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The Relationship between Plasma Homocysteine and Early Coronary Collateral Vessel Development after Acute Myocardial Infarction

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Aim: Homocysteine is known to inhibit endothelial cell proliferation, which is a key event in angiogenesis. Factors responsible for the presence or absence of coronary collateral circulation are poorly understood. Therefore, in this study we investigated the effect of plasma homocysteine level on the early formation of angiographically visible collaterals after acute myocardial infarction.

Materials and Methods: The study included 60 patients that had ST-segment elevation myocardial infarction (STEMI). All the patients underwent coronary angiography 1-4 days after admission (mean: 2.3 ± 1.2 days). Patients were graded according to Rentrop classification. Patients with grade 0 or 1 collateral vessels were classified as poor collaterals; patients with grade 2 or 3 collateral vessels were classified as good collaterals.

Results: In all, 35 (58.3%) patients had poor collateral vessel filling and the remaining 25 (41.7%) patients had good collateral filling. Plasma homocysteine concentration in patients with poor and good collateral formation was 18.2 ± 8.6 µmol/l and 12.7 ± 2.4 µmol/l, respectively (P = 0.008). There was a negative linear correlation between Rentrop subclasses and plasma homocysteine concentration (r = –0.391, P = 0.002). We assessed the effect of demographic variables, such as age, gender, hypertension, diabetes mellitus, smoking, lipid parameters, and plasma homocysteine concentration, on the development of collaterals. The only independent variable that affected the development of collaterals was homocysteine level (OR: 0.71; 95% CI = 0.57-0.89, P = 0.003).

Conclusions: This study demonstrates for the first time that there is an inverse relationship between the early development of collateral circulation after acute myocardial infarction and plasma homocysteine concentration.

Key Words: Collateral circulation, homocysteine, acute myocardial infarction

Homosistein ve Akut Miyokard İnfarktüsü Sonrası Erken Dönemde Koroner Kollateral Gelişimi

Amaç: Homosisteinin endotelyal hücre proliferasyonunu inhibe ettiği bilinmektedir. Koroner kollateral dolaşımın gelişimini etkileyen faktörler iyi bilinmemektedir. Bu çalışmada plazma homosistein düzeylerinin akut miyokard infarktüsü sonrası anjiyografik olarak saptanabilen kollaterallerin gelişimi üzerine tekisi araştırılmıştır.

Yöntem ve Gereç: Çalışmaya akut ST yükselmeli miyokard infarktüsü geçiren 60 hasta alınmıştır. Tüm hastalara hastaneye yatırıldıktan sonraki 1-4. günler arasında koroner anjiyografi yapılmıştır (ortalama 2,3 ± 1,2 gün). Kollateral damar gelişimi rentrop sınıflamasına göre derecelendirilmiş, 0 ve 1 kötü kollateral gelişimi, 2 ve 3 ise iyi kollateral gelişimi olarak gruplandırılmıştır.

Bulgular: 35 hastada (% 58,3) kötü kollateral gelişimi saptanmıştır. Geri kalan 25 hastada ise (% 41,7) kollateral gelişimin iyi olduğu görülmüştür. Ortalama plasma homosistein konsantrasyonu kötü ve iyi kollateral grublarında sırasıyla 18,2 ± 8,6 µmol/l ve 12,7 ± 2,4 µmol/l bulunmuştur (P = 0,008). Rentrop sınıfı ile homosistein düzeyi arasında anlamlı negatif korelasyon olduğu görülmüştür (r = –0,391, P = 0,002). Yaş, cinsiyet, hipertansiyon, diyabet varlığı, sigara alışkanlığı, plazma lipid parametreleri ve homosistein konsantrasyonlarının kollateral gelişimi üzerine etkisine bakıldığında, kollateral gelişini etkileyen tek bağımsız değişkenin homosistein olduğu görülmüştür (OR: 0,71; % 95 güven aralığı 0,57-0,89, P = 0,003).

Sonuç: Bu çalışma ile plazma homosistein konsantrasyonları ile akut miyokard infarktüsü sonrası erken dönemdeki kollateral gelişimi arasındaki negatif ilişkinin varlığı ilk kez gösterilmiştir.

Anahtar Sözcükler: Kollateral dolaşım, homosistein, akut miyokard infarktüsü

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Introduction

Homocysteine is a sulfur-containing amino acid derived from the demethylation of methionine. The atherosclerotic role of hyperhomocysteinemia was first established in 1969 by McCully, who reported premature extensive atherosclerosis in autopsied children that died due to homocysteinuria (1). It is now well known that high-level plasma homocysteine is an independent risk factor for peripheral vascular, cerebrovascular, and coronary artery disease (2-5). Hyperhomocysteinemia may exert multiple adverse effects on the cells of vascular walls. In several in vitro studies the addition of homocysteine to culture medium caused endothelial cell damage in a dose-dependent manner (6,7). Homocysteine is known to inhibit endothelial cell proliferation, which is a key event in angiogenesis (8). In the human heart mixed arteriogenic/angiogenic-type adaptation is an essential step in the development of collaterals (9).

The formation of coronary collaterals is an adaptive response of the coronary vascular system to arterial occlusion. This process is involved in restoring coronary blood flow and salvaging the myocardium in ischemic regions. Previous studies have shown that in cases of acute myocardial infarction, the presence of collaterals may limit the size of the infarct, preserve viability, and prevent ventricular aneurysm formation during an episode of acute coronary occlusion (10-13). Factors responsible for the presence or absence of collateral circulation are poorly understood. Therefore, in the present study we investigated the effects of plasma homocysteine level on the early formation of angiographically visible collaterals after acute myocardial infarction.

Materials and Methods

Patient Selection

The study included 60 patients that had ST-segment elevation myocardial infarction (STEMI). All the patients underwent coronary angiography 1-4 days after admission (mean: 2.3 ± 1.2 days). STEMI was diagnosed based on chest pain that persisted for more than 20 min and ST-segment elevation more than 1 mm in at least 2 standard limb leads or more than 2 mm in at least 2 contiguous precordial leads. STEMI was later confirmed by serum creatine kinase-MB fractions that increased to more than twice the upper limit of normal and serum troponin I levels above the upper limit of normal, according to the local quantitative or qualitative assays. Oxygen, aspirin, glyceryl trinitrate, morphine, and beta-blocker were administered to the patients. In addition, other appropriate pharmacologic agents were given to all the patients after thrombolytic therapy, which included heparin, clopidogrel, statin, and angiotensin enzyme inhibitor.

Exclusionary criteria were as follows: 1) Patients with a previous MI; 2) Patients with collateral formation due to a non-culprit lesion, as seen with coronary angiography; 3) Patients that previously underwent CABG or PCI; 4) Patients using folic acid or vitamin B complex supplements; 5) Patients with a history of folic acid or vitamin B complex deficiency; 6) Patients with cancer or renal insufficiency (creatinine ≥ 1.5 mg/dl).

Blood Sampling and Measurement of Plasma Homocysteine Level

Blood samples were collected from the antecubital vein at admission. Following coagulation for 1 h 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 using high-performance liquid chromatography with fluorescence detection (Chromsystems 45000 reagent kit; Agilent 1200, Germany). Hyperhomocysteinemia was defined as a plasma homocysteine concentration > 15 µmol/l. Lipid profiles, glucose, and creatinine concentrations were determined using routine laboratory methods.

Coronary Angiography and Grading of Coronary Collateral Filling

Standard angiography with at least 4 views of the left coronary system and 2 views of the right coronary artery was used for interpretation. Collateral vessels were graded according to Rentrop classification: 0, no filling of any collateral vessel; 1, filling of side branches of the artery to be perfused by collateral vessels, without visualization of the epicardial segment; 2, partial filling of the epicardial artery by collateral vessels; 3, complete filling of the epicardial artery by collateral vessels (14). All

angiographies were evaluated independently by 2 cardiologists blinded to the patients' identities and clinical data. When there was disagreement, a third cardiologist blinded to the initial 2 readings served as an arbitrator. The patients were classified into 2 groups according to collateral vessel grade. Patients with grade 0 or 1 collateral vessels were classified as poor collaterals; patients with grade 2 or 3 collateral vessels were classified as good collaterals.

Statistical Analysis

All statistical analyses were performed with SPSS v.13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD, and categorical variables were expressed as percentages. 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 and one way analysis of variance, with Bonferroni posteriori comparisons as appropriate. The chi-square test was used for the analysis of categorical variables. The relationship between Rentrop subclasses and plasma homocysteine levels was tested by Spearman's correlation. Multivariate logistic regression analysis was used to determine the independent variables that affected the development of collaterals. P values less than 0.05 were considered statistically significant.

Results

The study population consisted of 60 patients aged 32-77 years (47 males, 13 females). In all, 35 (58.3%) patients had poor collateral vessel filling and 25 (41.7%) had good collateral filling. The demographic characteristics of the study population are shown in the Table. There were no statistically significant differences between the groups in terms of gender, age, and lipid profile, or prevalence of hypertension, diabetes mellitus, and smoking. Plasma homocysteine concentration in patients with poor and good collateral formation was 18.2 ± 8.6 µmol/l and 12.7 ± 2.4 µmol/l, respectively (P = 0.008) (Figure 1). Among the entire study population there were 18 (30%) patients with grade 0 angiographic collaterals, 17 (28.3%) patients with grade 1, 17 (28.3%) patients with grade 2, and 8 (13.4%) patients with grade 3 angiographic collaterals. Mean plasma homocysteine concentration in individual Rentrop subclasses 0, 1, 2, and 3 were, respectively, 21 ± 10 µmol/l, 14.8 ± 5.1 µmol/l, 13.1 ± 2.1 µmol/l, and 11.5 ± 3.1 µmol/l, (P = 0.001, by ANOVA). There was a negative linear correlation between Rentrop subclasses and plasma homocysteine concentrations (r = –0.391, P = 0.002) (Figure 2).

Among the study population, 24 (40%) patients had a plasma homocysteine concentration > 15 µmol/l (upper limit of normal). Of these patients, 20 (83.3%) had poor

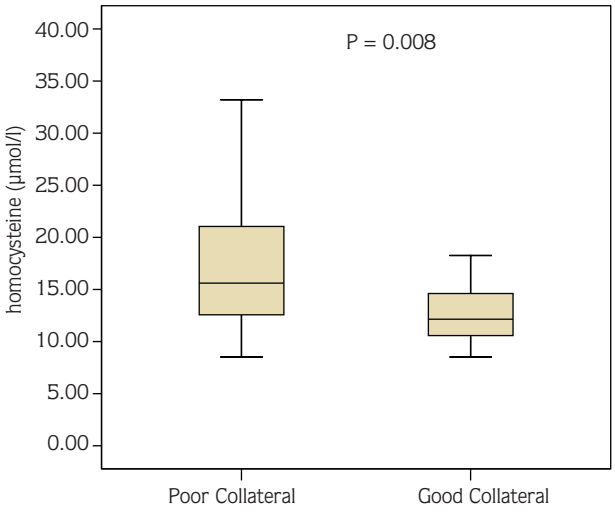

Figure 1. Plasma homocysteine concentration in the poor and good collateral groups.

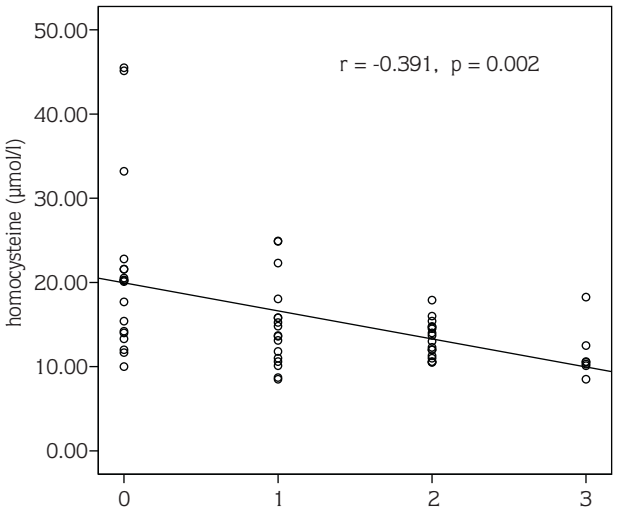

Figure 2. Relationship between plasma homocysteine concentration and Rentrop collateral classification (r = –0.391, P = 0.002).

Table. Characteristics of the study population.

	Poor collateral n = 35	Good collateral n = 25	P value
Age (years)	55 ± 10	58 ± 9	0.207
Gender (M/F)	5/30	8/17	0.122
Hypertension	14 (40%)	11 (44%)	0.795
Diabetes Mellitus	7 (20%)	6 (24%)	0.758
Smoking	25 (71.4%)	14 (56%)	0.276
Family history of CAD	8 (22.9%)	8 (32%)	0.384
Total cholesterol (mg/dl)	198.3 ± 43.6	187.1 ± 38.1	0.286
Triglycerides (mg/dl)	165.8 ± 113.4	182.7 ± 108.1	0.564
LDL (mg/dl)	125.5 ± 39	111 ± 29.6	0.124
HDL (mg/dl)	38.4 ± 6.4	37.2 ± 7.6	0.494
LVEF (%)	39.3 ± 9.1	41.3 ± 9.2	0.145

CAD: Coronary artery disease; F: female; HDL: high density lipoprotein, LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; M: male.

coronary collaterals, but in patients with a plasma homocysteine concentration < 15 µmol/l, this rate was only 41.7% (P = 0.002). Of patients in the good collaterals group, 84% had a plasma homocysteine concentration < 15 µmol/l. In the poor collaterals group 42.9% of the patients had a plasma homocysteine concentration < 15 µmol/l (P = 0.002).

We assessed the effect of demographic variables, such as age, gender, hypertension, diabetes mellitus, smoking, lipid parameters, and plasma homocysteine concentration, on the development of collaterals. The only independent variable that affected the development of collaterals was homocysteine level (OR: 0.71; 95% CI = 0.57-0.89, P = 0.003).

Discussion

In the present study increased plasma homocysteine concentration was an independent predictor of poor early collateral development after acute myocardial infarction. This is the first study to document that patients with poor early collateral formation after acute myocardial infarction had higher levels of plasma homocysteine than those with good collateral formation.

Coronary collateral circulation is an alternative source of blood supply to a myocardial area jeopardized by ischemia. Coronary collateral development has a potential protective role due to its association with smaller infarcts, less ventricular aneurysm formation, improved ventricular function, fewer future cardiovascular events, and improved survival in patients with acute myocardial infarction (10-13). During the early phase of acute myocardial infarction patients will show marked angiographic heterogeneity in collateral formation that is independent of the status of coronary artery occlusion (15). Collateral formation may vary from complete to absent during the early phase of acute myocardial infarction; however, the mechanism underlying these large differences between individual patients in the extent and adequacy of collateralization remains unclear.

In the present study we investigated age, gender, plasma homocysteine concentration, lipid parameters, hypertension, diabetes mellitus, and smoking as determinants of early collateral development after acute myocardial infarction. Plasma homocysteine concentration was the only independent variable that affected the development of collaterals. There was an inverse relation between plasma homocysteine concentration and collateral formation. Duan et al. reported that hyperhomocysteinemia impaired angiogenesis in vivo in a rat model (16). Their study was the first to provide evidence that hyperhomocysteinemia inhibits ischemia-induced angiogenesis in vivo.

Following a search of the literature, we located only 2

studies that investigated the association between homocysteine concentration and collateral formation in humans (17,18). Nagai et al. studied the effect of plasma homocysteine concentration on collateral circulation in 49 single-vessel coronary artery disease patients (17). Nineteen patients had single-vessel total occlusion. They noted significantly higher plasma homocysteine concentration in the poor collateral group. According to their study the independent factors that affected the development of collateral circulation in patients with single-vessel disease were homocysteine concentration, duration of angina pectoris, and degree of stenosis. The other study, which included 56 cases of pure single-vessel chronic total occlusion, reported no significant difference in plasma homocysteine concentration between the poor and good collateral groups (18).

Homocysteine is a risk factor for the development of coronary artery disease (4,5). Laboratory studies suggest that an elevated homocysteine concentration is both atherogenic and thrombogenic (19). There may be several possible mechanisms by which hyperhomocysteinemia impairs angiogenesis. First, hyperhomocysteinemia-induced endothelial dysfunction may account for the impaired angiogenesis. Homocysteine reduces endothelium-dependent vasodilatation by elevating plasma levels of asymmetric dimethylarginine, a potent inhibitor of nitric oxide (NO) synthase (20). Homocysteine impairs endothelium-derived NO formation, not only in large conduit arteries, but also in microvessels in vivo. Endothelium-derived NO is an important regulator of angiogenesis. For example, endothelium-derived NO maintains endothelial cell integrity and the expression of integrin $_{v\ 3,}$ thus promoting endothelial podokinesis and migration (21,22). Angiogenesis induced by vascular endothelial growth factor was attenuated by inhibitors of NO synthase (23).

Second, hyperhomocysteinemia-induced production of reactive oxygen radicals may contribute to further impairment of angiogenesis (24). Enhanced generation of oxygen radicals in the hyperhomocysteinemia state might further degrade NO. Third, homocysteine itself might directly inhibit endothelial cell proliferation and/or migration (8). Outinen et al. demonstrated that homocysteine induced arrested growth in human endothelial cells in vitro (25). Taken together, endothelial dysfunction, decreased NO bioactivity, and increased oxidative stress seem to account for impaired angiogenesis in the hyperhomocysteinemia state in vivo.

One of the main limitations of the present study is that the angiographically visualized collaterals were only part of the total collateral circulation, because collateral vessels less than 100 μm in diameter cannot be evaluated angiographically. Another limitation is the small size of the study population.

In conclusion, this study demonstrates for the first time that there is an inverse relationship between the early development of collateral circulation after acute myocardial infarction and plasma homocysteine concentration.

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