

## Premature Ventricular Contractions Strike Back

*Las extrasístoles ventriculares contraatacan*

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### A BIT OF HISTORY

Historically, premature ventricular contractions (PVCs) were considered precursors of sudden cardiac death and, for many years, their mere presence was taken as an indication for prescribing antiarrhythmic agents. The concept that ventricular fibrillation (VF) and ventricular tachycardia (VT) are preceded by PVCs arose when coronary care units were created to treat the complications of acute myocardial infarction (AMI). For many years, this concept of premonitory arrhythmias was extended, despite the lack of evidence, to other heart diseases. In addition, the traditional studies evaluating AMI outcome showed that PVCs were independent predictors of sudden and non-sudden death. (1) Studies in the post-thrombolytic era concluded that ventricular arrhythmia was associated with adverse outcome. (2) Finally, studies in ischemic heart disease showed that PVC could be suppressed with antiarrhythmic agents but at the expense of greater all-cause mortality. (3)

Subsequent studies using amiodarone in ischemic heart disease, as the EMIAT or the CAMIAT trials, failed to demonstrate any benefit with this drug. (4, 5)

Since then, no significant progress or working hypothesis has emerged about the role of PVCs in the outcome of patients. No new agents were developed in this field and the treatment of PVCs with drugs has remained as something trivial for the past 20 years. The concept of optimizing the treatment of the underlying condition has prevailed, especially with beta blockers, together with implantation of cardioverter defibrillator devices in patients at high risk of sudden death, with or without sustained ventricular tachycardia.

### PATHOPHYSIOLOGY AND TREATMENT

In the population of patients without heart disease, ventricular arrhythmia is uncommon; it is usually detected in a routine medical exam and has favorable outcome. (6) Nevertheless, PVCs may be very fre-

quent occasionally and accompanied by symptoms. In general, chronic antiarrhythmic therapy may be ineffective and poorly tolerated, and non-pharmacological treatment can be considered.

In most cases, PVCs have a focal origin. This means that, independently of the electrophysiological mechanism involved (abnormal automatism, triggered activity or reentrant mechanism), the electric impulse has a focal origin, and from this site the impulse propagates centrifugally to the rest of the ventricles. (7)

Endocardial mapping of the electrical activity with electrode catheters can demonstrate the activation pattern and detect the earliest electrogram or signal during PVCs and, thus, their site of origin.

The challenge of modern electrophysiology is to carry out a thorough exploration of the area of interest. Electroanatomical mapping has been facilitated with the incorporation of three-dimensional navigation systems which transform the records obtained by catheters in color maps which make target location easier. (8) The patient must have a significant number of PVCs during the procedure. Once the target has been identified, radiofrequency energy can be applied during the same procedure with an ablation catheter to eliminate the tissue and suppress PVCs or produce a significant reduction of the arrhythmia.

The results and findings of catheter-based therapy have been deeply studied in the population without heart disease, in which the anatomical distribution of ventricular arrhythmia is well-known. Most PVCs originate from the right ventricular (RV) outflow tract, followed by the left ventricular outflow tract including the sinuses of Valsalva and less common sites of origin are the left bundle branch fascicles, the RV moderator band and the left ventricular (LV) epicardium. (9) Nowadays, catheter ablation can cure 70-90% of patients. (9, 10) In a recent publication, we have demonstrated that catheter ablation using three-dimensional navigation systems is a feasible approach in our setting to eliminate PVCs in symptomatic pa-

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tients. (8) The complexity and the results depend on many factors. Location of the site of origin is paramount: ablation of PVCs originating from the RV entails a simpler procedure with higher rate of success than those originating from the LV. All the sites of origin can be easily predicted by analyzing the electrocardiogram (ECG). Left bundle branch block pattern in V1, the positive vertical axis indicating the outflow tract origin and the QRS transition in precordial leads (R/S-wave amplitude ratio  $\geq 1$ ) are the most relevant algorithms. Ventricular arrhythmias originating from the RV present late precordial transition (lead V4) while those with LV origin present lead V1 or V2 transition. (9, 11, 12) For this reason, it is important to be patient while taking the ECG, trying to record PVCs in all the leads.

Of importance, radiofrequency catheter ablation can abolish PVCs in selected symptomatic patients with very frequent ventricular arrhythmia.

#### **PREMATURE VENTRICULAR CONTRACTIONS AND VENTRICULAR DYSFUNCTION**

The relationship between LV dysfunction (LVD) and PVCs is the second phenomenon to consider. Although in patients with ventricular dysfunction, PVCs were systematically considered a consequence of the underlying cardiomyopathy, the results of catheter ablation are surprisingly demonstrating that this reasoning is not always correct.

In 2000, a publication reported the first case of dilated cardiomyopathy with high density of PVCs where radiofrequency catheter ablation resulted in complete recovery of ventricular function. (13) Since then, several reports have been published about this condition known as “PVC-induced cardiomyopathy” which consists of presumed idiopathic left ventricular dysfunction with frequent PVCs, which after radiofrequency catheter ablation significantly improves ventricular function parameters. (9, 14) These patients usually have monomorphic PVCs originating from the right or left ventricular outflow tracts. (15) In patients with polymorphic PVCs originating from other sites, the arrhythmia may probably be secondary to a different cardiomyopathy. Different meta-analyses of patients with apparently idiopathic cardiomyopathy confirm that ventricular function recovers with improvement of ventricular volumes after catheter ablation of PVCs. (10, 16) In these studies, in the subgroup of patients with ventricular dysfunction and ejection fraction  $<50\%$ , successful PVC ablation increased the absolute value of ejection fraction by 12%. (16) A significant number of PVCs is necessary to produce a deleterious effect. This PVC burden is better expressed as PVC percentage over the total number of beats in 24-hour Holter monitoring. Today, any Holter analysis software calculates this value. The critical value seems to be  $>20\%$ ; yet, some authors propose lower values, about 10% to 13%. (17) Although PVCs with left bundle branch block pattern that would pro-

duce a “dyssynchrony invasion” were initially associated with LVD, they have also been reported with other QRS patterns. (15) Irregularity seems to be a key factor. An animal model using a special epicardial pacemaker capable of simulating PVCs, induced LVD that reverted after pacing, compared with a control group of animals with implanted pacemaker but disabled premature pacing algorithm. (18) Independently of the mechanism involved, depletion of intracellular calcium may be the final pathway, similar to other tachycardiomyopathies. A recently published population-based study including more than a thousand patients without structural heart disease and PVCs reported that PVCs emerged as an independent predictor of long-term mortality. (19)

Obviously, there are still many questions: we do not know the proportion of patients with ventricular arrhythmia that will develop LV dysfunction, the precise cutoff point value to define frequent PVCs and the time of disease progression to determine groups at higher risk to initiate treatment. However, current information is useful to think that the phenomenon exists and that left ventricular dimensions and function should be monitored in patients with very frequent PVCs and in case of abnormalities, consider treatment.

Another point could be raised: if frequent PVCs can induce a certain degree of ventricular impairment in a normal heart, which would be the impact in a patient with ventricular dysfunction secondary to a certain condition as previous AMI? Could PVCs add “cardiomyopathy” to cardiomyopathy?

Although this aspect is controversial, according to recent information, ejection fraction increased after a significant reduction in the number of PVCs after ablation. (20, 21) Another study documented that ejection fraction increased from 32% to 43% in a population of patients with ischemic cardiomyopathy and idiopathic cardiomyopathy referred for invasive treatment. (22) These novel reports show lower success rates than those in patients without heart disease and with procedures technically more complex and challenging. Probably, magnetic resonance imaging could determine in which patients LV dysfunction would recover after ablation depending on the magnitude of fibrosis detected by late gadolinium enhancement. Some authors are performing radiofrequency catheter ablation of PVCs in patients with indication of implantable cardioverter defibrillator (ICD) for primary prevention due to severe left ventricular dysfunction (mostly of nonischemic etiology). In this population with very frequent PVCs, ejection fraction improves in a high proportion of patients and the indication of ICD could be withheld. (20, 22, 23)

#### **CONCLUSION**

There is still a long way to go. The information here presented should be confirmed by randomized trials including larger number of patients. Yet, and un-

doubtedly, if the deleterious effect of frequent PVCs is confirmed, "PVC-induced cardiomyopathy" added to the underlying heart disease could provide more damage across time. Could this be the mechanism involved to explain the worse outcome of patients with left ventricular dysfunction and frequent PVCs?

I think PVCs strike back. Apart from the old concept that the influence of PVCs is mainly electrical, they can also induce a mechanical phenomenon as ventricular dysfunction. Although a witch hunt is not necessary to treat PVCs, it is important to know the outcomes of radiofrequency catheter ablation. This procedure suppresses the arrhythmia using a physical technique which does not affect cardiac function directly, avoiding the unwanted effect of antiarrhythmic drugs and offering the possibility of testing the potential benefit of eliminating ventricular arrhythmias.

#### Conflicts of interest

None declared

(See authors' conflict of interest forms in the web/ Supplementary Material).

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