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REVIEW

Frequent Ventricular Ectopy: Implications and Outcomes

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Frequent ventricular ectopy is a common clinical presentation in patients suffering idiopathic ventricular outflow tract arrhythmias. These are focal arrhythmias that generally occur in patients without structural heart disease and share a predilection for characteristic anatomic sites of origin. Mechanistically, they are generally due to cyclic adenosine monophosphate (cAMP)-mediated triggered activity. As a result, there is typically an exercise or catecholamine related mode of induction and often a sensitivity to suppression with adenosine.

Treatment options include clinical surveillance, medical therapy with anti-arrhythmic agents or catheter ablation. Medical therapy may offer symptomatic benefit but may have side-effects and usually results in burden reduction rather than eradication of ectopy. Catheter ablation using contemporary mapping techniques, whilst associated with some inherent procedural risk, is a potentially curative and safe option in most patients.

Although usually associated with a good prognosis, some patients may develop an ectopy-mediated cardiomyopathy or, rarely, ectopy-induced polymorphic ventricular arrhythmias; catheter ablation is the treatment of choice in those patients.

Keywords Ventricular ectopy • Premature ventricular complex • Catheter ablation • Ectopy mediated cardiomyopathy

Introduction

Ventricular ectopic beats or premature ventricular complexes (PVCs) result from premature depolarisations arising from ventricular-derived myocardial cells. Whilst most PVCs arise from ventricular myocardium, conduction tissue distal to the bifurcation of the bundle of His, such as the bundle branches, fascicles or Purkinje fibres are also potential sites of origin for these arrhythmias.

Occasional PVCs have long been recognised as a ubiquitous phenomenon in the population, occurring in patients with and without structural heart disease (SHD) [1,2]; the prevalence increases with age. Healthy subjects under 30 years of age undergoing a 24-hour Holter monitor have a 16.7% prevalence of at least one PVC, increasing to a 69% prevalence in those over the age of 75 [3,4].

Frequent PVCs, however, are less common and can manifest as salvos, non-sustained or sustained ventricular tachycardia (VT). Some patients with idiopathic PVCs may develop an ectopy-mediated cardiomyopathy (EMC) or rarely PVC-induced polymorphic VT or ventricular fibrillation (VF). This review will focus on the clinical and pathophysiological characteristics of idiopathic VAs and the implications and options for therapy.

Ventricular Ectopy – A Historical Background

In the 1970s, PVCs were shown to be detrimental in patients with SHD, particularly in those with coronary artery disease (CAD) post-myocardial infarction (MI) [5,6]. Studies

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demonstrated up to a four-fold mortality increase in post-MI patients with >10 PVCs/hr [7]. In that era, attempts were made to medically suppress PVCs with 38% of cardiologists prescribing anti-arrhythmic agents for asymptomatic PVCs in the post-MI setting [8]. This practice was abolished following the publication of the landmark Cardiac Arrhythmia Suppression Trial (CAST) study in which the use of Class Ic agents (encainide and flecainide) to treat frequent PVCs in this population resulted in a 2.38% relative risk increase in all-cause mortality [9]. The increased mortality rate was due to both arrhythmic and non-arrhythmic cardiac causes implicating both pro-arrhythmic and negatively inotropic properties of these agents [10–12]. It was then appreciated that the association between post-MI PVCs and mortality may have simply been a marker of disease severity.

Subsequent studies demonstrated that, in contrast to the post-MI setting, frequent PVCs occurring in healthy patients without SHD were not associated with increased mortality [13–15]. Kennedy et al. followed 73 asymptomatic patients with PVCs, in whom cardiac disease was excluded by extensive non-invasive investigations, and found similar long-term prognoses to that of the general population over a 10-year period [16]. By the turn of the 21st century, the prevailing view was that PVCs in the absence of SHD were innocuous and, in most cases, did not warrant any specific therapy. These PVCs were considered part of the spectrum of idiopathic VAs and were recognised by characteristic sites of origin, particularly the right and left ventricular outflow tracts (RVOT/LVOT), the latter including sites within the LV ostium including the aortic sinuses of Valsalva, the aortomitral continuity, the superior mitral annulus and the LV summit [17]. A recent series, however, suggested that even these apparently benign PVCs may have implications for the development of heart failure and mortality, at least on a population level [18].

Whilst chronic tachyarrhythmias had long been recognised as a reversible cause of dilated cardiomyopathy (DCM) [19,20], the concept that frequent PVCs could directly result in impaired left ventricular (LV) function in the absence of sustained tachycardia was raised as a possibility when Singh et al. demonstrated improvement in LV function following suppression of PVCs with amiodarone in patients with idiopathic DCM [21]. This novel concept of an ectopy-mediated cardiomyopathy (EMC) was further supported in the early 2000s with case reports demonstrating reversal of LV dysfunction in individual patients following elimination of PVCs by radiofrequency ablation (RFA) [22,23].

Ectopy Mediated Cardiomyopathy

Ectopy-mediated cardiomyopathy (EMC) is a reversible cause of DCM that occurs in the setting of frequent PVCs. In contrast to tachycardia-mediated cardiomyopathy, patients with EMC can develop LV dysfunction even though the heart rate is not significantly elevated.

Whilst EMC has traditionally been considered a relatively rare cause of DCM, a recent analysis of 1,139 patients in the Cardiovascular Health Study suggests that PVCs play a greater contributory role to LV dysfunction in the population than previously appreciated [18]. Subjects in the highest quartile of PVC burden (0.12–17.7%) had three times greater odds of having a decrease in LVEF and 48% increased risk of developing incident congestive heart failure (CHF) at 5 years compared to those in the lowest quartile. Extrapolation of this data would imply that the population-level risk of CHF due to PVCs may be as high as 8.1%, suggesting that PVCs may be co-contributory to LV dysfunction in more patients than previously appreciated.

As cardiomyopathy itself can result in PVCs, the mere presence of PVCs in the setting of LV dysfunction is not proof of EMC. In clinical practice, the diagnosis is a retrospective one confirmed following documented improvement in LV function after PVC suppression. The evidence for this condition consists of multiple retrospective case control studies demonstrating reversal of LV systolic dysfunction following successful PVC suppression in the modern era of catheter ablation [Table 1] [24–30]. In these studies, control patients with documented ongoing ectopy did not show an improvement in LV function.

In our series of patients undergoing PVC ablation in the setting of impaired LV systolic function, the median PVC burden decreased from 29.2% to 1.3% ($p < 0.001$) resulting in an improvement in LVEF from a median of 40% to 52% ($p < 0.001$) [Figure 1] [29]. Other series have reported similar improvements [24–28,30]. Even in patients with LV dysfunction that preceded the development of frequent PVCs, including those with established scar on delayed enhancement cardiac magnetic resonance (cMRI) imaging, catheter ablation results in some improvement in LVEF (8% vs 13% improvement in patients without pre-existing cardiomyopathy) [31].

The success of PVC ablation has led to interest in determining which patients with frequent PVCs are at risk of developing EMC. Numerous risk factors, derived from studies of highly selected patients referred for catheter ablation of PVCs, have been proposed that include age, male gender, PVC burden, PVC QRS duration, pleomorphic PVCs, specific PVC sites of origin (including LV and epicardial locations), symptom status, PVC coupling interval, and body mass index [24–26,28,29,32–40]. The only risk factor that appears to be a robust predictor of EMC in most (but not all) series is PVC burden. Baman et al. demonstrated a PVC burden of >24% best separated those with and without EMC and that no patients with EMC had a PVC burden <10% [24]. Most other factors are inconsistently and variably reported in the literature which likely reflects bias due to differences in study populations and referral patterns [29] [Table 2].

In the absence of large prospective studies of EMC, animal models may provide insights into mechanisms underlying the development of EMC and potential therapeutic targets [41–43]. Preliminary data from our laboratory suggests that

Table 1 Studies demonstrating efficacy of radiofrequency ablation in patients with ectopy-mediated cardiomyopathy.

Study	Year	No. of patients LV dysfunction (% Total)	PVC sites of origin	No. undergoing successful RFA	PVC burden in patients with EMC		LVEF (%)		Mean follow-up time (months)
					Pre-RFA	Post-RFA	Pre-RFA	Post-RFA	
Yarlagadda et al. [28]	2005	8/27 (30%)	RVOT	7/8 (88%)	17,541 beats/day	507 beats/day	39	62	8
Bogun et al. [25]	2007	22/60 (37%)	RVOT (52%), LVOT (15%), other (22%)	18/22 (82%)	35%	0.7%	34	59	6
Taieb et al. [27]	2007	6/6 (100%)	RVOT (33%), LVOT (17%), other (50%)	5/6 (83%)	17,717 beats/day	268 beats/day	42	57	6
Baman et al. [24]	2010	57/174 (37%)	RVOT (38%), LVOT (51%), other (27%)	46/57 (81%)	33%	1.9%	35	54	4
Hasdemir et al. [26]	2011	17/249 (7%)	RVOT (68%), LVOT (32%)	9/12 (75%)	29.4%	1.3%	38	53	3 to 4
Zhong et al. [30]	2014	146/510 (29%)	RVOT (21%), LVOT (16%), other (48%)	58/146 (40%)	23,554 beats/day*	1,755 beats/day*	53¶	56¶	7
Lee et al. [29]	2018	54/152 (36%)	RVOT (39%), LVOT (25%), other (36%)	43/54 (80%)	29.2%	1.3%	40	52	7 (median)

Abbreviations: PVC, premature ventricular complex; LVEF, left ventricular ejection fraction; RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract; RFA, radiofrequency ablation; LV, left ventricular; EMC, ectopy-mediated cardiomyopathy.

*Average PVC burden.

¶Average LVEF only reported for entire study population (including patients with normal LVEF).

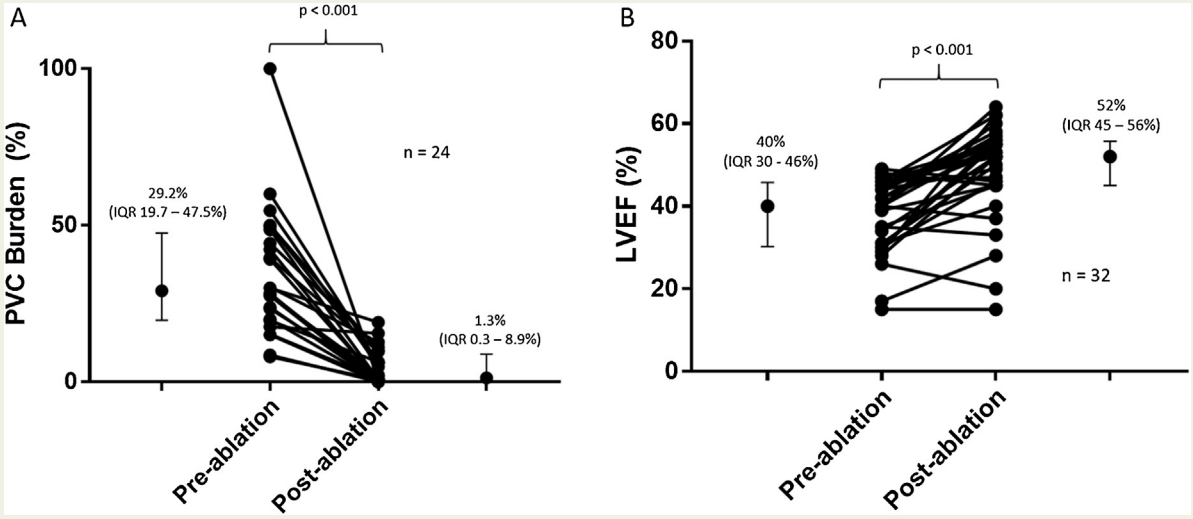

Figure 1 Pre- and post-procedural PVC burden (Panel A) and left ventricular ejection fraction (Panel B) in patients with left ventricular dysfunction undergoing PVC ablation.
Abbreviations: PVC, premature ventricular complex; LVEF, left ventricular ejection fraction.
Used with permission from Lee et al. Ventricular Ectopy in the Context of Left Ventricular Systolic Dysfunction: Risk Factors and Outcomes Following Catheter Ablation. Heart, Lung and Circulation. DOI: https://doi.org/10.1016/j.hlc.2018.01.012.

PVC associated LV dyssynchrony may be a critical factor in determining the severity of LV dysfunction [44,45].

Pathophysiology

Focal idiopathic VA typically arise from triggered activity due to delayed afterdepolarisations (DADs) [46]. DADs are premature depolarisations of the cell membrane that occur during Phase IV of the action potential (AP). Mechanistically, they occur due to diastolic intracellular calcium (Ca^{2+}) overload leading to transient disturbances in membrane voltage.

During normal ventricular myocyte depolarisation, cellular contraction is mediated by excitation-contraction coupling following accumulation of intracellular Ca^{2+}. A small amount of Ca^{2+} enters the cell via the membranous L-type Ca^{2+} during Phase II of the AP. This triggers release of stored Ca^{2+} within the sarcoplasmic reticulum (SR) into the cytosol via ryanodine (RyR2) receptors – a process termed Ca^{2+}-induced-Ca^{2+}-release [47]. The accumulated cytosolic Ca^{2+} then interacts with Ca^{2+}-binding proteins leading to myofilament contraction. Cytosolic Ca^{2+} is then sequestered back into the SR by the SR Ca^{2+} adenosine triphosphatase pump (SERCA), a process mediated via phosphorylation of phospholamban [48]. An additional regulator of cytosolic Ca^{2+} is the Na^{+}/Ca^{2+} exchanger (NCX), which extrudes excess Ca^{2+} from the cell in exchange for Na^{+} entry [49].

Pathological processes that lead to diastolic intracellular Ca^{2+} overload therefore promote increased activity of NCX. A net inward current (I_{NCX}) arises as three Na^{+} ions enter the cell for every one Ca^{2+} ion extruded, resulting in positive oscillations of membrane voltage (DADs) which, if they reach threshold voltage, may trigger an early action potential resulting in a PVC [50].

Mechanistically, DADs in the setting of focal idiopathic VA tend to be cAMP-mediated. Activation of cAMP-dependent protein kinase A results in phosphorylation of multiple targets including the L-type Ca^{2+} channel, phospholamban and the RyR2 receptor, the net effect of which is increased intracellular Ca^{2+} accumulation within the cytosol and SR [46]. These pathways are summarised in Figure 2.

A specific characteristic of these arrhythmias is adenosine sensitivity. Focal idiopathic VAs may be terminated by adenosine via action on the adenosine A1 receptor which inhibits production of adenylyl cyclase and thus cAMP [51]. β-blockers and vagal manoeuvres have similar downstream effects on cAMP, whilst calcium channel blockers (CCBs) prevent cytosolic Ca^{2+} accumulation by blocking the L-Type Ca^{2+} channel directly [52]. Conversely, these arrhythmias can be induced with catecholamines which increase cAMP or rapid pacing which increases diastolic Ca^{2+} loading.

Clinical Presentation

Some patients with frequent PVCs present with symptoms directly relating to ectopy, some with symptoms from LV systolic dysfunction and others as an incidental finding during investigations for other reasons. Patients with frequent PVCs and structurally normal hearts predominantly present with palpitations, fatigue, dyspnoea and/or dizziness [29]. Syncope is uncommon, but possible in the setting of sustained VT with or without underlying SHD. Patients presenting in the context of LV dysfunction often present with signs and symptoms of clinical heart failure [29].

Table 2 Proposed risk factors for ectopy-mediated cardiomyopathy as reported by previous studies. uni – by univariate analysis, multi- by multivariate analysis.

Study	n (CMP/normal)	Variable										
		Age	Male gender	BMI	PVC burden	PVC QRS duration	Pleomorphic PVCs	PVC interpolation	PVC coupling interval	Site or origin	Symptom duration	Asymptomatic
Yarlagadda (2005) [28]	8/19	Yes (uni)	No	-	No	-	No	-	-	No	-	-
Bogun (2007) [25]	22/38	-	-	-	Yes (uni)	-	-	-	-	-	-	-
Kanei (2008) [35]	21/87	No	No	-	**Yes (multi)**	-	-	-	-	No	-	-
Baman (2010) [24]	57/117	No	Yes (uni)	-	**Yes (multi)**	-	No	-	-	No	-	-
Del Carpio (2011) [33]	17/53	No	No	-	Yes (uni)[a]	**Yes (multi)**	Yes (uni)	-	-	No	No	-
Hasdemir (2011) [26]	17/232	No	Yes (uni)	-	Yes (uni)	-	-	-	-	-	-	Yes (uni)
Olgun (2011) [37]	21/30	No	No	-	**Yes (multi)**	-	-	**Yes (multi)**	-	-	-	-
Yokokawa (2012) [40]	76/165	No	Yes (uni)	-	**Yes (multi)**	-	-	-	-	-	**Yes (multi)**	**Yes (multi)**
Yokokawa (2012) [86] -	113/181	No	Yes (uni)	-	**Yes (multi)**	**Yes (multi)**	-	-	-	**Yes – epicardial (multi)**		**Yes (multi)**
Carballeira (2014) [32]	17/28	No	No	-	No	**Yes (multi)**	-	-	No	**Yes – non-outflow tract (multi)**	No	-
Kawamura (2014) [36]	51/163	No	No	**Yes (multi)**	**Yes (multi)**	No	-	-	**Yes** – maximum CI (uni), **CI dispersion (multi)**	No	-	-
Latchamsetty (2015) [68] **Yes (multi)**	245/940	No	**Yes (multi)**	-	**Yes (multi)**	-	No	-	**-**	**Yes – epicardial (multi)**		-
Blaye-Felice (2016) [39] -	96/72	No	Yes (uni)	-	**Yes (multi)**	No	Yes (uni)	Yes (uni)	Yes (uni)	**Yes – epicardial (multi)**		-

Table 2. (continued).

Study	n (CMP/normal)	Variable									
		Age	Male gender	BMI	PVC burden	PVC QRS duration	Pleomorphic PVCs	PVC interpolation	PVC coupling interval	Site or origin	Symptom duration	Asymptomatic
Hamon (2016) [34]	36/71	No	Yes (uni)		Yes (multi)	Yes (multi)	No	Yes (uni)	No	Yes – epicardial (multi)	-	-
Park (2017) [38]	28/116	No	Yes (multi)	No	Yes (multi)	Yes (multi)	No	-	No	Yes – LV (multi)	No	[b]NA
Lee et al (2017)	54/98	Yes (uni)	Yes (multi)	No	Yes (uni)	Yes (uni)	No	-	Yes – minimal (uni)	Yes – non RVOT/		infundibular (uni)
No	No											

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Abbreviations: BMI, body mass index; PVC, premature ventricular complex; RVOT, right ventricular outflow tract; VT, ventricular tachycardia; CI, coupling interval; CMP, cardiomyopathy.

[a]PVC burden was significant on multivariate analysis only when another factor (non-sustained VT) was removed.

[b]This study presented the results of a multivariate analysis in symptomatic patients only.

Assessment

All patients with frequent PVCs require an assessment for the presence of SHD, both as a potential cause and consequence of the PVCs, and determination of arrhythmia burden. Additionally, the 12-lead QRS morphology of the PVC should be analysed to determine the PVC origin and number of different morphologies, which may facilitate appropriate discussion of PVC risk as well as the specific potential risks of ablative treatment of them. Since PVCs have a focal origin, the electrocardiogram (ECG) QRS morphology is remarkably accurate in predicting the site of origin. The ECG should be acquired as continuous 12-channel rhythm strip so that the QRS morphology is available on all leads for each morphology PVC.

The sinus rhythm QRS morphology may also provide clues as to the presence of an underlying substrate. T-wave inversion and/or a prolonged S-wave upstroke ≥55 ms (parietal block) in the right precordial leads (V1–V3) and epsilon waves may suggest the presence of arrhythmogenic right ventricular cardiomyopathy [53]. Loss of R-wave progression or regional Q-waves can offer clues as to the presence of prior MI scar, whilst early transition or presence of a large S-wave in V6 can suggest a basal-lateral scar often seen in non-infarct cardiomyopathies [54,55].

Transthoracic echocardiography (TTE) provides an important assessment of both global and regional ventricular as well as valvular function and should be routinely performed. If the TTE is normal and the PVC is of a single morphology with typical RVOT or aortic cusp site of origin, further investigation is typically not necessary. However, in patients with unusual PVC sites of origin (e.g. tricuspid annulus, LV summit, papillary muscles), multiple PVC morphologies, sustained VT or LV dysfunction, cardiac magnetic resonance imaging (cMRI) may be useful to localise and assess for any underlying myopathic substrate, particularly the presence of myocardial fibrosis [56,57]. Admittedly, in patients with very frequent PVCs, gating difficulties may impair scan quality. In patients with newly diagnosed LV dysfunction, either non-invasive stress testing or coronary angiography should be performed to exclude the presence of coronary artery disease.

Assessment of the PVC burden is important for determining the aetiological relevance of ventricular ectopy to the patient's clinical presentation as well as the likelihood of response to therapy [58]. A 24-hour Holter monitor study will usually suffice, however, repeat or extended monitoring may be required in cases where significant fluctuation in PVC burden is suspected [59]. For patients in whom the PVC burden is borderline (<10%) and/or questionably related to the clinical presentation, symptom-rhythm correlation should be sought via extended monitoring with continuous or patient activated event recorders [60].

Indications for Treatment

There are three indications for treatment in patients with idiopathic focal ventricular arrhythmias: i) symptoms from PVCs or VT, ii) presumed EMC, and iii) polymorphic VT/VF due to

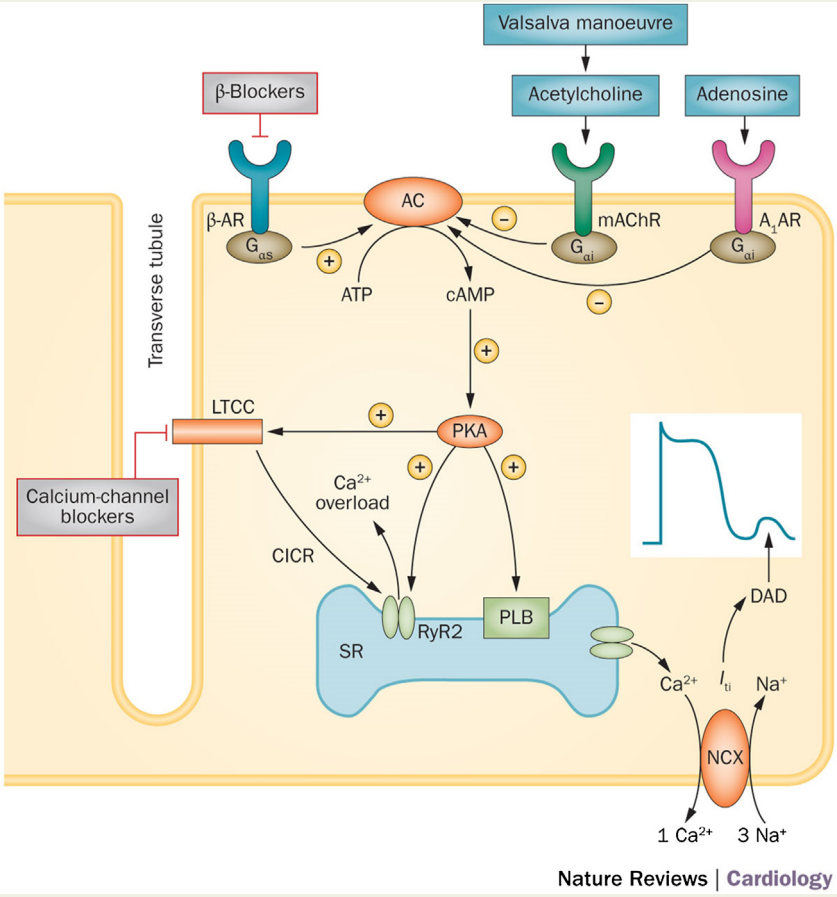

Figure 2 Cellular mechanisms underlying idiopathic premature ventricular complexes.
Abbreviations: β-AR, β-adrenergic receptor; AC, adenylyl cyclase; ATP, adenosine triphosphate; mAChR, muscarinic acetylcholine receptor; A_1AR, adenosine A1 receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; LTCC, L-Type Ca2+ channel; SR, sarcoplasmic reticulum; RyR2, ryanodine receptor; CICR, calcium induced calcium release; PLB, phospholamban; NCX, sodium-calcium exchanger; DAD, delayed after depolarisation.
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malignant PVCs. Asymptomatic patients with a low PVC burden do not require specific therapy. Patients with a high burden and normal LV size and function should undergo repeated Holter and echocardiographic monitoring, typically at yearly intervals, to detect changes in LV function. One may consider treating these patients with β-blockers if they are effective in suppressing PVCs and without side-effects, but there is no current data to definitively support that this prevents the future development of cardiomyopathy. For symptomatic patients, treatment options include medical therapy or catheter ablation. Risk stratification for sudden cardiac death (SCD) is only required in patients with LV dysfunction or malignant arrhythmias.

Treatment Options – Medical Therapy

The literature examining the effect of β-blockers and non-dihydropyridine calcium channel blockers (CCBs) on PVCs is limited. In a randomised control trial (RCT) of 52 patients, atenolol was shown to reduce mean PVC burden from 24,082 to 16,153 beats/day; 6 out of 25 (24%) patients in the study group had a >80% reduction in PVC burden [61]. In a non-randomised trial of 16 patients, diltiazem reduced average PVC frequency from 15,245 to 7564 beats/day, with eight patients (50%) having a significant response (defined as ≥65% PVC burden reduction) [62].

β-blockers and CCBs are options aimed at improving symptoms via reduction in PVC burden, however they rarely completely suppress PVCs. Nonetheless, their long-demonstrated safety profile makes them reasonable first line agents in patients with frequent or symptomatic PVCs who prefer an initial non-interventional approach to management. Patients with frequent PVCs in the context of SHD should be treated with guideline-directed medical therapy (GDMT) including a heart failure-specific β-blocker; CCBs are contraindicated in this setting.

Class I and III anti-arrhythmic agents are more efficacious than β-blockers and CCBs in reducing PVC burden but are associated with more side-effects. Propafenone (Class Ic) was shown to be more effective than either metoprolol or verapamil in a prospective, cross-over trial of 84 patients with idiopathic PVCs. Patients had a mean PVC burden of 13,767 beats/day at baseline which was reduced to 4,110 beats/day on propafenone compared to 12,482 and 9,241 beats/day on metoprolol and verapamil respectively. Fifteen patients (18%) had a complete eradication of PVCs whilst on propafenone [63]. Flecainide is also effective in suppressing PVCs. Whilst Class Ic agents are contraindicated in the post-MI setting, a small recent series provides limited evidence that, in patients without CAD, use of these agents can be considered in patients with mild LV dysfunction presumed to be due to EMC [64]. A double blind RCT of 56 patients demonstrated a 77–83% reduction in PVC frequency with sotalol compared to placebo. Twenty-two patients (59%) in the study group had a ≥75% reduction in PVC burden compared to two patients (11%) in the placebo group [65]. Amiodarone has demonstrated efficacy in reducing PVC burden in patients with SHD, but long-term therapy is limited by the considerable side-effect profile [21,66] and, therefore, this agent should be reserved for patients with significant cardiomyopathy that cannot be treated with other methods and should be prescribed at the lowest effective dose (50 mg daily may suffice).

Patients on Class I or III anti-arrhythmic agents can expect a reduction in PVC burden exceeding that of β-blockers and CCBs [30]. Complete suppression of PVCs occurs in the minority of patients. These agents are reasonable options in patients who do not wish to undergo catheter ablation especially if β-blockers and CCBs have been ineffective.

Treatment Options – Catheter Ablation

Whilst the aim of medical therapy is improvement in symptoms via a reduction in PVC burden, catheter ablation is potentially curative by directly targeting the abnormal cells from which the clinical PVCs arise. In a randomised trial of 330 patients with RVOT PVCs, the recurrence rate over 1 year of PVCs (defined as >300 beats/day) was significantly lower in those who underwent radiofrequency ablation (RFA) than those who were treated medically with either propafenone or metoprolol (19.4 vs 88.6%, $p < 0.001$) [30]. Similarly, Zhong et al. have demonstrated, in a retrospective series of 510 patients, significantly greater PVC burden reduction with catheter ablation compared to Class I/III anti-arrhythmic agents (93% vs 82%, $p = 0.04$). More than double the proportion of patients with EMC normalised their LV function following catheter ablation compared to those on medical therapy (47% vs 21%, $p = 0.003$) [67].

Although prospective RCTs are lacking, retrospective studies in patients with possible EMC are consistent in demonstrating greater degrees of PVC burden reduction, higher PVC cure rates and greater improvements in LV function following catheter ablation compared to medical therapy [25,30]. Zhong et al. demonstrated improvement in LV function following catheter ablation even when the average LV ejection fraction was apparently 'normal' (LVEF 53.0 to 55.9%, $p < 0.001$) consistent with the idea that some patients may have had a subclinical form of EMC [30]. This improvement was not seen in the group treated with medical therapy.

Outcomes in patients undergoing catheter ablation in the contemporary mapping era are excellent with a large multicentre retrospective cohort study demonstrating an overall acute success rate of 84% [68]. However, some anatomical sites may pose challenges during ablation. Premature ventricular complexes arising from the LV summit or crux may be difficult to ablate due to access constraints, inability to deliver adequate power and/or proximity to coronary vessels [68,69]. Ablation of endocavitary structures such as the LV papillary muscles can be challenging due to deep protected arrhythmic foci and/or poor catheter stability [70,71]. Adjunctive tools such as intracardiac echocardiography, irrigated tip catheters and percutaneous epicardial access may be helpful in such situations. Whilst RF energy is the most commonly employed ablation modality, cryoablation may have a role when catheter stability is poor (e.g. LV papillary muscle PVCs) or when the PVC is in proximity to an important structure (e.g. parahisian PVCs and the AV node) [71,72].

Contemporary catheter ablation techniques are reasonably safe, however as with any invasive procedure there are complications that may occur. In a multicentre study of 1,185 patients from eight centres, complications occurred in 62 patients (5.2%) of which 29 (2.4%) were considered major complications. Most complications (2.8%) were related to vascular access. Cardiac tamponade occurred in 0.8% of cases. No deaths occurred in this series. Complication rates were similar across all PVC sites of origin except for epicardial PVCs which were associated with higher rates of pericardial tamponade [68].

Implications – Management

In our experience, the management of patients presenting with frequent PVCs can be guided by three factors: the PVC burden, symptoms and the presence or absence of LV dysfunction [Table 3]. Asymptomatic patients with a low PVC burden (<10% daily) can be offered reassurance; those with a potentially significant PVC burden (≥10% daily) can undergo clinical surveillance. Repeat ambulatory monitoring, cardiac imaging and clinical assessment at yearly intervals is reasonable to assess for changes in PVC burden and to monitor for the development of symptoms or LV dysfunction. Importantly, LV dilatation often occurs before frank LV dysfunction. An increasing LV volume in patients with frequent PVCs, even with preserved ejection fraction, may be considered a reason to initiate therapy [30].

Symptomatic patients with normal LV function are offered medical therapy or catheter ablation, depending on PVC

Table 3 **Algorithm outlining therapeutic options in patients with frequent premature ventricular complexes.**

	PVC burden	PVC symptoms	LV systolic function	Management	
				Arrhythmia therapy	**Risk stratification**
Frequent PVCs	<10%	Asymptomatic	Normal	**Reassurance**	-
			Depressed	**GDMT* alone (preferred)** Consider catheter ablation and/or medical therapy (if PVCs thought to be contributory to LV dysfunction)	Consider ICD if meets primary prevention criteria
		Symptomatic	Normal	**Catheter ablation or medical therapy**	-
			Depressed	**Catheter ablation or medical therapy + GDMT***	Consider ICD if meets primary prevention criteria
	≥10%	Asymptomatic	Normal	**Clinical surveillance**	-
			Depressed	**Catheter ablation (preferred) + GDMT*** Consider medical therapy if patient preference or failed/high risk ablation	Consider ICD if persistent LV dysfunction and meets primary prevention criteria
		Symptomatic	Normal	**Catheter ablation or medical therapy**	
			Depressed	**Catheter ablation (preferred) + GDMT*** Consider anti-arrhythmic agents if patient preference or failed/high risk ablation	Consider ICD if persistent LV dysfunction and meets primary prevention criteria

Abbreviations: PVC, premature ventricular complex; GDMT, guideline directed medical therapy; ICD, implantable cardiac defibrillator; LV, left ventricular; ACE, angiotensin-converting-enzyme inhibitor.

*Guideline directed medical therapy (GDMT) for LV systolic dysfunction includes an ACE-inhibitor (or angiotensin II receptor blocker+/− neprilysin inhibitor), heart failure β-blocker ± aldosterone antagonist.

origin and patient preference. Patients with a technically challenging site of PVC origin (e.g. summit or parahisian) are typically offered medical therapy initially, with catheter ablation or antiarrhythmic agents reserved for continued symptoms. Those with more straightforward RVOT sites of origin can be offered catheter ablation as first line therapy. For those who elect medical therapy and have side-effects or continued symptoms, catheter ablation is typically the next step. In some patients in whom the PVC burden is low (<10% daily), it is also possible that the PVCs may be incidental and unrelated to the clinical presentation. Symptom-rhythm correlation should be sought prior to initiation of definitive therapy.

Patients with significant PVC burden (>10% daily) and LV dysfunction, in whom no other cause of cardiomyopathy is identified (i.e. patients with potential EMC), should be offered therapy targeting PVCs regardless of symptoms, in addition to guidelines-directed medical therapy (GDMT). We recommend curative catheter ablation as first line therapy in most patients, as medical therapy rarely results in complete PVC suppression. However, for cases in which PVC ablation is predicted to be challenging, a trial of medical therapy may be reasonable before undergoing a higher risk procedure. The causal relationship between PVCs and LV dysfunction is unclear in patients with a low burden (<10% daily) [25], but if no other cause of cardiomyopathy is identified, eradication of PVCs may still be helpful. This may be the case, even when delayed enhancement on CMR suggests a degree of established myocardial fibrosis. However, patients should be counselled that LV function may not improve despite effective PVC suppression [58].

Risk Stratification – Who Needs an Implantable Cardiac Defibrillator?

In contrast to the setting of macro-re-entrant scar-based VT, patients with focal idiopathic VAs in the absence of SHD are, in general, not at increased risk of SCD. Implantable cardiac defibrillators (ICDs) are not therefore required in most cases.

For patients with frequent PVCs and SHD, ICD indications are consistent with primary prevention guidelines in the general heart failure population. However, LV function should first be reassessed following a waiting period of at least 6 months following successful ablation, as many patients will no longer meet ICD criteria if LV function improves [73]. An ICD is reasonable if significant LV dysfunction persists after this point. Recovery is expected by 4

months after successful ablation in most patients with EMC, though delayed recovery occurs in about one third of cases (up to 45 months) [74]. Patients not meeting primary prevention criteria but with concerning features such as multiple PVC morphologies, rapid VT with syncope or significant scar burden on CMR may be considered for an ICD following discussion of the potential risks and benefits.

Management – Special Circumstances

Frequent PVCs in the Setting of Pre-Existing Cardiomyopathy

Patients with pre-existing (both post-MI and non-ischaemic) cardiomyopathies may also present with frequent PVCs. These patients may have a form of mixed cardiomyopathy with EMC contributing to LV dysfunction. Sarrazin et al. demonstrated improvement in LVEF from 38% to 51% ($p = 0.0001$) in a series of 15 post-infarction patients with frequent PVCs, whilst El Kadri demonstrated similar improvements (mean LVEF 34% to 46%, $p < 0.0001$) in 18 patients with non-ischaemic cardiomyopathy [75,76]. In the latter group, most PVCs originated from sites of scar. Therefore, patients with frequent PVCs in these settings should be considered for catheter ablation and be assessed for a response to therapy prior to ICD consideration. The presence of scar or late gadolinium enhancement on CMR does not necessarily indicate irreversibility of LV dysfunction.

Malignant PVCs

Uncommonly, PVCs may provoke life-threatening arrhythmias such as polymorphic VT or VF (Figure 3). Patients may present with syncope or resuscitated SCD due to polymorphic VT/VF initiated by what otherwise appears to be an idiopathic PVC. Some series have demonstrated these malignant PVCs to have shorter coupling intervals [77,78], but there is significant overlap with benign PVCs [79]. This phenotype overlaps with that of idiopathic VF, though Purkinje fibre rather than outflow tract origin is more common in the latter [80]. For patients with PVC-triggered polymorphic VT/VF, we recommend catheter ablation of the triggering PVC [81]. Depending on LV function and inducibility of other arrhythmias, ICD implantation can be considered, particularly in the setting of myocardial scar, syncope or cardiac arrest. However, in patients with complete PVC elimination, normal LV function, no evidence of myocardial scar and no inducible VT/VF, then medical therapy and close surveillance may suffice. The decision whether to place an ICD in such cases needs to be individualised, typically after a detailed discussion of the risks and benefits between a patient and their physician.

Frequent PVCs in the Setting of Biventricular Pacing

Frequent PVCs are a potential cause of non-response to cardiac resynchronisation therapy (CRT) in patients with long-standing cardiomyopathy, as they may both contribute to cardiomyopathy and limit effective biventricular pacing [82]. Although contemporary devices have algorithms that attempt to mimic biventricular pacing following a PVC, the haemodynamic effect of the resultant fused or pseudofused complexes are unlikely to be as effective as a true biventricular paced beat. Importantly, the percentage of ventricular pacing reported by most biventricular devices does not necessarily correspond to the percentage of effective biventricular pacing, as PVC fused and pseudofused beats will be counted as the former. Contemporary CRT devices from one device company uses an algorithm that attempts to present the percentage of effective biventricular pacing, however this may still misclassify about a quarter of pseudofused beats as effective biventricular pacing [83]. The gold standard to assess the effect of PVCs on biventricular pacing remains direct visualisation of 12-lead Holter ECG channels for evidence of PVC fusion and pseudofusion.

Lakkireddy et al. demonstrated symptomatic benefit and improved LV function in 65 patients with CRT who underwent catheter ablation for frequent PVCs [84]. Catheter ablation should be considered in these patients with persistent

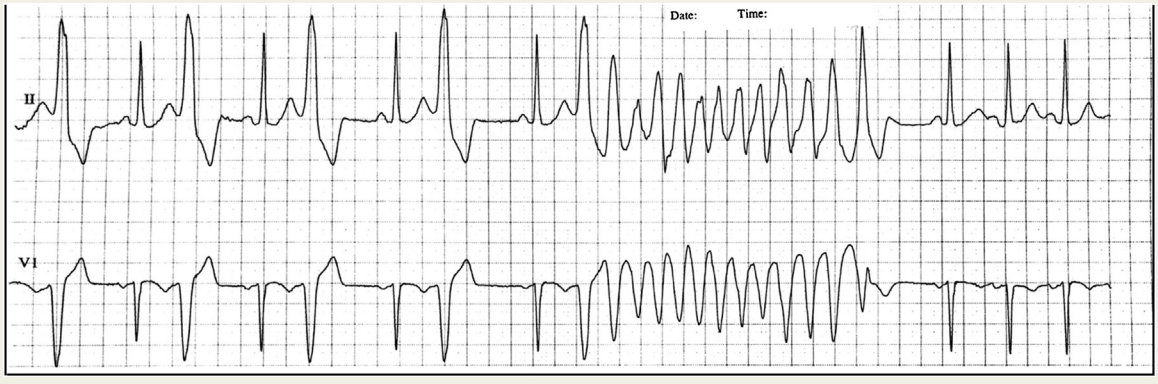

Figure 3 Ventricular ectopy from the right ventricular outflow tract initiating polymorphic ventricular tachycardia in a patient who presented with witnessed syncope and was found to be in ventricular fibrillation.

cardiomyopathy and biventricular devices especially if frequent PVCs limit effective biventricular pacing to improve CRT response rates [85].

Conclusions

Frequent premature ventricular complexes are a focal arrhythmia usually occurring in structurally normal hearts. In some patients, however, there may be an associated cardiomyopathy in which the PVCs may play a causative role (ectopy-mediated cardiomyopathy). Consequently, all patients with frequent PVCs should be assessed for PVC burden, symptom status and the presence of structural heart disease. Whilst therapeutic options include medical therapy and catheter ablation, the latter is more effective and potentially curative, particularly in patients with LV dysfunction. The prognosis in these patients is good and ICDs are rarely indicated in this population.

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