Eliminating Ventricular Tachycardia by Targeting Premature Ventricular Contractions in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Innocent Bystander or Heart of the Matter?

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Arrhythmogenic right ventricular dysplasia/cardio-myopathy (ARVD/C) is an electrophysiological curiosity. Unlike most forms of ventricular tachycardia (VT) due to a structural pathogenesis, it commonly originates from the right ventricle (RV) rather than the left ventricle, and in contrast to most forms of malignant ventricular arrhythmias due to a molecular defect, ARVD/C develops from mutations in desmosomal proteins rather than ion channels. Therefore, ARVD/C stands alone as an example of a cardiomyopathy, which is expressed primarily in the RV and is associated with VT and sudden cardiac death.

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In general, ARVD/C is an autosomal dominant disease. The precise correlation between mutations in desmosomal proteins and disease expression is unclear, but desmosomal proteins are integral to cell adhesion, are involved with transcriptional regulation of genes that govern adipogenesis and apoptosis, and facilitate electrical conductivity between cells through regulation of gap junctions.1 Pathologically, there is a progressive loss of cardiomyocytes with fibrofatty replacement. Although initially confined to the RV, and in particular, to the RV inflow tract, the RV outflow tract and apex, progression of fibrofatty replacement in the remainder of the RV and left ventricle may occur. This process begins in the subepicardium and midmyocardium, and subsequently migrates to the subendocardium. Because of the presence of patchy scar interspersed with normal myocardium, the demonstration of entrainment during tachycardia, as well as the presence of anatomic barriers like the tricuspid annulus, is well established as the arrhythmogenic mechanism of VT in ARVD/C.2 Most, but not all, of these circuits are due to macroreentry, with a minority due to focal re-entry.3,4 The study by Philips et al5 in this issue of the journal suggests that activation mapping and pace mapping of frequent premature ventricular contractions (PVCs) can identify focal sites where successful ablation of VT is achieved. Before examining this premise in greater detail, it is useful to summarize briefly the contemporary approaches to ablation for VT in patients with ARVD/C.

The ablation approach for VT due to ARVD/C is determined by its hemodynamic consequences. Stable VT is amenable to activation and entrainment mapping. Preferred sites for ablation include those associated with isolated mid-diastolic potentials during tachycardia, which can be entrained with concealed fusion, have a postpacing interval within 30 ms of the VT cycle length, and a stimulus-to-QRS/VT cycle length ratio of 30% to 70%. These findings are consistent with a central/proximal isthmus site. Terminating VT by targeting this area during ablation provides confirmatory evidence that it is a critical site for the arrhythmia. Isthmus may be relatively broad and often require transection with linear lesions, usually connecting 2 regions of scar, or scar and an anatomic barrier, such the tricuspid annulus.

For hemodynamically unstable VT, substrate mapping is performed during sinus rhythm and regions of scar and border regions are delineated with 3-dimensional mapping systems. Bipolar electrograms with voltages <1.5 mV are identified as abnormal, and those with voltages <0.5 mV are designated as scar. Scar can be further interrogated for isolated channels of slow conduction by adjusting the abnormal voltage window between 0.3 and 0.5 mV at the upper end and 0.1 mV at the lower end (<0.1 mV is designated as dense scar). In areas of low voltage, particular attention is focused on fractionated electrograms, split potentials, and delayed potentials whose onset occurs after inscription of the QRS complex, either in sinus rhythm or during right ventricular pacing. These electrogarams are further characterized and often targeted for ablation, particularly if pace mapping from the site results in a QRS morphology that matches the clinical VT with a stimulus-to-QRS interval >40 ms. In the absence of a prolonged stimulus-to-QRS interval but with a 11/12 or 12/12 matching pace map, the location is identified as a presumed exit site. Ablation is sometimes, but not always, successful at these sites, as they may be disparate from a critical isthmus site.

Several findings suggest the presence of an epicardial source of VT in patients with ARVD/C. These include a relative paucity of abnormal endocardial electrograms, late termination of VT during endocardial ablation, and the presence of a Q wave or QS configuration in leads I and V2 (anterior RV epicardial sites) or Q waves leads II, III, or aVF (inferior RV epicardial sites).6 Endocardial unipolar mapping is another useful method for identifying the presence of...
abnormal RV epicardial bipolar voltages in these patients. Right ventricular endocardial unipolar voltages <5.5 mV identify extensive RV epicardial bipolar abnormalities.\(^7\)

In contrast to the endocardium, normal epicardial voltage is defined as ≥1.0 mV (at a distance ≥1.0 cm from a major branch of a coronary artery).\(^8\) The criterion for dense scar remains the same as it is for endocardium, 0.5 mV. As epicardial fat overlying normal myocardium insulates the underlying tissue, attenuated low-amplitude signals can be mistaken for abnormal myocardial tissue. Therefore, truly abnormal fractionated electrograms on the epicardial surface are defined by a duration ≥80 ms. A successful epicardial ablation strategy is to ablate late potentials within a circumscribed radius (2–3 cm) of the critical isthmus, as identified by entrainment mapping or pace mapping.\(^8\)

In the present study, Philips and colleagues hypothesized that there is a strong association between VT in ARVD/C and baseline PVCs.\(^5\) Their patients were characterized by having frequent PVCs, with a median of approximately 7000/day among the 16 patients who comprise the study group. Fifteen of the 27 induced VTs required isoproterenol alone or during concurrent burst pacing to induce VT. Nine of 16 patients had adrenergically facilitated VT induced, which was identical in morphology to the patients’ baseline PVCs. Ablation at the site of earliest activation (which was confined to the scar border), and was coincident with a good or perfect pace–map match of the PVC, abolished VT and reduced the number of PVCs. Freedom from VT at 2 years approached 75% of patients. The authors suggest that PVC mapping and ablation can facilitate ablation of catecholamine-induced VT in ARVD/C.

The findings in this study are potentially valuable and may prove to have broader application to a larger universe of patients with VT and ARVD/C in subsequent studies. That being said, several assertions in the discussion deserve further comment. These matters pertain to interpretation of the data and do not detract from the validity or significance of the results. The authors assert that the characteristics of focal VT in ARVD/C may not be reliably distinguished from idiopathic right ventricular outflow tract VT in that both arrhythmias are due to triggered activity. They argue that the following observations support their hypothesis that focal VT in ARVD/C is due to triggered activity: (1) VT is initiated with isoproterenol with or without burst pacing and does not require extrastimuli, (2) VT shows varying rates during incremental infusion of isoproterenol, (3) there is a lack of progressive fusion during pacing at sites with good or perfect pace maps that correspond to sites of earliest activation during VT, and (4) following ablation at the earliest site of PVC activation, VT is no longer inducible.

To clarify, initiation of tachycardia with isoproterenol alone or during burst pacing does not differentiate between VT due to triggered activity and re-entry. The literature is replete with examples of induction of VT due to triggered activity with ventricular extrastimuli, and conversely, with induction of reentrant VT with isoproterenol or with burst pacing.\(^3\)–\(^12\) Similarly, oscillation of VT cycle length during catecholamine stimulation can be seen in either automatic, triggered, reentrant, or accelerated idioventricular rhythms. Furthermore, as the authors report in the present study,\(^5\) pacing during VT from a border zone of scar associated with presystolic activation (10–20 ms) results in a perfect or near-perfect pace map. However, contrary to the authors’ interpretation, these findings are consistent with pacing from an exit site of a reentrant tachycardia; therefore, pacing from such a site would not be expected to show progressive fusion (QRS fusion). Finally, the authors report that adenosine failed to terminate sustained VT in any patient, a finding that is inconsistent with catecholamine-mediated triggered activity. Therefore, in the aggregate, the evidence in this study supports re-entry as the operative mechanism of VT in these patients with ARVD/C. Finally, interpretation of the results is confounded by the ablation methodology. The putative ablation strategy was guided by an implicit presumption that 2 mechanisms were possibly operative for a given arrhythmia in a given ARVD/C patient, because following focal ablation (for presumed triggered activity), further ablation was performed at all sites with isolated delayed potentials (for presumed re-entry).

Despite some interpretative differences, the study by Philips et al\(^7\) represents a commendable addition to the catheter ablation literature on VT in ARVD/C. In this sense, the present study has similarities to that of Bogun et al\(^13\) who demonstrated that postinfarction PVCs often arise from infarct scar tissue in those patients who also have sustained VT, and that the site of origin of the PVC correlates with the exit site of reentrant VT. As in the present study, catheter ablation of the PVC origin frequently abolished inducibility of clinical VT. Although differences in the definition of scar tissue and border zone between the 2 studies may account for some discrepancies in labeling a PVC origin as from scar or border zone tissue (scar=bipolar voltage <1.0 mV\(^{13}\) versus <0.5 mV\(^5\)), and the histological characteristics of scar and border zone may differ between patients with infarcts and ARVD/C, the clinical message is essentially the same. Patients with either ischemic heart disease or ARVD/C and frequent PVCs whose morphology is similar to that of the clinical VT may be amenable to an ablation approach that targets the PVC (which originates from the exit site of the reentrant VT circuit). Confirmation of the appropriate ablation site requires a match of the PVC and VT morphologies during pace mapping, presystolic activation of the PVC, and a stimulus to QRS interval that is consistent with an exit site.

Disclosures

None.

References


**KEY WORDS:** Editorials ■ arrhythmia (mechanisms) ■ arrhythmogenic right ventricular dysplasia ■ catheter ablation ■ ventricular tachycardia
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