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EDITORIAL COMMENT

Navigating frequent idiopathic premature ventricular contractions: Lessons learned from clinical practice

Portuguese title: Extrassistolia ventricular idiopática frequente: experiências e Llções da prática clínica

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A young 25-year-old athlete sits across from you, concerned but otherwise healthy and asymptomatic, presenting with 25,000 premature ventricular contractions a day on Holter. His echocardiogram and treadmill stress test are pristine. You wonder: "Is this truly a benign finding? Does this patient warrant treatment?"

Questions like these are increasingly common in modern cardiology, where wearable devices, advanced imaging and genetics blur the boundary between truly *benign ectopy* and *subclinical*

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disease. Idiopathic premature ventricular contractions (PVC) are among the most commonly encountered arrhythmias in clinical practice. They can arise from various sites within the ventricles, even from the epicardium, but the most frequent include the outflow tracts, aortic root, atrioventricular rings, and the Purkinje fibres. The definition of idiopathic PVC is somewhat contentious, with some referring to them as those occurring in "apparently normal hearts" based on echocardiography and stress testing. However, these examinations are insufficient to reliably exclude structural heart disease as they lack sensitivity for detecting ventricular fibrosis, which is usually associated with increased sudden cardiac death (SCD) risk. Fibrosis, as defined by cardiac magnetic resonance imaging (CMR), may be present in up to one-quarter of patients with normal echocardiogram, with its presence and extent strongly correlated with long-term risk of ventricular tachycardia, regardless of left ventricular ejection fraction (1). Hence, a normal CMR is crucial for identifying truly idiopathic PVCs — those without ventricular scarring. Indeed, CMR is uniquely positioned to stratify SCD risk across nearly all scenarios involving frequent or sustained ventricular arrhythmias or structural heart disease. In my own practice, I consider CMR indispensable whenever evaluating patients with frequent PVCs from sites other than the septal right ventricular outflow tract. This single step may confirm the arrhythmia is truly idiopathic and prevent diagnostic and therapeutic errors that might otherwise follow.

Findings from observational studies in the general population have suggested that frequent PVCs are associated with increased risk of SCD and total cardiac death (2). This is not surprising, as frequent PVCs often represent a marker of underlying heart disease. However, whether frequent, truly idiopathic PVCs (i.e., with a normal CMR) are entirely benign remains a matter of debate. Some studies showed that idiopathic PVC patients have a similar prognosis as age- and sex- control-matched groups of the general population (3), with even a relatively high rate of spontaneous resolution (4). Conversely, others questioned the benignity of frequent idiopathic PVCs and showed that these can be a cause of cardiomyopathy. It is generally

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accepted that a PVC burden exceeding ~10% may associate with increased risk of LV dilatation and dysfunction (5, 6), and these patients warrant routine monitoring of the heart function regardless of symptoms. The extent of LV dyssynchrony caused by the ectopic beats strongly correlates with the degree of LV dysfunction. Thus, PVCs with longer QRS duration are typically more concerning. Accordingly, active surveillance is prudent even in asymptomatic patients with frequent idiopathic PVCs, given the potential risk of PVC-induced cardiomyopathy.

Treatment of frequent idiopathic PVCs is warranted when patients are symptomatic and may also be reasonable in well-selected asymptomatic patients with very high PVC burden. Beta-blockers, calcium channel blockers and class I antiarrhythmic drugs (such as Flecainide), as well as catheter ablation are the available treatment options. When considering medication, beta-blockers are the preferred drug in the setting of adrenergically mediated PVCs (e.g., higher burden during increased heart rate or exercise). In addition to lowering heart rate and partly suppressing PVC, beta-blockers can reduce the cyclic wall stress associated with the strong post-extrasystolic potentiation after each compensatory pause. Calcium channel blockers (CCB) tend to be preferred for fascicular PVCs. However, beta-blockers and CCB are often ineffective or poorly tolerated, especially at lower heart rates, and other treatment strategies may be required.

Flecainide is a potent inhibitor of the Nav1.5 sodium channels in cardiac muscle fibres, which are crucial for the rapid upstroke of the action potential. Traditionally, the administration of Class IC antiarrhythmic drugs has been contraindicated in patients with structural heart disease or coexisting coronary artery disease, owing to the results of the Cardiac Arrhythmia Suppression Trial (CAST) (7). However, CAST is now considerably outdated, and caution should be exercised in generalizing its results. It is unknown whether Flecainide is harmful in post-myocardial infarction patients on modern heart failure therapy, but there is certainly no evidence linking Flecainide to increased mortality in patients without underlying heart disease. On the contrary, preliminary data has shown Flecainide to be safe and reasonably effective in

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patients with stable coronary artery disease (8) and those with PVC-induced cardiomyopathy (9). Notably, in two previous randomized studies involving adult (10) and paediatric (11) patients without structural heart disease, Flecainide demonstrated superior efficacy in suppressing PVCs compared to carvedilol and metoprolol, respectively. However, there is still limited evidence on whether Flecainide is superior to beta-blockers.

In this context, Mauro Trindade Ave and colleagues propose a new randomized crossover study (12) to: first, compare the efficacy of Flecainide and Carvedilol in reducing idiopathic PVCs and their clinical consequences; and second, to assess whether there is any potential interaction between the H558R polymorphism of the SCN5A gene and the efficacy of Flecainide. The H558R polymorphism, a common loss-of-function variant present in more than 20% of the population in heterozygosity, has been associated not only with increased susceptibility to atrial fibrillation (AF) (13, 14) but also with greater efficacy and reduced toxicity of Flecainide in AF patients (14). Patients with ≥1000 idiopathic PVCs causing symptoms and/or a slight reduction in LV ejection fraction will be included in the study. Limitations include those inherent to the crossover design, the low number of patients, the modest PVC threshold required for study admission, and the fact that patients in the Flecainide group will be allowed to be on low-dose beta-blockers. Nevertheless, the study is expected to provide valuable insights into whether patients may benefit more from Flecainide than beta-blockers. In addition, if the interaction between the H558R polymorphism and Flecainide efficacy proves clinically significant, this will be another step toward genotype-guided antiarrhythmic therapy — an approach that can bring precision medicine into the realm of everyday arrhythmia management.

From my clinical experience, Flecainide has shown reasonable efficacy in treating idiopathic PVCs. I almost always start with a low dose (50 mg twice daily) in combination with a low-dose beta-blocker. Tolerance is generally good. When ineffective, I may consider increasing the dose of Flecainide or, more rarely, switching to Propafenone. The latter may be less

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effective than Flecainide (15) and requires more frequent dosing due to its shorter half-life. I never consider switching to Sotalol due to serious concerns about QT prolongation, proarrhythmia, and potentially increased mortality (16). Likewise, Amiodarone is almost always ruled out. Today, it is clear that long-term Amiodarone use for idiopathic PVCs or AF is rarely justified (17, 18). Regrettably, however, it remains overprescribed for these indications, despite its high toxicity and modest efficacy compared to catheter ablation. Ironically, although Amiodarone is often prescribed to avoid ablation, the risk of serious toxicity from Amiodarone exceeds the risk of complications from PVC or AF ablation in experienced hands. Amiodarone has been associated with toxicity affecting the thyroid, liver, lungs, central and peripheral nervous system, eyes, and skin. The rate of adverse events can reach 50% with long-term use. Thyrotoxicosis, pulmonary fibrosis, hepatitis, and polyneuropathy are among the most serious complications, but corneal microdeposits, optic neuritis, photosensitivity, memory impairment, ataxia, tremor, and skin discoloration are also possible side effects. Most importantly, amiodarone toxicity can occur at any point during therapy or even within six months of discontinuation. It may be difficult to diagnose, sudden and unpredictable, and potentially fatal. Therefore, in the setting of idiopathic PVCs, Amiodarone should almost never be used as a first-line treatment.

Catheter ablation remains the most attractive option for treating symptomatic PVCs when performed by experienced operators (19). It offers the possibility of a cure and freedom from chronic medication. Operator experience cannot be overstated, as it is crucial for maintaining a favourable benefit-risk ratio and justifying ablation as a first-line treatment. The procedure is fundamentally safe in experienced centers, but complications can still occur and must be thoroughly explained to the patient beforehand. PVCs originating from the outflow tracts or aorto-mitral continuity are generally more amenable to catheter ablation due to better accessibility and catheter stability. However, those arising from the papillary muscles or the LV summit remain challenging, even for the most experienced operators, with lower acute

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success rates and a higher risk of recurrence. Catheter ablation is a class I indication for frequent symptomatic PVCs of RVOT or fascicular origin, with a class IIa indication for PVCs from other regions. Asymptomatic patients with a PVC burden >20% and no evidence of structural heart disease may also be considered on an individual basis.

Returning to our young athlete — the answer to whether his PVCs are benign may soon depend as much on his genotype as on his imaging. As our diagnostic tools grow sharper, an experienced physician should get more comfortable with knowing not just *what* to treat, but *whom* to treat — and *how much evidence* is enough to act. In symptomatic patients, catheter ablation remains the most effective and potentially curative treatment when performed by experienced operators, offering freedom from chronic medication. However, Flecainide, stigmatized following CAST, may yet reclaim its place as a rational, targeted therapy in patients who are poor ablation candidates or prefer a pharmacological approach.

Declarations of interest: None

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