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ORIGINAL PAPER

Myocardial disarray and fibrosis across hypertrophic cardiomyopathy stages associate with ECG markers of arrhythmic risk

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Aims

Myocardial disarray, an early feature of hypertrophic cardiomyopathy (HCM) and a substrate for ventricular arrhythmia, is poorly characterized in pre-hypertrophic sarcomeric variant carriers (SARC+LVH−). Using diffusion tensor cardiac magnetic resonance (DT-CMR) we assessed myocardial disarray and fibrosis in both SARC+LVH− and HCM patients and evaluated the relationship between microstructural alterations and electrocardiographic (ECG) parameters associated with arrhythmic risk.

Methods and results

Sixty-two individuals (24 SARC+LVH−, 24 HCM, and 14 matched controls) were evaluated with multi-parametric CMR including stimulated echo acquisition mode DT-CMR, and blinded quantitative 12-lead ECG analysis. Mean diastolic fractional anisotropy (FA) was reduced in HCM compared with SARC+LVH− and controls (0.49 ± 0.05 vs. 0.52 ± 0.04 vs. 0.53 ± 0.04, $P = 0.009$), even after adjustment for differences in extracellular volume (ECV) ($P = 0.038$). Both HCM and SARC+LVH− had segments with significantly reduced diastolic FA relative to controls (54 vs. 25 vs. 0%, $P = 0.002$). Multiple repolarization parameters were prolonged in HCM and SARC+LVH−, with corrected JT interval (JTc) being most significant (354 ± 42 vs. 356 ± 26 vs. 314 ± 26 ms, $P = 0.002$). Among SARC+LVH−, JTc duration correlated negatively with mean diastolic FA ($r = -0.6$, $P = 0.002$). In HCM, the JTc interval showed a stronger association with ECV ($r = 0.6$ $P = 0.019$) than with mean diastolic FA ($r = -0.1$ $P = 0.72$). JTc discriminated SARC+LVH− from controls [area under the receiver operator curve 0.88, confidence interval 0.76–1.00, $P < 0.001$], and in HCM correlated with the European Society of Cardiology HCM sudden cardiac death risk score ($r = 0.5$, $P = 0.014$).

Conclusion

Low diastolic FA, suggestive of myocardial disarray, is present in both SARC+LVH− and HCM. Low FA and raised ECV were associated with repolarization prolongation. Myocardial disarray assessment using DT-CMR and repolarization parameters such as the JTc interval demonstrate significant potential as markers of disease activity in HCM.

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Structured Graphical Abstract

Key Question

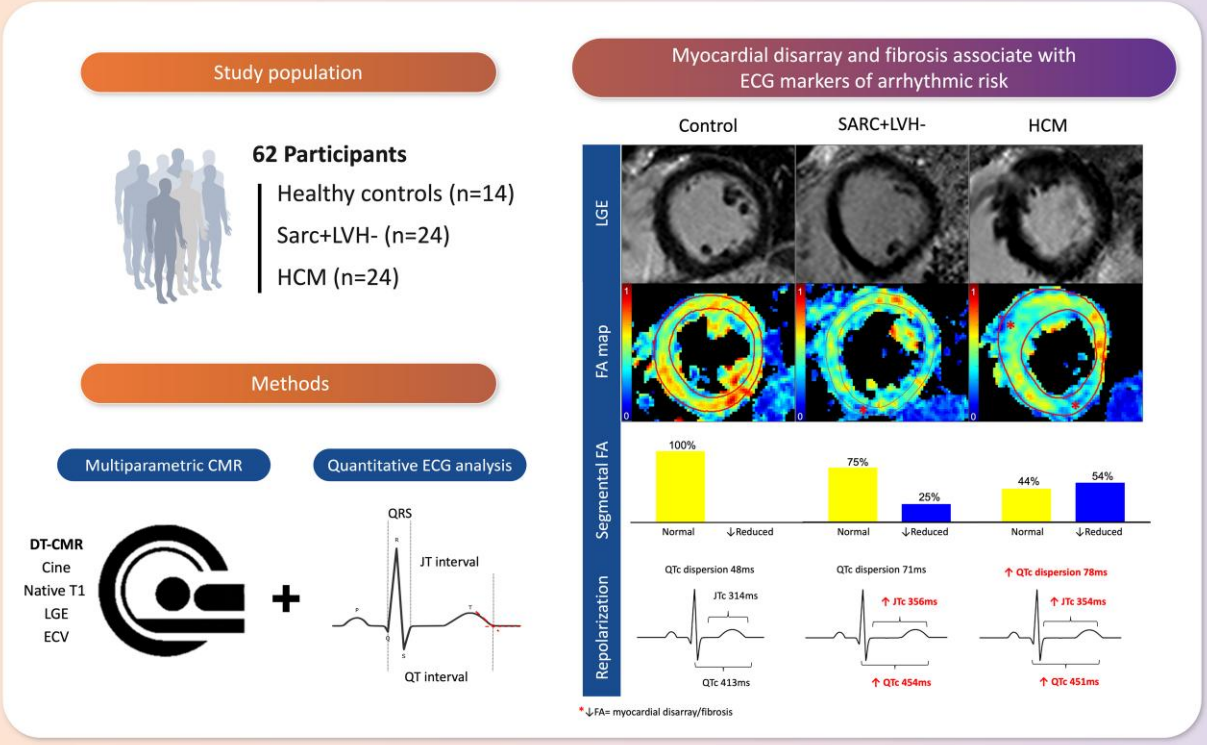
Is DT-CMR sensitive to microstructural abnormalities in pre-hypertrophic sarcomeric variant carriers (SARC+LVH-) as well as hypertrophic cardiomyopathy (HCM) patients, and is there an association with 12-lead ECG markers of arrhythmic risk?

Key Finding

Low diastolic FA, suggestive of myocardial disarray, is present in both SARC+LVH- and HCM patients. Low FA in SARC+LVH- and raised ECV in HCM patients were associated with repolarization abnormalities (JTc and QTc interval prolongation).

Take-home Message

DT-CMR and quantitative ECG analysis demonstrate significant potential as novel, sensitive and prognostically important markers of disease activity across HCM stages.



Keywords hypertrophic cardiomyopathy • sarcomere • cardiac magnetic resonance imaging • arrhythmia • sudden cardiac death • repolarization • ECG

Introduction

Myocardial disarray, a hallmark feature of hypertrophic cardiomyopathy (HCM) is an important substrate for ventricular arrhythmia. It is known that myocardial disarray can develop before the onset of hypertrophy in patients,[1,2] with emerging evidence indicating its presence even in pre-natal animal models.[3] Despite this, myocardial disarray remains poorly characterized in pre-hypertrophic sarcomeric variant carriers (SARC+LVH–), and the mechanisms by which it predisposes to ventricular arrhythmia are yet to be fully elucidated.

Several studies have explored the electrophysiological disruption caused by myocardial disarray, specifically with regards to myocardial conduction and action potential propagation.[4–6] Changes in fibre orientation and gap junction distribution are thought to lead to regional variations in conduction velocity and alterations in conduction pathways. These alterations in turn lead to myocardial repolarization heterogeneity, thereby facilitating an environment vulnerable to re-entrant arrhythmia.

Diffusion tensor cardiac magnetic resonance (DT-CMR) imaging has now made it possible to non-invasively estimate the burden of myocardial disarray. By tracking the directionality and magnitude of water

diffusion through myocardial tissue, DT-CMR enables voxel-wise assessment of myocardial microstructure. Two key DT-CMR parameters; fractional anisotropy (FA) and mean diffusivity (MD) are sensitive to microstructural alterations caused by myocardial disarray and fibrosis.[7–9] FA is a scalar value of the directionality in diffusion of water molecules (with 1 representing perfect alignment or 'isotropy', and 0 complete disorganisation or 'anisotropy'), and MD measures the magnitude of water diffusion (which increases with greater disruption of myocardial architecture). In recent years, our group and others have demonstrated that HCM patients exhibit reduced FA, even after adjustment for fibrosis and indicative of myocardial disarray.[7,10,11] We also showed that low FA independently associated with ventricular arrhythmia, suggesting a possible link between the extent of myocardial disarray and arrhythmic events.

Although DT-CMR is promising, its current status remains within the research domain, with limited clinical applicability. This is partly due to the need for complex hardware, software and expertise to interpret the data. In contrast, surface 12-lead electrocardiography (ECG) is a well-established and universally adopted clinical and diagnostic screening tool used in the management of both SARC+LVH− and overt HCM patients. Abnormalities in repolarization on ECG have long been associated with ventricular arrhythmia and sudden cardiac death (SCD) in HCM,[12–16] and as with myocardial disarray, have been shown to precede hypertrophy.[17,18] We hypothesize that myocardial disarray may influence repolarization parameter duration and heterogeneity on 12-lead ECG, including in SARC+LVH− patients. Establishing a relationship between myocardial disarray burden and ECG alterations could be of significant clinical value and provide mechanistic insight into the role of microstructural changes in HCM in arrhythmogenesis.

In this study, we aimed to characterize the extent of myocardial disarray in SARC+LVH− and HCM patients relative to healthy controls using DT-CMR. We additionally probed the relationship between myocardial disarray burden and ventricular repolarization using quantitative ECG analysis.

Methods

Study population

Twenty-four pre-hypertrophic (pathogenic or likely pathogenic) sarcomeric variant carriers (SARC+LVH−), 24 patients with HCM, and 14 age and gender-matched controls were included this study. SARC+LVH− and HCM patients were recruited from the inherited cardiac conditions service at the John Radcliffe Hospital, Oxford, UK. All SARC+LVH− and HCM patients underwent genetic testing to establish presence/absence of pathogenic and likely pathogenic sarcomeric variants (Sarc+ status) by the Oxford Medical Genetics Laboratory. Patients who tested positive for variants in genes associated with HCM phenocopies, e.g. TTR (amyloidosis) or GLA (Fabry disease) were excluded, as were cases with variants of uncertain significance. SARC+LVH− patients and healthy controls had confirmed left ventricular (LV) wall thickness < 13 mm, and HCM patients ≥ 15 mm (or ≥ 13 mm in case of positive family history/genetic test) on CMR. HCM patients with significant resting outflow tract obstruction (LV outflow tract gradient ≥ 50 mm Hg based on echocardiographic assessment) were excluded. Any participants who had past medical history of significant cardiac disease including severe hypertension (HTN), moderate/severe valvular dysfunction or ischaemic heart disease, and those with contraindications to CMR scanning were also excluded. The study was approved by the National Research Ethics Committee (REC ref 12/LO/1979). All participants provided written informed consent.

CMR protocol

CMR scans were performed using a 3T Siemens Trio scanner (Siemens Healthineers, Erlangen, Germany). The standard protocol included cine imaging, DT-CMR, pre- and post-contrast T1 mapping using a Shortened Modified Look-Locker Inversion recovery (ShMOLLI) sequence,[19] and late gadolinium enhancement (LGE) imaging.

DT-CMR was performed using a previously described stimulated echo acquisition mode (STEAM) sequence[7] to obtain a single mid-ventricular short axis slice at the diastolic pause. The same mid-ventricular slice position was used during pre- and post-contrast T1 acquisitions to obtain native T1 and extracellular volume (ECV) mapping.

CMR analysis

LV volumetric, functional, and fibrosis analysis was performed using cvi42 (Circle Cardiovascular Imaging, Calgary, Canada). Focal fibrosis was estimated from the extent of enhanced myocardial pixels (defined as signal intensity > 5 standard deviations (SDs) above a normal reference region of interest[20]). Significant LGE burden was defined as > 15% of LV mass based on increased risk of adverse clinical events.[20,21] DT-CMR data underwent rigorous quality control by two experienced observers (EMT, RA). No case required repeat MRI acquisition. DT-CMR post-processing was performed using a custom-built in-house software developed using MATLAB (MathWorks, MA, USA)[7] to obtain mean slice and segmental diastolic FA, mean slice and segmental MD, as well as helix angle gradient (HA, a measure of the helical arrangement of cardiomyocytes) and absolute diastolic sheetlet normal angles (SA, a measure of myocardial sheetlet orientation). Strain correction was not attempted due to the questionable validity of assuming that microscopic myocyte strain is accurately represented by macroscopic myocardial strain.[22] Previous work has shown that MD is strain-dependent, but that diastolic FA appears largely unaffected by strain.[23] All segmental analysis was performed using the standard American Heart Association (AHA) 16-segment model.

ECG analysis

Participants underwent standard 12-lead resting digital ECG using the CARDIOVIT FT-1 Schiller ECG system (Baar, Switzerland). Standard measurements of ECG axes, amplitudes and intervals were obtained for all leads from the ECG reports. Two independent ECG analysts (AHAS and MA), both senior physicians who were blinded to clinical data, interpreted the ECG according to the Minnesota Code of Electrocardiographic findings.[15] Specific ECG intervals were manually analysed using Adobe Acrobat Pro DC (version 2022.001.20085). Each digitized ECG was magnified to 400% for optimum resolution. Parameters measured included: the QT interval duration (ventricular depolarization and repolarization), QT dispersion (repolarization homogeneity), QTP (ventricular depolarization and repolarization), QTP dispersion (repolarization homogeneity), and JT interval duration (ventricular repolarization). The terminal end of the T wave was determined using the tangent method, defined as the intersection between the isoelectric line and the line drawn along the steepest angle of the descending arm of the T wave.[16] This technique has previously been used by our group to study associations between quantitative ECG parameters and multi-parametric CMR data.[24] Heart rate-corrected intervals were generated using the Bazett's formula [Corrected QT interval (QTc) = $QT/\sqrt{R-R}$ interval in second]. The inter-rater correlation coefficient between the two observers for corrected QT (QTc) and JT interval (JTc) were 0.88 and 0.86, respectively.

Statistical analysis

Statistical analyses were performed using SPSS Version 27.0 (IBM, Armonk, NY, USA). Normality was determined using the Kolmogorov–Smirnov test. Parametric continuous variables were presented as mean ± standard deviation (SD), and non-parametric variables as median with inter-quartile range (IQR). Categorical data were described using frequency and percentages. Difference between cohorts was assessed using either the independent Student's *t*-test or Mann–Whitney *U* test and Kruskal–Wallis test or ANOVA (with *post hoc* Bonferroni correction) as appropriate.

Associations between categorical variables were determined using the χ^2 test for independence or the Fischer's exact test. Correlation between continuous variables were analysed using Pearson's correlation coefficient (r) for parametric data and Spearman's rank correlation coefficient (rho) for non-parametric data. Linear regression using analysis of covariance (ANCOVA) with Bonferroni correction for multiple comparisons was performed to account for potential confounders. Associations between continuous variables derived from regression models were expressed as standardized β coefficients. Statistical significance was set at $P < 0.05$.

Results

Study population baseline characteristics

Demographic and clinical data are shown in Table 1. All three groups had comparable gender proportions, mean age, body mass index (BMI), and resting heart rate. The majority of HCM patients (79%) were on either beta blockers or (non-dihydropyridine) calcium channel blockers, with four patients also on concurrent low dose disopyramide. Two-thirds (18/24) of HCM patients possessed pathogenic sarcomeric variants (SARC+HCM). HCM patients had greater LV maximum wall thickness (MWT) compared with SARC+LVH− and controls, as well as greater LV ejection fraction, greater LV mass index and left atrial diameter. Pathological LGE was only present in HCM patients, where it was visually apparent in 41% of cases, however only a fraction (13%) had significant LGE burden (≥ 15% of LV mass). Native T1 was raised in HCM and SARC+LVH− patients compared with controls (1208 ± 35 vs. 1196 ± 22 vs. 1175 ± 17 ms, respectively, $P = 0.003$). ECV was also raised in HCM relative to SARC+LVH− patients and controls (30 ± 3 vs. 28 ± 2 vs. 27 ± 2%, $P = 0.039$). HCM patients with pathogenic or likely pathogenic variants (SARC+HCM) had lower LVEF and greater LGE burden than the SARC-HCM sub-group (see Supplementary data online, *Table S1*). In both SARC+HCM and SARC+LVH− patients approximately two-thirds of likely pathogenic/pathogenic variants were in the MYBPC3 gene, with the remainder involving MYH7, apart from a single Troponin I case in the SARC+HCM group.

DT-CMR parameters in SARC+LVH−, HCM, and control subjects

Mean diastolic FA was lower in HCM patients compared with both SARC+LVH− patients and healthy controls [0.49 ± 0.05 vs. 0.52 ± 0.04 vs. 0.53 ± 0.04, $P = 0.009$ (Table 1 and *Figure 1A*)], including after adjustment for ECV ($P = 0.038$). Even in patients where visible replacement fibrosis was absent (i.e. no LGE) in the myocardium, HCM patients exhibited lower mean diastolic FA relative to SARC+LVH− and healthy controls (see Supplementary data online, *Figure S1*). At a segmental level, 6/24 (25%) SARC+LVH− patients had segments with significantly reduced FA (defined as < 2 SD below control mean). A higher proportion of overt HCM 13/24 (54%) patients had abnormal

Table 1 Baseline demographic and clinical parameters

	Controls (14)	SARC+LVH (24)	HCM (24)	Sarc+LVH− vs. controls *P*-value	HCM vs. controls *P*-value	3-way comparison *P*-value
Demographics						
Male *n* (%)	11 (79)	13 (54)	18 (75)	0.132	0.803	0.187
Age	32 ± 8	32 ± 9	36 ± 11	0.859	0.234	0.322
BMI	23 ± 3	24 ± 4	26 ± 4	0.288	0.013	0.050
Hazard ratio (HR)	61 ± 13	63 ± 7	60 ± 10	0.454	0.386	0.463
HTN *n* (%)	0	0	4 (17%)		0.033	
Anti-arrhythmic therapy	0	3 (13)	19 (79)	0.283	< 0.001	< 0.001
ESC SCD risk score			3.3 ± 1.9%			
CMR findings						
LV MWT (mm)	11 ± 1	10 ± 1	22 ± 5	0.145	< 0.001	< 0.001
LV EDVI (mL/m^2)	90 ± 17	83 ± 15	81 ± 9	0.216	0.046	0.157
LV EF (%)	66 ± 6	67 ± 6	76 ± 5	0.776	< 0.001	< 0.001
LV mass index (g/m^2)	56 ± 13	51 ± 13	73 ± 20	0.289	0.010	< 0.001
LA diameter (mm)	31 ± 7	32 ± 6	37 ± 6	0.805	0.002	< 0.001
LGE present *n* (%)			10 (41)			
LGE > 15% of LV mass *n* (%)			3 (13)			
Native T1 (ms)	1175 ± 17	1197 ± 22	1208 ± 35	0.052	0.002	0.003
ECV (%)	27 ± 2	28 ± 2	30 ± 3	0.076	0.014	0.039
Mean diastolic FA	0.53 ± 0.04	0.52 ± 0.04	0.49 ± 0.05	0.535	0.009	0.009
Low segmental FA *n* (%)	0	6 (25)	13 (54)	0.041	< 0.001	0.002
Mean MD (× 10^{-3} mm^2/s)	1.20 ± 0.08	1.28 ± 0.08	1.30 ± 0.10	0.006	0.005	0.007
SA (°)	69 ± 7	59 ± 14	47 ± 10	0.031	< 0.001	< 0.001
HA (°/mm)	8 ± 2	7 ± 3	7 ± 1	0.061	0.076	0.087

Values are mean ± SD or *n* (%).
EDVI, end diastolic volume index; EF, ejection fraction; LA, left atrial; LVOT, left ventricular outflow tract.

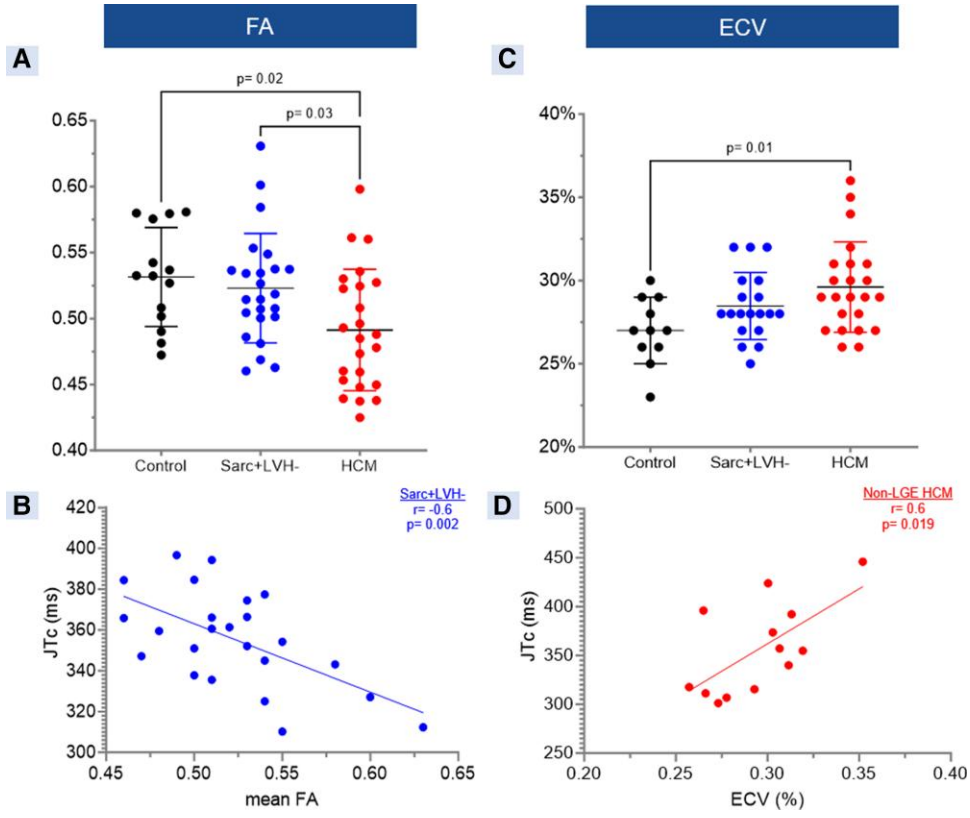


Figure 1 Mean diastolic FA and ECV correlation with JTc interval in SARC+LVH– and HCM. (*A*) Mean diastolic FA across groups. (*B*) Correlation between mean diastolic FA and JTc duration in pre-hypertrophic variant carriers. (*C*) Mean ECV across groups. (*D*) Correlation between mean ECV and JTc duration in HCM patients. ECV, extracellular volume; FA, fractional anisotropy; JTc, J point → T wave tangential line, corrected for heart rate; HCM, hypertrophic cardiomyopathy; SARC+LVH, pre-hypertrophic sarcomeric variant carriers.

segmental FA (*Figure 2*), both in patients with and without LGE (80 and 36%, respectively). There was no specific pattern in the location of low FA segments within the SARC+LVH– cohort, but in the overt HCM group abnormal segments were concentrated in the anteroseptum.

In SARC+LVH–, low segmental FA was not accompanied by raised segmental ECV in most cases (5/6 cases). In the HCM cohort, 5/13 (38%) of low FA segments did not have significantly raised ECV. There was no significant difference in mean or segmental FA in HCM patients according to sarcomeric status (see Supplementary data online, *Table S1*).

Mean MD was raised in both HCM patients (including those without LGE) and SARC+LVH– relative to healthy controls (1.30 ± 0.1 vs. 1.28 ± 0.08 vs. 1.20 ± 0.08, $P = 0.007$; Table 1. Given that impaired myocardial strain is associated with lower MD on STEAM DT-CMR,[23] we evaluated if diastolic myocardial strain was also abnormal in SARC+LVH– and HCM patients. Only HCM patients, but not SARC+LVH–, had impaired global longitudinal and circumferential diastolic strain (see Supplementary data online, *Table S2*). Despite adjusting for diastolic strain, MD was still raised in HCM patients relative to controls ($P = 0.02$).

In terms of secondary DT-CMR parameters, we noted an increase in diastolic absolute SA between HCM and controls (circular mean $47 \pm 10°$ vs. $59 \pm 14°$ vs. $69 \pm 7°$, $P < 0.001$) indicating more radially orientated sheetlet populations in the HCM patients, compared with both SARC+LVH– and controls. There was no significant difference in HA between groups. Mean diastolic FA correlated with LV wall thickness ($r = -0.352$, $P = 0.005$), LV mass ($r = -0.381$, $P = 0.002$) and LGE mass ($r = -0.497$, $P < 0.001$).

ECG parameters in SARC+LVH–, HCM, and control subjects

ECG characteristics are depicted in Table 2. PR interval and ventricular depolarization (QRS) durations were comparable between groups. In contrast, a significant higher frequency of qualitative ST/T wave abnormalities and prolongation of most repolarization parameters were observed in SARC+LVH– and overt HCM patients relative to healthy controls. In terms of quantitative parameters, QTc, QTPc, and JTc durations were prolonged in both SARC+LVH– and HCM cases relative to healthy controls, as was QTc dispersion, which was significantly longer in HCM patients compared with controls. The prolongation of these parameters was evident in SARC+LVH– and HCM patients even in the absence of regular anti-arrhythmic or QT prolonging medication use (see Supplementary data online, *Table S3*). There was no significant sex difference in any of the repolarization parameters within this cohort, and an increase in repolarization parameter durations was also observed in SARC+LVH– and HCM patients relative to healthy controls when sexes were analysed separately (see Supplementary data online, *Tables S4 and S5*). *Figure 3* shows scatter plots displaying differences in QTc interval, QTc dispersion, and JTc interval across the three groups.

Within the HCM group, patients with pathogenic sarcomeric variants tended to have longer repolarization parameters than those without. As a result, a more pronounced stepwise prolongation of repolarization parameters was evident between healthy controls, SARC+LVH– and SARC+HCM patients (Table 3). The clearest increase

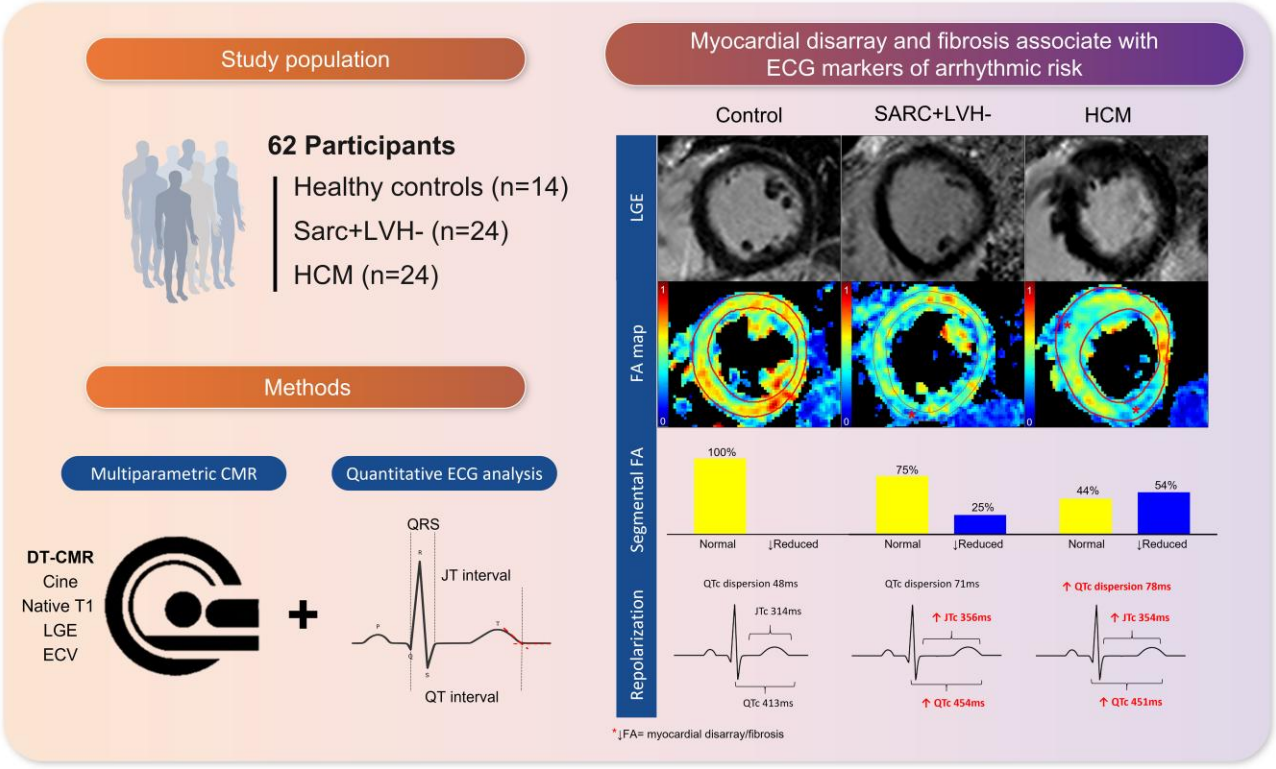


Figure 2 Microstructural abnormalities detected using DT-CMR in both SARC+LVH– and overt HCM are associated with prolongation of repolarization parameters linked to arrhythmic risk (main illustration). DT-CMR, diffusion tensor cardiac magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; SARC+LVH–, pre-hypertrophic sarcomeric variant carriers.

Table 2 ECG analysis results

	Controls (14)	SARC+LVH– (24)	HCM (24)	SARC+LVH– vs. controls *P*-value	HCM vs. controls *P*-value	3-way comparison *P*-value
Qualitative ECG parameters						
Sinus rhythm	14 (100)	24 (100)	24 (100)			
Abnormal ECG	1 (2)	9 (38)	17 (63)	0.115	< 0.001	< 0.001
LVH voltage criteria	0	7 (29)	9 (38)	0.07	0.014	0.053
Pathological Q waves	0	3 (13)	5 (21)	0.536	0.088	0.220
LBBB/RBBB	0	1 (4)	2 (8)	0.99	0.303	0.541
ST/T wave abnormalities	1 (8)	5 (21)	16 (67)	0.640	< 0.001	< 0.001
Quantitative ECG parameters						
PR interval (ms)	155 ± 24	150 ± 17	165 ± 21	0.451	0.239	0.052
QRS duration (ms)	94 ± 8	91 ± 16	98 ± 13	0.652	0.328	0.258
QTc (ms)	413 ± 27	454 ± 29	451 ± 50	< 0.001	0.026	0.013
QTc dispersion (ms)	48 ± 20	71 ± 27	78 ± 41	0.017	0.027	0.033
QTPc (ms)	340 ± 24	373 ± 28	375 ± 46	0.002	0.021	0.021
QTPc dispersion (ms)	40 ± 16	66 ± 18	88 ± 81	< 0.001	0.064	0.057
JTc (ms)	314 ± 26	356 ± 26	354 ± 42	< 0.001	0.006	0.002
cTPe (ms)	89 ± 10	102 ± 15	105 ± 10	0.023	0.185	0.678

Values are mean ± SD or *n* (%).
cTPe, corrected T wave peak → T wave end; ECG, electrocardiogram; JTc, ventricular repolarization (J point → T wave tangential line); LBBB, left bundle branch abnormality PR, atrial depolarization (*P* wave → R wave); QTc, ventricular depolarization + repolarization (Q wave → T wave tangential line); QTPc, ventricular depolarization + repolarization (Q wave → T wave peak).

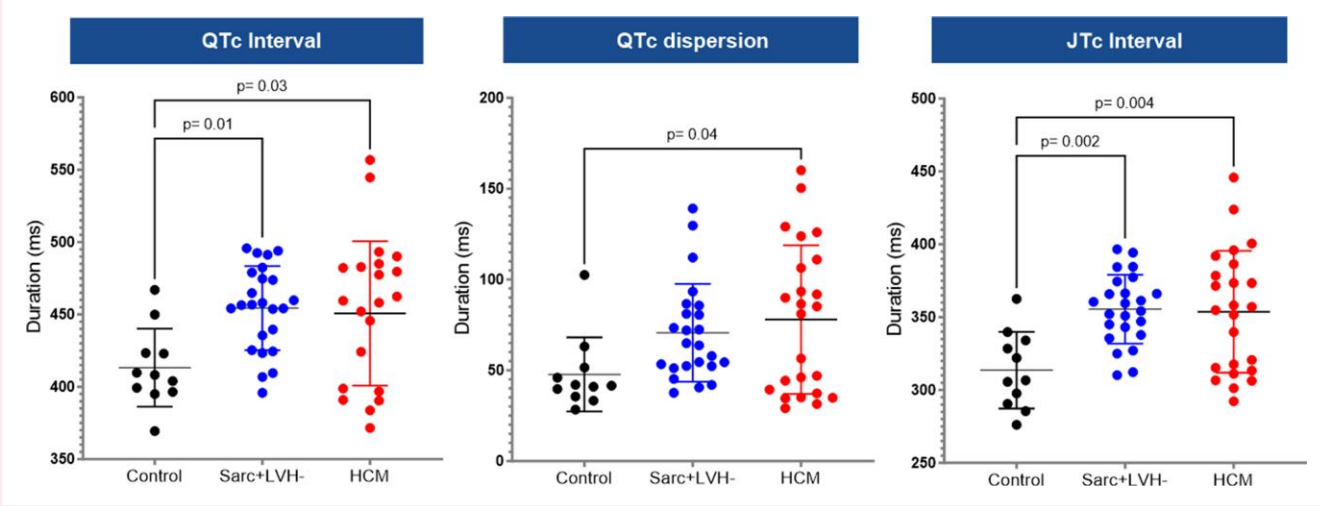


Figure 3 QTc interval, QTc dispersion, and JTc interval across groups. JTc, J point → T wave tangential line, corrected for heart rate; QTc, Q wave → T wave tangential line, corrected for heart rate.

and distinction from healthy individuals were seen with the JTc interval; this was significantly prolonged in both SARC+LVH− and overt HCM patients (354 ± 42 vs. 356 ± 26 vs. controls 314 ± 26 ms, $P = 0.002$). Both the QTc and JTc intervals showed significant correlation with the European Society of Cardiology (ESC) SCD risk score in HCM patients ($r = 0.418$, $P = 0.042$ and $r = 0.494$, $P = 0.014$, respectively). The JTc interval also demonstrated substantial diagnostic potential in discriminating SARC+LVH− from healthy controls with an area under the curve of 0.88 (95% confidence interval (CI) 0.76 – 1.00, $P <$ 0.001), with a JTc interval ≥ 342 ms delivering the highest combined sensitivity (75%) and specificity (91%) (*Figure 4*). A JTc interval ≥ 342 ms had a positive predictive value of 95% and a negative predictive value of 63% for discriminating variant carriers from controls.

Relationship between DT-CMR and repolarization parameters

In SARC+LVH− patients, there was a clear negative correlation between FA and the JTc interval ($r = -0.6$, $P = 0.002$) (*Figure 1B*) and to a lesser degree the QTc interval ($r = -0.5$, $P = 0.012$). This association was not as strong in HCM patients and absent in healthy controls (see Supplementary data online, *Figure S2*). MD did not show significant associations with any repolarization parameters in the SARC+LVH− group. In the HCM group, MD was associated with longer JTc and QTc intervals, and greater QTc dispersion, even after accounting for strain in the linear regression model (JTc $\beta = 0.407$, $P = 0.04$, QTc $\beta = 0.385$, $P = 0.036$, and QTc dispersion $\beta = 0.54$, $P = 0.03$).

Relationship between markers of fibrosis and repolarization parameters

The presence of replacement fibrosis on LGE imaging did not significantly affect the duration of repolarization parameters in HCM patients. In contrast, repolarization parameters, particularly the JTc and QTc intervals demonstrated a strong positive correlation with ECV (both $r = 0.6$, $P = 0.019$), an indicator of interstitial fibrosis which was elevated in HCM (*Figure 1D*). This was also the case for QTc dispersion ($r = 0.7$, $P = 0.01$) (see Supplementary data online, *Figure S3*). This relationship between repolarization parameters and ECV was not seen in SARC+LVH− patients.

Discussion

This study assessed the sensitivity of DT-CMR in detecting microstructural changes in SARC+LVH− and HCM patients and examined whether a standard 12-lead ECG can be used to detect the presence of microstructural abnormalities in early and late phases of disease. Our findings indicate that: (i) myocardial disarray, inferred from reduced FA on DT-CMR, is detectable in one in four SARC+LVH− patients as well as the majority of HCM patients, (ii) relative to controls, SARC+LVH− patients and overt HCM patients had a higher frequency of qualitative ECG abnormalities and more prolonged repolarization intervals (i.e. QTc and JTc intervals), and (iii) the JTc interval is associated with disarray and fibrosis as a continuum in pre-hypertrophic variant carriers and HCM patients and may serve as a promising marker for risk stratification in patients.

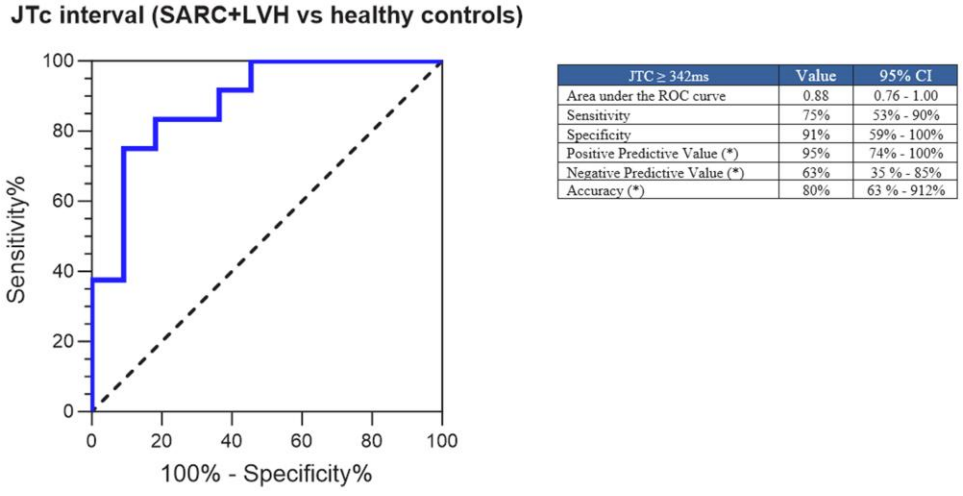
Myocardial disarray in SARC+LVH− patients

In our study, a substantial subset of SARC+LVH− patients (25%) exhibited low segmental FA compared with healthy individuals. Our analysis showed that SARC+LVH− patients exhibited higher mean MD in contrast to controls, a measure potentially suggestive of cellular hypertrophy and early interstitial expansion. In the absence of significant fibrosis in our SARC+LVH− patients, we have interpreted the reduced FA to primarily represent localized regions of myocardial disarray. These findings are in line with published histology from post-mortem studies which have shown the presence of disarray in SARC+LVH− patients[2] and demonstrated its patchy nature within the myocardium in HCM.[25] Previous work from our group has identified low FA as a marker of myocardial disarray in overt HCM, which also correlates independently with the risk of ventricular arrhythmias.[7] Complementing our findings, a recent study by Joy *et al.* employed a spin-echo DT-CMR sequence and similarly found reduced (systolic) FA in SARC+LVH− patients.[26] Other indicators of microstructural changes, such as diffuse fibrosis, have also been observed in this group; however, the evidence remains inconsistent. For example, Ho *et al.*[27] noted an increased ECV, indicative of diffuse fibrosis, in SARC+LVH− patients, whereas Joy's study and ours did not find significant ECV differences.

Table 3 ECG analysis results (incl. only SARC+HCM)

	Controls (14)	SARC+LVH− (24)	SARC+HCM (16)	SARC+LVH− vs. controls *P*-value	SARC+HCM vs. controls *P*-value	3-way comparison *P*-value
Qualitative ECG parameters						
Sinus rhythm	14 (100)	24 (100)	16 (100)			
Abnormal ECG	0	9 (38)	10 (63)	0.115	0.004	< 0.001
LVH voltage criteria	0	7 (29)	4 (25)	0.07	0.113	0.117
Pathological Q waves	0	3 (13)	4 (25)	0.536	0.113	0.156
LBBB/RBBB	0	1 (4)	1 (6)	0.99	0.99	0.692
ST/T wave abnormalities	1 (8)	5 (21)	10 (63)	0.640	0.006	0.003
Quantitative ECG parameters						
PR interval (ms)	155± 24	150 ± 17	167 ± 22	0.451	0.208	0.043
QRS duration (ms)	94 ± 8	91 ± 16	98 ± 14	0.652	0.400	0.382
QTc (ms)	411 ± 14	454 ± 29	458 ± 44	< 0.001	0.006	0.003
QTc dispersion (ms)	48 ± 20	71 ± 27	84 ± 43	0.017	0.017	0.021
QTPc (ms)	340 ± 24	373 ± 28	379 ± 42	0.002	0.009	0.007
QTPc dispersion (ms)	40 ± 16	66 ± 18	96 ± 94	< 0.001	0.064	0.040
JTc (ms)	314 ± 26	356 ± 26	360 ± 40	< 0.001	0.002	< 0.001
cTPe (ms)	89 ± 10	102 ± 15	119 ± 88	0.023	0.284	0.315

Values are mean ± SD or *n* (%).
cTPe, corrected T wave peak → T wave end; ECG, electrocardiogram; JTc, ventricular repolarization (J point → T wave tangential line); LBBB, left bundle branch abnormality PR, atrial depolarization (*P* wave → R wave); QTc, ventricular depolarization + repolarization (Q wave → T wave tangential line); QTPc, ventricular depolarization + repolarization (Q wave → T wave peak).



JTC ≥ 342ms	Value	95% CI
Area under the ROC curve	0.88	0.76 - 1.00
Sensitivity	75%	53% - 90%
Specificity	91%	59% - 100%
Positive Predictive Value (*)	95%	74% - 100%
Negative Predictive Value (*)	63%	35 % - 85%
Accuracy (*)	80%	63 % - 912%

Figure 4 Receiver operator characteristic curve—diagnostic ability of JTc interval in discriminating SARC+LVH− from healthy controls. JTc, J point → T wave tangential line, corrected for heart rate; SARC+LVH−, pre-hypertrophic sarcomeric variant carriers.

Discrepancies between these studies may stem from variations in patient selection, particularly regarding the stage of disease in cohorts. Nonetheless, our findings collectively imply that DT-CMR may detect disarray before diffuse fibrosis becomes apparent, underscoring its potential as an early marker for disease progression and clinical surveillance.

Myocardial repolarization abnormalities in SARC+LVH− and HCM patients

Using quantitative ECG analysis, we were able to show that repolarization is significantly delayed (evidenced by QTc and JTc interval prolongation) and more heterogeneous (indicated by increased QTc dispersion)

in SARC+LVH− patients in comparison to controls. Importantly, none of these patients were on medications that could prolong their QT interval. Within the array of ECG parameters, JTc exhibited the highest diagnostic performance in discriminating HCM patients from controls. We also demonstrate as expected, that prolongation and heterogeneity of repolarization is more pronounced in overt HCM cases, despite most of these patients being on anti-arrhythmic medications that serve to stabilize ventricular repolarization.

In this study, we show that manual measurements on 12-lead ECG can elucidate subtle delays in these repolarization parameters prior to the onset of hypertrophy in variant carriers and demonstrate repolarization prolongation with the evolution of the HCM phenotype. Although previous studies have described ECG changes including repolarization abnormalities in HCM, they tended to focus on those with established hypertrophy, and ECG analysis has been mostly qualitative in nature with only limited quantitative ECG analysis undertaken.[17,26,28,29] Those that did focus on repolarization intervals such as the QTc interval, QTc dispersion, and JTc interval in overt HCM found, similar to us, an association between prolongation of these parameters and SCD risk.[13,15,30–32] More recently, studies using advanced automated ECG analysis techniques have demonstrated prolongation of activation time (a measure of depolarization onset) and increased duration and dispersion of repolarization parameters in both overt HCM and SARC+LVH− patients.[33–36] However, caution is needed when making direct comparisons between studies due to differences in ECG analysis approaches (e.g. use of tangent method for estimation of QTc interval in our study), including the specific parameters measured, as well as variations in group characteristics, such as the mean age of HCM cohorts. For example, in another study by Joy *et al.*,[34] which included a larger cohort (211 patients), the QRS duration was shorter in the SARC+LVH− group compared with controls, while the QTc interval remained similar—potentially suggesting subtle repolarization prolongation. Although the JTc interval was not measured, this combination of shorter QRS and unchanged QTc duration could theoretically indicate JTc prolongation, aligning with our findings. Interestingly, in their study, repolarization parameters obtained via CMR-guided electrocardiographic imaging (ECGi), such as the activation recovery interval and repolarization time, were not prolonged in SARC+LVH− patients. However, it is important to note that both parameters incorporate parts of the QRS complex, meaning they reflect a composite of both depolarization and repolarization durations, rather than repolarization alone. While complex CMR-integrated ECG mapping techniques like ECGi play an important role in probing intricate conduction abnormalities in HCM, our study used the simpler, widely available 12-lead ECG to demonstrate that parameters such as the JTc interval can potentially differentiate sub-clinical HCM (SARC+LVH−) from controls. It is also noteworthy that we identified meaningful differences in ECG parameters with a modestly sized cohort, which highlights the sensitivity of these easy-to-extract measures.

Relationship between disarray, fibrosis, and repolarization parameters

Among SARC+LVH− patients, we found a significant inverse correlation between FA and JTc interval duration, providing further evidence that myocardial disarray may be complicit in repolarization prolongation (in conjunction with other factors such as ionic remodelling and aberrations in calcium handling[6]). However, this association was less pronounced in overt HCM patients and we postulate this divergence may be due to the more prominent roles of myocyte hypertrophy, progressive interstitial fibrosis[37] and microvascular dysfunction[28]—rather than disarray—in altering repolarization in more advanced disease. This is further supported by the strong correlation seen in overt HCM patients between repolarization parameters (JTc interval and QTc dispersion) and recognized markers of interstitial fibrosis such as ECV and T1. This relationship between interstitial fibrosis and myocardial repolarization (specifically QTc dispersion) was also observed by Hurtado-de-Mendoza *et al.*[37] in their ECG and CMR study of 112 overt HCM patients. Similarly, Österberg *et al.*[28] also observed an association between an ECG risk-score incorporating QTc duration and LGE burden in early stage HCM. Most noteworthy of all and consistent with our work is a comprehensive study by Kuroda *et al.*,[12] which employed both qualitative and quantitative ECG analyses, Holter monitoring, and histological evaluations, and identified T wave alternans as indicative of a higher burden of myocardial disarray and fibrosis on histology. Recent investigations have also highlighted the potential for qualitative ECG alterations in SARC+LVH− individuals as predictors of disease progression and penetrance.[38–40] The strong correlation observed between repolarization intervals and FA in our study suggests that these intervals might serve as reliable indicators of disease severity and could potentially forecast long-term disease progression.

Clinical relevance

With the advent of disease-modifying interventions such as small molecule modulators of cardiac myosin and gene therapies, the early identification of individuals exhibiting microstructural changes—those potentially on the cusp of developing HCM—has gained paramount importance. Our study highlights the potential of myocardial disarray imaging and quantitative ECG analysis to serve as early markers of disease activity in HCM, providing measures that can contribute to more nuanced clinical surveillance of variant carriers. Traditionally, qualitative 12-lead ECG analysis has anchored the diagnostic process for HCM, serving as an essential tool for familial screenings and risk evaluations, especially for individuals considering competitive athletic sports. Our findings suggest that more granular insight into microstructural changes (both myocardial disarray and fibrosis) can be inferred from specific quantitative ECG deviations across the disease spectrum. Our observations align with established literature indicating that repolarization abnormalities are closely related to microstructural abnormalities like fibrosis,[12,28,37] and mirror documented associations with other prognostic markers including strain abnormalities[41] and arrhythmic burden.[13,31,35] Future endeavours however are needed to validate our observations in larger cohorts, with comparative analyses of other risk assessment strategies.

Limitations

Our study, albeit small and cross-sectional in nature, provided some valuable insights into the relationship between myocardial microstructure and repolarization changes in both Sarc+LVH− and HCM patients. However, these observations cannot be directly attributed to disease progression without longitudinal follow-up. For a more comprehensive understanding of causal relationships between microstructural alterations and repolarization anomalies, in-depth histological validation and electrophysiological studies are imperative. It is also worth noting that cardiac DT-CMR remains a research technique, work on standardisation of approach and improvements in acquisition and data processing are pre-requisites to future longitudinal, multi-centre clinical studies necessary for it to enter the clinical domain.

Conclusion

Low diastolic FA, suggestive of myocardial disarray, is present in both SARC+LVH− and HCM patients. Low diastolic FA in SARC+LVH− and raised ECV in HCM patients associated with prolongation of repolarization. Myocardial disarray assessment using DT-CMR and prolongation of key repolarization parameters such as the JTc interval

demonstrates significant potential as novel, sensitive, and prognostically important markers of disease activity across HCM stages. These techniques may come to support more nuanced surveillance of SARC+LVH− patients and improved risk stratification of overt HCM patients.

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Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest: None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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