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Clinical Investigations

Changes of the Left Ventricle after Myocardial Infarction—Estimation with Cine Magnetic Resonance Imaging during the First Six Months

MARTIN KONERMANN, M.D., BERND M. SANNER, M.D., ECKARD HORSTMANN, M.D., JÜRGEN GRÖTZ, M.D., FRANK LASCHEWSKI, M.D., WOLFGANG JOSEPHS, M.D., HANS J. ODENTHAL, M.D., ALEXANDER STURM, M.D.

Department of Internal Medicine, University of Bochum, Marienhospital, Herne, Germany

Summary

Background: In recent years, the interest of cardiologists has focused increasingly on the morphologic and functional changes of the left ventricle after myocardial infarction (MI), due to their great prognostic significance for the patient.

Hypothesis: The aim of this study was to evaluate changes in left ventricular morphology and function during the first 6 months following MI.

Methods: In all, 61 patients (17 women, 44 men, age 36–83 years) were examined with cine magnetic resonance imaging (CMRI) 1, 4, and 26 weeks after myocardial infarction. Thirty-two patients had anterior MI and 29 patients had posterior MI. According to enzyme-derived infarct weight, 15 patients had small infarcts (<20 g), 19 had intermediate-sized infarcts (20–40 g), and 27 patients had large infarcts (>40 g). CMRI was performed in the true short axis of the left ventricle. In each examination, left ventricular end-diastolic and end-systolic volume indices (LVEDVI, LVESVI), stroke volume index (LVSVI), ejection fraction (LVEF), and regional thickness, mass, and motility of the myocardial wall—diastolic thickness (IDdia), infarct mass (IM) and motility (IMOT) of the infarct area and diastolic and systolic thickness (VDdia, VDsys), muscular mass (VM), and motility (VMOT)—were determined. In addition, patients were divided into subgroups according to New York Heart Association (NYHA) functional status at baseline.

Results: In the total group, LVEDVI increased from 73.9 ± 23.5 ml/m^2 to 85.4 ± 28.1 ml/m^2 ($p < 0.001$) and LVESVI from 40.5 ± 19.4 ml/m^2 to 51.2 ± 29.0 ml/m^2 ($p < 0.001$). In the subgroups the development depended on infarct size and location. LVSVI and LVEF remained more or less constant except for large anterior infarctions. All changes of the myocardial wall depended on infarct size and location: In all patients IDdia decreased from 10.4 ± 1.6 mm to 8.9 ± 1.7 mm ($p < 0.001$), IMOT from 2.0 ± 1.6 mm to 0.5 ± 2.9 mm ($p < 0.001$). IM increased from 41 ± 21 g to 45 ± 25 g ($p < 0.001$). In the total group, VDdia increased from 11.9 ± 1.6 mm to 12.4 ± 1.8 mm ($p < 0.05$), VDsys from 16.6 ± 2.5 mm to 17.2 ± 3.1 mm ($p < 0.05$). In the subgroups changes varied: VDdia and VDsys decreased markedly in large anterior wall infarctions. VM increased in the total cohort from a mean of 246 ± 66 g to 276 ± 80 g ($p < 0.001$). VMOT decreased from 7.1 ± 2.4 mm to 6.3 ± 2.7 mm ($p < 0.05$). Loss of motility was most pronounced in anterior infarctions. The volume–mass ratio, a measure of the success of compensation of volume increase by myocardial hypertrophy, decreased in small infarcts, remained unchanged in intermediate infarcts, and increased in large infarcts. There was a trend toward improvement of the NYHA functional status during the observation period.

Conclusions: Changes of the left ventricular chamber during the first 6 months following MI are dependent on its size and location, with large anterior infarctions having the worst course. Myocardial wall remodeling is also dependent on infarct size and location, and the volume–mass ratio increases in the presence of large areas of necrosis, indicating the noncompensatory effect of myocardial hypertrophy. However, these changes have no clinical effect during the first half year after MI.

Key words: remodeling, left ventricular function, left ventricular wall, myocardial infarction, cine magnetic resonance imaging

Address for reprints:

Priv.-Doz. Dr. med. Martin Konermann
Department of Medicine
Ruhr University of Bochum
Marien Krankenhaus
Marburger Str. 85
D 34127 Kassel
Germany

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Introduction

In recent years, the interest of cardiologists has focused increasingly on the morphologic and functional changes of the left ventricle after myocardial infarction (MI), due to their great prognostic significance for the patient.[1–5] The positive

results of recently published interventional investigations evaluating angiotensin-converting enzyme (ACE) inhibitor therapy—SAVE, SOLVD, and AIRE[6–8]—as well as preliminary data of early intervention after MI—GISSI 3[9] and ISIS 4—have considerably increased interest in the basic pathophysiologic and morphologic changes.

Despite the fact that sufficient experimental data on the time course of remodeling are available,[10–22] follow-up investigations in humans are required because animal models are not necessarily transferable to humans.[10,15] Only few studies have been carried out on changes of the myocardial wall in humans,[23–27] and due to methodological limitations they supplied only incomplete data. To date, large systematic studies are scarce.[3–5,28–31]

X-ray ventriculography, echocardiography, and radionuclide angiography—the methods applied in these studies—have limitations. X-ray, an appropriate method for the evaluation of dimensions and function of the left ventricle, is ill suited for the analysis of the ventricular wall[32,33] and has the additional drawbacks of being invasive and involving exposure to radiation and contrast media, and thus cannot be frequently repeated. Two-dimensional echocardiography can well delineate cardiac walls and ventricular cavity, is without undue strain for the patient, and can be repeated an unlimited number of times; however, reproducibility is suboptimal[34,35] and, depending on the anatomic situation regarding ultrasound transmission, satisfactory imaging quality was obtained in studies examining consecutive patient populations only in up to 70%.[36] Radionuclide angiography has limited spatial resolution and the disadvantage of radiation exposure, which makes it appear less suited for follow-up studies.[3,30,32]

Cine magnetic resonance imaging (cine-MRI) is largely free of these limitations. It is noninvasive, without the need of exposure to ionizing radiation or contrast media, and is well-tolerated biologically.[37] It has excellent reproducibility.[38–40] Next to electron-beam computed tomography, which again implies exposure to contrast media and x-rays, it is the only method that allows simultaneous imaging of wall and cavity in all segments of the heart. This allows better evaluation of functional interrelationship of both compartments than is possible by other methods.[38,41,42] Its reliability could be demonstrated in comparative studies,[43–45] particularly in deformed hearts after MI.[42,45]

It was therefore the aim of the present investigation to assess, by means of cine-MRI, the morphologic and functional changes of the left ventricular chamber and wall in patients during the first 6 months after transmural MI.

Methods

Patient Population

In all, 65 patients (19 women, 46 men, age 36–83 years) with first transmural MI [definition: creatine kinase (CK)>150 U/l, increase of CK-MB>10%, typical pain, Q wave in the surface electrocardiogram (ECG), and monophasic ST elevation by 6 mm in the chest leads, 2 mm in aVL, or 3 mm in II, III, aVF] were included. Patients who had been subjected to thrombolytic or interventional therapy were excluded, since enzyme analyses for calculating infarction size are less reliable after this treatment and MRI does not adequately differentiate necrotic from stunned tissue. Other criteria for exclusion were major arrhythmia, cardiac pacemaker insertion, and clinical signs of heart failure stage IV of the New York Heart Association (NYHA) classification 1 week post infarction. For better comparability of the data, patients received daily standardized therapy with isosorbide dinitrate 60–100 mg, atenolol 0–100 mg, aspirin (ASA) 100 mg and furosemide 0–80 mg daily. Within this framework, the dosage was adjusted according to individual requirements. Any therapy beyond this regimen led to exclusion from the study.

Technical Examinations

One week (Days 6–8), 4 weeks (Days 26–30), and 6 months (Week 25–27) after MI, patients were examined by cine-MRI (Signa, General Electric, U.S.A., 1.5 Tesla). At first, axial search slices of the thorax were taken by the spin echo technique. Then the first cine-MRI was performed as oblique slice in the true long axis of the left ventricle (4–6 slices simultaneously, slice thickness 10 mm, interslice distance 5 mm, 16 signal excitations/cardiac cycle, TE 17 ms, TR 31 ms, flip angle 30°, two repeated measurements). From the slice with the largest cavity (Fig. 1), slices in the double oblique plane in the true short axis of the left ventricle were

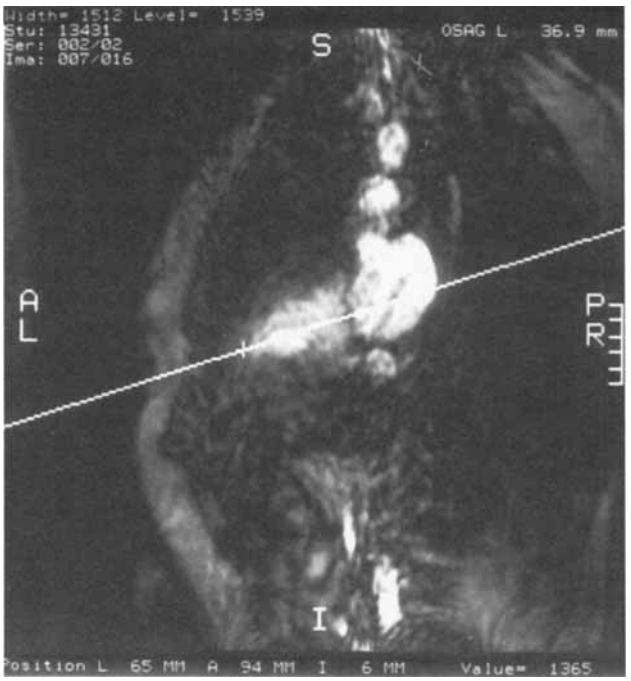

FIG. 1 Cine magnetic resonance image of the end-diastolic left ventricle in the true long axis. Auxiliary line drawn to determine position of short axis slices perpendicular to this line. For technique refer to text.

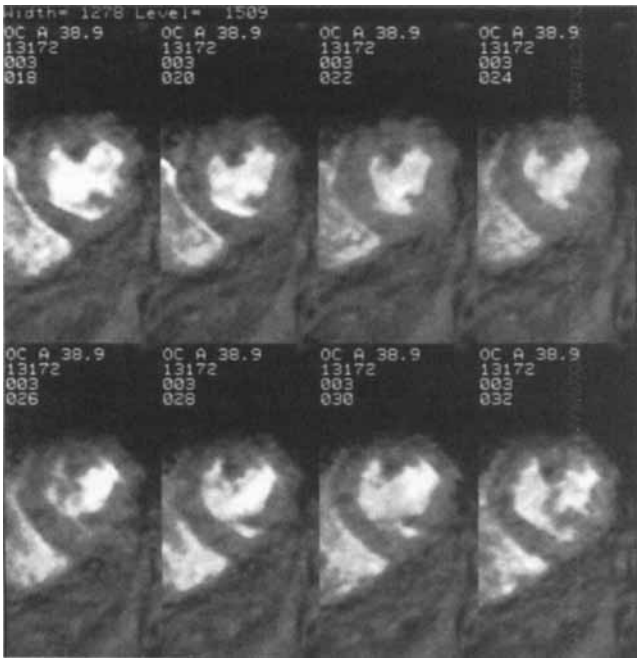

FIG. 2 Cine magnetic resonance images of the true short axis of the left ventricle, upper left end-diastole, upper right end-systole, at the level of the papillary muscles. For technique refer to text.

taken employing identical technique (Fig. 2). To permit exact reproducibility, the first slice was always positioned in the mitral plane. Examination time was 40–60 min depending on cardiac size and heart rate.

Analysis

Infarct size was calculated by enzyme analysis using the CK-integral method.[46] Serum CK after hospital admission was performed at 4-h intervals until normal values were reached. Employing average elimination constants, CK-mass flow was calculated from the integral of the measured values and, taking into account individual volumes of distribution, expressed in gram equivalent.[46] Following an earlier study,[47] infarct weight < 20 g was designated as small, of 20–40 g as medium-sized, and >40 g as large infarct.

Analysis of cine-MRI images was performed with the help of a cardiological computer (AVD-System, Siemens, Germany). End-diastolic and end-systolic images of the left ventricular short axis were identified according to their size and temporal relationship to the ECG, enlarged 2.5 times, and copied on x-ray film. Endo- and epicardial contours were traced manually on the computer, and planimetry was done. Left ventricular volumes were obtained by adding all intraendocardial planes, multiplied by slice thickness (1 cm) and interslice distance (0.5 cm). For better comparability volumes were expressed as indices related to body surface.

Myocardial thickness was determined both in diastole and systole by direct measurement in six segments of the left ventricular circumference. Motility was ascertained by subtracting the systolic from the diastolic distance of the endocard from the center focus of the left ventricular cavity. Following other authors,[48,49] infarct area was defined as an area with systolic increase of thickness <2 mm. In this region, thickness and motility were measured once again at three places (center and edges) in each slice.

Infarct volume was determined by planimetry of the infarct areas of all layers forming part of the necrosis, multiplied by the layer thickness (10 mm) and the layer distance (5 mm). Total myocardial volume was calculated by subtraction of all intraendocardial from all intraepicardial planes multiplied by slice thickness and slice distance. The volume of the viable myocardium was ascertained by subtraction of the infarct volume from the total wall volume. Myocardial weight was determined by multiplication by the specific weight of cardiac muscle (1.05 g/cm^3).

At each examination, left ventricular end-diastolic and end-systolic volume index (LVEDVI, LVESVI), stroke volume index (LVSVI), ejection fraction (LVEF), diastolic thickness (IDdia), mass (IM) and motility (IMOT) of the infarct zone, diastolic and systolic thickness (VDdia, VDsys), mass (VM) and motility (VMOT) of the vital myocardium, and the volume–mass ratio (VMR) as ratio of end-diastolic volume and left ventricular muscle mass were determined.

In addition, patients were divided into subgroups according to NYHA functional status at baseline.

Results were expressed as mean values with one standard deviation. Comparisons between the examinations were made by analysis of variance with repeated measures. Within-group differences were analyzed by the Scheffe's F test. A value of $p < 0.05$ was considered statistically significant.

Results

Four patients, all with large anterior infarctions, died before the end of the study period. Of the remaining 61 patients, 32 had anterior and 29 had posterior MI. Fifteen infarcts were small, 19 of medium size, and 27 grouped as large. In the subgroups there were 5 small, 12 intermediate, and 15 large anterior infarcts, and 10 small, 7 intermediate, and 12 large posterior infarcts.

Cavity

Left ventricular end-diastolic volume index: In the entire group, LVEDVI increased continuously during the observation period. Differences between each follow-up examination were significant (Table I).

The subgroups showed variable results. With small infarctions, ventricular size did not increase. In intermediate posterior infarcts, there was a small but nonsignificant increase in volume. In intermediate anterior infarcts, there was ventricular enlargement which was not significant after 4 weeks, but turned significant after that and over the entire study period. In

large infarctions, a marked increase in volume was noted, significant at all follow-up examinations and particularly pronounced in anterior wall necrosis.

Left ventricular end-systolic volume index: LVESVI showed similar results (Table II). In the entire cohort, mean values increased between all examinations. Differences were significant.

Here, too, the subgroups differed markedly. Again, small infarcts demonstrated no systolic volume increase of the left ventricle, while large infarcts showed a distinct increase in size, especially anterior wall infarctions. Intermediate-size infarcts of the posterior wall demonstrated a measurable but not significant increase in volume while those of the anterior wall had a significant increase in systolic volume at all follow-up examinations.

Left ventricular stroke volume index: The difference between LVEDVI and LVESVI is called stroke volume index. This index did not change essentially either in the entire study group or in the subgroups. Only large anterior infarcts demonstrated a slight decrease which, however, was not significant (Table III).

Left ventricular ejection fraction: In view of the lesser change in LVSVI than in LVEDVI, LVEF was expected to decrease in the entire study group (Table IV). However, the decrease observed was not significant between the first and second examinations but only in the further course of the study, with a significant overall difference.

Here, too, the results varied according to infarct size and location. Small infarctions rather had a tendency to increase LVEF over the observation period. With posterior infarcts there was a slight decrease that was only significant for large areas of necrosis during the second follow-up interval. With anterior infarcts, LVEF decreased markedly, yet it did not decrease significantly in intermediate-sized infarcts. Overall, it is notable that ejection fraction was more dependent on infarct size than were left ventricular volumes.

TABLE I Mean values and standard deviation of left ventricular end-diastolic volume index at individual examinations, entire group, and subgroups (ml/m^2)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 LVEDVI	73.9 (20.9)	62.8 (4.5)	71.2 (15.6)	88.7 (31.3)	66.9 (17.2)	71.9 (15.7)	69.6 (9.6)
p E1/E2	[c]	NS	NS	[c]	NS	NS	[c]
E2 LVEDVI	79.4 (23.5)	62.2 (7.3)	75.4 (17.7)	101.3 (31.3)	67.1 (15.4)	74.9 (15.4)	76.2 (11.6)
p E2/E3	[c]	NS	[b]	[c]	NS	NS	[c]
E3 LVEDVI	85.4 (28.1)	61.8 (6.4)	82.5 (19.4)	114.6 (35.2)	65.1 (14.9)	78.6 (17.5)	82.4 (12.7)
p E1/E3	[c]	NS	[b]	[c]	NS	NS	[c]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; LVEDVI = left ventricular end-diastolic volume index; p = statistical value between the examinations; NS = not significant.

TABLE II Mean values and standard deviation of left ventricular end-systolic volume index at individual examinations, entire group, and subgroups (ml/m^2)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 LVESVI	40.5 (19.4)	29.2 (3.6)	36.3 (11.2)	59.7 (28.7)	29.4 (8.6)	36.0 (7.3)	37.5 (7.9)
p E1/E2	[c]	NS	[a]	[c]	NS	NS	[b]
E2 LVESVI	45.0 (24.0)	25.0 (7.4)	40.5 (14.2)	73.0 (30.2)	27.6 (9.2)	37.6 (9.0)	41.5 (7.0)
p E2/E3	[c]	NS	[a]	[b]	NS	NS	[b]
E3 LVESVI	51.2 (29.0)	24.6 (3.2)	46.2 (16.4)	87.1 (32.2)	26.4 (9.8)	42.4 (14.7)	48.2 (9.1)
p E1/E3	[c]	NS	[a]	[c]	NS	NS	[b]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; LVESVI = left ventricular end-systolic volume index; p = statistical value between the examinations; NS = not significant.

TABLE III Mean values and standard deviation of left ventricular stroke volume index at individual examinations, entire group, and subgroups (ml/m^2)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 LVSVI	33.3 (7.7)	33.6 (2.9)	34.9 (7.5)	28.9 (10.9)	37.5 (9.8)	35.9 (8.8)	32.1 (6.0)
p E1/E2	NS	NS	NS	NS	NS	NS	NS
E2 LVSVI	34.4 (8.7)	37.2 (6.2)	34.9 (7.5)	28.3(8.4)	39.5 (10.5)	37.3 (8.4)	34.5 (6.0)
p E2/E3	NS	NS	NS	NS	NS	NS	NS
E3 LVSVI	34.2 (9.1)	37.2 (6.1)	36.3 (11.9)	27.5 (7.1)	38.7 (10.8)	36.1 (4.0)	34.3 (6.4)
p E1/E3	NS	NS	NS	NS	NS	NS	NS

[a] $p<0.05$.
[b] $p<0.01$
$p<0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; LVSVI = left ventricular stroke volume index; p = statistical value between the examinations; NS = not significant.

TABLE IV Mean values and standard deviation of left ventricular ejection fraction at individual examinations, entire group, and subgroups (%)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 LVEF	46.8 (10.7)	53.4 (3.4)	49.7 (7.6)	35.0 (12.2)	56.0 (4.4)	49.7 (2.9)	46.3 (7.0)
p E1/E2	NS	NS	NS	[b]	NS	NS	NS
E2 LVEF	46.1 (13.0)	60.2 (9.3)	47.5 (8.5)	29.8 (10.1)	58.9 (8.4)	50.1 (5.4)	46.3 (2.4)
p E2/E3	[c]	NS	NS	[a]	NS	NS	[a]
E3 LVE	43.2 (14.7)	60.0 (5.2)	44.8 (10.6)	24.5 (7.2)	59.4 (10.1)	48.3 (6.5)	41.6 (5.2)
p E1/E3	[c]	NS	NS	[a]	NS	NS	[a]

[a] = $p<0.05$.
[b] = $p<0.01$.
[c] = $p<0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; LVEF = left ventricular ejection fraction; p = statistical value between the examinations, NS = not significant.

Infarct Area

The good correlations between the infarction weight measured enzymatically or by MRI in this study, published elsewhere,[45] showed the reliability of the latter and could exclude measurement of stunned or hibernating myocardium as an infarcted area.

Diastolic diameter of infarct zone: Diastolic thickness of the infarct area was averaged from all measurements in the infarct zone. It decreased continuously in the entire study population and in the subgroups (Table V). The results were largely dependent on infarct size and location: while the decrease of IDdia in small posterior infarctions was not significant—neither between the individual follow-up examinations nor over the total observation period— it was significant in small anterior infarcts over the total observation period. In the other subgroups, the level of significance increased markedly after large infarcts.

Infarct mass: Table VI shows the mean values and standard deviations of the infarct mass in all subgroups at the three examination dates. In the entire study population as well as in the subgroups, there was an increase in infarct mass between the first and the second examination, and a slight decrease between the second and the third examination, dependent on the size of myocardial necrosis.

Infarct motility: IMOT was measured at three places (center and edges). For calculation, only 50% of the edge values was taken into account since in these areas there is passive motion of the adjacent vital myocardium. Mean values and standard deviations are shown in Table VII.

IMOT decreased in all subgroups even in small infarcts, largely dependent on infarct size and location.

Vital Myocardium

Diastolic and systolic thickness: Diastolic and systolic thickness of the myocardium were calculated by adding the thickness of vital myocardial wall of the two segments adjacent to and of the segment opposite the myocardial necrosis, as well in the slice imaging the center of the necrosis as in the

TABLE V Mean values and standard deviations of the mean diastolic thickness of the infarction zone at individual examinations, entire group, and subgroups (mm)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 IDdia	10.4 (1.6)	12.4 (1.3)	9.6 (1.0)	9.4 (1.5)	11.1 (1.9)	10.6 (1.0)	11.1 (1.4)
p E1/E2	[c]	NS	[b]	[c]	NS	NS	[c]
E2 IDdia	9.4 (1.6)	11.5 (1.5)	8.9 (1.1)	7.9 (1.3)	10.7 (1.5)	9.8 (0.8)	9.6 (0.9)
p E2/E3	[c]	NS	NS	[b]	NS	[a]	[c]
E3 IDdia	8.9 (1.7)	10.8 (1.6)	8.5 (1.2)	7.1 (1.2)	10.7 (1.5)	9.3 (0.8)	8.8 (0.6)
p E1/E3	[c]	[a]	[b]	[c]	NS	[a]	[c]

[a] $p < 0.05$.
[b] = $p < 0.01$.
[c] = $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; IDdia = mean diastolic diameter of the infarct zone; p = statistical value between the examinations; NS = not significant.

TABLE VI Mean values and standard deviations of the infarction mass at individual examinations, entire group, and subgroups (g)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 IM	41 (21)	13 (8)	34 (6)	62 (14)	15 (5)	35 (6)	58 (9)
p E1/E2	[c]	[a]	[c]	[c]	[a]	[b]	[c]
E2 IM	47 (24)	14 (8)	40 (8)	71 (16)	17 (6)	41 (9)	66 (10)
p E2/E3	[c]	[b]	[c]	NS	[b]	[c]	[c]
E3 IM	45 (25)	13 (8)	38 (8)	72 (18)	15 (6)	39 (9)	63 (10)
p E1/E3	[c]	[b]	[c]	[c]	[b]	[c]	[c]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; IM = infarction mass; p = statistical value between the examinations; NS = not significant.

TABLE VII Mean values and standard deviations of the mean motion of the infarction zone at individual examinations, entire group, and subgroups (mm)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 IMOT	2.0 (1.6)	4.3 (2.6)	1.9 (0.8)	0.6 (1.1)	3.1 (1.3)	2.0 (1.1)	2.2 (1.4)
p E1/E2	[c]	NS	[a]	[c]	NS	NS	[c]
E2 IMOT	1.1 (1.9)	3.3 (1.4)	0.9 (1.1)	−1.0 (1.4)	3.5 (1.1)	1.5 (1.2)	0.6 (0.7)
p E2/E3	[b]	NS	NS	[b]	NS	NS	[a]
E3 IMOT	0.5 (2.9)	4.2 (2.5)	0.5 (0.8)	−2.7 (2.7)	3.8 (1.2)	0.9 (0.4)	0.1 (0.9)
p E1/E3	[c]	NS	[b]	[c]	NS	[a]	[c]

[a] $p < 0.05$.
[b] = $p < 0.01$.
[c] = $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; IMOT = mean motion of the infarct zone; p = statistical value between the examinations; NS = not significant.

two adjacent slices, and then dividing the result by nine. Table VIII shows the results and the diastolic-systolic thickening of vital myocardium at the three examinations.

In the total study population, wall thickness increased markedly during the first 4 weeks, but not afterward, so that the increase of wall thickness during the first 6 months after

TABLE VIII Mean values and standard deviations of the mean thickness of the vital myocardium at individual examinations, entire group, and subgroups (mm)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 VDdia	11.9 (1.6)	12.0 (1.4)	11.6 (1.6)	12.0 (1.7)	11.8 (2.0)	11.7 (1.9)	12.2 (1.6)
p E1/E2	[b]	[a]	[b]	NS	NS	NS	NS
E2 VDdia	12.4 (1.6)	13.4 (1.1)	12.7 (1.2)	11.7 (1.6)	12.2 (2.3)	12.4 (1.5)	12.6 (1.3)
p E2/E3	NS	NS	NS	NS	[a]	NS	NS
E3 VDdia	12.4 (1.8)	13.7 (0.8)	13.0 (1.3)	11.3 (1.8)	12.4 (2.3)	12.8 (1.8)	12.3 (1.7)
p E1/E3	[a]	[b]	[c]	NS	NS	NS	NS
E1 VDsys	16.6 (2.5)	17.4 (2.7)	16.4 (2.5)	16.8 (2.5)	17.0 (2.7)	15.7 (2.4)	16.3 (2.8)
p E1/E2	[b]	[a]	[c]	NS	NS	[a]	NS
E2 VDsys	17.4 (2.7)	18.8 (1.6)	18.0 (2.6)	16.2 (3.2)	17.4 (2.9)	17.5 (2.3)	17.4 (2.6)
p E2/E3	NS	NS	NS	NS	NS	NS	NS
E3 VDsys	17.2 (3.1)	19.5 (1.8)	18.0 (3.1)	15.8 (3.7)	17.8 (2.7)	17.7 (2.9)	16.7 (2.7)
p E1/E3	[a]	NS	[b]	NS	NS	[a]	NS
E1 Ddia/sys	4.7 (0.9)	5.4 (1.3)	4.8 (0.9)	4.8 (0.8)	5.2 (0.7)	4.0 (0.5)	4.1 (1.2)
p E1/E2	NS	NS	NS	NS	NS	NS	NS
E2 Ddia/sys	5.0 (1.1)	5.4 (0.5)	5.3 (1.4)	4.5 (1.6)	5.2 (0.6)	5.1 (0.8)	4.8 (1.3)
p E2/E3	NS	NS	NS	NS	NS	NS	NS
E3 Ddia/sys	4.8 (1.3)	5.8 (1.0)	5.0 (1.8)	4.4 (1.0)	5.4 (0.4)	4.9 (1.1)	4.4 (1.0)
p E1/E3	NS	NS	NS	NS	NS	NS	NS

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; VDdia = diastolic diameter of the vital myocardium; VDsys = systolic diameter of the vital myocardium; Ddia/sys = diastolic-systolic thickening of the vital myocardium; p = statistical value between the examinations; NS = not significant.

myocardial infarction was all in all only moderate. In the subgroups, changes varied: in small and intermediate-sized infarcts, wall thickness increased steadily while diastolic-systolic thickening remained the same. In large posterior infarcts, wall thickness increased during the first 4 weeks and showed a slight decrease in the following 5 months without reaching statistical significance. In large anterior infarctions, wall thickness and diastolic-systolic thickening decreased continuously, although not significantly.

Mass: Table IX shows the mean values and standard deviations of the mass of the vital myocardium at the different examinations.

VM increased significantly in the total study group. The increase was significant in small infarcts over the entire study

TABLE IX Mean values and standard deviations of the mass of the vital myocardium at individual examinations, entire group, and subgroups (g)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 VM	246 (66)	180 (44)	201 (53)	246 (63)	205 (32)	163 (53)	196 (58)
p E1/E2	[c]	NS	[b]	[c]	[c]	[a]	[a]
E2 VM	262 (71)	183 (42)	213 (54)	260 (65)	212 (32)	167 (53)	205 (63)
p E2/E3	[c]	NS	[c]	[c]	NS	[b]	[c]
E3 VM	276 (80)	188 (43)	230 (55)	287 (71)	215 (37)	179 (53)	224 (67)
p E1/E3	[c]	NS	[c]	[c]	NS	[b]	[c]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; VM = mass of the vital myocardium; p = statistical value between the examinations; *NS = not significant.*

period and in intermediate-sized and large infarcts at all follow-up examinations, dependent on size and location of the infarct.

Motility: VMOT was calculated in the same way as VDdia and VDsys, that is, by averaging the values of three specific segments in three slices. The results are given in Table X.

It decreased in the total study population. Results differed widely in the subgroups: VMOT increased steadily in small anterior infarctions, especially during the first 4 weeks. In intermediate-sized posterior myocardial wall infarcts, it increased during the first 4 weeks and decreased afterward; in the other subgroups, VMOT decreased steadily. Loss of motility was most pronounced in anterior myocardial wall infarcts.

Volume–mass ratio: VMR, calculated from the ratio of left ventricular end-diastolic volume and left ventricular muscle mass, is an index for compensatory myocardial hypertrophy to balance volume increase. In the entire group, this value was not subject to significant change (Table XI).

In the subgroups this was different. While the ratio became smaller—at times significantly so—in smaller infarcts, it stayed about the same with intermediate-sized necroses. With large infarcts, most pronouncedly on the anterior wall, the ratio increased markedly.

Clinical Course

At first examination, 13 patients were in NYHA class I, 38 in NYHA class II, and 10 in NYHA class III. This changed to 23 patients in class I, 35 in class II, and 3 in class III at the second examination, and 28 patients in NYHA class I, 30 in class II, and 3 in class III at the final examination.

The average NYHA classification at baseline was 2.0, at the second examination it was 1.7, and at the third examination it was 1.6. Changes between baseline and second examination were highly significant, and significant between the second and third examinations. There were no significant differences with respect to infarct size and location.

TABLE X Mean values and standard deviations of the mean motion of the vital myocardium at individual examinations, entire group, and subgroups (mm)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 VMOT	7.1 (2.4)	6.3 (2.7)	7.7 (2.5)	5.8 (2.6)	9.2 (1.6)	7.0 (1.2)	6.7 (1.6)
p E1/E2	NS	NS	NS	NS	[b]	NS	NS
E2 VMOT	6.8 (2.4)	8.7 (2.1)	6.9 (1.7)	5.2 (3.2)	7.9 (1.6)	7.7 (2.1)	6.6 (1.7)
p E2/E3	[b]	NS	[a]	[a]	NS	NS	NS.
E3 VMOT	6.3 (2.7)	9.5 (2.1)	6.1 (2.0)	4.4 (3.1)	7.8 (2.2)	6.9 (2.1)	5.7 (2.1)
p E1/E3	[a]	NS	NS	[a]	[a]	NS	NS

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; VMOT = motion of the vital myocardium; p = statistical value between the examinations; NS = not significant.

TABLE XI Mean values and standard deviation of left ventricular volume–mass ratio at individual examinations, entire group and subgroups (ml/gm)

		Anterior infarction			Posterior infarction		
	All	Small	Moderate	Large	Small	Moderate	Large
E1 VMR	0.58 (0.15)	0.64(0.15)	0.58 (0.15)	0.53 (0.14)	0.61 (0.15)	0.66 (0.15)	0.55 (0.13)
p E1/E2	NS	NS	NS	[a]	[a]	NS	NS
E2 VMR	0.58 (0.14)	0.61 (0.15)	0.56 (0.14)	0.56 (0.13)	0.59 (0.14)	0.66 (0.16)	0.56 (0.12)
p E2/E3	NS	NS	[a]	[c]	NS	NS	[b]
E3 VMR	0.59 (0.14)	0.60 (0.15)	0.58 (0.14)	0.60 (0.15)	0.55 (0.11)	0.66 (0.15)	0.59 (0.14)
p E1/E3	NS	NS	[a]	[c]	NS	NS	[b]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
Abbreviations: E1, 2, 3 = examination 1, 2, 3; VMR = volume–mass ratio of the left ventricle; p = statistical value between the examinations; NS = not significant.

Discussion

It is well known that the size of the left ventricle increases after MI. This was demonstrated in animal experiments, particularly with rats, because their coronary arteries, like those of human beings, are end arteries.[12, 17, 20, 47]

In humans, investigations with various techniques have been reported (teleradiography, angiography, echocardiography, radionuclide ventriculography, and SPECT). All these studies have yielded valuable information and insight into the process of remodeling in humans, yet they all have limitations with respect to methods, number of patients, or observation period. They all have in common that no reliable data on changes in the myocardial wall could be obtained.

It is not surprising that quantitative studies about changes of myocardial wall in humans do not exist since there are no examination techniques—with the exception of magnetic resonance imaging (MRI) and electron beam computed tomography—that can reliably determine the structures of the myocardial wall in all segments, and are moreover reproducible.[32, 35, 50, 51] Even the studies using MRI are mostly descriptive; only one author treats changes of the infarct area during the first 4 weeks.[47]

The present study thus is the first to investigate systematically, in a larger cohort and over a prolonged period of time, the remodeling of the left ventricle after myocardial infarction in humans by a method that makes it possible to obtain exact morphologic and functional data of left ventricular cavity and walls by one single examination. Thus, it can demonstrate the interdependence of these data in a reliable way not possible with any other method.

Changes of the Cavity

In the total study population, LVEDVI and LVESVI increased over the entire study period. The increase of 7.5% of LVEDVI and of 11% of LVESVI during the first 4 weeks is less marked than the one Kleber found by echocardiography in anterior wall infarctions.[4] During the ensuing 5 months, however, volume increase was distinctly higher in the present study (7.5% of LVEDVI, 15% of LVESVI). The reason for these divergent results is explained by the fact, that, for methodological reasons, Kleber excluded patients with large anterior wall infarctions.[4] In our investigation, this subgroup showed the greatest volume increase during the late phase (Tables I and II).

Subgroup analysis revealed a decrease in the size of the left ventricular cavity in small infarcts. The same phenomenon was observed by Gaudron *et al.*[29] It can be explained by the fact that activation of the neurohumoral mechanisms during the early postinfarction period subsequently normalizes, thereby terminating initial volume overload.[52, 53]

With intermediate-sized, and particularly with large necroses, volumes increased. Here a distinct dependency on the size of the infarct but also on infarct location is noted. Pirolo[54] observed the same in an autopsy study and reasoned that the anterior free wall offers less resistance to infarct expansion than either the posterior wall or the septum. We, however, could demonstrate that increase of the infarcted zone after 4 weeks progresses much more slowly,[55] so that this is not the only reason for greater left heart dilatation of anterior infarcts during the late phase. Dilatation of the surviving myocardium must also play an essential role.

In the present investigation there was an interval of 3 weeks between the first and the second examination, and an interval of 22 weeks between the second and the third examination. The almost identical differences of the measured values between the two examinations allow the conclusion that volume increase of the left ventricle develops at a much faster rate during the first weeks following MI than during subsequent months.

In large infarctions, especially of the anterior wall, LVEDVI was greater at the first examination than in the other subgroups, which points to the fact that early dilatation of the left ventricle takes place in the first week post infarction, as could already be shown in an earlier study.[47] This can be explained by expansion of the infarcted area, which is particularly marked during the initial phase and which in animal experiments leads to a more rapid enlargement of the ventricular cavity than the more slowly evolving excentric hypertrophy and fiber slippage of the viable myocardium that is predominant during the late phase.[6, 8, 10, 56–58]

Stroke volume remained quite constant in the entire group and in all subgroups. This coincides with the results of Gaudron *et al.*[29] who also observed no deterioration of LVSVI during the first 6 months following MI independent of its size. Ejection fraction, however, showed divergent results on subgroup analysis. While in small necroses it increased continuously, it decreased slightly in intermediate-sized infarcts, and markedly so in large infarcts, particularly of the anterior wall (Table IV).

It is evidently an effect of postinfarction remodeling to maintain cardiac function by compensating for the loss of contractile tissue by volume expansion, thus maintaining stroke volume constant. This is achieved during the first half year following MI. In accordance, we as well as Gaudron *et al.*,[29, 59] could observe that clinical behavior did not deteriorate in this period.

Yet concomitant with infarct size there is also an increase in the rate of left ventricular volume which maintains cardiac pump function. It could be shown[29] that this is the basis for deterioration of left ventricular function during the further course of the healing process, which is heralded by diminishing ejection fraction.

Changes of the Infarct Area

The thickness of the infarct area decreased steadily in all subgroups, most pronouncedly during the first 4 weeks after MI, and largely dependent on size and location of the necrosis (Table V). Due to the remodeling that took place during the first week post infarction, thickness of the infarct zone was smallest in large infarcts as early as at the first examination. This corresponds to the results of animal studies on rats and dogs.[57, 58, 60, 61] Thickness of the infarct area decreased further

during the following months. These findings prove that—contrary to similar processes in animals—remodeling of the infarct zone in humans is not concluded after a few weeks but continues during the following months, as has already been assumed by Braunwald and Pfeffer.[1]

Infarct mass increased markedly in intermediate-sized and large necroses during the first 4 weeks (Table VI). Since the infarct area became thinner at the same time, this indicates an expansion of the infarct area that is already known from animal experiments[10, 18, 62] and autopsy studies in humans.[23, 63] Afterward, almost all subgroups showed a decline of infarct mass indicating shrinking processes.[64] Only in large anterior infarctions did infarct mass continue to increase after the first 4 weeks, even though much more slowly than before. This can be explained by, first, the extent of the myocardial necrosis, and second, the fact that the anterior free wall offers less resistance to infarct expansion than either the septum or the posterior wall, which are reinforced by the right ventricle and the diaphragm.[23] Thus extent and duration of expansion of the infarct zone seem to depend on size and location of the necrosis.

Motility of the infarct area was also largely related to size and location of the necrosis (Table VII). This is probably mainly due to an impaired contractility of the vital myocardium since the motions of the transmural infarction area—the sole subject of this study—can only be partly attributed to remaining contractility of the infarct zone. The negative motility in large anterior myocardial wall infarctions corresponds to a systolic bulging since aneurysms develop more often in these infarctions.

Changes of the Vital Myocardium

Thickness of the vital myocardium increased in all subgroups except in large anterior infarctions, mainly during the first 4 weeks. After that, wall thickness decreased slightly in large posterior myocardial wall infarcts, especially during systole. In large anterior infarctions, myocardial thickness decreased from the beginning (Table VIII). This indicates the dependence of dilatation and loss of contractile function of the viable tissue on the size and location of the necrosis.

Mass of the vital myocardium also increased in all subgroups (Table IX), markedly dependent on size and location of the infarct zone. It is noteworthy and has not been described to date that a hypertrophy of the vital myocardium also ensues in small necroses, especially during the first 4 weeks. Since these small infarctions are functionally insignificant, the hypertrophy of the vital myocardium is probably due to early phase neurohumoral volume load and sympathetic activity leading to stimulation of myocardial growth.[53]

The effect of myocardial hypertrophy is a counterbalance for the increased wall stress caused by volume expansion.[15, 53] The volume–mass ratio, an index representing the global left ventricular wall stress, can be used as a measure of the effectiveness of this compensatory mechanism (Table XI). Our results indicate for the first time in humans that in small and medium-sized infarcts compensation is successful, while it fails in large posterior infarcts during the late phase and in large anterior infarcts already in the early post-infarction period. Thus the extent of compensatory myocardial hypertrophy depends on size and location of the necrosis.

Contractility of the vital myocardium can be derived from diastolic-systolic thickening and from motility (Tables VIII and X). While there was no significant change of myocardial thickening in small infarcts, it decreased in large infarctions, dependent on its location. Motility decreased by 24% in anterior infarcts and by 15% in posterior infarcts. Thus, even contractility of the vital myocardium depends on size and location of the infarction.

When comparing the changes in size of the left ventricle and those of the infarct area and of the vital myocardium, it becomes obvious that during the first 4 weeks the correlation is best between ventricular size and infarct area size, and afterward between size of the left ventricle and vital myocardium. This applies to the entire study population and to all subgroups with the exception of large anterior infarcts where correlations do not differ that widely. It can be concluded that the increase in ventricular size is caused mainly by dilatation of the infarct area during the early phase post infarction and by dilatation of the vital myocardium during the later period. These findings confirm those of earlier studies by Pfeffer *et al.*[19] and Roberts *et al.*[64] on rats as well as those of Erlebacher *et al.* using echocardiography[24, 65] and Lamas using x-ray ventriculography[26] on humans. Only in large anterior myocardial wall infarctions are both compartments of the infarcted ventricle involved more evenly during both phases.

Conclusions

The increase in size of the left ventricle during the first half year following myocardial infarction depends primarily on infarct size, but also on its location. The effect is the maintenance of stroke volume and of cardiac pump function reflected in the unchanging clinical behavior of the patients during this period. With declining ejection fraction in large infarcts, expected deterioration is heralded.

Size and location of the infarction also are relevant for changes of necrotic and vital parts of the left ventricular wall, with large anterior infarctions having the worst course. However, even small, hemodynamically insignificant infarcts showed changes of the architecture of the left ventricle; these were most pronounced in the early phase after infarction, probably due to neurohumoral activation.

The increase in left ventricular muscle mass compensates for increased wall stress caused by volume expansion. Myocardial hypertrophy is also dependent on size and location of the infarct, and the compensation of wall stress is not successful in large infarctions—with anterior necroses early during the postinfarction period.

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