REVIEW

Ventricular Ectopy in the Normal Heart. An Elusive Menace or a Harmless Variant?

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Abstract

Premature ventricular complexes (PVCs) are a common feature specially at increasing age. In the normal heart they are usually benign, but in some cases, they may be associated with sudden cardiac death or risk of heart failure. Although the pathophysiological mechanisms of these effects are not yet fully clarified, PVCs' potential to cause a form of cardiomyopathy is now widely accepted. In this brief review we present the main evidence regarding ventricular ectopy and its consequences, in individuals without pre-existing heart disease. ***Rhythmos 2020;15(3): 47-51.***

Key Words: premature ventricular complexes; cardiomyopathy; antiarrhythmic drugs; catheter ablation

Abbreviations: CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; PVCs = premature ventricular complexes; RBBB = right bundle branch block; RVOT = right ventricular outflow

Introduction

Premature ventricular complexes (PVCs) are a common feature specially at increasing age. They are found in 0.6% of the apparently healthy young individuals <20 years old, increasing up to 2.7% at 50 years of age, when screening utilizes the 12-lead electrocardiogram (ECG). If longer monitoring systems are applied, PVCs are observed in 40%-75% of the general population. [1-5] In subjects with structural heart disease, most researchers agree that frequent PVCs, multiform PVCs, or nonsustained ventricular tachycardia (NSVT) are associated with worse prognosis in the presence of ischemic heart disease (IHD).[6] In hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, complex ventricular ectopy and NSVT also contribute to the total arrhythmic risk, although in dilated cardiomyopathy, the picture is less clear. [7-8] In individuals with a normal heart however, data have been somewhat conflicting, with the resultant scientific view swinging between different positions over the years. [9] We hereby attempt a brief review of the evidence, focusing on the implications of ventricular ectopy in the normal heart.

Prognosis

The effect of ventricular ectopy in prognosis, in the absence of apparent heart disease, has been a matter of debate for some time. To begin with, there are many different ways to define the term "frequent PVCs"; in this context, we adopt the criteria used in the relevant 2017 AHA/ACC/HRS Guidelines, i.e. the presence of at least 1 PVC on a 12-lead ECG or >30 PVCs per hour,[3] unless determined otherwise. The impact of ventricular ectopy was assessed in several studies. In the 80's and early 90's studies yielded neutral results. [10-12] Exercise-induced ventricular ectopic beats were seen to increase with age especially in men, but did not affect the incidence of cardiac events (angina pectoris, nonfatal myocardial infarction, cardiac syncope or cardiac death) and non-cardiac mortality respectively, over a mean follow-up period of 5.6 years.[11] In a study enrolling healthy (history, clinical examination, stress ECG) elderly people (>60 years old), angina pectoris, nonfatal myocardial infarction and sudden cardiac death did not differ between individuals with and without ventricular ectopic beats over a mean follow-up period of 10 years. [12] More recent data, however, have shifted our conclusions towards a less benign influence of this arrhythmia. A study of over 29000 individuals, including patients with coronary heart disease (CHD), showed that frequent ventricular ectopy (seven or more ventricular premature beats per minute, ventricular bigeminy or trigeminy, ventricular couplets or triplets) during recovery after exercise predicted an increased risk of death (adj. HR=1.5, mean follow-up 5.3 years) [13]. In a subset of the community-based cohort study "Cardiovascular Health Study" (1,139 participants), higher frequency of PVCs was associated with LVEF decline, increased incident CHF, and increased mortality.[14] In a study from Taiwan, multifocal PVCs were found to have an increased incidence of mortality (hazard ratio - HR: 1.642, 95% confidence interval [CI]: 1.327–2.031), hospitalization (HR: 1.196, 95% CI: 1.059–1.350), cardiovascular hospitalization (HR: 1.289, 95% CI: 1.030–1.613), new-onset heart failure (HF; HR: 1.456, 95% CI: 1.062–1.997), transient ischemic accident (HR: 1.411, 95% CI 1.063–1.873), and new-onset atrial fibrillation (AF; HR: 1.546, 95% CI: 1.058–2.258) compared to the group without PVC, and a higher rate of mortality (HR: 1.231, 95% CI: 1.033–1.468) and all cause-hospitalization

(HR: 1.147, 95% CI: 1.025–1.283) compared with patients with uniform PVC, within a follow up period of nearly 10 years. [15] Non sustained VT was independently associated with death (HR: 1.362, CI: 1.071– 1.731), hospitalization for cardiovascular events (HR: 1.527,CI: 1.171–1.992), ischemic stroke (HR: 1.436, CI: 1.014–2.032), transient ischemic attacks (TIA) (HR 1.483, CI: 1.069–2.057), and new-onset heart failure (HF) (HR: 1.716, CI: 1.243–2.368).[16] Data from the ARIC study also revealed that participants with VPCs (recorded on a single 2-minute ECG) were >2 times as likely to die due to CHD than were those without VPCs, regardless of the CHD status at baseline.[17] Finally, a meta-analysis comprising 106000 subjects from the general population concluded that the overall adjusted relative risk for sudden cardiac death comparing participants with frequent VPCs versus those without frequent VPCs was 2.64 (95% CI: 1.93 to 3.63) and for total cardiac death it was 2.07 (95% CI: 1.71 to 2.50).[18]

PVC-Induced Cardiomyopathy (PIC)

The idea of PVCs being responsible for some sort of cardiomyopathy was introduced in late 90's when it was suggested that the suppression of frequent PVCs might be associated with improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy.[19] On the other hand, the burden of ventricular ectopy capable of producing impairment in ventricular function is not precisely defined, probably because PVC abundance exerts a continuous effect on myocardial performance. [20] Improvement in left ventricular ejection fraction (LVEF) has been documented after successful ablation of right ventricle outflow tract (RVOT) sites in patients with as low as 5500 PVCs/24h, [21] but a threshold of PVC burden of 10% represent a common assumption with regard to the cardiomyopathy induction. [22, 23]

An issue that has to be clarified is that no universal definition of PVC-induced cardiomyopathy (PIC) exists. In the literature relevant definitions include either having an abnormal LVEF which improved by at least 15% or 10% or normalization of LVEF>50% after an effective ablation procedure. [24,25] The mechanism by which PVCs produce cardiac dysfunction also remains unclear. Several potential explanations have been offered. Initially it was proposed that PVCs act similarly to sustained tachycardias to produce a tachycardia-mediated cardiomyopathy; the average rate however is near-normal and sustained ventricular arrhythmias are rare. The dyssynchronous ventricular contraction has also been accounted for the development of myocardial dysfunction, acting via remodeling pathways. Moreover, frequent PVCs, which are typically nonperfusing, may result in a volume strain on the heart, mimicking valvular regurgitation. According to these mechanisms, the underlying electrical phenomena which constitute the hazardous nature of ventricular ectopics may be PVC QRS duration (>150 ms), PVC coupling interval (<450 ms) and the presence of interpolated PVCs, [26-30] as recently reviewed. [31] Another feature which may have some influence on the development of cardiomyopathy is the site of origin of PVCs. Ventricular complexes arising from the right ventricle were associated with a significant reduction in LV function at a PVC burden of ≥10%, while PVCs originating from the LV were associated with a significant reduction in LVEF at a PVC burden of ≥20%. [28] Non-outflow tract origin is also a possible predictor of the development of PVC-induced cardiomyopathy. [27]

PVCs and Cardiomyopathy: cause or effect?

So far, we have argued that frequent PVCs may cause some form of cardiomyopathy. Traditionally, however, this condition has been a diagnosis of exclusion, because PVCs can be observed in the setting of pre-existing cardiomyopathy. In that case PVCs indicate a poorly functioning ventricle, but they can cause further deterioration of the myocardial performance. In a case series of 15 patients with ischemic cardiomyopathy, successful catheter ablation improved the mean LVEF from 38% to 51%. Among these patients, cardiac magnetic resonance imaging (MRI) demonstrated less delayed gadolinium enhancement as compared with control patients with similar baseline LVEF, but without frequent PVCs. [32] Similar findings have been published in patients with non-ischemic cardiomyopathy, where successful ablation of PVCs improved the mean LVEF from 33.9% to 45.7%. [33] Thus, cardiomyopathy and ventricular ectopy can co-exist and negatively affect each other. Penela et al proposed several characteristics to distinguish between PVC-exacerbated cardiomyopathy and pure PVC-induced cardiomyopathy: intrinsic QRS duration >130 ms, LV end-diastolic diameter >63 mm, or baseline PVC burden <17% individually demonstrated 85% sensitivity and 98% specificity for PVC-exacerbated cardiomyopathy, and thus predicted only partial improvement in EF with successful PVC suppression. [34]

Malignant ventricular arrhythmias

The most common type of sustained ventricular arrhythmia in normal hearts is monomorphic VT originating from the outflow tract of the right ventricle.

However, malignant arrhythmias triggered by PVCs have been observed, namely ventricular fibrillation (VF) and polymorphic ventricular tachycardia. [35, 36] In up to 75% of these cases, PVCs mostly arise from the RVOT, the papillary muscles or the moderator band, but the His-Purkinje system, the right ventricular anterior wall and the left ventricular outflow tract (LVOT) have also been recognized as potential sites of origin. [23,37] Non-ischemia triggered PVC-induced VF is rare, representing an estimated 5% of resuscitated sudden death, a percentage rising to 23% in cases with preserved EF. [38] The underlying mechanism is presumed to relate to early afterdepolarizations caused by inward calcium currents. Such ionic disturbances occur more readily in Purkinje cells and may be potentiated via mechanical stretch. [39,40] Other explanations have also been proposed, but they all still seek confirmation in humans. [23]

Diagnostic evaluation

Patients with PVCs should receive a detailed clinical and laboratory assessment including clinical personal and family history, laboratory tests, 12-lead ECG and transthoracic ultrasound imaging. An exercise stress test can also provide useful information, since exercise-induced PVCs have been correlated with increased risk of CV death in several studies. It is noteworthy that certain morphological patterns are shown to be more aggressive, such as multifocal PVCs and PVCs with RBBB morphology. [41,42] All these conventional techniques may miss subtle or early stage abnormalities, which would have reclassified some cases as non-idiopathic. This is the weak spot of the whole concept of the "normal heart"; the definition differs according to the imaging modality. Cardiac Magnetic Resonance (CMR) is currently considered the most accurate noninvasive method for the assessment of myocardial performance, structure, geometry and arrhythmic substrate and thus normality should be defined with regard to this method. In a recent study, 68% of 162 patients with exercise-induced PVCs without structural heart disease on routine diagnostic work up had evidence of areas of late gadolinium enhancement with a sub-epicardial or midmyocardial distribution consistent with previous myocarditis, compared to only 9% of controls. Moreover, in 37% of such cases myocardial edema consistent with acute inflammatory process was also detected. [43] Focal abnormalities such as inflammatory or early cardiomyopathy changes have been noted in almost half of the patients with frequent PVCs and unremarkable ECG and echocardiographic findings.[44] Male gender, older age, family history of sudden cardiac death or cardiomyopathy, multifocal PVCs, exercise-induced PVCs and RBBB morphology have been shown to predict CMR lesions in patients with apparently idiopathic premature ventricular complexes. [45]

Treatment

If the patient fulfills the criteria of idiopathic ventricular arrhythmia, treatment options depend on the presence of symptoms or complications. First line treatment for PVCs consists of a beta blocker, a non-dihydropyridine calcium channel blocker (recommendation grade I) or an antiarrhythmic agent (recommendation grade IIa). If monomorphic VT has been documented, (originated from outflow tract, papillary muscle or Interfascicular Reentrant VT), catheter ablation is offered as a second choice, when antiarrhythmics are ineffective, not tolerated, or the patient denies medical therapy. If the patient has been successfully resuscitated from sudden cardiac death due to idiopathic polymorphic VT or VF, ICD implantation is the treatment of choice. [3] In case of suspected PVC-induced cardiomyopathy, providing that PVCs are frequent enough, exceeding 15% of total beats per day, ectopic suppressing therapy is indicated. Beta blockers and non-dihydropyridine calcium channel blockers are not particularly effective, [45,46] while class I antiarrhythmic drugs, although effective, their significant side-effects in case of coexisting structural heart disease have hamper their use. Amiodarone can be administered; it is however accompanied by significant toxicity in the long-term setting. For these reasons, catheter ablation is increasingly employed and it has been shown superior compared to metoprolol and propafenone. [46] Unfortunately, not all PVCs are equally amenable to ablation. The recent 2019 HRS/EHRA/APHRS/LAHRS Expert Consensus on CA of VAs, recommends catheter ablation of idiopathic PVCs in patients with symptomatic PVCs originating from RVOT as first line therapeutic approach over AAD therapy, but when PVCs arise from other sites than RVOT (including LVOT, epicardial OT or LV summit) or in a polymorphic pattern, ablation is deferred until drug failure or patient refusal to comply. [47]

Conclusion

Premature ventricular complexes are benign in nature in most cases, in the absence of structural heart disease. In some instances, however, they may be associated with sudden cardiac death or risk of heart failure, depending on their origin, daily burden and electromechanical characteristics. Cardiac evaluation should be detailed, in

order to avoid elusion of a subtle cardiomyopathy, and ought to include a cardiac MRI scan. When PVCs are frequent, highly symptomatic or causing deterioration of myocardial performance, treatment is warranted and it consists in antiarrhythmic agent administration as a first line management. Catheter ablation is becoming more popular, but techniques need to improve in order to increase efficacy when uncommon origin sites have to be ablated.

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