The Fault Is in Our Scars
LGE and Ventricular Arrhythmia Risk in LV Dysfunction*

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In this issue of iJACC, Desertori et al. (1) present a meta-analysis of the association between myocardial scar detected by cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) and ventricular arrhythmia (VA) risk. The study included 2,850 patients from 19 different studies and 423 arrhythmic events over a median 2.8 years of follow-up. The authors defined a composite arrhythmic event endpoint that included sudden death, aborted sudden death, ventricular tachycardia, ventricular fibrillation, and appropriate implantable cardioverter-defibrillator (ICD) therapy for VA. Using this endpoint, the authors’ meta-analysis found that patients without LGE had an annual composite arrhythmia event rate of 1.7% compared with the annualized event rate of 8.6% in patients with LGE (1).

With respect to the potential impact of LGE-based risk stratification for VA, the most obvious application is identification of optimal candidates for ICDs for primary prevention of sudden cardiac arrest. Although the strong association between LGE findings and VA risk is clear, application of these results in clinical practice for ICD risk stratification is much less straightforward because of the heterogeneity of these studies. In addition to the different endpoints used, ICD indications varied among the studies, and cardiac resynchronization defibrillators were sometimes implanted. Furthermore, the patients enrolled ranged from those with severe LV dysfunction to those with only mild LV dysfunction, and some patients in these studies did not even meet criteria for ICD implantation. Even so, the consistently strong associations across studies between LGE and VA risk suggest that LGE may have significant utility for this purpose in the future.

The potential impact of LGE for risk stratification in ischemic cardiomyopathy (ICM) is highlighted by the fact that nearly two-thirds of the patients in the National Cardiovascular Data Registry (NCDR) ICD Registry (version 1) had ischemic heart disease, and more than one-half of those patients had prior myocardial infarction (2). One challenge with respect to using LGE for risk stratification in ICM patients is that it is not practical to use absence of LGE to identify a low-risk cohort, as shown by the 100% prevalence of LGE in the 5 studies (included in this meta-analysis) that analyzed only ICM patients. Fortunately, there are other important indicators of risk based on LGE in ICM patients, including total scar mass, total scar as a percentage of LV volume, gray zone mass, infarct transmurality, and the peri-infarction-to-core infarction mass ratio. Of note, in the studies with non-ischemic cardiomyopathy (NICM), the presence (versus absence) of LGE (or midwall LGE), total scar mass, or scar volume as a percentage of LV volume were typically used.

Although LGE results can be analyzed in a number of sophisticated ways with respect to risk stratification for VA, perhaps the most intriguing approach is to analyze the gray zone (also called the peri-infarct zone or border zone). Although gray zone criteria with CMR have varied among studies, gray zone tissue is generally defined as tissue with a lower signal intensity than the infarct core but with a greater signal intensity than normal tissue. The gray zone consists of less dense scar with greater potential arrhythmic potential and is a prominent feature in areas of scar in patients with prior myocardial infarction. In ICM, the gray zone typically surrounds the “core” area of scar and is thus located at the border zone between scar and normal tissue. From a

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

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physiologic standpoint, the gray zone consists of scar tissue interspersed with islands of viable myocardium. Conduction in this mixed tissue is heterogeneous, and dispersion of repolarization may be increased. These tissue characteristics are conducive to re-entry through viable channels in the scar. In simplistic terms, arrhythmia circuits associated with scar utilize viable tissue within the scar because completely dead tissue cannot conduct electricity. Hence, the gray zone, in which the proportion of viable tissue relative to scar is greater, presents more possibilities for arrhythmia circuits.

From a physiologic standpoint, the extent of the gray zone has been strongly associated with inducibility of ventricular tachycardia during a standard ventricular stimulation protocol performed during an invasive electrophysiology study (3). This physiology is also evident during catheter ablation of ventricular tachycardia, in which viable channels of myocardium are targeted for ablation if they meet established pacing and electrogram-based criteria for being part of the ventricular tachycardia circuit (4). In addition, it has recently been demonstrated that detailed computer modeling of electrical conduction in infarcts in swine based on LGE imaging can accurately predict ventricular tachycardia morphology and circuit location (5), suggesting that current methods for gray zone analysis may eventually be replaced by even more sophisticated analytic methods to identify potential arrhythmia circuits based on LGE findings.

Several studies in the current meta-analysis (1) showed that the gray zone was strongly associated with VA risk. The threshold level used to identify a high-risk LGE pattern in gray zone mass in ICM patients was 16.7 g (median value) in one meta-analysis study, while another meta-analysis study in a mixed ICM/NICM cohort with cardiac resynchronization therapy defibrillators found that a gray zone mass of <9.5 g combined with a total scar volume less than 16% of the LV volume identified patients at very low risk for appropriate ICD therapies. A ratio of gray zone mass to core infarct mass <0.6 also identified low-risk patients in another study of patients with standard ICDs. In addition, one of the NICM studies found that a threshold value of 6.1% for overall scar volume conveyed an increased risk of major adverse cardiac
events. With respect to total scar volume in ICM, the design of a prior incomplete clinical trial of patients with coronary artery disease and mild to moderate LV dysfunction was based on a threshold of a 10% scar volume to identify those at higher risk for VA (6).

Considering the burden of heart failure, the large volume of ICDs implanted every year (2), and the cost associated with these ICDs, the use of LGE to identify optimal ICD candidates could have a large public health impact. LGE data could be used to identify current patients who may not need an ICD even though they have LV dysfunction and guideline-based primary prevention criteria for ICD implantation. Alternatively, the use of LGE in risk stratification algorithms could expand the pool of ICD candidates by identifying patients with lesser degrees of LV dysfunction but higher VA risk. LGE findings could also aid in patient selection for prophylactic ventricular tachycardia ablation or antiarrhythmic drug therapy early after ICD implantation.

Before we can use LGE to guide therapy, we must achieve consensus regarding the optimal measure of VA risk based on LGE in ICM and NICM. Randomized clinical trials will be needed to test the hypothesis that LGE findings can help identify patients who currently have a guideline-based primary prevention indication for an ICD but may not experience improved survival with an ICD, as well as other patients without a current ICD indication who are actually at increased VA risk and may benefit from an ICD (Figure 1). These clinical studies should also evaluate whether LGE adds to risk scores (7,8) and other risk stratification tools that we already have. Furthermore, we need to acknowledge that not all patients will be able to receive CMR with gadolinium because of chronic kidney disease or contraindications to CMR.

In summary, the current research supports a strong association between LGE findings on CMR and subsequent VA in the setting of LV dysfunction, and the scar gray zone appears to be at least as important as total scar volume for risk stratification. In fact, all the studies in the meta-analysis showed that LGE findings conveyed increased risk for VA, and LGE findings were often still associated with VA risk after adjustment for other factors. Consequently, the findings from this meta-analysis (1) indicate that the “fault” in heart failure patients with respect to VA really does lie in the extent and characteristics of their myocardial scars and that randomized clinical trials are needed to determine whether LGE can determine which patients are most likely to benefit from clinical interventions designed to decrease morbidity and mortality from VA.

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KEY WORDS cardiac magnetic resonance, implantable cardioverter-defibrillator, late gadolinium enhancement, sudden death, ventricular tachyarrhythmia