Why Does Catheter Ablation of Premature Ventricular Contractions in Arrhythmogenic Right Ventricular Cardiomyopathy Fail?

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined cardiomyopathy characterized by ventricular arrhythmias (VA) of predominant right ventricular (RV) origin and, pathologically, by a loss of cardiomyocytes with fibrofatty replacement that typically progresses from the subepicardial RV layers to the midmyocardium and subendocardium.[1] Frequent premature ventricular contractions (PVCs) are a common clinical manifestation of the disease, and represent one of its diagnostic criteria.[2] A high PVC burden has also been independently correlated with long-term risk of life-threatening VA in patients with a definite diagnosis of ARVC and no previous history of sustained VA/sudden cardiac death (SCD) and, recently, included in a multiparametric longitudinal SCD risk prediction model.[3] [4]

Surprisingly, there is a paucity of published studies focusing on different management strategies for PVCs in patients with ARVC. Multiple prior studies have documented a substantial benefit of catheter ablation (CA) to achieve suppression of sustained VT, mostly after failure of antiarrhythmic drug (AAD) therapy .[5,6] [7] Owing to the more extensive epicardial pathological substrate, endocardial only approaches have led to suboptimal results,[8] [9,10] and a combined endocardial and epicardial approach has been shown to provide good long-term outcomes with an overall VT-free survival ranging from 45% to 91% (average follow-up 41 months, range 11 to 88 months) (**Table**).[5,6] [11] [12,13] The extent to which these results can be extrapolated to the treatment of PVCs warrants adequate investigation.

In this issue of the *Journal of Cardiovascular Electrophysiology* , Assis et al. report novel and important information on the efficacy of CA for symptomatic PVCs in patients with ARVC. The authors retrospectively analyzed eight ARVC patients with a moderate-to-high burden of symptomatic PVCs (range 5%-25% within 24-h) who underwent CA at their institution. Most patients (62.5%) had previously failed AAD therapy (class I or III agents, none treated with amiodarone), and presented an average of 2.7±1 distinct PVC morphologies, all with a left bundle branch block configuration (87.5% with an inferior axis). Acute procedural success was achieved in 50%, whereas complete long-term success (defined as >80% reduction in the PVCs burden at follow-up monitoring) in 2 (25%) at a median follow-up of 345 days; of these, only 1 patient was maintained off AAD therapy.

Overall, the results of this study are compelling: CA of PVCs was not associated with a clinical benefit in the large majority of patients included in this series. The authors concluded that CA pf PVCs should be reserved only for highly symptomatic ARVC patients who have failed AAD therapy. From a mechanistic perspective, the study by Assis et al. provides several intriguing insights. For instance, it is notable that the PVCs were all localized within areas of abnormal substrate, and no patient had concomitant idiopathic PVCs from areas of normal voltage and/or intracavitary structures. With this in mind, a substrate-based ablation approach should have been effective in eliminating the PVCs similarly to what has been reported for reentrant VTs. On the other hand, an extensive endo-epicardial substrate-based ablation approach may not be appropriate for patients presenting only with symptomatic PVCs and no documentation of VT and may also be associated with pro-arrhythmia. Notably, two patients that presented with multiple distinct PVC morphologies and extensive endo-epicardial abnormal substrates were treated with supplemental substrate modification at the time of the index procedure and developed new VT during follow-up.

In the presence of a mappable arrhythmia, most operators would opt for a more targeted approach focused on the site of origin of the VA detected with detailed activation mapping and pace mapping. However, these techniques may have limitations in the context of focal PVCs arising from areas of abnormal substrate. For instance, prior investigations have documented that the spatial resolution of pace mapping within the abnormal substrate, defined as the area subtending sites with matching 12-lead ECG pace maps, averages 3.6-3.8 cm^2.[14] [15] In addition, multiple distinct QRS morphologies may also be observed from the same pacing site within the scar due to the presence of multiple exit sites and/or preferential conduction routes that may be dependent on different pacing rates/coupling intervals.[16]Activation mapping is without doubt the most reliable approach to identify the site of origin of focal PVCs, but requires a high intraprocedural ectopic burden, and the depth of anesthesia may affect the frequency of PVCs available to map. In the study by Assis et al. epicardial mapping and ablation were performed in 88% of cases (7 out of 8 patients); as the authors also point out, the use of general anesthesia to facilitate epicardial access and increase patient's comfort during epicardial mapping and ablation may have greatly influenced the ability to perform a detailed activation map in the epicardium and ultimately impact the procedural success. Of note, the same group of investigators has previously reported excellent results with catheter ablation of focal sustained VTs in a series of patients with ARVC, with a cumulative freedom from recurrent VT of 85% at 1 year and 75% ay 2 years.[3] As the procedural approach to focal sustained VT and PVCs is the same, the discrepancy in the observed outcomes may reflect unique mapping challenges that prevented an adequate PVC localization in the present study.

In summary, the study by Assis et al. adds novel and clinically relevant data. This is the first study to

systematically evaluate the role of CA to treat PVCs in ARVC and the results do not appear to support the widespread use of CA for the treatment of symptomatic PVCs in patients with ARVC. Additional investigations are needed to better comprehend the reasons for the poor outcomes described in this study and to reconcile these findings with prior reports documenting good results with CA of reentrant and focal VT in ARVC.

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Table. Principal studies documenting the efficacy of endo-epicardial catheter ablation of VT in ARVC.

Study	**Study type**	**N. of patients**	**% Epicardial ablation**	**Median follow-up, months**	**V**
Garcia et al. 2009 [11]	Single center	13	100	18	23
Bai et al. 2011 [13]	Multicenter	49	53	40	15
Berruezo et al. 2012 [12]	Single center	11	100	11	9
Philips et al. 2012 [17]	Multicenter	87	26	72	55
Santangeli et al. 2015 [5]	Single center	62	63	40	29
Wei et al. 2017 [19]	Single center	48	26	79	44
Santangeli et al. 2019 [20]	Multicenter	32	72	46	19
Mahida, et al. 2019 [21]	Multicenter	75	53	36	29
Mathew, et al. 2019 [22]	Single center	47	64	50	46
Lin et al. 2019 [23]	Single center	91	26	32	38
Summary		**827**		**41**	**31**

*Cumulative VT recurrence rate for both endocardial-only and endo-epicardial groups. Outcomes separated by ablation strategies were not reported.