Deformation imaging and three-dimensional echocardiography : implications on clinical management of patients with ischemic heart disease

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CHAPTER 2

Prognostic implications of left ventricular regional function heterogeneity assessed with two-dimensional speckle tracking in patients with ST-segment elevation myocardial infarction and depressed left ventricular ejection fraction

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ABSTRACT

The aim of the current study was to evaluate the prognostic implications of myocardial tissue heterogeneity assessed with two-dimensional speckle-tracking echocardiography in patients three months after first ST-segment elevation myocardial infarction (STEMI) with left ventricular ejection fraction (LVEF) ≤35%. For this purpose, a total of 79 patients with first STEMI and LVEF ≤35% at three months postinfarction were evaluated. Based on left ventricular (LV) speckle-tracking longitudinal strain echocardiography, the infarct core, border zone, and remote zone at baseline and three months' follow-up were defined. Patients were followed for the occurrence of the composite end point of appropriate implantable cardioverter-defibrillator (ICD) therapy and/or cardiac mortality. During a median follow-up of 46 months, 13 patients (17%) reached the composite end point. At baseline, patients with and without events showed comparable values of LV longitudinal strain at the infarct, border, and remote zones. However, at three months' follow-up, patients with events showed significantly more impaired longitudinal strain at the border zone (–6.8 ± 3.1% vs. –10.5 ± 4.9%, p=0.002), whereas LVEF was comparable (28 ± 6% vs. 31 ± 4%, p=0.09). The median three-month LV longitudinal strain at the border zone was –9.4%. Multivariate Cox regression analysis demonstrated that three-month longitudinal strain >–9.4% at the border zone was independently associated with the composite end point (hazard ratio 3.94, 95% confidence interval 1.05–14.70, p=0.04). In conclusion, regional longitudinal strain at the border zone three months post-STEMI is associated with appropriate ICD therapy and cardiac mortality.

INTRODUCTION

Myocardial tissue heterogeneity has been associated with sudden cardiac death and all-cause mortality in patients with ischemic heart disease.[1-4] Among several pathophysiologic mechanisms of ventricular arrhythmias, myocardial scar has been associated with increased risk for fatal arrhythmias.[5] Especially, the border zone between the myocardial scar tissue and preserved viable myocardial tissue is an important anatomic substrate for the occurrence of re-entrant ventricular arrhythmias.[5,6]

An implantable cardioverter-defibrillator (ICD) for primary prevention early after myocardial infarction is a class I indication for patients who have symptoms of heart failure (New York Heart Association (NYHA) functional class II–III) and left ventricular ejection fraction (LVEF) ≤35% at least 40 days after the index infarct.[7] However, the results of randomized controlled trials including patients immediately after STEMI have not convincingly shown the benefit of ICD in this population.[8,9] LVEF was an established criterion to select patients for ICD implantation in those trials and is included in current guidelines.[7] However, LVEF has proved to have limited specificity in identifying patients who will benefit from ICD.[10,11] Evaluation of myocardial tissue heterogeneity with novel imaging techniques has shown improved accuracy for the prediction of ventricular arrhythmias.[12-14] Recently, two-dimensional (2D) speckle-tracking echocardiography has been introduced as a novel technique to assess regional myocardial function and heterogeneity in the infarct core, border zone, and remote area in patients with stable ischemic chronic heart disease.[3,14] However, changes in tissue heterogeneity early after myocardial infarction and its impact on long-term outcome of patients have not been explored. Therefore, the objective of the current study was to evaluate the prognostic implications of myocardial tissue functional heterogeneity, assessed with 2D speckle-tracking echocardiography at three months' follow-up, after first ST-segment elevation myocardial infarction (STEMI) in patients with a LVEF ≤35% postinfarction.

PATIENTS AND METHODS

Patient population

Patients presenting with a STEMI at the Leiden University Medical Center were included in an ongoing registry (MISSION!).[15] All patients were treated with primary percutaneous coronary intervention according to the institutional MISSION! protocol, which is based on American College of Cardiology/American Heart Association and European Society of Cardiology guidelines. According to this protocol, optimal medical therapy was initiated early during hospitalization, 2D echocardiography was performed within 48 h of admission, and all patients were followed at the outpatient clinic at three, six, and 12 months. A repeat 2D echocardiography was performed at three months.

In the present evaluation, patients with a first STEMI and LVEF ≤35% at three months' follow-up were included (Figure 1). During follow-up, patients who experienced ventricular arrhythmias (sustained monomorphic ventricular tachycardia or ventricular fibrillation) or survived an out-of-hospital cardiac arrest received an ICD device as secondary prevention (after exclusion of any completely reversible cause). Patients who developed NYHA II–III heart-failure symptoms and showed a LVEF ≤35% or had NYHA functional class I and a LVEF ≤30% received an ICD device as primary prevention, as recommended by current guidelines.[7]

In addition, global and regional left ventricular (LV) longitudinal strain was assessed at baseline and at three months' follow-up with 2D speckle-tracking echocardiography. The infarct core, peri-infarct or border zone, and the remote areas were identified. The association between regional LV longitudinal strain and the occurrence of the combined end point (cardiac mortality or appropriate ICD therapy) was evaluated. Patients who presented with appropriate ICD therapy before the three-month echocardiogram, who received cardiac resynchronization therapy, or who had suboptimal image quality for speckle-tracking analysis or inaccurate speckle tracking were excluded.

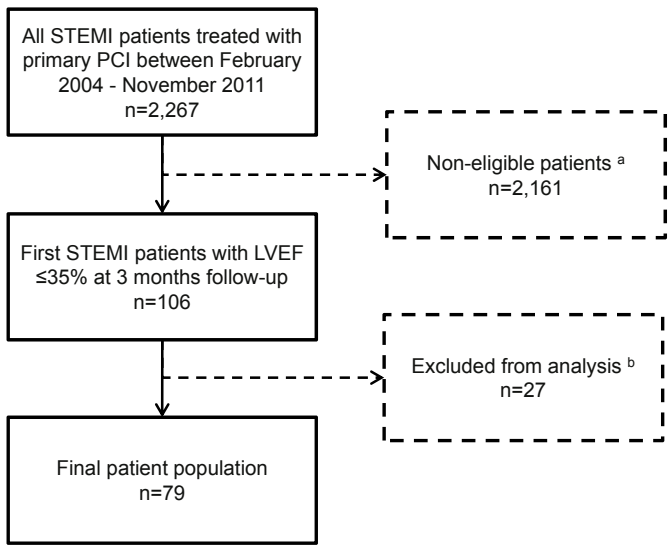

Figure 1. Flowchart of the patient population. [a] Patients were not eligible if they had a myocardial infarction prior to inclusion in the MISSION! registry, if echocardiography was not available at baseline and/or 3 months, and if left ventricular ejection fraction (LVEF) at 3 months was >35%. [b] Reasons for exclusion were (1) implantation of a cardiac resynchronization therapy device with defibrillator capabilities (n=15), (2) speckle-tracking analysis was not feasible at baseline and/or 3 months' follow-up (n=5), (3) presentation of appropriate implantable cardioverter-defibrillator therapy before the 3-month echocardiogram (n=1), and (4) inclusion of baseline and/or 3-month echocardiograms in a previous study (n=6).[3] *PCI* = percutaneous coronary intervention; *STEMI* = ST-segment elevation myocardial infarction.

Clinical and echocardiographic data were collected at the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center) and the echocardiography database, respectively, and retrospectively analyzed. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent.

Echocardiography

Images were obtained at rest with the patient in the left lateral decubitus position using a commercially available system (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway). Data acquisition was performed with a 3.5-MHz transducer at a depth of 16 cm in the standard parasternal and apical views. During breath hold, M-mode and 2D images were obtained and saved in cine-loop format. Data analysis was performed offline (EchoPAC version 111.0.0; General Electric-Vingmed). LV volumes and function were assessed by tracing the LV end-systolic volumes and end-diastolic volumes in the apical four- and two-chamber views. Using the biplane Simpson's method, LVEF was calculated.[18] Mitral regurgitation was graded as mild (vena contracta width <0.3 cm), moderate (vena contracta width 0.3–0.69 cm), or severe (vena contracta width ≥0.7 cm).[19] Diastolic function was assessed by positioning the Doppler sample volume between the tips of the mitral leaflets and acquiring the pulsed-wave Doppler spectral signal of the mitral valve inflow. Peak early (E) and late (A) diastolic velocities and E-wave deceleration time were assessed. E' was measured with tissue Doppler imaging at the septal side of the mitral annulus in the apical four-chamber view and E/E' ratio was calculated.[20] Finally, maximal left atrial volume was measured according to the biplane Simpson's technique in the apical four- and two-chamber views and indexed to the body surface area, as recommended.[18]

Speckle tracking: global LV longitudinal strain and regional tissue heterogeneity

To evaluate global and regional longitudinal LV function, 2D speckle-tracking analyses were performed on standard routine gray-scale images of apical four-chamber, two-chamber, and long-axis views using Q-analysis (EchoPAC version 111.0.0; General Electric-Vingmed).[21] For reliable analysis, images were recorded with a frame rate ≥40 frames per second. First, the LV end-systolic frame was defined by establishing the closure of the aortic valve in the apical long-axis view. Thereafter, the time between R-wave and aortic valve closure was automatically measured and used as a reference for strain analysis at the two- and four-chamber views. The LV endocardial border was automatically traced at end-systole after manual definition of the mitral annulus and LV apex with three index points in all three apical views. The width of the region of interest was manually adjusted to include the entire myocardium. The myocardium was then automatically tracked throughout the cardiac cycle by the software, allowing for manual adjustment of the region of interest to ensure proper myocardial tracking. The software indicated the segments that have poor tracking and allowed for their exclusion. The global and the regional values of peak systolic

LV longitudinal strain were provided by the software in a 17-segment "bull's eye" plot. As described previously, an infarct segment was defined as a longitudinal strain value >–5%.[3,14] All segments immediately adjacent to an infarct segment were defined as border segments. A remote segment was defined as any segment that was not an infarct or border segment. Thereafter, the longitudinal strain values at the infarct, border, and remotes zones were manually averaged (Figure 2).[3]

Previous work has reported intra- and interobserver variabilities for global longitudinal strain analysis in our laboratory as mean absolute differences ± 1 standard deviation of 1.2 ± 0.5% and 0.9 ± 1.0%, respectively.[3] Furthermore, to define the segmental reproducibility, segmental strain measurements were repeated for 10 randomly selected patients (170 segments) at least 1 month apart by the same observer on the same echocardiographic images and by a second independent observer. For segmental strain assessment, the intra- and interobserver variability were 0.08 ± 2.36% and –0.02 ± 2.67%, respectively.

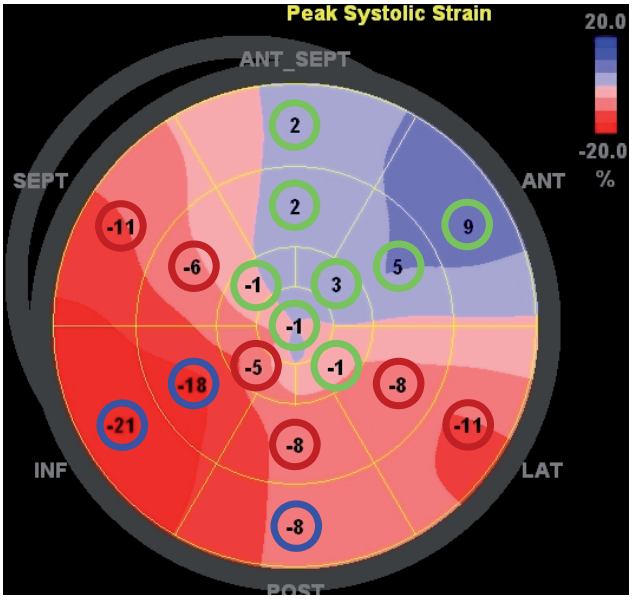

Figure 2. Graphic representation of a 17-segment "bull's eye" plot that was automatically generated by two-dimensional speckle-tracking echocardiography. Eight left ventricular segments (basal anteroseptal, basal anterior, midanteroseptal, midanterior, apical anterior, apical lateral, apical septal, and apical cap) were classified as infarct segments as defined by a segmental longitudinal strain value >–5%. The border segments were the basal lateral, basal septal, midlateral, midseptal, midposterior, and apical inferior. Remote segments were all other segments not defined as infarct or border segments. *ANT* = anterior wall; *ANT_SEPT* = anteroseptal wall; *INF* = inferior wall; *LAT* = lateral wall; *POST* = posterior wall; *SEPT* = septal wall.

Follow-up and end point definitions

After discharge, patients were followed according to the institutional STEMI protocol.[15] By reviewing medical records, retrieval of survival status through municipal civil registries, and telephone interviews, data on the occurrence of adverse events after discharge were collected, including all-cause mortality, cardiac mortality, implantation of ICD devices, and appropriate ICD therapies, with the date of the three-month echocardiogram as the follow-up onset. Appropriate ICD therapy was defined as antitachycardia pacing or shock for ventricular tachycardia or ventricular fibrillation. This was documented from the ICD

device interrogation printouts and confirmed by independent clinical cardiologists. From the ICD device interrogation printouts, time to appropriate ICD therapy was calculated. A composite end point of cardiac mortality or appropriate ICD therapy was used. Patients without data in the last six months were considered lost to follow-up. Data of these patients were included up to the last date of follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median with 25th and 75th percentiles where appropriate. Categorical data are expressed as frequencies and percentages. To obtain a Gaussian distribution, peak troponin T and peak creatine phosphokinase (CPK) levels were log-transformed. These transformed data were used in statistical tests that required normality (or symmetry). Data were then back-transformed to the original data scales and expressed as median with interquartile ranges.

Patients were divided into two subgroups based on event status (cardiac mortality or appropriate ICD therapy, whichever came first) during long-term follow-up: patients suffering from events and patients without events. Baseline and three-month clinical and echocardiographic data were compared between these subgroups with the unpaired Student's *t* test and χ^2 test. Subsequently, baseline and three-month LV longitudinal strain measurements were compared in the two subgroups with the paired *t* test.

In addition, event rates of the composite end point were analyzed and displayed using cumulative incidence curves. Based on the median value of longitudinal strain measured at the border zone at three months' follow-up, patients were dichotomized into two groups and the groups were compared using cause-specific Cox regression modeling.

Finally, univariate and multivariate Cox proportional-hazards analyses were performed to assess the association between myocardial tissue heterogeneity assessed by 2D speckle-tracking echocardiography, global longitudinal strain, and LVEF with the composite end point. Competing risks were approached by cause-specific hazard modeling. Significant ($p<0.05$) univariate variables were included in a multivariate Cox regression model. The number of variables included were limited to the number of events to avoid overfitting the model. To avoid multicollinearity between univariate parameters, a correlation coefficient of <0.7 was set. Relative risks, expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs), were derived from a Cox regression model. To evaluate the relative merits of tissue heterogeneity assessed by 2D speckle-tracking echocardiography, global longitudinal strain, and LVEF to predict the occurrence of the combined end point, three-month LV longitudinal strain measurements, global longitudinal strain values, and LVEF were introduced separately to a clinical model containing age and peak CPK as univariate variables. Thereafter, the Harrell's *c* statistic for each model was calculated.

All statistical tests were two-sided and $p<0.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS software (version 17.0; SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 106 patients presenting with a first STEMI and LVEF ≤35% at three months' follow-up were eligible for the current study. Fifteen patients received a cardiac resynchronization therapy device with defibrillator capabilities and, accordingly, were excluded from the analysis. Furthermore, in five patients (5%), speckle-tracking analysis was not feasible at baseline and/or three months' follow-up. One patient presented with appropriate ICD therapy before the three-month echocardiogram and was also excluded. Finally, another six patients were excluded, since the echocardiograms of these patients (the baseline echocardiogram of three patients and the three-month echocardiogram of another three patients) were already included in a previous study.[3] Therefore, the final patient population included 79 patients. Baseline clinical and echocardiographic characteristics of the total patient population are summarized in Table 1. Most patients were men (81%) and the mean age of the patients was 61 ± 11 years. At baseline, mean LVEF was 36 ± 7% and moderate to severe mitral regurgitation was observed in 11 patients (14%).

Follow-up

In total, 42 patients (53%) received an ICD device during follow-up after STEMI. The median duration between the date of admission for the index infarction and the date of device implantation was six months (interquartile range 3–11 months). The reason for ICD implantation was primary prevention in 93% of the recipients (n=39) and secondary prevention in 7% (n=3).

Long-term follow-up was completed in all patients and the median follow-up duration was 46 months (interquartile range 26–60 months). During follow-up, eight patients (10%) presented with appropriate ICD therapy for ventricular tachycardia/fibrillation. All-cause mortality rate in the overall population was 13% (n=10). Cardiac cause of death was reported in six patients while the remaining four patients died of noncardiac cause. A total of 13 patients (17%) reached the composite end point of cardiac mortality or appropriate ICD therapy.

The study population was divided into two groups: patients with events (cardiac mortality or appropriate ICD therapy) and patients without events. Baseline clinical and echocardiographic characteristics of these patients are summarized in Table 1. Patients with events had higher peak cardiac enzymes compared with patients without events (6,543 (interquartile range 4,126–9,085) vs. 3438 (interquartile range 1,997–5,392) U/L, p=0.007

and 14.2 (interquartile range 10.8–22.3) vs. 8.5 (interquartile range 4.5–15.1) μg/L, p=0.04 for peak CPK and peak cardiac troponin T levels, respectively). No significant differences were observed in LVEF between patients with and without events (33 ± 7% vs. 36 ± 7%, p=0.16).

Table 1. *Patients' characteristics*

	Total patient population (n=79)	Events (n=13)	No events (n=66)	p*
Clinical characteristics				
Age (years)	61 ± 11	56 ± 9	62 ± 11	0.06
Male gender	64 (81%)	12 (92%)	52 (79%)	0.26
Killip class ≥2	7 (9%)	3 (23%)	4 (6%)	0.05
QRS duration (ms)	103 ± 22	113 ± 25	101 ± 21	0.12
Medical history				
Current smoking	33 (42%)	9 (69%)	24 (36%)	0.03
Diabetes	16 (20%)	3 (23%)	13 (20%)	0.78
Family history of CAD	36 (46%)	6 (46%)	30 (46%)	0.96
Hypercholesterolemia	14 (18%)	4 (31%)	10 (15%)	0.19
Hypertension	33 (42%)	3 (23%)	30 (46%)	0.14
Coronary angiography				
LAD as culprit vessel	58 (73%)	12 (92%)	46 (70%)	0.09
Multivessel disease	48 (61%)	9 (69%)	39 (59%)	0.49
TIMI 2–3 flow	77 (98%)	13 (100%)	64 (97%)	0.53
Laboratory tests				
Peak CPK level (U/L)	3,962 (2,174–5,678)	6,543 (4,126–9,085)	3,438 (1,997–5,392)	0.007
Peak cTnT level (μg/L)	9.8 (4.7–15.9)	14.2 (10.8–22.3)	8.5 (4.5–15.1)	0.04
eGFR (mL/min/1.73 m^2)	96 ± 33	113 ± 38	93 ± 32	0.06

Table 1. *Patients' characteristics (continued)*

	Total patient population (n=79)	Events (n=13)	No events (n=66)	p*
Medication at discharge				
ACE-inhibitors/ARBs	78 (99%)	12 (92%)	66 (100%)	0.02
Antiplatelets	79 (100%)	13 (100%)	66 (100%)	1.00
β-Blockers	72 (91%)	11 (85%)	61 (92%)	0.37
Statins	78 (99%)	13 (100%)	65 (99%)	0.66
Antiarrhythmics class I	1 (1%)	0 (0%)	1 (2%)	0.66
Antiarrhythmics class II	71 (90%)	11 (85%)	60 (91%)	0.49
Antiarrhythmics class III	3 (4%)	0 (0%)	3 (5%)	0.43
Antiarrhythmics class IV	1 (1%)	0 (0%)	1 (2%)	0.66
Echocardiography				
LVESV (mL)	83 ± 34	90 ± 34	82 ± 34	0.46
LVEDV (mL)	129 ± 47	134 ± 43	128 ± 48	0.69
LVEF (%)	36 ± 7	33 ± 7	36 ± 7	0.16
Global longitudinal strain (%)	–10.8 ± 2.9	–8.9 ± 3.7	–11.1 ± –2.6	0.01
LAVI (mL/m^2)	20 ± 7	16 ± 5	21 ± 8	0.01
E/A ratio	1.00 ± 0.44	1.07 ± 0.35	0.98 ± 0.46	0.51
DT (ms)	182 ± 70	179 ± 81	183 ± 68	0.87
E/E' ratio	16 ± 9	13 ± 5	17 ± 9	0.17
Moderate to severe MR grade	11 (14%)	2 (15%)	9 (14%)	0.87
ICD recipients	42 (53%)	11 (85%)	31 (47%)	0.01

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage).
ACE = angiotensin-converting enzyme; *ARB* = angiotensin receptor blocker; *CAD* = coronary artery disease; *CPK* = creatine phosphokinase; *cTnT* = cardiac troponin T; *DT* = deceleration time; *E/A* = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); *E/E'* = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); *eGFR* = glomerular filtration rate estimated with the Cockcroft–Gault formula; *ICD* = implantable cardioverter-defibrillator; *LAD* = left anterior descending coronary artery; *LAVI* = left atrial indexed volume; *LVEDV* = left ventricular end-diastolic volume; *LVEF* = left ventricular ejection fraction; *LVESV* = left ventricular end-systolic volume; *MR* = mitral regurgitation; *TIMI* = Thrombolysis In Myocardial Infarction.
* p-values are given for the comparisons of patients with and without the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy).

Table 2. *Echocardiographic characteristics at 3 months' follow-up*

	Events (n=13)	No events (n=66)	p*
LVESV (mL)	143 ± 48	107 ± 32	0.001
LVEDV (mL)	198 ± 64	154 ± 44	0.003
LVEF (%)	28 ± 6	31 ± 4	0.09
Global longitudinal strain (%)	–7.4 ± 2.3	–11.6 ± 3.6	<0.001
LAVI (mL/m^2)	33 ± 10	27 ± 10	0.07
E/A ratio	2.49 ± 1.61	1.19 ± 0.78	0.02
DT (ms)	154 ± 50	210 ± 95	0.04
E/E' ratio	34 ± 22	19 ± 12	0.03
Moderate to severe MR grade	8 (62%)	27 (41%)	0.17

Data are presented as mean ± standard deviation or as number (percentage).
DT = deceleration time; *E/A* = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); *E/E'* = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); *LAVI* = left atrial indexed volume; *LVEDV* = left ventricular end-diastolic volume; *LVEF* = left ventricular ejection fraction; *LVESV* = left ventricular end-systolic volume; *MR* = mitral regurgitation.
* p-values are given for the comparisons of patients with and without the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy).

Echocardiographic characteristics at three months' follow-up for patients with and without events are illustrated in Table 2. At three months' follow-up, patients with events had larger LV volumes than patients without events, whereas LVEF was comparable in patients with and without events (LVEF 28 ± 6% vs. 31 ± 4%, p=0.09). Compared with patients without events, diastolic function was significantly more impaired in patients with events (E/A ratio 2.49 ±1.61 vs. 1.19 ± 0.78, p=0.02; deceleration time 154 ± 50 vs. 210 ± 95 ms, p=0.04; E/E' ratio 34 ± 22 vs. 19 ± 12, p=0.03). Finally, the percentage of patients with moderate to severe mitral regurgitation was comparable in patients with and without events (62% vs. 41%, p=0.17).

Time course of tissue heterogeneity after STEMI

Longitudinal strain values at the infarct, border, and remote zones in patients with and without events are summarized in Table 3 and Figure 3. All segments were considered to have good tracking and, therefore, no segments were excluded. Although both baseline and three-month global longitudinal strain values were different between patients with and without events, no change was observed from baseline to three months' follow-up in patients without events (from –11.1 ± 2.6% to –11.6 ± 3.6%, p=0.28), whereas patients with events demonstrated a trend toward more impaired global longitudinal strain values (from –8.9 ± 3.7% to –7.4 ± 2.3%, p=0.09) (Table 3).

Table 3. *The course of LV longitudinal strain values at the infarct, border, and remote zones, and global longitudinal strain in STEMI patients*

LV longitudinal strain	Events (n=13)	No events (n=66)	p*
Baseline			
Infarct zone (%)	1.4 ± 1.9	0.6 ± 4.0	0.28
Border zone (%)	–9.4 ± 1.3	–10.5 ± 2.4	0.13
Remote zone (%)	–15.3 ± 2.1	–15.4 ± 3.0	0.96
Global (%)	–8.9 ± 3.7	–11.1 ± 2.6	0.01
3 months			
Infarct zone (%)	–3.6 ± 4.4†	–6.3 ± 5.9†	0.12
Border zone (%)	–6.8 ± 3.1†	–10.5 ± 4.9	0.002
Remote zone (%)	–10.0 ± 5.0†	–13.1 ± 4.9†	0.06
Global (%)	–7.4 ± 2.3	–11.6 ± 3.6	<0.001

Data are presented as mean ± standard deviation.
LV = left ventricular; *STEMI* = ST-segment elevation myocardial infarction.
* p-values are given for the comparisons of patients with and without the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy).
† p<0.05 compared with baseline values.

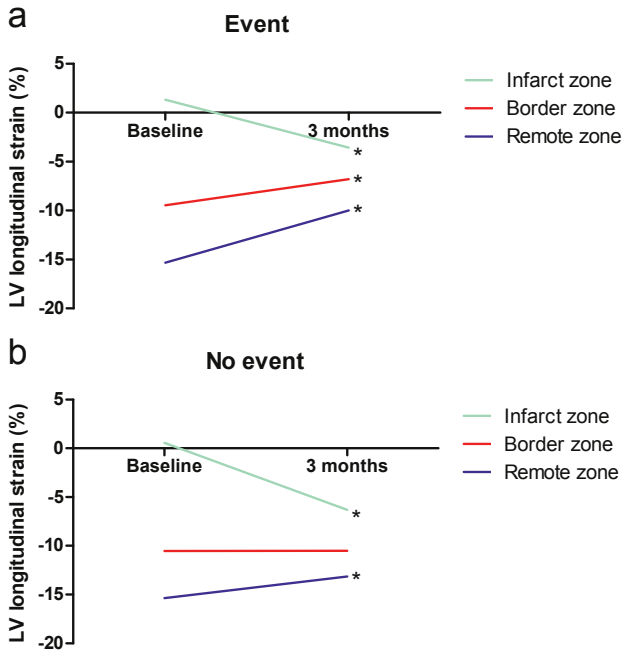

Figure 3. Time course of tissue heterogeneity in patients with events (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy) (a) and patients without events (b). Asterisks denote p<0.05 compared with baseline values. *LV* = left ventricular.

Baseline longitudinal strain values at the infarct, border, and remote zones were comparable in patients with and without events. However, at three months' follow-up, the border zone showed significantly more impaired longitudinal strain values in patients with events than in patients without events; the infarct and remote zones in patients with events showed a trend toward a more impaired function (infarct zone –3.6 ± 4.4% vs. –6.3 ± 5.9%, p=0.12; border zone –6.8 ± 3.1% vs. –10.5 ± 4.9%, p=0.002; remote zone –10.0 ± 5.0% vs. –13.1 ± 4.9%, p=0.06). Importantly, in patients with events, longitudinal strain values at the border zone significantly worsened from baseline to three months' follow-up. However, longitudinal strain values at the border zone in patients without events did not change during the three months of follow-up.

Tissue heterogeneity and outcome after STEMI

The cumulative incidence curves of the composite end point are shown in Figure 4, with the patient population dichotomized based on the median value of –9.4% measured at the border zone three months postinfarction. The patient population was censored when cardiac mortality or appropriate ICD therapy occurred, whichever came first. Patients with more impaired three-month LV longitudinal strain at the border zone (>–9.4%) showed a significantly worse long-term outcome compared with patients with a border zone ≤–9.4% (HR 4.52, 95% CI 1.24–16.50, p=0.02). The 12-, 24-, and 36-month cumulative incidence rates of the composite end point for patients with more impaired three-month longitudinal strain at the border zone were 13%, 21%, and 24%, respectively; in patients with longitudinal strain at the border zone ≤–9.4%, the 12-, 24-, and 36-month cumulative incidence rates of the composite end point were 2%, 5%, and 5%, respectively (Figure 4). Every 1% increase in longitudinal strain value at the border zone at three months' follow-up was associated with an increased risk of the composite end point of 16% (p=0.01).

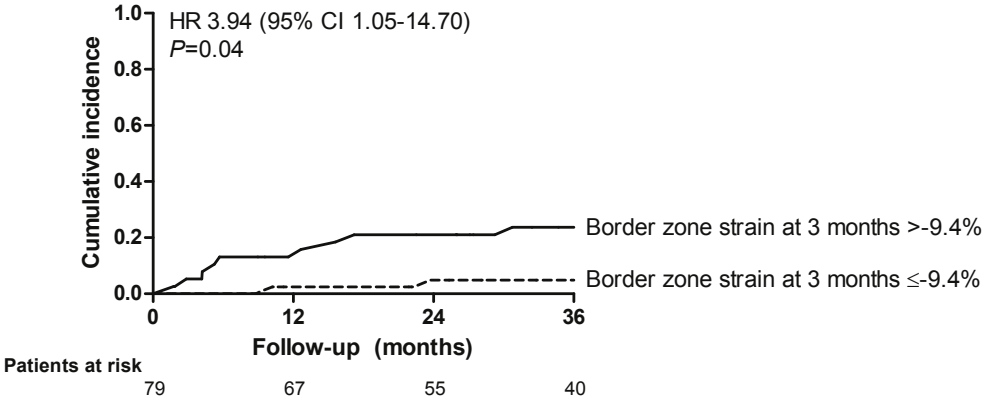

Figure 4. Cumulative incidence curves for the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy) in patients dichotomized based on the median value of the left ventricular longitudinal strain values at the border zone at 3 months' follow-up of –9.4%. *CI* = confidence interval; *HR* = hazard ratio.

Significant univariate parameters of cardiac mortality or appropriate ICD therapy were Killip class ≥2, smoking, peak CPK and peak cardiac troponin T levels, estimated glomerular filtration rate, three-month LV end-systolic volume, LV end-diastolic volume, LVEF, global longitudinal strain, E/A ratio, deceleration time, and E/E' ratio and three-month longitudinal strain values at the border zone. In Table 4, three multivariate models are presented assessing the association between the composite end point and three-month LVEF or three-month global longitudinal strain or three-month longitudinal strain at the border zone, adjusted for clinical variables (age and peak CPK). While three-month LVEF was no longer independently associated with the composite end point, three-month longitudinal strain at the border zone >–9.4% was independently associated with an almost fivefold increased risk of cardiac mortality or appropriate ICD therapy after STEMI (HR 3.94, 95% CI 1.05–14.70, p=0.04). Moreover, three-month global longitudinal strain was independently associated with the composite end point (HR 1.49, 95% CI 1.18–1.89, p=0.001). The relative merits of the three models were assessed by calculating the Harrell's *c* statistic. The multivariate model including three-month LVEF provided a *c* statistic of 0.81 for the composite of cardiac mortality and appropriate ICD therapy. A *c* statistic of 0.90 was provided for the multivariate model including three-month global longitudinal strain. The multivariate model including three-month longitudinal strain values at the border zone provided a *c* statistic of 0.85 for the composite end point.

Table 4. *Predictors of cardiac mortality and appropriate ICD therapy in STEMI patients*

	Multivariate analyses	
	HR (95% CI)	**p**
Model 1		
Age (years)	0.98 (0.93–1.04)	0.47
Peak CPK level (U/L)	3.85 (1.29–11.46)	0.02
LVEF at 3 months (%)	0.94 (0.85–1.04)	0.22
Model 2		
Age (years)	0.97 (0.92–1.03)	0.33
Peak CPK level (U/L)	2.03 (0.83–4.99)	0.12
Global longitudinal strain at 3 months (%)	1.49 (1.18–1.89)	0.001
Model 3		
Age (years)	0.98 (0.93–1.03)	0.37
Peak CPK level (U/L)	3.64 (1.34–9.89)	0.01
LV strain at border zone at 3 months >–9.4%	3.94 (1.05–14.70)	0.04

CI = confidence interval; *CPK* = creatine phosphokinase; *HR* = hazard ratio; *ICD* = implantable cardioverter-defibrillator; *LV* = left ventricular; *LVEF* = left ventricular ejection fraction; *STEMI* = ST-segment elevation myocardial infarction.

DISCUSSION

The present study demonstrated that patients with a first STEMI who remained with a LVEF ≤35% at three months' follow-up and showed a more impaired function of the border zone, assessed with speckle-tracking longitudinal strain, had an increased risk for ventricular arrhythmias and/or cardiac mortality.

LVEF versus speckle-tracking echocardiography for risk stratification of patients with STEMI

Current guidelines recommend ICD implantation for primary prevention in patients at least 40 days after STEMI who have symptoms of heart failure (NYHA class II–III) and LVEF ≤35%.[7] Although LVEF is an established parameter for the selection of patients for ICD, several studies have reported its limited specificity for the identification of patients who will benefit from ICD therapy.[10,11,22] In addition, a time-dependent benefit from ICD therapy after myocardial infarction has been described in several randomized trials only immediately after STEMI and in remote infarctions (≥18 months).[23-26] On the other hand, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and Immediate Risk Stratification Improves Survival (IRIS) trial, in which ICD therapy was randomly assigned to patients immediately after myocardial infarction, did not show benefit from ICD implantation in this subset of patients.[8,9] These studies suggest that the mechanisms of ventricular arrhythmias may change over time after STEMI. Further changes in the tissue characteristics of the scar and surrounding areas may alter the substrate, forming regional re-entry circuits that favour the occurrence of ventricular arrhythmias at follow-up.[27-29] Therefore, characterization of myocardial tissue, including the infarct core, border, and remote zones, has been proposed to improve the risk stratification of patients after STEMI.

Speckle-tracking echocardiography has been introduced to evaluate more subtle changes in regional and global LV function. In the present evaluation, regional longitudinal strain assessed at three months after STEMI was an independent determinant of long-term outcome in STEMI patients with LV dysfunction, whereas LVEF was not. Specifically, longitudinal strain at the border zone three months after infarction was independently associated with appropriate ICD therapy and/or cardiac mortality. With the use of this tool the risk stratification of STEMI patients may improve, identifying the patients who may benefit from ICD implantation. Although these results are promising, the small patient population and the low number of patients reaching the end point in the present study preclude us to generalize the results.

Border zone as determinant of ventricular arrhythmias

Previous studies have demonstrated that the peri-infarct or border zone is the origin of re-entrant ventricular tachycardia following myocardial infarction.[30] This arrhythmogenic anatomic substrate consists of dense, fibrous scar tissue incapable of depolarization,

interspersed with bundles of surviving myocytes capable of depolarization.[30] Contrast-enhanced magnetic resonance imaging has shown to accurately identify the border zone in patients with ischemic heart disease, which was independently associated with arrhythmic events.[2,6,13,31] Moreover, with the developments in echocardiographic deformation imaging techniques, similar evaluations of regional tissue function and heterogeneity, related to the presence of infarct core, border, and remote zones, can be performed.[3,14] In 424 ICD recipients with chronic ischemic heart failure, Ng et al.[3] assessed the regional myocardial function in the infarct, border, and remote zones using 2D speckle-tracking imaging. After adjustment for clinical and other echocardiographic parameters, longitudinal strain at the border zone was an independent predictor of all-cause mortality and ventricular arrhythmias during follow-up.[3]

However, these studies have been performed in patients with chronic heart disease and remote myocardial infarctions. The present study evaluated changes in regional function during the three months after STEMI, when myocardial scar is still developing and further changes in extracellular matrix have not yet taken place.[28,29] Importantly, in patients who presented with appropriate ICD therapy or died of a cardiac cause during long-term follow-up, the border zone, assessed by speckle-tracking longitudinal strain, significantly impaired over time. In addition, the border zone at three months' follow-up was independently associated with adverse outcome.

Limitations

The present study has several limitations. First, the relatively small sample size and the retrospective observational single-center design of the study preclude us to generalize the results. Therefore, the present evaluation should be considered as a hypothesis-generating study, with the results to be confirmed in larger multicenter study populations with strict enrollment before this technique can be implemented in guidelines and daily clinical routine.[32] Furthermore, despite the relatively low intra- and interobserver variability of global longitudinal strain,[3] the relatively wide limits of agreement of segmental longitudinal strain indicate that the implementation of segmental analysis in daily clinical practice demands further improvement of the technique. Moreover, test/retest variability data were not available. Finally, definition of infarct core, infarct border zone, and remote zone by means of speckle-tracking echocardiography may be less accurate than with contrast-enhanced cardiac magnetic resonance imaging.

CONCLUSIONS

The longitudinal strain value at the border zone three months after STEMI is associated with appropriate ICD therapy or cardiac mortality and may be useful in risk-stratifying patients following STEMI.

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