Noninvasive myocardial blood flow assessment: Another marker of arrhythmic risk?

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Received Jun 30, 2017; accepted Jul 3, 2017
doi:10.1007/s12350-017-0989-6

See related article, pp. 417–427

Left ventricular ejection fraction (LVEF) is one of the most important predictors of risk for cardiac arrest and sudden cardiac death (SCD) and is currently used as the main parameter to determine which patients will benefit from prophylactic ICD placement.[1] However, LVEF alone has limited sensitivity and specificity for assessing arrhythmic risk. Many patients receiving an ICD based on current guidelines (LVEF $\leq$ 35%) do not use it over several years of follow up.[2] Advances in heart failure therapy may further diminish the benefit derived from ICD placement in some groups, as suggested by the recent DANISH study.[3] On the other hand, it is well known that some patients with relatively preserved LVEF have a high risk of SCD.[4,5]

Programmed ventricular stimulation to assess for inducible arrhythmias is an invasive technique that has been used to identify high-risk patients with ischemic heart disease and moderate LV dysfunction, who may benefit from ICD implantation.[6] In addition, several noninvasive modalities for refining arrhythmic risk have been investigated over the years: (a) the arrhythmogenic substrate can be assessed by ECG parameters (QRS fractionation, signal-averaged ECG) and imaging techniques (MRI, echocardiography, SPECT, PET); (b) autonomic function can be assessed by heart rate variability, heart rate turbulence and baroreceptor sensitivity, while MIBG-SPECT and HED-PET can image autonomic innervation; (c) ventricular repolarization as a measure of electrical vulnerability can be assessed by microvolt T-wave alternans, QT interval dispersion and other markers; (d) rhythm monitoring can detect subclinical arrhythmias; and (e) genetic testing can identify high-risk subgroups, especially in certain nonischemic cardiomyopathies.[7]

Many imaging modalities can assess the arrhythmogenic substrate.[8] Global longitudinal strain on echocardiography has been shown to predict ventricular arrhythmias independent of LVEF in patients with ischemic and nonischemic cardiomyopathy.[9,10] Late gadolinium enhancement (LGE) on cardiac MRI permits quantification and characterization of the total scar burden. The amount of midwall scar identified by LGE has been shown to associated with arrhythmic events in nonischemic cardiomyopathy.[11] In ischemic cardiomyopathy, in addition to scar burden, intermediate intensity regions (gray zones) on LGE that presumably represent heterogeneous scar with a mixture of viable and nonviable myocardium may predict arrhythmic risk.[12] PET and SPECT imaging allow noninvasive assessment of ischemic burden, scar and hibernating myocardium in post-MI patients, providing incremental prognostic value beyond LVEF in predicting SCD.[13,14]

In this issue of the Journal, Ghannam et al. retrospectively studied 159 patients with ICDs, to explore the relationship between noninvasive myocardial blood flow (MBF) measurement using rubidium-82 during PET imaging and ventricular arrhythmias.[15] 65% of these patients had ischemic cardiomyopathy and nearly three out of four had an ICD implanted for primary prevention. Over a median follow up of 1.4 years, ventricular arrhythmias occurred in 44 patients (27%). Impaired stress MBF (less than 1.9 mL/g/min) and resting EF were found to be associated with an increased risk of ventricular arrhythmias, while summed rest score (SRS) and summed stress score (SSS) were not predictive. In the subset of 110 pts with LVEF $<$ 35%, stress MBF remained an independent predictor of ventricular arrhythmias, while residual EF, SSS, and SRS were not.

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J Nucl Cardiol 2019;26:428–30.
1071-3581/$34.00

The authors should be congratulated on a well-designed study that demonstrates the potential utility of noninvasive measurement of stress MBF in arrhythmic risk stratification. Prior studies have shown that diminished MBF is associated with adverse clinical outcomes.[16] However, the association between MBF and ventricular arrhythmias has not been well studied. In patients with ischemic cardiomyopathy, Rijnierse et al. found that impaired hyperemic MBF predicted patients who are likely to have inducible VT with programmed electrical stimulation.[17] While both studies are similar in that they showed a relationship between stress MBF and ventricular arrhythmias, the endpoint in the current study was spontaneous ventricular arrhythmia noted on ICD diagnostics, in contrast to inducible arrhythmias in the other study.

This study also adds to our understanding of the complex relationship between blood flow, ischemia, and arrhythmias in patients with cardiomyopathy.[18] How does stress MBF predict ventricular arrhythmias while measures of scar and ischemia (SRS and SSS) do not? Perhaps, low stress MBF by PET identifies a more arrhythmogenic substrate, or perhaps it might reflect a higher propensity for triggers during periods of hyperemia due to underlying microvascular dysfunction.

This is a small, observational study prone to the usual limitations of retrospective analyses such as selection bias and referral bias. Another important limitation is that this study included patients with both ischemic and nonischemic cardiomyopathy. As pointed out by the authors, the small sample size precluded independent subgroup analyses, and one could argue that the predictive value of MBF might differ in these subgroups of patients. However, a counter point would be that is common to find several patients with 'mixed' ischemic and nonischemic cardiomyopathy, and that stress MBF has practical value in predicting arrhythmic risk in a real-world setting.

There are some important cautionary points to be noted with the primary endpoint of this study, i.e., survival free of ventricular arrhythmia. First, detection and therapy of ventricular arrhythmia by devices is dependent on programming parameters including rate, duration, zones, and discriminators.[19] Programming of devices in this study is not reported and, without a standardized protocol, is likely to have been heterogeneous. With more conservative programming, episodes that 'required' device therapy might have terminated spontaneously.[20] Second, it should be noted that the episodes of VF noted on device diagnostics may not represent clinical VF. Device classification of ventricular arrhythmia as VT and VF is predominantly based on rate: a regular monomorphic VT that is fast enough to be detected in the VF zone is classified as VF by the device. Third, device detected VT/VF episodes may not be an accurate reflection of arrhythmic or SCD risk. The sample size and follow up duration obviously limited using sudden cardiac death as an independent endpoint. Ventricular arrhythmia burden (i.e., the number and duration of episodes) may have been a reasonable measure of arrhythmic risk, but patients in this study were censured after the first occurrence of a ventricular arrhythmic episode, making no distinction between patients with one or multiple episodes. Larger, prospective studies with standardized device programming and more meaningful endpoints can address some of these limitations.

The arrhythmic risk stratification tool box keeps growing and the search for the best strategy for refining risk continues. As we move towards complex algorithms for risk stratification, it is crucial to identify two groups of patients: (a) high-risk patients with an EF above the current ICD threshold, who might benefit from ICD placement, and (b) low-risk patients among those with LVEF in the ICD range, in whom the ICD may not be cost-effective.[21] It is in this area that tools such as stress MBF assessment by PET and LGE by cardiac MRI hold promise.

Disclosure

The authors have no conflicts of interest to disclose. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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