Clinical Investigations

Preinfarction Angina Prevents Left Ventricular Remodeling in Patients Treated with Thrombolysis for Myocardial Infarction

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Summary

Background: It has been shown that preinfarction angina may have beneficial effects on infarct size and mortality. However, there are no studies that have serially assessed the impact of preinfarction angina on left ventricular (LV) function in a large series of patients.

Hypothesis: The study was undertaken to determine whether preinfarction angina (within 7 days before infarction) influences LV remodeling.

Methods: In all, 119 consecutive patients with acute myocardial infarction were serially evaluated by 2-dimensional echocardiography (on Days 1, 2, 3, and 7; at 3 and 6 weeks; and at 3, 6, and 12 months following infarction). Left ventricular volumes were determined using Simpson’s biplane formula and normalized for body surface area. Wall motion score index and sphericity index were calculated for each study. Coronary angiography was performed before discharge.

Results: Preinfarction angina was detected in 39 of 119 patients. Initial echocardiographic and clinical data as well as the incidence of patent infarct-related artery and collaterals were similar for patients with and without preinfarction angina. In the subset of thrombolysed patients, patients with preinfarction angina showed decrease of LV end-diastolic and end-sys-

tolic volumes during the follow-up period ($p = 0.033$ and $p = 0.001$, respectively), and improvement of wall motion score index ($p < 0.001$) and ejection fraction occurred ($p = 0.001$), without changing of LV shape ($p > 0.05$); in addition, patients with preinfarction angina had smaller LV volumes and higher ejection fraction than did those without angina, from 3 weeks onward. These favorable effects were not detected in patients not treated with thrombolysis.

Conclusions: These data indicate that preinfarction angina has an inhibiting effect on long-term LV remodeling in patients who underwent thrombolysis for first acute myocardial infarction. It appears that preinfarction angina has no impact on infarct size and early postinfarction LV function.

Key words: preinfarction angina, left ventricular remodeling

Introduction

Progressive left ventricular (LV) dilation and complex alterations in LV geometry, a process known as remodeling, can occur following acute myocardial infarction (MI).¹ These changes influence left ventricular systolic function and prognosis. We have recently demonstrated² that LV dilatation can be detected in the earliest phase of MI. The magnitude and the rate of postinfarction remodeling is affected by numerous factors, including infarct location, infarct-related artery patency, and therapy.^{3–7}

Recently, several studies have assessed the impact of preinfarction angina on infarct size,^{8,9} postinfarction LV function,^{10–13} and clinical outcome,^{14–16} with controversial results.^{17–19} However, data are scarce regarding the impact of preinfarction angina on changes in LV function during long-term follow-up. Thus, the issue of the effects of preinfarction angina on LV remodeling has not been clarified yet.

This study sought to determine the relationship between preinfarction angina and LV remodeling after acute MI during 1-year follow-up.

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Methods

Study Patients

The initial study group consisted of 131 consecutive patients with acute MI, originally reported previously,² who met the following criteria: (1) age ≤ 70 years, (2) chest pain lasting > 30 min, (3) ST-segment elevation ≥ 2 mm in at least two electrocardiographic leads, (4) elevation of creatine kinase and/or MB isoenzyme, and (5) echocardiogram performed within 24 h from onset of pain. Five patients with inconclusive history of preinfarction angina and seven patients who died during the first days after infarction were not included in the study. Thus, the final study group consisted of 119 serially evaluated patients.

The history of preinfarction angina was obtained on hospital admission by the attending cardiologist. Preinfarction angina was defined as the presence of resting or exercise-induced typical chest pain, lasting < 30 min and relieved spontaneously or by sublingual nitroglycerin, during the week before infarction. None of the patients was hospitalized for anginal pain in the week preceding infarction.

Therapy

Thrombolytic therapy (intravenous streptokinase 1,500,000 U over 30–60 min) was administered in 77 of 119 patients; the remaining 42 patients were not treated with thrombolysis at the discretion of their attending cardiologist, because they were admitted late after the onset of pain or had contraindications for thrombolysis. The use of thrombolysis, nitrates, beta blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digoxin was similar in patients with and without preinfarction angina. It is important to note that few patients in our study were treated with intravenous nitroglycerin (24/119, 20%) and with ACE inhibitors (12/119, 11%).

Echocardiograms

Two-dimensional echocardiography was performed on Days 1, 2, 3, and 7; at 3 and 6 weeks; and at 3, 6, and 12 months following MI. All examinations were performed with an Acuson 128 machine (Mountain View, Calif., USA), using a 2.5 MHz transducer, and were stored on VHS video tapes for later analysis. Left ventricular end-diastolic and end-systolic volumes and ejection fraction were determined from apical 2- and 4-chamber views using the Simpson's biplane formula.²⁰ Tracing of endocardial borders in end-diastole and end-systole was performed on the Acuson 128 machine in the technically best cardiac cycle. The volumes were normalized for body surface area and expressed as indices. Assessment of wall motion score index was performed by dividing the left ventricle into 16 segments,²⁰ and segmental wall motion was graded as follows: normal motion at rest (score = 1); hypokinetic:

marked reduction in endocardial motion and systolic thickening (score = 2); akinetic: virtual absence of inward motion and systolic thickening (score = 3); and dyskinetic: paradoxical wall motion away from the center of the left ventricle in systole (score = 4). Wall motion score index was calculated by summation of individual segment scores divided by the number of interpreted segments.

In the beginning and at the end of the study, LV sphericity indices in diastole were determined using the modified Lamas formula,²¹ which describes sphericity of a shape as a ratio of its volume to that of the smallest enclosing sphere (sphericity index = $6V/\pi L^3$, where L = long axis of the left ventricle and V = volume of the left ventricle).

Coronary Angiography

In 104 of 119 patients enrolled in the study before hospital discharge, coronary angiography was performed to determine the presence of collateral circulation and infarct-related artery patency. The remaining patients did not undergo coronary angiography because they refused it or died before the scheduled procedure. Perfusion of the infarct-related artery was assessed using Thrombolysis in Myocardial Infarction (TIMI) criteria.²² Successful reperfusion was defined as TIMI 3. Significant coronary artery stenosis was defined as $> 70\%$ area stenosis of the major epicardial coronary artery.

Statistical Analysis

The chi-square test was used for comparison of nonparametric data and the unpaired t -test was used to compare continuous variables between patients with and without preinfarction angina. Paired t -test was used to compare initial LV volumes, ejection fraction, and wall motion score and sphericity indices, with results at the end of the follow-up.

Analysis of variance (ANOVA), with post hoc analysis by the Newman-Keuls test, was used to analyze repeated measures of ventricular volumes, ejection fraction, and wall motion score and sphericity indices.

Results

Of 119 patients enrolled in the study, 39 had a history of preinfarction angina ≤ 7 days before infarction. Patients' characteristics are shown in Table I. Patients with angina ≤ 7 days were slightly older than those without angina ($p = 0.045$). Although 1-year mortality was not statistically different in patients with or without preinfarction angina, it should be noted that there were no deaths among patients with angina ≤ 7 days.

Left Ventricular Function and Remodeling

Initial left ventricular volumes, ejection fraction, and wall motion score and sphericity indices were similar between groups (Table II).

TABLE I Patient characteristics

	Angina + (n = 39)	Angina 0 (n = 80)
Age (years)	57.1 ± 7.9	53.7 ± 9.0 ^a
Sex	19F/30M	23F/57M
Hypertension	10/39	36/79
Diabetes	5/39	14/79
Smoking	27/39	40/79
Anterior infarct	14/39	34/80
Q-wave infarction	31/39	74/80
Peak creatine kinase (U/l)	925 ± 607	1164 ± 856
Killip class >I	6/39	15/80
Thrombolysis	24/39	53/80
1-year mortality	0/39	5/80

Age and creatine kinase are expressed as mean ± 1 standard deviation.

^a p < 0.05, between groups.

TABLE II Initial echocardiographic data (Day 1)

	Angina + (n = 39)	Angina 0 (n = 80)	p Value
End-diastolic volume index (ml/m ²)	58.6 ± 10.9	62.0 ± 12.5	NS
End-systolic volume index (ml/m ²)	31.7 ± 10.2	34.0 ± 11.5	NS
Ejection fraction (%)	47 ± 10	46 ± 10	NS
Wall motion score index	1.5 ± 0.3	1.6 ± 0.3	NS
Sphericity index	0.36 ± 0.07	0.38 ± 0.06	NS

Data are expressed as mean ± 1 standard deviation.

Abbreviation: NS = not significant.

TABLE III Echocardiographic data for the whole study group^a

	Day 1	1 Year	p Value
End-diastolic volume index (ml/m ²)			
Angina +	58.4 ± 11.8 ^b	61.4 ± 17.3	NS
Angina 0	61.6 ± 13.0	73.7 ± 24.57	<0.001
End-systolic volume index (ml/m ²)			
Angina +	30.4 ± 9.9 ^b	39.1 ± 13.2	NS
Angina 0	33.4 ± 12.3	40.2 ± 21.5	0.001
Ejection fraction (%)			
Angina +	49 ± 9 ^b	54 ± 8	0.008
Angina 0	47 ± 11	48 ± 11	NS
Wall motion score index			
Angina +	1.5 ± 0.3 ^b	1.3 ± 0.3	0.001
Angina 0	1.5 ± 0.3	1.4 ± 0.4	0.036
Sphericity index			
Angina +	0.36 ± 0.07 ^b	0.38 ± 0.07	NS
Angina 0	0.38 ± 0.06	0.41 ± 0.09	0.001

Data are expressed as mean ± standard deviation.

^a Only patients with both Day 1 and 1-year echocardiographic data were included in this analysis (25 patients with angina ≤ 7 days and 54 without angina).

^b p > 0.05 vs. patients without angina.

Patients without angina increased LV volumes and sphericity index, without changes in ejection fraction and wall motion score index during follow-up (Table III). On the other hand, patients with preinfarction angina did not change initial LV volumes and shape and showed improvement in ejection fraction and regional wall motion (Table III).

However, in the subset of thrombolysed patients, those with preinfarction angina showed a decrease in LV volumes during the follow-up period, as well as improvement of wall motion score index and ejection fraction without changing LV shape (Table IV); in addition, according to ANOVA, patterns of changes of LV end-diastolic volume (F = 6.6, p = 0.0001), end-systolic volume (F = 8.4, p < 0.00001), ejection fraction (F = 3.8, p = 0.002), and wall motion score index (F = 12.2, p < 0.00001) in patients with and without preinfarction angina were strikingly different throughout the study period (Fig. 1A–D). Patients with preinfarction angina had smaller LV volumes and higher ejection fraction than did those without angina, from 3 weeks onward (Fig. 1A–D). These favorable effects were not detected in patients not treated with thrombolysis (Table V, Fig. 2A–D).

Angiographic Data

Incidence of collaterals, multivessel coronary artery disease, and late infarct-related artery patency were similar between groups (Table VI).

TABLE IV Echocardiographic data for patients treated with thrombolysis^a

	Day 1	1 Year	p Value
End-diastolic volume index (ml/m ²)			
Angina +	60.1 ± 9.7 ^b	56.8 ± 9.2	0.033
Angina 0	59.2 ± 9.2	69.1 ± 17.9	0.001
End-systolic volume index (ml/m ²)			
Angina +	31.6 ± 8.2 ^b	25.1 ± 5.3	0.001
Angina 0	30.6 ± 9.5	36.3 ± 17.2	0.009
Ejection fraction (%)			
Angina +	49 ± 8 ^b	56 ± 6	0.001
Angina 0	49 ± 10	49 ± 11	NS
Wall motion score index			
Angina +	1.5 ± 0.3 ^b	1.1 ± 0.2	<0.001
Angina 0	1.5 ± 0.3	1.4 ± 0.4	NS
Sphericity index			
Angina +	0.37 ± 0.08 ^b	0.38 ± 0.07	NS
Angina 0	0.36 ± 0.05	0.40 ± 0.08	0.016

Data are expressed as mean ± standard deviation.

^a Only patients with both Day 1 and 1-year echocardiographic data were included in this analysis (17 patients with angina ≤ 7 days and 34 without angina).

^b p > 0.05 vs. patients without angina; patients with preinfarction angina were older (58.1 ± 8.9 vs. 52.3 ± 9.2 years, p = 0.034); other patient characteristics listed in Table I, as well as the therapy, were similar in both groups.

Abbreviation as in Table II.

FIG. 1 (A) Impact of preinfarction angina on left ventricular end-diastolic volume index during 1-year follow-up in patients treated with thrombolysis. * $p < 0.001$ between groups. (B) Impact of preinfarction angina on left ventricular end-systolic volume index during 1-year follow-up in patients treated with thrombolysis. * $p < 0.001$ between groups. (C) Impact of preinfarction angina on left ventricular ejection fraction during 1-year follow-up in patients treated with thrombolysis. * $p < 0.001$ between groups; † $p < 0.01$ between groups. (D) Impact of preinfarction angina on left ventricular wall motion score index during 1-year follow-up in patients treated with thrombolysis. * $p < 0.001$ between groups.

TABLE V Echocardiographic data for patients not treated with thrombolysis^a

	Day 1	1 Year	p Value
End-diastolic volume index (ml/m ²)			
Angina +	52.9 ± 14.5 ^b	71.1 ± 25.9	0.008
Angina 0	65.8 ± 17.3	81.7 ± 31.9	0.001
End-systolic volume index (ml/m ²)			
Angina +	27.6 ± 13.1 ^b	37.5 ± 20.4	0.033
Angina 0	38.3 ± 14.8	46.9 ± 26.5	0.038
Ejection fraction (%)			
Angina +	49 ± 10 ^b	50 ± 12	NS
Angina 0	43 ± 10	46 ± 11	NS
Wall motion score index			
Angina +	1.5 ± 0.3 ^b	1.5 ± 0.4	NS
Angina 0	1.6 ± 0.3	1.5 ± 0.4	NS
Sphericity index			
Angina +	0.35 ± 0.05 ^b	0.38 ± 0.07	NS
Angina 0	0.40 ± 0.07	0.44 ± 0.11	0.034

Data are expressed as mean ± 1 standard deviation.

^a Only patients with both Day 1 and 1-year echocardiographic data were included in this analysis (8 patients with angina ≤ 7 days and 20 without angina).

^b $p > 0.05$ vs. patients without angina; patients with preinfarction angina were older (61.1 ± 1.9 vs. 55.1 ± 8.4 years, $p = 0.006$); other patient characteristics listed in Table I, as well as the therapy, were similar in both groups.

Abbreviation as in Table II.

FIG. 2 (A) Impact of preinfarction angina on left ventricular end-diastolic volume index during 1-year follow-up in patients not treated with thrombolysis. (B) Impact of preinfarction angina on left ventricular end-systolic volume index during 1-year follow-up in patients not treated with thrombolysis. (C) Impact of preinfarction angina on left ventricular ejection fraction during 1-year follow-up in patients not treated with thrombolysis. (D) Impact of preinfarction angina on left ventricular wall motion score index during 1-year follow-up in patients not treated with thrombolysis.

TABLE VI Angiographic data

	Angina + (n = 35)	Angina 0 (n = 69)	p Value
Patent infarct-related artery	23/35	32/69	NS
Multivessel coronary artery disease	16/35	30/69	NS
Collaterals	8/34	24/68	NS

Abbreviation as in Table II.

Discussion

Recent studies have revealed evidence that preinfarction angina has a beneficial effect on infarct size^{8,9} and LV function¹⁰⁻¹³ after acute MI. More important, a better short-^{14,15} and long-term¹⁶ outcome has been reported in patients with preinfarction angina. On the other hand, some studies have found no beneficial,¹⁷ or even unfavorable, effect of preinfarction angina on clinical outcome.^{18,19,23} This controversy may be related to various definitions of preinfarction angina used in these studies, including different time windows for positive history (ranging from 1 day up to 3 months preceding infarction). In addition, in some studies no distinction between

chronic stable angina and angina of recent onset was made; thus, they did not evaluate the same mechanisms that may affect LV function.

Previously published studies that analyzed LV function at one point of time after infarction provided no precise answers regarding the pattern of LV dilatation that may continue over months and years after infarction.

Our data revealed that, for the whole study group, LV remodeling during the year following infarction was only slightly affected by the presence of preinfarction angina. The increase in LV volumes and the change in LV shape were limited in patients with preinfarction angina in contrast to those without angina, indicating that the remodeling process was diminished. It should be noted, however, that, in contrast to patients without preinfarction angina, end-systolic volume was not increased in those with angina. Keeping in mind that LV end-systolic volume is a strong predictor of mortality after infarction,²⁴ this limiting effect on end-systolic volume increase could be at least partly responsible for the zero mortality observed in patients with preinfarction angina.

Of importance is the fact that we found that beneficial effect of preinfarction angina was significantly more pronounced in patients treated with thrombolysis. In this subset of patients, the remodeling process was halted during the year following in-

faction in those with preinfarction angina. All analyzed echocardiographic parameters of LV function and shape were favorably affected by preinfarction angina: patients with angina had decreased left ventricular volumes, improved ejection fraction, no change in LV shape, and reduced extent of regional wall motion asynergy. It should be noted that this favorable effect was not apparent before the third week after infarction, indicating that preinfarction angina has no influence on initial infarct size and early LV function, but prevents late LV remodeling.

It has been shown that some drugs, such as intravenous nitrates and angiotensin-converting enzyme inhibitors,^{6,7} may influence LV remodeling after infarction. Since few patients in our study were treated with these drugs, it is less likely that they could demonstrate a significant effect on the remodeling process in this series of patients.

Recently, it has been demonstrated that patients with preinfarction angina have more rapid reperfusion²⁵ and lower incidence of reocclusion of the infarct-related artery¹² after thrombolysis. According to these studies, it can be proposed that this beneficial effect on LV remodeling may depend on faster coronary thrombolysis and maintained infarct-related artery patency in addition to or instead of myocardial preconditioning.^{9,15,26} Although initial infarct size, as assessed by wall motion score index and maximal creatine-kinase level, was similar in patients with and without preinfarction angina, it is suggested that faster and longer-lasting reperfusion in patients with angina may result in restriction of the remodeling process.

Limitations of the Study

This is a relatively small study, and the comparatively small number of patients in subgroups, considering the number of comparisons necessary, may influence the stability of the statistical estimates. Although the use of cardiovascular drugs was balanced in patients with and without preinfarction angina, the influence of any of them as a confounding factor could not be definitively discarded in such a small sample size.

It would also be interesting to determine whether the influence of preinfarction angina on LV remodeling was more pronounced in different patient populations (i.e., anterior vs. inferior infarctions). However, further dividing our study population would result in such small subgroups that this would further jeopardize meaningful statistical comparisons; therefore, larger studies are necessary to address these issues.

Conclusions

Our results indicate that preinfarction angina has an inhibiting effect on long-term left ventricular remodeling after a first acute myocardial infarction in patients treated with thrombolysis. On the other hand, it appears that preinfarction angina has no effect on infarct size and early postinfarction left ventricular function.

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