Beneficial effects of diltiazem during myocardial reperfusion: a randomized trial in acute myocardial infarction

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Key words:
Acute myocardial infarction; Diltiazem; Myocardial viability; Reperfusion injury.

Background. **Although in experimental models of coronary occlusion diltiazem administration has been shown to reduce the degree of stunning and of reperfusion injury, the majority of clinical trials has failed to demonstrate significant benefits. The aim of this study was to evaluate the effect of diltiazem, administered before coronary reperfusion, on infarct size, residual myocardial viability and recovery of left ventricular function.**

Methods. **We studied 90 patients admitted within 3 hours of the onset of symptoms of acute myocardial infarction. They were immediately randomized to either intravenous diltiazem (10 mg bolus + 10 mg/hour for 3 days) (group 1, n = 43) or placebo (group 2, n = 47) and subsequently treated with recombinant tissue-type plasminogen activator. All underwent serial echocardiograms upon admission, 4 days post-admission during low-dose dobutamine stress echo, at discharge and after 6 months. We calculated the dysfunction score (1 = hypokinesia, 2 = akinesia, 3 = dyskinesia) on admission and its percent reduction after dobutamine (viability) and at follow-up (recovery). The 12-lead electrocardiograms were continuously monitored for 3 days and coronary angioplasty was performed whenever the residual stenosis was > 60%.**

Results. **Upon admission, there were no differences in age, sex, infarct location and size, degree of ST-segment elevation, time from onset of symptoms and dysfunction score. Creatine kinase peaked early in 70% of patients in both groups; the incidences of recurrent ischemia, infarct-related vessel patency and the need for coronary angioplasty were also similar. The creatine kinase peak was significantly higher in group 2 (2931 ± 2456 vs 1726 ± 1004 IU/l, $p < 0.05$). Conversely, in group 1 the residual viability was significantly higher (51 ± 23 vs 36 ± 30% improvement in dysfunction score, $p < 0.05$) and the early recovery of regional function was significantly greater (35 ± 34 vs 18 ± 22% at discharge, $p < 0.05$). On the other hand, the delayed recovery was not significantly different (15 ± 29 vs 21 ± 32% from the time of discharge to 6 months of follow-up).**

Conclusions. **Intravenous diltiazem, started before coronary reperfusion, has beneficial effects on the infarct size, residual viability and recovery of regional function. If confirmed by larger trials, these preliminary results suggest the use of diltiazem as adjunctive therapy in patients with acute myocardial infarction and undergoing reperfusion.**

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Introduction

Thrombolytic therapy reduces the relative risk of all cause mortality from acute myocardial infarction[1-3]. Recent studies evaluating the effects of primary angioplasty suggest that further benefits may be obtained following effective reperfusion, especially if performed early after the onset of symptoms[4-6]. However, several questions regarding the possibility of preserving the myocardium from ischemic and reperfusion injury remain. Experimental data support the idea that reperfusion damage can be prevented or reduced by diltiazem[7-9], but whether the same result can be obtained in patients with acute myocardial infarction is still to be demonstrated. In fact, although diltiazem has been shown to improve the outcome of a non-Q wave myocardial infarction[10], where the infarct-related artery is very often patent, the role of this agent in improving left ventricular function recovery in patients with myocardial infarction undergoing reperfusion with thrombolysis or coronary angioplasty is still debated. In general, calcium channel blockers have not been shown to reduce the infarct size in humans. However, in most studies the agents were administered relatively late (≥ 4 hours after the onset of symptoms) and were rarely administered before reperfusion treatment. In two recent studies, diltiazem was administered either orally during streptokinase treatment[11] or intravenously during tissue-type plasminogen activator thera-

py[12]. The effects on left ventricular function were quite different in the two studies and the question of whether the observed beneficial effects of diltiazem were related to an anti-ischemic mechanism or to direct cardioprotection was not addressed. The aim of our study was to assess the effects of intravenous diltiazem, administered together with thrombolytic therapy, on the left ventricular function of patients with acute myocardial infarction. The study followed a randomized, placebo-controlled, double-blind design and left ventricular function was assessed by serial echocardiograms performed during admission and follow-up. Residual viability was evaluated by dobutamine stress echocardiography and the degree of myocardial injury was assessed on the basis of the peak level reached in serum cardiac enzymes.

Methods

In the study period, we enrolled all patients who met the following inclusion criteria: 1) age < 70 years, 2) an established diagnosis of acute myocardial infarction, documented by the presence of an ST segment elevation (> 2 mm in at least 2 leads, lasting > 30 min and not responsive to nitrates), a-dyskinesia of at least two ventricular segments on echocardiography and increased creatine kinase (CK) levels (more than twice the upper limit of normal), 3) no contraindication to thrombolytic therapy, 4) admission within 3 hours of symptom onset. We excluded patients with a previous myocardial infarction, coronary bypass surgery, heart failure or cardiogenic shock, bradycardia (heart rate < 50 b/min), atrioventricular block, sick sinus syndrome, low blood pressure (systolic blood pressure < 100 mmHg) and other cardiovascular conditions or severe hepatic, renal or hematological disorders. The study was approved by the Institutional Ethics Committee and each patient gave written informed consent to the investigation.

Study drug. Eligible patients were blindly assigned to receive either diltiazem or placebo according to a randomization block. We used commercially available vials (50 mg/3 ml, Tildiem, Sanofi-Synthelabo, Milan, Italy) or matching doses of placebo. In patients randomized to diltiazem, the drug was given as a 0.15 mg/kg bolus, followed by an infusion of 0.15 mg/kg/hour lasting 3 days. The maximum daily dose was 300 mg and was never exceeded. The infusion rate was reduced to 5 mg/hour in the presence of I degree atrioventricular block, bradycardia (< 50 b/min) or low blood pressure. The infusion was discontinued in the presence of a hepatic enzyme increase, II or III degree atrioventricular block or whenever unexpected adverse drug reactions developed. Besides diltiazem or placebo, all patients received intravenous nitrates, titrated according to blood pressure values, aspirin (an initial intravenous bolus of 300 mg followed by an oral daily dose of 100 mg), recombinant tissue-type plasminogen activator (100 mg; 15 mg bolus, 50 mg in 30 min, 35 mg in 60 min), and whole intravenous heparin (5000 IU bolus, followed by an infusion initially set at 1000 IU/hour). The maintenance heparin dose was adjusted on the basis of the values of the activated partial thromboplastin time ratio which were kept between 2.5 and 3.5.

In order to achieve adequate control of the heart rate (< 90 b/min) and blood pressure (< 140/90 mmHg), beta-blockers were administered. In the acute phase we administered propranolol (1 mg intravenous bolus every 15 min to a maximal intravenous dose of 5 mg) and subsequently, if tolerated, oral therapy with atenolol (from 25 to 100 mg/day according to the target heart rate and blood pressure).

Echocardiography. The study was primarily aimed at evaluating the effects of diltiazem on ventricular function as assessed by serial echocardiograms. These were obtained by a Hewlett Packard 5000 echocardiograph (Andover, MA, USA) immediately after admission (before thrombolysis), 7 days thereafter and 6 months post-discharge. All standard views were used for the assessment of wall motion but images were considered acceptable for analysis only when the endocardial borders were clearly identified on end-diastolic and end-systolic frames derived from the parasternal short-axis and 4- or 2-chamber apical views or from all three apical views. Images were coded and blindly assessed by two independent experienced cardiologists. The left ventricle was divided into 16 segments as previously described[13] and the regional wall motion was scored as follows: 0 = normal, 1 = hypokinetic (marked reduction in endocardial motion), 2 = akinetic (virtual absence of inward motion), 3 = dyskinetic (paradoxical systolic expansion). The dysfunction score was calculated by adding the values of the regional scores recorded on the admission echocardiogram (before thrombolysis) as well as on that taken 7 days post-admission. The absolute and relative percent differences of the dyssynergic score observed on admission and 7 days later were assumed to represent the amount of early myocardial recovery. However, the actual degree of myocardial salvage was derived from the extent of left ventricular function recovery observed on follow-up echocardiograms, obtained 6 months post-admission. Three days after enrollment, diltiazem or placebo as well as beta-blockers were gradually discontinued and a low-dose dobutamine test (5-10-20 μg/kg/min for 4 min) was performed under ECG and echocardiographic continuous monitoring. Whenever possible all standard views were obtained during the test. Relevant frames were digitized on line using dedicated software (HP 5000 echocardiography). Representative digitized cycles were reviewed off-line and displayed on a cine-loop format for analysis. Control images and those obtained at each dobutamine infusion rate were displayed, side-by-side, using a split screen format. A viability test was considered positive when the wall motion score de-

creased by 4 or more points at peak dobutamine. The difference between admission and peak dobutamine scores was assumed to represent the amount of myocardial viability.

Electrocardiography. Conventional ECGs (including right precordial and lateral leads) were obtained immediately after admission, as well as after intravenous nitrates. ECG was also performed and recorded after the diltiazem/placebo bolus, following thrombolysis and daily until discharge. The level of the ST segment was measured at the J point and the cumulative ST segment elevation was calculated from all leads except aVR. The ECG showing the maximum value of ST segment elevation was selected for comparison with subsequent tracings. The 12-lead ECG was also continuously monitored for 72 hours by the ST-Surveyor System (Mortara Rangoni, Milwakee, WI, USA). This monitoring equipment allows the detection of all significant ST segment changes (> 1 mm in ≥ 2 leads or ≥ 2 mm in 1 lead) lasting at least 3 min as well as the recording of all arrhythmic events. The 72 hours, 12-lead ST segment trend was stored on digital tape and analyzed by two independent cardiologists unaware of the treatment that the patient received. Particular attention was given to the immediate post-thrombolysis period and to the occurrence of ST segment shifts unrelated to positional changes and possibly related to recurrent ischemia[14,15].

Cardiac enzyme determinations and reperfusion criteria. Blood samples for the determination of total CK and CK-MB concentration were obtained every 4 hours during the first 24 hours and daily thereafter. Reperfusion was assumed to have occurred when at least three of the following criteria were fulfilled: 1) the occurrence of a CK-MB peak within 12 hours of symptom onset[16], 2) reduction of the cumulative ST segment elevation to < 50% the maximal initial value occurring at the end of thrombolytic treatment[14], 3) relief of chest pain, 4) occurrence of reperfusion arrhythmias (accelerated idioventricular rhythm, ventricular tachycardia in the absence of electrolyte disorders or bradyarrhythmias in inferior myocardial infarction and occurring within 6 hours of thrombolysis and simultaneously to ST segment elevation resolution).

In-hospital clinical evaluation and follow-up. Blood pressure (cuff sphygmomanometer) and heart rate were routinely recorded upon admission, 30 min, 1, 3, 6 and 12 hours after randomization and daily thereafter. The timing and duration of chest pain before and after admission were annotated and the occurrence of adverse events such as death, recurrent ischemia and the need for emergency revascularization (owing to refractory ischemia or hemodynamically severe ischemia) were recorded. The presence of heart failure was also recorded and scored as follows: 0 = absence of symptoms or of clinical or radiological (chest X-ray) signs, 1 = signs of pulmonary congestion only on chest X-ray, 2 = signs of pulmonary congestion and rales, 3 = rales, X-ray signs and dyspnea, 4 = cardiogenic shock. A follow-up visit was performed along with repeat echocardiography 6 months post-discharge.

Coronary arteriography. Unless indicated in an emergency setting (recurrent ischemia, severe left ventricular failure), coronary arteriography was performed before discharge 4-7 days post-admission. The femoral transcutaneous approach and the Judkins technique were usually employed. The severity of coronary stenosis of the infarct- and non-infarct-related vessels was assessed by directional coronary atherectomy and the TIMI grade flow in the culprit artery was assessed by two independent observers who were blinded to therapy.

Statistical analysis. Continuous variables are given as the mean ± SD. The frequency distribution is given for categorical data. The Student's t and χ^2 tests were used to test categorical variables. Continuous variables were tested by analysis of variance (ANOVA for repeated measures, two-sided, alpha = 0.05) when appropriate (analysis of left ventricular function indexes and evaluation of blood pressure and heart rate). Differences were considered statistically significant when the p value was < 0.05.

Results

Study population. Between March 1996 and December 1998, 281 patients with an acute myocardial infarction were admitted to our Coronary Care Unit: 191 patients were excluded because of 1) delayed admission (n = 35), 2) signs of heart failure (n = 25), 3) age (n = 20), 4) previous myocardial infarction (n = 26), 5) bradycardia-hypotension (n = 21), 6) ST segment depression (n = 20), 7) contraindications to thrombolysis (n = 10), 8) primary angioplasty (n = 30), and 9) cardiogenic shock (n = 4). Of the remaining 90 patients (76 males, 14 females), 43 were assigned to diltiazem (group 1) and 47 received placebo (group 2). The two groups were comparable for age, sex, presence of risk factors, infarct size and location, time from symptom onset and ejection fraction on admission. Their baseline characteristics are shown in table I.

Non-invasive assessment of reperfusion. Based on the evaluation of the different non-invasive markers (Table II), the occurrence of reperfusion, defined as the concomitant presence of at least three of these markers was similar in the two groups. However, although the percentage of patients exhibiting an early CK peak was similar, the peak values of total and CK-MB were significantly lower in group 1 ($p < 0.05$ and $p < 0.01$ respectively). Furthermore, although the ECG parameters of reperfusion were also similar, the occurrence of

Table I. Baseline characteristics of the two study groups.

	Group 1 (n = 43)	Group 2 (n = 47)
Sex (M/F)	27/16	39/8
Age (years)	56 ± 11	55 ± 11
Family history	15 (35%)	18 (38%)
Hypertension	22 (51%)	20 (43%)
Diabetes	14 (38%)	17 (36%)
Hypercholesterolemia		
(> 200 mg/100 ml)	18 (42%)	21 (43%)
Total cholesterol (mg/100 ml)	192 ± 35	203 ± 37
Triglycerides (mg/100 ml)	116 ± 46	138 ± 72
Blood glucose (mg/100 ml)	106 ± 34	117 ± 49
Cigarette smoking	28 (65%)	35 (74%)
Time from symptom onset		
to thrombolysis (min)	123 ± 63	144 ± 56
Anterior infarction (%)	56	51
ST segment elevation (mm)		
Admission	15 ± 10	15 ± 9
Peak	19 ± 12	20 ± 13
Post rt-PA	5 ± 6	6 ± 8
Admission echocardiography		
Ejection fraction (%)	48 ± 10	46.8 ± 8.4
Dysfunction score	15 ± 5.6	14.9 ± 6

rt-PA = recombinant tissue-type plasminogen activator.

repetitive ventricular arrhythmias was significantly lower in patients treated with diltiazem (35 vs 68%, p < 0.05).

Acute events. The adverse events observed during the 72-hour period following admission are summarized in table III. The incidence of acute ST segment re-elevation (i.e. occurring immediately after the termination of reperfusion therapy) was not significantly different in the two groups, whilst subacute ST segment changes (i.e. those observed during the first 72 hours post-admission) with either elevation or depression were slightly but not significantly less frequent in patients receiving diltiazem. The incidence of revascularization by either emergency or elective coronary angioplasty was similar. The in-hospital mortality, reinfarction rate, presence and severity of signs of heart failure and concomitant medications did not differ in the two groups, even though the optimal control of heart rate and blood pressure necessitated beta-blockers in a greater proportion of patients of group 2. In general, diltiazem was well tolerated and in only 1 patient did the occurrence of a transient I degree atrioventricular block prompt the down-titration of the study drug.

Table III. In-hospital events and concomitant therapy.

	Group 1 (n = 43)	Group 2 (n = 47)
Subacute ST segment elevation		
or depression	11 (26%)	15 (32%)
Emergency PTCA	7 (16%)	5 (11%)
Elective PTCA	25 (60%)	33 (70%)
Heart failure		
0 (absent)	33 (77%)	30 (64%)
1 (X-ray, asymptomatic)	4 (9%)	5 (11%)
2 (rales, asymptomatic)	2 (5%)	5 (11%)
3 (rales, symptomatic)	4 (9%)	7 (14%)
I degree atrioventricular block	3 (7%)	0
Concomitant therapy		
Beta-blockers	6 (14%)	13 (28%)
Nitrates	40 (93%)	42 (89%)
Heparin	43 (100%)	47 (100%)
ACE-inhibitors	10 (23%)	10 (21%)
Amiodarone	1 (2%)	2 (4%)

PTCA = percutaneous transluminal coronary angioplasty.

Effects of diltiazem on heart rate and blood pressure. The behavior of heart rate and systolic blood pressure during the different trial phases is shown in figure 1. Both upon admission and immediately before thrombolysis the two parameters did not significantly differ between the two groups. Immediately after thrombolysis, the systolic blood pressure was lower in patients receiving placebo, whilst in the diltiazem group the heart rate was lower from 3 to 12 hours after thrombolysis; however, the pressure-rate product, an index of myocardial oxygen consumption, did not significantly differ at baseline and throughout the study.

Table II. Prevalence of clinical markers of reperfusion and cardiac enzyme peak.

	Group 1 (n = 43)	Group 2 (n = 47)	p
Early CK peak	30 (70%)	33 (70%)	NS
50% reduction in ST			
segment elevation	35 (81%)	36 (77%)	NS
Reperfusion arrhythmias	15 (35%)	32 (68%)	< 0.05
Angina relief	38 (88%)	31 (66%)	NS
Reperfusion	30 (70%)	30 (64%)	NS
Time to CK peak (hours)	11 ± 3	11.2 ± 4	NS
CK peak (IU/l)	1726 ± 1004	2931 ± 2456	< 0.05
CK-MB peak (IU/l)	207 ± 107	402 ± 330	< 0.01

CK = creatine kinase.

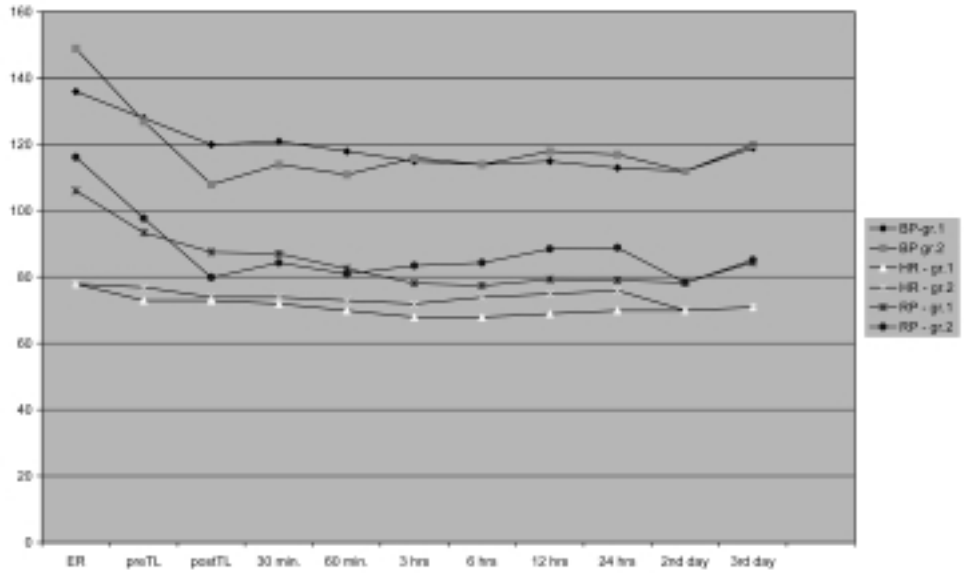

Figure 1. *Serial measurements of blood pressure (BP, mmHg), heart rate (HR, b/min) and rate-pressure product (RP, mmHg*b/min) at admission (emergency room-ER), before and after thrombolysis (TL) and during the 3-day diltiazem (group 1) or placebo (group 2) infusion period. No significant differences were observed.*

Coronary arteriography. Angiographic data are summarized in table IV. The severity of coronary artery disease was similar in the two groups. In particular, the presence of multivessel disease, the patency of the infarct-related vessel and the severity of residual stenosis were not significantly different. Furthermore, the need for percutaneous revascularization and the percentage of successful, uncomplicated procedures were also similar.

Rest and dobutamine stress echocardiography. Upon admission, both the ejection fraction (48 ± 10 vs 47 ± 8%) and dysfunction score (14 ± 5 vs 15 ± 6) were similar in the two groups (Fig. 2). At discharge, the ejection fraction was significantly improved in both groups (group 1 from 47 ± 10 to 59 ± 11%, group 2 from 47 ± 8 to 51 ± 10%, $p < 0.05$). Accordingly, the dysfunction score decreased significantly in group 1 (from 14 ± 5 to 9 ± 6, $p < 0.05$) and in group 2 (from 15 ± 6 to 13 ± 6, $p < 0.05$). The absolute reduction in the dysfunction score was greater in group 1 (-5.2 ± 3 vs -2.7 ± 1.5, $p < 0.01$), leading to a significance in the early recovery of the dyssynergic score (35 ± 34 vs 18 ± 22%, $p < 0.05$) (Fig. 3).

Three patients in each group did not undergo dobutamine stress echocardiography: 2 died in hospital, 2 had a left ventricular thrombus and 2 developed sustained ventricular arrhythmias in the post-acute phase. The percentage of patients exhibiting a significant improvement in systolic function after dobutamine was similar in the two groups (77% group 1, 75% group 2, p = NS) but the extent of the improvement measured as a change in the function score was significantly greater in the diltiazem group (51 ± 33 vs 36 ± 30%, $p < 0.05$).

Table IV. Angiographic data and cardiovascular events at 6 months of follow-up.

	Group 1 (n = 43)	Group 2 (n = 47)
Single-vessel disease	31 (72%)	33 (70%)
Patency of the infarct-related vessel	33 (77%)	32 (68%)
TIMI 3	30 (70%)	31 (66%)
Residual stenosis (%)	89 ± 15	88 ± 16
Angioplasty	32 (76%)	38 (81%)
Success rate	32 (100%)	37 (97%)
Cardiovascular events		
Death	3 (7%)	2 (4%)
Non-fatal reinfarction	2 (5%)	2 (4%)
Heart failure	7 (16%)	11 (23%)

Clinical outcome and follow-up. Two patients died of severe heart failure during admission (one of group 1, and one of group 2). One patient of group 1 died suddenly 3 months after discharge and 2 patients (one of each group) died of a reinfarction within 6 months. A non-fatal reinfarction occurred in 2 patients of each group at 6 months of follow-up. The prevalence of patients reporting symptoms of chronic heart failure (NYHA functional class II-III) was greater in group 2 although the difference did not reach statistical significance (16 vs 23%, p = NS). Finally, the benefit in terms of the left ventricular function observed on the pre-discharge echocardiogram was maintained at 6 months when both the score and the ejection fraction were found to have improved further, as shown in figure 2; this delayed recovery was similar in both groups (15 ± 29 vs 21 ± 32%, p = NS; Fig. 3).

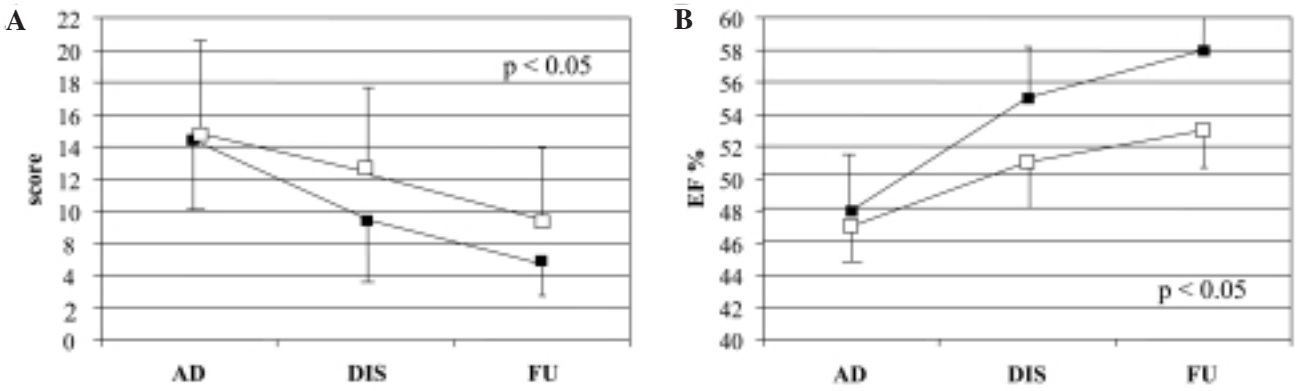

Figure 2. *Dysfunction score* (A) *and ejection fraction (EF)* (B) *in the diltiazem (■ group 1) and placebo (□ group 2) groups at admission (AD), before discharge (DIS) and at 6 months of follow-up (FU). Values are shown as mean ± standard error.*

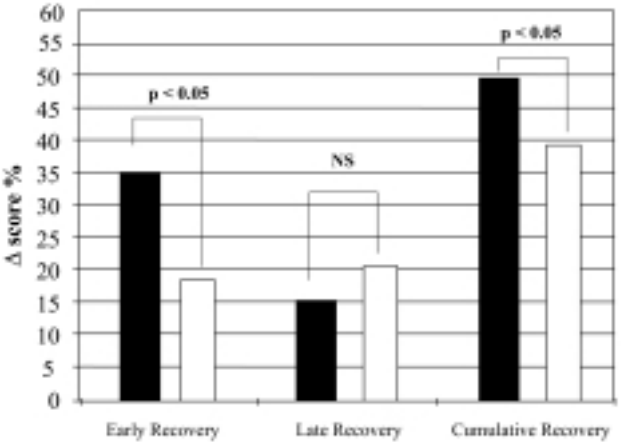

Figure 3. *Histograms of early and late recovery of regional wall motion abnormalities and myocardial viability in the diltiazem (■ group 1) and placebo (□ group 2) groups.*

Discussion

Background. Several randomized, placebo-controlled trials have shown that both thrombolysis and primary angioplasty performed early after acute myocardial infarction result in a decrease in the infarct size, improved ventricular function and reduced mortality[1-6]. Early recanalization of the infarct-related artery is a necessary condition for these effects to occur, though other phenomena such as the "no-reflow", prolonged stunning, reperfusion injury and vessel reocclusion may hinder the immediate and long-term benefits of reperfusion[17-19]. Thus, even after successful recanalization, adjunctive therapy would appear appropriate if the results of treatment are to be optimized and if the effects of acute thrombosis and reperfusion are to be minimized[20,21].

Effects of diltiazem on myocardial ischemic injury: experimental studies. Numerous investigations have been conducted to elucidate the effects of calcium channel blockers on regional myocardial ischemia and infarct size[7-9,22-26]. Among available agents, diltiazem causes a reduction in cytosolic and sarcoplasmic reticulum calcium levels. Free intracellular calcium is able to interact with many of the regulatory proteins that are implicated in the contraction/relaxation cycle and with several biochemical functions of myocardial cells. Increased calcium levels and pathological calcium-mediated activation of various proteins have been implicated as potential mediators of reperfusion injury which was reduced by diltiazem in several experimental studies. Furthermore, similar to other calcium channel blockers, this agent appears to exert a direct antioxidant effect[27,28], to preserve vasodilation even in the presence of endothelial dysfunction[29] and to reduce neutrophil accumulation[30] and myocardial stunning[31,32]. Indeed, previous studies have shown that diltiazem can significantly reduce the infarct size, particularly if administered before coronary occlusion[8,9], but also when given at reperfusion[30]. The latter effect is probably not only due to the properties listed above but also to the ability of diltiazem to resolve microvascular constriction[29], to exert antiplatelet[33,34] and antioxidant effects[27,28] and to prevent the release of thromboxane A_2 and endothelin-1 after reperfusion[34-37].

Role of diltiazem after myocardial infarction: clinical studies. Three well designed randomized trials conducted in patients with non-transmural myocardial infarction and unstable angina demonstrated that chronic oral diltiazem significantly improves the prognosis and event-free survival[11,38,39]. In the earlier studies conducted in patients with transmural myocardial infarction, the effect appeared much less clear and the drug was found to be even detrimental in patients with left ventricular failure[40,41]. However, most of those studies were performed in the pre-thrombolytic era, the drug was administered late (hours or days after symptom onset) and the trials were mainly targeted on secondary prevention rather than being aimed at demonstrating a cardioprotective effect. Nicolau et al.[11] conducted a study in which oral diltiazem was given concomitantly with intravenous streptokinase. In patients

with grade 3 TIMI flow, diltiazem appeared to somewhat improve functional recovery: however, since the agent was administered orally, the achievement of effective plasma levels is uncertain. More recently, Theroux et al.[12] assessed the effects of intravenous diltiazem in a group of 59 patients undergoing thrombolysis with tissue-type plasminogen activator. The drug was given immediately before administration of the thrombolytic agent: the infusion was continued for 48 hours and followed by oral administration for 4 weeks. The study was placebo-controlled and showed a significant decrease in cardiac events (death, myocardial infarction or recurrent ischemia) in the group of patients treated with the active drug. There was no difference in ventricular function between the two groups, though the patients with anterior myocardial infarction receiving diltiazem had a greater reduction of the infarct area, as assessed by myocardial perfusion scintigraphy. Given the small size of the study population, the observed reduction in cardiac events is somewhat surprising, although most of the difference was attributable to the reduced need for emergency revascularization because of recurrent ischemia. Therefore, the positive prognostic result observed in this trial probably relates to the rather conservative approach used by the investigators who elected to perform coronary arteriography and myocardial revascularization only in case of documented residual ischemia. Recently, the results of INTERCEPT, a prospective placebo-controlled study on chronic therapy with diltiazem, have confirmed the favorable effects after thrombolysis in the secondary prevention of nonfatal cardiovascular events[42].

Cardioprotective effect of diltiazem in reperfused myocardial infarction. The aim of our trial was to investigate the cardioprotective effect of diltiazem in the setting of reperfusion by means of tissue-type plasminogen activator after acute myocardial infarction. We selected patients presenting early after symptom onset in whom the probability of successful reperfusion was expected to be high: indeed the prevalence of clinical signs of early recanalization was in the region of 70-80% and the angiographic patency rate was also quite high. Furthermore, the size of the area at risk was sufficiently large to allow the detection of a significant cardioprotective effect, if present. In the first hours of the acute phase, before effective reperfusion by thrombolysis, diltiazem could have determined a significant anti-ischemic effect; the more frequent use of beta-blockers in group 2 might have equally protected from ischemia, as suggested by a comparable double product in the two groups during the acute phase. Besides, continuous 12-lead ECG monitoring allowed the detection of recurrent ischemia after thrombolysis and careful recording of the blood pressure and heart rate enabled evaluation of the hemodynamic effects of diltiazem. Finally, aggressive detection and treatment of residual stenosis of the infarct-related vessel helped to prevent recurrent ischemia and reinfarction, thus allowing the assessment of "pure" cardioprotective effects independent of other confounding factors.

In patients receiving diltiazem, we observed a significant reduction in enzyme release as well as a reduced prevalence of "reperfusion" arrhythmias. These effects were probably mediated by a reduction in the intracellular calcium overload. Furthermore, the global and regional contractile function was better preserved and the extent of residual viable tissue within the infarct area was significantly increased. The beneficial effect on contractile function was maintained even at long-term follow-up and translated into a lower incidence of symptomatic heart failure and into a better functional status. It could not be explained by a greater prevalence of reperfusion nor by a lesser incidence and severity of recurrent ischemia, suggesting that diltiazem exerted a primary cardioprotective effect and preserved myocardial cell integrity. This contention is further supported by the observation that throughout the in-hospital study period the heart rate and systolic blood pressure did not significantly differ between the two groups.

Limitations of the study. Firstly, the relatively small patient sample limits the results to a particular subset of patients presenting with myocardial infarction. However, the inclusion criteria were highly selective, all patients were enrolled consecutively and the two groups appeared well balanced for both demographics and clinical presentation. Secondly, the administration of concomitant treatment was left to the discretion of attending physicians, though, with regard to this aspect, no significant differences were observed. Future larger studies should compare diltiazem to other cardioprotective agents such as classical beta-blockers or, possibly, Na^+/K^+ exchange inhibitors[43].

Conclusions. Intravenous infusion of diltiazem initiated before coronary reperfusion by thrombolysis appeared to reduce the infarct size, to preserve residual viability and to improve contractile function. These effects seem to be unrelated to the anti-ischemic properties of the drug but should probably be attributed to a direct "cardioprotective" action. Larger trials are needed to confirm our results and to assess the effects of this intervention on the long-term outcome and prognosis.

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