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Echocardiographic Deformation Analysis for the Prediction of Sudden Cardiac Death and Life-Threatening Arrhythmias After Myocardial Infarction

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OBJECTIVES This study sought to hypothesize that global longitudinal strain (GLS) as a measure of infarct size, and mechanical dispersion (MD) as a measure of myocardial deformation heterogeneity, would be of incremental importance for the prediction of sudden cardiac death (SCD) or malignant ventricular arrhythmias (VA) after acute myocardial infarction (MI).

BACKGROUND SCD after acute MI is a rare but potentially preventable late complication predominantly caused by malignant VA. Novel echocardiographic parameters such as GLS and MD have previously been shown to identify patients with chronic ischemic heart failure at increased risk for arrhythmic events. Risk prediction during admission for acute MI is important because a majority of SCD events occur in the early period after hospital discharge.

METHODS We prospectively included patients with acute MI and performed echocardiography, with measurements of GLS and MD defined as the standard deviation of time to peak negative strain in all myocardial segments. The primary composite endpoint (SCD, admission with VA, or appropriate therapy from a primary prophylactic implantable cardioverter-defibrillator [ICD]) was analyzed with Cox models.

RESULTS A total of 988 patients (mean age: 62.6 ± 12.1 years; 72% male) were included, of whom 34 (3.4%) experienced the primary composite outcome (median follow-up: 29.7 months). GLS (hazard ratio [HR]: 1.38; 95% confidence interval [CI]: 1.25 to 1.53; $p < 0.0001$) and MD (HR/10 ms: 1.38; 95% CI: 1.24 to 1.55; $p < 0.0001$) were significantly related to the primary endpoint. GLS (HR: 1.24; 95% CI: 1.10 to 1.40; $p = 0.0004$) and MD (HR/10 ms: 1.15; 95% CI: 1.01 to 1.31; $p = 0.0320$) remained independently prognostic after multivariate adjustment. Integrated diagnostic improvement (IDI) and net reclassification index (NRI) were significant for the addition of GLS (IDI: 4.4% [$p < 0.05$]; NRI: 29.6% [$p < 0.05$]), whereas MD did not improve risk reclassification when GLS was known.

CONCLUSIONS Both GLS and MD were significantly and independently related to SCD/VA in these patients with acute MI and, in particular, GLS improved risk stratification above and beyond existing risk factors. (J Am Coll Cardiol Img 2013;■:■–■) © 2013 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) and life-threatening ventricular arrhythmias (VA) are rare but devastating complications following acute myocardial infarction (MI). Primary prevention with an implantable cardioverter-defibrillator (ICD) is recommended in patients with left ventricular ejection fraction (LVEF) ≤35% and symptomatic congestive heart failure (HF) at least 40 days after an acute MI (1). Although the absolute risk for SCD is highest in patients with significantly reduced LVEF (2), a significant proportion of SCD events occur in patients with LVEF >35%, which underscores the need for improved risk stratification early in the course of acute MI (3).

Increased risk for SCD or VA after acute MI has been associated with scar burden (4), scar tissue inhomogeneity (5), as well as electrical abnormalities such as increased T-wave alternans (6). The pathophysiological process leading to SCD or VA is thought to be re-entrant currents originating in the scar region and the peri-infarct area (7). Echocardiographic deformation analysis with assessment of myocardial dispersion (MD) assessed by the SD of time to peak longitudinal strain has been shown to predict arrhythmic events in patients with ischemic heart disease undergoing ICD implantation (8). Global longitudinal strain (GLS) correlates with infarct size (9) and predicts death and HF after acute MI (10). However, to the best of our knowledge, no prior studies have assessed the importance of these echocardiographic deformation parameters in specific relation to SCD or VA in a large, unselected, contemporary population of acute MI. We hypothesized that the early measurement of GLS as a sensitive measure of myocardial injury, as well as MD reflecting inhomogeneous contraction, would predict SCD or VA independently and incrementally to LVEF in a contemporary cohort of patients with acute MI.

ABBREVIATIONS AND ACRONYMS

GLS = global longitudinal strain

HF = heart failure

ICD = implantable cardioverter-defibrillator

IDI = integrated diagnostic improvement

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

MD = mechanical dispersion

MI = myocardial infarction

NRI = net reclassification improvement

SCD = sudden cardiac death

VA = ventricular arrhythmia

METHODS

Study design and patient population. We prospectively included patients referred for invasive coronary angiography due to either ST-segment elevation or non–ST-segment elevation MI at 2 tertiary cardiac centers in the region of Copenhagen, Denmark. All patients provided written informed consent. Exclusion criteria were age <18 years, noncardiac disease with a life expectancy <1 year, and an inability to provide written informed consent. Furthermore, patients in whom atrial fibrillation, paced rhythm, or severe aortic stenosis were noted at the time of echocardiographic examination were excluded from the analyses.

Information on diabetes, hypertension, history of ischemic heart disease or MI, and objective signs of HF (Killip class) were acquired from chart review. Findings in relation to coronary angiography, including culprit lesion, number of diseased vessels, left main involvement, and type of revascularization (percutaneous coronary intervention, coronary artery bypass grafting, or no intervention) were registered. QRS duration was obtained from 12-lead electrocardiography obtained before discharge. Peak troponin I was measured in 250 patients (25.3%), and peak troponin T was measured in 738 patients (74.7%). The study protocol was approved by the regional scientific ethics committee (reference no. H-D-2009-063).

Echocardiography. Echocardiography was performed within 48 h of admission to the tertiary center. Echocardiographic cine loops were obtained by the recording of 3 consecutive heart cycles. All examinations were performed on a Vivid e9 system (General Electric, Horten, Norway). Images were obtained at a frame rate of at least 60 frames/s and analyzed offline (Echopac BT 11.1.0, General Electric). All analyses were performed by a single experienced operator (M.E.) who was blinded to follow-up information.

Volumetric measurements (LVEF, LV end-diastolic volume [EDV], and LV end-systolic

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volume) were determined using the biplane Simpson model. LV mass index was calculated from the LV linear dimensions in the parasternal view. All volumetric analyses were performed in accordance with European Association of Echocardiography/American Society of Echocardiography recommendations (11).

Strain analysis. Two-dimensional speckle tracking was performed on 3 apical views (long-axis, 4-chamber, and 2-chamber). Aortic valve closure was identified on continuous-wave Doppler recording through the aortic valve. The region of interest was adjusted to cover the thickness of the myocardium. The LV was subsequently divided into 17 segments covering the entire myocardium, and GLS was calculated as the mean of the global peak systolic strain from each of the 3 views. Careful inspection of tracking and manual correction, if needed, were performed; if tracking was unsatisfactory, the segment was excluded from the analysis. If GLS could be assessed only in 2 of 3 apical projections, we calculated the overall GLS as the mean of these 2. If GLS could not be assessed in at least 2 of the apical projections, the patient examination was classified as having image quality insufficient for strain measurements. Mechanical dispersion was calculated as the SD of the time from the peak R-wave to peak negative strain during the entire cardiac cycle in all segments (Fig. 1). Segments without shortening during the entire cardiac cycle were excluded. However, segments with stretching in systole and subsequent shortening were included in the measurements of time to peak strain. If 6 or more segments did not have sufficient tracking, the patient was excluded from the analyses.

Follow-up and endpoint definition. The primary outcome was a composite of definite or suspected SCD, admission with documented VA, or appropriate ICD discharge only in patients with a primary prophylactic ICD. Information on all-cause mortality was obtained from the Danish Civil Registration System, and cause of death was ascertained from hospital and pre-hospital patient records by 2 independent reviewers who were blinded to echocardiographic data, and in cases of disagreement, a third reviewer was consulted. ICD therapy was evaluated from device interrogation by an experienced cardiac electrophysiologist blinded to the echocardiographic data. No patients were lost to follow-up.

Statistical analyses. All data are reported as mean ± SD or median (first and third quartiles [Q1 to Q3]). Baseline characteristics are given according to quartiles of GLS and MD. Categorical data were tested with the Cochran-Armitage trend test and continuous variables analyzed with analysis of variance or the Kruskal-Wallis test in cases of skewed distribution. All tests were 2-sided and statistical significance was defined as $p < 0.05$. Interobserver and intraobserver reproducibility of GLS and MD was assessed by two readers (M.E. and U.M.M.) in 20 randomly selected patients by Bland-Altman analysis (12).

Cause-specific Cox regression models allowing for competing risks were used to identify univariate predictors of the primary composite outcome. These predictors were then added to a multivariate model to assess any independent information of GLS and MD. A final parsimonious model was obtained by backward selection using $p < 0.10$ for retention. The competing risk associated with the primary composite outcome was death from all causes other than SCD. Unadjusted cumulative incidence curves were calculated for the primary composite outcome stratified by tertiles of GLS and MD. Interactions were analyzed between the covariates in the final parsimonious model. The added values of GLS and MD were assessed using reclassification analysis,

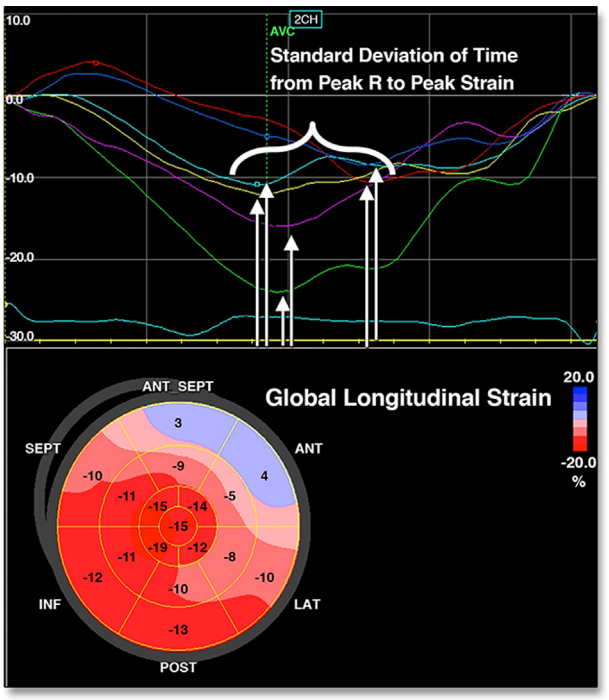

Figure 1. Representative Example of the Calculation of GLS and MD

MD was calculated as the SD of time to peak regional negative strain. ANT = anterior; GLS = global longitudinal strain; INF = inferior; LAT = lateral; MD = mechanical dispersion; POST = posterior; SEPT = septal.

Table 1. Baseline Characteristics According to Tertiles of GLS

	GLS <–15.5% (n = 330)	−15.5% < GLS <−12% (n = 329)	GLS >–12% (n = 329)	p Value
Age, yrs	61.15 ± 11.8	61.01 ± 12.1	65.57 ± 11.8	<0.0001
Male	223 (67.6)	255 (77.5)	236 (71.7)	0.0167
Hypertension	133 (40.3)	141 (42.9)	180 (54.7)	0.0004
Previous MI	36 (10.9)	37 (11.2)	49 (14.9)	0.2265
Diabetes	33 (10.0)	42 (12.8)	54 (16.4)	0.0496
Medical history prior to MI				
ACEi/ARB	71 (21.5)	74 (22.5)	94 (28.6)	0.0725
Beta-blocker	34 (10.3)	31 (9.4)	48 (14.6)	0.0835
ASA/clopidogrel	43 (13.0)	50 (15.2)	57 (17.3)	0.3073
Killip class >1	14 (4.2)	24 (7.3)	103 (31.3)	<0.0001
ECG findings				
HR	67.73 ± 10.7	70.33 ± 11.9	80.01 ± 13.5	<0.0001
QRS duration, ms	94.98 ± 15.6	97.82 ± 18.0	101.06 ± 23.3	0.0008
QTc duration, ms	418.50 ± 36.5	426.60 ± 30.1	431.35 ± 30.1	<0.0001
QRS >120 ms	12 (3.6)	17 (5.2)	29 (8.8)	0.0147
Infarct classification				
Non-STEMI	133 (40.3)	98 (29.8)	80 (24.3)	<0.0001
STEMI	197 (59.7)	231 (70.2)	249 (75.7)	
Troponin T, µg/l	1.0 (0.3–2.5)	2.1 (0.5–4.6)	4.6 (1.6–9.0)	<0.0001
Troponin I, µg/l	10.3 (2.7–50.6)	33.9 (8.2–145.2)	136.0 (23.7–277.8)	<0.0001
LAD involvement	78 (23.7)	108 (32.8)	213 (64.7)	<0.0001
3VD/LM involvement	37 (11.2)	45 (13.7)	78 (23.7)	<0.0001
Intervention				
No PCI	81 (24.5)	66 (20.1)	62 (18.8)	
PCI	65 (19.7)	52 (15.8)	46 (14.0)	0.0420
Primary PCI	184 (55.8)	211 (64.1)	221 (67.2)	
CABG	21 (6.4)	28 (8.5)	34 (10.3)	0.1842
Echocardiography findings				
LVEDV, ml	80.69 ± 22.7	85.99 ± 25.1	97.93 ± 34.4	<0.0001
LVESV, ml	34.59 ± 12.5	42.15 ± 16.1	58.11 ± 28.4	<0.0001
LVEF, %	57.54 ± 7.3	51.74 ± 8.2	42.55 ± 10.3	<0.0001
LVMI, g/m2	84.83 ± 20.0	89.30 ± 22.5	100.90 ± 30.5	<0.0001
MD, ms	49.39 ± 12.4	56.73 ± 13.9	64.40 ± 18.7	<0.0001

Values are mean ± SD, n (%), or median (Q1–Q3).
3VD = 3-vessel disease; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; ECG = electrocardiography; GLS = global longitudinal strain; LAD = left anterior descending; LM = left main; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVMI = left ventricular mass index; MD = mechanical dispersion; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

with calculations of integrated diagnostic improvement (IDI) and category-free continuous net reclassification improvement (NRI_0) allowing for censored data (13). Landmark analysis was performed at 90 days after the index event. Finally, the stability of the parsimonious model was assessed by fitting the model in 1,000 bootstrap replicates of the original dataset. This allowed for an evaluation of the consistency of the associations between the selected covariates and the outcome when small changes in the data were introduced. All statistical analyses were performed using R software (R Development Core Team 2011 R Foundation, Vienna, Austria), with the following packages: Survival, RiskRegression, Hmisc, CAR, survIDINRI, and Publish.

RESULTS

Patient characteristics and outcome. A total of 1,106 patients were enrolled in the study, of whom 56 (5.1%) were excluded prior to strain analyses due to atrial fibrillation (n = 40), ventricular paced rhythm (n = 8), or severe aortic stenosis (n = 8). Of 1,054 patients, 66 were excluded due to missing values in the regional strain traces of >5 segments, leaving 988 patients (mean age: 62.6 ± 12.1 years; 72% male), with a total of 16,488 tracked segments. During a median follow-up of 29.7 months (Q1 to Q3: 23.5 to 32.7), a total of 80 (8.1%) deaths occurred, of which 26 were attributed to SCD (32.5%). Three patients (0.3%) were admitted with VA or successfully resuscitated after SCD, of whom none died during follow-up and all received a secondary prophylactic ICD. A total of 30 patients (3%) had a primary prophylactic ICD implanted during follow-up, of whom 6 (20%) had appropriate therapy (shock: 4; antitachycardia pacing: 2). Of the 30 patients with a primary prophylactic ICD, 2 experienced SCD, with 1 patient having previously received appropriate therapy and 1 without previous appropriate therapy. Thus, a total of 34 patients (3.4%) experienced the primary composite outcome (SCD: 25; VA: 3; appropriate ICD therapy: 6).

Intra observer and interobserver mean differences (95% CI) in agreement for GLS were −0.7 ± 2.5% and −0.05 ± 1.3%, respectively, and for MD were −1.4 ± 7.5 ms and 1.3 ± 10.8 ms, respectively.

Deformation analysis for the prediction of SCD or VA. Impaired GLS and prolonged MD were associated with increasing age, higher prevalence of comorbidities, wider QRS, larger infarct size, more severe angiographic findings, and increasingly worsening measures of LV systolic function (Table 1, Online Table 1). The correlation between LVEF and GLS (r: −0.67; p < 0.0001) was stronger than between LVEF and MD (r: −0.22; p < 0.0001) and GLS and MD (r: 0.40; p < 0.0001) (Figs. 2 and 3). Patients experiencing SCD/VA compared with those without an event were more likely to have had low LVEF (42.4 ± 13.5% vs. 51.4 ± 10.1%), impaired GLS (−9.9 ± 4.0 ms vs. −13.9 ± 3.5 ms), and high MD (70.7 ± 29.7 vs. 56.1 ± 15.3) (Table 2).

On univariate Cox analysis, LVEF (HR: 0.93; 95% CI: 0.90 to 0.96; p < 0.0001), GLS (HR: 1.38; 95% CI: 1.25 to 1.53; p < 0.0001), and MD (HR/10 ms: 1.38; 95% CI: 1.24 to 1.55; p < 0.0001) were significantly associated with SCD/VA. However, GLS exhibited a higher Wald value (40.0) compared with MD (32.7) and LVEF (24.9).

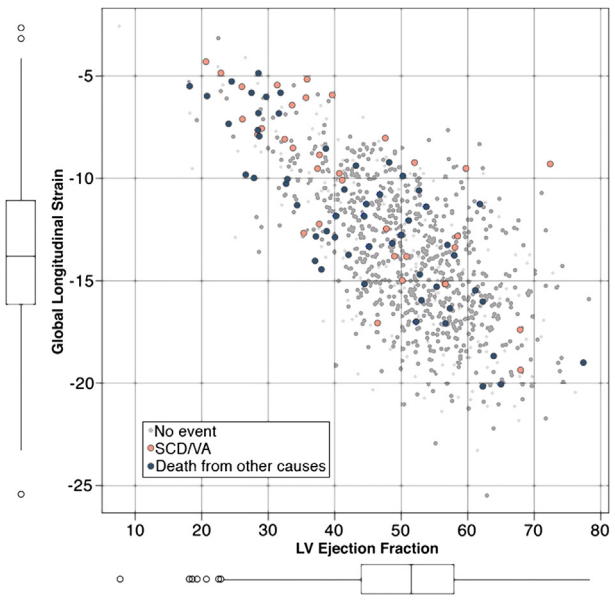

Figure 2. Clinical Outcomes of GLS

Scatterplot of GLS versus left ventricular (LV) ejection fraction, with plotting of clinical outcomes. SCD/VA = sudden cardiac death/ventricular arrhythmias. Other abbreviation as in Figure 1.

On multivariate analysis, age (HR: 1.04; 95% CI: 1.01 to 1.08; p = 0.0210), GLS (HR: 1.24; 95% CI: 1.10 to 1.40; p = 0.0004), and MD (HR/10

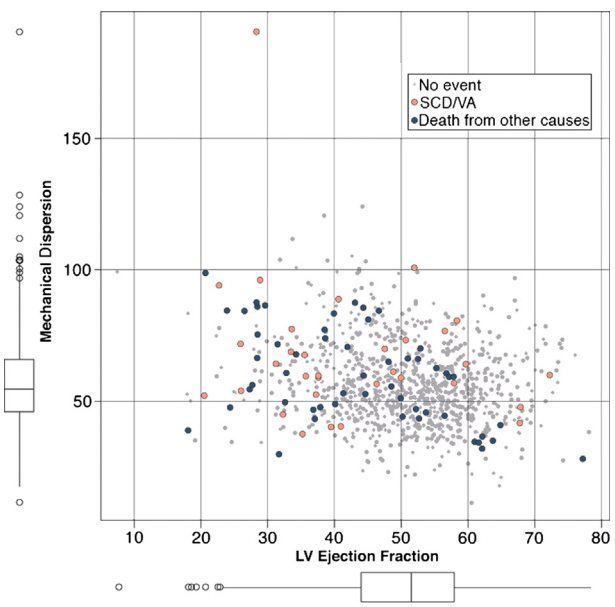

Figure 3. Clinical Outcomes of MD

Scatterplot of MD versus LV ejection fraction, with plotting of clinical outcomes. Abbreviations as in Figures 1 and 2.

Table 2. Baseline Characteristics According to Outcome

	No Event (n = 900)	SCD or VA (n = 34)	Death From Other Cause (n = 54)	p Value
Age, yrs	61.7 ± 11.8	69.7 ± 10.3	73.0 ± 10.8	<0.0001
Male	654 (72.7)	23 (67.6)	37 (68.5)	0.6662
Hypertension	399 (44.3)	21 (61.8)	34 (63.0)	0.0048
Previous MI	101 (11.2)	10 (29.4)	11 (20.4)	0.0012
Diabetes	112 (12.4)	6 (17.6)	11 (20.4)	0.1762
Medical history prior to MI				
ACEi/ARB	208 (23.1)	12 (35.3)	19 (35.2)	0.0404
Beta-blocker	94 (10.4)	8 (23.5)	11 (20.4)	0.0066
ASA/clopidogrel	125 (13.9)	11 (32.4)	14 (25.9)	0.0010
Killip class >1	108 (12.0)	13 (38.2)	20 (37.0)	<0.0001
ECG findings				
HR	72 ± 13	76 ± 17	75 ± 11	0.0412
QRS duration, ms	97 ± 19	108 ± 23	104 ± 19	0.0024
QTc duration, ms	425 ± 33	424 ± 32	433 ± 29	0.1502
QRS >120 ms	45 (5.0)	9 (26.5)	4 (7.4)	<0.0001
Infarct classification				
Non-STEMI	276 (30.7)	14 (41.2)	21 (38.9)	0.2088
STEMI	624 (69.3)	20 (58.8)	33 (61.1)	
Troponin T, µg/l	2.1 (0.5–5.2)	5.0 (0.5–10.9)	2.4 (0.3–6.9)	0.2551
Troponin I, µg/l	36.1 (6.8–179.5)	75.0 (15.1–210.0)	30.0 (7.2–91.3)	0.6899
LAD involvement	363 (40.4)	18 (52.9)	18 (33.3)	0.1882
3VD/LM involvement	137 (15.2)	10 (29.4)	13 (24.1)	0.0238
Intervention				
No PCI	185 (20.6)	11 (32.4)	13 (24.1)	
PCI	148 (16.4)	6 (17.6)	9 (16.7)	0.4946
Primary PCI	567 (63.0)	17 (50.0)	32 (59.3)	
CABG	73 (8.1)	5 (14.7)	5 (9.3)	0.3855
Echocardiography findings				
LVEDV, ml	87.0 ± 27.4	108.0 ± 40.2	96.1 ± 36.1	0.0004
LVESV, ml	43.5 ± 20.8	64.6 ± 32.6	56.7 ± 30.9	<0.0001
LVEF, %	51.4 ± 10.1	42.4 ± 13.5	43.5 ± 13.4	<0.0001
LVMI, g/m2	90.2 ± 24.4	105.2 ± 32.5	107.9 ± 32.4	<0.0001
GLS, %	−13.9 ± 3.5	−9.9 ± 4.0	−11.7 ± 4.0	<0.0001
MD, ms	56.1 ± 15.3	70.7 ± 29.7	59.6 ± 18.2	0.0018

Values are mean ± SD, n (%), or median (Q1–Q3).
Abbreviations as in Table 1.

ms: 1.15; 95% CI: 1.01 to 1.31; p = 0.0320) were independently prognostic in relation to SCD/VA, while LVEDV and QRS >120 ms were borderline significant (p < 0.10) and thus were retained in the model as previously described (Table 3). The cumulative incidence functions of SCD/VA according to tertiles of GLS and MD are shown in Figure 4. As a sensitivity analysis, we excluded patients with antitachycardia pacing therapy only from the primary composite outcome. The results for neither GLS nor MD on univariate analysis (GLS, HR: 1.38 [95% CI: 1.25 to 1.53; p < 0.0001]; MD, HR/10 ms: 1.38 [95% CI: 1.24 to 1.55; p < 0.0001]) or on multivariate analyses (GLS, HR: 1.24 [95% CI: 1.10 to 1.40; p = 0.0004]; MD, HR/10 ms: 1.15 [95% CI: 1.01 to 1.31; p = 0.0320]) changed significantly as a result of this.

Subgroup analyses according to LVEF. Among patients with LVEF <35% (n = 84), SCD/VA occurred in 11 patients (13.1%) during follow-up, and 67.6% (n = 23) of the SCD/VA events occurred in patients with LVEF >35% (n = 904). In patients with LVEF <35%, only GLS (HR: 1.64; 95% CI: 1.13 to 2.39; p = 0.0092) and MD (HR/10 ms: 1.17; 95% CI: 1.01 to 1.37; p = 0.0413) retained independent prognostic information. In patients with LVEF >35%, age (HR: 1.05; 95% CI: 1.01 to 1.09; p = 0.0104), LVEDV (HR/10-mL increase: 1.21; 95% CI: 1.06 to 1.38; p = 0.0045), and GLS (HR: 1.21; 95% CI: 1.05 to 1.40; p = 0.0092) remained independently prognostic (Table 4).

Reclassification. Adding GLS to a model containing the significant and borderline significant variables from the multivariate model age, LVEDV and QRS >120 ms resulted in significant IDI (4.4%; p < 0.05) and NRI_0 (29.6%; p < 0.05) (data not shown). The subsequent addition of MD did not yield further improvement in risk classification, with IDI = 0.02% (p = NS) and NRI_0 = −0.02% (p = NS). Because the multivariate model was data driven and derived in our population only, reclassification was also assessed by adding GLS and MD to LVEF and Killip class >1, which are widely used in daily clinical risk stratification. When adding GLS to LVEF and Killip class >1, significant improvement in reclassification occurred (IDI: 2.4% [p < 0.05]; NRI_0: 21.0% [p < 0.05]), whereas adding MD to LVEF, Killip class >1 and GLS resulted in no further improvement (IDI: 2.4% [p = NS]; and NRI_0: 0.3% [p = NS]). Landmark analysis at 90 days' follow-up demonstrated that GLS was independently associated with SCD/VA (HR: 1.85; CI: 1.23 to 2.79; p = 0.003) after adjustment for LVEF and Killip class >1. However, when replacing GLS with MD, there was only a borderline significant association with short-term risk for SCD/VA (HR: 1.03; 95% CI: 1.00 to 1.05; p = 0.055). Bootstrap validation of the parsimonious model in 1,000 randomly regenerated samples of the original dataset revealed that GLS was consistently associated with SCD/VA, whereas the other covariates in the model were less so (Fig. 5).

Table 3. Univariate and Multivariate HR (95% CI) for the Primary Composite Endpoint SCD/VA

Covariate	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age per yr	1.06	1.03–1.09	0.0003	1.04	1.01–1.08	0.0210
Male	0.77	0.38–1.58	0.4807			
Killip class >1	4.29	2.15–8.58	<0.0001			
LAD involvement	1.43	0.89–2.31	0.1386			
3VD or LM involvement	2.27	1.09–4.75	0.0293			
Diabetes	1.44	0.60–3.49	0.4138			
Previous MI	3.08	1.47–6.45	0.0028			
Troponin	1.26	0.92–1.71	0.1462			
QRS >120 ms	6.30	2.94–13.49	<0.0001	2.20	0.95–5.14	0.0641
LVEF	0.93	0.90–0.96	<0.0001			
LVEDV/10-ml increase	1.21	1.11–1.32	<0.0001	1.11	1.00–1.23	0.0612
LVESV/10-ml increase	1.28	1.17–1.40	<0.0001			
WMSI/0.1 increase	1.39	1.25–1.55	<0.0001			
GLS	1.38	1.25–1.53	<0.0001	1.24	1.10–1.40	0.0004
MD/10 ms	1.38	1.24–1.55	<0.0001	1.15	1.01–1.31	0.0320

CI = confidence interval; HR = hazard ratio; SCD/VA = sudden cardiac death/ventricular arrhythmia; WMSI = wall motion score index; other abbreviations as in Table 1.

DISCUSSION

This study demonstrated in a large cohort of patients with acute MI that early measurement of GLS was an independent and consistent predictor of SCD/VA. Adding GLS to already known risk factors resulted in significantly improved risk reclassification, whereas MD as a marker of contraction in homogeneity provided less additional information.

GLS and MD as markers of arrhythmic risk. VA and SCD after acute MI and in patients with chronic ischemic HF have been shown to be closely related to the extent of myocardial scarring and scar tissue heterogeneity assessed by cardiac magnetic resonance (4). The border zone between viable myocardium and necrotic scar tissue contains areas where viable and necrotic areas are interwoven (14,15), which slows conduction and forms a substrate of post-MI VA (16). The close relationship between GLS and infarct size after acute MI and in chronic ischemic heart disease has previously been demonstrated (9,17). Regional differences in myocardial electrical

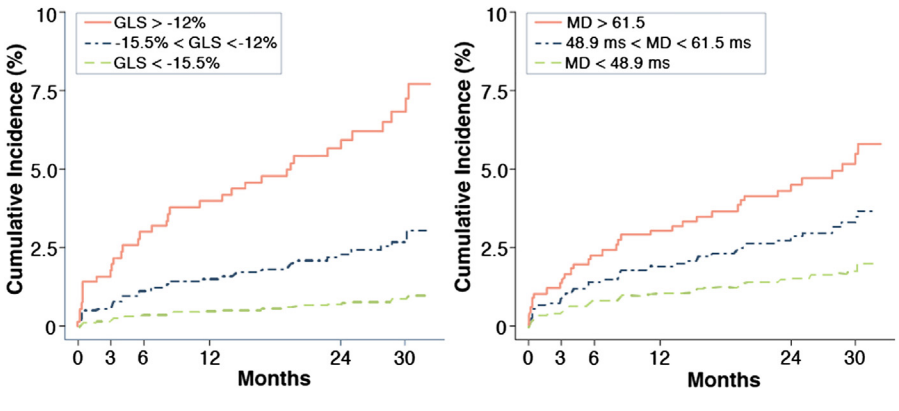

Figure 4. Cumulative Incidence Function of the Primary Composite Outcome SCD/VA

Cumulative incidence stratified according to tertiles of GLS **(left)** and MD **(right)**. Abbreviations as in Figures 1 and 2.

Table 4. Multivariate HR (95% CI) for the Primary Composite Endpoint SCD/VA according to LVEF <35% and LVEF >35%

Covariate	HR	95% CI	p Value
LVEF<35%			
Age/yrs	1.04	0.96–1.12	0.3201
MD/10 ms	1.17	1.01–1.37	0.0413
QRS >120 ms	2.12	0.57–7.89	0.2634
LVEDV/10-ml increase	0.93	0.76–1.13	0.4585
GLS	1.64	1.13–2.39	0.0092
LVEF >35%			
Age/yrs	1.05	1.01–1.09	0.0104
MD/10 ms	0.99	0.76–1.29	0.9387
QRS >120 ms	1.74	0.52–5.78	0.3651
LVEDV/10-ml increase	1.21	1.06–1.38	0.0045
GLS	1.21	1.05–1.40	0.0092

Abbreviations as in Tables 1 and 3.

activity caused by infarct tissue could be reflected by a more heterogeneous myocardial contraction pattern, which has been shown to predict appropriate ICD therapy in post-MI patients with both primary and secondary prophylactic indications (8). We demonstrated that GLS was an independent predictor of SCD/VA and superior to existing echocardiographic parameters, including LVEF. Furthermore, MD as a measure of heterogeneous contraction was also independently related to SCD/VA, albeit not as consistently and strongly as GLS. Adding MD to a model already including GLS did not significantly improve reclassification, and analysis of bootstrap replicates revealed that MD was a less stable predictor than was GLS.

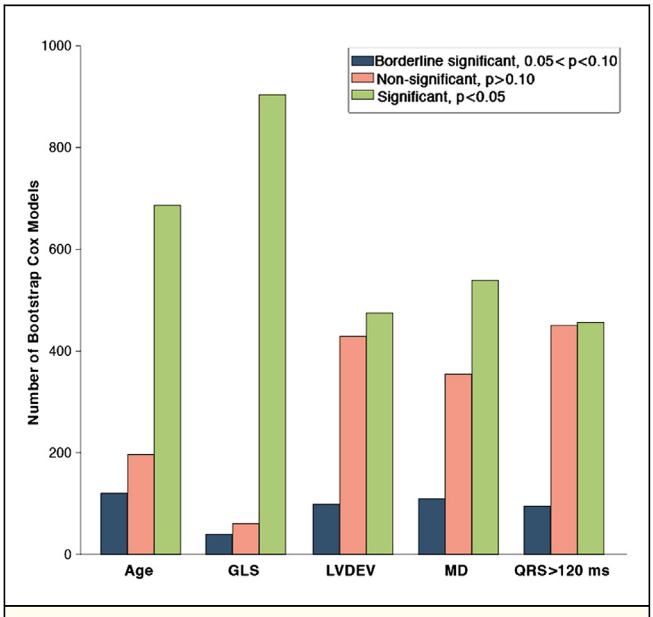

Figure 5. Bar Plot of Bootstrap Validation of the Final Parsimonious Model

The model including age, GLS, LV end-diastolic volume (EDV), MD, and QRS >120 ms was fitted in 1,000 randomly regenerated bootstrap samples of the original dataset. The significance level of each covariate was assessed in each model and counted. Significant association **(green)** was defined as $p < 0.05$; borderline significance **(blue),** as $0.05 < p < 0.10$; and nonsignificance **(pink),** as $p > 0.10$. Abbreviations as in Figures 1 and 2.

Our findings are partly in contrast to those from the study by Haugaa et al. (8). Impaired myocardial segments with smaller strain amplitude often exhibit a flatter curve shape, with smaller strain rate values and prolonged time to peak strain. Identifying the time to peak negative value in such segments will inherently be associated with more variation than in a viable segment with normal deformation. Thus, measurement error alone will contribute to increased values of MD in an LV, with several segments exhibiting impaired strain. The independent prognostic value of MD found in our study, despite these limitations, confirm that the important prognostic information specific to SCD/VA described by Haugaa et al. (8) also pertains to patients with acute MI. However, our bootstrap validation suggests that MD may be a difficult parameter to integrate into daily clinical practice or as a selection criterion for future randomized trials. Haugaa et al. (8) measured MD in patients at varying time points after the MI and the time course of MD after acute MI has not been studied. However, it has been demonstrated, that GLS improves in most patients over 6 to 12 months (18). Thus, the prognostic value of MD relative to GLS might improve with increasing time from the index MI. Indeed our landmark analysis suggests that GLS but not MD was significantly associated with short-term risk for SCD/VA within the first 90 days after MI. A recent multicenter study by Haugaa et al. (19) with contributions from our group suggests that with further time elapsed from the index acute MI, MD may become increasingly important relative to GLS.

Arrhythmia risk prediction after acute MI. The risk for SCD in patients with reduced LVEF is highest in the early aftermath of acute MI as demonstrated in the VALIANT (Valsartan in Acute Myocardial Infarction Trial) trial (2). A substudy of that trial suggested that the cause of SCD in the early phase after acute MI was dominated by recurrent MI and cardiac rupture, whereas after 3 months, arrhythmic SCD became more prevalent (20). The DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) trial failed to demonstrate an overall survival advantage with ICD implantation

early after MI (21). Accordingly, guidelines recommend ICD implantation in eligible patients at least 40 days after the MI (1). However, in both of these trials, only patients with depressed LVEF (DINAMIT) and or clinical HF (VALIANT) were included; thus, the estimates of the relative proportions of SCD etiologies may not necessarily apply to our contemporary MI population, in which only 8.5% had LVEF <35%. The conundrum of greater early risk for SCD/VA after acute MI, lack of survival advantage with early ICD implantation in low LVEF, and the potential for substantial recovery in LV function over time poses a significant challenge. Adding deformation-based indices of LV function to LVEF in the early phase of acute MI could potentially identify high-risk subjects in whom wearable defibrillators (22) could be worn until such time as either LV function is improved or ICD implantation is indicated.

Cardiac magnetic resonance remains the gold standard for quantitative measurement of myocardial scarring. However, due to limited healthcare resources and availability of magnetic resonance imaging, implementing an evaluation of scar burden in all patients with acute MI is prohibitive. The potential gatekeeping role of early echocardiographic deformation imaging in more complex imaging strategies in patients with acute MI should be investigated further.

Study limitations. The primary outcome SCD/VA was rare in our study, which highlights the difficulties of studying novel SCD/VA risk-stratification tools in a prospective way in acute MI. The low number of events renders the multivariate models uncertain, with a high risk for overfitting and potentially discarding covariates with real prognostic value due to low power. The etiology of SCD may not necessarily be ventricular tachyarrhythmia originating in myocardial scar areas; indeed new MI triggering ventricular tachycardia or ventricular fibrillation may account for a significant number of SCD events. Myocardial rupture has also been shown to account for a significant proportion of early SCD, although this complication may be more common in the subset of patients with low LVEF (20). The high degree atrioventricular block may account for a significant proportion of SCD (23), and the relationship between conduction abnormalities after acute MI and deformation patterns is unresolved. Measurements of GLS and MD were performed using a proprietary system (EchoPac, General Electric); however, both GLS and regional myocardial timing intervals can be measured with good reproducibility across different platforms and software algorithms (24,25).

CONCLUSIONS

Early assessment of GLS and MD significantly improves the prediction of SCD/VA in contemporarily managed patients with acute MI. GLS appears to be a particularly promising measure of risk for SCD/VA and, importantly, acts as an early identifier of individuals with LVEF <35 at low risk for malignant arrhythmias.

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Key Words: acute myocardial infarction ■ myocardial strain ■ sudden cardiac death ■ ventricular arrhythmias.

▶ APPENDIX

For a supplemental table, please see the online version of this issue.