Association of left ventricular tissue heterogeneity and intramyocardial fat on computed tomography with ventricular arrhythmias in ischemic cardiomyopathy

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BACKGROUND Gray zone, a measure of tissue heterogeneity on late gadolinium enhanced–cardiac magnetic resonance (LGE-CMR) imaging, has been shown to predict ventricular arrhythmias (VAs) in ischemic cardiomyopathy (ICM) patients. However, no studies have described whether left ventricular (LV) tissue heterogeneity and intramyocardial fat mass on contrast-enhanced computed tomography (CE-CT), which provides greater spatial resolution, is useful for assessing the risk of VAs in ICM patients with LV systolic dysfunction and no previous VAs.

OBJECTIVE The purpose of this proof-of-concept study was to determine the feasibility of measuring global LV tissue heterogeneity and intramyocardial fat mass by CE-CT for predicting the risk of VAs in ICM patients with LV systolic dysfunction and no previous history of VAs.

METHODS Patients with left ventricular ejection fraction $\leq$35% and no previous VAs were enrolled in a prospective, observational registry and underwent LGE-CMR. From this cohort, patients with ICM who additionally received CE-CT were included in the present analysis. Gray zone on LGE-CMR was defined as myocardium with signal intensity (SI) > peak SI of healthy myocardium but <50% maximal SI. Tissue heterogeneity on CE-CT was defined as the standard deviation of the Hounsfield unit image gradients (HU/mm) within the myocardium. Intramyocardial fat on CE-CT was identified as regions of image pixels between −180 and −5 HU. The primary outcome was VAs, defined as appropriate implantable cardioverter-defibrillator shock or sudden arrhythmic death.

RESULTS The study consisted of 47 ICM patients, 13 (27.7%) of whom experienced VA events during mean follow-up of 5.6 $\pm$ 3.4 years. Increasing tissue heterogeneity (per HU/mm) was significantly associated with VAs after multivariable adjustment, including for gray zone (odds ratio [OR] 1.22; $P = .019$). Consistently, patients with tissue heterogeneity values greater than or equal to the median ($\geq$22.2 HU/mm) had >13-fold significantly increased risk of VA events, relative to patients with values lower than the median, after multivariable adjustment that included gray zone (OR 13.13; $P = .028$). The addition of tissue heterogeneity to gray zone improved prediction of VAs (area under receiver operating characteristic curve increased from 0.815 to 0.876). No association was found between intramyocardial fat mass on CE-CT and VAs (OR 1.00; $P = .989$).

CONCLUSION In ICM patients, CE-CT–derived LV tissue heterogeneity was independently associated with VAs and may represent a novel marker useful for risk stratification.

KEYWORDS Contrast-enhanced computed tomography; Intramyocardial fat; Ischemic cardiomyopathy; Left ventricular tissue heterogeneity; Ventricular arrhythmia

Introduction

Ventricular arrhythmias (VAs) in patients with ischemic cardiomyopathy (ICM) are an important cause of morbidity and mortality. Because left ventricular ejection fraction (LVEF) alone has been shown to be an inadequate measure of the underlying myocardial phenotype predisposing to VAs, late gadolinium enhanced–cardiac magnetic resonance (LGE-CMR) imaging has emerged as an important tool for the identification of arrhythmogenic substrate.[1] Regions of LGE with intermediate signal intensity (SI), termed gray zones, represent areas of transition from normal myocardium to scar. As a measure of tissue heterogeneity on LGE-CMR, gray zone extent has been shown to predict VAs in patients with ICM.[2–6]

Contrast-enhanced computed tomography (CE-CT), a more readily available imaging technique, provides greater spatial resolution than LGE-CMR, with shorter imaging times, and potentially can distinguish a broader range of

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KEY FINDINGS

- Gray zones on late gadolinium enhanced–cardiac magnetic resonance (LGE-CMR) imaging have been shown to predict ventricular arrhythmias (VAs) in ischemic cardiomyopathy (ICM) patients.

- However, no studies have described whether left ventricular (LV) tissue heterogeneity on contrast-enhanced computed tomography (CE-CT), which provides greater spatial resolution with shorter imaging times, is useful for assessing the risk of VAs in ICM patients with LV systolic dysfunction and no previous VAs.

- The present proof-of-concept study is the first to demonstrate that CE-CT–derived global LV tissue heterogeneity is independently associated with VAs in patients with ICM, LV systolic dysfunction, and no previous history of VAs, and may improve prediction of VAs when used in conjunction with LGE-CMR–derived gray zone.

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arrhythmogenic tissue substrate, particularly intramyocardial fat. Thus, a more extensive range of Hounsfield units (HU) on CE-CT may be a prognostically important indicator of myocardial tissue heterogeneity. A recent study investigated the role of right ventricular (RV) tissue heterogeneity on CT for detecting areas with late potentials as a surrogate for ventricular tachycardia (VT) substrate in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).[7] However, no studies have described whether left ventricular (LV) tissue heterogeneity on CE-CT is associated with the clinical outcome of VAs in ICM patients, particularly those with LV systolic dysfunction and no previous VAs. Additionally, although intramyocardial fat is recognized to develop progressively after myocardial infarction and may be arrhythmogenic, no studies have examined the relationship between intramyocardial fat mass on CE-CT and the occurrence of VAs in a cohort of ICM patients with LV systolic dysfunction and no previous VAs.[8–14]

Accordingly, in this proof-of-concept study, we aimed to determine the feasibility of measuring global LV tissue heterogeneity and intramyocardial fat mass by CE-CT for predicting the risk of VAs in ICM patients with LV systolic dysfunction and no previous history of VAs.

Methods
Patient population
We performed a retrospective analysis of the prospective observational Left Ventricular Structural Predictors of Sudden Cardiac Death Registry (ClinicalTrials.gov Identifier NCT01076660), which enrolled 382 patients at 3 sites: Johns Hopkins Medical Institutions (Baltimore, MD); Christiana Care Health System (Newark, DE); and the University of Maryland (Baltimore, MD), as previously reported.[15]

Patients with clinical criteria for a primary prevention implantable cardioverter-defibrillators (ICD), based on LVEF ≤35% and no history of sustained VAs, were enrolled; 328 patients were concurrently enrolled in the PROSE-ICD (Prospective Observational Study of Implantable Cardioverter Defibrillators [ClinicalTrials.gov Identifier NCT00733590]) Registry.[16] Patients underwent LGE-CMR using a standard protocol, as previously described.[6] For the present study, patients with ICM who additionally received clinically indicated CE-CT (commonly obtained for indications such as suspicion for pulmonary embolism and evaluation of aortic aneurysm) were included. CE-CTs were obtained using Omnipaque 350 mg iodine per milliliter, with a dose of 100–120 cc. Bolus tracking technique was used to acquire images. The institutional review boards approved the protocol at each site, and all participants provided informed consent. The research reported in this paper adhered to the Helsinki Declaration guidelines.

Clinical follow-up and endpoint
Patients were evaluated every 6 months and after ICD shock events. ICDs were interrogated in person or via remote transmission, and all arrhythmic events were adjudicated by 2 clinical cardiac electrophysiologists blinded to patient data. Each electrophysiologist independently determined the rhythm at the time of initial detection and after therapy delivery. Disagreements regarding the diagnosed rhythm were reviewed by a third electrophysiologist for final adjudication. The primary endpoint was VA events, defined as appropriate ICD shock or sudden arrhythmic death. ICD programming parameters were not prescribed but were determined by implanting electrophysiologists, as is the case for other contemporary ICD trials. Deaths were classified according to the most proximate cause after review of available ICD interrogations, medical records, death certificates, autopsy reports, and eyewitness accounts.

Scar analysis on LGE-CMR
Patients underwent LGE-CMR as part of the prospective observational studies described earlier. All LGE-CMR images were acquired according to previously reported protocols.[6] Scar analysis consisted of measurements of gray zone and infarct core, using methodology previously described.[6] SI threshold values to define scar regions were determined from a semi-automatic full-width half-maximum approach. Gray zone was defined as myocardium with SI > peak SI of healthy myocardium but <50% of maximal SI. Infarct core was defined as myocardium with SI >50% of maximal SI.

CE-CT image processing
For the present study, patients with ICM who additionally received CE-CT were included, as described earlier. The outline for CE-CT image processing is detailed in Figure 1. Each CE-CT image was resampled into short-axis slices at an isotropic resolution of 0.35 × 0.35 × 0.35 mm. Short
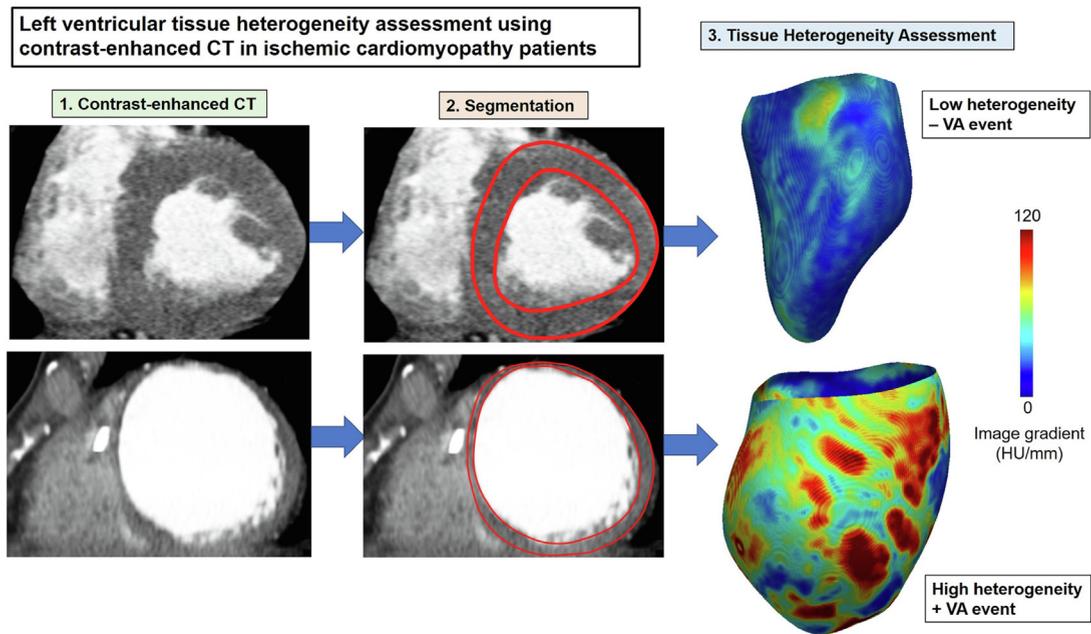
Figure 1   Contrast-enhanced computed tomography (CT)-derived left ventricular tissue heterogeneity analysis workflow. Segmentations were performed using a semi-automated approach. Image gradients were calculated across the entire myocardium. Tissue heterogeneity was computed as the standard deviation of the image gradient values across the whole myocardial volume. VA = ventricular arrhythmia.

axial slices were segmented with a semi-automated method by manually placing control points that are used to generate a smooth interpolated surface, as previously described.[13] Segmentations were carefully performed to exclude any blood pool, papillary muscles, and epicardial adipose tissue. Voxels that had values <−180 HU and >250 HU within the segmented myocardium were defined as artifacts. If artifacts persisted after this thresholding approach, additional manual contours were used to delineate these artifact regions. All artifact voxels were excluded.

LV tissue heterogeneity analysis and intramyocardial fat identification on CE-CT

The primary objective of the present study was to examine the utility of measuring CE-CT–derived LV tissue heterogeneity in patients with ICM. Specifically, the aim was to assess whether CE-CT–derived LV tissue heterogeneity is associated with VA events, independent of the established parameter of LGE-CMR–derived gray zone. For further perspective on our data, we also assessed whether the combination of LV tissue heterogeneity and gray zone provides additional prognostic information relative to gray zone alone.

LV tissue heterogeneity on CE-CT was computed in 2 steps, consistent with methodology previously reported.[7] Image gradients, defined as magnitudes of change in HU/mm between neighboring voxels, were first calculated across the entire myocardium. These image gradients reflect differences between abnormal and non-injured myocardial tissues. Next, the standard deviation of image gradient values in the entire myocardium was computed. This mea-

surement, representing global LV tissue heterogeneity across the entire myocardium, describes the degree of variation in the myocardium and is expected to be higher in patients with more heterogeneous tissue distributions. We incorporated an assessment of wall thickness into our LV tissue heterogeneity analysis. Using CE-CT, wall thickness was computed at each point as the distance between endocardium and epicardium. The wall thickness for a given patient was then computed as the average across all wall thickness measurements. Additionally, we examined histopathologic correlates of CE-CT–derived tissue heterogeneity in 2 patients who underwent LV assist device placement and thus had available histopathologic studies.

A secondary objective of our study was to assess whether total LV intramyocardial fat mass by CE-CT was associated with the risk of VAs in ICM patients with LV systolic dysfunction and no history of VAs. Total LV intramyocardial fat mass on CE-CT was defined as the total mass of voxels of tissue in the myocardium with values between −180 and −5 HU, as previously described.[12,13] Because noise can have negative HU and be mistakenly identified, intramyocardial fat volumes <1 mm³ were removed as well, consistent with previously reported methodology.[12,13]

Statistical analysis

Continuous data are given as mean ± SD, and categorical variables are given as percentages. Continuous variables were evaluated by t tests, and categorical variables were compared using the χ^2 or Fisher exact test. Univariable and multivariable logistic regression analyses, adjusted for relevant clinical covariates, were performed to evaluate the

Table 1 Baseline characteristics and imaging findings

	All (n = 47)	VA+ (n = 13)	VA– (n = 34)	P value
Demographics				
Age (y)	61.4 ± 11.9	54.7 ± 12.3	63.9 ± 10.9	**.029**
Male	39 (83.0)	12 (92.3)	27 (79.4)	.203
White	32 (68.1)	8 (61.5)	24 (70.6)	.562
Body mass index (kg/m²)	28.1 ± 4.7	28.2 ± 4.6	28.1 ± 4.7	.956
Cardiac risk factors				
Hypertension	34 (72.3)	7 (53.8)	27 (79.4)	.098
Hyperlipidemia	37 (78.7)	10 (76.9)	27 (79.4)	.855
Diabetes mellitus	17 (36.2)	4 (30.8)	13 (38.2)	.625
Tobacco use	35 (74.5)	10 (76.9)	25 (73.5)	.807
Laboratory values				
Serum creatinine (mg/dL)	1.0 ± 0.28	1.1 ± 0.4	0.97 ± 0.2	.280
ECG parameters				
QRS duration (ms)	116.7 ± 29.7	118.9 ± 31.7	115.9 ± 29.4	.769
Medications				
Aspirin	42 (89.4)	11 (84.6)	31 (91.2)	.555
Beta-blocker	46 (97.9)	13 (100)	33 (97.1)	.310
Antiarrhythmic drugs	4 (8.5)	3 (4.2)	1 (2.9)	.094
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	43 (91.5)	12 (92.3)	31 (91.2)	.898
Biventricular ICD	4 (8.5)	2 (15.4)	2 (5.9)	.378
CMR indices				
LV ejection fraction (%)	27.7 ± 7.3	26.6 ± 7.7	28.2 ± 7.3	.512
LV end-diastolic volume (cc)	234.4 ± 73.4	281.5 ± 99.2	215.9 ± 51.2	**.040**
LV end-systolic volume (cc)	171.3 ± 62.1	210.4 ± 84.2	155.8 ± 43.5	**.043**
Gray zone (g)	13.8 ± 9.5	21.5 ± 9.1	10.9 ± 8.0	**.002**
Core scar (g)	22.2 ± 15.4	27.8 ± 12.9	20.0 ± 15.9	.095
CE-CT indices				
LV tissue heterogeneity (HU/mm)	25.3 ± 7.5	29.9 ± 9.6	23.6 ± 5.8	**.041**
Intramyocardial fat (g)	7.3 ± 8.2	7.3 ± 8.7	7.3 ± 8.1	.990
Wall thickness (mm)	7.4 ± 1.6	6.9 ± 1.4	7.5 ± 1.6	.178

Values are given as mean ± SD or n (%) unless otherwise indicated.
The bolded P-values represent statistically significant differences.
CE-CT = contrast-enhanced computed tomography; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LV = left ventricle; VA = ventricular arrhythmia.

association between parameters of interest and the primary endpoint. Receiver operating characteristic (ROC) analyses were conducted to assess the performance of parameters of interest in predicting the primary endpoint, with the Youden index used to determine optimal cutoff values. Pearson correlation coefficients were used to assess associations between continuous variables of interest. $P < .05$ was considered significant. Analyses were performed using Stata software Version 16.1 (StataCorp, College Station, TX).

Results
Baseline characteristics, LGE-CMR findings, and VA events
The study cohort consisted of 47 patients with ICM. Baseline characteristics are detailed in Table 1. Mean patient age was 61.4 ± 11.9 years, and the majority of patients (83%) were male. The four patients (8.5%) taking antiarrhythmic drugs had additional history of atrial arrhythmias. The average CMR-derived LVEF was 27.7% ± 7.3%. Mean LV end-diastolic volume and LV end-systolic volume were 234.4 ± 73.4 cc and 171.3 ± 62.1 cc, respectively. Patients with VA events were younger and presented with larger LV

end-diastolic volume and LV end-systolic volume. Gray zone mass on LGE-CMR was greater in patients with VA events. After mean follow-up of 5.6 ± 3.4 years for the cohort, 13 patients (27.7%) experienced VA events, with mean time to event of 2.7 ± 2.5 years. The subgroup of patients with VAs (n = 13) all received ICD shocks for VT. There were 2 patients who also received ICD shocks for ventricular fibrillation, and 2 patients additionally had sudden arrhythmic death. None of the patients in the subgroup without VAs (n = 34) received antitachycardia pacing or had VT below ICD detection.

LV tissue heterogeneity on CE-CT
Mean time from myocardial infarction to CE-CT acquisition was 7.5 ± 8.8 years. Mean global LV tissue heterogeneity on CE-CT for the cohort was 25.3 ± 7.5 HU/mm and was significantly greater in patients with VA events vs those without VA events (29.9 ± 9.6 vs 23.6 ± 5.8, respectively; $P = .041$) (Table 1). Mean wall thickness for the cohort, measured using CE-CT, was 7.4 ± 1.6 mm. Figure 1 shows examples of tissue heterogeneity in patients with and those without VA events.

Table 2 Risk factors for VA events in univariable and multivariable logistic regression analyses

Univariable models	OR	95% CI	*P* value
Parameter			
LV tissue heterogeneity (per HU/mm)	1.12	1.02–1.23	**.015**
Intramyocardial fat mass (per gram)	1.00	0.92–1.08	.989
Gray zone (per gram)	1.15	1.05–1.27	**.003**
Core scar (per gram)	1.03	0.99–1.08	.132
Multivariable models	**OR***	**95% CI**	***P* value**
Parameter (continuous)			
LV tissue heterogeneity (per HU/mm)	1.22	1.03–1.44	**.019**
Gray zone (per gram)	1.09	0.96–1.25	.185
Parameter (categorical)			
LV tissue heterogeneity (HU/mm) (≥median vs <median)	13.13	1.32–130.82	**.028**
Gray zone (g) (≥median vs <median)	1.26	0.11–13.83	.851

The bolded *P*-values represent statistically significant differences.

CI = confidence interval; HU = Hounsfield unit; LV = left ventricle; OR = odds ratio; VA = ventricular arrhythmia.

*Adjusted for age, sex, left ventricular end-systolic volume (LVESV), and wall thickness. Because left ventricular end-diastolic volume and LVESV were collinear, the variable with the stronger association, LVESV, was selected. We also performed sensitivity analyses for left ventricular ejection fraction, antiarrhythmic drugs, and cardiac resynchronization therapy use and found no significant difference in results.

In univariable analysis, increasing tissue heterogeneity on CE-CT was significantly associated with VAs (per HU/mm; OR 1.12; *P* = .015) (Table 2). Furthermore, in univariable analysis, gray zone on LGE-CMR had a significant association with VAs (per gram; OR 1.15; *P* = .003), whereas core scar was not associated with VAs (per gram; OR 1.03; *P* = .132).

Multivariable analysis confirmed the association of increasing tissue heterogeneity with VAs, including after adjustment for gray zone (per HU/mm; OR 1.22; *P* = .019) (Table 2). Consistently, patients with tissue heterogeneity values greater than or equal to the median (≥22.2 HU/mm) had >13-fold significantly increased risk of VA events, relative to patients with values lower than the median, including after adjustment for gray zone (Table 2).

ROC analyses, conducted to provide further perspective on our data, showed that the area under the curve (AUC) for gray zone alone was 0.815, with the AUC increasing to 0.876 when the combination of tissue heterogeneity and gray zone was assessed. The optimal cutpoint for tissue heterogeneity in our sample, based on the Youden index, was identified as 31.8 HU/mm, which correctly classified patients with VA events in 80.9% of cases, with sensitivity of 53.9% and specificity of 91.2%.

Furthermore, we examined histopathologic correlates of CE-CT–derived tissue heterogeneity in 2 patients with available histopathology following LV assist device placement. Apical core histopathology was correlated with the apical segment of the corresponding CE-CT. Relative to areas of low tissue heterogeneity on CE-CT, regions with high tissue heterogeneity on CE-CT corresponded with greater degrees of intramyocardial fat and fibrosis intermixed with normal myocardium (Figure 2).

LV intramyocardial fat mass on CE-CT

Mean total LV intramyocardial fat mass on CE-CT for the cohort was 7.3 ± 8.2 g, similar in patients with VA events vs those without VA events (7.3 ± 8.7 g vs 7.3 ± 8.1 g, respectively; *P* = .990) (Table 1). Increasing intramyocardial fat mass was found not to be associated with VAs (per gram; OR 1.00; *P* = .989) (Table 2).

Discussion

To our knowledge, the present proof-of-concept study is the first to demonstrate that CE-CT–derived global LV tissue heterogeneity is independently associated with VAs in patients with ICM, LV systolic dysfunction, and no history of VAs. CE-CT–derived LV tissue heterogeneity may represent a novel marker useful for risk stratification in ICM patients.

Previous work has focused on LGE-CMR–derived gray zones, which represent areas of transition from normal myocardium to scar and predict VAs in patients with ICM.[1–6] The delayed enhanced sequence on LGE-CMR is specifically aimed at identifying fibrosis and is less ideal for delineating intramyocardial fat. However, CE-CT, which provides higher spatial resolution with shorter imaging time, has the potential to delineate a broader range of arrhythmogenic tissue substrate, particularly intramyocardial fat, but is not optimal for providing detailed information regarding fibrosis. Thus, a more extensive range of HU on CE-CT may be a prognostically important marker of myocardial tissue heterogeneity, with CE-CT–derived tissue heterogeneity representing a measure distinct from LGE-CMR–derived gray zone.

However, few studies have described tissue heterogeneity based on CE-CT. One such study examined the association between RV tissue heterogeneity on CE-CT and abnormal electrograms in ARVC.[7] The authors found that regions of greater RV tissue heterogeneity on CE-CT identified late potentials on electroanatomic mapping. Hence, these results suggest that tissue heterogeneity on CE-CT may represent disorganized admixtures of diseased
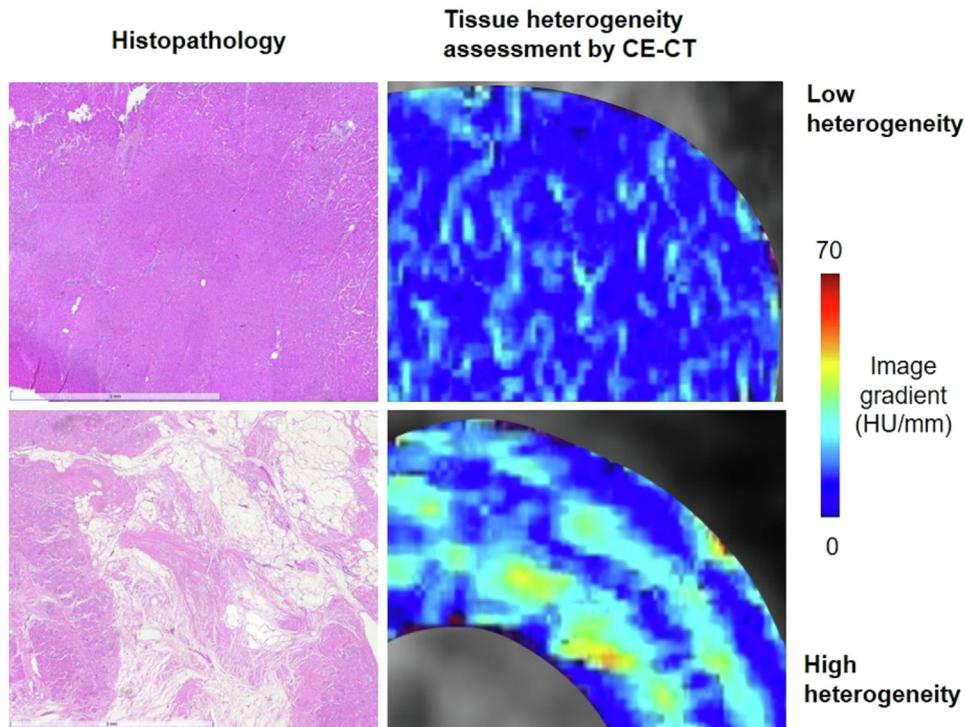
Figure 2 Histopathology corresponding to LV tissue heterogeneity assessment by contrast-enhanced computed tomography (CE-CT). **Top panels:** A mild degree of intramyocardial fat and fibrosis infiltrating normal myocardium corresponds with low tissue heterogeneity on CE-CT. **Bottom panels:** The presence of marked intramyocardial fat and fibrosis infiltrating normal myocardium corresponds with high tissue heterogeneity on CE-CT. HU = Hounsfield unit.

and non-diseased myocardium that give rise to abnormal conduction propagation.

The present study is the first to investigate the feasibility of CE-CT–derived global LV tissue heterogeneity in predicting arrhythmic outcomes in ICM patients. Our proof-of-concept study reveals a significant association between tissue heterogeneity identified on CE-CT and the clinical outcome of VAs, demonstrating a marked >13-fold increased risk of VAs in patients with increased tissue heterogeneity, independent of gray zone identified on LGE-CMR. ROC analyses, performed to provide further perspective on our data, suggest that the combination of tissue heterogeneity and gray zone improves prediction of VAs relative to gray zone alone, reflecting the differing information provided by CE-CT and LGE-CMR. Taken together, our findings indicate that tissue heterogeneity has the potential to provide additional prognostic information and predictive value when used in conjunction with gray zone. Furthermore, in contrast to a previous investigation of RV tissue heterogeneity on CT that was unable to discern the RV endocardial border, the present study included detailed contouring of both endocardial and epicardial surfaces of the LV.[7] Our study is also the first to provide information regarding histopathologic correlates of CE-CT–derived tissue heterogeneity in ICM patients, providing evidence that, in the context of the postinfarct substrate, tissue heterogeneity represents an admixture of fat, fibrosis, and healthy tissue.

Infiltrating adipose tissue has previously been identified in chronic infarcts.[8–11] A small number of studies examining the relationship between intramyocardial fat and VAs in ICM patients have specifically relied on cohorts receiving catheter ablation for the treatment of VT. These studies have shown that, in ICM patients undergoing VT ablation, fat deposition was associated with critical VT circuit sites.[12] Furthermore, a whole-heart computational study that investigated the arrhythmogenic propensity of patient-specific intramyocardial fat distributions demonstrated how fat-based substrate could harbor VT circuits in ICM patients undergoing VT ablation.[13] The amount of infiltrating fat was also a predictor of VT recurrence after VT ablation in ICM patients.[14] Unlike these studies, our cohort consists of ICM patients with LV systolic dysfunction without any previous VT and thus is more representative of a broader ICM population at high risk for VAs. Our results show a lack of association between total intramyocardial fat mass and arrhythmic outcomes. Additionally, because the development of intramyocardial fat is progressive in ICM, longer follow-up may be required to elucidate fully the relationship between intramyocardial fat and VAs in our population, which had no previous VAs.[8–11]

Importantly, our results highlight that, although total intramyocardial fat mass or infarct size (core scar) may not be associated with new VAs, the admixture of fat and fibrosis within healthy tissue, as represented by global tissue heterogeneity on CE-CT, is more clinically relevant for

outcomes in a cohort of ICM patients with LV systolic dysfunction and no previous VAs. This finding suggests that it is the heterogeneous distribution of the substrate that confers arrhythmogenicity, not necessarily the amount of remodeled tissue. Previous studies have shown that spatial complexity in regions of diseased myocardium is independently associated with VA events.[17] Importantly, because CE-CT is a more widely available imaging modality, the presence of high tissue heterogeneity on CE-CT may have clinical utility in identifying high-risk groups.

Although device programming parameters evolved over the course of the study due to changes in clinical practice, we only observed a slight decline over time in appropriate ICD therapies, as previously reported.[15] Antitachycardia pacing therapy rates are most influenced by ICD programming parameters and may not reflect sustained VA.[18] Thus we focused on clinically relevant, life-threatening arrhythmias terminated by an ICD shock that is associated with the highest mortality, consistent with previous analyses.[17]

Study limitations

This is a retrospective analysis; however, outcomes were collected in a prospective fashion. Because the prospective observational registry (Left Ventricular Structural Predictors of Sudden Cardiac Death [ClinicalTrials.gov Identifier NCT01076660]) enrolled patients with clinical criteria for primary prevention ICDs, based on LVEF ≤35% and no history of sustained VAs, we were unable to study patients with LVEF >35%. Artifacts and poor signal-to-noise ratios are inherent limitations of CE-CTs, and our thresholding approach and careful segmentations, as detailed, minimized the impact of artifacts and noise, consistent with previous methodology.[12,13] Detailed analysis of scar architecture was not possible with our CE-CTs; however, we incorporated wall thickness measurements into our analysis.

Our objective was to assess whether CE-CT–derived tissue heterogeneity is associated with VA events, independent of the established parameter of LGE-CMR–derived gray zone, and whether the combination of LV tissue heterogeneity and gray zone provides additional prognostic information relative to gray zone alone. However, we acknowledge that newer indices derived from cardiac magnetic resonance imaging have recently been reported.[19] Our study consists of a relatively small number of patients, and larger prospective studies are needed to assess the role of CE-CT for risk stratification in ICM patients. Histopathology was not available for all patients; nevertheless, available samples provide insight into what LV tissue heterogeneity on CE-CT represents at the histopathologic level.

Conclusion

CE-CT–derived global LV tissue heterogeneity is an independent predictor of VAs in ICM patients with LV systolic dysfunction and no history of VAs. Thus, CE-CT–derived tissue heterogeneity may represent a novel marker useful for risk stratification in ICM patients.

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