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EDITORIAL COMMENT

Post-Extrasystolic Potentiation for Individualizing Care of Premature Ventricular Contraction–Induced Cardiomyopathy*

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Although once considered a nuisance, only to be treated in the setting of intolerable symptoms, it is now well-recognized that frequent premature ventricular contractions (PVCs) can cause a cardiomyopathy and clinical heart failure (1). With the common use of PVC catheter ablation, we also now have a successful method that can eliminate the PVCs and lead to recovery of the dysfunctional myocardium. The problem, however, lies in the fact that the PVC-cardiomyopathy relationship is not consistent or predictable.

Many patients with frequent PVCs, probably the majority, never develop a cardiomyopathy (2). Some of these patients are symptomatic from palpitations, but there are many who have no awareness of the ectopy. Unfortunately, many of these asymptomatic patients, even more so than those with palpitations, will later develop a PVC-induced cardiomyopathy (3,4). There are several risk factors known to be associated with progression to a cardiomyopathy (**Figure 1**) (3–8). Despite this, it remains quite difficult to know who to treat without exposing the others to an invasive procedure that will not benefit them.

Perhaps more challenging are patients who already have a cardiomyopathy with a reduced left ventricular ejection fraction (LVEF). In a majority of these patients, the ectopic beats are not truly the source of the problem, but a reflection of a sick heart. More important, elimination of the PVCs will not lead to recovery in a heart irreparably damaged by ischemia, infiltrative disease, hypertension, or other processes.

However, when we do not have evidence of one of these other clear causes of cardiomyopathy, and the patient has frequent PVCs, an ablation procedure is commonly performed. Fortunately, many of these carefully selected patients do improve with reduction in the PVCs, although a substantial portion does not. Thus, the second major question in this confusing relationship is: which patients, with frequent PVCs and a reduced LVEF, will have a recovery in their LVEF after an effective ablation? There are some factors that may be predictive of EF recovery after catheter ablation (**Figure 1**) (9–12). Again, however, despite several potential clues, the situation remains murky with regard to prognostication.

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In this issue of *JACC: Clinical Electrophysiology*, Krishnan et al. (13) attempt to shed some light on these clinically important questions in their retrospective analysis of 61 patients with frequent PVCs who underwent a successful catheter ablation. Their study compares several clinical, electrocardiographic, and hemodynamic variables between 3 groups of patients: 1) normal LVEF; 2) LVEF <50% that recovered after ablation; and 3) LVEF <50% that did not recover after ablation. The LVEF in the study was determined by visual estimation of the echocardiographer, but they also required a change of >10% after

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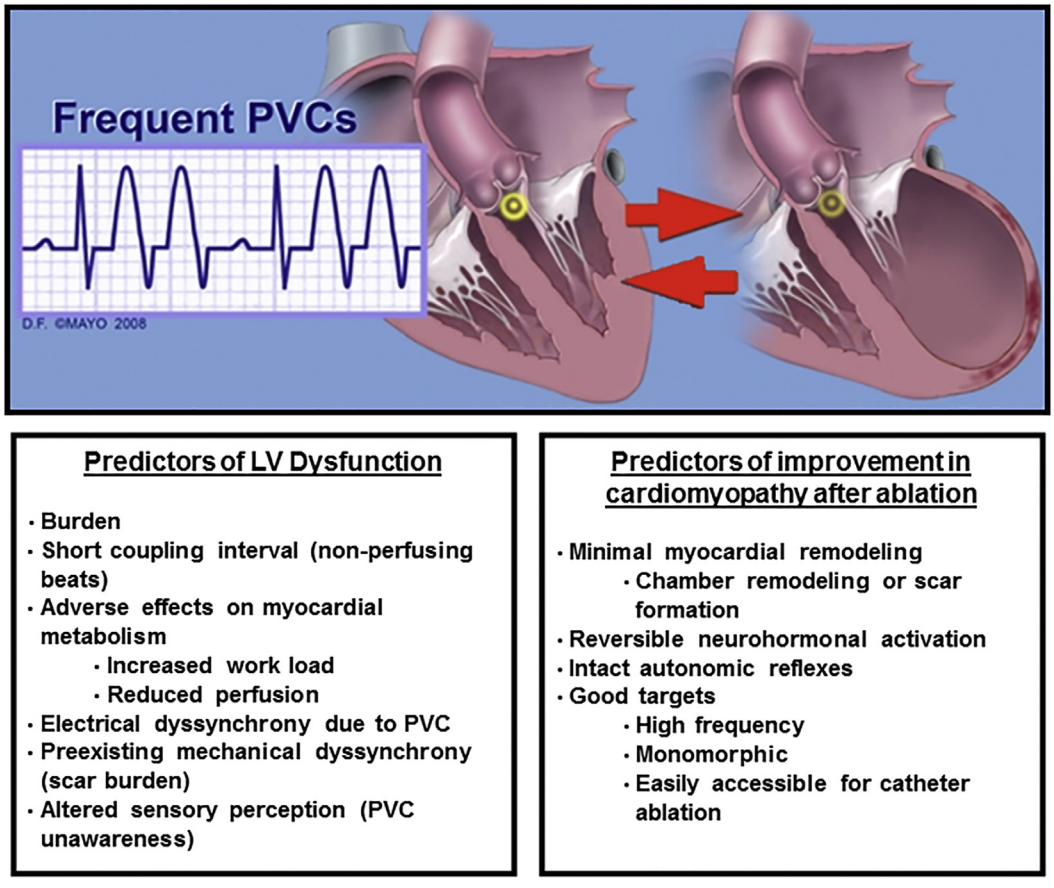
FIGURE 1 Prognostication in PVC-Induced Cardiomyopathy



Several factors have been associated with progression to cardiomyopathy in the setting of frequent premature ventricular contractions (PVCs) **(left)** as well as improvement of cardiomyopathy after ablation of PVCs **(right)**.

ablation to meet the criteria of recovery, which somewhat accounts for the imprecision of the assessment method.

The hemodynamic variables included invasive assessment of the degree of post-extrasystolic potentiation (PESP), which is the ultimate focus of the paper. PESP is the increase in blood pressure seen in the first sinus initiated beat that occurs after a PVC. This effect has been known and studied for decades, but was not fully elucidated previously in this setting (14). It seems to occur due to an increase in intracellular calcium and change in calcium handling. Although PESP has been defined variably in the past, the investigators in this study measured the difference between the blood pressure of the post-PVC beat and an average of normal sinus beats.

There were few significant differences in the baseline characteristics between the 3 groups beyond those that would be expected, such as the reduced LVEF groups having more heart failure symptoms and the normal LVEF group having more palpitations. A history of coronary artery disease was more common in the reduced LVEF groups; however, significant stenosis was ruled out as a cause of cardiomyopathy by angiography in all patients with a reduced EF. Despite a mention of magnetic resonance imaging assessment in the text, it does not seem that this evaluation was done very frequently based on the information in the table. The authors do note that none of the patients with a reduced LVEF had scar present on bipolar voltage mapping, which is somewhat surprising, but perhaps related to the highly selected group of patients. Alternatively, unipolar mapping may have shown different and potentially helpful findings (12).

The primary novel finding of the study was a significant difference in the magnitude of PESP between groups. The normal LVEF group and the recovered LVEF group had a similar increase in systolic blood

pressure with the post-PVC beat (12.1 and 11.5 mm Hg, respectively). The group of 14 patients that did not recover their LVEF after ablation had a much smaller increase in the post-PVC systolic blood pressure at only 5 mm Hg.

This finding may reflect the fact that the myocardium in the 17 patients who recovered their LVEF is just "stunned," and the post-PVC beat allows the muscle to demonstrate its capabilities if the cause of the cardiomyopathy were removed. In the patient where the LVEF does not recover, the minimal increase in systolic blood pressure may illustrate that there is limited myocardial reserve. The investigators' use of the PESP in this study is similar to how it was used years ago to assess the reserve of specific myocardial segments in patients with ischemic cardiomyopathy (14). It could also be considered similar to the use of dobutamine stress tests in patients with low-flow aortic stenosis. In both, an increased inotropic effect and lower vascular resistance is used to determine the myocardial reserve and the detrimental effect of a potential impediment to normal cardiac function.

Although these results seem intuitive, they could be considered at odds with some more recent data regarding PESP and cardiomyopathy. Recent studies have shown that patients with the presence of PESP, that is, an increase in post-PVC systolic blood pressure, have an increase in heart failure and mortality (15). Although this may seem paradoxical, it seems to be consistent, and likely relates to abnormal calcium handling in those patients. It is important to highlight that the study by Krishnan et al. (13) discussed includes an intervention. Thus, the patients with a recovered LVEF may have eventually had worse outcomes were it not for the ablative therapy. Also, the method of PESP measurement, the group definitions, the underlying disease, and the outcomes were quite different than other studies investigating PESP, which vastly reduces comparability.

Ultimately, if the results of this study are reproduced in a larger group of patients, it may represent a useful clinical assessment tool. Blood pressure was measured invasively in this study, but PESP has been measured by noninvasive methods in prior studies (15). This difference could be quite valuable in the common scenario of a patient with an undefined, nonischemic cardiomyopathy and frequent, asymptomatic PVCs. If noninvasive PESP assessment demonstrated a large effect, it would motivate the patient and physician to pursue ablation. Alternatively, a small PESP effect may reassure everyone that the ablation is likely to have minimal effect on recovery, which is especially helpful in elderly patients or those with multiple comorbidities where the risk of complications is greater. Even the invasive measurement could be helpful in deciding how aggressive to be when treating a PVC in a risky location, such as near a coronary artery or a proximal His-Purkinje location, although it would likely be important to have performed the PESP assessment before sedation, as was done in this study.

Last, the other significant parameter identified in the multivariable analysis should not be ignored despite the lack of novelty. The QRS duration, a marker of electrical and thus mechanical dyssynchrony, was noted to be longer in the patients who did not recover their LVEF, which has been seen in prior studies (9). The reproducibility of this finding is important and, with continued definition of cutoff points, should be a useful differentiator. Furthermore, although PVC burden was the only variable found to significantly discriminate between those with normal and reduced LVEF before ablation, the QRS duration was nearly significant and numerically quite different. In a larger study, it may be proven to be helpful in this regard as well.

Ultimately, the investigators in this study have identified a novel use for PESP and strengthened the validity of QRS duration, both of which may ultimately be proven to be highly beneficial in the individualized treatment of patients suffering from frequent PVCs.

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