Management of premature ventricular complexes

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Learning objectives

- Care pathways for management of premature ventricular complexes (PVCs) including screening for structural heart disease, PVC burden, cause and effect relation with left ventricular dysfunction when present.
- Site of origin for common PVCs.
- Role of pharmacological therapy and catheter ablation.
- Risk stratification for sudden cardiac death.

INTRODUCTION

Premature ventricular complexes (PVCs) are the most common arrhythmias in daily practice. At the cellular level, ventricular myocytes spontaneously depolarise to create an extrasystole 'out of sync' with the cardiac cycle.[1] The prevalence depends on the characteristics and comorbidities of the population, the method by which the population is studied and the duration of observation. PVCs have been described in 1% of clinically normal people on standard electrocardiography (EKG) and 40%–75% of healthy people assessed by short-term ambulatory monitoring.[2] Atherosclerosis Risk in Communities, a large population-based study of 15 792 Americans aged 45–65 years, demonstrated a higher prevalence of PVCs with age, structural heart disease (SHD), hypertension, African–American ethnicity, male sex and lower education.[3]

PVCs are generally benign in patients without SHD.[4 5] However, PVCs can be a trigger for life-threating arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) causing sudden cardiac death (SCD), especially in patients post-myocardial infarction (MI). Risk stratification for PVCs varies in specific populations with underlying cardiac disease, family history, genetic variants and sometimes coupling interval. The differing implications with these variables is the basis of this review.

SYMPTOMS

The symptoms of PVCs are variable. Patients often have palpitations described as fluttering, pounding, skipping beats or often a strange sensation in the neck. Others may have fatigue, shortness of breath or change of stamina and endurance. The increased stroke volume of the post-PVC beat may cause chest discomfort. Non-sustained or sustained episodes of VT may be associated with presyncope or syncope.

In contrast, many patients are asymptomatic, sometimes even with bigeminal PVCs or non-sustained VT. Symptoms can often be non-specific when patients with frequent PVCs and even preserved left ventricular (LV) function may report a 'vague fatigue' associated with higher N-terminal pro B-type natriuretic peptide and circumferential end-systolic wall stress. These have been shown to resolve after a successful ablation.[6]

PVCS WITH AND WITHOUT SHD

At the outset, one should establish whether PVCs exist in the presence or absence of SHD. Studies have shown that patients with frequent PVCs after MI have higher risk of mortality and SCD.[7 8] Does PVC suppression in this situation help? The prospective Cardiac Arrhythmia Suppression Trial (CAST) randomised patients after an MI to PVC suppression with encainide, flecainide or placebo.[9] Pharmacological PVC suppression had adverse effects on the treatment group by increasing mortality from arrhythmic and non-arrhythmic cardiac causes. This raised concerns for proarrhythmic and negative inotropic properties of these agents, restraining use of class IC antiarrhythmic drugs (AADs) in patients with SHD.

Amiodarone has been used for patients with frequent PVCs after MI in two prospective randomised controlled trials, the European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Arrhythmia (CAMIAT) investigations. Both trials showed that amiodarone reduced the incidence of VF or arrhythmic death among survivors of acute MI with frequent PVCs but no reduction in all-cause mortality.[10 11] Neither trial supported the prophylactic use of amiodarone in these patients but showed a rationale for its use for symptomatic PVCs or in patients with impaired LV function.

EKG and echocardiography are most commonly used to screen for SHD. Stress testing, nuclear imaging and late gadolinium enhancement with cardiac MRI (LGE-CMR) are useful for further evaluation of ischaemia, inflammation and scars. Patients with pleomorphic PVC have a higher prevalence of scarring.[12] Most patients with low burden of monomorphic PVCs (generally <5%) in the absence of SHD have a fairly benign course.

PVC-INDUCED CARDIOMYOPATHY

We first shared our experience with PVC ablation in 23 patients showing positive impact of successful ablation on LV function in patients with frequent ventricular ectopy.[13] Prior anecdotal studies had shown that frequent PVCs lead to impairment of LV function which can be reversible.[14] Bogun *et al* showed a positive impact of PVC suppression versus a control group[15] and all this has increased our understanding about 'PVC-induced cardiomyopathy' (PIC).[16]

The diagnosis of PIC is based on the presence of LV systolic dysfunction with frequent PVCs and absence of an alternate cause. If the chronology of

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events is known and PVCs antedate the LV dysfunction, the diagnosis is more obvious. The diagnosis is less obvious when the cardiomyopathy and frequent PVCs are discovered simultaneously, especially if the PVC burden is not very high. In such situations, the diagnosis of PIC is made in hindsight when PVC suppression by an ablation or AADs reverses the LV dysfunction.

Patients with a pre-existing cardiomyopathy can also have worsening of LV dysfunction with frequent ventricular ectopy. In our opinion, this is a situation where the 'PVC aggravated cardiomyopathy'. The existence of this phenomenon is supported by a study of El Kadri *et al*[17] showing that patients with pre-existent cardiomyopathy and a PVC burden of >5% had significant improvement if not normalisation of LV dysfunction by PVC suppression. The PVCs in these patients most often originated within or close to the scar. In contrast, there is currently not much evidence to show LGE-CMR in patients with PIC but in patients with a PVC-aggravated cardiomyopathy, there is more obvious scarring. This could be a significant physiological and prognostic difference between the two.

What burden of PVCs predisposes to LV dysfunction or worsening left ventricular ejection fraction (LVEF)? Baman *et al* showed that a PVC burden of >24% was thought to best separate the recovery of LV function after catheter ablation.[18] In general, a burden of 16%–26% has been reported to be responsible for a PIC though rarely a burden as low as 4% has been reported as a culprit. We feel that it is reasonable to be suspicious in a patient with a burden of 10% or more with a drop in LVEF in most cases,[19–21] and suppression of these can lead to partial or complete reversal of cardiomyopathy.

What predisposes some patients to have a cardiomyopathy and not others? The 'burden of PVCs' continues to be the most significant risk factor. Other factors identified are a duration of the QRS complex greater than 140 ms,[22–25] an epicardial origin,[23 26] the duration for which PVCs have been present, interpolated PVCs, asymptomatic status (frequent PVCs may go unrecognised and untreated longer), male sex and lack of circadian variability. The odds ratio (OR) for developing PIC with very frequent PVCs is about 4 in patients with a duration of 30–60 months and 20 in patients with a duration of over 60 months.[27] PVC suppression in patients with PIC results in a significant improvement or normalisation of LVEF and, hence, likely to confer survival benefit.

The proposed mechanisms for PIC are mechanical interventricular dyssychrony, intraventricular torsional changes, abnormal diastolic filling and elevation of heart rates.[28] In animal studies using swine and canine models, a PIC develops in a few weeks with pacing in a bigeminal pattern from a programmed pacemaker.[25 29 30] Pacing from certain locations such as the epicardium resulted in lower LV function as well as greater fibrosis in the ventricle compared with pacing from the right ventricular (RV) endocardium.[28] At the cellular level, the changes involve the calcium currents and changes in the sarcoplasmic reticulum.[31]

MANAGEMENT OF PVCS

Diagnostic evaluation

Initial evaluation should include assessment for symptoms, exacerbating and relieving factors, signs of heart failure, ambulatory monitoring to assess PVC burden, an ischaemia evaluation to rule out coronary artery disease, an echocardiogram to assess the LV volumes, valves, LVEF and RV function for any cardiomyopathy. We prefer a 12-lead holter to assess PVC burden and morphology analysis to determine whether the PVCs are monomorphic or pleomorphic. This helps define the best candidates for an ablation as patients with one or two morphologies with a reasonably high burden per focus are likely most appropriate. A cardiac MRI is fairly reasonable in patients with frequent PVCs and a cardiomyopathy or in patients with suspicion for an underlying SHD like an RV or LV cardiomyopathy, sarcoid or other infiltrative diseases. A positron emission tomography (PET) scan should be considered in inflammatory disorders like sarcoid where immunosuppressive therapy would be the first-line therapy. An exercise stress test should be considered when there is suspicion for catecholaminergic polymorphic ventricular tachycardia (CPVT).

Proposed management algorithm

In figure 1, we propose a management algorithm for patients with frequent PVCs. After the initial diagnostic evaluation, we first separate out patients who have PVC-induced sustained ventricular arrhythmias like VT or VF. PVC suppression is essential in patients where short coupled PVCs induce sustained VT or VF.[32 33] Due to the curative nature and more durable results, we consider catheter ablation as a first-line approach in these patients. If unsuccessful, AAD therapy would be the next step. Due to the continuing risk of VF in these patients, an implantable cardioverter defibrillator (ICD) is an important complementary need. Patients with low risk sustained VT like those from the ventricular outflow, fascicular VT and papillary muscle VT without underlying SHD are at low risk of SCD and usually do not need an ICD, but PVC/VT suppression with ablation or AADs is reasonable.

For other patients, it is useful differentiate those who have normal LV function from those with LV dysfunction. In patients with PIC or PVC aggravated cardiomyopathy, guideline-directed medical therapy for LV dysfunction should be initiated regardless of PVC burden. The PVC burden could be considered as low (<5%), moderate (5%–20%) or high (>20%). This is based on the fact that patients with a burden of 5% or more have shown association with worsening LV function. A conservative cut-off of 10%

(instead of 5%) could also be considered reasonable as most patients with a burden of less than 10% tolerate them well.

Given robust data for improvement of LV function in patients where moderate or high burden of PVCs is associated with LV dysfunction or heart failure, strong consideration should be given to catheter ablation or pharmacological suppression in these patients. We usually try to avoid long-term AADs, though there are no randomised data to compare the two. Attention to secondary factors (electrolytes, metabolic, heart failure, ischaemia, etc) and behavioural modifications (caffeine, alcohol, nicotine, stress and deconditioning) is important.

PVC suppression with ablation or AADs is a more challenging decision for patients with preserved LV function. The presence of symptoms and reduced quality of life attributable to the PVCs is a reasonable indication for PVC suppression. Palpitations, skipped beats, haemodynamic instability with short runs of non-sustained VT and chest discomfort from post-PVC pauses are more specific symptoms. Non-specific symptoms like fatigue, reduced effort tolerance and shortness of breath are common, but establishing a cause and effect relation with the PVCs can be a challenging art of clinical medicine.

It is not proven whether using strain analysis as a measure of LV function can help make decisions about PVC suppression in patients with normal LVEF, though there is evidence that PVC suppression can improve measures of strain. In asymptomatic patients or those with non-specific symptoms like fatigue and with lack of alternative causes, a careful and unbiased discussion of the risks and benefits of an ablation or AADs could be considered in patients with a high burden of PVCs. Many such patients report improvement in energy levels and effort tolerance after ablation. A higher threshold for ablation may exist for more difficult PVCs as those from the papillary muscle or with epicardial origin. The other option is close surveillance of LV function as up

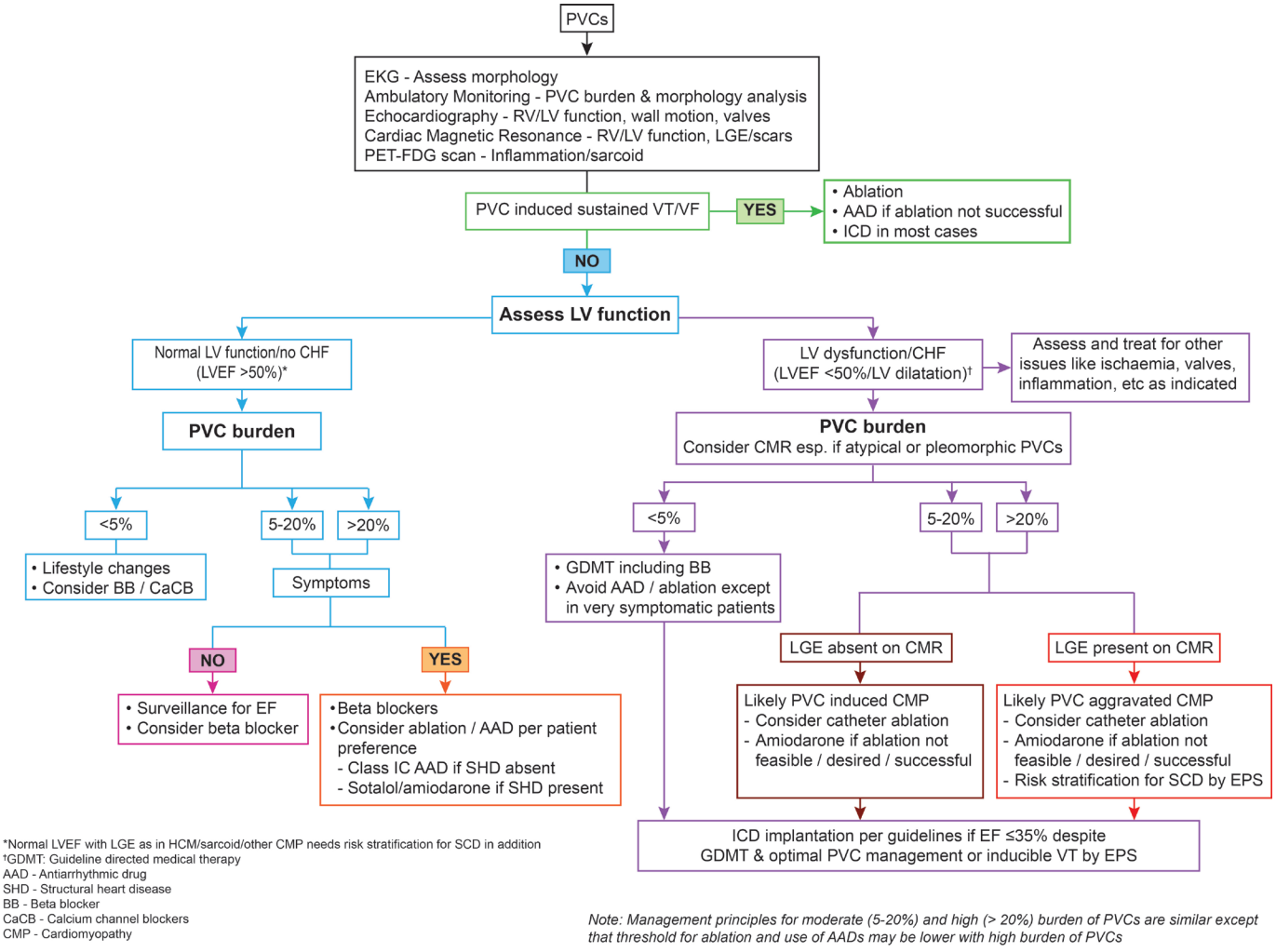

Figure 1 Flowchart showing a comprehensive algorithm to help in management of a patient with PVCs. BB, beta blocker; CaCB, calcium channel blocker; CHF, congestive heart failure; CMR, cardiac magnetic resonance ; EF, ejection fraction; EKG, electrocardiography; EPS, electrophysiologic study; FDG, fluorodeoxyglucose; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; PET, positron emission tomography; PVC, premature ventricular complex; RV, right ventricular; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

to a third of patients with frequent PVCs develop LV dysfunction with time.[24]

Options for PVC suppression

Pharmacological therapy

Beta blockers (BBs) are often used as first-line therapy.[34 35] They do not affect myocardial ion channels but may help by suppression of sympathetically driven excitation, negative inotropic effects and slowing sinus rates. Calcium channel blockers may help fascicular PVCs. However, either or the combination offers relief in less than 25% patients.[36 37] Hamon and colleagues reported that patients with fast HR-dependent PVCs (number of PVC higher during daytime) had a favourable benefit from BBs, whereas PVCs in patients without any correlation with the mean HR did not improve significantly. Interestingly, patients with slow HR-dependent PVCs (number of PVC increased during night-time) actually worsened with BBs.[38]

Class IC and class III AADs have reported better suppression of PVCs compared with BBs. Class IC drugs are avoided in patients with impaired LV function and SHD because of the increased mortality seen in the Cardiac Arrhythmia Suppression Trial[9] but may offer relief in patients without SHD. The use of class IC AADs in patients with PIC could become a consideration as studies have shown a significant improvement in PVC burden (36% down to 10%) and LVEF (37% up to 49%) with these drugs.[37] We may need to refine the role of these drugs in the modern era with the availability of the LGE-CMR.

Among class III AADs, amiodarone reduced PVC burden and the risk of arrhythmic deaths in the EMIAT and CAMIAT trials. Amiodarone can be used for symptom and PVC suppression in these patients but offers no survival benefit. It had shown improvement in arrhythmic deaths, but this was likely offset by an increase in non-arrhythmic deaths.[10 11] In patients with PIC, the CHF-STAT trial showed reduction in PVC burden with amiodarone in up to 69% patients, but the discontinuation rate was as high as 27%.[39]

Catheter ablation

Many advances in catheter ablation for ventricular arrhythmias have lowered threshold for invasive therapy. Accurate 3D mapping systems, epicardial access, irrigated tip ablation catheters, contact force assessment by catheter tips, use of intracardiac echo and image integration have revolutionised this field. Catheter ablation can be curative, but the potential benefit must be evaluated against the risk of major complications as vascular injury, cardiac tamponade, coronary artery injury or stroke; overall in the range of 1%–3%.[40] Assessment for ablation includes understanding of symptoms, heart failure status, LV function, risks of sustained VT/VF, haemodynamic compromise with the arrhythmia and a careful assessment of the EKG to assess the site of origin of the PVCs and surrounding structures to assess risk of collateral damage.

EKG assessment for site of origin

In most patients with PVCs without SHD, the underlying mechanism is focal abnormal automaticity or triggered activity. Activation occurs from the site of origin and propagates normal healthy myocardium to present characteristic EKG morphology from that site. Numerous reports have been published to predict sites of origin of PVCs,[41–44] and the common morphologies are summarised in table 1. The outflow tract represents the most common origin for idiopathic PVCs. The vast majority originate from the anterior and superior septal aspect of the right ventricular outflow tract (RVOT). In 15% of patients, the arrhythmia originates from the left ventricular outflow tract and may be best approached from the aortic cusps.[45] PVCs may often originate from an epicardial site and EKG characteristics can help predict an epicardial origin.[46]

Mapping and ablation

The favoured technique for successful ablation entails locating the site of earliest intracardiac activation, commonly known as 'Activation mapping'. 'Pace mapping' may be used when the PVC burden is low. In this technique, the mapping catheter is advanced to the area of interest and pacing is performed to achieve an identical match of the surface QRS. Activation mapping is more reliable and the intracardiac signal at the site of successful ablation usually precedes the onset of QRS by about 25–30 ms or more. Pace mapping is less reliable but may be useful if the PVC burden during the

Table 1 Electrocardiography patterns for common PVCs (usually typical)

Site of PVC origin	Pattern in V1	Axis	Other features
RVOT free wall	LBBB	Inferior axis	QS in V1, transition V4–V5 Notching in inferior leads
RVOT septum	LBBB	Inferior axis	QS in V1, transition V3–V4, narrower QRS, notching absent
Para Hisian	LBBB or RBBB depending on right or left exit	Inferior axis	PVCs are narrow, polarities often similar to that of QRS in sinus rhythm with subtle differences
LVOT including aortic cusp and LV summit	LBBB or RBBB	Inferior axis	rS, qR or R in V1, V2 or V3 transition, maximum deflection index >0.55 from LV summit
Posterior fascicle	RBBB	Left superior axis	Can often present as VT
Anterolateral papillary muscle	RBBB	Right superior or inferior axis	QRS may be narrow

LBBB, Left Bundle Branch Block; LV, Left Ventricular; LVOT, Left Ventricular Outflow Tract
; PVC, Premature Ventricular Complex; RBBB, Right Bundle Branch Block; RVOT, Right Ventricular Outflow Tract
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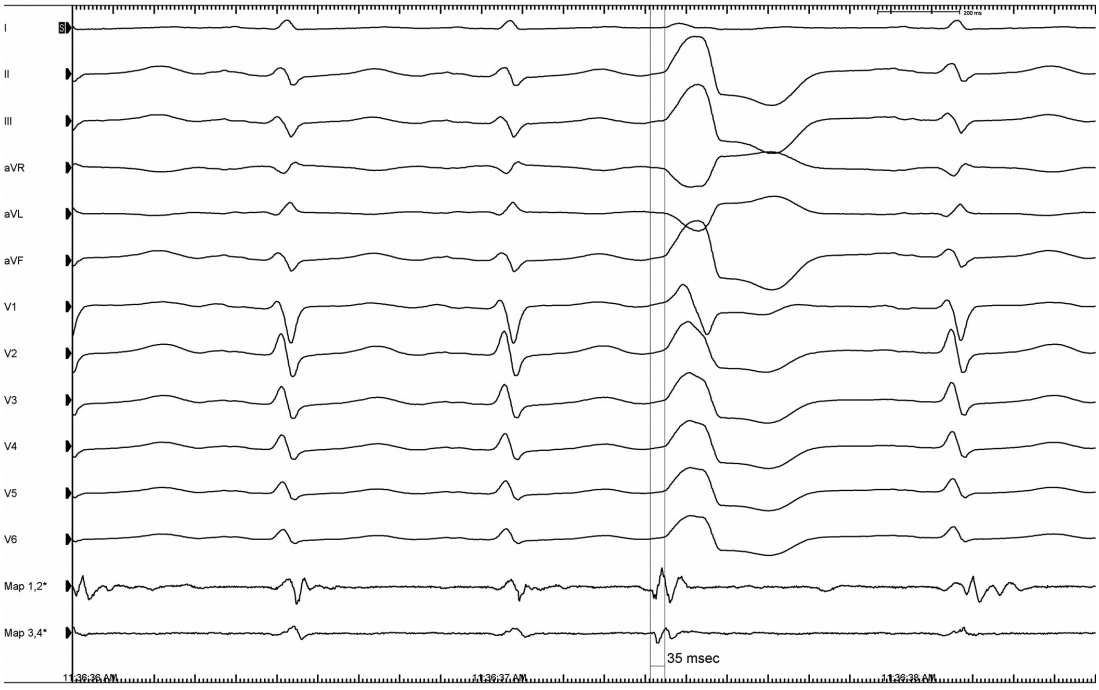

Figure 2 Activation mapping: 12-lead electrocardiography (leads labelled on the left margin) at 100 mm/s in a patient with frequent PVCs. The PVC has an LBBB (left bundle branch block) -like pattern, early transition in the precordial leads with a left inferior axis. The distal electrode on the mapping catheter (maps 1 and 2) located in the right coronary cusp shows an activation signal during the PVC. The first vertical line shows the onset of the local electrogram, which precedes the onset of the surface QRS (shown by the second vertical line) by 35 ms. PVC, premature ventricular complex.

procedure is not high enough to facilitate activation mapping. Figures 2 and 3 demonstrate the use of activation and pace mapping, respectively in a patient with frequent PVCs that were successfully mapped and ablated from the right coronary cusp. Figure 4 shows successful elimination of the PVCs 4.6 seconds after the start of delivery of radiofrequency energy.

Success for PVC ablation can vary significantly based on the site of origin and approachability of the focus. A recent multicenter study[47] showed overall success rate of 85% with a complication

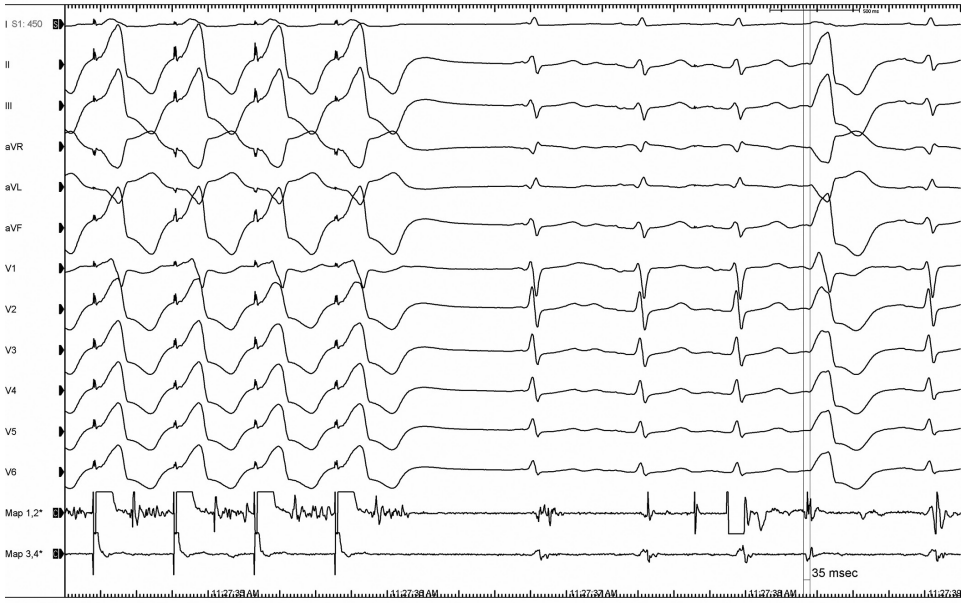

Figure 3 Pace mapping: 12-lead electrocardiography at a 50 mm/s with the mapping catheter at the same location as in figure 2. The first four complexes show paced beats from this location as identified by the pacing spikes preceding the QRS complex. After cessation of pacing, there is normal sinus rhythm with a single spontaneous PVC. The paced morphology of the QRS shows a near-perfect pace match (96% with software) with the spontaneous clinical PVC when compared on the 12 surface leads. PVC, premature ventricular complex.

Figure 4 Ablation: the patient is having PVCs in a quadrigeminal pattern as seen on the 12-lead electrocardiography at 10 mm/s starting on the left portion of the screen. Delivery of radiofrequency energy starts at the first vertical bar and results in prompt termination of the PVCs which are last seen once at 4.6 s after the onset of ablation, and there is subsequently no PVCs on the right side of the screen. After completion of ablation, the patient did not have any clinical PVCs during the procedure or on follow-up. PVC, premature ventricular complex.

rate of about 2.4%. The predictors of success were an origin from the RVOT and presence of a single morphology. The predictors for failure include epicardial or papillary muscle origin and presence of multiple morphologies. Successful ablation of PVCs in patients with PIC is usually associated with either normalisation of LV function or an improvement in the LV ejection fraction by over 10%–15%. In the study, the LVEF improved by more than 10% in 67% of patients, by 1%–10% in 18% and no improvement was seen in 15% of patients. Understanding of these data enhances our ability to discuss the risks/benefits of PVC ablation with patients and individualise treatment based on their symptoms, LV function and preference.

PVCS AND RISK OF SCD

In general, PVCs in the absence of any SHD have a benign prognosis, especially when monomorphic and from typical sites like the outflow tract, papillary muscles and the LV fascicles. Certain factors may indicate that the PVCs are less likely to be benign, and these are mentioned in table 2.

Table 2 Factors predicting PVCs as potentially non-benign or atypical

Clinical	Existence of any underlying structural heart disease
	Existence of late gadolinium enhancement in the right or left ventricle on CMR
ECG features	Frequent PVCs greater than 10% burden
	Wider QRS duration (greater than 140 ms)
	Multiple morphologies of PVCs (pleomorphic)
	Atypical sites of origin
	Short coupling interval predisposing to an 'R on T' phenomenon
	Epicardial origin

CMR, Cardiac Magnetic Resonance; PVC, premature ventricular complex.

These patients may need additional surveillance or attention.

Patients with *PVC-induced VF* (often associated with short coupled PVCs) continue to be at high risk for subsequent return of PVCs even after a successful ablation or to have PVCs from other foci. They merit implantation of a defibrillator to reduce the risk of SCD. Such PVCs can rarely be seen from the outflow tract or often from the injured Purkinje tissues after an MI or coronary bypass surgery. Often times, patients with PVCs from sites like the RVOT, fascicles and papillary muscles may be associated with non-sustained or sustained monomorphic VT of similar morphology. These patients usually do not have any SHD or LGE-CMR and tend to have a benign prognosis. Most often, they are not at an increased risk of SCD. The arrhythmias can be well suppressed with an ablation or pharmacological therapy and a defibrillator can be avoided.

In patients with PVCs and a cardiomyopathy (typically greater than 5%–10% burden), the PVC burden is the strongest predictor for development of LV dysfunction. Hence, in patients with PIC or *PVC-aggravated cardiomyopathy*, risk stratification for SCD should be done after best attempts at reducing the PVC burden and appropriate guideline-directed medical therapy has been instituted for a while (usually at least 3 months). A defibrillator would be reasonable if the LV ejection fraction continues to be low (usually ≤35%) despite the aforementioned efforts.

Conventionally, the utility of an electrophysiological study (EPS) has not been favoured for risk stratification in patients with non-ischaemic cardiomyopathy. Recent data have shown some promise of programmed stimulation in patients with frequent

Key messages

- Isolated monomorphic premature ventricular complexes (PVCs) without structural heart disease are generally benign.
- Frequent PVCs can cause reversible cardiomyopathy or aggravate an existing cardiomyopathy.
- Short coupled PVCs can trigger sustained ventricular fibrillation. These are often from the Purkinje tissue or rarely the outflow tract.
- Beta blockers are considered first-line therapy but have low efficacy. Catheter ablation and AADs are reasonable to suppress PVCs in appropriate patients.
- Ablation is often curative and success depends on location and accessibility of PVCs.
- Implantable defibrillators are reasonable in patients at higher risk of sudden cardiac death.

PVCs and LV dysfunction in the presence of LGE-CMR. A combination of SHD as detected by LGE-CMR and an inducible VT at EPS has been found to independently predict risk of an adverse outcome and help select patients who may benefit from an ICD in patients with frequent PVCs and LV dysfunction. Further studies in larger number of patients, preferably in randomised controlled trials will be needed to substantiate these data.[48] Risk stratification should be further individualised for inheritable disorders like arrhythmogenic RV cardiomyopathy, Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy and CPVT as per their individual guidelines.

CONCLUSION

The majority of PVCs in daily practice are benign, especially in the absence of SHD. An EKG, echo, stress test, CMR and PET scan are appropriate tools to establish any SHD based on the appropriate clinical setting. Ambulatory monitoring is best to assess PVC burden, morphology analysis and to establish cause and effect relation of the symptoms to the PVCs. In asymptomatic patients with normal LV function and absence of SHD, careful surveillance is appropriate. PVC-induced sustained ventricular arrhythmias, PIC or PVC-aggravated cardiomyopathy are best treated with PVC suppression. Catheter ablation may be a reasonable first-line therapy in these patients.

Randomised controlled trials are lacking, but the 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society Ventricular Arrhythmia guidelines support catheter ablation as a class I recommendation in patients with frequent PVCs causing LV dysfunction where AADs are not effective, tolerated or preferred.[34] Catheter ablation and AADs are reasonable in symptomatic patients with normal LV function. Risk stratification for SCD should be based on objective criteria for the respective clinical setting. There may be a role for programmed stimulation in patients with LGE-CMR, but more data are needed to support it as the standard of care.

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