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EDITORIAL COMMENT

Substrate Mapping for Functionally Defined Ventricular Re-Entry*

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Ablation of ventricular tachycardia (VT) by targeting the substrate identified during sinus or paced rhythm evolved because many VTs are hemodynamically unstable, precluding extensive activation and entrainment mapping. In addition, some VTs are not inducible in the electrophysiology (EP) laboratory, such that a substrate-guided approach is the only option. How best to identify the VT substrate and the extent of ablation required remains a subject of ongoing investigations. These strategies are based on targeting surrogates for the re-entry substrate derived largely from studies of post-infarction VT. Over the years, most clinical studies of pathophysiology have come from patients who have inducible VTs that can be studied in the EP laboratory. Mapping findings are consistent with re-entry circuits that have a critical isthmus defined by nonconducting scar with loops for conduction outside the isthmus completing the circuit. Fibrosis that separates myocyte bundles and causes circuitous paths for conduction also contributes to slow conduction time through these regions. A structural substrate lends itself to recognition during sinus rhythm. Cassidy et al. (1) associated abnormal low-voltage, delayed, and fragmented sinus rhythm electrograms with infarcts associated with VT. Subsequently a number of electrogram targets have been used: late potentials, electrogram evidence of poorly coupled fibers, regions of greater voltage surrounded by lower voltage, and homogenization of the entire low-voltage region. Regions of slow conduction can also be recognized from long stimulus to QRS interval during pace mapping, which, when present at slow pacing rates, further supports existence of a structural contribution to slow conduction. Reproduction of VT morphology during pacing at such sites has been taken as evidence for participation of that isthmus in VT (1,2).

Although the association of electrophysiological markers with VT re-entry circuits is well supported by studies using ablation, current techniques cannot reliably distinguish bystander regions from re-entry circuit sites, and ablation is performed over broad areas, exceeding what may be necessary. The accuracy of substrate mapping may also be affected by the reliance on markers associated with structural abnormalities (3). Although re-entry paths defined by fixed conduction block due to fibrosis is consonant with the common clinical observation of reproducibly inducible VT of the same morphology and cycle length in many patients, it is well established that the conduction block that defines re-entry pathways is not necessarily fixed. Dillon et al. (4) and Wit et al. (5) have shown that re-entrant VT induced 3 to 5 days after infarction in canine models often take a figure-of-8 type of configuration with the central isthmus defined by lines of functional conduction block. Re-entry is facilitated by differential conduction velocities in the infarct region due to anisotropic conduction accentuated by interstitial fibrosis, and nonuniform refractory periods (4). In these circuits, conduction of the circulating wavefront is slowest,

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not in the center of the isthmus, but rather at the exit and entrance to the isthmus, where the excitation wave has the greatest curvature (6). Conduction is very slow perpendicular to the lines of block as well. Hence, anatomic and functional conduction slowing and block are important contributors to re-entry.

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In this issue of *JACC: Clinical Electrophysiology*, Anter et al. (7) shed light on the potential relationship between substrate mapping findings and functionally determined re-entry circuits. They examined the electrogram features and conduction properties of the 8- to 10-week-old infarct supporting inducible VT in vivo in a porcine model. Using a high-resolution multipolar mapping catheter with 0.4-mm^2 electrodes with 2.5-mm interelectrode spacing (Rhythmia Mapping System, Boston Scientific, Marlborough, Massachusetts), activation during sinus rhythm was compared with that during induced sustained VT. The areas of slowest conduction velocity (CV) with greatest wavefront curvature during VT were designated "critical zones" for re-entry. The sinus rhythm conduction properties and electrograms of these zones and of the VT isthmus regions were compared with noncritical zone sites. Areas of fixed block were present in 37.5% of isthmuses, but most were defined by functional block. Abnormal multicomponent electrograms and electrograms containing a high frequency "near-field" and separate far-field components (defined as local abnormal ventricular activity potentials) were common in regions that were isthmus sites and critical regions for VT, but were also common in areas that were "bystanders" relative to the VT induced, such that the specificity of these electrograms was relatively poor (<70%). A novel aspect of the study is the use of high-resolution mapping to assess ventricular activation and calculate estimates of conduction velocity across the infarct region, exposing heterogeneous conduction velocity. "Steep activation gradient" regions were defined as having >50% slowing of conduction velocity over 5 mm. Identification of these regions had better sensitivity and specificity for critical zones for VT compared with the electrogram characteristics.

The present study highlights the potential contribution of high-density mapping for better definition of arrhythmia substrates. Is high-density mapping for assessment of conduction velocity in sinus rhythm a better method for identifying the VT substrate, perhaps identifying markers for both functionally determined as well as anatomically defined re-entry circuits related to scar? The outcome of ablation guided by this type of mapping remains to be tested in humans or an animal model. Is identification of the substrate for functional re-entry important in humans? It seems likely that some VT circuits are functionally defined, and some are partially functionally defined. Although the functional refractoriness and slow conduction that maintain re-entry are closely linked to the anatomical substrate, slow conduction and block are more likely at faster heart rates. Will "substrate mapping" at slow sinus rates detect the VT substrate for circuits that are functionally defined? Perhaps faster inducible VTs are more likely to be from functionally defined re-entry circuits. Some of the more rapid VTs induced with vigorous programmed stimulation are, however, likely nonspecific, with low probability for clinical recurrence. Watanabe et al. (8), in a recent study of patients undergoing VT ablation, found that induction of VT with a cycle length ≤30 ms + right ventricular effective refractory period measured at 400-ms drive cycle length was not associated with an increased risk of VT recurrence after ablation. Not all clinically relevant VTs are inducible in the EP laboratory, and our EP laboratory-based knowledge is likely biased toward those that are slower and perhaps more likely to be anatomically defined. Further study is needed.

As new mapping tools emerge, careful evaluation will be needed and the limitations understood. Recording techniques markedly influence electrogram characteristics, such that application of substrate markers defined using one system may not translate to a different system. Electrogram characteristics are influenced by electrode dimensions, interelectrode distance, and the recording dipole position relative to activation wavefront direction (3). The validity of bipolar voltage below 0.5 mV representing "dense scar" and >1.5 mV indicating "normal" myocardium was established using a large, 3.5- to 4-mm tip electrode and a 1-mm ring electrode that contain substantial contributions from far-field signals boosting local voltage, and that may not detect low-voltage signals from small channels of myocardium. Correlative magnetic resonance imaging studies show substantial variability in the relationship between endocardial electrogram amplitude and the degree of fibrosis present across the ventricular wall. An electrogram amplitude of <1.5 mV is reliably associated with some fibrosis, but substantial fibrosis can be present in regions of greater electrogram amplitude. Use of small electrodes improves detection of low-amplitude near-field signals,

but loses far-field information, which may be needed to detect substrates deep to the endocardial mapping site, which are common in the nonischemic cardiomyopathies.

With current technology for VT ablation, 20% to 60% of patients with scar-related VT have recurrence at 2 years. New techniques to improve identification of ablation targets are welcome, particularly those that identify the arrhythmia substrate without requiring initiation of VT. The present study that correlates activation features in sinus rhythm to functionally determined re-entry around infarct scars in an animal model is progress in the right direction. Further work to determine whether use of this method for substrate mapping will improve ablation success is warranted.

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