FIBRINOLYTIC ACTIVITY IN ACUTE MYOCARDIAL INFARCTION

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SUMMARY

Purpose: *Hemostatic variables are recognized to have critical importance in the pathogenesis of ischemic heart disease (IHD). A possible defect in the fibrinolytic mechanism may constitute an independent risk factor for the development of acute myocardial infarction (AMI). The aim of this study was to investigate the overall hemostatic parameters and fibrinolytic activity, in particular, and the possible relationship between the hemostatic parameters and fibrinolysis in patients with AMI.* ***Methods:*** *We measured the fibrinolytic activity, fibrinogen, and some other hemostatic parameters in the acute stage and at day 10 of AMI in 33 patients and in 12 age and sex matched healthy controls. Dilute blood clot lysis time was used to determine overall fibrinolytic activity.* ***Results:*** *Seventy-three % of the patients in the first 24-48 hours and 69 % of the patients at day 10 were shown to have decreased fibrinolytic activity. None of the individuals in the control group had decreased fibrinolytic activity. Plasma fibrinogen levels were significantly higher in patients with acute myocardial infarction than in the control group. No increase in fibrin degradation products were determined in the patients with AMI.* ***Conclusion:*** *Fibrinolytic activity was found to be decreased and fibrinogen to be increased in patients with AMI, and these results are concordant with the previous reports in the literature regarding the association of AMI and decreased fibrinolytic activity. The exact cause of decreased fibrinolytic activity remains to be elucidated.*

Key Words: *Fibrinolysis, Atherosclerosis, Myocardial Infarction.*

INTRODUCTION

Being an important cause of mortality and morbidity, ischemic heart disease (IHD) has attracted enormous attention of the scientists. Several mechanisms have been suggested to explain the pathogenesis of IHD. Platelets, lipids, the response of the endothelial cell to injury, certain growth factors such as platelet derived growth factor (PDGF), and the complex interaction or the combination of these are known to be involved in atherogenesis (1,2,3,4).

Since fibrinogen and fibrin formation have an essential role in the formation and propagation of the atherom plaque, the fibrinolytic activity also has an essential importance in atherogenesis, particularly in the

acute thrombosis stage, which is the final stage in the development of acute myocardial infarction (AMI). However, the role of impaired fibrinolysis has been appraised to be related to a reduction of defensive capacity to thrombosis and atherosclerosis, while hypercoagulability and the role of platelets have been investigated comprehensively as a pathogenic mechanism in atherosclerosis (5).

The aim of this study was to search the overall hemostatic parameters and the fibrinolytic activity, in particular, in AMI. The probable variations in the hemostatic parameters and their relationship with the fibrinolytic activity were also investigated.

PATIENTS AND METHODS

Thirty-three patients (26 males and 7 females, with the age of 37 to 85) admitted to the coronary intensive care unit of Gazi University Hospital with the definitive diagnosis of AMI were included in the study. The diagnosis of AMI was suspected on the basis of clinical grounds and confirmed by the presence of appropriate new-onset ECG changes and elevated creatinine kinase MB isoenzymes. The patients who presented within 6 hours after the onset of chest pain, who did not have a malignant disease or thrombophlebitis diagnosed previously, with no history of recent operation, with normal liver chemistries and who did not receive heparin treatment were included in the study protocol. Twelve healthy volunteers (7 men and 5 women aged 34 to 65 years) were included in the study as the control group. None of them had a history of cardiac disease, liver disease, kidney disease, hypertension, diabetes mellitus, recent surgery or malignant disease. They were not taking any drugs known to affect the coagulation system, and they all had normal electrocardiograms.

Blood samples were drawn within the first 24-48 after AMI and on the 10th day of AMI in the patient group, in the morning after an overnight fast and without venous occlusion. Only the euglobulin or dilute blood clot lysis time (DBCLT) was repeated 10 days after the initial sampling in the control group. Fibrinolytic activity was determined on the day of sampling by DBCLT. DBCLT is a simple global test for fibrinolytic activity, performed after depletion of the inhibitors. The euglobulin fraction of plasma was precipitated with 1% acetic acid, and dissolved in borate solution. This euglobulin fraction of plasma was clotted with the addition of $CaCl_2$ and incubated in 37°C. Clots were observed regularly for lysis, which is expected to occur within 90 minutes to 6 hours in persons with normal fibrinolytic activity (6) .

In addition to DBCLT, serum glucose, cholesterol, ALT, AST, AP, total protein, albumin, globulin, LDH and total/direct bilurubin levels were determined with the appropriate methods in the biochemistry laboratory. Erythrocyte sedimentation rate (Westergreen method), complete blood count (Autoanalyser system Coulter-STKS), prothrombin time and partial thromboplastin time, fibrin degradation products, and fibrinogen were also tested.

Statistical analysis: The analysis of the data for determining the significance of the difference between the control and the two AMI groups was performed with analysis of variance. Student's t test was employed for comparing the data within the AMI group (initial and the 10^{th} day data) . The effect of the all other parameters to DBCLT was investigated by Spearman's rank correlation test. A non-parametric test, Mann Whitney-U test, was performed for analysing the effect of cigarette smoking.

RESULTS

The main characteristics of the 33 patients and 12 control subjects are listed in Table 1. Conventional risk factors and the other variables are shown in Table 2. Age distribution was similar for patients with AMI and control subjects, while male sex was more prominent in the AMI group. DBCLT was prolonged (longer than 240 min.) in 24 patients (73%), in the first 24-48 h. after AMI and in 22 patients (67%) at day 10 of AMI. All the people in the control group had DBCLT within the normal limits. DBCLT, both in the initial and the 10^{th} day analysis, were significantly prolonged in AMI patients when compared to the control group ($F=15.261$; $p=0.000$, $p<0.001$ and $F=13.228$; $p=0.000$, $p<0.001$, respectively). However, there was no statistically significant difference in the DBCLT between the first 24-48 h. and at day 10 of AMI ($p=0.925$ $p> 0.05$).

Both the systolic and diastolic blood

Table 1 : Demographic and epidemiological data

	Patients with AMI (n = 33)	Control subjects (n = 12)
Mean age (years)	57 ± 12	52 + 12
Sex ratio (M/F)	26 / 7	5 / 7
History of hypertension	11 (33.3 %)	
History of diabetes mellitus	7 (21.2 %)	
Previous AMI or unstable angina pectoris	17 (51.2 %)	
Medical therapy used		
Aspirin	33 (100 %)	
Beta blockers	17 (51 %)	
Ca antagonists	25 (75.7 %)	
Nitrates	33 (100 %)	

Table 2 : Conventional risk factors, coagulation and fibrinolytic parameters .

	Control n : 12	AMI (24-48 hours) n : 33	AMI (10th day) n : 33
Systolic blood pressure (mmHg)	125 ± 12	142 + 32	---
Diastolic blood pressure (mmHg)	75 ± 8	83 + 16	---
Cigarette (gr/day)	7.5 ± 3.3	17 + 16	---
Bleeding time (minute)	4.2 ± 0.5	3.97 + 0.6	3.64 + 0.6
Hematocrit (%)	44.6 ± 4.9	42.7 + 5.5	42.4 + 5.1
Prothrombin time (second)	11.4 ± 0.7	11.7 + 0.7	11.7 + 0.8
PTT (second)	35.6 ± 3.1	39 + 3.6	40 + 3.9
Platelet ($x10^9$/L)	232.67 ± 88	258 + 90	308 + 109
Total lipid (mg/dl)	729 ± 174	664 + 163	670 + 137
Cholesterol (mg/dl)	228 ± 55.8	201 + 37	203 + 34
Fibrinogen (mg/dl)	424 ± 65.8	445 + 95	512 + 134
DBCLT* (minute)	140.8 ± 19 (I) 141.6 ± 17 (II)		

* DBCLT: euglobulin-dilute blood clot lysis time, (I) the initial sampling, (II) the fibrinolytic activity 10 day apart in the control group.

Table 3 : Fibrinolytic activity in low and high risk patients.

DBCLT (minutes)	control n : 12	Low risk group (DBP < 90mm Hg) n : 22	High risk group (DBP ³ 90mm Hg) n : 11
Acute stage (initial 24-48 hours)	141 + 19	273 + 62	305 + 62
Day 10 of AMI	142 + 17	275 + 63	299 + 59

DBP: diastolic blood pressure

pressures were significantly higher in the AMI group. When the patient population was divided into two risk groups, the patients with diastolic blood pressure lower than 90 mmHg, being the low risk group, and the patients with diastolic blood pressure above 90 mmHg, being the high risk group, there was no difference between the two groups in respect to fibrinolytic activity. Fibrinolytic activity was decreased in both the low and high risk groups when compared to the control group (Table 3).

There was no difference between the control and AMI groups with respect to hematocrit, prothrombin time, and lipid-cholesterol levels. PTT was found to be significantly prolonged both in the first 24-48 h. and at the 10^{th} day of AMI (though within the normal range : 36-42 sec) when compared to the

control group (F=0.411 p= 0.004, p< 0.01 and F=1.025; p= 0.000 p<0.001, respectively). There was no significant difference between the initial and 10th day PTT values in the AMI group.

The initial bleeding time in the AMI group was not different from the control group, however the bleeding time on the 10th day of AMI was significantly shorter than the control group (F=0.006, p=0.009, p<0.01). The 10th day bleeding time in the AMI group was significantly shorter than the initial bleeding time (p=0.01, p<0.01).

The initial platelet count in the AMI group was not different from the control group, however the 10^{th} day platelet count was significantly higher (though within the normal limits) than the control group (F=0.729, p=0.026, p<0.05). The platelet count on the 10^{th} day of AMI was significantly higher than the initial values in the AMI subjects (p=0.000, p< 0.001).

Fibrin degradation product levels were below the threshold levels both in the patient and control groups. Plasma fibrinogen concentrations at the 24-48 h. of AMI was not significantly different from the healthy control subjects whereas the 10^{th} day fibrinogen levels in the AMI group were significantly higher than the control subjects (F= 7.5999; p= 0.009, p< 0.01). Plasma fibrinogen levels were found to be significantly higher on the 10th day of AMI than the initial fibrinogen levels (p=0.001, p<0.001).

Smoking habits were assessed as gram tobacco per day, based on the fact that a cigarette contains 1 g of tobacco and was found to be significantly more prevalent and higher in the AMI group (F=0.253, p=0.033, p<0.05).

DISCUSSION

Coronary artery thrombosis has a central role in the pathogenesis of AMI (7). While the role of hypercoagulability is well established in the pathogenesis of AMI (8), the role of impaired fibrinolysis was considered to be only a minor contributory factor as a reduction in the normal defensive mechanisms until recently (5).

The fibrinolytic activity was determined with the DBCLT in this study and was found to be significantly decreased in the group of patients with AMI, both in the first 24-48 hours and at day 10 of AMI. The fibrinolytic activity in the control group was within normal limits. This study is concordant with the literature regarding the association of decreased fibrinolytic activity and atherosclerosis. However, whether decreased fibrinolytic activity is the cause or consequence of atherosclerosis remains to be elucidated.

AMI, attacking the patients with decreased fibrinolytic activity, may be an explanation for decreased fibrinolytic activity. On the other hand, the decrease in the fibrinolytic activity may be the result of the acute phase response occurring in the course of AMI. And finally, certain risk factors such as diabetes, hypertension, or hypercholesterolemia may contribute to the decrease in the fibrinolytic activity.

Decreased fibrinolytic activity has been reported to be due to decreased synthesis and release of tissue plasminogen activator (TPA) in atherosclerotic endothelium (9). However, in the group of patients with normal coronary angiograms, in which coronary artery thrombus occurs in the absence of atherosclerosis, it is not reasonable to explain decreased fibrinolysis as a consequence of atherosclerosis (10). It is also interesting that fibrinolytic activity is found to be decreased, particularly in this group of patients.

A strong long-term relation between low fibrinolytic activity and the incidence of IHD in younger men has been shown in a study in which 1380 male patients between ages 40- 64 were followed prospectively. The risk of AMI was found to be increased significantly in the individuals with decreased fibrinolytic activity (11). This association remained to be significant after adjusting for plasma fibrinogen.

Increase in fibrinogen and plasminogen activator inhibitor-1 (PAI-1) levels may be the consequence of the acute phase response in AMI, which may cause decreased fibrinolytic activity. Since the fibrinolytic activity is determined with DBCLT in this study and the euglobulin fraction of the plasma is deprived of the inhibitors including PAI-1, it seems unlikely that the decreased fibrinolytic activity in our study is due to increased PAI-1 levels. Although PAI-1 levels were not studied in this research, fibrinogen was determined and was found to be increased in AMI patients. The increase in the fibrinogen levels were correlated with the decreased fibrinolytic activity.

Furthermore, in a previous study, AMI

patients with decreased fibrinolytic activity were followed for 3 months to 3 years and the decreased fibrinolytic activity was found to persist, which refutes the fact that acute phase response -which does not keep on this long- is the only cause of the decreased fibrinolytic activity (12).

Enhanced coagulation and /or decreased fibrinolytic activity plays a significant role in the pathogenesis of atherosclerosis. Increased Factor VIII, Factor VII, vWF and fibrinogen levels have been demonstrated in AMI patients previously (8).

Although the coagulation parameters were not determined in this study, the prothrombin time, which shows the thrombin formation and the reflects the coagulation process to some extent, was shown to be similar in the AMI patients and the control group.

On the other hand, PTT, which reflects the activities of FVII, FIX, FXII, was found to be significantly longer than the control group in AMI patients. Although this seems rather contradictory with the anticipated hypercoagulability, the absence of clinical bleeding diathesis in the patients reminds the possibility of decreased FXII levels, hence decreased intrinsic fibrinolysis as the cause of prolonged PTT. It is well known that decreased FXII level is associated with thrombosis instead of bleeding diathesis due to decreased fibrinolysis. Increased risk of reinfarction has been reported in AMI patients with decreased FXII levels (13). Suzuki and Tanaka showed the decreased levels and activity of FXII and high molecular weight kininogen levels in patients with AMI (14). Though enhanced fibrinolysis may be the cause of decreased FXII levels, the absence of FDP in our patients excludes this possibility.

The decreased fibrinolytic activity in the AMI patients in this study may be the consequence of the exhaustion of plasmin due to enhanced fibrinolysis; however, the absence of FDP makes this explanation unlikely as increased FDP would be expected in enhanced fibrinolysis.

Certain risk factors of atherosclerosis such as obesity, smoking, hypercholesterolemia, hypertension or diabetes may be the cause of decreased fibrinolytic activity. However, no such association has been documented in this study.

Platelet count is higher on the 10th day of AMI just as it is in other inflammatory disorders. As 90% of the total PAI-1 is located in platelets, and invitro studies show that platelet PAI contributes to the inhibition of tPA (5), an increase in platelet count may be expected to decrease fibrinolytic activity. However as DBCLT is performed with plasma deprived of inhibitors and furthermore the decreased fibrinolytic activity in this study was found to be independent from the platelet count.

On the other hand, the significantly shorter bleeding time in the patient group suggests the role of increased platelet reactivity , which has been showed in atherosclerosis by other means, in the pathogenesis of AMI.

In conclusion; fibrinolytic activity has been shown to be decreased in patients with AMI, once again supporting the association of AMI and decreased fibrinolytic activity. The exact mechanism(s) of decreased fibrinolytic activity remains to be elucidated. Decreased fibrinolytic activity may be the consequence of increased fibrinogen and other coagulation factors, decreased FXII or TPA, or increased PAI-1. Considering the successful results with fibrinolytic therapy early in the treatment of AMI, modifying this increased fibrinolytic activity may improve mortality and morbidity by preventing the development or recurrence of AMI.

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