

INVITED REVIEW

State-of-the-art look at premature ventricular complex diagnosis and management: Key messages for practitioners from the American College of Cardiology Electrophysiology Council

Ventriküler erken vuruların tanı ve tedavisinde son durum: Amerikan Kardiyoloji Cemiyeti Elektrofizyoloji Konseyi dokümanından klinisyenlere anahtar mesajlar

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Summary– Premature ventricular complexes (PVCs) are one of the most common arrhythmias seen in daily practice. Although PVCs are generally considered benign, they can lead to the development of cardiomyopathy and, rarely, can be associated with sudden cardiac death. Recently, the American College of Cardiology Electrophysiology Council published a state-of-the-art review on PVCs to provide diagnostic and therapeutic considerations for clinical practice. Presented are some important points about the diagnosis, approach, and treatment of PVCs.

Premature ventricular complexes (PVCs) are one of the most common arrhythmias observed in daily practice. Although PVCs are generally considered benign, they can lead to the development of cardiomyopathy (CMP) and, rarely, can be associated with sudden cardiac death (SCD). The American College of Cardiology Electrophysiology Council has published a state-of-the-art review on PVCs.^[1] This article is a brief summary of the document and some key points on the diagnosis and management of PVCs.

Epidemiology and Pathophysiology

Some 1% of 12-lead electrocardiograms (ECGs) may demonstrate PVCs and the frequency may be 40% to 75% in 24- or 48-hour Holter monitoring of healthy individuals.^[2] PVCs can occur via 3 different mechanisms. In structurally normal hearts, delayed afterdepolarizations can cause the triggered activity. Re-entry

Özet– Ventriküler erken vurular (VEV), klinikte en sık karşılaşılan aritmilerden birisidir. Genellikle iyi huylu olarak kabul edilmesine rağmen, kardiyomiyopati gelişimine sebep olabilir ve nadiren de ani kardiyak ölüm ile ilişkili olabilir. Yakın zamanda Amerika Kardiyoloji Koleji Elektrofizyoloji Konseyi VEV'lere ilişkin tanısal ve tedavi edici hususlar hakkında klinik pratiğe ilişkin son durumu bildiren bir derleme yayınlamıştır. Biz bu yazıda güncel raporların ışığında VEV'lerin tanısı, yaklaşım ve tedavi yöntemleri hakkında önemli noktaları sunduk.

is the main mechanism in patients with structural heart disease (SHD), due to heterogeneous conduction. Finally, abnormal automaticity describes the spontaneous initiation of the action potential and can be seen in parasystole or ischemia-reperfusion states.^[1]

Clinical Management

Some patients with PVC are asymptomatic and the PVC is detected incidentally during an ECG examination for another reason. Others may experience dizziness, fatigue, dyspnea, syncope, or heart failure symptoms. An evaluation of medical and family history can provide valuable information about the underlying condition or inherited arrhythmia. Diagnostic tests can provide important clues for patients with PVC in terms of the presence, frequency, characterization, determination of the underlying etiology, and the need for treatment.

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Diagnostic Tests

Electrocardiography

A 12-lead surface ECG can provide information of underlying SHD, such as arrhythmogenic right ventricular cardiomyopathy/dysplasia, and it can offer valuable clues about the possible origin of PVC. QRS width, QRS axis, bundle branch block pattern, and precordial transition are parameters frequently used to determine localization in an ECG.^[1] There are practical algorithms for defining the origin of a PVC (Fig. 1a, b).

Ambulatory monitoring

Ambulatory monitoring is used to determine the burden of PVCs in a 24-hour period. Whether PVCs are unifocal or multifocal, the presence of non-sustained or sustained ventricular tachycardia (VT) and the PVCs' relationship to symptoms can be evaluated using ambulatory monitorization. Single or serial 24-hour Holter monitoring can be used, or a longer duration of 48 or 72 hours. The origin of ventricular arrhythmia, changes in the QT interval and the ST segment can be determined with 12-lead Holter monitoring.^[1]

Echocardiography

Echocardiography is a practical tool used to evaluate cardiac structure and function. In the presence of a frequent ectopic rhythm, the left ventricular ejection fraction (LVEF) should be assessed carefully. The LVEF should be measured in non-PVC cycles, the second beat of 2 consecutive sinus rhythm beats, or an average LVEF measurement can be used in the presence of ventricular bigeminy.^[1]

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is superior to echocardiography in terms of the early detection of SHD and scar analysis. Late-gadolinium enhancement (LGE)-cardiac MRI is a successful means of identifying any form of SHD, microvascular obstruction, myocardial edema, or fibrosis. A recent meta-analysis and systematic review has shown that LGE can predict ventricular arrhythmic events.^[3] Cardiac MRI can distinguish between areas of fibrosis caused by ischemic and non-ischemic CMP. Unlike ischemic CMP, scar distribution in non-ischemic CMP is typically in the epicardium and mid-wall, and is not compatible with the coronary artery distribution.^[4]

Exercise testing

Exercise testing is useful in the assessment of underlying structural abnormalities, ischemic heart disease, and familial arrhythmic conditions. In a pediatric patient group without underlying heart disease, suppression of PVCs with light exercise was associated with benign prognosis.^[5] However,

in patients with known or suspected cardiovascular disease, PVCs during exercise testing or the recovery phase of exercise testing may be associated with an increased risk of cardiac events and mortality.^[6-8]

Coronary angiography

Coronary angiography is indicated in patients with positive exercise testing or symptoms consistent with myocardial ischemia. It is also useful for evaluating the proximity to coronary arteries during catheter ablation (CA), especially in the aortic cusps, the coronary sinus, the middle cardiac vein, or the epicardial approach via the subxiphoid route. Computed tomography coronary angiography may be of limited quality in patients with frequent PVCs due to PVC-related motion artifacts.^[1]

Fluorodeoxyglucose cardiac positron emission tomography

Fluorodeoxyglucose positron emission tomography (FDG-PET) is a technique used to evaluate myocardial ischemia and inflammation. However, false positive results can occur in the evaluation of myocardial inflammation with this technique. A cardiac MRI may not show changes in the early stages of myocarditis; therefore, both LGE-cardiac MRI and FDG-PET used together can increase diagnostic accuracy, especially in cases of a high suspicion of myocarditis.^[1]

Electrophysiology studies

An electrophysiological study may aid in risk stratification of SCD. It is also the basic technique to determine the mechanism and localization of PVCs.

Abbreviations:

3D	Three-dimensional
AAD	Antiarrhythmic drug
CA	Catheter ablation
CMP	Cardiomyopathy
ECG	Electrocardiogram
FDG-PET	Fluorodeoxyglucose positron emission tomography
LGE	Late-gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PVC	Premature ventricular complex
RF	Radiofrequency
SCD	Sudden cardiac death
SHD	Structural heart disease
VT	Ventricular tachycardia

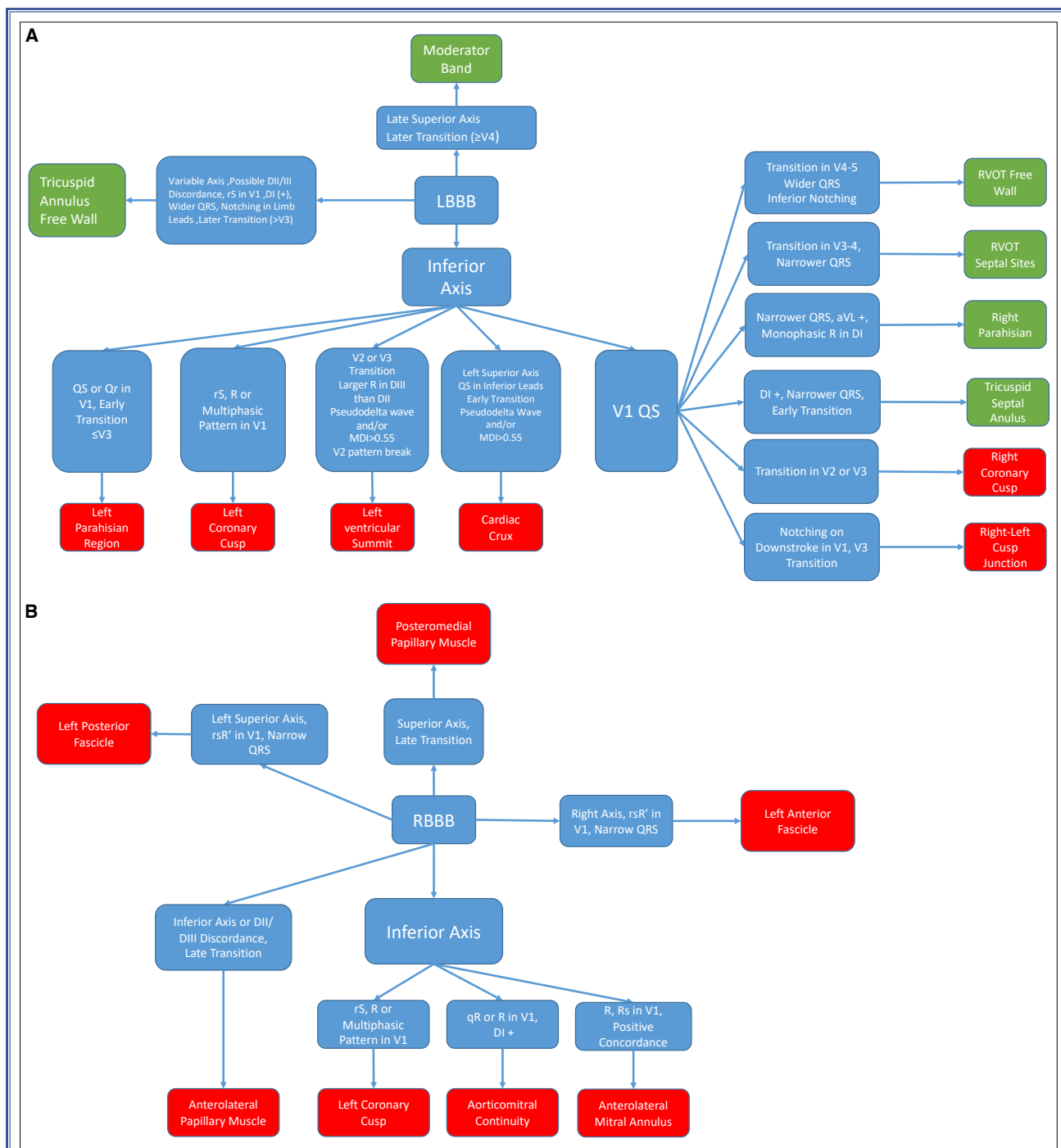


Figure 1. Twelve-lead electrocardiography findings used to determine idiopathic PVC localization. **(A)** Left bundle branch block, **(B)** right bundle branch block. Green boxes indicate right-sided premature ventricular contractions (PVCs) and red boxes indicate left-sided PVCs. LBBB: Left bundle branch block; MDI: Maximum deflection index; PVC: Premature ventricular contraction; RBBB: Right bundle branch block; RVOT: Right ventricle outflow tract.

PVCs associated with the triggered mechanism are often sensitive to catecholamines. Drugs used for sedation and pain control may suppress PVCs and sympathomimetic agents may be required. Programmed stimulation can be particularly useful for PVCs with

a re-entry mechanism. A change in the beat-to-beat conduction interval occurs as a result of variable conduction across the myocardial tissue and indicates a re-entry mechanism. Three-dimensional (3D) mapping systems help to understand the electroanatomical

configuration of the ventricle, show electroanatomical activation, and can aid in successful ablation despite infrequent PVCs.^[1]

Characterization of Benign and Non-Benign PVCs

Especially in SHD, PVCs may be predictors of life-threatening arrhythmias and SCD. Underlying structural, electrical, or ischemic diseases; very frequent or complex PVCs, such as couplets, triplets, and nonsustained VT; multifocal PVCs; an increasing number of PVCs during exercise; non-outflow tract PVCs and non-left ventricular (LV) fascicular PVCs; short coupling intervals; and wider PVCs indicate a potentially non-benign character in a PVC.^[1]

PVCs in Patients with No Underlying SHD

PVCs in the absence of SHD are referred to as an idiopathic PVC. Idiopathic PVCs generally have a benign nature, although they carry a potential risk for CMP and, very rarely, cause polymorphic VT/ventricular fibrillation. An idiopathic PVC tends to be monomorphic and typically originates from the right ventricular outflow tract, left ventricular outflow tract, left ventricular fascicles or, less commonly, from the mitral and tricuspid annuli.^[1]

In symptomatic patients with a PVC in a normal heart, beta blockers and non-dihydropyridine calcium channel blockers have a Class I recommendation.^[9] Antiarrhythmic drugs (AADs) are generally avoided, with a Class IIa recommendation that includes benefits and potential adverse effects. If drug therapy is ineffective, not tolerated, or undesired, CA is a highly effective treatment recommended as Class I.

PVCs in Patients with Underlying SHD

PVC and cardiomyopathy

Before making the diagnosis of PVC-induced CMP, any underlying form of SHD should be excluded and the frequency of PVCs should be evaluated. There is no precise cut-off value for PVC burden that causes CMP development. Some studies have suggested that a PVC load of 10% to 24% or more than 10,000 PVCs per day may be predictive of CMP development.^[10,11] However, speckle-tracking studies have shown that a more than 8% daily PVC load may be associated with impaired global longitudinal strain.^[12] Not just the frequency of PVCs, but also the presence of nonsustained

VT, interpolated PVCs, retrograde P waves, QRS duration of PVC, epicardial origin and right ventricular origin compared to left ventricular origin, male gender, older age, higher body mass index, lack of circadian variability of PVC, lack of symptoms, and longer coupling intervals have been associated with LV dysfunction.^[1] Suppression of PVCs with CA with the suspicion of LV dysfunction due to frequent PVCs can improve LV function, even in the presence of SHD.^[1,13]

Myocarditis

Myocarditis may be accountable for unexplained ventricular arrhythmias, including PVCs. Acute and chronic myocarditis may be an underlying etiology of PVCs.

Ischemic heart disease

Myocardial infarction (MI) can be a substrate for frequent PVCs that cause LV dysfunction. In patients with ischemic heart disease, a PVC burden can adversely affect LV function and the LVEF can improve after successful ablation.

Treatment

General recommendations and medications

Lifestyle changes, such as avoidance of caffeine, tobacco, alcohol, and anxiety, may reduce the burden of a PVC.^[1] Electrolyte disturbances, such as hypokalemia and hypomagnesemia, may be predisposing factors for PVCs. Beta-blockers or non-dihydropyridine calcium channel blockers can improve symptoms and they can decrease the burden of PVCs. They should be used in the minimum effective dose. In patients without SHD who are unresponsive to beta blockers or calcium channel blockers, AADs, primarily flecainide and propafenone, may be considered to reduce the frequency of PVCs and to improve symptoms. Note that, Class Ia and Ic AADs are contraindicated in patients with SHD. Amiodarone has been shown to be effective in patients with a PVC with reduced LVEF, but it has not demonstrated any effect on mortality.^[1]

Catheter ablation

CA is commonly used to eliminate PVCs and to improve PVC-related consequences. The indications for CA in PVC treatment are presented in Table 1. Electrical information showing the focus of the PVC is combined with images from fluoroscopy, 3D systems,

Table 1. Catheter ablation indications for premature ventricular contractions^[11]**Idiopathic outflow tract PVCs**

- Frequent and symptomatic PVCs originating from RVOT (Class I B-NR)
- If antiarrhythmic medication is ineffective, not tolerated, or patient's choice;
- In patients with symptomatic PVCs originating from RVOT (Class I B-NR)
- In patients with symptomatic PVCs originating from endocardial LVOT and sinus of Valsalva (Class IIa B-NR)
- In patients with symptomatic PVCs originating from epicardial outflow tract or LVOT summit (Class IIa B-NR)

Non-outflow tract PVCs in the absence of structural heart disease

- If antiarrhythmic medication is ineffective, not tolerated, or patient's choice
- In patients with symptomatic PVCs originating other than from RVOT (tricuspid anulus, moderator band, parietal band, or papillary muscle) (Class I B-NR)
- In patients with symptomatic PVCs originating other than from LVOT (mitral annulus, papillary muscles, or aortic-mitral continuity) (Class I B-NR)
- In patients with symptomatic PVCs from epicardial venous system (Class IIa B-NR)
- In patients with symptomatic PVCs from para-Hisian site (Class IIa B-NR)
- In patients with symptomatic PVCs originating from posterior-superior process of LV, catheter ablation from the LV endocardium, right atrium, or coronary sinus can be useful. (Class IIa C-LD)

PVCs with or without left ventricular dysfunction

- If antiarrhythmic medication is ineffective, not tolerated, or not preferred for long-term therapy
 - In patients with cardiomyopathy suspected to be caused by with frequent and predominately monomorphic PVCs (Class I B-NR)
 - In patients with structural heart disease and PVCs, the PVCs are suspected to be a contributing factor of cardiomyopathy (Class IIa B-NR)
- In patients with focally triggered ventricular fibrillation refractory to antiarrhythmic therapy and triggered by a similar PVC (Class IIa B-NR)
- If very frequent unifocal PVCs are limiting optimal biventricular pacing in nonresponders to cardiac resynchronization therapy (Class IIa C-LD)

LV: Left ventricle; LVOT: Left ventricular outflow tract; PVC: Premature ventricular complex; RVOT: Right ventricular outflow tract.

Level of evidence B-NR: Data derived from one or more non-randomized trials or meta-analysis of such studies; C-LD: Non-randomized observational studies with limitations in design or execution or metanalysis of such studies.

or intracardiac echocardiography. Activation mapping and pace mapping techniques are useful in localizing the origin of PVCs. Radiofrequency (RF) energy is more effective, but cryoablation is safer in hazardous locations near the conduction system.

A PVC can originate from the endocardium, mid-myocardium, or the epicardium. Particularly PVCs in cases of non-ischemic CMP, such as idiopathic dilated CMP, myocarditis, sarcoidosis, Chagas disease, and Brugada syndrome, are generally associated with midmyocardial or epicardial origins. Post MI-related PVCs often have endocardial origins, though they may also have midmyocardial or epicardial origins.^[14] The presence of a subepicardial or midmyocardial scar seen on contrast-enhanced computed tomography or a

cardiac MRI, some surface ECG features (such as a maximum deflection index of ≥ 0.55 or pseudo-delta waves of ≥ 34 ms in precordial leads) favor an epicardial origin. In addition, endocardial unipolar voltage mapping can reliably identify an epicardial substrate in the absence of endocardial bipolar abnormalities. The presence of a ventricular thrombus in preprocedural imaging is an indication for epicardial access.^[1,14]

The most common complications of CA for PVC are vascular complications, such as hematoma, pseudoaneurysm, or arteriovenous fistula (1.3%), followed by pericardial complications, such as cardiac tamponade (0.8%).^[15] Cerebral emboli or intracerebral bleeding are major neurological complications of CA (0–2.7%). Atrioventricular blocks can occur when

energy is delivered close to the conduction system (0.1%).^[15] Coronary injury may occur during catheter manipulations or ablation in the aortic root. Heart failure and pulmonary edema may develop as a result of external irrigation, sympathetic response due to ablation, or VT induction. Valvular injury is also less frequently seen (up to 0.7%). This complication may occur as a result of retrograde passage of the aortic valve with an ablation catheter, ablation of the aortic valve region, entrapment of the ablation catheter in the mitral or tricuspid valve, and ablation of the papillary muscles. During subxiphoid transpericardial puncture, an inadvertent right ventricle puncture, laceration or puncture of an epicardial coronary artery or vein, or coronary artery spasm may occur. As a result of RF ablation or cryoablation in the epicardial space, coronary artery injury or spasm or phrenic nerve paralysis may be seen.^[14]

The CA endpoints for PVCs are considered to be the elimination and non-inducibility of PVCs with a catecholamine infusion or electrical stimulation. Generally, acute procedural success is defined by the elimination of PVCs at least 30 minutes after the last ablation. Ambulatory monitoring plays a role in determining the success of procedure rates and recurrence. In most clinical studies, ablation success is defined as 80% reduction in the PVC burden compared with pre-ablation. Higher CA success rates are observed in PVCs originating from the right ventricular outflow tract and the cusp region. However, the PVCs originating from the papillary muscle or epicardial region are hard to ablate and have lower success rates. Multifocal PVCs are also associated with ablation failure and longer procedure duration.

Intracardiac echocardiography helps to verify catheter stability and catheter contact during ablation of PVCs originating from the papillary muscle.^[16] Cryoablation can also be beneficial in the ablation of PVCs originating from the papillary muscle by providing stable contact with tissue; it creates less damage than RF ablation and the recurrence rate with cryoablation is higher. Cryoablation may be preferred in cases where there is a high risk of coronary artery injury or AV block.

Conclusion

PVCs and symptoms related to PVCs are frequently seen in clinical practice. They can occur in patients

with or without SHD. When planning treatment, it is very important to evaluate any underlying structural heart disease, PVC burden, and the relationship of PVC to symptoms. Beta blockers and AADs can be used in medical treatment. When medical treatment is ineffective, not tolerated, or not desired by the patient, CA treatment can be an option to be considered when performed in experienced centers with high success and low complication rates.

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