Relation of homocysteine levels with patency and flow rate of infarct related artery in patients receiving fibrinolytic therapy

Fibrinolitik tedavi alan hastalarda homosistein düzeyleri ile enfarktüsle ilişkili arterin açıklığı ve akım hızının ilişkisi

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ABSTRACT

Objective: Elevated homocysteine levels induce a hypercoagulable state and make the clot more resistant to fibrinolysis. In this prospective observational study, we investigated the influence of homocysteine levels on infarct-related artery (IRA) patency and flow as determined with regard to thrombolysis in myocardial infraction (TIMI) flow grade and corrected TIMI frame count (CTFC).

Methods: Sixty-one patients who received fibrinolytic therapy for a first ST elevation myocardial infarction (STEMI) within 12 hours of chest pain were included. Coronary angiography was performed according to the Judkins technique within 72 hours after fibrinolytic therapy. Total plasma homocysteine level was determined by the high-performance liquid chromatography method with fluorescence detection. Statistical analysis was performed using Chi-square, Student's t and Pearson correlation tests. Logistic regression analysis was used to determine the predictors of IRA occlusion.

Results: Of the 61 patients, 22 (36.1%) had an occluded IRA (group 1), 39 (63.9%) had a patent IRA (group 2). Mean plasma homocysteine levels were found to be significantly higher in the group 1 compared to the group 2 (18.5±9.6 µmol/L vs 14.3±5 µmol/L, p=0.04). In addition, we found a significant positive correlation between CTFC and plasma homocysteine levels (r=0.415; p<0.01). In multiple logistic regression analysis, high levels of plasma homocysteine (OR=1.2; 95% CI 1.1-1.25; p=0.03) and being a non-smoker (OR=5.9; 95% CI 1.1-31.6; p=0.03) were found to be significant independent predictors of having an occluded IRA.

Conclusion: There is an inverse relation between plasma homocysteine levels and IRA patency and flow in patients receiving fibrinolytic therapy for STEMI. *(Anadolu Kardiyol Derg 2010; 10: 410-5)*

Key words: Homocysteine, fibrinolytic therapy, infarct-related artery, logistic regression analysis

ÖZET

Amaç: Yüksek homosistein düzeyleri mevcut pıhtıyı fibrinolize daha dirençli hale getirmektedir. Bu prospektif gözlemsel çalışmada, homosistein düzeylerinin, TIMI (thrombolysis in myocardial infarction) akım derecesi ve TIMI kare sayısına göre değerlendirilen enfarktüs ile ilişkili arter (EİA) açıklık ve akım hızı üzerine etkisini araştırdık.

Yöntemler: ST yükselmeli miyokart enfarktüsü nedeniyle, göğüs ağrısının ilk 12 saati içinde fibrinolitik tedavi alan 61 hasta çalışmaya alındı. Fibrinolitik tedavi sonrası 72 saat içinde Judkins tekniği ile koroner anjiyografi yapıldı. Total plazma homosistein düzeyi flörosan saptama ile yüksek performanslı likit kromatografi metodu ile belirlendi. İstatistiksel analiz Ki-kare, Student t test, Pearson korelasyon testi kullanılarak yapıldı. EİA oklüzyonu öngördürücülerinin belirlemesinde lojistik regresyon analizi kullanıldı.

Bulgular: Çalışmaya alınan 61 hastanın 22'sinde (%36.1) EİA tıkalı (grup 1), 39'unda (%63.9) EİA açık (grup 2) saptandı. Ortalama plazma homosistein düzeyleri grup 1 de grup 2 ile kıyaslandığında daha yüksekti (18.5±9.6 µmol/L'ye karşın 14.3±5 µmol/L, p=0.04). Ayrıca düzeltilmiş TIMI kare sayısıyla plazma homosistein düzeyleri arasında anlamlı bir pozitif korelasyon vardı (r=0.415; p<0.01). Lojistik regresyon analizinde ise yüksek plazma homosistein düzeyleri (OO=1.2; %95GA 1.1-1.25; p=0.03) ve sigara içme alışkanlığının olmaması (OO=5.9; %95GA 1.1-31.6; p=0.03) tıkalı EİA için bağımsız risk faktörleri olarak bulundu.

Sonuç: ST yükselmeli miyokart enfarktüsü nedeniyle fibrinolitik tedavi alan hastalarda plazma homosistein düzeyleri ile EİA açıklık ve akım hızları arasında ters ilişki vardır. *(Anadolu Kardiyol Derg 2010; 10: 410-5)*

Anahtar kelimeler: Homosistein, fibrinolitik tedavi, enfarktüs ile ilişkili arter, lojistik regresyon analizi

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Introduction

Homocysteine is an intermediary amino acid produced by conversion of methionine to cysteine. Several clinical studies have associated elevated plasma homocysteine levels to increased risk of cardiovascular diseases such as coronary artery disease (CAD), peripheral artery disease and venous thrombosis (1, 2). In patients with acute coronary syndrome, elevated plasma homocysteine levels were associated with hypercoagulability and increased platelet aggregation (3, 4). Recent studies have investigated the association of increased homocysteine levels with markers of thrombosis and fibrinolysis in individuals without evidence of CAD and have shown that an increase in homocysteine levels was associated with elevated plasma levels of D-Dimer as well as tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) antigen (5-7). Homocysteine inhibits thrombolysis by decreasing the effectiveness of t-PA. To the best of our knowledge, the relationship between plasma homocysteine level and infarct-related artery (IRA) flow in patients receiving fibrinolytic therapy was not investigated before.

In this study, we investigated the influence of homocysteine levels on IRA patency and flow as determined with regard to thrombolysis in myocardial infarction (TIMI) flow grade and corrected TIMI frame count (CTFC) in patients with acute myocardial infarction (MI) receiving fibrinolytic therapy.

Methods

Patients

In this prospective observational study, 61 patients who received fibrinolytic therapy for first ST elevation myocardial infarction (STEMI) within 12 hours of chest pain were included. Of 61 patients, 32 (52.5%) had anterior, 25 (41%) - inferior and 4 (6.6%) had inferoposterior MI localization. To avoid other variables that could influence the plasma concentrations of total homocysteine, we excluded patients using folic acid, vitamin B complex supplements, fibrates or nicotinic acid, patients with a history of folic acid or vitamin B complex deficiency, and patients with cancer or renal failure (creatinine ≥1.5 mg/dl). The following criteria were used for the diagnosis of STEMI: chest pain for more than 20 min and ST segment elevation more than 1 mm in at least two standard limb leads or 2 mm in at least two contiguous precordial leads. Streptokinase (1.5 MU intravenously over 60 min) was given unless the patient was hypotensive on presentation (systolic blood pressure < 90 mmHg) or streptokinase intolerance or allergy was likely. Intravenous front-loaded t-PA was given in these circumstances. STEMI diagnosis was later confirmed by elevation of cardiac enzymes either with creatine kinase-MB and troponin-I. All patients were given anti-ischemic therapy including aspirin, beta- blocker, statin and heparin.

The study was approved by the Ethics Committee of our institution. Written informed consent was obtained from patients and controls.

Laboratory analyses

Blood samples were collected from antecubital vein before fibrinolysis. Following coagulation for one hour at room temperature, the samples were centrifuged for 10 min at 3000 rpm. The plasma was collected and kept at -70°C until further analysis. Total plasma homocysteine level was determined by the high-performance liquid chromatography method with fluorescence detection (Chromsystems 45 000 reagent kit; Agilent 1200, Germany). Lipid profiles, glucose and creatinine concentrations were determined by routine laboratory methods.

Coronary angiography

Coronary angiography was performed according to the Judkins technique within 72 hours after fibrinolytic therapy and images of coronary tree were obtained in standardized routine projections. Two experienced cardiologists who had no knowledge of patients' clinical characteristics and plasma homocysteine levels reviewed all angiographic images. Decisions were made by consensus. The IRA was identified by electrocardiography at admission to hospital, ventriculographic contraction abnormalities, and angiographic findings. IRA patency and flow were graded according to the TIMI classification (8). A patent vessel was defined by a TIMI flow grade ≥2. A CTFC was measured only in patent arteries according to the methods first described by Gibson et al. (9). Briefly, the number of cineangiographic frames, recorded at 30 frames per second, required for the leading edge of the column of radiographic contrast to reach a predetermined landmark, is determined. Left anterior descending coronary artery (LAD) is usually longer than other major coronary arteries, and the TIMI frame count for this vessel is often higher. To obtain CTFC for LAD, TIMI frame count was divided by 1.7. The first frame is defined as the frame in which fully concentrated dye occupies the full width of the proximal artery lumen, touching both borders of the lumen, and has forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal landmark. In the LAD, the landmark used is the most distal branch nearest to the apex of the ventricle, commonly referred to as the "pitchfork" or "whale's tail". The right coronary artery (RCA) distal landmark is the first branch of the posterolateral RCA after the origin of the posterior descending artery, regardless of the size of this branch. If a significant stenosis is present within the posterior descending artery, the landmark is the first branch of the posterior descending artery itself beyond the stenosis. The original TIMI grading system and CTFC method were developed for the assessment of IRA after reperfusion, thus the distal landmark in the circumflex system was defined as the most distal branch of the artery containing infarct related stenosis. Depending upon infarct related stenosis, the distal landmark could be in the first marginal, a more distal marginal or the distal portion of circumflex artery. In general, CTFCs in the LAD and circumflex arteries were assessed in a right anterior oblique projection with caudal angulation and the RCA in a left anterior oblique projection with cranial angulation.

Statistical analysis

All statistical analyses were performed with SPSS version 13 (SPSS INC., Chicago, Illinois, USA). Continuous variables were expressed as mean±SD, and categorical variables were expressed as a percentage. The Kolmogorov-Smirnov test was used to compare empirical distribution of continuous variables. Comparison of continuous variables between groups was performed using Student's t-test. The Chi-square test was used for the analysis of categorical variables. The correlation between plasma homocysteine levels and CTFC was assessed by the Pearson correlation test. Multiple logistic regression analysis, with the IRA as the dependent variable, and plasma homosistein level, non-smoker, diabetes mellitus, age and hypertension as independent variables, was performed to evaluate the independent predictors of IRA occlusion. P values less than 0.05 were considered as statistically significant.

Results

Of the 61 patients (mean age 56.6±9.7 years, 78.7% male, 21.3% diabetics, 65.6% smokers, 41% hypertensives) constituting our study population, 22 (36.1%) had an occluded IRA (group 1), and 39 (63.9%) had a patent IRA (group 2). There were no significant differences between the two groups with regard to age, sex, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides and presence of hypertension, diabetes mellitus, and family history of CAD (Table 1).

The percentage of smokers was higher in patients with a patent vessel (group 2) than in patients with an occluded vessel (group 1) (p=0.01). The infarct related artery patency was 75% in smokers, and 42.9% in non-smokers (p=0.02). There was a non-significant difference between the groups in left ventricular ejection fraction (EF) (p=0.22). In group 1, mean time between chest pain and onset of reperfusion therapy was greater than in group 2 (p=0.04) (Table 1). Peak creatine phosphokinase -MB value was somewhat higher in group 1 compared with group 2 (248±127 U/l vs 196±130 U/l; p=0.20). Mean homocysteine levels in group 1 were significantly higher when compared to group 2 (18.5±9.6 µmol/L v 14.3±5 µmol/L; p=0.04) (Fig. 1).

Association of homocysteine with clinical variables, IRA patency and flow

There was no correlation between homocysteine levels and EF (r=-0.147; p=0.28). A significant correlation between homocysteine level and peak creatine phosphokinase-MB (r=0.37; p<0.05) was seen.

When homocysteine levels were assessed with respect to TIMI flow grade, mean homocysteine levels of patients with grade 0 or 1 TIMI flow were 18.5±9.6 µmol/L, while they were 16.5±4.1 µmol/L in patients with grade 2 TIMI flow and 11.6±1.8 µmol/L in those with grade 3 TIMI flow. The difference between homocysteine levels of the group with TIMI 0 or 1 flow and the group with TIMI 3 flow was statistically significant (p=0.01). Than in group 2.

Table 1. Baseline characteristics of the groups

Variables	Group 1 (occluded IRA) (n=22)	Group 2 (patent IRA) (n=39)	*p
Age, years	57±11	56±9	0.78
Male, n (%)	17 (77.3)	31 (79.5)	0.84
Hypertension, n (%)	10 (45.5)	15 (38.5)	0.59
Diabetes mellitus, n (%)	7 (31.8)	6 (15.4)	0.13
Smoking, n (%)	10 (45.5)	30 (76.9)	0.01
Family history for CAD, n (%)	8 (36.8)	9 (23.1)	0.27
Total cholesterol, mg/dl	188.1±44.2	196.3±36.7	0.43
Triglyceride, mg/dl	178.5±98.3	169.5±116.8	0.76
LDL-cholesterol, mg/dl	112.4±35.9	123.3±35.2	0.25
HDL-cholesterol, mg/dl	36.1±7.4	38.7±6.5	0.17
Time to reperfusion, h	4.6±2.8	3.1±2.2	0.04
LVEF, %	38.0±8.6	41.0±9.2	0.22

Data are presented as mean±SD and numbers (percentages)
*Chi - square and unpaired Student's t tests
CAD - coronary artery disease, HDL - high-density lipoprotein, IRA - infarct-related artery, LVEF - left ventricular ejection fraction, LDL - low-density lipoprotein

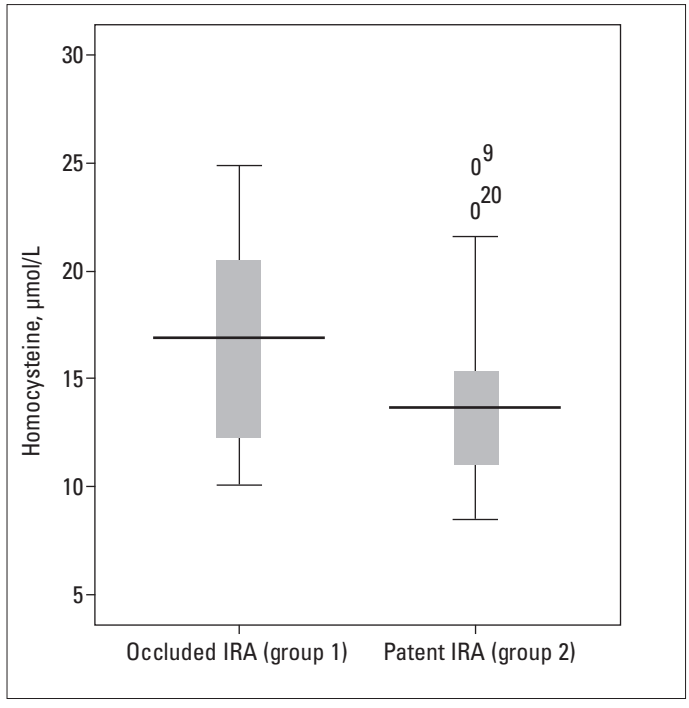

Figure 1. Comparison of plasma homocysteine levels between groups
*Student's t test, p=0.04
IRA - infarct-related artery

Mean CTFC was 30.9±11.8 in all patients with patent IRA. There was a significant positive correlation between homocysteine levels and CTFC (r=0.415; p<0.01) (Fig. 2). In other words, as homocysteine levels increased CTFC increased, namely the flow in patent IRA slowed down. However, no significant correlation was detected between other parameters and CTFC. When the patients were allocated to homocysteine levels <15 µmol/L and

homocysteine levels >15 µmol/L, mean CTFC values in those with homocysteine levels < 15 µmol/L were significantly lower than those with homocysteine levels ≥15 µmol/L (30.9±11.8 v 43.6±16.7; p<0.01) (Fig. 3). There was no difference in CTFC values in patent IRA between smokers and non-smokers (36.1±10.8 v 35.5±16.1, respectively; p>0.05).

Predictors of IRA occlusion

In multiple logistic regression analysis, being a non-smoker (OR=5.9; 95%CI 1.1-31.6; p=0.03) and high homocysteine levels (OR=1.2; 95%CI 1.1-1.25; p=0.03) were detected as independent predictors of occluded IRA. Diabetes mellitus, age, and hypertension were not predictors of occluded IRA (Table 2).

Discussion

In this study, we demonstrated a significant relationship between plasma homocysteine levels and IRA patency and flow after fibrinolysis in acute STEMI.

Several epidemiologic studies have shown that elevated homocysteine is a risk factor for coronary artery disease (CAD) (1, 2). In in vitro models, elevated homocysteine levels induced a hypercoagulable state by reducing thrombomodulin level, protein C activity and heparin sulfate level, as well as inhibiting the binding of tissue plasminogen activators to endothelial cells (10-13). Hyperhomocysteinemia was associated with activation of coagulation systems in patients with premature atherosclerotic arterial disease and with thrombin generation in patients with acute coronary syndrome (3, 4). In hyperhomocysteinemic rabbits, fibrin clots are composed of thinner and more tightly packed fibers compared with normal animals (14). Furthermore, the clots formed from purified fibrinogen from homocysteinemic rabbits were lysed more slowly by plasmin than the clots from control fibrinogen. Whole blood thromboelastographic profiles obtained from rats fed with a folate-depleted diet showed that hyperhomocysteinemia is associated with increased maximum clot firmness (15). Clots formed from human plasma incubated in vitro with homocysteine have also been reported to have a more compact structure, with shorter and more frequently branched fibers, than those formed in absence of homocysteine (16). These changes would make the clot more resistant to fibrinolysis. In a study, plasma homocysteine levels significantly correlated with plasma fibrin clot permeation and clot susceptibility to fibrinolysis both in apparently healthy subjects and in patients with advanced CAD (17). These associations were observed regardless of whether the subjects studied took low-dose aspirin or not. In patients with CAD, one month after a first STEMI, homocysteine plasma levels inversely correlated with t-PA activity and patients with mild hyperhomocysteinemia showed a markedly decreased t-PA activity (18). Consistent with all these data in literature, in our study, mean homocysteine levels in the patient group with occluded IRA were higher than the group with patent IRA. Furthermore, there was a significant positive correlation between CTFC and homocysteine levels in the group with patent IRA. So, a slower IRA flow was seen in those with high homocysteine levels. A slower IRA flow in these patients may be due to increased thrombus burden in IRA or impaired microcirculatory perfusion. It was demonstrated that plasma homocysteine concentration was associated with the burden of intracoronary thrombus, resulting in increased coronary obstruction and decreased distal flow (19). The direct toxic effect of homocysteine on endothelium increases thrombus burden and the atherogenic effect of homocysteine may lead to impaired microcirculatory perfusion. We do not know why the plasma homocysteine level increases in these patients, there may be a need to genetically research.

Another remarkable finding in our study is that IRA patency is seen at a higher rate in smokers. Actually, this finding is consistent with the data in literature (20-22). Smoking is associated with a hypercoagulable state, particularly higher fibrinogen, compared to non-smokers (23). This may predispose smokers to thrombotic vessel occlusion at an earlier stage of atheromatous disease than non-smokers, leading to coronary occlusions

Table 2. Results of logistic regression analysis in predicting occluded IRA in patients receiving fibrinolytic therapy

Variables	Odds ratio (95% CI)	p
Age, years	1.06 (0.89-1.13)	0.27
Diabetes mellitus, n (%)	1.52 (0.076-1.79)	0.21
Hypertension, n (%)	1.28 (0.32-5.1)	0.71
Non-smoker, n (%)	5.9 (1.1-31.6)	0.03
Homocysteine, µmol/L	1.2 (1.1-1.25)	0.03

IRA - infract-related artery

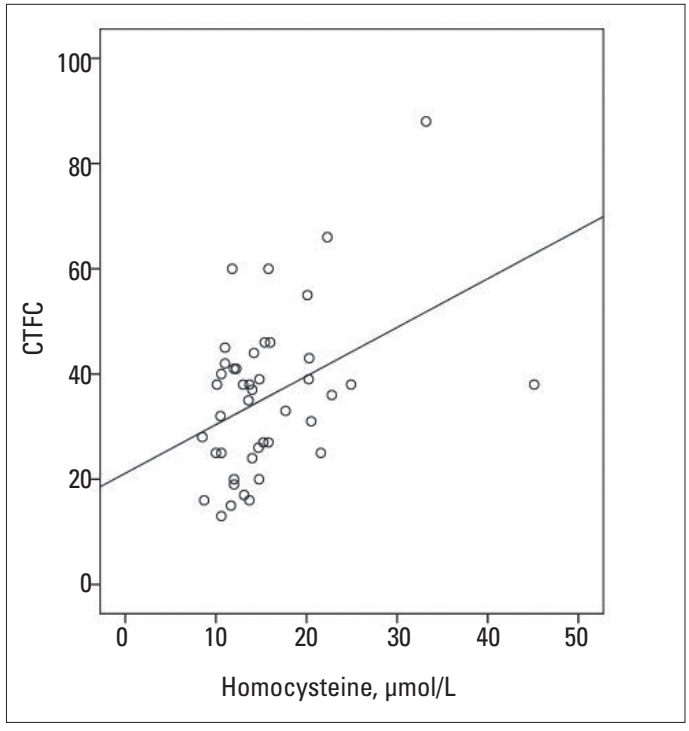

Figure 2. Correlation of plasma homocysteine and corrected TIMI frame count

*Pearson correlation test

CTFC - corrected TIMI frame count

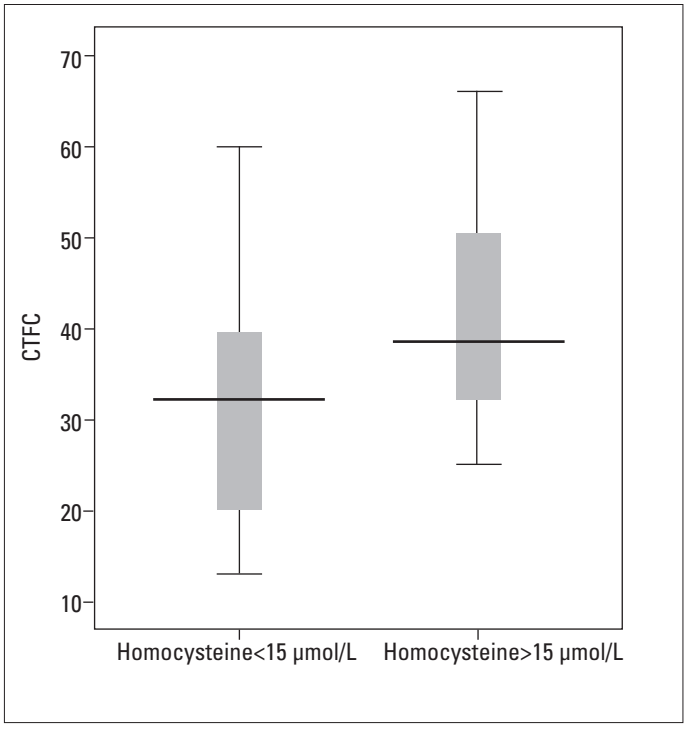

Figure 3. Comparison of corrected TIMI frame count between patients with homocysteine levels < 15 µmol/L, and patients with homocysteine levels >15 µmol/L

*Student's t test, p<0.01
CTFC - corrected TIMI frame count

which are more susceptible to thrombolysis. Alternatively, smokers may have a more complete fibrinolytic response to thrombolysis, leading to improve vessel recanalization for the same degree of stenosis compared to non-smokers. Although IRA patency was more frequent in smokers in our study, CTFC, namely flow in IRA was similar in smokers and non-smokers.

Study limitations

The most important limitation of our study is a small number of patients. Moreover, coronary angiography after fibrinolytic therapy was performed within the first 72 hours (mean 34 hours) in our study.

Conclusion

There is an inverse relation between plasma homocysteine levels and IRA patency and flow in patients receiving fibrinolytic therapy for acute STEMI. Findings in our study support the consideration that high plasma homocysteine levels negatively affect the coronary vessel patency after fibrinolytic therapy.

Conflict of interest: None declared.

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