Influence of Thrombolytic Therapy on the Incidence of Left Ventricular Thrombi after Acute Anterior Myocardial Infarction: Role of Successful Reperfusion

MEHMET ILERI, M.D., İZZET TANDOĞAN, M.D., FERİDUN KOŞAR, M.D., ERTAN YETKİN, M.D., YAHYA BÜYÜKAŞIK, M.D., EMİNE KÜTÜK, M.D.

Department of Cardiology, Türkiye Yüksek İhtisas Hospital, Ankara, Turkey

Summary

Background: Previous studies have reported controversial results regarding the effectiveness of systemic thrombolysis in preventing left ventricular (LV) thrombus after acute myocardial infarction (MI).

Hypothesis: This study was performed to evaluate the influences of thrombolysis, and particularly successful reperfusion, on the incidence of LV thrombus formation after acute anterior MI.

Methods: In all, 191 patients suffering from a first attack of acute anterior MI were prospectively evaluated by two-dimensional echocardiography and coronary angiography, performed at the end of the first week and within the first two weeks of MI, respectively. Of these, 98 who presented within 12 h of onset of symptoms received intravenous streptokinase (1.5 million IU), while the remaining 93 patients who, either because of contraindications or late admission, did not receive thrombolytic treatment served as control group. All patients received aspirin and full-dose anticoagulation with intravenous heparin. Successful reperfusion in the streptokinase group was assessed by enzymatic and electrocardiographic evidence.

Results: The overall incidence of LV thrombi was 24.6% (47/191). When all patients were evaluated, no statistically significant difference was found between the frequency of LV thrombi in the patients who had thrombolysis (22.4%) and those who did not (26.8%), despite a trend toward the formation of fewer thrombi in the initial group ($p > 0.05$). However, the patients who had successful reperfusion with streptokinase ($n = 64$) had significantly reduced incidence of LV thrombi compared with those who did not receive throm-

bolytic therapy (20 vs. 26.8%, $p < 0.05$). Stepwise multivariate analysis suggested that LV abnormal wall motion score ($p = 0.01$) and presence of LV aneurysm were independent predictors of LV thrombus formation in patients with acute anterior MI.

Conclusion: Not all patients who received streptokinase for acute anterior MI, but only those with successful reperfusion had reduced incidence of LV thrombi. The favorable effects of thrombolysis on LV thrombus formation are probably due to the preservation of global LV systolic function.

Key words: left ventricular thrombus, acute anterior myocardial infarction, thrombolytic therapy, reperfusion

Introduction

Left ventricular (LV) mural thrombus formation is a well recognized complication of acute anterior myocardial infarction (MI). Data concerning the influence of thrombolytic treatment on the occurrence of thrombi remain controversial. Accordingly, the aim of this study was to determine whether the use of the thrombolytic agent streptokinase reduces the incidence of LV thrombus early after acute anterior MI and to examine the clinical and echocardiographic predictors of this complication.

Materials and Methods

In all, 191 consecutive patients (130 men, 61 women, mean age $\pm$ standard deviation 65 ± 11 years) who were admitted to our clinic between June 1996 and September 1997 with a first episode of acute transmural anterior MI were included in this study. The diagnosis of acute anterior MI was based on the typical chest pain lasting > 30 min and that was unrelieved with intravenous nitroglycerin, accompanied by a new ST-segment elevation of > 2 mm in at least two contiguous anterior precordial leads of the electrocardiogram (ECG) and followed by two-fold elevation of serum creatine kinase with a myocardial band (MB) $> 5\%$. Criteria of exclusion were (1) history of previous MI, (2) evidence of valvular heart disease or cardiomyopathy, and (3) complete left bundle-branch block.

Address for reprints:

Dr. Mehmet Ileri
Samur Sok 30/10
Öncebeci Mahallesi 06600
Ankara, Turkey

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The patients who were admitted to the coronary care unit within 12 h of the onset of chest pain and who had no contraindication received 1.5 million IU streptokinase intravenously in 60 min. Immediately after thrombolytic treatment, an initial intravenous bolus of 5000 IU heparin was injected and followed by continuous infusion for 3 to 5 days, beginning at 1000 IU/h and maintaining activated partial thromboplastin time at 1.5 to 2 times of normal. Antiplatelet therapy with aspirin (150 mg) was started on admission in all patients. The remaining patients who did not receive streptokinase either because of contraindications or late arrival served as the control group. These patients received only heparin and aspirin in the same manner described above.

A 16-lead ECG (standard precordial leads and peripheral leads V₇, V₈, V_{3R}, and V_{4R}) was obtained from all patients immediately after admission and at least every 4 h for the first 24 h. Creatine kinase-MB (CK-MB) isoenzyme was measured every 4 h for the first 24 h, every 8 h for the next 24 h, and once a day until Day 7. Time-to-peak release of CK-MB isoenzyme was calculated by plotting the CK-MB (IU/l) against time in hours. The ECG resolution of maximal ST-segment elevation by at least 50% within 2 h from the start of streptokinase administration and the occurrence of peak plasma CK-MB level within 12 h from the onset of symptoms were considered as noninvasive markers of reperfusion in patients receiving thrombolytic treatment. The clinical features analyzed included age, gender, risk factors for coronary artery disease (hypertension, cigarette smoking, serum cholesterol > 250 mg/dl, diabetes mellitus, and family history) and history of angina pectoris before MI.

Two-dimensional echocardiography was performed in all patients at the end of the first week of admission. The diagnosis of LV thrombi was based on the detection of an echo-dense mass with definite margins, adjacent to asynergic myocardium and distinguishable from cardiac structures (e.g., muscle trabeculation) and false masses resulting from technical artifacts. Left ventricular aneurysm was defined as a demarcated bulge of the contour of the left ventricular wall during both diastole and systole, which showed akinesia and dyskinesia. The regional wall motion of the left ventricle was assessed by dividing it into 16 segments and graded visually by using the following score system: 0 = normal, 1 = hypokinesia, 2 = akinesia, 3 = dyskinesia. The sum of these graded scores was expressed as abnormal wall motion (AWM) score for each patient. Left ventriculography and selective coronary angiography were performed by the Judkins technique in all patients within 10 days of the MI. The location of the left anterior descending artery disease was classified as proximal if it was located in front of the first major septal perforator and distal if it was located behind the major septal perforator or at a large diagonal branch. The left anterior descending artery was defined as occluded if there was Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow and patent if there was TIMI grade 2 or 3 flow. Total occlusion of the artery was accepted when there was TIMI grade 0 flow. All patients gave informed consent, and the study protocol was in agreement with the guidelines of the Ethics Committee of our institution.

TABLE I Clinical characteristics of the patients with acute anterior myocardial infarction according to treatment modality

Clinical variables	With streptokinase (n = 98) (%)	Without streptokinase (n = 93) (%)	p Value
Age (years)	65 ± 0.9	64 ± 13	NS
Male	67 (68.3)	63 (67.7)	NS
Risk factors			
Family history	17 (17.3)	19 (20.4)	NS
Hypertension	40 (40.8)	49 (52.6)	NS
Diabetes mellitus	24 (24.5)	21 (22.5)	NS
Smoking	48 (48.9)	38 (40.8)	NS
Hypercholesterolemia	56 (57.1)	50 (53.7)	NS
Previous angina	52 (53)	50 (53.7)	NS
Time from onset of chest pain to arrival at hospital (h)	6 ± 3	13 ± 37	p < 0.005

Abbreviation: NS = not significant.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Univariate analysis was performed with the chi-square test for categorical data and with the unpaired *t*-test for continuous variables. Multivariate analysis of significant univariate factors was performed by stepwise linear regression. A *p* value < 0.05 was considered significant.

Results

Frequency of Left Ventricular Thrombi; Relation to Thrombolytic Treatment and Reperfusion

Of 191 patients, 98 received streptokinase plus heparin and aspirin, and 93 received only heparin plus aspirin. There was no difference between the treatment groups with respect to age, gender, coronary risk factors, and history of previous angina. The time from onset of chest pain to arrival at hospital was 6 ± 3 h for the patients who received thrombolytic treatment and 13 ± 37 h for those who did not (Table I). Reperfusion was achieved in 64 (65.3%) and not achieved in 34 (34.7%) patients who received streptokinase.

When all study patients were evaluated, the overall incidence of LV thrombi was 24.6% (47/191). No statistically significant difference was found regarding frequency of LV thrombi between the groups who received streptokinase (22/98, 22.4%) and those who did not (25/93, 26.8%) despite a trend toward fewer thrombi observed in the streptokinase group (*p* > 0.05). However, when the patients who received streptokinase were divided into two subgroups according to achievement of reperfusion, it was found that those with reperfusion had significantly lower frequency of LV thrombi (13/64, 20.3%) than either the patients without reperfusion (9/34,

TABLE II Percent prevalences of left ventricular thrombus for occluded and patent infarct-related coronary arteries in patients with and without streptokinase treatment

Patients (n = 191)	LV thrombus (n = 47) (24.6%)	p Value
With streptokinase (n = 98)		
Occluded (n = 39)	11 (28%)	0.03
Patent (n = 59)	11 (19%)	
Without streptokinase (n = 93)		
Occluded (n = 69)	20 (29%)	0.035
Patent (n = 24)	5 (21%)	

Abbreviations: Occluded = TIMI 0–1 flow, Patent = TIMI 2–3 flow, LV = left ventricular.

26.4%) or those who did not receive streptokinase (25/93, 26.8%) ($p = 0.035$ and $p = 0.01$, respectively).

Coronary Angiographic Findings in Relation to Left Ventricular Thrombus Formation

As shown in Table II, patients with TIMI 2–3 flow who received thrombolytic therapy had a significantly lower frequency of LV thrombus than those with an occluded vessel (19 vs. 28%, $p = 0.03$). Similarly, patients without streptokinase who had a patent infarct-related coronary artery (i.e., spontaneous thrombolysis) had fewer LV thrombi than those who had an occluded artery (21 vs. 29%, $p = 0.035$). It is interesting that the incidence of LV thrombus was similar in patients with patent infarct-related arteries whether or not they received streptokinase (19 vs. 21%, $p > 0.05$).

Comparison between the Patients with and without Left Ventricular Thrombus

There were no significant differences regarding age, gender, coronary risk factors, peak CK-MB levels, and LV end-diastolic pressures in ventriculography between the patients with and without LV thrombus (Table III). However, the patients with LV thrombus had a larger infarct size evidenced by higher AWM score than those without LV thrombus (9.2 ± 2.8 vs. 4.7 ± 2.1 , $p = 0.0008$). Patients with LV thrombus showed a higher frequency of LV aneurysm than those without LV thrombus (80.8 vs. 13.2%, $p = 0.00027$). A proximal lesion of the left anterior descending artery was observed more often in patients with than in those without LV thrombus (42.5 vs. 17.3%, $p = 0.001$). Twenty-three patients (48.9%) with LV thrombus and 46 patients (31.9%) without LV thrombus had total occlusion of the left anterior descending artery ($p = 0.035$). Stepwise multivariate analysis of the patients' AWM score, LV aneurysm, and angiographic parameters (characteristics of left anterior descending artery lesion) revealed AWM score and frequency of LV aneurysm to be independent predictors of LV thrombus formation in patients with acute anterior MI ($p = 0.01$ and $p = 0.002$, respectively).

TABLE III Characteristics of patients with and without left ventricular thrombus complicating acute anterior myocardial infarction

Clinical variables	Thrombus present (n = 47)(%)	Thrombus absent (n = 144)(%)	p Value
Age (years)	66 ± 11	64 ± 12	NS
Male	32 (68)	98 (68)	NS
Risk factors			
Family history	10 (21.2)	23 (16)	NS
Hypertension	17 (36.1)	72 (50)	NS
Diabetes mellitus	14 (29.9)	31 (21.5)	NS
Smoking	26 (55.3)	60 (41.6)	NS
Hypercholesterolemia	28 (59.5)	78 (54.1)	NS
AWM score	9.2 ± 2.8	4.7 ± 2.1	$p = 0.0008$
LV aneurysm	38 (80.8)	19 (13.2)	$p = 0.00027$
Peak CK-MB (IU/l)	2492 ± 2122	2212 ± 1938	NS
Thrombolytic treatment	26 (55.3)	72 (50)	NS
LAD			
Proximal occlusion	20 (42.5)	25 (17.3)	$p = 0.001$
Total occlusion	23 (48.9)	46 (31.9)	$p = 0.035$
EDP (mmHg)	15 ± 6	13 ± 7	NS

Values given as mean $\pm$ SD.

Abbreviations: AWM score = abnormal wall motion score, LV = left ventricular, CK = creatine kinase, LAD = left anterior descending artery, NS = not significant, EDP = end-diastolic pressure.

Discussion

This study resulted in three main findings: (1) the use of systemic thrombolytic therapy itself was not associated with a significant reduction in the formation of LV mural thrombi after acute anterior MI; (2) in a particular subgroup of the patients who received thrombolytic treatment, that is, those with successful reperfusion of the infarct-related artery, had significantly reduced incidence of LV thrombi; (3) the degree of LV wall motion abnormality and presence of LV aneurysm were found to be strongly associated with thrombus formation.

Left ventricular thrombus formation is a frequent complication after acute anterior MI. Consistent with previous studies^{1–3} reporting an incidence of between 28 and 54%, our results have also shown a high incidence (24.6%) of LV thrombus formation. Previous studies have reported controversial results about the effectiveness of systemic thrombolysis in preventing LV thrombus after acute MI. Some investigators reported a significant reduction in LV thrombus formation after thrombolysis,^{4–7} while others did not.^{8–10, 12} The conflicting results in these studies may be in part due to the type and timing of the adjunctive antithrombotic therapy as well as to the heterogeneity of the patient population. In most series, the thrombolytic agent was followed by high-dose heparin in contrast to the control group who received either no antithrombotic therapy or only low-dose heparin.^{4–6, 8} In our study, all patients regardless of whether they were treated with streptokinase or not immediately received full-dose anticoagulation with high-dose intravenous heparin and aspirin.

Few other studies have evaluated prospectively the effect of reperfusion and/or infarct-related artery patency after thrombolytics on the formation of LV thrombi in acute anterior MI.⁷⁻¹³ Some studies showed no significant reduction in the frequency of LV thrombi after reperfusion,⁸⁻¹² while others reported a significant inverse relationship between thrombi formation and successful coronary reperfusion.^{7,13} In our study, when all patients who received thrombolytic treatment were evaluated as a whole, the incidence of LV thrombus did not appear to change significantly with respect to treatment modality. However, the patients who had successful thrombolysis, that is, evidence of reperfusion, had significantly decreased frequency of LV thrombi compared with those who received only heparin and aspirin. Thrombolytics have been suggested to inhibit the formation of LV thrombi either by direct lysis of primordial thrombi or by reduction of infarct size.^{8,14,16} Our findings support the second mechanism. Early reperfusion may save global cardiac function by salvaging the jeopardized myocardium and thus limiting LV blood stasis. In stepwise multivariate analysis, AWM score and presence of LV aneurysm were found to be the independent predictors of LV thrombus formation, but the use of streptokinase did not appear to be an independent predictor. Similarly, coronary angiographic findings in the late term showed that patients who had patent infarct-related arteries, whether treated with thrombolytics or not, had lower frequencies of LV thrombus formation than those who had occluded coronary vessels. Consequently, the formation of LV thrombus is probably determined more often by LV systolic function than by the use of thrombolytics. This is consistent with the finding that only those patients with successful reperfusion had reduced frequency of this complication, probably due to the limitation of the infarct size. Left ventricular aneurysm formation was another strong predictor of thrombus formation, because it leads to blood stasis in the left ventricular cavity.

The main limitation of our study was the lack of a randomized design. The patients who arrived at the coronary care unit within 12 h of the onset of chest pain received thrombolytic treatment, whereas others did not. Since previous studies have shown that early intervention with high-dose heparin prevents the formation of LV thrombus in acute MI,¹⁴ earlier intravenous heparin and aspirin therapy in the streptokinase group may contribute to the tendency of reduced thrombi formation in these patients. However, randomization of patients with acute MI with regard to streptokinase treatment is obviously unethical.^{15,17} Therefore, patients admitted later to the coronary care unit, in whom administration of streptokinase was not indicated, constituted the control group.

Conclusions

Present data indicate that the patients who received intravenous streptokinase for acute anterior MI and achieved successful reperfusion had a reduced incidence of LV thrombus

formation. Possibly, limitation of the infarct size is the mechanism by which streptokinase prevents this complication.

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