Cardiac resynchronization therapy (CRT) has made a major impact on clinical outcomes in many patients with heart failure with widened QRS complexes and reduced ejection fraction (EF), even in those who are mildly symptomatic. Assessing risk for ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients treated with CRT continues to be of great interest. Despite its known limitations, EF remains the only imaging parameter to guide implantable cardioverter-defibrillator therapy for the primary prevention of ventricular arrhythmias. Other echocardiographic parameters have been proposed as risk markers of VT/VF, which are additive to EF, including low relative wall thickness,2 global longitudinal strain (GLS),3,4 mechanical dyssynchrony5 and, more recently, peak strain dispersion6,7 (Figure). However, none of these echocardiographic markers has emerged to substantially influence patient care, and the prediction of VT/VF remains one of the largest challenges in cardiology.

See Article by Biering-Sørensen et al

Low Inferior Wall Strain as a Marker of Risk for Arrhythmias in MADIT-CRT Trial (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy)

The MADIT-CRT trial has generated an impressive number of substudies that have contributed substantially to the current knowledge of mildly symptomatic patients with heart failure treated with CRT.1 MADIT CRT randomized 1064 patients with QRS ≥130 ms wide and EF ≤30% to either CRT-D (≈66%) and to implantable cardioverter-defibrillator alone (≈33%). Biering-Sørensen et al8 in this issue of Circulation: Cardiovascular Imaging investigated the role of regional myocardial dysfunction by speckle-tracking strain echocardiography and the relation to ventricular arrhythmia outcome in a MADIT CRT post hoc subanalysis. Strain analysis software was applied to the apical 4-chamber and 2-chamber views to determine segmental peak longitudinal strain for the septal, lateral, anterior, and inferior myocardial walls. The end point tested was the first event of appropriate antitachycardia pacing for VT or appropriate shock for VF. They found that after multivariate adjustment, anterior and inferior longitudinal strains were independently associated with VT/VF. The main finding in this study was that reduced strain in the inferior wall was independently associated with VT/VF and provided incremental prognostic information over clinical and echo parameters. Specifically, patients with an inferior strain worse than −7% had a 2-2-fold increased risk VT/VF, hazard ratio, 2.10 (95% confidence interval, 1.63–2.69), P<0.001. In patients randomized to CRT, the relationship between regional septal strain and risk of VT/VF was modified by CRT (P=0.008 for the interaction). However, they found that CRT did not modify the relationship between regional strain and risk of VT/VF for other myocardial walls. This interaction of CRT and baseline strain limited to the septum appeared unexpected because effective CRT has been shown to impact global left ventricular (LV) reverse remodeling.

What could be the mechanism for this association between VT/VF and diminished inferior wall strain? The authors speculated that the inferior wall, because it is relatively flat, exhibits a higher radius of curvature and comparatively higher wall stress than other regions in cardiac disease.8 This altered regional curvature in myopathic ventricles may lead to increased stretch, which is arrhythmogenic. Furthermore, they speculated that the inferoposterior regions of the LV are innervated by greater amount of parasympathetic afferents, and a deceased or ailing myocardium in these regions may alter or destroy the parasympathetic fibers, leading to autonomic dysfunction of the heart with higher arrhythmic potential. An alternate hypothesis is that low values of regional strain may indicate myocardial scar and that LV lead positioned within or adjacent to scar are associated with arrhythmia risk. However, an analysis of lead position was not included to test this hypothesis. Interestingly, this study showed no differences between ischemic and nonischemic patients with regard to inferior wall strain and prediction for arrhythmic events. Because assessment of regional or global scar burden was not part of MADIT-CRT and lower strain values can represent scar, or profound nonischemic myocardial dysfunction, the role of inferior wall scar and risk for VT/VF remains unclear.

Other Markers of Risk in CRT Patients

One of the most widely used parameters for prognostic utility from strain echocardiography is GLS.9 Most recently, low
GLS was found to be of prognostic importance in a study of 755 patients in the EchoCRT trial (Echocardiography Guided Cardiac Resynchronization Therapy), enrolled with narrow QRS, reduced EF, and baseline echocardiographic dyssynchrony. Among these patients, those with the lowest quartile of GLS values (worse than −6.2%) had a substantial increased risk of death with CRT-On, compared with those in CRT-Off control groups (P=0.007). In particular, low GLS was shown to be additive to low EF as a marker of risk for harm from CRT in these patients with QRS width of <130 ms and baseline mechanical dyssynchrony. Although not clearly elucidated, there is a suggestion that the increased mortality observed in EchoCRT was related to arrhythmias.

The MADIT-CRT investigators have investigated other markers for ventricular arrhythmias in their study patients, previously. They presented recently that decreased relative wall thickness was a marker of VT/VF and also the combined end point of ventricular arrhythmias and death. Other findings reported from this same trial have shown an association of ventricular arrhythmias and degree of EF reduction, non-apical RV lead location, and unchanged or worsening of dyssynchrony after device implantation. Because each of these features has been examined individually to date, the relative importance of these markers by comparison or in combination remains unknown to most precisely determine VT/VF risk in the MADIT-CRT study.

**Echocardiographic Mechanical Dyssynchrony and Risk for Arrhythmias**

The MADIT-CRT study is in contrast to several studies on different patient populations from different institutions that have shown echocardiographic measures of differences in regional timing, generally referred to as dyssynchrony as a marker of risk for VT and VF. There is mechanistic support for regional dyssynchrony to represent myocardial scar or increases in regional shear stress that may be related to the genesis of VT or VF. The MADIT-CRT investigators have previously reported that the SD of the time-to-peak longitudinal strain as a marker of dyssynchrony at baseline was not associated with subsequent VT of VF. Although the MADIT-CRT trial is the largest CRT study to date with continuous rhythm monitoring and adjudicated VT/VF events, two thirds of the patients were randomized to CRT-implantable cardioverter-defibrillator. CRT is a powerful therapy, with the ability to profoundly change regional timing and improve myocardial synchrony. Therefore, dyssynchrony at baseline could only be tested for its predictive of VT/VF in patients in the implantable cardioverter-defibrillator control group and not adequately reflective in patients treated with CRT that modulates arrhythmia risk. Recent studies have shown that dyssynchrony after CRT implantation was importantly associated with VT/VF, both when using peak strain dispersion or other measures of dyssynchrony. Importantly, these studies showed that reduced dyssynchrony after CRT was associated with reduction in risk for ventricular arrhythmias, which has also been previously shown in the MADIT-CRT population. There were some methodological limitations to consider in this present study. In contrast to previous studies on mechanical dispersion using 16 segments and high frame rates, data from only 4- and 2-chamber views were included (12 segments) with lower temporal resolution. The lower frame rates may smoothen and soften the strain curves that may influence time-to-peak longitudinal strain measurements. The precise reasons for the difference in the results of MADIT-CRT analysis of mechanical dyssynchrony and VT/VF and other studies are not known, and accordingly further future investigation is warranted.

**Potential Confounding Variables in the MADIT-CRT Analysis**

Decreased strain in the inferior myocardial wall was significantly associated with a higher proportion of male sex, higher heart rate, higher proportion of previous ventricular arrhythmias, higher proportion of diabetes mellitus, higher proportion with ischemic cardiomyopathy, higher blood urea nitrogen, lower systolic blood pressure, higher proportion of right bundle branch block, and higher B-type natriuretic peptide. In addition, lower inferior wall strain was significantly associated with impaired echocardiographic measures of LV structure and function, including larger LV mass, larger LV end-diastolic volume index, lower EF, lower GLS, and worse diastolic function. In summary, markers of risk for ventricular arrhythmias are complex and overlapping. The observation that lower inferior wall strain was associated with a striking increase in risk for VT/VF in the MADIT-CRT patient population is intriguing. However, important questions remain unanswered. Are LV regions really different in terms of arrhythmogenesis, independently of global function? Why is low strain in the inferior wall most arrhythmogenic? What is the role of scar and what is the relationship between low strain and scar? How do other markers of risk for VT/VF relate to reduced inferior wall
strain? Future studies to answer these questions are warranted to advance the mechanistic understanding needed to further reduce risk and enhance clinical outcomes in patients treated with CRT.

**Disclosures**

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**References**


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Ventricular Arrhythmias and Reduced Echocardiographic Inferior Wall Strain: Is Regional Function an Important Risk Marker?

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