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Citation

Abou, R., Prihadi, E. A., Goedemans, L., Geest, R. van der, Mahdiui, M. el, Schaliij, M. J., ... Delgado, V. (2020). Left ventricular mechanical dispersion in ischaemic cardiomyopathy: association with myocardial scar burden and prognostic implications. *European Heart Journal - Cardiovascular Imaging*, 21(11), 1227-1234. doi:10.1093/ehjci/jeaa187

Version: Publisher's Version

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Left ventricular mechanical dispersion in ischaemic cardiomyopathy: association with myocardial scar burden and prognostic implications

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Received 9 April 2020; editorial decision 28 May 2020; accepted 16 June 2020; online publish-ahead-of-print 30 July 2020

Aims

Left ventricular (LV) mechanical dispersion (MD) may result from heterogeneous electrical conduction and is associated with adverse events. The present study investigated (i) the association between LV MD and the extent of LV scar as assessed with contrast-enhanced cardiac magnetic resonance (CMR) and (ii) the prognostic implications of LV MD in patients after ST-segment elevation myocardial infarction.

Methods and results

LV MD was calculated by echocardiography and myocardial scar was analysed on CMR data retrospectively. Infarct core and border zone were defined as $\geq 50\%$ and 35–50% of maximal signal intensity, respectively. Patients were followed for the occurrence of the combined endpoint (all-cause mortality and appropriate implantable cardioverter-defibrillator therapy). In total, 96 patients (87% male, 57 ± 10 years) were included. Median LV MD was 53.5 ms [interquartile range (IQR) 43.4–62.8]. On CMR, total scar burden was 11.4% (IQR 3.8–17.1%), infarct core tissue 6.2% (IQR 2.0–12.7%), and border zone was 3.5% (IQR 1.5–5.7%). Correlations were observed between LV MD and infarct core ($r = 0.517$, $P < 0.001$), total scar burden ($r = 0.497$, $P < 0.001$), and border zone ($r = 0.298$, $P = 0.003$). In total, 14 patients (15%) reached the combined endpoint. Patients with LV MD > 53.5 ms showed higher event rates as compared to their counterparts. Finally, LV MD showed the highest area under the curve for the prediction of the combined endpoint.

Conclusion

LV MD is correlated with LV scar burden. In addition, patients with prolonged LV MD showed higher event rates. Finally, LV MD provided the highest predictive value for the combined endpoint when compared with other parameters.

Keywords

myocardial infarction • left ventricular • mechanical dispersion • scar burden • prognosis

Introduction

Myocardial infarct size is an important determinant of poor outcome after ST-segment elevation myocardial infarction (STEMI).¹ Among several methods to assess infarct size,² late gadolinium

contrast-enhanced cardiac magnetic resonance (LGE-CMR) is considered the gold standard.³ Furthermore, LGE-CMR allows for the characterization of infarct tissue heterogeneity, differentiating between infarct core and border zone.⁴ Left ventricular (LV) mechanical dispersion (MD) by two-dimensional (2D) speckle tracking

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echocardiography (STE) measures the timing of peak segmental myocardial shortening and has been proposed as parameter reflecting the heterogeneity of the electrical conduction.^{5,6} Prolonged LV MD after myocardial infarction has been associated with poor outcomes.^{5–8} However, the association between total myocardial scar and heterogeneity of myocardial scar tissue as assessed with LGE-CMR and LV MD measured with STE has not been investigated. Therefore, our aim is to investigate (i) the association between LV MD and the extent of LV scar burden as evaluated by LGE-CMR and (ii) the prognostic implications of LV MD compared to LGE-CMR variables in a contemporary STEMI group.

Methods

Population

Patients with first acute STEMI and treated with primary percutaneous coronary intervention (PCI) between February 2004 and April 2017 were evaluated retrospectively. All patients were treated according to the institutional, guideline-based, clinical care track protocol (MISSION!).⁹ LGE-CMR was performed in a subgroup of patients at the discretion of the treating physician to evaluate cardiac function and the extent of myocardial scar. For this substudy, STEMI patients with analysable 2D STE analysis and LGE-CMR were evaluated. Patients with prior myocardial infarction, coronary artery bypass grafting, non-feasible 2D STE analysis, or LGE-CMR performed within 30 days of index myocardial infarction were excluded (Figure 1).

Clinical data

Patient demographics and clinical characteristics were recorded. The culprit lesion was identified on invasive coronary angiography at the time of intervention. The final thrombolysis in myocardial infarction flow after primary PCI was registered. Multi-vessel disease was defined as the presence of more than $\geq 50\%$ luminal narrowing in more than one coronary artery. Cardiovascular medications at hospital discharge were optimized according to contemporary guidelines and titrated at the discretion of the treating physician.^{10,11} Cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) were implanted during follow-up in accordance with current guidelines.^{12–14} The institutional review board of the Leiden University Medical Center approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent (C13.029). All data used for this study was acquired for clinical purposes and handled anonymously.

Conventional transthoracic echocardiography

Two-dimensional transthoracic echocardiography was performed in patients at rest in the left lateral decubitus position using commercially available ultrasound systems (Vivid 7 and E9; General Electric Vingmed, Horten, Norway). Data acquisition was performed with 3.5-MHz or M5S transducers. Standard M-mode, 2D, colour, pulsed and continuous wave Doppler images were acquired and stored digitally for offline analysis (EchoPac BT13; GE Medical Systems, Horten, Norway). LV ejection fraction (LVEF) was calculated from the apical four- and two-chamber views using the Simpson's biplane method.¹⁵

Two-dimensional speckle tracking echocardiography

From 2D echocardiographic data, LV global longitudinal strain (GLS) was quantified by 2D STE from the apical four-, two-, and long-axis views. The endocardial borders were traced at the end-systolic frame and an automated tracking algorithm outlined the myocardium in successive frames throughout the cardiac cycle.¹⁶ The software automatically tracks and accepts segments of good tracking quality and rejects poorly tracked segments, while allowing the observer to manually override its decisions based on visual assessment of tracking quality (Figure 2). LV MD was defined as the time from onset of the Q/R wave on the electrocardiogram to peak longitudinal strain.⁸ LV MD was defined as the standard deviation of time to peak longitudinal strain in 17 LV segments and generated automatically by the software (Figure 2).

Late gadolinium contrast-enhanced cardiac magnetic resonance

CMR was performed on a 1.5-T Gyroscan ACS-NT/Intera MR system or on a 3.0-T Ingenia MR system (Philips Medical Systems, Best, the Netherlands). A standardized protocol was followed, including cine CMR in long-axis (two- and four-chamber views) and short-axis reconstructions. Contrast-enhanced images were acquired 15 min after bolus injection of gadolinium (Magnevist, Schering, Berlin, Germany) (0.15 mmol/kg) with an inversion-recovery 3D turbo-field echo sequence with parallel imaging. The heart was imaged in one or two breath-holds with 20–24 imaging levels in short-axis views.⁴

For image analysis, the MASS software (research version 2012, LKEB, Leiden University Medical Centre, Leiden, the Netherlands) was used for offline analysis. Myocardial scar was assessed by signal intensity. First, the endocardial and epicardial contours were traced on the short-axis images. Papillary muscles were considered as part of the ventricular cavity, and epicardial fat was excluded. Subsequently, the maximum signal intensity within the infarcted region was determined, while allowing the observer to manually override its decisions based on visual assessment. LV end-diastolic volume and LV mass were computed automatically. LGE was defined by a signal intensity $\geq 35\%$ of maximal myocardial signal intensity (total scar burden). In addition, results were subdivided into infarct core ($\geq 50\%$ of maximal signal intensity) and border zone (35–50% of maximal signal intensity, which reflects infarct tissue heterogeneity) (Figure 3).⁴

Follow-up and endpoints

Clinical data were collected from the Cardiology Department Information System (EZIS chipsoft & EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands). The occurrence of ICD therapy was assessed by device interrogation. Appropriate ICD therapy was defined as ICD shocks in response to ventricular tachycardia/fibrillation and anti-tachycardia pacing. Furthermore, all-cause mortality was reported including cardiac and non-cardiac mortality. Patients were followed-up from the moment of admission to the occurrence of the composite endpoint of appropriate ICD therapy and all-cause mortality.

Statistical analysis

The data that support the findings of this study are available on reasonable request to the corresponding author. Continuous variables with normal distribution are reported as mean $\pm$ standard deviation. Non-normally distributed data are presented as median and interquartile range (IQR), whereas categorical variables are reported as frequencies and percentages. Bivariate correlation analysis was performed to evaluate the correlation between LV MD and the extent of LV scar burden (total scar

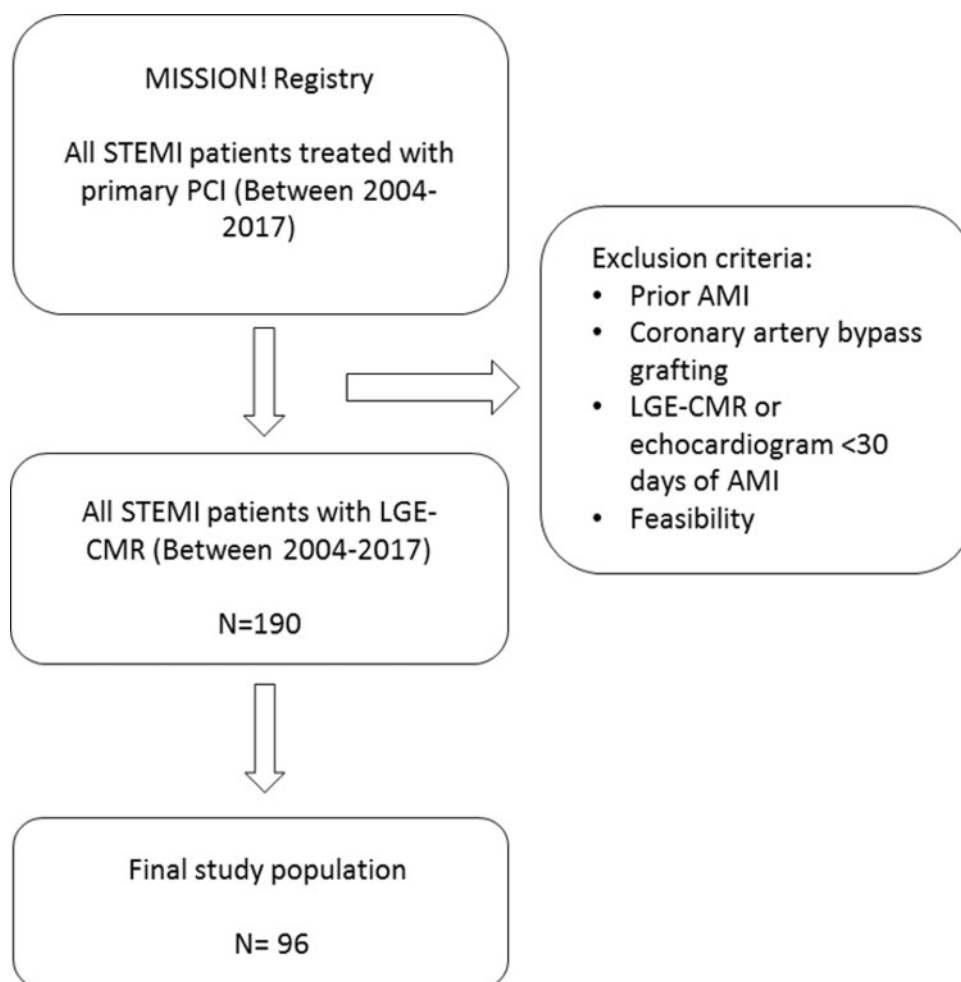


Figure 1 Flowchart of study population. AMI, acute myocardial infarction; LGE-CMR, late gadolinium contrast-enhanced cardiac magnetic resonance; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

burden, infarct core, and border zone). The study population was divided into two groups according to the median LV MD (≤ 53.5 ms). Cumulative event rates were analysed with the Kaplan–Maier method and compared between groups with the log-rank test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate and compare the discriminative power of various echocardiographic variables to predict the combined endpoint. Statistical analysis was performed on SPSS for Windows v20.0 (IBM, Armonk, New York) and MedCalc v17.6 (MedCalc software, Belgium). A two-tailed P -value <0.05 was considered statistically significant.

Results

Population

A total of 96 patients (mean age 57 ± 10 years, 87% male) were included in this study (Table 1). The median levels of peak troponin T and creatine phosphokinase were 5.3 ng/L (IQR 2.4–8.8 ng/L) and 1917 U/L (IQR 1165–4030), respectively. Multi-vessel disease was

observed in 57 (59%) patients and the culprit lesion was the left anterior descending coronary artery in 49 (51%) patients. At discharge, 97% of patients were treated with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, 93% received beta-blockers, and 100% used statins. A total of 4 (4%) patients received an ICD, whereas 6 (6%) patients received CRT during the follow-up period (Table 2).

Left ventricular mechanical dispersion and scar burden

Table 3 demonstrates the findings from 2D echocardiography and LGE-CMR data. The median interval from index infarction to echocardiography was 104 days (IQR 92–181), whereas the median interval from index infarction to LGE-CMR was 74 days (IQR 51–132). The mean LVEF for the study population was $49 \pm 10\%$ and the mean LV GLS was $-14.5 \pm 3.8\%$. In addition, the median LV MD was 53.5 ms (IQR 43.4–62.8).

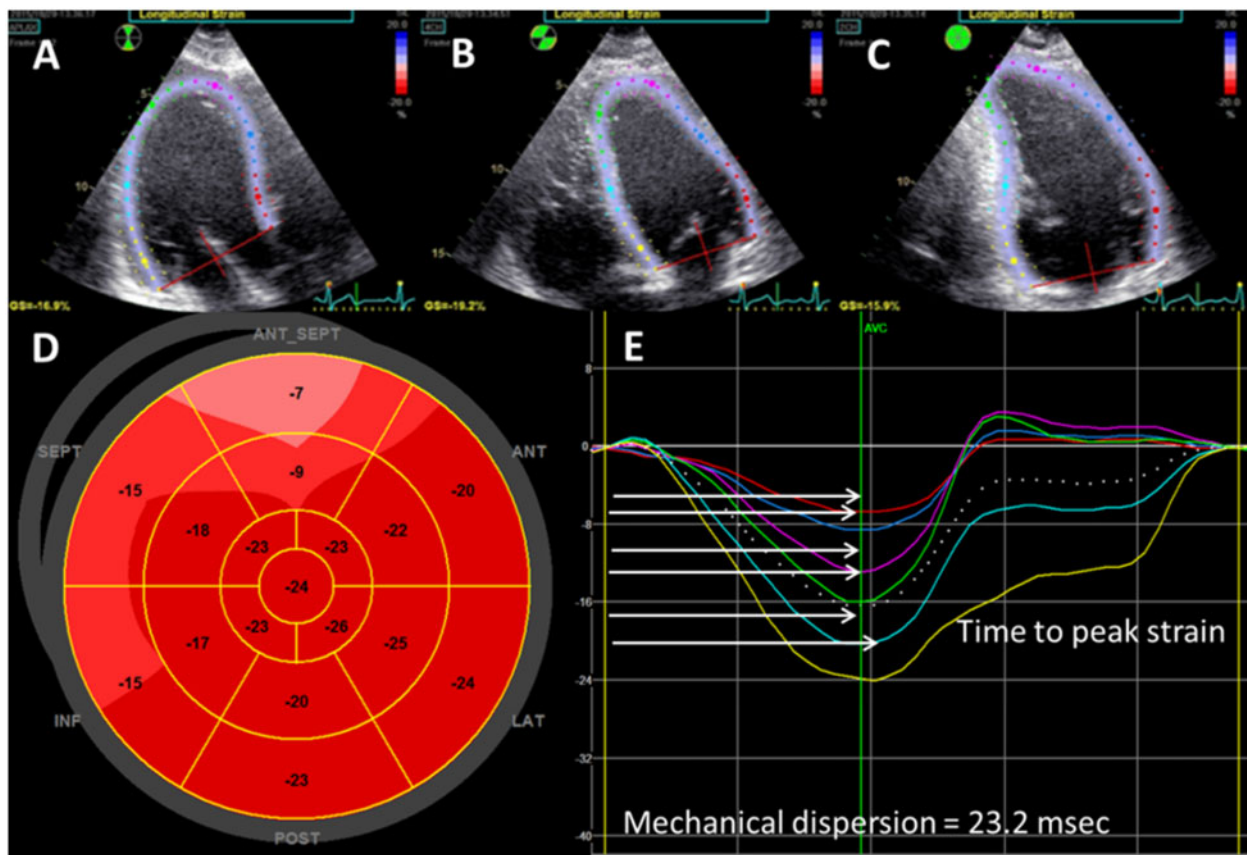


Figure 2 Left ventricular mechanical dispersion. Example of patient after anterior infarction. (A) Speckle tracking analysis of apical long-axis; (B) speckle tracking analysis of apical four-chamber view; (C) speckle tracking analysis of apical two-chamber view. (D) Bull's eye plots for global value of longitudinal strain which is calculated as the average of the 17 regional strain values, (E) mechanical dispersion (23.2 ms) with time to peak negative strain in all left ventricular segments.

On LGE-CMR, the total scar burden was 11.4% (IQR 3.8–17.1), the percentage of infarct core tissue was 6.2% (IQR 2.0–12.7), whereas the median extent of the border zone was 3.5% (IQR 1.5–5.7) (Table 3). LV MD was significantly correlated with infarct core ($r=0.517$, $P<0.001$), total scar burden ($r=0.497$, $P<0.001$), and border zone ($r=0.298$, $P=0.003$).

Follow-up and events

A total of 11 patients (12%) died and 3 (3%) patients experienced appropriate ICD therapy during a median follow-up of 6.8 (IQR 6.0–8.3) years. Kaplan–Meier curves for the combined endpoint are shown in Figure 4, with the population divided into two groups according to the median LV MD (≤ 53.5 ms vs. >53.5 ms). The cumulative survival rates were significantly higher for patients with LV MD (>53.5 ms) as compared to patients with LV MD (≤ 53.5 ms) (log-rank $P<0.001$). On ROC curve analysis, LV MD provided the highest area under the curve (AUC) for predicting the combined endpoint (AUC = 0.847, $P<0.001$), followed by LV GLS (AUC = 0.822, $P<0.001$), total scar burden (AUC = 0.768, $P=0.002$), infarct core (AUC = 0.763, $P=0.003$), and border zone (AUC = 0.687, $P=0.032$) (Figure 5, Table 4). In contrast, LVEF showed poor discrimination to

identify the patients who will present with an event. In a bi-variable model, the AUC for LV MD was significantly different from that of LVEF ($P<0.001$). However, there were no significant differences in the AUC for LV GLS, total scar score, infarct core, and border zone when compared with LV MD ($P>0.05$, for all) (Table 4).

Discussion

The present study showed that LV MD is significantly related with total scar burden, infarct core, and border zone in STEMI patients. In addition, patients with prolonged LV MD showed higher event rates. Finally, prolonged LV MD provided the highest predictive value for the combined endpoint when compared with other echocardiographic and LGE-CMR-derived parameters.

Association between left ventricular mechanical dispersion and scar burden

LGE-CMR has been proven to accurately quantify the extent of LV myocardial scar and is a powerful prognostic parameter in patients with ischaemic heart disease.^{17,18} It has been suggested that the

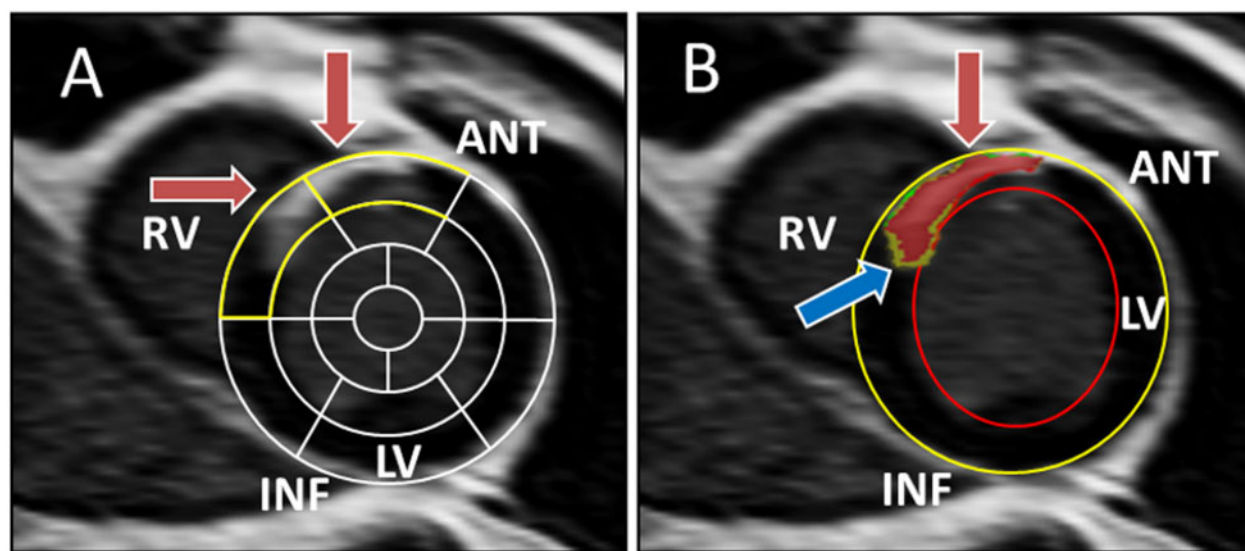


Figure 3 Left ventricular scar calculated by signal intensity on LGE-CMR. (A) Transmurular hyperenhancement on the short-axis view of the apical level of a patient with anterior infarction. Hyperenhancement is indicated by the red arrow within the yellow segments. (B) The endocardial (red) and epicardial (yellow) contours, which were drawn manually on the short-axis images to perform the analysis on signal intensity. The red area, as indicated by the red arrow, indicates the infarct core. The orange area as indicated by the blue arrow indicates the border zone. Ant, anterior; Inf, inferior; LV, left ventricle; RV, right ventricle.

anatomical substrate for ventricular arrhythmias post-myocardial infarction is predominantly determined by the scar heterogeneity, which provides a substrate for a re-entry circuit.¹⁹

A recent meta-analysis including 1105 patients demonstrated that the occurrence of ventricular arrhythmias were predominantly observed in patients with a greater extent of LV scarring.²⁰ However, it remains unclear which scar characteristics are prognostic in the prediction of ventricular arrhythmias. Some studies have shown that the extent of the infarct core scar is most predictive of events, while other studies have shown that the border zone (grey zone) is more important.^{4,19,21–24} Some of this variability may be attributed to different populations (acute STEMI vs. chronic ischaemic heart disease) and different definitions for quantifying LV scar. Furthermore, the presence or reactive fibrosis, measured with native T1 mapping techniques has been associated with the occurrence of ventricular arrhythmias. Chen *et al.*²⁵ showed in 130 patients (71 with ischaemic heart failure), that for every 10-ms increment in non-contrast T1 (native) value, the risk of appropriate ICD therapy or documented sustained ventricular arrhythmia increased by 10% (hazard ratio 1.10; confidence interval 1.04–1.16). Therefore, new non-invasive parameters may further aid in early recognition of patients at risk of adverse outcomes.

Recently, LV MD by 2D STE has appeared as a relative novel parameter in the risk stratification of various cardiac diseases. It is hypothesized that the extent of tissue heterogeneity causes heterogeneous electrical conduction, which is associated with ventricular arrhythmias and mortality in various cardiac diseases.^{5–8,26–30}

A previous study by Leong *et al.*³¹ demonstrated that LV MD was independently associated with the occurrence of ventricular arrhythmias in 206 patients with ischaemic heart disease. Interestingly, Leong

et al. demonstrated that a higher total percentage of LGE as evaluated by CMR was associated with prolonged LV MD, indicating a larger burden of LV fibrosis.³¹ These findings were corroborated by a recent study measuring LV MD with feature tracking CMR.⁷ In 130 STEMI patients after first STEMI evaluated with feature tracking CMR and LGE CMR, Muser *et al.*⁷ showed a correlation between myocardial infarct size and LV MD ($r = 0.50$, $P < 0.001$).

Left ventricular mechanical dispersion and clinical implications

LV dyssynchrony can be observed in patients after myocardial infarction and has been associated with myocardial infarct size and poor outcome.^{32,33} Although current guidelines still include the use of LVEF as the main functional parameter to manage patients after STEMI, 2D STE has been shown to be of incremental value over LVEF in this group of patients.^{5,6,34}

Of 988 patients post-myocardial infarction, Ersbøll *et al.*²⁶ reported the occurrence of ventricular arrhythmias or sudden cardiac death in 34 patients. Patients presenting with ventricular arrhythmias or sudden cardiac death showed more prolonged LV MD than patients who were free of those events (70.7 ± 29.7 ms vs. 56.1 ± 15.3 ms).²⁶ Similarly, a study by Haugaa *et al.*⁵ evaluated 569 patients after myocardial infarction (at least 40 days after) and demonstrated that patients with ventricular arrhythmias ($n = 15$; ventricular tachycardia and sudden death) showed more prolonged LV MD than their counterparts (63 ± 25 ms vs. 42 ± 17 ms).⁵ On multivariable analysis, both studies reported that LV MD was independently associated with the endpoint. We report a relative lower event rate ($n = 14$; $n = 3$ ICD therapy, $n = 11$ death) and slightly lower value of LV MD when compared with

Table 1 Baseline characteristics of the study population

Variables	Total population (n = 96)
Clinical characteristics	
Age (years)	57 ± 10
Male gender, n (%)	83 (87)
Heart rate discharge (bpm)	71 ± 12
Systolic blood pressure, discharge (mmHg)	112 ± 16
Diastolic blood pressure, discharge (mmHg)	70 ± 10
Cardiovascular risk factors	
Hypertension, n (%)	40 (42)
Hypercholesterolaemia, n (%)	21 (22)
Family history of CAD, n (%)	43 (45)
Diabetes mellitus, n (%)	10 (10)
Current smoker, n (%)	46 (48)
Biochemical markers	
Peak CPK (U/L)	1917 (1165–4030)
Peak cTnT (ng/L)	5.3 (2.4–8.8)
eGFR (mL/min/1.73 m ²)	103 ± 35
Glucose (mmol/L)	8 (7–10)
Coronary angiography	
Killip class ≥2, n (%)	4 (3)
TIMI flow 2–3, n (%)	95 (99)
RCA, n (%)	32 (33)
Left main, n (%)	1 (1)
LAD, n (%)	49 (51)
LCX, n (%)	14 (15)
Multi-vessel disease, n (%)	57 (59)

Data are presented as mean ± standard deviation, number (percentage), or as median (25th–75th percentile).

Hypertension was defined as office blood pressure ≥140/90 mmHg or previous pharmacological treatment. Hypercholesterolaemia was defined as total cholesterol 190 mg/dL or previous pharmacological treatment. Diabetes mellitus was defined as fasting blood glucose ≥7.0 mmol/L, 2-h oral glucose tolerance test glucose ≥11.1 mmol/L, or previous pharmacological treatment.

CAD, coronary artery disease; CPK, creatine phosphokinase; cTnT, cardiac troponin T; (e)GFR, glomerular filtration rate estimated with the Cockcroft–Gault formula; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

the aforementioned studies.^{5,26} This can be explained by differences in study populations: while the present study includes patients with STEMI treated with primary PCI, the other studies included more heterogeneous populations (STEMI and non-STEMI) that received different therapies (not all of them received PCI) and with different follow-up time.

In the present study, LV MD provided the highest accuracy for predicting the endpoint followed by LV GLS and CMR derived parameters. In contrast, LVEF showed poor discrimination to identify patients at risk for events. As early detection of myocardial fibrosis possibly leads to early identification of patients at risk for adverse events, LV MD by 2D STE appears to be a promising marker of LV fibrosis and outcome.

Table 2 Medical management of the study population

Variables	Total population (n = 96)
Medications at discharge	
Aspirin, n (%)	91 (95)
Thienopyridines, n (%)	96 (100)
ACEi/ARBs, n (%)	93 (97)
β-blockers, n (%)	93 (97)
Statins, n (%)	96 (100)
Device therapy	
ICD, n (%)	4 (4)
CRT, n (%)	6 (6)
Index infarction to CRT (days)	208 (132–1145)

Data are presented as mean ± standard deviation, number (percentage), or as median (25th–75th percentile). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

Table 3 Findings at echocardiography and contrast-enhanced magnetic resonance imaging

Variables	Total population (n = 96)
Echocardiography	
Heart rate (bpm)	64 ± 13
BSA (m ²)	2.0 ± 0.2
Left ventricular end-systolic volume (mL)	56 (43–78)
Left ventricular end-diastolic volume (mL)	117 ± 34
Left ventricular ejection fraction (%)	49 ± 10
Left ventricular global longitudinal strain (%)	-14.5 ± 3.8
Left ventricular mechanical dispersion (ms)	53.5 (43.4–62.8)
Index infarction to echocardiography (days)	104 (92–181)
LGE-CMR	
Left ventricular end-diastolic volume (mL)	137 ± 44
Left ventricular mass (kg/m ²)	159 ± 42
Total percentage of left ventricular scar tissue (%)	11.4 (3.8–17.1)
Percentage of left ventricular infarct core (%)	6.2 (2.0–12.7)
Percentage of left ventricular border zone (%)	3.5 (1.5–5.7)
Index infarction to LGE-CMR (days)	74 (51–132)

Data are presented as mean ± standard deviation, number (percentage), or as median (25th–75th percentile).

BSA, body surface area; LGE-CMR, late gadolinium contrast-enhanced cardiac magnetic resonance.

Study limitations

The current study was retrospective in nature and the data were generated from a single centre. T1 mapping techniques were not applied in this study cohort and therefore the association between reactive fibrosis and ventricular arrhythmias could not be evaluated. Furthermore, CMR was performed relatively early after STEMI when compared with transthoracic echocardiography. Therefore, LV MD may improve due to functional recovery in a later stage. In addition,

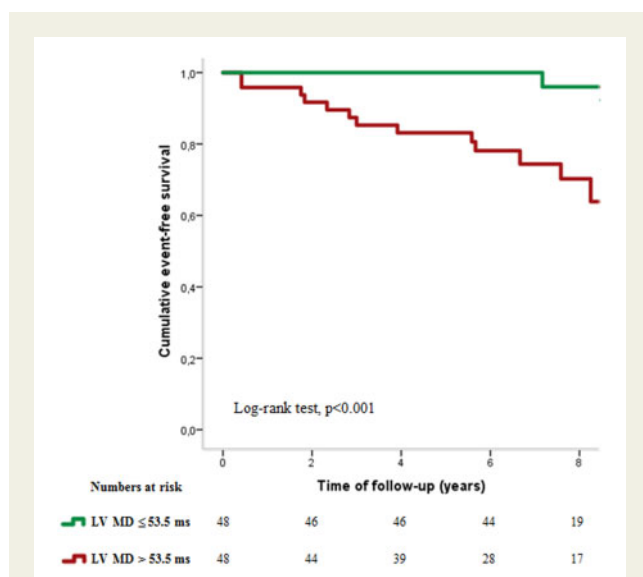


Figure 4 Kaplan–Meier survival curves for combined endpoints according to left ventricular mechanical dispersion. Patients were classified in two separate groups according to the median LV MD (≤ 53.5 ms vs. > 53.5 ms).

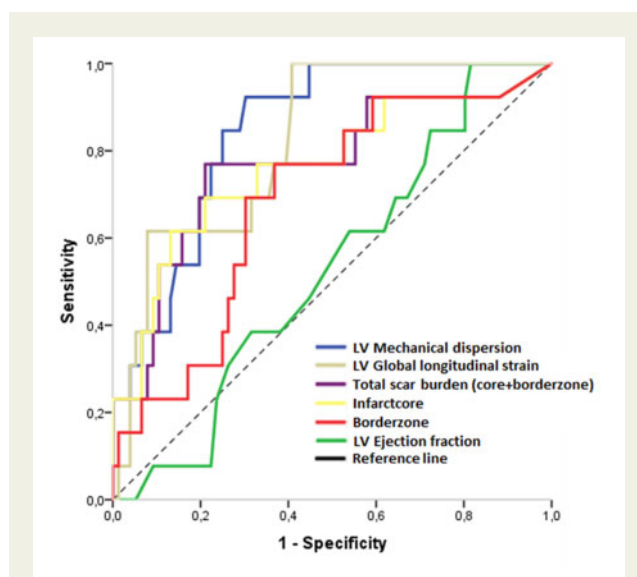


Figure 5 Receiver operating characteristics curves for combined endpoint. This figure demonstrates receiver operating characteristics curves for several echocardiographic parameters and parameters derived from cardiac magnetic resonance.

Table 4 Receiver operating characteristics curve analysis for combined endpoint

Univariable model					Bivariable model	
Variables	Sensitivity	Specificity	AUC	P-value	Variables	P-value
LV MD	0.923	0.618	0.847	<0.001	LVEF vs. LV MD	<0.001
LVEF	0.077	0.776	0.529	0.741	LV GLS vs. LV MD	0.7217
LV GLS	0.615	0.895	0.822	<0.001	TSB vs. LV MD	0.3920
TSB	0.769	0.789	0.768	0.002	Infarct core vs. LV MD	0.3672
Infarct core	0.769	0.618	0.763	0.003	Border zone vs. LV MD	0.0744
Border zone	0.769	0.618	0.687	0.032		

AUC, area under the curve; GLS, global longitudinal strain; LV, left ventricle; MD, mechanical dispersion; TSB, total scar burden.

the measurements of LV MD may not be generalizable for all vendors and the cut-off value of LV MD provided in this study may not be applicable in other study populations. Finally, the number of events during follow-up was relatively small. Data on specific cause of death were not available. Further studies including larger sample size are needed.

Conclusions

LV MD is correlated with total scar burden, infarct core, and border zone. In addition, patients with prolonged LV MD showed higher rates of all-cause mortality and ICD therapy. Finally, LV MD provided the highest predictive value for the combined endpoint of all-cause mortality and ICD therapy when compared with other parameters.

Conflict of interest: The department of Cardiology received unrestricted research grants from Abbott Vascular, Bayer, Bioventrix, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare and Medtronic. V.D. received speaker fees from Abbott Vascular, Edwards Lifesciences, GE Healthcare and Medtronic. N.A.M. and J.J.B. received speaker fees from Abbott Vascular. All the remaining authors declared no conflict of interest.

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