

ORIGINAL RESEARCH

Strain Echocardiography Improves Risk Prediction of Ventricular Arrhythmias After Myocardial Infarction

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OBJECTIVES The aim of this study was to test the hypothesis that strain echocardiography might improve arrhythmic risk stratification in patients after myocardial infarction (MI).

BACKGROUND Prediction of ventricular arrhythmias after MI is challenging. Left ventricular ejection fraction (LVEF) <35% is the main parameter for selecting patients for implantable cardioverter-defibrillator therapy.

METHODS In this prospective, multicenter study, 569 patients >40 days after acute MI were included, 268 of whom had ST-segment elevation MIs and 301 non-ST-segment elevation MIs. By echocardiography, global strain was assessed as average peak longitudinal systolic strain from 16 left ventricular segments. Time from the electrocardiographic R-wave to peak negative strain was assessed in each segment. Mechanical dispersion was defined as the standard deviation from these 16 time intervals, reflecting contraction heterogeneity.

RESULTS Ventricular arrhythmias, defined as sustained ventricular tachycardia or sudden death during a median 30 months (interquartile range: 18 months) of follow-up, occurred in 15 patients (3%). LVEFs were reduced ($48 \pm 17\%$ vs. $55 \pm 11\%$, $p < 0.01$), global strain was markedly reduced ($-14.8 \pm 4.7\%$ vs. $-18.2 \pm 3.7\%$, $p = 0.001$), and mechanical dispersion was increased (63 ± 25 ms vs. 42 ± 17 ms, $p < 0.001$) in patients with arrhythmias compared with those without. Mechanical dispersion was an independent predictor of arrhythmic events (per 10-ms increase, hazard ratio: 1.7; 95% confidence interval: 1.2 to 2.5; $p < 0.01$). Mechanical dispersion and global strain were markers of arrhythmias in patients with non-ST-segment elevation MIs ($p < 0.05$ for both) and in those with LVEFs >35% ($p < 0.05$ for both), whereas LVEF was not ($p = 0.33$). A combination of mechanical dispersion and global strain showed the best positive predictive value for arrhythmic events (21%; 95% confidence interval: 6% to 46%).

CONCLUSIONS Mechanical dispersion by strain echocardiography predicted arrhythmic events independently of LVEF in this prospective, multicenter study of patients after MI. A combination of mechanical dispersion and global strain may improve the selection of patients after MI for implantable cardioverter-defibrillator therapy, particularly in patients with LVEFs >35% who did not fulfill current implantable cardioverter-defibrillator indications. (J Am Coll Cardiol Img 2013;6:841–50) © 2013 by the American College of Cardiology Foundation

Although survival after acute coronary syndromes has improved impressively since the introduction of modern revascularization treatment, mortality due to sudden cardiac death (SCD) remains significant. Efforts aimed at predicting and preventing SCD are of high priority (1). SCD is most frequently caused by ventricular arrhythmias resulting from electrical changes in infarcted myocardium and may be prevented by an implantable cardioverter-defibrillator (ICD) (2,3).

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However, the selection of patients for ICD therapy is challenging. Reduced left ventricular (LV) function is an important predictor of SCD, and LV ejection fraction (LVEF) is the most established cardiac mechanical parameter to select patients for ICD therapy, using LVEF <35% as a predictor of adverse outcomes in patients after myocardial infarction (MI) (4). Although LVEF is a helpful predictor of heart failure and death, the ability to predict ventricular arrhythmias is relatively limited (5). The majority of patients dying suddenly after MI have LVEFs >35%, reflecting poor sensitivity of LVEF as a risk-stratifying parameter (6,7).

Better treatment strategies for acute MI have resulted in an increasing number of post-MI patients with preserved LV function. Risk stratification tools targeting patients with relatively preserved ventricular function are therefore needed. These tools may be refined methods of assessing cardiac function and methods targeting mechanisms of ventricular arrhythmias and electromechanical changes.

Myocardial strain derived by echocardiography can accurately quantify regional myocardial function and the timing of contraction (8). It has been demonstrated that the measurement of global strain is more accurate than LVEF in quantifying LV function after MI (9,10) and in predicting mortality (11) and ventricular arrhythmias (12). We therefore

hypothesized that global strain, as a more sensitive measure of impaired LV function, might improve risk stratification in SCD.

Ischemic injuries ultimately lead to inhomogeneous ventricular electrical conduction and contraction. Strain echocardiography can detect subtle changes in the timing of myocardial contraction. We recently reported that mechanical dispersion, a parameter of inhomogeneous ventricular contraction, predicted arrhythmic events in post-MI patients with ICDs better than and independently of LVEF (12). This method is presumed to reflect the electromechanical changes in scarred myocardium. The aim of the present multicenter study was to explore whether strain echocardiography might improve arrhythmic risk stratification in a prospectively included cohort of post-MI patients.

METHODS

This prospective, multicenter study was performed at 5 different centers (Oslo University Hospital, Rikshospitalet, Oslo, Norway; Sørlandet Hospital, Arendal, Norway; Rigshospitalet, Copenhagen, Denmark; Gentofte Hospital, Gentofte, Denmark; and University Hospital Gasthuisberg, Leuven, Belgium). The inclusion criterion was >40-day survival after acute MI, defined as ST-segment elevation or non-ST-segment elevation myocardial infarction (NSTEMI) with elevations in cardiac biomarkers and typical symptoms (13). Echocardiographic examinations were performed at least 40 days after the acute MI (4,14,15). Exclusion criteria were age <18 years, more than mild valvular regurgitation or stenosis, and coronary artery bypass graft surgery before echocardiographic examination. Patients undergoing ventricular pacing were excluded from the analyses.

All patients underwent coronary angiography in the acute phase of MI. Culprit lesion and number of diseased vessels were determined by the judgment of the physician performing angiography.

All patients were given optimal pharmacological therapy as appropriate, including acetylsalicylic acid, clopidogrel, beta-blockers, statins, and angiotensin-

ABBREVIATIONS AND ACRONYMS

GLS = global longitudinal strain

ICD = implantable cardioverter-defibrillator

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

PPV = positive predictive value

PSSI = post-systolic strain index

SCD = sudden cardiac death

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converting enzyme inhibitors or angiotensin receptor blockers.

Arrhythmic events during follow-up were defined as documented sustained ventricular tachycardia, ventricular fibrillation, and SCD. Survival was assessed by medical charts if patients were within the uptake area of the hospital and by the Norwegian death registry Folkeregisteret and corresponding registries and institutions in Denmark and Belgium.

Written informed consent was given by all participants. The study was approved by the Regional Committee for Medical Research Ethics.

Echocardiography. Echocardiography was performed at each center >40 days after MI using Vivid 7 and Vivid 9 systems (GE Vingmed Ultrasound AS, Horten, Norway) and analyzed using commercially available software (EchoPAC; GE Vingmed Ultrasound AS). LVEF was assessed using Simpson's biplane method.

By speckle-tracking echocardiography, longitudinal strain was obtained from apical 4-chamber, 2-chamber, and long-axis views. Three cardiac cycles from each view were recorded. Strain analyses were performed offline at 2 different centers (Oslo University Hospital and Sørlandet Hospital) by 3 independent observers blinded to clinical data (K.H.H., B.L.G., and C.H.E.). Peak strain was assessed in 16 LV segments at aortic valve closure (peak systolic strain) (16). Peak systolic strain from each segment was averaged to global longitudinal strain (GLS) from a 16-segment LV model (17). Post-systolic strain index (PSSI) was calculated from a ratio as (peak post-systolic strain – peak systolic strain)/peak strain during the cardiac cycle (18). If

peak strain (the most negative strain value) occurred during systole, post-systolic strain was defined as zero. The time interval from the electrocardiographic peak R-wave to peak negative strain during the cardiac cycle was assessed in each LV segment (Fig. 1) (12). Mechanical dispersion was defined as the standard deviation of time to peak negative strain from the 16 LV segments, reflecting myocardial contraction heterogeneity (19). Segments with only positive strain, as in dyskinetic segments, and segments with strain curves oscillating around the zero line, as in akinetic segments, were not included in time measurements. Automated software for calculations of mechanical dispersion, GLS, and PSSI was used in this study.

Electrocardiography. Electrocardiograms were recorded at the time of echocardiographic examinations and, therefore, >40 days after the acute MI. QRS durations and QT intervals were measured from 12-lead electrocardiograms recorded at 50 mm/s. QT intervals were heart rate corrected using Bazett's formula.

Troponin analyses. Of 5 participating centers, 3 used troponin T with a reference value of 0.01 µg/l. Two centers used troponin I with a reference value 0.13 µg/l. The maximum troponin level measured during the MI was recorded. Troponin T levels were available in 326 patients and troponin I levels in 171 patients.

Statistical analyses. Continuous data are presented as mean ± SD or as median (interquartile range [IQR]). Comparisons of means were analyzed using unpaired Student *t* tests. Mann-Whitney *U* tests were used for nonparametric data (SPSS version 18, SPSS, Inc., Chicago, Illinois). Proportions were

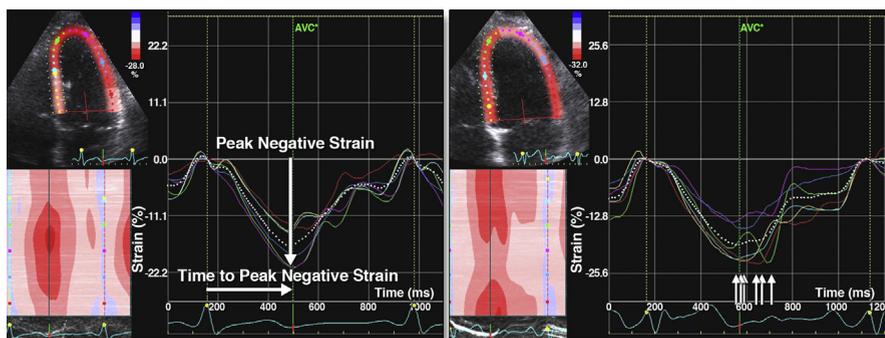


Figure 1. Strain Curves in Patients After MI

Strain curves from the apical 4-chamber view in a patient after myocardial infarction (MI) without arrhythmic events during follow-up (left) and a patient after MI who died of ventricular fibrillation during follow-up (right). White vertical arrows indicate the timing of peak negative strain. The patient who died of ventricular fibrillation showed a more dispersed contraction pattern. The dispersion is also shown in the color-coded images below the 2-dimensional 4-chamber views. The patient who died of ventricular fibrillation (right) showed a more inhomogeneous color coding compared with the survivor (left).

compared using chi-square or Fisher exact tests. Cox regression analysis was performed to identify predictors of arrhythmic events. The multivariate regression was performed by including significant variables from the univariate model ($p < 0.05$). Collinearity was found between LVEDV, LVESV, and LVEF and between GLS and PSSI. These parameters were therefore not included in multivariate analyses together. Separate models were created for LVEF, LVEDV, LVESV, and GLS together with mechanical dispersion. C-statistics were calculated from receiver-operating characteristic curves (20). The value closest to the upper left corner of the receiver-operating characteristic curve was defined as the cutoff value for optimal sensitivity and specificity to identify arrhythmic events. Kaplan-Meier survival analyses with follow-up censored at 24 months were performed for patients with mechanical dispersion above and below 47 and 75 ms, which represented the mathematical and clinical optimal cutoff values. The incremental effect of adding mechanical dispersion to LVEF for predicting arrhythmic events was evaluated with the use of net reclassification index (21). We stratified the risk for arrhythmic events into low risk (0% to <1%), intermediate risk (1% to 3%), and high risk (>3%). Overall model improvement was assessed by the log-likelihood chi-square increase (SAS version 9.2; SAS Institute Inc., Cary, North Carolina) macro of Bergstralh et al. (Mayo Clinic, Rochester, Minnesota). Reproducibility is expressed using intraclass correlation coefficients. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics and mortality data. Clinical characteristics are presented in Table 1. Of 569 patients, 268 had ST-segment elevation MIs and 301 had non-ST-segment elevation MIs. During a median follow-up period of 30 months (IQR: 18 months), 15 patients (3%) experienced ventricular tachyarrhythmias. Of these 15 patients, 10 died suddenly, 4 had documented ventricular tachycardias requiring cardioversion, and 1 received appropriate shock therapy for ventricular tachycardia from an ICD implanted for a primary prevention indication. Two of the patients requiring cardioversion for ventricular tachycardia died. Mortality due to arrhythmias, therefore, was 12 patients. Total mortality was 5% ($n = 25$). The 13 patients who did not die of arrhythmias died of malignancies ($n = 6$), heart failure ($n = 3$), subsequent MI ($n = 1$), alcohol

Table 1. Baseline Characteristics of 569 Patients After MI

Age, yrs	61 ± 11
Women	194 (34%)
Heart rate, beats/min	64 ± 12
STEMI	268 (47%)
Follow-up time, mo	30 (18)
Beta-blockers	524 (92%)
ACE inhibitors/AT2 receptor blockers	349 (61%)
Amiodarone	3 (0.5%)
Troponin T, µg/l	1.7 (5.0)
Troponin I, µg/l	53.0 (132.4)
Angiographic findings	
LAD coronary artery	182 (32%)
Circumflex coronary artery	82 (14%)
RCA	161 (28%)
>1 vessel	81 (14%)
No significant stenosis	63 (11%)

Values are mean ± SD, n (%), or median (interquartile range). ACE = angiotensin-converting enzyme; AT2 = angiotensin II; LAD = left anterior descending; MI = myocardial infarction; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

abuse ($n = 1$), infection ($n = 1$), and an unknown cause ($n = 1$).

Arrhythmic risk prediction by echocardiographic parameters. Echocardiography was performed at study inclusion a median of 4 months (IQR: 3 months) after the MI. LVEFs were reduced in patients with arrhythmic events ($p < 0.01$; Table 2). GLS was markedly lower in those with arrhythmic events ($p = 0.001$), and mechanical dispersion and PSSI were increased ($p < 0.001$ for both) (Table 2). In those with LVEFs >35% ($n = 541$), GLS, mechanical dispersion, and PSSI differed significantly between those with ($n = 12$) and without ($n = 529$) arrhythmic events (GLS: $-16.7 \pm 2.9\%$ vs. $-18.5 \pm 3.3\%$, $p = 0.05$; mechanical dispersion: 59 ± 26 ms vs. 41 ± 17 ms, $p < 0.001$; PSSI: 0.093 ± 0.076 vs. 0.042 ± 0.056 , $p < 0.01$), whereas LVEF did not differ ($54 \pm 12\%$ vs. $57 \pm 9\%$, $p = 0.38$).

Mechanical dispersion was a strong and independent predictor of arrhythmic events by Cox regression analyses (Table 3). By including mechanical dispersion, PSSI, and LVEF in the model, only mechanical dispersion ($p < 0.01$) remained predictive of arrhythmias, while LVEF ($p = 0.48$) and PSSI ($p = 0.21$) were not significant predictors. By including mechanical dispersion together with LVEF only, mechanical dispersion was a significant predictor ($p < 0.001$), whereas LVEF was not ($p = 0.21$). Furthermore, separate inclusion of LVEDV ($p = 0.25$) and LVESV ($p = 0.06$)

Table 2. Echocardiographic and ECG Findings in 569 Patients After MI

	Post-MI Patients Without Arrhythmias (n = 554)	Post-MI Patients With Arrhythmias (n = 15)	p Value
Echocardiographic findings			
LVEDV, ml	103 ± 32	126 ± 51	0.011
LVESV, ml	47 ± 22	73 ± 46	<0.001
LVEF, %	55 ± 11	48 ± 17	0.009
GLS, %	-18.2 ± 3.7	-14.8 ± 4.7	0.001
Mechanical dispersion, ms	42 ± 17	63 ± 25	<0.001
PSSI	0.049 ± 0.73	0.142 ± 0.135	<0.001
ECG findings			
QRS duration, ms	95 ± 16	97 ± 14	0.67
QTc interval, ms	421 ± 39	429 ± 33	0.49
STEMI/NSTEMI	260/294	8/7	0.79
Troponin T	1.8 (4.9)	0.5 (7.6)	0.53

Values are mean ± SD or n. The p values are from Student unpaired t tests, Fisher exact tests, and Mann-Whitney U tests.
 ECG = electrocardiographic; GLS = global longitudinal strain; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NSTEMI = non-ST-segment elevation myocardial infarction; PSSI = post-systolic strain index; QTc = corrected QT; other abbreviations as in Table 1.

showed that only mechanical dispersion predicted arrhythmic events ($p < 0.001$).

Even when excluding patients with LVEFs <35% ($n = 28$), mechanical dispersion remained an excellent and independent predictor of arrhythmic events ($p < 0.01$), indicating that mechanical dispersion may serve as a risk marker in the vast majority of post-MI patients currently not fulfilling primary ICD indications. Mechanical dispersion was increased in those with arrhythmic events compared with those without also when excluding all patients with QRS durations >120 ms ($n = 17$) (60 ± 21 ms vs. 41 ± 17 ms, $p < 0.001$).

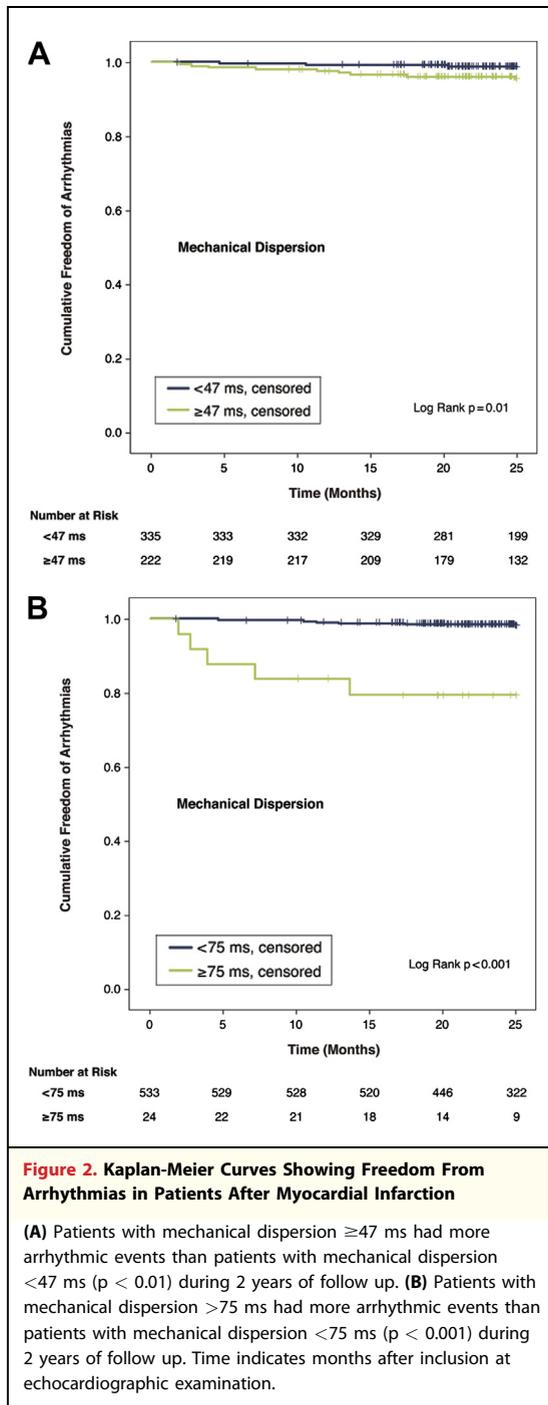
Mechanical dispersion and PSSI discriminated between those with and without arrhythmic events, with a C-statistic of 0.75 for both. The statistically optimal cutoff value for mechanical dispersion

was ≥ 47 ms and identified those with arrhythmic events with sensitivity of 80% and specificity of 62%. Twelve of 15 patients with arrhythmic events had mechanical dispersion ≥ 47 ms ($p < 0.01$). Arrhythmia-free survival was significantly better in those with mechanical dispersion <47 ms (log-rank $p = 0.001$) (Fig. 2A). However, 210 patients without arrhythmic events also had mechanical dispersion ≥ 47 ms, indicating low specificity for clinical use (positive predictive value [PPV] 5%). An arbitrary value for mechanical dispersion of >75 ms increased PPV to 17% and increased specificity to 96% (Fig. 2B). The C-statistics were 0.71 for GLS and 0.64 for LVEF. The statistically calculated optimal LVEF was <57%. In all, 28 patients had LVEFs <35%, and 3 of these had arrhythmic events (PPV 11%). To increase the prediction of

Table 3. Cox Regression Analysis for Ventricular Arrhythmias in 569 Patients After Myocardial Infarction

	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, per yr	1.0 (1.0-1.1)	0.06		
LVEDV, per 10-ml increase	1.2 (1.0-1.3)	0.03		
LVESV, per 10-ml increase	1.3 (1.1-1.5)	<0.001		
LVEF, per 5% decrease	1.4 (1.1-1.7)	0.004	1.2 (0.9-1.5)	0.26
GLS, per 1% increase	1.2 (1.1-1.4)	<0.001	1.0 (0.8-1.2)	0.79
Mechanical dispersion, per 10-ms increase	1.8 (1.4-2.2)	<0.001	1.7 (1.2-2.5)	<0.01
PSSI, per 1%	1.1 (1.0-1.1)	<0.001		

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.



arrhythmic events, we combined our parameters of GLS and mechanical dispersion. GLS worse than -16% has been shown to indicate permanent myocardial dysfunction after MI (9). GLS worse than -16% and mechanical dispersion > 75 ms increased PPV from 17% for mechanical dispersion alone to 21% and was markedly better than PPV for LVEF alone (11%).

The addition of mechanical dispersion to a risk classification model based on LVEF alone resulted in the correct reclassification of 3 patients with arrhythmic events to the high-risk category and 222 patients without arrhythmic events to the low-risk category (net reclassification index 0.35, $p = 0.02$) (Table 4). Adding mechanical dispersion to GLS resulted in a modestly improved reclassification (0.18, $p = 0.18$).

Analyses of all-cause mortality ($n = 25$) showed lower LVEF ($48 \pm 16\%$ vs. $57 \pm 11\%$, $p < 0.001$), reduced GLS ($-15.5 \pm 4.9\%$ vs. $-18.2 \pm 3.6\%$, $p = 0.001$), increased mechanical dispersion (56 ± 26 ms vs. 42 ± 17 ms, $p < 0.001$), and increased PSSI (0.115 ± 0.131 vs. 0.049 ± 0.072 , $p < 0.001$) in those who died.

ST-segment elevation MI versus non-ST-segment elevation MI. In separate analyses of patients with ST-segment elevation MI, LVEF and GLS were reduced and mechanical dispersion and PSSI increased in those with arrhythmic events (Table 5). In patients with NSTEMIs, however, only strain parameters such as GLS, mechanical dispersion, and PSSI were markers of arrhythmias, whereas LVEF was not, indicating the potential role of strain echocardiography in the risk stratification of patients with NSTEMIs (Table 5).

Feasibility and reproducibility. Strain amplitudes could be assessed in 91% and time measurements in 88% of all myocardial segments. In 12 patients, strain measurements were not assessed, because of poor image quality. Interobserver and intraobserver intraclass correlation coefficients were 0.90 and 0.92, respectively, for GLS measurements and 0.82 and 0.89, respectively, for measurements of mechanical dispersion.

DISCUSSION

This study showed that strain echocardiography added prognostic value in arrhythmic risk stratification of patients after MI. Low LVEF was associated with arrhythmic events but failed as a predictor in those with relatively preserved function. GLS was a more sensitive predictor of arrhythmic events compared with LVEF and was useful also in patients with LVEFs $> 35\%$. Mechanical dispersion, a novel risk-stratifying parameter, reflects contraction heterogeneity and was an excellent predictor of arrhythmic events independently of LVEF. Prediction of arrhythmias improved considerably when using a combination of the parameters global strain and mechanical dispersion compared with the use of LVEF alone.

Table 4. Reclassification for the Total Cohort on the Basis of Models Using LVEF and Mechanical Dispersion in Patients After Myocardial Infarction With or Without Arrhythmic Events During 30 Months of Follow-Up

Model With LVEF	Model With Mechanical Dispersion			Total
	Low Risk	Intermediate Risk	High Risk	
Patients with arrhythmic events				
Low risk	0	0	1	1
Intermediate risk	0	5	2	7
High risk	1	1	5	7
Total	1	6	8	15
Patients without arrhythmic events				
Low risk	9	19	4	32
Intermediate risk	151	166	47	364
High risk	23	48	77	148
Total	183	233	128	544

Net reclassification improvement 0.35 (p = 0.02).
 Abbreviation as in Table 2.

Myocardial function and risk stratification of ventricular arrhythmias. In patients after MI, LVEF is an established marker of prognosis, with a value <35% indicating worse prognosis. Current ICD indications in patients after MI rely almost entirely on LVEF (4). However, it is well known that arrhythmic risk stratification by LVEF is insufficient (5,7). In addition to the limited sensitivity of LVEF, specificity is limited. Buxton et al. (5) reported that 2-year predicted arrhythmic death risk in post-MI patients whose only risk factor was

LVEF <30% was 5%, indicating that only 1 of 15 patients who satisfied current guidelines for a primary prophylactic ICD would benefit from ICD therapy (7). We found slightly better prediction using LVEF, with 3 of 28 patients with LVEFs <35% experiencing arrhythmic events. However, in those with relatively preserved ventricular function (LVEF >35%), LVEF was not useful as a predictor of arrhythmic events. A statistical cutoff for LVEF of <57% for the detection of arrhythmic events, as found in our study, is not clinically useful.

Table 5. Echocardiographic Findings in 301 Patients After NSTEMI and 268 Patients After STEMI

	Patients Without Arrhythmias	Patients With Arrhythmias	p Value
NSTEMI	294	7	
LVEDV, ml	108 ± 30	100 ± 39	0.51
LVESV, ml	46 ± 21	50 ± 38	0.60
LVEF, %	58 ± 11	54 ± 20	0.33
GLS, %	-17.8 ± 3.3	-14.7 ± 4.5	0.02
Mechanical dispersion, ms	44 ± 16	71 ± 30	<0.001
PSSI	0.047 ± 0.066	0.159 ± 0.065	<0.001
STEMI	260	8	
LVEDV, ml	97 ± 34	152 ± 50	<0.001
LVESV, ml	48 ± 25	96 ± 45	<0.001
LVEF, %	53 ± 10	43 ± 13	<0.01
GLS, %	-18.5 ± 4.0	-14.9 ± 5.1	0.01
Mechanical dispersion, ms	40 ± 18	55 ± 19	0.02
PSSI	0.051 ± 0.080	0.127 ± 0.179	0.01

Values are n or mean ± SD. The p values are from Student unpaired t tests and Fisher exact tests.
 Abbreviations as in Tables 1 and 2.

An emerging parameter in assessing LV function is GLS. GLS has been shown to be more accurate than LVEF in quantifying myocardial function in patients with acute MI and in those with chronic MI (9). Furthermore, it has been shown that GLS predicts mortality and ventricular arrhythmias better than LVEF in cardiac patients (10,11). Despite the small number of events in our study, we found that GLS was a marker of arrhythmic events in patients with LVEFs >35%. Similarly, GLS was a marker of arrhythmic events in patients with NSTEMIs, whereas LVEF was not. These results indicate that GLS may be a more accurate marker to detect small changes in myocardial function, which may be important in arrhythmic risk stratification.

The better prediction of GLS can be explained by the more detailed information of myocardial function obtained using this method. GLS is derived from 3 echocardiographic apical views and averaged from 16 LV segments. LVEF is derived from volumetric measurements made at 2 different phases of the cardiac cycle and from only 2 apical views. Subtle, but important, remodeling in smaller regions of the left ventricle may therefore be missed by LVEF. Our findings are in accordance with previous studies showing that GLS can detect subtle myocardial changes of prognostic importance in patients after MI (16,22,23) and improve arrhythmic risk stratification (12).

Although measurements of GLS represent a refinement of LVEF, mechanical dispersion represents a novel approach in the risk assessment of ventricular arrhythmias. Mechanical dispersion predicted arrhythmias in patients after MI independently of GLS and PSSI and, furthermore, independently of more traditional echocardiographic parameters such as LVEF, LVEDV, and LVESV. Importantly, statistical analysis of reclassification found that adding mechanical dispersion to LVEF resulted in superior classification of patients experiencing arrhythmic events as well as patients not experiencing events. It is important to acknowledge that we did not aim to exclude patients from ICD therapy but to evaluate patients with arrhythmic risk who do not fulfill current ICD indications. In addition to mechanical dispersion, PSSI was a marker of ventricular arrhythmias. This finding underscores that post-systolic events are important in arrhythmogenesis in patients after MI. The presence of post-systolic strain will increase mechanical dispersion. Mechanical dispersion reflects myocardial contraction heterogeneity, subtle as shown in patients with long-QT syndrome (19,24) or apparent such as dyssynchrony in patients with dilated

cardiomyopathy (25) and after MI (12). We recently showed associations between mechanical dispersion and increased risk for ventricular arrhythmias in various cardiac diseases (12,19,24,26). In this study, we explored the ability of mechanical dispersion to act as an independent predictor of arrhythmias in a large cohort of prospectively included patients after MI. Interestingly, mechanical dispersion predicted arrhythmic events independently of LVEF and was an excellent predictor also in patients with preserved LV function. Furthermore, mechanical dispersion remained a marker of arrhythmias when excluding patients with wide QRS intervals. Increased mechanical dispersion could therefore not be attributed to the presence of bundle branch block.

Electrical and mechanical alterations are ultimately associated. Mechanical dispersion can be regarded as the mechanical consequence of electrical alterations and tissue abnormalities. One might speculate that mechanical dispersion represents fundamental arrhythmogenic risk due to inhomogeneous electrical conduction and repolarization (26).

Clinical implications. We propose that echocardiographic evaluation should be performed in patients in stable condition after acute MI. Measurements of LVEF should be supplemented by strain analyses. In patients not fulfilling current ICD criteria with GLS worse than -16% , mechanical dispersion should be analyzed, and a value >75 ms may act as a threshold. In this study, the combination of these parameters improved the PPV of arrhythmic events to 21% from 11% by LVEF alone. This strategy may improve the selection of patients after MI for primary ICD therapy. Future studies may address whether strain echocardiography in the acute phase after MI provides prognostic information.

In our study, almost 50% of deaths were sudden and of probable arrhythmic origin. This underscores that risk stratification of arrhythmias in patients after MI is of vital importance. This study did not aim to exclude patients who fulfilled primary indications for ICD implantation. Our results supported current guidelines, showing that LVEF $<35\%$ was a marker of adverse outcomes. However, additional strain analyses of these patients could offer ICD therapy to further patients at risk. GLS has emerged as an accurate parameter of LV function and has been implemented in routine clinical practice at several centers worldwide. Our study suggests that the use of GLS may refine risk stratification in patients after MI and be of particular importance in patients with NSTEMIs.

Study limitations. The event rate in our population was low, and our results need to be replicated in larger

datasets and in high-risk patients. A possible explanation for the low event rate is that all patients in this study underwent coronary angiography at the time of acute MI and were revascularized if indicated. The low event rate in this study also means that multi-variable regression analyses should be interpreted with care. Furthermore, because of current ICD indication guidelines (4), patients were included >40 days after MI, which may have influenced survival data.

Strain analyses require experience and training, similar to other echocardiographic measurements. In our study, 3 independent observers performed strain analyses, with excellent interobserver reliability.

Strain analyses are time consuming, but incremental improvements in software applications have reduced the time needed for analyses. We used fully automated software for calculations of mechanical dispersion and GLS in this study. The time needed for strain analyses in each patient was approximately 5 min. For clinical use, without saving data for research purposes, about 3 min were necessary for each patient.

Vendor differences in absolute strain values may result in different clinical cutoff values for GLS. Time measurements, however, as used for mechanical dispersion, do not differ significantly among vendors (27).

CONCLUSIONS

Mechanical dispersion improved the risk classification of ventricular arrhythmias and predicted arrhythmias independently of LVEF in this prospective study of post-MI patients. The combination of mechanical dispersion and GLS increased the prediction of arrhythmic events. Strain echocardiography may potentially save additional lives by the more appropriate selection of patients for ICD therapy who do not fulfill current ICD indications.

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