**Editorial**

**123I-Meta-Iodobenzylguanidine Guanidine–Guided Ventricular Tachycardia Ablation Will Expanding the Target Improve the Aim?**

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Catheter ablation is an established therapeutic approach for ventricular tachycardia (VT), especially in patients with drug-refractory VT. Despite advances in modern state-of-the-art ablation techniques and greater operator experience, the VT recurrence rate after ablation still approaches 50% at 6 months in a large series. The majority of current VT ablation strategies rely heavily on targeting anatomic and scar-based substrate and include activation and substrate mapping; the latter particularly helpful for patients with hemodynamically unstable or noninducible VT. However, these techniques are limited by multiple technical and nontechnical factors, including challenges posed by the complex 3-dimensional morphology of scar, particularly in an intramyocardial location, possible artifacts because of poor catheter contact, low spatial resolution, and the time-consuming nature of the techniques themselves. Furthermore, VT substrate not only is anatomic and scar-based but also has physiological components, including ischemia, inflammation, metabolism, and autonomic innervation, which are generally not considered when delineating potential targets for VT ablation. These factors may, in part, explain the high rate of VT recurrence after ablation and highlight the need to consider incorporating functional targets such as those available with several noninvasive imaging modalities into electroanatomic mapping to refine targets for catheter ablation of VT.

**In this issue of Circulation: Arrhythmia and Electrophysiology, Klein et al** present a single-center experience demonstrating the feasibility of integrating iodine-123-labeled-meta-iodobenzylguanidine (123I-mIBG) scintigraphy with voltage mapping for postinfarction VT ablation in 15 patients. Areas defined as denervated by 123I-mIBG were 2.5× larger than scar identified by bipolar voltage mapping. On the contrary, the voltage-defined border zone tended to be larger than the 123I-mIBG transition zone, but this difference was not statistically significant. By bipolar voltage mapping, 36% of VT ablation sites were located in healthy myocardium. In contrast, all VT ablation sites had abnormal denervation defined by 123I-mIBG scintigraphy.

The results of the current study are consistent with our existing knowledge of denervated but viable tissue and its associated risk of ventricular arrhythmias, which provides a sound rationale for using 123I-mIBG scintigraphy in concert with voltage and scar-based mapping for VT ablation. 123I-mIBG is a guanethidine derivative that is taken up into the postganglionic presynaptic sympathetic nerve terminals, is stored in synaptic vesicles, and is not metabolized by monoamine oxidase. The specificity of 123I-mIBG for the sympathetic nervous terminals has been demonstrated in animal models, in which experimental disruption of sympathetic nerve integrity dramatically reduced myocardial 123I-mIBG retention. Similarly, in humans, myocardial 123I-mIBG retention was markedly reduced in the denervated, transplanted hearts. Thus, 123I-mIBG provides a measurement of cardiac sympathetic innervation and denervation, which is relevant given the susceptibility of sympathetically denervated myocardium to ventricular arrhythmias. Cardiac sympathetic fibers are highly sensitive to ischemia compared with myocytes. Thus, after myocardial infarction, the area of sympathetic denervation may be more extensive than the area of myocardial necrosis. Viable but denervated tissue seems to be markedly sensitive to sympathetic stimulation and may predispose to ventricular arrhythmias. In patients with previous myocardial infarction, the risk of ventricular arrhythmias correlates with the extent of mismatch between 123I-mIBG and thallium-201 single photon emission computed tomographic perfusion defects, but not with infarct size. 123I-mIBG imaging, especially in conjunction with scar measurement, therefore, has the potential to identify larger zones of VT susceptibility. Whether larger targets will translate to consistently better results is unknown.

Although the association between sympathetic denervation and increased incidence of ventricular arrhythmias has been demonstrated in several studies, Klein et al are the first to incorporate regional 123I-mIBG uptake with voltage mapping for VT ablation. This is a significant step forward in applying a multidisciplinary approach toward VT ablation that incorporates additional pathophysiological considerations beyond anatomic scar assessment, as discussed above. The finding that all VT ablation sites had abnormal innervation defined by 123I-mIBG scintigraphy but less than two thirds were in abnormal areas defined by voltage mapping suggests the potentially greater accuracy of 123I-mIBG scintigraphy in predicting the location of VT substrate. A common limitation of combining invasive anatomic and noninvasive functional data is coregistration; however, the investigators were able to identify...
and successfully use 3 landmark pairs for this purpose in all patients. The 6-month VT recurrence rate of this novel combined 123I-mIBG and electroanatomic approach in the pilot study by Klein et al was 43%, which is slightly lower than that observed in studies using electroanatomic mapping alone (50%). However, this recurrence rate is still high, and perhaps further refinements to this combined approach and greater operator experience will increase the success rate.

Although several areas of the study by Klein et al require further investigation, 2 areas in particular deserve special mention. First, the 123I-mIBG transition zone is a novel measurement in 123I-mIBG imaging that has not been validated outside of their study and should be externally validated. Second, the scar zone in the study of Klein et al was estimated by voltage mapping alone. Scar may also be assessed by several noninvasive imaging techniques, which could easily be combined with 123I-mIBG imaging and potentially further improve the results of VT ablation. Peri-infarct gray zone by delayed contrast-enhanced cardiac magnetic resonance imaging reflects viable myocardium within areas of dense scar tissue, is an independent predictor of ventricular arrhythmia and implantable cardioverter defibrillator discharge, and is more commonly seen in patients with VT than controls. Real-time integration of cardiac magnetic resonance imaging with electroanatomic mapping to guide VT ablation has been successfully attempted in 23 patients with ischemic cardiomyopathy with good correlation between cardiac magnetic resonance scar and areas of low voltage. Similarly, CT-guided VT ablation has been attempted, but its wide-spread use has been limited by additional radiation exposure, and inconsistent delayed enhancement in chronic infarcts and metal artifacts in patients with cardiac devices. F-18 fluorodeoxyglucose positron emission tomography (PET) and thallium-201 single photon emission computed tomography–derived myocardial scar have also been used to guide VT ablation but were unable to differentiate between scar and border zone owing to the limited spatial resolution of single photon emission computed tomography and the registration errors of both single photon emission computed tomography and PET with voltage mapping. In addition, none of these imaging techniques have been combined with concomitant assessment of sympathetic innervation. The combination of ≥1 of these noninvasive imaging modalities with sympathetic and voltage mapping may better define the area of viability-sympathetic innervation mismatch that could provide a better target for VT ablation than current techniques. An additional imaging consideration is the use of PET-based characterization of the sympathetic myocardial innervation with C-11 hydroxyephedrine, which shares many of the kinetic properties described above for 123I-mIBG but with greater specificity for neuronal binding sites. In the multicenter Prediction of ARhythmic Events with Positron Emission Tomography (PARAPET) study of 204 patients with ischemic cardiomyopathy, the extent of sympathetic denervation quantified by PET C-11 hydroxyephedrine was independently associated with the propensity for sudden cardiac arrest, even after adjusting for ejection fraction and infarct size. The greater spatial resolution of PET and its robust built-in attenuation correction may provide better delineation of VT ablation zones.

Ultimately, the most important consideration is clinically significant VT recurrence and patient outcomes. The latter are understandably not available in the pilot study by Klein et al but should be included in future larger studies. Furthermore, in their study, the VT recurrence rate post ablation was only slightly lower and still >40% at 6 months. Further progress in clinical outcomes should be demonstrated to justify the additional cost and radiation exposure of additional 123I-mIBG imaging. In this study, only patients with ischemic VT were enrolled, and whether similar results would be generalizable to other patients undergoing VT ablation needs further exploration.

In summary, in their pilot study, Klein et al demonstrated the feasibility of a novel approach integrating 123I-mIBG–based assessment of cardiac innervation with voltage mapping for VT ablation and demonstrated improved but still suboptimal VT recurrence rate for postinfarct VT ablation. Nevertheless, the investigators are paving the way for integrating molecular imaging of sympathetic denervation and other functional measurements in various electrophysiological procedures. Functional imaging not only helps to discriminate normal from abnormal myocardium, and to localize ablation sites, but also provides insight into the pathophysiology of the arrhythmia and to identify future potential targets of therapy.

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References


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