Potential influence of pre-infarction angina on myocardial viability and residual ischemia

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Key words:
Ischemia; Pre-infarction angina; Viability.

Background. **The effects of recent pre-infarction angina on myocardial viability and residual ischemia are unknown. This study evaluates them in 90 patients with a first Q-wave myocardial infarction using early dobutamine stress echocardiography.**

Methods. **Patients were classified according to the absence or presence of recent pre-infarction angina, defined as chest pain lasting < 30 min during a period of 7 days before the acute myocardial infarction. The infarct zone wall motion score index was calculated at baseline and at low- and peak-dose dobutamine stress echocardiography. All subjects underwent coronary angiography.**

Results. **Patients with unheralded myocardial infarction showed, in comparison with patients with recent pre-infarction angina, a significantly higher peak of creatine kinase serum levels (2630 ± 1360 vs 1865 ± 1562 IU/l, p = 0.002) and a higher number of leads with pathologic Q waves (3.2 ± 1.3 vs 2.8 ± 0.8, p = 0.002). The groups did not differ with regard to the infarct zone wall motion score index at rest (2.15 ± 0.42 vs 2.18 ± 0.31, p = 0.72) and at low- (1.86 ± 0.52 vs 1.80 ± 0.41, p = 0.55) and peak-dose (2.24 ± 0.55 vs 2.19 ± 0.58, p = 0.68) dobutamine stress echocardiography. The prevalence of myocardial viability (31 vs 48%, p = 0.15), homozonal (52 vs 58%, p = NS) or heterozonal ischemia (36 vs 23%, p = NS) was not statistically different between the groups of patients without and with recent pre-infarction angina. The angiographic patterns were similar.**

Conclusions. **Recent pre-infarction angina is associated with a smaller infarct size but it does not seem to influence the ventricular contractile improvement or residual ischemia, detected at early dobutamine echocardiography, in patients with a first Q-wave myocardial infarction.**

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Introduction

Recent studies have shown that in patients with acute myocardial infarction the presence of new-onset angina is associated with more rapid reperfusion after thrombolytic therapy[1], a smaller infarct size[2], a favorable effect on the in-hospital outcome[3], and a positive influence on infarct expansion[4]. In animal models this positive effect has been considered as the clinical equivalent of ischemic preconditioning[5]. In these instances, repeated brief episodes of ischemia and reperfusion seem to be able to protect the myocardium from more persistent subsequent coronary occlusion[6]. These findings are in contrast with previous studies which have shown no benefits[7] or even deleterious effects[8-10] of pre-infarction angina. However, the influence of prior myocardial infarction, risk factors and multivessel coronary artery disease has not always been considered and the definition of pre-infarction angina has often included chronic as well as unstable angina. Furthermore, the effect of recent pre-infarction angina on the recovery of myocardial function and its influence on the jeopardized myocardium in patients with recent acute myocardial infarction has not been defined yet. Dobutamine-atropine stress echocardiography allows the evaluation of segmental wall motion abnormalities during inotropic stimulation; besides it is safe and reliable in detecting residual ischemia[11] and the contractile reserve[12] even in patients with a recent acute myocardial infarction[13,14]. The aim of this study was to analyze the effects of recent pre-infarction angina on both viability and residual ischemia in patients with a first Q-wave myocardial infarction using early dobutamine stress echocardiography.

Methods

Study population. The study involved 90 consecutive patients (79 men, 11 women,

mean age 60 ± 9 years, range 41-76 years) undergoing dobutamine stress echocardiography. All patients fulfilled the following criteria: 1) first acute Q-wave myocardial infarction diagnosed on the basis of chest pain, a diagnostic rise in serum creatine kinase levels (at least twice the normal values) and acute evolutionary ST-segment changes in more than 2 leads; 2) presence of at least two akinetic left ventricular segments at baseline echocardiography; 3) absence of intraventricular conduction defects, ventricular preexcitation, right or left ventricular hypertrophy, significant valvular heart disease and those factors known to influence the QRS complex; 4) acceptable acoustic window; 5) no contraindication to dobutamine stress (occurrence of early post-infarction angina or acute left ventricular failure, severe systemic hypertension, ventricular arrhythmias).

Patients reporting typical chest pain lasting < 30 min during a period of 7 days before the acute myocardial infarction were defined as having recent pre-infarction angina. This timeframe was chosen for two main reasons: 1) because the majority of patients with intermittent chest pain, who develop myocardial infarction, report unstable symptoms during the preceding week[7], 2) to exclude the influence of any collateral circulation, as it has been shown that the latter is established in about 2 weeks[15]. The data concerning pre-infarction angina were collected during an interview the day after the index event. All patients were informed about the nature of this protocol and gave their written consent. The ECGs on which the Q-wave analysis was based were collected 7 ± 2 days after the acute myocardial infarction.

Dobutamine stress echocardiography. Dobutamine-atropine echocardiography was performed 7 ± 2 days after the acute myocardial infarction and after withdrawal of cardioactive drugs. Dobutamine was infused at incremental doses of 5, 10, 20, 30 to 40 μg/kg/min, each dose for 3 min. Atropine was administered at the end of the last stage when the heart rate had not reached 85% of the maximal age-predicted value. The cuff blood pressure was measured every 3 min. The following had been considered as the test's endpoints: 1) achievement of 85% of the maximal age-predicted heart rate, 2) new or worsening wall motion abnormalities, 3) severe angina, 4) sustained ventricular or supraventricular arrhythmias, 5) systemic hypertension (> 220/130 mmHg) or hypotension (drop in systolic blood pressure > 20 mmHg compared to the previous step). All patients completed the dobutamine stress test.

Echocardiographic analysis. Two-dimensional echocardiography was performed with the patient in the left lateral position using a Hewlett Packard Sonos 2500 echo system (Palo Alto, CA, USA) with a 2.5 or 3.5 MHz transducer. Images from four standard views of the left ventricle (parasternal long and short axis, apical 4 and 2 chamber views) were obtained. All echocardiograms were monitored, recorded on videotape and blindly interpreted by two skilled physicians. In case of disagreement a third investigator reviewed the images. This permitted consensus to be reached in all cases. In accordance with the guidelines of the American Society of Echocardiography[16], the left ventricle was divided into 16 segments and the analysis was performed using the 16-segment model and the following scoring system: 1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis. An echocardiographic wall motion score index, defined as the sum of the scores of the segments divided by the number of the segments considered, was calculated in basal conditions and at low and peak doses of dobutamine. The infarct zones were defined according to a previous study and consisted, for both anterior and inferior infarction, of 9 segments[17]. The infarct zone wall motion score index was defined as the sum of the scores of the segments divided by 9. Viability was considered to be present when both wall motion and thickness improved in at least two adjacent akinetic or dyskinetic segments. To reduce the effects of variability, the change from hypokinesia to normal contraction was not considered[18]. Homozonal ischemia was defined as the extension of akinesia to at least one normal or hypokinetic segment in the infarct area[19] or as contractile deterioration, after initial improvement, to at least akinesia at low doses of dobutamine in a minimum of two baseline akinetic segments. Akinesia deteriorating to dyskinesia was not considered indicative of myocardial ischemia[20]. Heterozonal myocardial ischemia was defined as the appearance of new areas of akinesia/dyskinesia in a non-infarct-related region. Intraobserver and interobserver calibration for regional wall motion analysis during dobutamine stress echocardiography had been previously performed in our laboratory on the basis of the evaluation of a group of 100 patients with coronary artery disease: the interobserver agreement was 93%, the intraobserver agreement was 95%.

Coronary angiography. Coronary angiography was performed according to the Judkins technique in all patients before discharge (within 2 weeks of the onset of acute myocardial infarction). Significant stenosis was defined as a decrease in diameter > 50% according to the caliper technique[21]. The collateral circulation was graded according to Rentrop's classification[22]. Two blinded investigators analyzed the angiogram data. The left ventricular ejection fraction was calculated at contrast ventriculography.

Statistical analysis. Data are presented as mean values ± SD. Patients were divided into two groups according to the absence (0) or presence (+) of recent pre-infarction angina. Continuous variables were compared using a two-tailed Student's t-test. A χ^2 test with Yates' correction was used for comparison of categorical variables. A p value of < 0.05 was considered statistically significant.

Results

Study patients. The infarct location was anterior in 50 patients. Thrombolytic treatment was administered to 59 subjects. Recent pre-infarction angina occurred in 48 patients. Patients with unheralded myocardial infarction showed, in comparison with patients with recent pre-infarction angina, a significantly higher peak of creatine kinase serum levels and a higher number of leads with pathologic Q waves, as shown in table I. The area under the 24-hour creatine kinase curve was 4571 ± 2797 and 3105 ± 2548 IU/l 24 hours in the group without and with recent pre-infarction angina respectively (p = 0.01), as shown in figure 1. As reported in table I, there were no differences in risk factors between the groups. In patients submitted to thrombolysis the time interval between onset of symptoms and the beginning of lytic therapy was 4 ± 1.9 and 3.6 ± 1.6 hours in patients without and with recent pre-infarction angina respectively (p = 0.45).

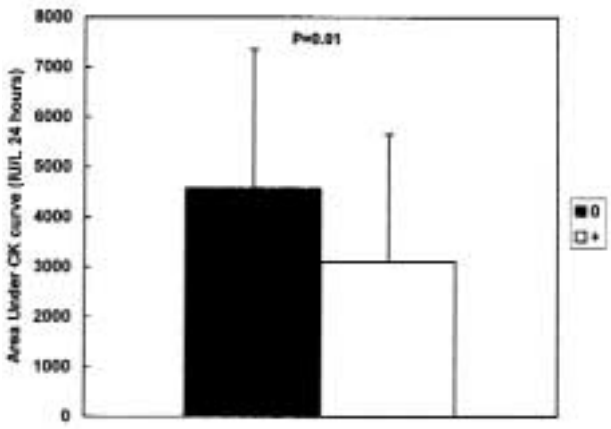

Figure 1. *Comparison between the areas under the 24-hour creatine kinase (CK) curve in patients without (0) or with (+) recent pre-infarction angina.*

Angiographic data. The mean luminal diameter stenosis of the involved vessel was 79 ± 35%. Collateral vessels were noted in 15 patients. The angiographic patterns did not show significant differences between the groups. The percentage stenosis of the infarct-related coronary artery was 75 ± 32 vs 82 ± 37% for patients without or with recent pre-infarction angina respectively (p = NS). Total occlusion of the infarct-related artery was present in 8 patients without and in 9 patients with recent pre-infarction angina (p = NS) while in 5 patients without and in 4 patients with recent pre-infarction angina, there was no residual stenosis of the infarct-related coronary artery (p = NS). A patent but stenotic infarct-related coronary artery was found in 29 patients without and in 35 patients with recent pre-infarction angina (p = NS). A type 0 collateral circulation was found in 35 patients without and in 40 patients with recent pre-infarction angina. A type 1 collateral circulation was found in 5 patients without and in 6 patients with recent pre-infarction angina. A type 2 collateral circulation was found in 2 patients without and in 2 patients with recent pre-infarction angina. No patient presented with a type 3 collateral circulation. The prevalence of one, two and three vessel disease was the same in both groups. The left ventricular ejection fraction was 49 ± 9 and 49 ± 8% in patients without and with recent pre-infarction angina respectively (p = NS).

Dobutamine stress echocardiography. All patients completed dobutamine stress echocardiography. The endpoints were: heart rate > 85% in 71 (79%) patients, a maximal dose of dobutamine and atropine in 9 (10%), hypotension in 4 (4%), hypertension in 1 (1%), multi-

Table I. Patient's selection: baseline clinical data and risk factors in patients without (0) and with (+) recent pre-infarction angina.

	Recent pre-infarction angina		p
	0 (n=42)	+ (n=48)	
Age (years)	61 ± 10	59 ± 9	0.31
Men/women	36/6	43/5	0.81
Thrombolysis (yes/no)	30/12	29/19	0.38
Peak creatine kinase (IU/l)	2630 ± 1360	1865 ± 1562	0.002
Peak creatine kinase MB (IU/l)	225 ± 136	154 ± 133	0.001
No. leads with pathologic Q waves	3.2 ± 1.3	2.8 ± 0.8	0.002
Site of AMI (anterior/inferior)	22/20	28/20	0.72
Data of stress test after AMI (days)	7.1 ± 2	7.8 ± 2	0.14
Hypertension	18 (43)	21 (50)	1.00
Diabetes	7 (17)	8 (17)	1.00
Smoking	19 (45)	24 (50)	0.81
Hypercholesterolemia	19 (45)	20 (42)	0.89
Family history of coronary artery disease	7 (17)	7 (14)	1.00
Obesity	6 (14)	11 (23)	0.43

Data are expressed as mean ± SD or number (%) of patients. AMI = acute myocardial infarction.

ple abnormalities in 3 (3%) and chest pain in 2 (2%). At low doses, myocardial viability developed in 36 (40%) patients. At the peak dose, homozonal ischemia and heterozonal ischemia developed in 50 (55%) and 26 (29%) patients respectively. Dobutamine stress data are reported in table II. Patients with and without recent pre-infarction angina showed a similar wall motion score index and infarct zone wall motion score index at rest and at the low- and peak-dose dobutamine stress test; the prevalence of myocardial viability, homozonal and heterozonal ischemia and chest pain were not statistically different between the groups. The infarct zone wall motion score index calculated at rest and at low- and high-dose dobutamine stress echocardiography in patients with or without recent pre-infarction angina is shown in figure 2. Among patients with reversible dysfunction, 3 in the group without and 5 in the group with recent pre-infarction angina had sustained improvement at low doses of dobutamine without changes at high doses, while 10 patients in the group with unheralded acute myocardial infarction and 16 in the group with recent pre-infarction angina showed a biphasic response (p = NS).

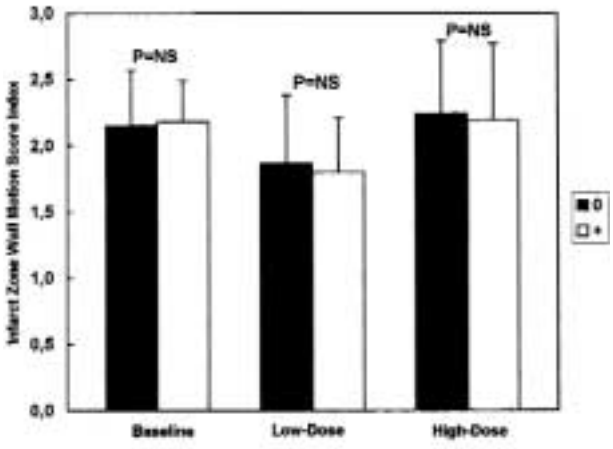

Figure 2. *Comparison between infarct zone wall motion score index at rest and at low and high doses of dobutamine in patients without (0) or with (+) recent pre-infarction angina.*

Discussion

We found that recent pre-infarction angina occurred in 53% of patients with a first acute Q-wave myocardial infarction. This result does not differ from previous studies which reported an incidence of pre-infarction angina ranging from 44 to 65%[7,23-25].

Infarct size and ventricular function. The effect of pre-infarction angina on the infarct size has been previously evaluated. As reported in table III[1,4,9,23,26], most of the studies concluding that episodes of chest pain before acute myocardial infarction are cardioprotective[1-4] found a smaller infarct size as determined by a lower peak of creatine kinase serum levels in patients with pre-infarction angina. Our data are in line with these results. We also found, in agreement with Kloner et al.[3], a significantly higher number of Q waves on the ECGs of patients with unheralded acute myocardial infarction, suggesting a larger infarct size.

The benefits of pre-infarction angina in terms of its effect on ventricular function are still controversial. According to some authors[2-4,27], they seem to be more evident only in the subgroup of patients with anterior infarction. Napoli et al.[26] were not able to find any differences in both ejection fraction and number of hypokinetic segments 24 hours following an acute myocardial in-

Table II. Dobutamine echocardiographic test data in patients without (0) and with (+) recent pre-infarction angina.

	Recent pre-infarction angina		p
	0 (n=42)	+ (n=48)	
Baseline heart rate (b/min)	68 ± 13	72 ± 13	0.23
Baseline systolic blood pressure (mmHg)	123 ± 20	130 ± 19	0.10
Low-dose heart rate (b/min)	76 ± 15	75 ± 17	0.93
Low-dose systolic blood pressure (mmHg)	134 ± 24	138 ± 25	0.37
Peak heart rate (b/min)	137 ± 14	133 ± 19	0.23
Peak systolic blood pressure (mmHg)	144 ± 30	150 ± 32	0.32
Baseline WMSI	1.71 ± 0.28	1.70 ± 0.20	0.93
Low-dose WMSI	1.50 ± 0.33	1.46 ± 0.24	0.55
Peak WMSI	1.83 ± 0.40	1.81 ± 0.31	0.79
Baseline infarct zone WMSI	2.15 ± 0.42	2.18 ± 0.31	0.72
Low-dose infarct zone WMSI	1.86 ± 0.52	1.80 ± 0.41	0.55
Peak infarct zone WMSI	2.24 ± 0.55	2.19 ± 0.58	0.68
Myocardial viability	13 (31%)	23 (48%)	0.15
Homozonal myocardial ischemia	22 (52%)	28 (58%)	0.72
Heterozonal myocardial ischemia	15 (36%)	11 (23%)	0.26
Chest pain	11 (26%)	18 (37%)	0.35

Data are expressed as mean ± SD or number (%) of patients. WMSI = wall motion score index.

Table III. Peak creatine kinase serum levels (IU/l) in patients without (0) or with (+) pre-infarction angina as reported in the literature.

Author	No. patients	0	+	p	T
Andreotti et al.[1]	23	2395 ± 1615	1180 ± 783	0.03	< 1 week
Anzai et al.[4]	129	2819 ± 2515	1824 ± 1458	0.016	< 1 month
Pierard et al.[9]	732	1569 ± 1099	1454 ± 1142	NS	< 1 month
Yoshikawa et al.[23]	256	1510 ± 1310	1170 ± 1140	NS	Not specified
Napoli et al.[26]	90	1250 ± 1436	1078 ± 1373	0.0001	< 2 days

T = duration of pre-infarction angina before the index event.

farction. However, from the third day until 1 month of follow-up, the two parameters expressing left ventricular function, behaved significantly better in patients with new-onset angina. Other authors[24,28] found a higher ejection fraction in the group of patients with pre-infarction angina lasting > 1 week, but this finding was absent in the group with pre-infarction angina lasting < 1 week[28] in comparison with the group without it. Our data do not differ from the results of Kloner et al.[3] and Pierard et al.[9] who found no differences in left ventricular ejection fraction between the groups of patients with or without new-onset angina. Differences in the population selection criteria, study protocol and definition of antecedent angina may account for the different results. Table IV[2-4,23,24,27,28] summarizes the results of the main studies regarding the left ventricular ejection fraction in patients with or without recent pre-infarction angina.

We did not find any differences in angiographic patterns between the groups. Our results appear to be in line with those of some major studies[2,4,28], but in contrast with those of others[3,23]. With regard to the presence of a collateral circulation, our findings are comparable to previous studies[2-4,27,29] as no difference in patients with or without new-onset angina was found.

Viability and residual ischemia. The most important finding of our study is that recent pre-infarction angina does not seem to be associated with an improved contractile recovery or with a higher incidence of residual ischemia as assessed at early dobutamine stress echocardiography. In fact, the prevalence of homozonal and heterozonal ischemia as well as of myocardial viability was not statistically significant different between the groups with and without recent-onset angina. Although a trend favoring patients with recent pre-infarction angina was found during the analysis of myocardial viability, the wall motion score index and infarct zone wall motion score index, calculated at low doses of dobutamine, were similar. These findings, together with the exclusion of the confounding influence of collateral flow, are not consistent with the hypothesis that ischemic preconditioning may produce an effect on reversible dysfunction or on residual ischemia in patients with a recent acute Q-wave myocardial infarction. It has been reported that preconditioning may not have occurred when reperfusion is missing[24,28]. However we did not find any significant differences regarding the number of patients submitted to thrombolytic treatment and the percentage of residual stenosis of the involved coronary artery between the groups with or without recent pre-infarction angina. Our data appear to be in contrast with those of Napoli et al.[26] and Nakagawa et al.[29]. Napoli et al.[26] concluded that in patients with new-onset angina preceding acute anterior myocardial infarction, recovery of left ventricular function may occur earlier. In fact, they found the new-onset angina group to have fewer hypokinetic segments, a more significant improvement in the wall motion score and a higher ejection fraction as detected at serial echocardiography. However it is worth noting that, with regard to the number of hypokinetic segments, differences with the group with unheralded acute myocardial infarction disappear within

Table IV. Left ventricular ejection fraction (%) in patients without (0) or with (+) pre-infarction angina as reported in the literature.

Author	No. patients	0	+	p	T	Site of infarction
Ottani et al.[2]	24	49 ± 8	53 ± 11	NS	< 1 day	Anterior
Anzai et al.[4]	129	52 ± 13	55 ± 11	NS	< 1 month	Anterior
Kloner et al.[3]	416	51 ± 1	52 ± 1	NS	< 2 days	Anterior + inferior
Yoshikawa et al.[23]	256	51 ± 15	57 ± 12	0.05	Not specified	Anterior + inferior
Matsuda et al.[24]	31	32 ± 15	47 ± 16	0.05	< 2 weeks	Anterior
Iwasaka et al.[27]	53	43 ± 15	57 ± 13	0.001	< 1 week	Anterior + inferior
Hirai et al.[28]	27	38 ± 3	47 ± 4	NS	< 1 week	Anterior

T = duration of pre-infarction angina before the index event.

3 months of follow-up. Furthermore, Napoli's study population significantly differs from ours in at least three aspects: 1) only patients with acute anterior myocardial infarction undergoing thrombolysis were included; 2) the definition of new-onset angina included only patients with chest pain within 48 hours before myocardial infarction; 3) as coronary angiography was performed only in a small number of patients (25%), the confounding role of multivessel disease or of a collateral circulation was not excluded. However it must be remarked that the contractile reserve may change if dobutamine stress echocardiography is repeated during a later phase of myocardial infarction. Nakagawa et al.[29] performed left ventriculography during the acute phase and 28 days after acute myocardial infarction. They found that the early and late ejection fractions were not statistically different in groups without and with antecedent angina pectoris, but the latter had a significant improvement in left ventricular function, independently of collateral circulation. However, as serial echocardiograms have shown that areas of reversible dysfunction may not recover before a few days or even a few weeks have elapsed[30] and since no information was available after 30 days, it cannot be excluded that the benefits of new-onset angina resulting in a faster improvement of contractile recovery, are not detectable after this period.

Study limitations. Our study did not include patients with early post-infarction angina, acute left ventricular failure and ventricular arrhythmias because in such patients dobutamine stress echocardiography would have been contraindicated: the selection of patients with very low in-hospital complications could have influenced the results. Recent pre-infarction angina is not an objective parameter and it is not easy to evaluate it accurately. Silent ischemia, another important component of the whole ischemic burden, was not recorded. Finally, the small cohort of patients may have limited the findings of the study.

Conclusions. Recent pre-infarction angina is associated with a smaller infarct size but it does not seem to influence the ventricular contractile improvement or residual ischemia, detected at early dobutamine echocardiography, in patients with a first acute Q-wave myocardial infarction.

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