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Arrhythmia (R Kabra, Section Editor)

Approach to Management of Premature Ventricular Contractions

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Abstract

Purpose of review Premature ventricular contractions (PVCs) are arrhythmias with presentation ranging from asymptomatic and benign to symptomatic, frequent and capable of inducing cardiomyopathy. Work in the late 1970s–1980s showed that they could be representative of underlying coronary artery disease, hypertension, or left ventricular hypertrophy. Furthermore, their presence is independently linked to an increased risk of stroke and sudden cardiac death. Since characterization of PVC-induced cardiomyopathy 21 years ago, there has been progressive interest in treating PVCs. This review aims to present an approach that practitioners can use for the treatment of PVCs.
Recent findings Recent efforts have focused on optimizing techniques for mapping and ablation of PVCs in patients with symptoms or reduced LVEF. However, an understanding of the medical treatment options is necessary because medical management is still the first line of therapy. The practitioner will need to weigh the risks and benefits of these strategies in order to help the patient determine the best course of action.
Summary PVCs are recognized as a clinically significant arrhythmia, and evolving treatment strategies can improve cardiovascular outcomes. This review provides a concise summary of the current state of PVC treatment.

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Introduction

Premature ventricular contractions (PVC) are a common, age-related [1, 2], form of dysrhythmia and can be found in 50% of people even in the absence of underlying heart disease [3, 4, 5••]. They were long considered benign until the late 1980s when data from the Multiple Risk Factor Intervention Trial showed an association between one or more PVCs in a 2-min rhythm strip and increased frequency of sudden cardiac death in a 7.50-year follow-up [6]. Subsequently, publications from the Atherosclerosis Risk in Communities cohort showed that the presence of PVCs on a 2-min electrocardiogram independently predicted a 2-fold increase in the risk of death related to coronary heart disease and was associated with an increased risk of LV hypertrophy, hypertension, and stroke [1, 7–9].

The concept of PVC-induced cardiomyopathy was first introduced by Duffee and colleagues in 1998, when they described how suppressive medical therapy improved LV systolic function in idiopathic dilated cardiomyopathy [4, 10]. Later work showed that PVCs could further reduce systolic function in patients with prior structural heart disease [4, 11, 12] and that PVC-induced cardiac dysfunction can be cumulative [13]. The PVC burden required to induce cardiomyopathy is unclear, but studies have shown reproducible LV dysfunction in patients with > 10,000–20,000 PVCs per day [4, 5••]. Further characterization of PVCs in two retrospective studies of PVC-induced cardiomyopathy showed that lack of palpitations and increased QRS duration are independent predictors of reduced LV function [14]. Several other potentially concerning variables have been evaluated, but none have consistently shown significance in clinical studies [4]. However, work in animal models of PVC-induced cardiomyopathy showed that PVC burden and LV dyssynchrony are integral to the pathophysiology [15–17].

PVCs are still considered to be benign by most providers, unless the patient expresses concern about symptoms, or there is evidence of reduced LVEF with no other etiology. In patients with no symptoms and normal LVEF, reassurance with close follow-up is the recommended approach [4]. Several studies have shown adequate symptom control with beta blockers and calcium channel blockers [4]. In addition, a study has shown a benefit for flecainide and mexiletine in the reduction of PVC burden [18]. Another study has shown some evidence that amiodarone may be helpful [12, 19], but its usefulness is limited due to long-term side effects. In a prospective clinical study, radiofrequency ablation reversed more of the PVC-induced LV dysfunction than antiarrhythmic medications [19]. As such, PVC ablation has become the primary modality for treating PVCs in patients with bothersome symptoms or reduced LVEF with an otherwise unexplained pathophysiology. In this review, we will discuss the treatment options, as diagramed in Fig. 1, and review new advances in the field that are making PVC treatment more successful.

Treatment

Risk factor management

Premature ventricular contractions (PVCs) have been associated with several medical comorbidities, most of which are modifiable and should be considered either prior to or in conjunction with pharmacologic therapy or interventional procedures.

- Hypertension: Hypertension has been associated with increased frequency of PVCs, with even stronger correlation in patients with both daytime and nocturnal hypertension as well as left ventricular hypertrophy [1, 8, 20, 21]. Participants in the Systolic Hypertension in the Elderly Program (SHEP) were also followed for the presence of ventricular ectopy. This study examined a population over the age of 60 years old and found a statistically significant association with left ventricular hypertrophy as well as systolic hypertension greater than 160 mmHg with increased frequency of PVCs [22]. There are no prospective studies to demonstrate that

treatment of hypertension decreases frequency of PVCs directly [23]. It could however be postulated that reduction in left ventricular hypertrophy afforded by treatment for hypertension may have a more direct effect on PVC burden reduction.

- Alcohol: Alcohol consumption has been associated with numerous cardiac arrhythmias including PVCs [24]. In a study of over 17,000 Japanese office workers with no prior known cardiac disease, PVCs were seen in 1.7% of individuals. Those that endorsed consuming between 0 and 19 g/day of alcohol (approximately one drink) demonstrated an odds ratio of 1.73 (95% CI 1.149–2.633, *P* value 0.009) for the presence of PVCs [25]. A cross-sectional cohort analysis of 3028 visitors to the 2015 Munich Octoberfest demonstrated a trend towards increased PVC prevalence which failed to reach statistical significance [26•]. Similarly, the prospective Cardiovascular Health Study was unable to demonstrate a statistically significant relationship between acute alcohol intoxication with increased frequency of PVCs [27].
- Obstructive Sleep Apnea: Obstructive sleep apnea (OSA) is an underdiagnosed condition with increasing prevalence that can lead to rapid fluctuations in blood pH, systemic oxygenation, intrathoracic pressure, and sympathetic tone [28]. Several studies have documented an association between OSA or sleep-disordered breathing and the occurrence of ventricular arrhythmias [29, 30] including non-sustained ventricular

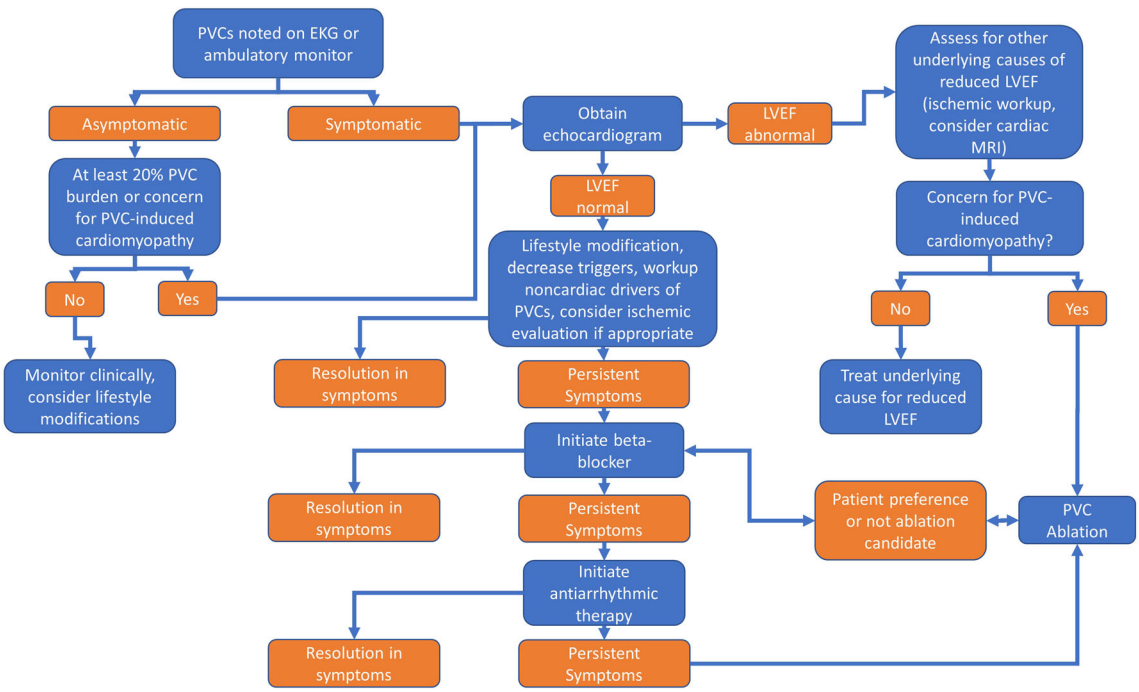

Fig 1. Overview of the management of premature ventricular contractions. Demonstrated here is a practical approach to the management of premature ventricular contractions. It should be noted that there is no one specific "cutoff" of PVC burden which places every patient at higher risk of PVC-induced cardiomyopathy. If clinical suspicion for PVC-induced cardiomyopathy exists regardless of active symptoms, workup and treatment if appropriate remain indicated. The authors recommend thorough discussion of risks and benefits of each respective therapy prior to initiation.

tachycardia and PVCs. Furthermore, patients with OSA that undergo catheter ablation for ventricular tachycardia and/or PVCs have been shown to have a higher risk of recurrence of their ventricular arrhythmia compared with patients without OSA [31]. Treatment of OSA with continuous positive airway pressure has been associated with decreased frequency of premature ventricular contractions specifically in patients with heart failure [32]. At the time of this writing, the most recent guidelines from the European Society of Cardiology published in 2015 do not suggest deviation from the usual management of ventricular arrhythmias in patients with OSA [33••]. In the 2017 version of the AHA/ACC/HRS guideline for the management of patients with ventricular arrhythmias, there are no specific recommendations regarding OSA [5••].

- Smoking: Smoking status is strongly linked to an increased risk of cardiovascular morbidity and mortality [34]. Few observational studies have specifically analyzed the relationship between PVCs and smoking. Given the degree of cardiovascular morbidity contributed by smoking, we recognize that it is difficult to adjust for all confounders to isolate the effect of smoking on PVC burden. The previously mentioned Cardiovascular Health Study did demonstrate a statistically significant increase in PVC burden (18% increase in PVCs associated with active smoking status, 95% CI 3 to 36%, *P* value 0.02) [27].
- Caffeine consumption: Caffeine has properties similar to theophylline and acts primarily as an adenosine receptor antagonist [35]. A very small prospective crossover trial of caffeine consumption and its effects on PVC burden from the 1990s failed to show a significant relationship. Since that time, a large systematic review and meta-analysis did not identify any meaningful interaction between caffeine consumption and PVC burden [36]. This was also the finding of a later published analysis from the Cardiovascular Health Study which failed to detect differences in PVC burden across various levels of coffee, tea, and chocolate consumption on 24-h ambulatory electrocardiography monitoring [37].
- Electrolyte management: Maintaining adequate serum potassium and magnesium levels is a relatively safe and cost-effective means of decreasing PVC burden. The Framingham Heart study revealed that potassium and magnesium levels were both statistically significantly associated in an inverse relationship with PVC burden after adjustment for age, sex, smoking, alcohol consumption, coffee consumption, and systolic blood pressure [38].

Pharmacologic treatment

- Beta blockers: Should pharmacologic therapy be required for treatment of symptomatic PVCs, beta blockers are considered first-line therapy [5••]. Beta blockers do not directly affect myocardial ion channels. Beta blockers suppress PVCs by several mechanisms including suppression of sympathetically driven myocardial excitation, negative inotropic effect, and slowing of the sinus rate [33••, 39–41]. Specific beta blockers which have been recommended for use in the management of PVCs include atenolol (25–100 mg orally daily or twice daily), bisoprolol (2.5–10 mg orally

once daily), carvedilol (3.125–25 mg orally every 12 h), metoprolol (25–100 mg extended-release orally daily or every 12 h), and nadolol (40–320 mg orally daily) [5••]. A study of 416 patients with frequent PVCs on Holter monitors found that beta blockers are effective at reducing PVCs associated with fast heart rates, but increase PVCs associated with slower heart rates [42]. While no specific beta blocker has been studied for relative effectiveness in suppressing PVCs, the authors of this paper generally favor using metoprolol or carvedilol primarily given their benefits in patients with heart failure [43], relatively inexpensive cost, and widespread availability. The most common serious side effects include hypotension, dizziness, fatigue, depression, and decompensated heart failure. Beta-blockers are contraindicated in patients with bradycardia, high-degree atrioventricular block, and decompensated heart failure.

- Calcium channel blockers: The non-dihydropyridine calcium channel blockers verapamil and diltiazem are Vaughn Williams Class IV antiarrhythmic drugs which decrease conduction velocity in the sinoatrial node and atrioventricular node, as well as increase the refractoriness of the atrioventricular node. For this reason, they do not have a well-documented role in the management of PVCs [44]. However, two exceptions to this are PVCs or ventricular tachycardia originating from either the right ventricular outflow tract or the fascicles of the left bundle branch, where calcium channel blockers have a more established role [5••, 33••, 45•, 46]. Verapamil is administered either intravenously as 2.5–5 mg every 15–30 min or as a sustained-release oral formulation of 240–480 mg daily [5••]. Diltiazem can be administered intravenously at 5–10 mg every 15–30 min, or as either an oral immediate-release formulation of up to 60 mg every 6 h or an extended-release formulation of up to 360 mg every 24 h [5••]. Important side effects of both diltiazem and verapamil include hypotension, atrioventricular conduction block, bradycardia, headache, constipation, and dyspepsia. Importantly, both diltiazem and verapamil should be avoided in patients with reduced left ventricular ejection fraction as they may precipitate a heart failure exacerbation due to their negative inotropic and chronotropic properties.
- Flecainide and propafenone: Flecainide and propafenone are Vaughn Williams Class 1C antiarrhythmic drugs which act by reversibly inhibiting voltage-gated sodium channels and dissociate relatively slowly from their targets. Flecainide has been shown to be effective in the treatment of PVCs, with one study achieving at least 70% reduction in PVC burden [18]. Flecainide is traditionally dosed at 100 mg every 12 h when used for suppression of ventricular ectopy and major side effects include widening of the QRS interval, atrioventricular block, dizziness, tremor, and visual disturbances [33••, 45•]. Propafenone can be administered in an immediate-release tablet at a dose of 150–300 mg every 8 h or an extended-release tablet of 225–425 mg every 12 h. The major side effects of propafenone are similar to flecainide given their similar mechanism of action, with the additional risk of drug-induced Brugada syndrome [5••, 33••, 45•]. It should be noted that flecainide and other class 1C antiarrhythmic medications are contraindicated in the presence of prior myocardial infarction due to increased risk of mortality [47, 48].

- Amiodarone: Amiodarone is classified as a Vaughn Williams Class III antiarrhythmic medication that has properties of sodium channel blockade, calcium channel blockade, and potassium channel blockade, as well as alpha and beta receptor blockade. In general, the sodium channel and beta receptor blockades are thought to occur first, while the later effects are mostly potassium channel blockade [45•, 49]. The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial investigators saw an 84% incidence of meaningful reduction in PVC burden with amiodarone compared with 35% with placebo in patients with PVCs after myocardial infarction [50]. Reduction in PVC frequency with amiodarone has also previously been shown in asymptomatic patients with reduced left ventricular systolic function [12] and in symptomatic patients with generally preserved left ventricular systolic function [19]. For the treatment of PVCs, amiodarone is generally used in an oral formulation with a total daily dose of 1200 mg divided into three doses for 1–2 weeks, followed by a maintenance dose of 400 mg daily [5••, 45•]. Patients should have baseline thyroid function testing, hepatic function testing, and pulmonary function testing performed prior to initiation of chronic amiodarone therapy due to the possibility of developing long-term toxicity in these organ systems. Side effects can include hypotension, bradycardia, atrioventricular block, slowing of sustained ventricular tachycardia, increased ventricular defibrillation threshold, nausea, skin discoloration, ataxia, and tremor in addition to liver toxicity, thyroid toxicity, and pulmonary toxicity mentioned above [5••, 45•].
- Sotalol: Sotalol, like amiodarone, has multiple antiarrhythmic effects and is classified as a Vaughn Williams Class III antiarrhythmic medication. Sotalol is formulated as a racemic mixture of D-sotalol and L-sotalol, where D-sotalol primarily has potassium channel block effects while L-sotalol acts predominately as a beta blocker [45•, 51]. Sotalol has been shown to decrease PVC burden by as much as 80–85% [52, 53]. Sotalol is administered orally at a starting dose between 80 and 120 mg every 12 h with escalation up to 160 mg every 12 h allowing 3 days at each dose to allow steady-state ascertainment of QTc prolongation. An electrocardiogram is obtained 2 h after each dose for the first five doses and QTc interval is manually calculated to ensure safety. Notable side effects other than QTc prolongation include hypotension, bradycardia, exacerbation of heart failure in predisposed individuals, fatigue, syncope, dyspnea, and depression [5••, 45•].

Interventional procedures

Catheter ablation of premature ventricular contractions

Catheter ablation of ventricular arrhythmias in general have undergone several advances in the last decade prompting a new expert consensus statement which is published online as of May 2019 [54••]. PVC ablation begins with careful preprocedural planning, including a definitive understanding of the mechanism of the particular PVC, and the underlying anatomic substrate. The majority of idiopathic PVCs tend to arise from the

RVOT followed by the LVOT, with other typical origins including the mitral or tricuspid annulus, papillary muscles, RV moderator band, and Purkinje network [55]. Dixit and colleagues devised a reproducible algorithm for localizing focal PVCs in the ventricle and associated ventricular structures [56]. This algorithm along with subsequent work enables very specific localization of PVCs to defined structures in the ventricle within a radius of 1–2 cm [54••]. More recent emerging data showed that multipoint electrocardiographic imaging (ECGI) can more accurately pinpoint the origin of focal and reentrant arrhythmias [57]. As part of the standard work up, all patients with frequent PVCs should undergo transthoracic echocardiography and ischemic evaluation to determine if these PVCs could be related to underlying structural disease, like mitral valve prolapse, or potentially reversible ischemia [54••, 58]. In the case of PVCs related to prior myocardial injury, late gadolinium enhancement on cardiac MRI can identify myocardial scar, and fiber disarray [58••, 59]. In addition, advances in multidetector CT scanners have increased the resolution of cardiac imaging to a level that regions of scar, and surviving myocardium can be differentiated based on the relative wall thickness [60]. When these techniques are overlaid with the electroanatomic mapping system and intracardiac echocardiography, they create a detailed roadmap that enables exact localization of focal ventricular arrhythmias.

Current PVC ablation techniques are based on the identification and ablation of the earliest focal endocardial or epicardial electrical signal preceding the clinical PVC [54••]. Activation maps of these early signals are highly dependent on the frequency of PVCs in the electrophysiology lab. Therefore, part of the planning for this procedure should include discontinuation of any antiarrhythmic medication by at least 5 half-lives prior to the ablation, and avoidance of any periprocedural sedative medications [54••, 61]. PVC induction via isoproterenol, epinephrine, or phenylephrine infusion and programmed electrical stimulation is helpful to increase PVC frequency, but can be limited by nonspecific results [54••]. In the absence of frequent PVCs, pace mapping is a suitable, but less accurate way to determine the origin of these PVCs [62]. Current electroanatomic mapping systems have built-in template matching algorithms which will quantify the percentage of morphologic correlation between the clinical VT and a paced beat [54••, 63]. High-density electroanatomic mapping using the ORION Catheter from Boston Scientific, the HD Grid catheter from St. Jude, or the Pentaray catheter from Biosense Webster has significantly increased the accuracy of signal detection for better accuracy, but these catheters can cause nonspecific ectopy in the ventricles [54••]. Once a suitable target has been identified, an ablation catheter is then used to deliver unipolar radiofrequency energy to the site. In cases of intramural ectopic foci, half normal saline has been used to increase current density into the tissue resulting in a deeper lesion. Alternatively, simultaneous unipolar and bipolar ablation strategies have been described to improve ablation of deep tissue like that of the ventricular septum or papillary muscles [54••].

The most common complications of PVC ablation are vascular including hematomas, pseudoaneurysms, and arteriovenous fistulas in less than 1% of cases [64, 65]. Other less common complications include cardiac

perforation with subsequent pericardial effusion/tamponade, damage to the conduction system with possible atrioventricular block [66], damage to other nearby structures which could result in valvular regurgitation, or even coronary artery injury. These risks are mitigated by careful electroanatomic mapping, force-sensing catheters, intracardiac echocardiography, and conservative ablation strategies, including limited power burns for shorter durations when there is concern [64, 65]. In rare cases of PVCs from an epicardial source, surgical access can enable the provider to dissect adhesions or reflect nearby structures for unimpeded access to the site of origin. Finally, all left-sided ablations carry an inherent risk of possible thromboembolism or air embolism [65]. The proceduralist must maintain an adequate level of anticoagulation in the patient with routine checks of the activated clotting time and remain vigilant about keeping all access and flush lines bubble free.

A direct comparison between PVC ablation and medical management is not currently available; however, a study comparing ablation with antiarrhythmic therapy in atrial fibrillation showed that the two options are cost neutral after 2 years due to the decreased recurrence rate with ablation [67]. An observational study of patients who failed medical therapy showed that successful PVC ablation improved quality of life and reduced health care costs [68].

Other treatments

Renal sympathetic denervation

Increased sympathetic tone has an established role in the burden of ventricular arrhythmias and PVCs. A prospective observational study from 2015 demonstrated a reduction in the frequency of ventricular arrhythmia after renal sympathetic denervation [69]. Shortly after this, a case report focusing on PVC burden after renal sympathetic denervation [70] demonstrated a greater than 90% reduction in PVC burden in a patient on sotalol for PVC management. Long-term data are insufficient to recommend renal sympathetic denervation for routine management of refractory PVCs. It is also difficult to separate the anti-hypertensive effects of renal sympathetic denervation from its anti-sympathetic effects, as both are likely playing a role in diminishing PVC burden.

Emerging therapies

- Recent work from Robinson and colleagues showed that stereotactic body radiation therapy reduced ventricular tachycardia burden by 99% in patients with scar-mediated ventricular tachycardia [71, 72]. This data highlights an evolving strategy [73] showing the potential benefits of radiation therapy for the treatment of ventricular arrhythmias [71, 72]. It is too early to speculate on the likelihood of complications or long-term success rates at this time.
- There is a great deal of interest in pulsed electric fields that induce cardiomyocyte apoptosis or necrosis when delivered to myocardium depending on the characteristics of the generated field [74]. The first human study with this technology showed that it successfully isolated the pulmonary

veins of all study patients [75]. Although cardiac data in humans is limited, this technology has been used previously to treat cancer and is considered very safe because the tissue injury is specific to the tissue being treated [74].

- In some areas of the heart, successful ablation is not possible due to thick myocardial tissue with an intramural focus of ectopy. To better ablate in these areas, like the LV summit, a retractable needle-tipped catheter has been designed to enable creation of deeper lesions [76, 77]. It is too early to speculate on the likelihood of complications or long-term success rates at this time.

Compliance with Ethical Standards

Conflict of Interest

Michael P. O'Quinn, Anthony J. Mazzella, and Prabhat Kumar each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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