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IN DEPTH

Evaluation and Management of Premature Ventricular Complexes

ABSTRACT: Premature ventricular complexes (PVCs) are extremely common, found in the majority of individuals undergoing long-term ambulatory monitoring. Increasing age, a taller height, a higher blood pressure, a history of heart disease, performance of less physical activity, and smoking each predict a greater PVC frequency. Although the fundamental causes of PVCs remain largely unknown, potential mechanisms for any given PVC include triggered activity, automaticity, and reentry. PVCs are commonly asymptomatic but can also result in palpitations, dyspnea, presyncope, and fatigue. The history, physical examination, and 12-lead ECG are each critical to the diagnosis and evaluation of a PVC. An echocardiogram is indicated in the presence of symptoms or particularly frequent PVCs, and cardiac magnetic resonance imaging is helpful when the evaluation suggests the presence of associated structural heart disease. Ambulatory monitoring is required to assess PVC frequency. The prognosis of those with PVCs is variable, with ongoing uncertainty regarding the most informative predictors of adverse outcomes. An increased PVC frequency may be a risk factor for heart failure and death, and the resolution of systolic dysfunction after successful catheter ablation of PVCs demonstrates that a causal relationship can be present. Patients with no or mild symptoms, a low PVC burden, and normal ventricular function may be best served with simple reassurance. Either medical treatment or catheter ablation are considered first-line therapies in most patients with PVCs associated with symptoms or a reduced left ventricular ejection fraction, and patient preference plays a role in determining which to try first. If medical treatment is selected, either β-blockers or nondihydropyridine calcium channel blockers are reasonable drugs in patients with normal ventricular systolic function. Other antiarrhythmic drugs should be considered if those initial drugs fail and ablation has been declined, has been unsuccessful, or has been deemed inappropriate. Catheter ablation is the most efficacious approach to eradicate PVCs but may confer increased upfront risks. Original research remains necessary to identify individuals at risk for PVC-induced cardiomyopathy and to identify preventative and therapeutic approaches targeting the root causes of PVCs to maximize effectiveness while minimizing risk.

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Premature ventricular complexes (PVCs) are observed in the majority of individuals monitored for more than a few hours, and the absence of a PVC will likely become more of a rare phenomenon as longer monitoring devices are used. The direct-to-consumer wearables with ECG capabilities, such as the Apple Watch and the Alivecor Kardia device, will only produce more strips revealing these early ventricular beats for clinicians to consider. Although the optimal approaches to the evaluation and treatment of PVCs sometimes remain uncertain, we now have a deeper understanding of PVCs and better methods to treat them than ever before in history. Whenever possible, investigating the cause of the PVCs is important to both optimize the care of the PVCs and identify other processes that may influence the patient's overall health. This review will summarize the state-of-the-art knowledge on the subject to help provide clinically relevant guidance and acknowledge many remaining unknowns and ongoing opportunities for future discovery.

Of note, the Heart Rhythm Society consensus recommends the term "premature ventricular complex" and not "ventricular premature depolarization" or "premature ventricular contraction" to standardize the literature and acknowledge that electric activity may not lead to mechanical contraction.[1]

PREVALENCE

Many of the studies that describe the prevalence of PVCs arise from databases of ECGs or Holter monitor studies among those seeking clinical care, where the prevalence is expected to be elevated. In one of the first large population-based assessments performed in 1962, a study of 122 043 US Air Force personnel showed that 7.8 per 1000 exhibited a PVC during a 48-second ECG, with an increasing prevalence with age.[2] In a more contemporary cohort of a multiethnic community-based study of men and women 45 to 64 years of age (ARIC [Atherosclerosis Risk in Communities] study), we observed at least 1 PVC in 252 (1.8%) of 14 000 conventional 10-second ECGs from participants without heart failure.[3] In the Cardiovascular Health Study, a community-based cohort of individuals at least 65 years of age, 243 of 4710 (5.2%) patients manifested an ECG during their baseline 10-second ECG after those with prevalent heart failure were excluded.[3] It is not surprising that the prevalence of PVCs increases as monitoring duration increases. In the ARIC study, a 2-minute ECG detected PVCs in 5.5% of the population.[4] In the Framingham Heart Study, evidence of PVCs or other more complex ventricular arrhythmias was observed in 12% of individuals without coronary disease monitored for 1 hour.[5] In one of the few community-based cohorts with 24-hour Holter monitoring, a population-based study of healthy adults aged 25 to 41 years in Lichtenstein found at least one PVC in 69% of participants; the median PVC count was 2, and the 95th percentile was 193 PVCs.[6] In a random sample of 1139 community-dwelling Americans enrolled in the Cardiovascular Health Study who underwent 24-hour Holter monitoring, we showed that PVCs comprised a median 0.011% of all heartbeats (interquartile range, 0.002%–0.123%).[7] We also found that, among those with a second 24-hour Holter study in this same community-based population 5 years later, the median number of PVCs per hour increased from 5 (interquartile range, 0.1–4.7) to 1.2 (interquartile range, 0.1–13.8).[8] Last, perhaps most commensurate with the common use of wearable patch ECG monitoring, Heckbert et al[9] recently described their findings after fitting 1122 MESA (Multi-Ethnic Study of Atherosclerosis) participants with Zio patches (iRhythm Technologies), observing at least 1 PVC in 99.5% of those elderly (mean age of 75 years) individuals. They describe a median PVC count of 1.9/hour (interquartile range, 0.3–12). In terms of overall healthcare use, we found that 35 817 (0.2%) of 16.8 million California residents seen in emergency departments, hospitals, or outpatient surgery centers between 2005 and 2009 had a healthcare code for a PVC.[10]

PREDICTORS

Although the term "predictors" can imply a causal relationship, it is important to emphasize that the majority of studies on this subject simply report characteristics that are statistically significantly associated with the presence of PVCs or a greater PVC frequency. Most of these studies are cross-sectional, because the presence of PVCs is nearly always ascertained during the baseline visit. An analysis using the ARIC study cohort demonstrated that older age, male sex, black race, a history of hypertension, evidence of other heart disease (defined as either a history of coronary disease or taking either digitalis or other antiarrhythmic drug), a higher heart rate, lower educational attainment, and hypomagnesemia were each associated with the presence of at least 1 PVC during a 2-minute ECG recording.[11] Other lifestyle factors, notably smoking, were not included in these analyses. Among 1412 community-dwelling individuals with Holter studies and echocardiograms, we found that increasing age, a taller height, and a lower left ventricular ejection fraction (LVEF) were each associated with an increasing frequency of PVCs after multivariable adjustment (Figure 1).[8] In addition, and also after adjusting for those factors, an elevated systolic blood pressure, performing less regular physical activity, and smoking were identified as potentially modifiable risk factors associated with increasing PVCs. Several hundred of those participants underwent a follow-up Holter study 5 years later, enabling a rare opportunity to assess predictors of increasing PVC counts

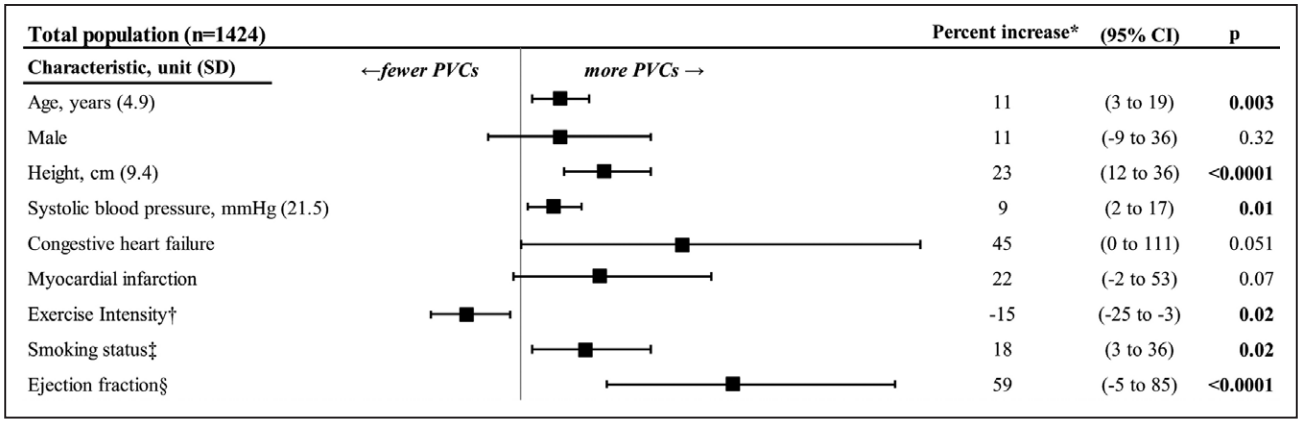

Figure 1. Multivariate adjusted predictors of PVC frequency.
The model includes all covariates listed. *Percent increase in PVCs per hour per SD of continuous covariate or the presence (versus absence) of each categorical variable. †Dichotomized into high- and intermediate-intensity exercisers versus low-intensity exercisers and no exercisers. ‡Dichotomized into ever smokers versus never smokers. §Dichotomized into abnormal and borderline ejection fraction versus normal ejection fraction. PVC indicates premature ventricular complex. Reprinted from Kerola et al[8] with permission. Copyright © 2018, the American Heart Association.

in the community: a history of a myocardial infarction, a lower LVEF, an elevated diastolic blood pressure, and smoking were each associated with an increasing frequency of PVCs over time after multivariable adjustment.[8] Compatible with those observations, a study of 2048 young, healthy individuals from the Principality of Liechtenstein with Holter studies described significant relationships between older age, taller height, lower levels of education, smoking, less physical activity, and a larger waist-to-hip ratio with more PVCs.[6] In brief, the most consistent immutable or at least unavoidable risk factors for PVCs appear to be advancing age and a taller height. Potentially modifiable risk factors observed across various cohorts and methodological approaches include a higher blood pressure, less physical activity, and smoking.

MECHANISMS

The actual mechanism of PVCs in many cases is not known, and more than 1 process may ultimately be responsible. There are 3 basic mechanisms that might be operative, including triggered activity, automaticity, and reentry. The mechanism may have clinical relevance when considering behavioral triggers, other underlying diseases, the potential effectiveness of certain medicines, and understanding the approaches (and therefore patient experiences) pertinent to catheter ablation procedures.

Triggered activity is generally attributed to afterdepolarizations mediated by increases in intracellular calcium.[12] Early afterdepolarizations, occurring in the plateau phase of the action potential, classically arise in the setting of prolonged repolarization, resulting in the PVCs that may initiate torsades de pointes in those with congenital or acquired forms of the long-QT syndrome.[13] Delayed afterdepolarizations occur at repolarized membrane potentials and are classic manifestations of digitalis toxicity[14] or catecholaminergic polymorphic ventricular tachycardia.[15] Activation of cAMP-dependent protein kinase A more often results in phosphorylation of multiple targets that may lead to increased intracellular calcium.[16] Caffeine is known to result in delayed afterdepolarizations through the release of calcium from the sarcoplasmic reticulum.[17] Adenosine, via action on the adenosine A1 receptor, which itself inhibits production of adenylyl cyclase (and hence cAMP), can terminate triggered PVCs.[18] Because catecholamines also activate cAMP, β-blockers may reduce PVCs arising from triggered activity.[16] Last, nondihydropyridine calcium channel blockers (diltiazem and verapamil) may prevent triggered PVCs by reducing cytosolic calcium accumulation through blockage of L-type calcium channels.[16]

In contrast with a triggered mechanism, PVCs arising from automaticity may exhibit parasystole.[19] Here, the PVCs should march through at the same cycle length, independent of the underlying rhythm. It is important to note that the absence of a PVC may occur intermittently because of ventricular refractoriness related to the separate underlying rhythm, and therefore multiples of the parasystolic PVC interval should be considered before excluding automaticity. The mechanistic cause of the automaticity itself may be multifactorial, including an exaggerated version of normal automaticity inherent to all cardiomyocytes (such as attributable to intrinsic catecholamines or extrinsic inotropes[20]), and, relative electric isolation attributable to some poorly conducting barrier such as fibrosis, as well.[21] The clear and consistent predilection for PVCs to arise from certain anatomic regions, such as the outflow tract, has led to recent speculation that the ultimate origins of the ectopic focus may relate to shared embryological development with cell or tissue types physiologically destined for automaticity, such as specialized conduction tissue.[22]

Although reentry is usually considered most pertinent to sustained arrhythmias, it can play a role in single PVCs. Reentry requires 2 distinct electric pathways and either transient or permanent unidirectional block in 1 limb. Those pathways may be anatomically quite distinct, such as a right ventricular PVC blocking in the retrograde limb of the right bundle (commonly attributable to phase 3 block), crossing the ventricular septum through cardiomyocytes, conducting in a retrograde fashion up the left bundle, and then continuing on down the right bundle, producing a bundle-branch reentry complex (recognized as having a typical, usually left, bundle-branch block appearance). A similar phenomenon may occur involving the left anterior and left posterior fascicles, resulting in a fascicular PVC (recognized as having the appearance of a right bundle-branch block with left anterior hemiblock if exiting the left posterior fascicle or left posterior hemiblock if exiting the left anterior fascicle). Instead, in the absence of anatomically well-defined pathways, different tissue properties, such as 2 adjacent regions with different conduction velocities and refractory periods, may suffice to host reentry. In general, an area of scar, or a series of electrically connected cardiomyocytes meandering through an area of fibrosis, may provide a pathway that conducts much more slowly than surrounding healthier tissue during a sinus beat, such that the resultant exiting depolarizing wave front would meet myocardium that was no longer refractory, producing a PVC.

EVALUATION

Patients with PVCs typically come to clinical attention for 1 of 2 reasons: symptoms or an incidental finding on medical examination. Symptoms may include palpitations (which may manifest as chest discomfort, a sensation of an intermittently strong heartbeat, or a sensation of skipped or irregular heartbeats), presyncope, dyspnea, and fatigue.[23] The symptom is often not attributable to the PVC itself, but rather the sensation of the particularly strong heartbeat that occurs because of the prolonged ventricular filling time after that PVC, resulting in an enhanced stroke volume along the Frank-Starling curve and potentiated calcium release. Patients may describe this as an abrupt feeling of needing to catch their breath or the heart stopping. Many people with PVCs never feel them, and some individuals will notice some PVCs and not others. PVC symptoms are an area ripe for original investigation. The proportion of those with asymptomatic versus symptomatic PVCs is not known, and neither the predictors nor the precise mechanisms underlying noticeable versus occult PVCs are understood.

Symptoms may also occur more indirectly, not because of the PVCs themselves, but rather because of the consequences that ensue. As will be discussed in-depth in the prognosis and management sections, patients with more frequent PVCs may present with symptoms of heart failure and volume overload.[7,24,25]

Patients may rarely present with abrupt syncope or sudden arrhythmic death attributable to PVC-induced ventricular fibrillation.[26] Even those apparently benign forms of PVCs, such as those arising from the right ventricular outflow tract, may trigger polymorphic ventricular tachycardia or ventricular fibrillation.[27,28] Whether these represent something malignant about the PVC (such as a particularly short coupling interval[29]), a vulnerability to these tachyarrhythmias in response to a PVC, or a combination remains unknown. Although there are no established guidelines to identify patients with PVC at the highest risk of PVC-triggered ventricular fibrillation, the clinical pearl is to consider PVCs as potentially playing a causal role when ventricular fibrillation is observed.

A family history is important to elucidate any possible inherited disorders that may be associated with PVCs and a risk for sudden death. As an initial screen, it is often useful to recommend asking about any first-degree family members who either died suddenly or at an early age. A positive family history in a patient with PVCs should heighten suspicion for arrhythmogenic right ventricular dysplasia and possibly for other inherited cardiomyopathies.

In the absence of symptoms, PVCs may manifest as an irregular pulse or as an incidental finding on ECG. Both patients and healthcare providers may be alarmed by apparent bradycardia ascertained by a palpable pulse alone, occurring because of intermittent, poorly perfused PVCs. It can be useful to explain this phenomenon to patients to help them (and their providers) feel more comfortable with their prescribed β-blockers or calcium channel blockers, which, in this case, may counterintuitively result in an increase in the palpable pulse rate. Understanding this mechanism can similarly be instructive in appreciating how some patients may experience substantial fatigue because of frequent PVCs, where, despite a normal number of electric complexes per minute, there exists a hemodynamically relevant effective bradycardia.

A careful physical examination, including simply lingering for a few heartbeats during cardiac auscultation, can be the critical assessment that first identifies evidence of a PVC. Similarly, that physical examination may be the first indication of PVC frequency, which ultimately may prove to be clinically relevant. Given the established relationship between PVCs and heart failure, it is important to assess for physical signs of reduced systolic function, a dilated left ventricle, and volume overload.

PVCs can be diagnosed only by ECG. The 12-lead ECG is useful to provide the initial evidence of PVC

frequency and remains the best noninvasive tool to determine the PVC location. When a PVC is suspected from either the history or physical examination, it is useful to continue to run a rhythm strip over 30 to 50 seconds in the hopes of determining a better sense of PVC frequency and to catch the PVC during recording of all 12 contemporaneous leads to allow for the most accurate morphology assessment. Attention to the remainder of the ECG may also reveal clues to the underlying substrate: careful measurement of the QT interval is mandatory, precordial T-wave inversion beyond lead V_2 or right ventricular conduction delay may be indicative of arrhythmogenic right ventricular dysplasia,[30] pathological Q waves can reflect discrete areas of scar, an early precordial transition accompanied by a prominent S wave in V_6 may signal a basolateral scar observed in nonischemic cardiomyopathy,[31] and conduction disease may be a manifestation of cardiac sarcoidosis.[32] It is also important to emphasize that PVCs arising from common sites, such as the right ventricular outflow tract, may commonly trigger ventricular fibrillation in patients with the Brugada syndrome[33] and torsade de pointes in patients with the long-QT syndrome.[33,34]

Although 24-hour Holter monitoring was long considered the gold standard in assessing PVC frequency, recent evidence has demonstrated that substantial daily variation may occur and that up to 6 days of monitoring may be required before the maximum daily PVC frequency is observed.[35] In general, a single wearable ECG patch is likely sufficient and the most useful for this purpose. It is important for practitioners to recognize that some wearable ECG monitors may be true event monitors that capture only rate- or rhythm-based irregularities as snapshots in time without full disclosure of every beat, precluding an assessment of PVC burden. A true continuous recording is most useful both to provide an accurate PVC count and to determine the percentage of PVCs in the context of the total sinus beats over the same time period. Those monitors are also more apt to detect and characterize episodes of ventricular tachycardia. Ambulatory monitoring is also helpful in matching patient symptoms with (or without) the occurrence of PVCs and to determine the number of different PVC morphologies.

Understanding the PVC location may provide clues to underlying cardiac disease, may help direct medical therapy, and may be relevant to counseling patients regarding relative risks and effectiveness of catheter ablation procedures (Figure 2). The most common PVC location in the general community remains unknown, and the data regarding frequency of various PVC types arises mainly from series of patients seeking medical care. PVCs from the outflow tract appear to be the most common.[1,16] Outflow tract PVCs characteristically exhibit negative QRS complexes in both aVL and aVR, consistent with a vector that is predominately arising from the top of the heart, and, by the same token, the inferior leads will all be positive. Right ventricular outflow tract PVCs will have a left bundle-branch morphology, meaning a predominately negative QRS in V_1. If the precordial transition (the precordial lead that first exhibits a QRS that is more positive than it is negative) occurs at V_4 or later and the other limb-lead criteria just described are present, the PVC is almost certainly arising from the right ventricular outflow tract.[16,36] If an otherwise similar PVC has a precordial transition that occurs in V_1 or V_2, it is almost certainly left-sided, most likely arising from the right or left coronary cusp (or just in-between the 2). If an otherwise similar PVC precordial transition occurs at V_3, it may be either right or left sided.[16,36] The distinction is relevant to both the effectiveness and the risks of potential catheter ablation, which, as will be described in more detail later in this article, are both more favorable for right-sided PVCs. Understanding these morphological characteristics is also relevant because right ventricular PVCs that are not arising from the right ventricular outflow tract may be a sign of underlying pathology, such as arrhythmogenic right ventricular dysplasia, sarcoidosis, or other infiltrative diseases. For example, although idiopathic PVCs may arise from various locations within the right ventricle in the absence of structural heart disease, a frequent left bundle-branch, late-precordial transition (more positive than negative starting in V_4) PVC that is not negative in both aVR and aVL and that is negative in the inferior leads should prompt further evaluation with cardiac magnetic resonance imaging (MRI). Commonly observed PVC morphologies from the left ventricle include the papillary muscles,[37–39] which may often exhibit variable morphologies within the same patient, the left anterior or left posterior fascicles (which may occur because of either reentry or automaticity),[40] and along the mitral annulus.[41–43] PVCs also arise relatively frequently in proximity to venous structures, such as the great cardiac vein and anterior intraventricular vein[44–46] and from the crux of the heart, where all 4 chambers meet.[47]

An echocardiogram is indicated in nearly everyone referred to clinical attention because of PVCs to exclude structural heart disease, in particular, a reduced LVEF, and other underlying pathology that may either contribute to the genesis of the PVCs or render them more symptomatic. Because ordering an echocardiogram is a common default, this review may be most helpful in guiding some clinicians away from unnecessary testing. Some patients present with relatively rare PVCs that are just symptomatic enough to cause the patient concern but not so symptomatic that they prohibit any activities. If a patient is otherwise healthy and is physically active without limitation, does not have a history of syncope or symptoms compatible with ventricular tachycardia, does not have a family history of early or sudden death, and

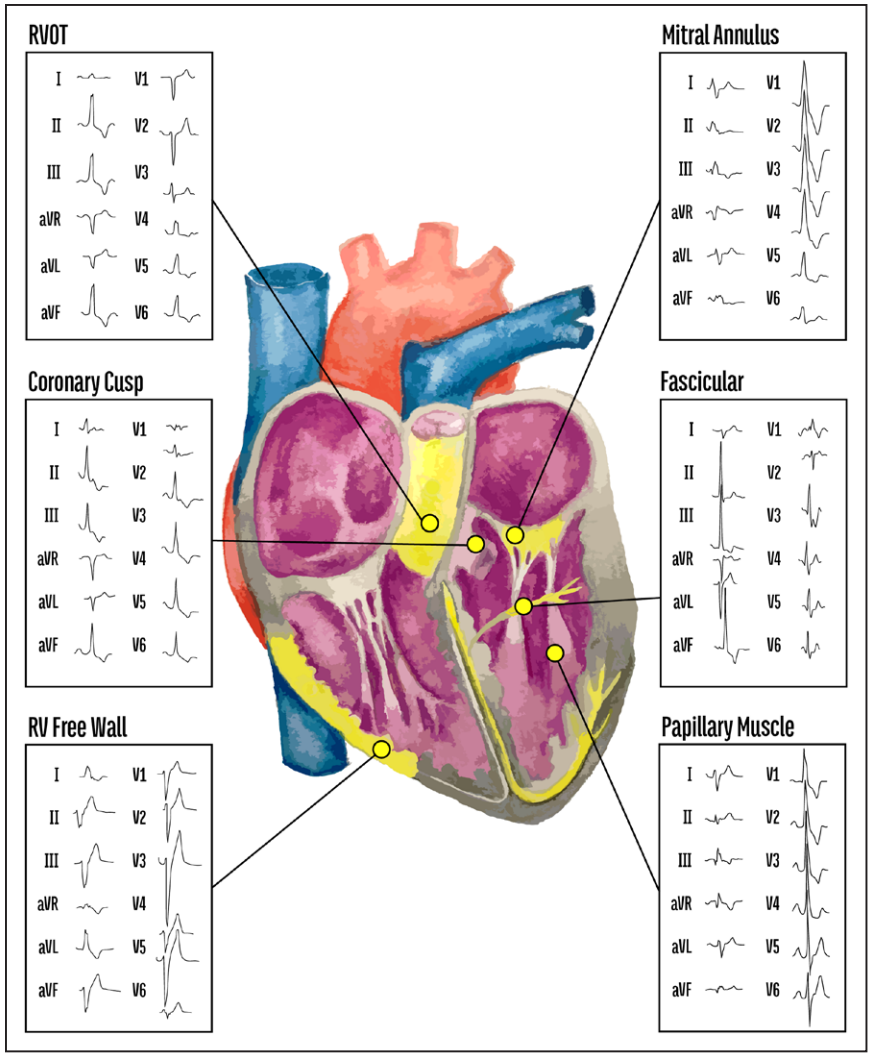

Figure 2. Example 12-lead ECGs from common locations of premature ventricular complexes.
RV indicates right ventricle; and RVOT, right ventricular outflow tract.

neither a resting ECG (with a long rhythm strip as described earlier) nor physical examination reveal any PVCs (in support of a low PVC burden) or other abnormalities, it is reasonable to stop there without ordering further testing. Patients can always be encouraged to return if, after reassurance, they develop worsening symptoms.

A cardiac MRI should be considered when the PVC is not arising from a common location (such as the right ventricular outflow tract) or when sustained ventricular tachycardia or reduced ventricular systolic function is present. Of note, cardiac MRI images may be difficult to interpret in the context of frequent PVCs because of gating difficulties. The MRI can be helpful in making a diagnosis of arrhythmogenic right ventricular dysplasia [48] or when there is a suspicion for cardiac sarcoidosis.[49] Even in the absence of a clear underlying diagnosis, delayed enhancement observed on a cardiac MRI can help visualize cardiac scar,[50,51] potentially helping to plan for and guide catheter ablation procedures.[52] Among those with evidence of delayed enhancement, a positron emission tomography scan may be particularly useful in assessing infiltrative and inflammatory processes.

PROGNOSIS

A seminal article in 1985 describing a mean 6.5 years of follow-up in 70 asymptomatic, healthy patients found to have ventricular ectopy concluded that there was no difference in prognosis in comparison with the general population.[53] Although the general impression for decades was that PVCs in otherwise healthy individuals were benign, studies consistently demonstrated that PVCs signaled a higher risk of death after myocardial infarction.[54–56] Given evidence that successful PVC suppression could result in an increased risk for death in CAST (Cardiac Arrhythmia Suppression Trial),[57] the notion that PVCs were causal, or at least should be considered a reasonable target of suppression for the purposes of improving prognosis, was abandoned.

In 1995, a randomized trial demonstrated that amiodarone suppressed PVCs and resulted in a significant increase in LVEF among patients who had heart failure with frequent cardiac ectopy.[58] Subsequently, starting in the early 2000s, case reports of successful catheter ablation of PVCs resulting in improvements in

and even complete resolution of systolic dysfunction were published.[59,60] Such studies were soon followed by case series of improvements in LVEF after catheter ablation among patients with a high burden of PVCs and reduced left ventricular systolic function, providing evidence that PVCs could play a causal role in heart failure (Figure 3).[24,61–64] Although these data could be ascribed to only a very specialized group of rare patients presenting for interventional electrophysiology procedures, contemporaneous evaluations of community-based populations extended concern that PVCs in general may portend a poor prognosis; in a multiracial community-based cohort study of >15 000 individuals, the presence of a PVC on a 2-minute monitoring strip predicted a higher risk of coronary heart disease events and death.[65] Using data from another community-based study, the Cardiovascular Health Study, and armed with baseline echocardiography data and a median follow-up of nearly 14 years, we demonstrated that a greater frequency of PVCs was associated with a 5-year reduction in LVEF, an overall increased risk for clinically relevant heart failure, and an increased risk for death (Figure 4).[7] We found that the overall population-attributable risk of heart failure related to PVCs was similar to coronary artery disease, and our analyses indicated that approximately one-third (albeit with the upper end of the 95% confidence interval including 68%) of the increased risk for death related to PVCs was mediated by incident heart failure.[7]

It is clear that there are many patients with frequent PVCs who never go on to develop systolic dysfunction or clinical heart failure. There is therefore tremendous interest in identifying individuals at risk. Most of this work has arisen from series of patients presenting for catheter ablation of their PVCs, and more work needs to be done in the community-based settings to better inform decision making in the general population.

Among patients presenting for clinical care for their heart failure and PVCs, a higher burden of PVCs has consistently been shown to be an important risk factor. It is important to emphasize the origins of this group (constrained to those presenting for clinical care, primarily to cardiologists), where the proportions of individuals with heart failure in the setting of PVCs is likely inflated in comparison with the general population. Although there is no clear single threshold cutoff, studies have suggested that optimal test characteristics for a PVC-induced cardiomyopathy occur at PVC burdens of 16% to 24%[24,66] and that most cases of PVC-induced cardiomyopathy occur at burdens >10%.[24,66–69] However, consistent with evidence that those with 6% PVCs can experience benefit in reducing their systolic dysfunction with catheter ablation, the reality is likely more complicated and nuanced, fitting with our previous community-based observation that the risk simply increases proportionally with burden.[7,70] Very likely, factors other than the PVC frequency determine an individual's propensity to develop systolic dysfunction in the face of PVCs. Again primarily from cross-sectional studies (or studies with follow-up only after catheter ablation) restricted to patients presenting with clinically relevant heart failure and PVCs, additional factors reported to be associated with PVC-induced cardiomyopathy include male sex,[71,72] asymptomatic PVCs,[71–73] a longer duration of palpitations,[71] interpolated PVCs,[74] a variable PVC coupling interval,[75] a longer PVC QRS duration,[66,76,77] and PVCs arising from the epicardium.[72,73] Because of the cross-sectional nature of most of these clinical case series, it can be difficult to disentangle cause and effect. In some, resolution of heart failure after successful PVC ablation demonstrates that the PVCs were the cause, whereas in others the PVCs may be a secondary manifestation or epiphenomenon of an underlying pathology that will not be reversed with ablation.

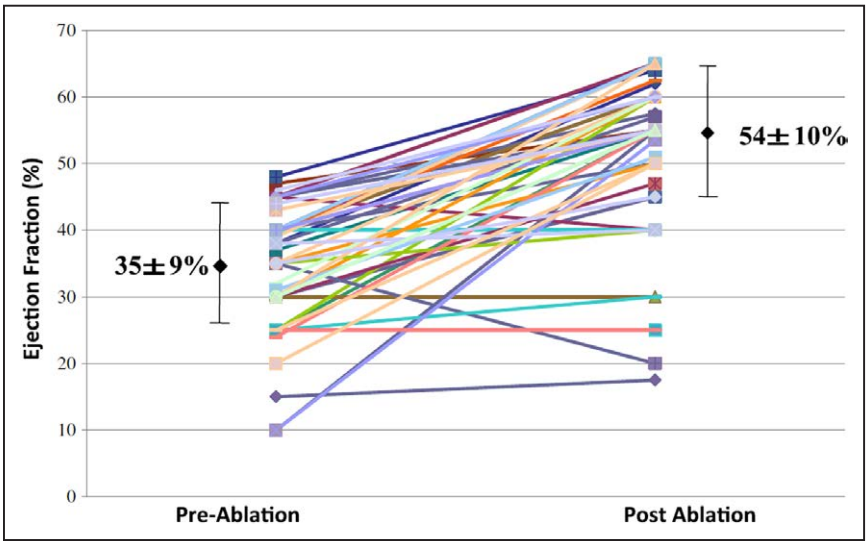

Figure 3. Change in ejection fraction among a series of patients with frequent premature ventricular complexes and reduced left ventricular systolic function after catheter ablation.
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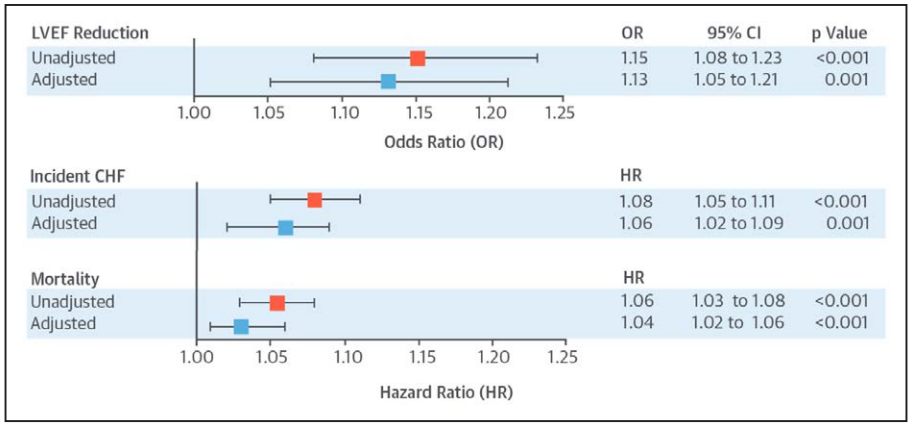

Figure 4. Associations between baseline percent PVCs and 5-year reduction in LVEF, incident heart failure, and mortality.
Squares represent unadjusted (salmon) and adjusted (blue) odds ratios (ORs) for log base 2–transformed percent of premature ventricular complexes (PVCs) as a predictor of any reduction in qualitative left ventricular ejection fraction (LVEF) between the baseline and 5-year echocardiograms or hazard ratios (HRs) for incident heart failure and mortality. Multivariable models included adjustment for age, sex, race, body mass index, and a history of hypertension, diabetes mellitus, coronary artery disease, β-blocker use, Holter-based atrial fibrillation, and number of Holter-based ventricular tachycardia episodes. Error bars indicate 95% CIs. HRs express the increase in risk per doubling of the percent of PVCs. CHF indicates congestive heart failure. Reprinted from Dukes et al[7] with permission. Copyright © 2015, the American College of Cardiology Foundation.

More difficult to study are the potential interactions between patient characteristics that may modify the relationship between PVCs and incident cardiomyopathy. We attempted to do this among nearly 17 million California residents, relying on the crude predictor of an *International Classification of Diseases, Ninth Revision* diagnosis of PVCs; we found that the absence of established cardiovascular risk factors heightened the risk of incident heart failure among those with PVCs.[10] Future research may determine whether there are genetic determinants, such as variants that enhance the risk of heart failure, that modify the influence of PVCs on cardiomyopathy risk.

Although the mechanism responsible for systolic dysfunction attributable to PVCs was initially attributed to a tachycardia-induced cardiomyopathy, careful measurements of actual heart rates (including the PVCs) has not borne this out.[25,74] The established risk factors, in particular, the wider QRS and epicardial PVC origins, have been interpreted to mean that PVC-induced left ventricular dyssynchrony may be the culprit. Albeit only in 45 patients presenting for treatment of their PVCs, one of the few studies to follow patients with normal baseline systolic function over time found a longer PVC QRS duration to be a particularly potent predictor of systolic function decline.[78] Elegant experiments in a swine model, where PVCs were induced with pacing from either the right ventricular apex or left ventricular epicardium, have provided compelling evidence that left ventricular dyssynchrony during PVCs appears to have an especially detrimental effect on left ventricular remodeling and systolic function.[79]

MANAGEMENT

In many cases, the most useful contribution a physician can provide a patient with PVCs is reassurance. In considering whether additional management beyond reassurance should be pursued, 3 key pieces of information are needed: (1) information regarding symptoms, (2) the burden of the PVCs (typically reported in PVCs as a percentage of all beats), and (3) the presence or absence of structural heart disease.

If the burden of PVCs is low, the evaluation as described earlier reveals no relevant underlying condition, and the ejection fraction is normal, reassurance alone may be reasonable and sufficient. In fact, determining therapy based on symptoms requires some important questions for the patient. In brief, treatment should not necessarily be given for symptoms alone. Often the patient is seeking evaluation because they experience a worrisome sensation with their PVCs and are concerned these symptoms may be a sign of something wrong or of some impending problem. It is important to distinguish those who would no longer be too bothered by their symptomatic PVCs once they are reassured that they are in no danger from those who have PVCs that are causing symptoms interfering with their quality of life even after receiving that reassurance. Clinicians may consider specifically asking their patients whether their PVCs would be bothersome enough to try a medicine or a procedure even if they could be convinced their PVCs posed no danger. PVC symptoms, even in the presence of a normal LVEF, that remain bothersome to patients after reassurance are indications for treatment.

Patients will often ask about lifestyle changes that might help them with their PVCs. The literature here is sparse. Although we have demonstrated a relationship between more exercise and fewer PVCs,[8] prospective trials proving a causal relationship have not been performed. It is possible that intensive and long-term exercise may result in increased PVCs among highly trained athletes,[80] but that observation should not be

extrapolated as a reason to avoid exercise given the clear net benefits of physical activity.[81] Similarly, we and others have found a positive relationship between smoking and PVCs,[6,8] providing yet one more reason to strongly counsel smoking avoidance and cessation. Studies regarding e-cigarettes and cannabis have not yet been performed, but, at the very least, advocating for a trial away from such substances may be useful. Expert guidelines commonly call for avoidance of caffeine.[82] Prineas et al[83] published a study in 1980 that demonstrated a statistically significant relationship between self-reported caffeine consumption and the presence of a PVC on a 2-minute ECG recording. Perhaps relevant, these participants consumed on average 5 cups of coffee per day. However, a randomized trial of 81 men with PVCs failed to show a reduction (on tests at the end of the study rather than during long-term, contemporaneous, ambulatory assessments) between those randomly assigned to 6 weeks of caffeine, alcohol, and smoking abstinence plus an exercise program versus those randomly assigned to control.[84] In an analysis of more than 1,000 community-dwelling individuals randomly assigned to 24-hour Holter monitoring, we were unable to detect any relationships between self-reported caffeine and PVC counts.[85] To assess potential real-time effects, we are currently conducting the CRAVE trial (Coffee and Real-time Atrial and Ventricular Ectopy) (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03671759), wherein individuals will be assigned to randomly selected days to consume versus avoid coffee while wearing a continuously recording ECG patch. For now, emphasizing the goal of enhancing quality of life in those with a normal LVEF, there is insufficient evidence to recommend a broad prohibition against caffeine. Instead, counseling moderation and even self-experimentation (with and without caffeine) for individual patients best addresses this quality-of-life issue.

If a patient has bothersome symptoms despite reassurance or a reduced LVEF, either medical treatment or catheter ablation are reasonable first options. In general, catheter ablation exhibits superior effectiveness,[67,86,87] but may represent greater up-front risks. In the presence of a structurally normal heart, the purpose of treatment is to improve quality of life; therefore, patient preference is appropriately a primary determinant in pursuing medical therapy or catheter ablation first.[1,82] The optimal approach to the asymptomatic patient with a high burden of PVCs and a normal LVEF remains unknown; in general, routine surveillance, such as with an annual in-person evaluation accompanied by an echocardiogram, is reasonable for these patients. Figure 5 provides a general guide to help frame decision making for the common patient with PVCs (with predominately monomorphic PVCs), acknowledging the importance of flexibility in individual cases, the need to address readily reversible processes, and the need for additional information gleaned from original research.

Medical Therapy

Either β-blockers or nondihydropyridine calcium channel blockers (diltiazem or verapamil) are considered first-line medicines for PVCs. Both have a long track record of safety in structurally normal hearts, and β-blockers may have additional benefits in the setting of coronary disease or a reduced LVEF. β-Blockers are particularly effective for sympathetically mediated, triggered PVCs, with data demonstrating effectiveness specifically in outflow tract PVCs.[82,88] Although better than placebo, randomized controlled clinical trials demonstrate that β-blockers result in a clinically meaningful reduction in symptomatic outflow tract PVCs in only 12% to 24%.[86,88] The nondihydropyridine calcium channel blockers have similarly demonstrated effectiveness in outflow tract PVCs and are considered particularly useful for fascicular ventricular arrhythmias.[82,89,90] In the patient with a structurally normal heart, it is reasonable to try a calcium channel blocker if a β-blocker fails (and vice versa). Failure of a drug may occur because of either insufficient effectiveness or medication intolerance. It is important to probe patients regarding side effects to medicines given the reasonable alternative of catheter ablation or other antiarrhythmic drugs. With either type of drug, patients may experience fatigue or presyncope. Although depression and erectile dysfunction may be less common with more selective β-blockers now commonly in use, it is important for healthcare providers to be aware of these possible side effects. The nondihydropyridine calcium channel blockers may result in gastrointestinal side effects, such as gastroesophageal reflux and constipation, and can cause leg swelling.

If these initial drugs fail, catheter ablation should be considered next. For the patient in need of treatment who strongly prefers to avoid catheter ablation, for whom catheter ablation has failed, or who may not be a good ablation candidate (because of frailty or multifocal PVCs), additional antiarrhythmic drugs to consider include flecainide, propafenone, sotalol, and amiodarone. Mexiletine may be used rarely, but its effectiveness is inferior to either other antiarrhythmic drugs or catheter ablation.[67,91] Flecainide and propafenone are well-tolerated, in general, and are often efficacious.[67,87,91] In extrapolating from the CAST study,[57] flecainide and propafenone are generally considered contraindicated in the presence of coronary disease, severe left ventricular hypertrophy, or heart failure.[92] Some practitioners will use propafenone in patients without coronary disease and mildly depressed systolic function.[67,93] Sotalol can suppress PVCs in most patients[94] and is a particularly reasonable choice in the presence

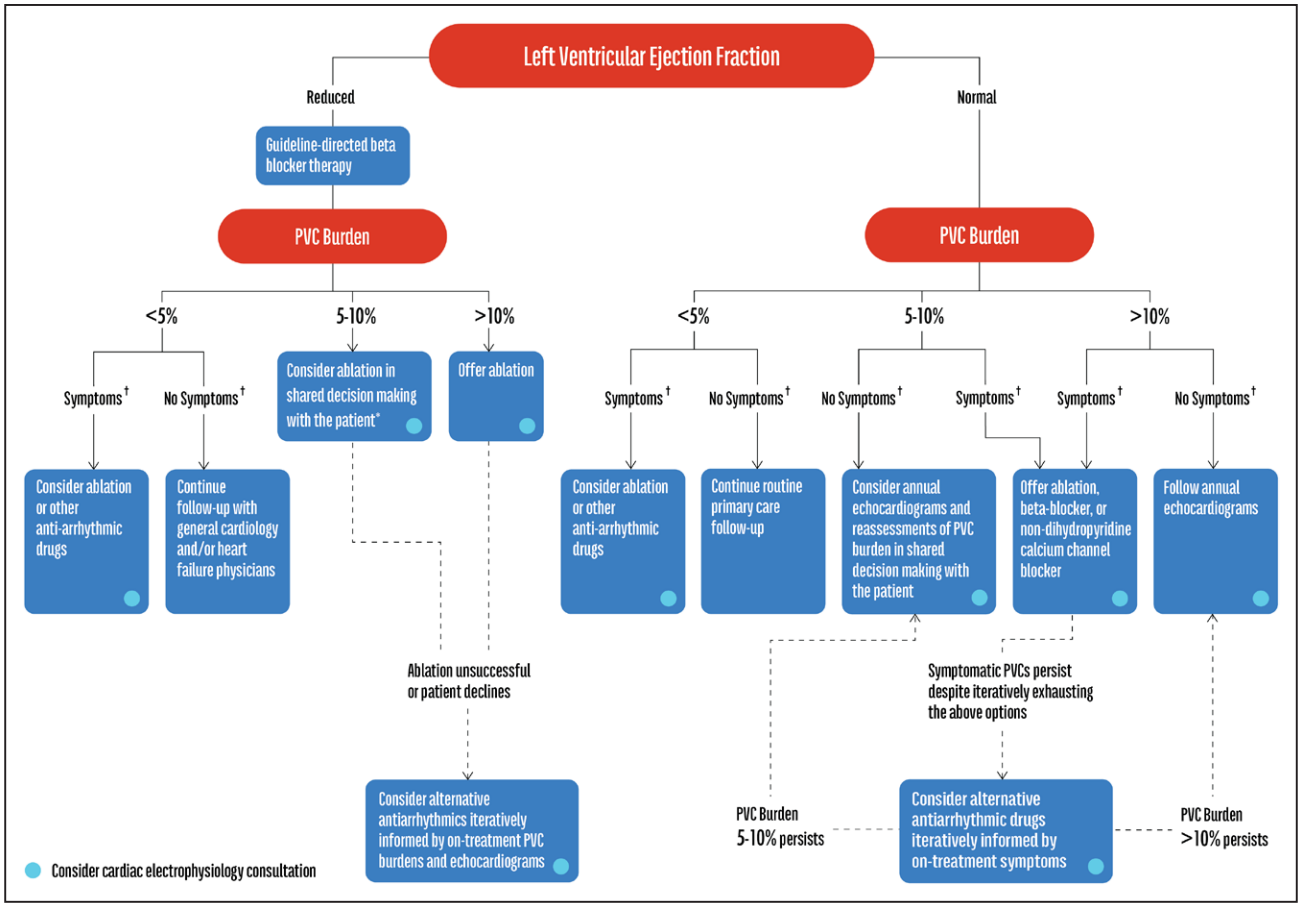

Figure 5. Suggested workflow in considering the evaluation and management of patients with predominantly monomorphic PVCs.
The workflow should be used after readily reversible causes of either PVCs or reduced ejection fraction have been addressed. *The absence of other clear causes for the reduced systolic function may support more aggressive attempts to determine whether PVC suppression results in improvement. †Symptoms refers to those that are sufficiently bothersome such that the patient prefers to pursue therapies even after understanding that those therapies are not needed for risk reduction. PVC indicates premature ventricular complex.

of coronary disease,[95] although careful monitoring of the QT interval is critical.[96] It is reasonable to admit all patients initiating sotalol, and, at the very least, there should be a low threshold to admit any patient at risk for QT prolongation. Although amiodarone is efficacious and is one of the few antiarrhythmic drugs that can be safely administered in the setting of severely reduced systolic function,[58] the associated side-effect profile, in particular, with long-term use, makes it substantially less preferable in younger patients. In general, amiodarone is reserved for older patients and for those with no other options.[97]

Catheter Ablation

In general, catheter ablation is more efficacious than medicines to treat PVCs, in particular, given a predominately monomorphic target.[67,86,87] Success of PVC ablation procedures range from approximately 80% to 95%.[1] Both the American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the treatment of ventricular arrhythmias[82] and the Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter ablation of ventricular arrhythmias[1] generally recommend either medicines or catheter ablation as first-line therapies for PVCs that are either symptomatic or likely responsible for systolic dysfunction. Specifically, catheter ablation is listed as a class I indication (meaning a strong recommendation where the benefit far exceeds the risk) to treat PVCs if medicines are not tolerated, not effective, or preferred by the patient. Complications of catheter ablation procedures for PVCs are observed in 0% to 5% of cases, in general,[64,72,86,98] mostly because of issues related to vascular access including hematoma, pseudoaneurysm, or atrioventricular fistula (which may often resolve without intervention). More rare but more severe complications include aortic dissection, atrioventricular block, myocardial infarction, cardiac tamponade, and stroke. The expert guidelines on catheter ablation recommend ablation of outflow tract PVCs originating from the left side of the heart, including the sinuses of valsalva, as a class IIa recommendation (moderate

strength of recommendation, where benefit still exceeds the risk, but not to the same degree as the class I indications reserved for PVCs in other locations). Part of this is because the left ventricular outflow tract is more complex, and epicardial access may be required more frequently. Although entering via the coronary sinus, the great cardiac vein, or anterior interventricular vein may provide conduits for ablation catheters that may negate the need for left ventricular or pericardial access, some of these left ventricular summit PVCs can be notoriously difficult PVCs to ablate, often because of the close proximity to the left main coronary artery.[44,99] Similarly, crux PVCs, or those arising from the direct center of the 4 chambers,[47] can be reached via the great cardiac vein or a subxiphoid epicardial approach, but achieving adequate temperatures to render an effective burn there may be problematic. In a small case series, we recently found that ≈60% of all left ventricular ablations resulted in new brain emboli (Figure 6)[100]; no new brain emboli were observed in right ventricular ablations. To test the hypothesis that a transseptal approach instead of the more conventional retrograde aortic approach might mitigate the risk of those lesions, we are now conducting a multicenter randomized trial funded by the Patient Centered Outcomes Research Institute (TRAVERSE [Transseptal or Retrograde Aortic Ventricular Entry to Reduce Systemic Emboli]; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03946072). In that study, we will also obtain neurocognitive tests in the hopes of elucidating the meaning of those otherwise subclinical brain emboli.

FUTURE DIRECTIONS

Basic, translational, and clinical investigators have all contributed substantially to our understanding of PVCs over the past few decades, but there is still much to learn. Although some of the basic mechanisms have been elucidated, we still do not understand why some people have a greater PVC frequency than others or exactly why some experience debilitating symptoms while others do not notice them at all. Identifying those at risk for PVC cardiomyopathy remains critical to optimize healthcare utilization workflows while mitigating that risk in appropriately selected patients. The tools routinely used for catheter ablation continue to improve and evolve; indeed, much of the effectiveness and complication rates reported earlier arose before the routine use of ultrasound-guided vascular access, phased-array intracardiac echocardiography, deflectable long sheaths, and irrigated catheters with contact force sensors, all of which have likely increased success rates while decreasing complications. The goal ultimately will be to determine the genetic and environmental factors responsible for problematic PVCs, enabling strategies aimed at prevention and targeted therapies that can effectively eradicate pathological PVCs with minimal risk.

CONCLUSIONS

PVCs are a commonly observed phenomenon that are best evaluated with a thorough history and physical examination and 12-lead electrocardiography,

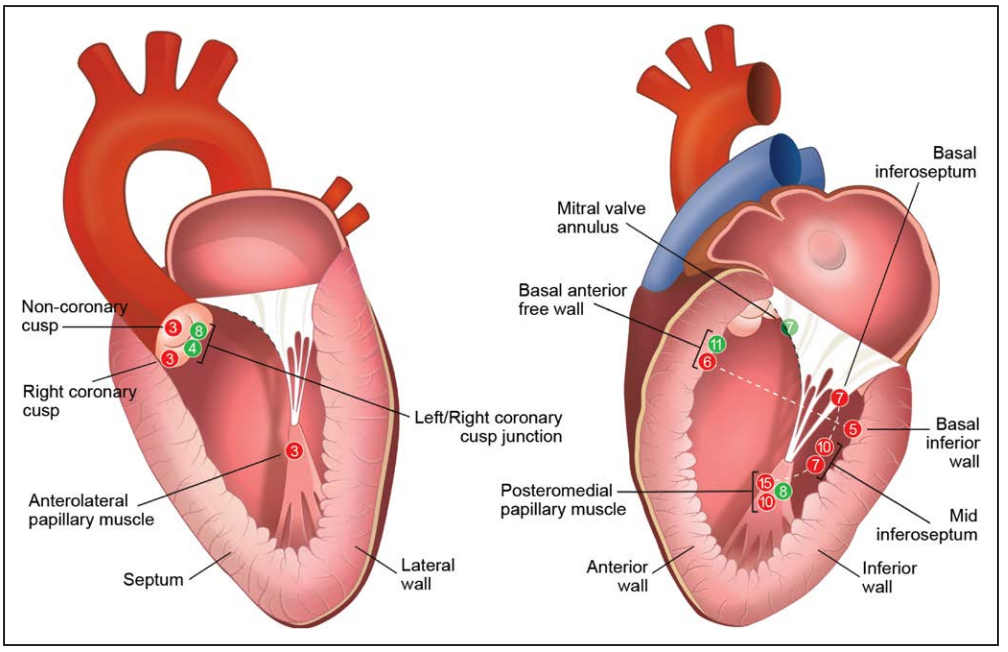

Figure 6. Left ventricular ablation locations by patient and presence of postprocedural cerebral emboli.
Ablation locations associated with cerebral emboli are depicted with red circles, and those locations without corresponding cerebral emboli are depicted with green circles. The number of lesions at each location appears in the circles. Lesions connected by a dashed white line are from the same patient and procedure. Reprinted from Whitman et al[100] with permission. Copyright © 2017, the American Heart Association.

usually supplemented with ambulatory monitoring and an echocardiogram. A cardiac MRI is useful in select patients. Although many patients with PVCs may require only reassurance, treatment is generally reserved for either symptomatic PVCs or concern for PVC-induced cardiomyopathy. PVC burden remains the most reliable PVC-associated predictor of incident heart failure, and additional research is needed to inform the optimal clinical application of other risk factors for PVC-induced cardiomyopathy. The potentially bidirectional and likely variable relationships between PVCs, cardiomyopathy, and their effect modifiers remain incompletely understood. Although interventional trials of lifestyle factors have not yet been completed to guide recommendations, observational data suggest that tobacco smoke and a sedentary lifestyle may promote more PVCs. Data regarding caffeine consumption are conflicting and not currently sufficiently strong to support a broad recommendation against caffeine consumption in general. β-Blockers, calcium channel blockers, or catheter ablation are each reasonable first-line strategies to treat PVCs, with the final decision driven by the specific patient characteristics and preferences. Additional antiarrhythmic drugs may be helpful in those with polymorphic PVCs and in those in whom other medicines and ablation are either contraindicated or have failed. Additional research is needed to identify the fundamental etiologies underlying PVCs, the differential PVC frequencies across individuals that are observed, the mechanisms explaining the presence or absence of symptoms, the optimal risk stratification for PVC cardiomyopathy, and the development of targeted prevention strategies and therapeutics aimed at the root cause of PVCs.

ARTICLE INFORMATION

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