except for amiodarone, caution is advised before using them for PVC suppression[114,115]. The drugs that indicate for the treatment of ventricular arrhythmias are labeled as being indicated for "**sustained**" or "life-threatening" ventricular arrhythmias. The use of drugs for the treatment of PVCs or non-sustained VT represents off-label usage[86]. Regardless of whether the patient has PVCs, non-sustained ventricular tachycardia, or both, the management approach is the same[86]. Chronic antiarrhythmic therapy may be ineffective and poorly tolerated[1]. Failure of a beta-blocker, a calcium channel blocker, or both often result in referral to a cardiologist or electrophysiologist[86]. There is strong evidence against suppressing PVCs with antiarrhythmics (SOR: A, randomized controlled trials [RCTs]) [36]. Nor is it clear that VPC suppression, if it could be safely performed, would decrease risks[33].

Antiarrhythmic Agents using in Suppressing of Frequent PVCs Increased the Mortality

Studies have evaluated whether suppressing PVCs with antiarrhythmic agents improves prognosis[36]. Both Cardiac Arrhythmia Suppression Trials (CASTI: encainide and flecainide; CAST II: moricizine) showed that suppressing frequent PVCs significantly increased mortality in the treatment groups[4,116]. According to the CAST report[117], when antiarrhythmic drugs such as flecainide and encainide were administered for the treatment of asymptomatic or mildly symptomatic ventricular arrhythmia occurring following MI, the mortality rate was significantly higher in patients given these drugs than in the placebo group. Randomized trials have shown that antiarrhythmic drugs suppress PVCs but increase the risk of SCD[118,119]; thus, the use of these drugs for PVCs suppression is not generally recommended[33]. Administration of AADs appears to worsen prognosis, and physicians' attention was called to conventional drug therapy for arrhythmia[120].

Nitroglycerin a New Therapy for Variable Ischemic PVCs

Recently, nitroglycerin was introduced by the author as a newer antiarrhythmic agent in two case reports. The first reported case (2017)[7] was a case of ischemic PVCs-bigeminy had shown a dramatic response to a

trace dose of intravenous nitroglycerin infusion. The second reported case (2019)[8] was another case of ischemic PVCs-quadrigeminy had shown a dramatic response to a trace dose of intravenous nitroglycerin infusion.

Catheter Ablation

The following are the possible indications for the treatment with catheter ablation: 1. Severe symptom control when the use of AADs is ineffective or unfavorable[1,29,30,86, 121,122]. 2. To prevent recurrence in PVC-triggered ventricular fibrillation[121,122]. 3. To potentially reduce the effects of PVC-induced cardiomyopathy[121,122]. 4. It may also be helpful when frequent PVCs interfere with cardiac resynchronization therapy[1,123]. 5. If the patients are not responding to cardiac resynchronization therapy due to suboptimal pacing due to PVCs[112]. 6. Catheter ablation of PVCs is recommended for highly selected patients who remain very symptomatic despite conservative treatment or for those with very high PVC burdens associated with a decline in LV systolic function[30]. 7. Unifocal PVCs arising from the RVOT is common and may increase with exercise and cause sustained or nonsustained VT[51]. 8. It may be considered as an adjunctive treatment[51]. Catheter ablation appears as an effective treatment option[9]. However, multiple studies indicate high efficacy of ablation with PVC elimination in 74–100% of patients [26,124-136]. Ablation is successful if the burden of PVCs, usually more than 10000/ 24 hours allows for meaningful mapping[29]. Ablation usually targets the RVOT or less frequently the LVOT[29]. 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[29]. However, these studies have typically included highly symptomatic patients typically with a very high burden of PVCs. Thus, catheter ablation should only be considered for patients who are markedly symptomatic with very frequent PVCs [129--137]. Although complete PVC elimination is the goal of ablation, it should be noted that partial success may still be associated with significant improvement in LV systolic function. The efficacy of catheter ablation may be reduced for patients with multiple morphologies of PVCs or those for whom the clinical PVC morphology cannot be induced at the time of the procedure. The published complication rates of catheter ablation for PVC suppression are generally low (1%)[30].

Implantable Cardioverter-Defibrillator (ICD)

In a small cohort of patients with ARVC, an ICD, and refractory VT, flecainide was recently demonstrated to reduce arrhythmia recurrence[138]. Risk of SCD from malignant ventricular arrhythmia should be considered in patients with SHD who have frequent PVCs. ICD may be indicated if risk stratification is met[51].

Conclusion

Premature ventricular contraction maybe benign and may be a serious arrhythmia. Early and rapid verification of premature ventricular contractions hurry avoidance of the serious outcome. Recent efficient use of nitroglycerin in many types of premature ventricular contractions make it for in front of future selection as an antiarrhythmic drug.

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