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Left Ventricular Dyssynchrony Acutely After Myocardial Infarction Predicts Left Ventricular Remodeling

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Objectives We sought to identify predictors of left ventricular (LV) remodeling after acute myocardial infarction.

Background Left ventricular remodeling after myocardial infarction is associated with an adverse long-term prognosis. Early identification of patients prone to LV remodeling is needed to optimize therapeutic management.

Methods A total of 178 consecutive patients presenting with acute myocardial infarction who underwent primary percutaneous coronary intervention were included. Within 48 h of intervention, 2-dimensional echocardiography was performed to assess LV volumes, LV ejection fraction (LVEF), wall motion score index, left atrial dimension, E/E′ ratio, and severity of mitral regurgitation. Left ventricular dyssynchrony was determined using speckle-tracking radial strain analysis. At 6-month follow-up, LV volumes, LVEF, and severity of mitral regurgitation were reassessed.

Results Patients showing LV remodeling at 6-month follow-up (20%) had comparable baseline characteristics to patients without LV remodeling (80%), except for higher peak troponin T levels ($p < 0.001$), peak creatine phosphokinase levels ($p < 0.001$), wall motion score index ($p < 0.05$), E/E′ ratio ($p < 0.05$), and a larger extent of LV dyssynchrony ($p < 0.001$). Multivariable analysis demonstrated that LV dyssynchrony was superior in predicting LV remodeling. Receiver-operating characteristic curve analysis demonstrated that a cutoff value of 130 ms for LV dyssynchrony yields a sensitivity of 82% and a specificity of 95% to predict LV remodeling at 6-month follow-up.

Conclusions Left ventricular dyssynchrony immediately after acute myocardial infarction predicts LV remodeling at 6-month follow-up. (J Am Coll Cardiol 2007;50:1532–40) © 2007 by the American College of Cardiology Foundation

The occurrence of left ventricular (LV) dilatation after acute myocardial infarction is not uncommon. Giannuzzi et al. (1) noted severe LV remodeling 6 months after infarction in 16% of the patients. The clinical importance of LV remodeling was emphasized by White et al. (2), who demonstrated that patients who died during follow-up after myocardial infarction had significantly larger LV volumes and lower left ventricular ejection fractions (LVEFs) than survivors. Furthermore, they indicated left ventricular end-systolic volume (LVESV) as the primary predictor of survival after myocardial infarction. As a consequence, early identification of patients with LV remodeling after acute myocardial infarction is of vital importance.

Previous studies demonstrated relations between preexisting hypertension, infarct size and anterior location of the infarct, and the occurrence of LV remodeling after myocardial infarction (3–6). Recently, Zhang et al. (7) demonstrated that myocardial infarction has a significant impact on LV synchronicity and that the degree of LV dyssynchrony is mainly determined by the infarct size. In this work, we hypothesize that LV dyssynchrony occurring early after myocardial infarction may predict LV remodeling at 6-month follow-up. In the current study, the relation between LV dyssynchrony, as assessed by speckle-tracking radial strain analysis, occurring early after myocardial infarction and LV remodeling at 6-month follow-up was evaluated.

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Methods

Patients. A total of 194 consecutive patients admitted with an acute myocardial infarction were evaluated. To acquire a homogenous study population, patients who were treated conservatively (n = 6) or who underwent thrombolysis (n = 4) or coronary artery bypass grafting (n = 2) in the acute setting were excluded from the study. Four patients died during follow-up and therefore did not have the follow-up assessment. These patients were excluded from the study. The final study population comprised 178 patients who all underwent primary percutaneous coronary intervention.

Study protocol. Two-dimensional (2D) echocardiography was performed within 48 h of admission (baseline) and at 6-month follow-up. At baseline, 2D echocardiography was used to assess LV volumes, LVEF, wall motion score index (WMSI), left atrial (LA) dimension, the mitral inflow peak early velocity (E)/mitral annular peak early velocity (E′), or E/E′ ratio, and severity of mitral regurgitation. Left ventricular dyssynchrony was quantified using speckle-tracking radial strain analysis. At 6-month follow-up, LV volumes, LVEF, and severity of mitral regurgitation were reassessed (8). The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Echocardiography. Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis images) and apical (2- and 4-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. The LV volumes (end-systolic and -diastolic) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (9). Left atrial dimension was measured at end-systole using M-mode (10).

Pulsed-wave mitral inflow Doppler was obtained by placing the Doppler sample volume between the tips of the mitral leaflets. The E/E′ ratio was obtained by dividing E by E′ at the basal septal segment (11).

Severity of mitral regurgitation was graded semiquantitatively from color-flow Doppler data in the conventional parasternal long-axis and apical views. Mitral regurgitation was characterized as: mild = 1+ (jet area/left atrial area <10%), moderate = 2+ (jet area/left atrial area 10% to 20%), moderately severe = 3+ (jet area/left atrial area 20% to 45%), and severe = 4+ (jet area/left atrial area >45%) (12).

The LV was divided into 16 segments. A semiquantitative scoring system (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia) was used to analyze each study. Global WMSI was calculated by the standard formula: sum of the segment scores divided by the number of segments scored (13,14).

All echocardiographic measurements were obtained by 2 independent observers without knowledge of the clinical status of the patient. Interobserver and intraobserver agreement for assessment of LV volumes was 90% and 93% for LVESV and 92% and 93% for left ventricular end-diastolic volume (LVEDV), respectively.

Speckle-tracking radial strain analysis. Radial strain was assessed on LV short-axis images at the papillary muscle level, using speckle-tracking analysis (15,16). This novel technique tracks frame-to-frame movement of natural acoustic markers on standard gray-scale images of the myocardium. Off-line analysis of radial strain was performed on digitally stored images.

Abbreviations and Acronyms

- **2D** = two-dimensional
- **E/E′** = mitral inflow peak early velocity/mitral annular peak early velocity
- **LA** = left atrium/atrial
- **LV** = left ventricle/ventricular
- **LVEDV** = left ventricular end-diastolic volume
- **LVEF** = left ventricular ejection fraction
- **LVESV** = left ventricular end-systolic volume
- **WMSI** = wall motion score index

The speckle-tracking software makes use of natural acoustic markers, or speckles, that are present on standard ultrasound tissue images. The software automatically subdivides the short-axis images of the LV into blocks of approximately 20 to 40 pixels containing stable patterns of speckles. These speckles move together with the myocardium and can be followed accurately from frame to frame (frame rate varied from 40 to 80 frames/s). A dedicated algorithm tracks the location of the speckles throughout the cardiac cycle, using correlation criteria and the sum of absolute differences (15). Local 2D tissue velocity vectors are then derived from the spatial and temporal data of each speckle. Myocardial strain can then be assessed from temporal differences in the mutual distance of neighboring speckles. The change in length/initial length of the speckle pattern over the cardiac cycle can be used to calculate radial strain, with myocardial thickening represented as positive strain, and myocardial thinning as negative strain.

To assess regional LV strain, a region of interest was drawn manually at the endocardial-cavity boundary on a single frame at end-systole. The speckle-tracking software then automatically created a second larger circle at the epicardial level, so that the region of interest spans the LV myocardium. The automatically-created circle width could be adjusted manually by the operator, depending on the LV wall thickness. Starting at the selected frame at end-systole, the speckle-tracking algorithm automatically tracked the region of interest and calculated radial strain throughout the cardiac cycle. Ultimately, the user-defined region of interest covered the entire myocardial wall during the entire cardiac cycle.

Finally, the traced endocardium was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior, respectively. The soft-

ware provided a score for all 6 segments marked in green for good quality and in red for poor quality. Signals from all 6 segments had to be of good quality to be able to adequately determine radial strain. Time-strain curves for all 6 segments were then constructed and time from QRS onset to peak radial strain was obtained. Consequently, the location of the earliest and latest activated segments was determined. Interobserver and intraobserver agreement for assessment of the absolute difference in time-to-peak radial strain for the earliest versus the latest activated segments was 87% for both.

Statistical analysis. Most continuous variables were not normally distributed (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25th and 75th percentiles. Categorical data are summarized as frequencies and percentages. LV remodeling at 6-month follow-up was defined as an absolute increase in LVESV of at least 15% (2,17,18). Differences in baseline characteristics between patients who developed LV remodeling versus those who did not were analyzed using Wilcoxon-Mann-Whitney tests, chi-square tests with Yates' correction or Fisher exact tests, as appropriate. Echocardiographic changes that occurred over time (LVESV, LVEDV, and LVEF) were studied by subtracting the baseline values from the values at 6-month follow-up for each individual patient. These changes were then summarized as median values together with 25th and 75th percentiles. Differences in changes between patients with and without LV remodeling were studied by applying the Wilcoxon-Mann-Whitney test.

Left ventricular dyssynchrony was defined as the absolute difference in time-to-peak radial strain for the earliest versus the latest activated segments. Univariable and multivariable linear regression analyses were performed to evaluate the relation between LV dyssynchrony at baseline and LVESV at 6-month follow-up, as well as the change in LVESV (indicating the magnitude of LV remodeling) after 6-month follow-up compared with the baseline value. The number of covariates in the final multivariable regression models was limited via a backward selection procedure, and all variables with a p value <0.15 were maintained.

Additionally, univariable and multivariable logistic regression analyses were applied (with a similar model-building process), relating LV dyssynchrony (continuous variable) to LV remodeling (dichotomous outcome). We realize that dichotomization of a continuous variable (LVESV) will result in loss of statistical power to reveal relevant relations. Still, these analyses are useful from a clinical point of view, as patients with a change in LVESV $\geq$15% constitute a cohort at increased risk of adverse events (17,18). Crude and adjusted odds ratios with their corresponding 95% confidence intervals are reported.

Left ventricular dyssynchrony was associated with LV remodeling. To determine the "optimal" threshold of LV dyssynchrony for the prediction of LV remodeling, receiver-operating characteristic (ROC) curve analysis was applied. This optimum was defined as the value for which the sum of sensitivity and specificity was maximized. As a result of the cutoff p value (<0.15) based on which covariates were included in the final multivariable regression model, the absoluteness of the obtained cutoff value for LV dyssynchrony can be discussed. All statistical tests were 2-sided. For all tests, a p value <0.05 was considered statistically significant.

Results

Baseline data of the study population. The study sample consisted of 178 patients (140 men, median age 61 years [25th, 75th percentiles: 53, 70 years]). During primary percutaneous coronary intervention, Thrombolysis In Myocardial Infarction flow grade III was obtained in all but 7 (4%) patients. The infarct-related artery was the left anterior descending coronary artery in 92 (52%) patients, the left circumflex coronary artery in 40 (22%) patients, and the right coronary artery in 44 (25%) patients. Multivessel disease was present in 95 (53%) patients.

At baseline, median WMSI was 1.50 (1.31, 1.63). Median peak cardiac troponin T and creatine phosphokinase levels were 6.5 μg/l (2.3, 10.3 μg/l) and 2,133 U/l (1,006, 3,570 U/l), respectively. Eight (4%) patients had a previous myocardial infarction.

Median LVESV and LVEDV were 66 ml (54, 83 ml) and 128 ml (106, 150 ml), respectively, whereas median LVEF was 47% (42%, 52%). Median LA dimension was 38 mm (35, 42 mm). The median E/E′ ratio at baseline was 12.4 (9.8, 16.2). In 8 (4%) patients moderate to severe mitral regurgitation (grade $\geq$2+) was observed.

Median LV dyssynchrony, as measured by speckle-tracking radial strain analysis, was 47 ms (13, 106 ms). In 14 (8%) of patients assessment of LV dyssynchrony using speckle-tracking radial strain analysis was not feasible due to poor quality of the 2D echocardiographic images.

LV remodeling at 6-month follow-up. In the entire patient population, median LVESV at 6-month follow-up was 63 ml (48, 80 ml) and median LVEDV was 128 ml (104, 152 ml), whereas median LVEF was 49% (43%, 56%). The number of patients with moderate to severe mitral regurgitation (grade $\geq$2+) was 13 (7%) at 6-month follow-up.

Patients were then divided into patients with LV remodeling (n = 36, 20%) and without LV remodeling (n = 142, 80 %) at 6-month follow-up. Baseline patient characteristics of these 2 groups are summarized in Table 1. At baseline, no significant differences were observed between the patients with and without LV remodeling except for the fact that peak levels of cardiac enzymes (reflecting enzymatic infarct size) were higher in the patients with LV remodeling.

The echocardiographic data of the patients with and without LV remodeling are shown in Table 2. At baseline, no significant differences in LV volumes and LVEF were observed. At 6-month follow-up, however, the LVESV

Table 1 Baseline Characteristics of Patients Without Versus With LV Remodeling (n = 178)

	No LV Remodeling (n = 142)	LV Remodeling (n = 36)	p Value
Age, yrs (25th, 75th percentiles)	61 (53, 69)	67 (56, 72)	NS
Gender, M/F (%)	110/32 (77/23)	30/6 (83/17)	NS
Previous MI (%)	6 (4)	2 (6)	NS
QRS duration baseline, ms	94 ± 13	96 ± 15	NS
Wide QRS ≥120 ms (%)	6 (4)	2 (6)	NS
Risk factors for CAD (%)			
Diabetes	13 (9)	4 (11)	NS
Hypertension	43 (30)	12 (33)	NS
Hyperlipidemia	27 (19)	6 (17)	NS
Smoking	76 (54)	16 (44)	NS
Family history of CAD	64 (45)	11 (31)	NS
Peak cTnT level, μg/l, (25th, 75th percentiles)	5.2 (1.9, 9.8)	10.1 (6.3, 15.3)	<0.001
Peak CPK level, U/l (25th, 75th percentiles)	1,893 (868, 3,236)	3,877 (1,816, 5,597)	<0.001
Infarct-related artery (%)			
LAD	70 (49)	22 (61)	NS
RCA	38 (27)	6 (17)	NS
LCX	33 (23)	7 (19)	NS
Multivessel disease	73 (51)	22 (61)	NS
Medication at 6-month follow-up (%)			
Beta-blocker	126 (89)	34 (94)	NS
ACE inhibitor/ARB	139 (98)	35 (97)	NS
Anticoagulants	142 (100)	36 (100)	NS
Statin	137 (96)	36 (100)	NS

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LV = left ventricular; MI = myocardial infarction; RCA = right coronary artery.

(according to the definition of LV remodeling) and LVEDV were significantly larger in the patients with LV remodeling. Moreover, the LVEF was significantly lower in the patients with LV remodeling. Moderate to severe mitral regurgitation (grade ≥2+) was more often present in the patients with LV remodeling.

At baseline, WMSI, E/E′ ratio, and LV dyssynchrony (Fig. 1) were the only baseline echocardiographic variables that were significantly different between patients with and without LV remodeling. In the patients with LV remodeling median WMSI was 1.56 (1.38, 1.69), whereas median WMSI in patients without LV remodeling was 1.50 (1.25, 1.63; $p < 0.05$). The median value for E/E′ ratio in patients with LV remodeling measured 14.8 (12.3, 18.4) and the patients without LV remodeling had a median E/E′ ratio of 11.7 (9.7, 15.7; $p < 0.05$).

Table 2 Echocardiographic Parameters of Patients Without Versus With LV Remodeling

	No LV Remodeling (n = 142)	LV Remodeling (n = 36)	p Value
Baseline			
LVESV, ml	64 (54, 70)	76 (54, 91)	NS
LVEDV, ml	128 (106, 148)	139 (108, 160)	NS
LVEF, %	47 (42, 52)	47 (42, 51)	NS
WMSI	1.50 (1.25, 1.63)	1.56 (1.38, 1.69)	<0.05
LA dimension, mm	38 (34, 42)	41 (37, 43)	NS
E/E′ ratio	11.7 (9.7, 15.7)	14.8 (12.3, 18.4)	<0.05
MR, moderate-severe (%)	6 (4)	2 (6)	NS
LV dyssynchrony, ms	31 (12, 77)	148 (134, 180)	<0.001
6-month follow-up			
LVESV, ml	58 (46, 74)	112 (70, 130)	<0.001*
LVEDV, ml	121 (103, 144)	170 (127, 202)	<0.001
LVEF, %	52 (46, 57)	39 (34, 44)	<0.001
MR moderate-severe (%)	7 (5)	6 (17)	<0.05

Values are expressed as n (25th, 75th percentiles) unless otherwise indicated. *Per definition.

E/E′ = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E′); LA = left atrial; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; WMSI = wall motion score index.

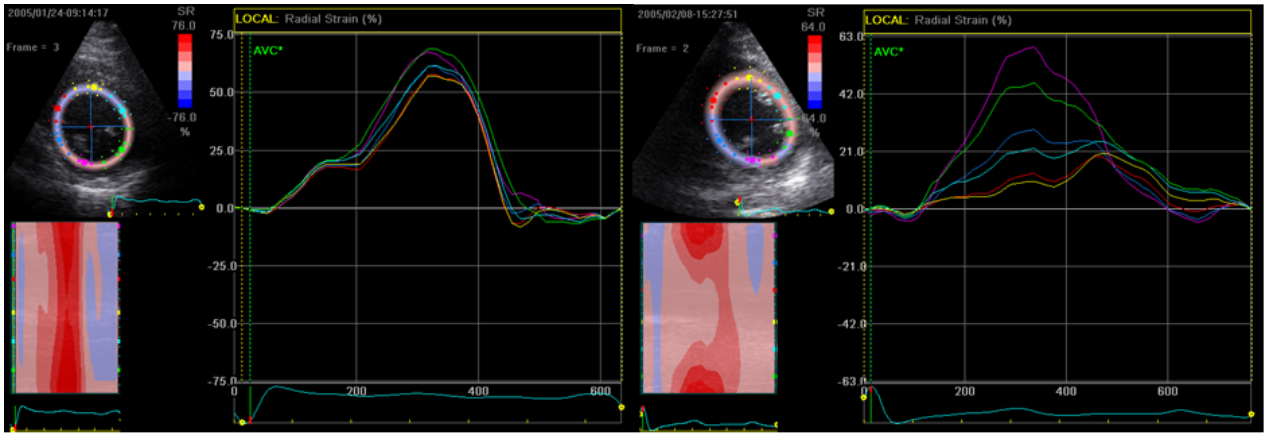

Figure 1 **Extent of LV Dyssynchrony Was Significantly Larger in Patients With LV Remodeling During Follow-Up Versus Those Without LV Remodeling**

Left panel demonstrates time-strain curves of a patient without dyssynchrony at baseline. This patient did not show left ventricular (LV) remodeling during follow-up (left ventricular end-systolic volume [LVESV] was 84 vs. 73 ml, baseline vs. 6-month follow-up). **Right panel** demonstrates time-strain curves of a patient with LV dyssynchrony at baseline (earliest activated segments: **purple, green,** and **dark-blue**, latest activated segments: **light-blue, yellow,** and **red**). This patient showed LV remodeling during follow-up (LVESV was 77 vs. 122 ml, baseline vs. 6-month follow-up).

Median LV dyssynchrony was 148 ms (134, 180 ms) in the patients with LV remodeling, compared with 31 ms (12, 77 ms) in the patients without LV remodeling ($p < 0.001$). The individual data are demonstrated in Figure 2.

Figure 3 shows the prevalence for each LV segment as being the latest activated segment in the patients with LV remodeling after 6-month follow-up. According to the high prevalence of the left anterior descending coronary artery as infarct-related artery, the anteroseptal and septal LV segments are activated late in a considerable proportion of the patients with LV remodeling.

Determinants of LV remodeling. Patients with more extensive LV dyssynchrony at baseline had a larger LVESV at 6-month follow-up (Fig. 4, left panel). This relation remained after adjustment for the baseline LVESV, peak level of cardiac troponin T, and history of hypertension (these variables had a p value <0.15 in the final model; the R^2 value of the final model was 0.73). Each 10-ms increase in LV dyssynchrony was associated with a 1.2 ml (95%

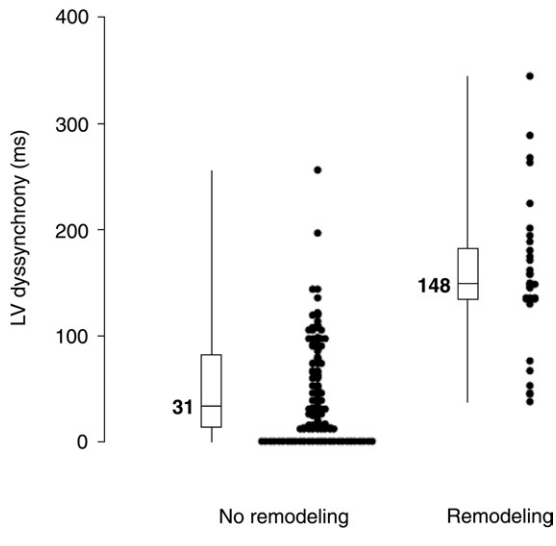

Figure 2 **LV Dyssynchrony in Patients Without Versus With LV Remodeling at 6-Month Follow-Up**

Box-whisker plot indicates median, first quartile, third quartile, and range. Median left ventricular (LV) dyssynchrony was significantly higher ($p < 0.001$) in the patients with LV remodeling versus without LV remodeling (148 ms [134, 180 ms] vs. 31 ms [12, 77 ms], respectively).

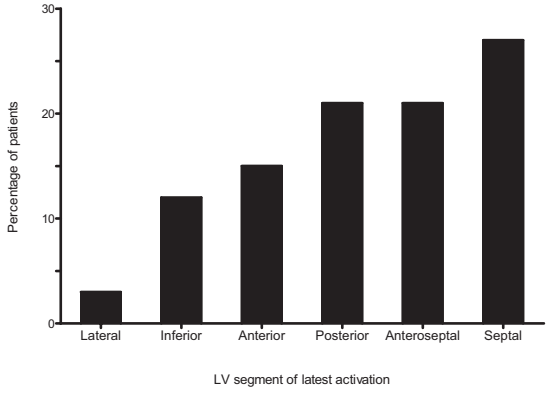

Figure 3 **Distribution of Latest Activated LV Segments in Patients With LV Remodeling**

According to the high prevalence of the left anterior descending coronary artery (LAD) as infarct-related artery, the anteroseptal and septal left ventricular (LV) segments are activated late in a considerable proportion of the patients with LV remodeling.

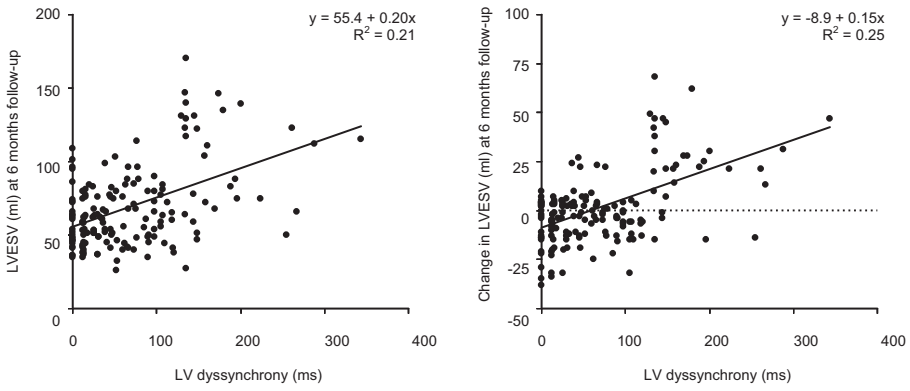

Figure 4 **Correlation Between LV Dyssynchrony at Baseline and LVESV and Change in LVESV at 6-Month Follow-Up**

A significant relation existed between baseline left ventricular (LV) dyssynchrony and absolute value for left ventricular end-systolic volume (LVESV) **(left panel)** and change in LVESV **(right panel)** at follow-up.

confidence interval [CI] 0.8 to 1.6 ml; $p < 0.001$) larger LVESV at 6 months.

Patients with more extensive LV dyssynchrony at baseline also had a higher change in LVESV in the 6-month period of follow-up (Fig. 4, right panel). Of note, the extent of LV dyssynchrony was largest in patients with significant LV remodeling (increase in LVESV ≥15%) (Fig. 5). After adjustment for the baseline LVESV, peak level of cardiac troponin T and history of hypertension, each 10-ms increase in LV dyssynchrony was associated with a 1.2 ml (95% CI 0.8 to 1.6 ml) higher change in LVESV (note that the "change model" had similar covariables as the "absolute value" model; the R^2 value of the final "change model" was 0.41).

Left ventricular dyssynchrony at baseline was also associated with an increased risk of LV remodeling at 6-month follow-up. Table 3 presents the univariable relations between a range of clinical and echocardiographic variables, and the incidence of LV remodeling at 6-month follow-up. Among the variables studied, LV dyssynchrony showed the strongest relation. This relation remained after adjustment for the peak level of cardiac troponin T ($p = 0.015$ in the final model), hypertension ($p = 0.10$), baseline LVESV ($p = 0.14$), and baseline LVEDV ($p = 0.14$). Each millisecond increase in LV dyssynchrony was associated with a 3% increased risk of LV remodeling (adjusted odds ratio 1.03 per ms; 95% CI 1.02 to 1.05; $p < 0.001$).

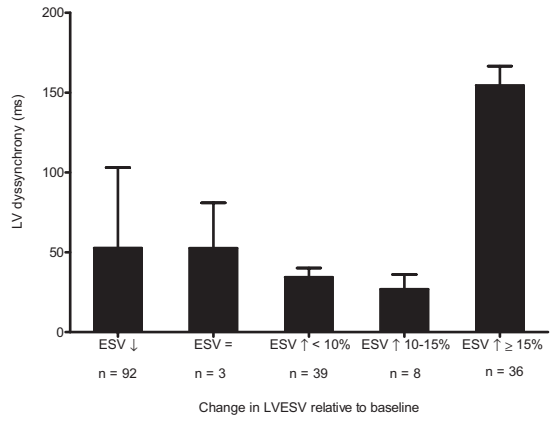

Figure 5 **The Extent of LV Dyssynchrony According to Changes in LVESV During Follow-Up**

Of note, the extent of left ventricular (LV) dyssynchrony was largest in patients with significant LV remodeling (increase in left ventricular end-systolic volume [LVESV] ≥15%). ESV = end-systolic volume.

Table 3 **Relation Between Clinical and Echocardiographic Parameters and LV Remodeling**

Baseline Variable	Odds Ratio	95% Confidence Interval	p Value
LV dyssynchrony, per ms	1.03	1.02–0.05	**<0.001**
Peak cTnT level, per μg/l	1.14	1.07–1.22	**<0.001**
Peak CPK level, per U/l	1.44	1.20–1.72	**<0.001**
E/E′ ratio	1.09	1.01–1.17	**0.019**
WMSI	8.11	1.39–47.0	**0.020**
Age, per year	1.03	1.00–1.07	0.073
LA dimension, per mm	1.07	0.99–1.15	0.081
LVESV, per ml	1.02	1.00–1.03	0.090
LVEDV, per ml	1.01	1.00–1.02	0.094
Positive family history	0.54	0.25–1.17	0.12
Culprit vessel LAD	1.96	0.73–5.26	0.18
QRS duration, per ms	1.01	0.99–1.04	0.39
Gender	1.45	0.56–3.80	0.45
Number of diseased vessels	1.20	0.78–1.97	0.46
MR	1.19	0.66–2.15	0.57
Culprit vessel LCX	1.34	0.41–4.40	0.63
LVEF, per %	0.99	0.94–1.04	0.72
Diabetes	1.24	0.38–4.06	0.72
Hypertension	1.15	0.53–2.51	0.72
Previous MI	1.33	0.26–6.90	0.73
Hyperlipidemia	0.85	0.32–2.25	0.75
Smoking	0.94	0.44–1.98	0.86

Values in bold indicate statistical significance.
Abbreviations as in Tables 1 and 2.

To identify the optimal extent of LV dyssynchrony that was predictive for LV remodeling at 6-month follow-up, ROC curve analysis was performed (Fig. 6). At a cutoff value of 130 ms for LV dyssynchrony, ROC curve analysis revealed a sensitivity of 82% with a specificity of 95% to predict LV remodeling at 6-month follow-up.

Discussion

The main findings of the present study can be summarized as follows: 1) 20% of the patients exhibited LV remodeling at 6-month after acute myocardial infarction; 2) patients in which LV remodeling occurred had higher baseline peak levels of cardiac enzymes, WMSI, E/E′ ratio, and a larger extent of LV dyssynchrony; and 3) baseline LV dyssynchrony of 130 ms or more, as assessed by speckle-tracking radial strain analysis, had a sensitivity of 82% and a specificity of 95% to predict LV remodeling at 6-month after acute infarction.

Prediction of LV remodeling. During follow-up, 20% of the study group showed remodeling of the left ventricle. Accordingly, in these patients LVESV and LVEDV increased, whereas LVEF declined. In the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)-3 Echo Substudy, Giannuzzi et al. (1) showed comparable results. Using the end-diastolic volume index as a marker of remodeling, the authors noted severe LV remodeling at 6-month after infarction in 16% of the patients.

Cardiac remodeling is recognized as an important trigger for the progression of cardiovascular disease. Increasing LVESV (index) and declining LVEF post-infarction are important predictors of mortality (2,19,20). White et al. (2) measured LV volumes, LVEFs, and severity of coronary occlusions and stenoses in 605 male patients younger than 60 years of age at 1 to 2 months after a first (n = 443) or recurrent (n = 162) myocardial infarction. During a follow-up period of 78 months, there were 101 cardiac deaths. Multivariable analysis showed that LVESV had greater predictive value for survival than LVEDV or LVEF. The LVESV was significantly larger in patients who died from a cardiac cause (122 ± 65 ml) than in survivors (72 ± 36 ml). Therefore, early identification of patients with LV remodeling after acute myocardial infarction is of vital importance. In order to identify patients at high risk, parameters with adequate predictive values are needed.

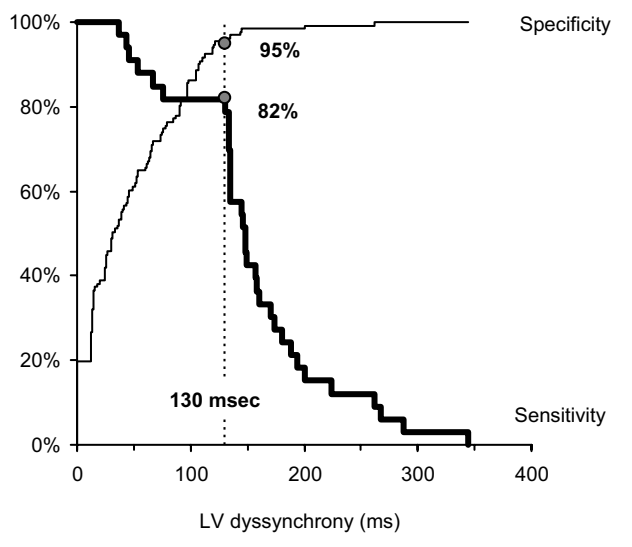

Figure 6 ROC Curve Analysis to Determine the Optimal Cutoff Value for LV Dyssynchrony to Predict LV Remodeling

Using a cutoff value of 130 ms, a sensitivity of 82% and a specificity of 95% were obtained to predict left ventricular (LV) remodeling. ROC = receiver-operating characteristic.

In the current study, it was shown that patients with LV remodeling had significantly higher peak levels of cardiac enzymes, WMSI, E/E′ ratio, and a significantly larger extent of LV dyssynchrony, compared with the patients without LV remodeling.

Significant relations have been described between cardiac troponin T levels after myocardial infarction and scintigraphic estimate of myocardial infarct size (21,22). The importance of the infarct size as a determinant of LV remodeling was previously noted by McKay et al. (3). The authors demonstrated that infarct size, as assessed by the extent of wall motion abnormalities, was directly proportional to the magnitude of LV remodeling during the acute phase of infarction.

The predictive value of infarct size was further confirmed by Popović et al. (5), who described initial infarct size after anterior wall acute myocardial infarction as a major determinant of infarct expansion and ventricular remodeling. Furthermore, the importance of the infarct-related artery patency as predictor for infarct expansion after anterior wall myocardial infarction was emphasized. Unfortunately, systematic information on vessel patency was not available in the current study.

The variables LA dimension and E/E′ ratio were evaluated for their relation with long-term LV remodeling. In previous studies, both variables demonstrated to be of clinical importance (10,11). In the present study, the influence of these variables on LV remodeling was limited, and LV dyssynchrony at baseline appeared superior for prediction of LV remodeling.

Recently, Zhang et al. (7) emphasized the significant impact of acute myocardial infarction on regional myocardial contractility and systolic LV synchronicity early in the course, even in the absence of QRS widening or bundle-branch block. The authors concluded that the degree of LV systolic dyssynchrony was mainly determined by the infarct size. The infarct size was assessed by contrast-enhanced magnetic resonance imaging and was significantly larger in patients with anterior infarction (n = 24) compared to inferior infarction (21.3 ± 12.1% vs. 13.3 ± 6.1%, respectively). Of note, a larger extent of LV dyssynchrony was demonstrated in patients with anterior than inferior myo-

cardial infarction (46.8 ± 13.9 ms vs. 34.6 ± 8.5 ms, p = 0.002).

LV dyssynchrony predicts long-term LV remodeling. A novel finding in the current study is that the extent of LV dyssynchrony was demonstrated to be an independent predictor of LV remodeling at 6-month follow-up. Moreover, multivariable analysis showed that LV dyssynchrony, measured at baseline after myocardial infarction, was superior to other variables in the prediction of LV remodeling. To identify a cutoff value to predict LV remodeling, we performed an ROC curve analysis and identified an optimal cutoff value of 130 ms. This cutoff value yielded a sensitivity and specificity of 82% and 95% to predict LV remodeling at 6-month follow-up. These findings suggest that assessment of LV dyssynchrony immediately after acute myocardial infarction may provide incremental predictive value for the identification of patients prone to the development of LV remodeling.

Speckle-tracking radial strain analysis to assess LV dyssynchrony. In the present study, the location of the earliest and latest activated segments was determined using speckle-tracking software applied to standard short-axis images. The definition of LV dyssynchrony was based on the absolute difference in time-to-peak radial strain for the earliest versus the latest activated segments. Speckle-tracking radial strain analysis is a novel technique that allows angle-independent measurement of regional strain and time-to-peak radial strain of different LV segments (15,16). Recently, this technique has been validated against magnetic resonance imaging (23). Furthermore, Suffoletto et al. (24) demonstrated that speckle-tracking radial strain analysis can quantify LV dyssynchrony, and can accurately predict response to cardiac resynchronization therapy. In contrast to tissue velocity imaging-derived strain, speckle-tracking radial strain is angle-independent and not limited by tethering (25). Therefore, speckle-tracking radial strain analysis permits an accurate quantification of regional wall strain, with a high reproducibility (23,25).

Clinical implications. Recently, numerous reports have been published on LV dyssynchrony, mainly in relation to prediction of response to cardiac resynchronization therapy (17). In these studies, the presence of LV dyssynchrony in severely dilated left ventricles is predictive for response to cardiac resynchronization therapy.

According to the present study, a significant degree of dyssynchrony is highly predictive for the long-term development of LV remodeling after acute myocardial infarction. This finding offers a unique possibility to identify patients at risk for LV remodeling early after infarction and to subsequently intensify treatment of these patients.

There is an important role for medical therapy in the prevention of LV remodeling after myocardial infarction, especially for angiotensin-converting enzyme inhibitors and beta-blockers (26–33). The SOLVD (Studies of Left Ventricular Dysfunction) prevention trial (27), for instance, demonstrated that enalapril (partially) reversed LV dilation in patients with LV dysfunction. Moreover, beta-blocker therapy has been shown to reduce the LVEDV and LVESV indexes in patients with LV dysfunction (32,33).

In addition to further optimization of medical therapy, early cardiac resynchronization therapy could be considered in patients with severe LV dyssynchrony early after acute myocardial infarction. However, it is currently unclear whether large infarction results in LV dilatation, or whether LV dyssynchrony is most important for LV dilatation. Only when LV dyssynchrony is the main determinant of LV dilatation, cardiac resynchronization may be beneficial. Further studies are needed to explore these issues.

Conclusions

Patients with LV remodeling after acute myocardial infarction show significant LV dyssynchrony at baseline compared with patients without LV remodeling. Using a cutoff value of 130 ms, a sensitivity of 82% and a specificity of 95% were obtained to predict LV remodeling at 6-month follow-up. Left ventricular dyssynchrony may be used to identify patients at high risk for development of LV remodeling after infarction.

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REFERENCES

1. Giannuzzi P, Temporelli PL, Bosimini E, et al. Heterogeneity of left ventricular remodeling after acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-3 Echo Substudy. Am Heart J 2001;141:131–8.
2. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.
3. McKay RG, Pfeffer MA, Pasternak RC, et al. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. Circulation 1986;74:693–702.
4. Pirolo JS, Hutchins GM, Moore GW. Infarct expansion: pathologic analysis of 204 patients with a single myocardial infarct. J Am Coll Cardiol 1986;7:349–54.
5. Popović AD, Neskovic AN, Marinkovic J, Thomas JD. Acute and long-term effects of thrombolysis after anterior wall acute myocardial infarction with serial assessment of infarct expansion and late ventricular remodeling. Am J Cardiol 1996;77:446–50.
6. Richards AM, Nicholls MG, Troughton RW, et al. Antecedent hypertension and heart failure after myocardial infarction. J Am Coll Cardiol 2002;39:1182–8.
7. Zhang Y, Chan AK, Yu CM, et al. Left ventricular systolic asynchrony after acute myocardial infarction in patients with narrow QRS complexes. Am Heart J 2005;149:497–503.
8. Liem SS, van der Hoeven BL, Oemrawsingh PV, et al. MISSION! Optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J 2007;153:14–1.
9. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
10. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 1995;92:835–41.

11. Naqvi TZ, Padmanabhan S, Rafii F, Hyuhn HK, Mirocha J. Comparison of usefulness of left ventricular diastolic versus systolic function as a predictor of outcome following primary percutaneous coronary angioplasty for acute myocardial infarction. Am J Cardiol 2006;97:160–6.
12. Thomas JD. How leaky is that mitral valve? Simplified Doppler methods to measure regurgitant orifice area. Circulation 1997;95:548–50.
13. Broderick TM, Bourdillon PD, Ryan T, Feigenbaum H, Dillon JC, Armstrong WF. Comparison of regional and global left ventricular function by serial echocardiograms after reperfusion in acute myocardial infarction. J Am Soc Echocardiogr 1989;2:315–23.
14. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83:1605–14.
15. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004;17:1021–9.
16. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004;17:630–3.
17. Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834–40.
18. Yu CM, Fung JW, Chan CK, et al. Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. J Cardiovasc Electrophysiol 2004;15:1058–65.
19. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. On behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569–82.
20. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. Circulation 1993;87:755–63.
21. Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kubler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. Heart 2002;87:520–4.
22. Panteghini M, Cuccia C, Bonetti G, Giubbini R, Pagani F, Bonini E. Single-point cardiac troponin T at coronary care unit discharge after myocardial infarction correlates with infarct size and ejection fraction. Clin Chem 2002;48:1432–6.
23. Amundsen BH, Helle-Valle T, Edvardsen T, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789–93.
24. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960–8.
25. Cho GY, Chan J, Leano R, Strudwick M, Marwick TH. Comparison of two-dimensional speckle and tissue velocity based strain and validation with harmonic phase magnetic resonance imaging. Am J Cardiol 2006;97:1661–6.
26. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation 1992;86:431–8.
27. Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Circulation 1993;88:2277–83.
28. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation 1995;91:2573–81.
29. Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. J Am Coll Cardiol 2000;36:2072–80.
30. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–77.
31. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
32. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997;349:375–80.
33. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation 2004;109:201–6.