Left Atrium Remodeling After Acute Myocardial Infarction (Results of the GISSI-3 Echo Substudy)

Bogdan A. Popescu, MD, Franco Macor, MD, Francesco Antonini-Canterin, MD, Pantaleo Giannuzzi, MD, Pier L. Temporelli, MD, Enzo Bosimini, MD, Francesco Gentile, MD, Aldo P. Maggioni, MD, Luigi Tavazzi, MD, Rita Piazza, MD, Luigi Ascione, MD, Ioana Stoian, MD, Eugenio Cervesato, PhD, and Gian L. Nicolosi, MD, for the GISSI-3 Echo Substudy Investigators*

To evaluate the existence, timing, and determinants of post-infarction left atrial remodeling, we studied a subgroup of 514 patients from the Third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Echo Substudy who underwent 4 serial 2-dimensional echocardiograms up to 6 months after acute myocardial infarction. This study is the first to demonstrate, in a large series of patients, the existence of early and late left atrial remodeling after low-risk acute myocardial infarction and the relation of left atrial remodeling to left ventricular remodeling. ©2004 by Excerpta Medica, Inc.

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Left atrial (LA) size is an important determinant of morbidity and mortality. This has been shown in the general population[1] and in patients with cardiomyopathies,[2] left ventricular dysfunction,[3] aortic stenosis,[4] mitral regurgitation,[5] or atrial arrhythmias.[6] Recently, LA volume has been described as an important predictor of survival after acute myocardial infarction (AMI).[7] Another study[8] has found that myocardial ischemia results in significant LA dilation, depressed LA systolic function, and altered LA diastolic stiffness. LA distention after infarction has been described in 22 patients by serial echocardiograms.[9] The existence, timing, and determinants of LA remodeling after infarction in a large sample of consecutive patients with low-risk AMI, all alive at 6-month follow up, have not been assessed, and that is the purpose of this report.

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The Third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) Echo Substudy initially evaluated 878 patients from among the 19,394 patients randomized within the GISSI-3 study.[10] Patients were initially considered eligible if they had confirmed AMI as previously reported[10] and echocardiograms suitable for quantitative analysis. The protocol required serial echocardiograms at 24 to 48 hours (mean ± SD 36 ± 8) from symptom onset (S1), at hospital discharge (12 ± 5 days; S2), at 6 weeks (48 ± 9 days; S3), and at 6 months (194 ± 17 days; S4) after AMI.[11] The protocol was approved by the local ethics committee. Patients were informed, and a consent statement was obtained from all.

All echocardiograms were submitted to the core laboratory at the Research Center of the National Association of Hospital Cardiologists (Associazione Nazionale Medici Cardiologi Ospedalieri) in Florence for an assessment of technical quality and suitability for quantitative analysis. All parameters analyzed were calculated as the mean of ≥3 measurements. For wall motion analysis, a 16-segment model was used according to recommendations by the American Society of Echocardiography.[12] Videotape analysis was performed centrally by 3 expert investigators unaware of patients' clinical, electrocardiographic, or angiographic data, who assigned the wall motion score by consensus. A percentage of wall motion abnormalities

TABLE 1 Baseline Characteristics of the Study Population (n = 514)

	n (%)
Men	428 (83.3%)
Age ≥70 yrs	122 (23.7%)
Site of AMI	
Anterior	151 (29.4%)
Inferoposterior	193 (37.5%)
Multiple locations	17 (3.3%)
Non–Q wave	102 (19.8%)
Undefined	38 (7.4%)
Not reported	13 (2.5%)
Killip class at admission	
1	446 (86.9%)
2	63 (12.3%)
3	4 (0.8%)
Previous AMI	66 (12.9%)
Systemic hypertension	185 (37.1%)
Diabetes mellitus	68 (13.5%)
Treatments	
Thrombolysis	360 (70.6%)
Intravenous β blockers	128 (25.2%)
Aspirin	444 (87.2%)

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*A list of investigators appears in Badano et al.[13]

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TABLE 2 Changes After Infarction in Echocardiographic Parameters During 6-Month Follow Up

	24–48 Hours (S1)	Before Discharge (S2)	6 Wks (S3)	6 Mo (S4)	Time Effect p Value
Left ventricular end-diastolic volume index (ml/m^2)	81 ± 20	85 ± 23	86 ± 25	87 ± 26	<0.001
Left ventricular end-systolic volume index (ml/m^2)	44 ± 16	46 ± 19	47 ± 21	48 ± 22	<0.001
Percentage of wall motion abnormalities	25 ± 15	23 ± 15	21 ± 15	20 ± 15	<0.001
Left ventricular ejection fraction (%)	47 ± 7	47 ± 8	47 ± 8	47 ± 9	0.59
Mitral regurgitation degree (0–3/3)	0.81 ± 0.57	0.88 ± 0.58	0.85 ± 0.56	0.85 ± 0.59	0.063
LA area index (cm^2/m^2)	9.48 ± 2.01	9.66 ± 2.12	9.74 ± 1.99	9.82 ± 2.01	<0.001
LA length (cm)	4.73 ± 0.58	4.77 ± 0.60	4.79 ± 0.57	4.81 ± 0.56	0.002
LA width (cm)	4.15 ± 0.53	4.25 ± 0.75	4.19 ± 0.50	4.24 ± 0.62	<0.001
LA sphericity index	1.15 ± 0.14	1.14 ± 0.15	1.15 ± 0.13	1.15 ± 0.14	0.40

Data are expressed as mean values ± SD (n = 514 patients).

TABLE 3 Clinical Events Recorded During Follow-up in the Study Population (n = 514)

	n (%)
In-hospital events	
Atrial fibrillation and/or atrial flutter	26 (5.1%)
Sustained ventricular tachycardia	6 (1.2%)
Second- and/or third-degree atrioventricular block	21 (4.1%)
Stroke	2 (0.4%)
After discharge	
Heart failure at 6 wks	106 (20.6%)
Heart failure at 6 mo	112 (21.8%)

was obtained by dividing the number of akinetic, dyskinetic, and aneurysmal segments by the total number of segments evaluated. Our inter- and intraobserver reproducibility values in wall motion score assessment were 89% and 93%, respectively.[13] Left ventricular diastolic filling pattern was obtained by pulse-wave Doppler by placing the sample volume between the tips of mitral leaflets in the apical 4-chamber view. Peak velocity of early filling, peak velocity at atrial contraction, their ratio, and deceleration time of early filling were measured. Mitral regurgitation was assessed by color Doppler flow mapping and graded as mild, moderate, or severe, as previously described.[14] Significant mitral regurgitation was defined as moderate or severe (2 to 3 of 3) mitral regurgitation. Echocardiographic images were then digitized to obtain endocardial contours and left ventricular cavity areas at end-diastole and end-systole from 2 apical orthogonal (4- and 2-chamber) views. Indexed left ventricular volumes and ejection fraction were determined as previously described.[11] From the apical 4-chamber view, the mediolateral (width, in the mid-cavity) and the superoinferior (length, from the posterior LA to the mitral annular level) LA diameters were measured at end-systole. An LA sphericity index was defined as the ratio of length/width. LA maximal end-systolic area was measured by tracing the outline of the atrial endocardium from the apical 4-chamber view. LA area index was calculated as LA area/body surface area (square centimeters per square meter). Timing of remodeling was defined as early when it occurred from S1 to S2 and as late when it occurred from S2 to S4. Overall LA area index changes (S4 − S1) were calculated, and the same was done for changes in left ventricular end-diastolic volume index, end-systolic volume index, ejection fraction, early-filling wave deceleration time, and degree of mitral regurgitation.

All continuous data are given as mean value ± SD. Differences between patients were assessed by unpaired *t* testing and frequency of parameters by the chi-square test. Differences between echocardiographic measurements between groups, changes over time within each group (time effect), and interaction effects were assessed by repeated measures analysis of variance. Linear regression analysis was used, and correlation coefficients were calculated by Pearson's method. Stepwise multivariate linear regression analysis was performed to assess the determinants of LA area index changes. Variables included in the multivariate analysis were selected based on the best results of the univariate analyses (at the significance level of $p < 0.10$). A p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS 11.5 for Windows (SPSS Inc., Chicago, Illinois).

Patients with reinfarction (n = 23, 2.6%), myocardial revascularization procedures during the 6-month period of the study (n = 75, 8.5%), and those with incomplete follow-up or echocardiograms inadequate for quantitative analysis (n = 230, 26.1%) were excluded. Thirty-six patients died during follow-up. The remaining 514 patients (428 men; mean age 61 ± 12 years) who underwent all 4 echocardiographic examinations represent the final study population. Baseline characteristics of the study group are presented in Table 1. Except for minor differences, these characteristics were comparable to those of the general population of the GISSI-3 trial who were discharged alive and followed up with echocardiograms at 6 months.[15]

Changes in echocardiographic parameters during follow-up are presented in Table 2. The prevalence of significant mitral regurgitation was low and did not change from S1 to S4 (6.2%, 9.9%, 8.4%, and 8.9%, respectively; p = 0.29). Clinical event occurrence during follow-up was also low and is presented in Table 3. By stepwise multivariate linear regression, statistically significant correlates of LA area index at S1 were age ($p < 0.001$), left ventricular end-diastolic

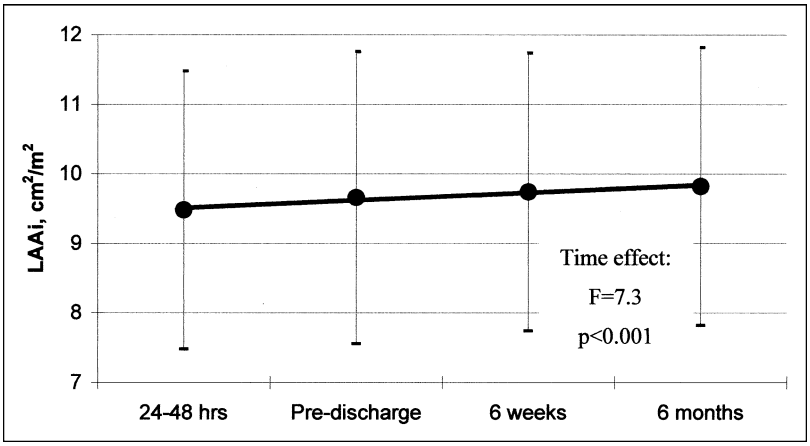

FIGURE 1. Postinfarction changes of LA area index (LAAi; square centimeters per square meter) during 6-month follow-up.

TABLE 4 Univariate Correlates of Overall Changes in Left Atrial Area Index (n = 514)

Variable	Univariate Analysis	
	r Coefficient	p Value
Age (yrs)	0.03	0.52
Left ventricular ejection fraction at S1	−0.10	0.02
Peak transmitral early filling velocity at S1	−0.05	0.25
Early/atrial filling velocity ratio at S1	−0.01	0.83
Early filling wave deceleration time at S1	0.01	0.77
Left ventricular end-diastolic volume index at S1	0.03	0.49
Left ventricular end-systolic volume index at S1	0.06	0.19
Percentage of wall motion abnormalities at S1	0.08	0.08
Peak creatine kinase at S1	0.08	0.06
Left ventricular ejection fraction change (S4 − S1)	0.04	0.37
Left ventricular end-diastolic volume index change (S4 − S1)	0.16	<0.0001
Left ventricular end-systolic volume index change (S4 − S1)	0.13	0.003
Early-filling wave deceleration time change (S4 − S1)	−0.07	0.15
Mitral regurgitation change (S4 − S1)	0.08	0.09

volume index at S1 (p = 0.001), early filling/atrial contraction ratio at S1 (p = 0.01), a history of myocardial infarction (p = 0.03), and peak early-filling wave at S1 (p = 0.03).

LA area index significantly increased throughout follow-up (Figure 1). The 2 LA diameters increased significantly from S1 to S4, whereas the LA sphericity index did not (Table 2). The LA area index increase was already significant at S2 (time effect: F = 5.7, p = 0.018). LA diameters increased from S1 to S2 (time effect for length increase: F = 3.7, p = 0.05; time effect for width increase: F = 12.2, p = 0.001), whereas the LA sphericity index remained unchanged (F = 2.1, p = 0.15). The LA area index increase from S2 to S4 was also significant (time effect: F = 5.2, p = 0.02). Although LA length continued to increase from S2 to S4 (time effect: F = 3.9, p = 0.049), LA width (F = 0.11, p = 0.73) and the LA sphericity index (F = 0.94, p = 0.33) remained unchanged.

The correlations of overall changes in the LA area index (S4 − S1) with different parameters by linear regression analysis are presented in Table 4. The increase in the LA area index from S1 to S4 was greater in patients with than in those without anterior myocardial infarction (p = 0.02). LA area index changes were not significantly related to gender, a history of AMI, diabetes mellitus, hypertension, blood pressure values or Killip class at admission, significant mitral regurgitation at S1, use of thrombolysis or intravenous β blockers, treatment assigned by randomization (lisinopril or glyceryl trinitrate), or heart failure occurrence at 6 months. By stepwise multivariate linear regression, overall changes in the left ventricular end-diastolic volume index emerged as the only independently significant correlate of overall changes in the LA area index (r = 0.16, p <0.0001).

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The GISSI-3 Echo Substudy,[16] part of a randomized, controlled, multicentric trial conducted in a large series of consecutive, low-risk patients, demonstrated the occurrence of left ventricular remodeling after infarction. The present study demonstrated the existence of LA remodeling after infarction in this population. Even without a control group of noninfarcted patients, the only independently significant correlate of changes in the LA area index was a change in the left ventricular end-diastolic volume index and the lack of a significant relation to age, hypertension, diabetes mellitus, or significant mitral regurgitation, which are strong arguments that changes in LA size during follow-up in this study most likely were due to cardiac remodeling after infarction.

Myocardial infarction results in complex alterations in ventricular architecture. Infarct expansion is observed most frequently in large, transmural infarcts.[17] The anterior-apical region is particularly vulnerable to expansion because it is the thinnest,[18] but the noninfarcted zone also demonstrates a progressive increase in end-diastolic lengths.[19] Our study provides evidence that remote remodeling involves more than the noninfarcted left ventricular tissue, and that LA remodeling is directly related to left ventricular remodeling.

Experimental[20] and clinical[15] studies have shown that left ventricular enlargement continues long after complete healing of the infarction. The progressive nature of left ventricular enlargement beyond the early convalescent period of the infarct is now confirmed for the left atrium. The present study demonstrates that remodeling after infarction involves the 2 left-sided heart chambers even in a low-risk population. Although weak, the correlation between LA and left ventricular remodeling was nevertheless highly significant, and left ventricular end-diastolic volume index

changes represented the only independently significant correlate of LA area index changes.

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Usefulness of Myocardial Contrast Echocardiography Derived Coronary Flow Reserve to Accurately Determine Severity of Left Anterior Descending Coronary Artery Stenosis

Michael Hickman, MBBS, Paramjit Jeetley, MBBS, and Roxy Senior, MD

Thirty-five patients underwent quantitative low-power myocardial contrast echocardiography to evaluate the severity of left anterior descending coronary artery stenosis. Coronary flow reserve and myocardial blood flow were able to accurately differentiate among angiographically derived grades of coronary stenosis. ©2004 by Excerpta Medica, Inc.

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Myocardial contrast echocardiography (MCE)–derived coronary flow reserve (CFR) in humans has been validated against Doppler flow wire recordings[1] using a high-power intermittent harmonic imaging technique. In the same study, a significant decrease in microbubble velocity was shown to correlate with an increasing severity of coronary stenosis. However, this technique is time consuming and requires prolonged acquisition times, with the possible deterioration of image quality as a result of respiratory and movement artifacts. Furthermore, background tissue noise is frequently a problem with high-power imaging techniques. The use of low-power imaging reduces unwanted background tissue signal, and because microbubbles are minimally destroyed, images may be acquired at every cardiac cycle to assess replenishment during a single breath-hold, thereby limiting respiratory artifacts. These factors enable the more accurate quantification of destruction-replenishment curves. Therefore, we have hypothesized that low-power MCE can accurately assess myocardial blood flow (MBF) at rest and during hyperemia and thus differentiate among varying grades of coronary stenosis in humans.

From the Department of Cardiovascular Medicine, Northwick Park and St. Mark's Hospitals, Harrow, United Kingdom. Dr. Senior's address is: Department of Cardiovascular Medicine, Northwick Park Hospital, Watford Road, Harrow, Middlesex HAI 3UJ, United Kingdom. E-mail: roxy.senior@virgin.net.

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