Relationship between elevated serum gamma-glutamyltransferase activity and slow coronary flow

Yüksek serum gama-glutamiltransferaz aktivitesi ile yavaş koroner akım arasındaki ilişki

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Objectives: We evaluated the relationship between coronary blood flow and serum gamma-glutamyltransferase (GGT) activity in patients with slow coronary flow (SCF).

Study design: The study included 90 patients (47 men, 43 women; mean age 50.8±9.4 years) with SCF and 88 patients (45 men, 43 women; mean age 51.4±8.8 years) with coronary artery disease (CAD), whose diagnoses were made by coronary angiography. Patients with CAD had normal coronary flow. Coronary flow was quantified using the corrected TIMI frame count (TFC) method and serum levels of gamma-glutamyltransferase were measured. The results were compared with those of a control group consisting of 86 age- and sex-matched patients who had normal coronary arteries and normal coronary flow.

Results: The three groups were similar with respect to body mass index, presence of hypertension and diabetes mellitus, lipid profiles, and fasting glucose. The use of medications was significantly more common in the CAD group ($p<0.01$). Compared to the control group, serum GGT activity was significantly increased in both SCF and CAD groups ($p<0.01$), but these two groups did not differ significantly in this respect ($p=0.71$). The TFCs for all the epicardial coronary arteries and the mean TFC were significantly higher in the SCF group ($p<0.01$). Patients with CAD and the controls had similar TFC parameters. The mean TFC showed a positive and moderate correlation with serum GGT activity ($r=0.326$; $p<0.001$). In regression analysis, serum GGT activity was found as the only independent predictor of the mean TFC ($\beta=0.309$; $p<0.001$).

Conclusion: We have shown for the first time an association between increased serum GGT activity and SCF. Further clinical studies are needed to clarify the physiopathologic role of serum GGT activity in SCF.

Key words: Blood flow velocity; coronary angiography; coronary circulation; coronary disease; gamma-glutamyltransferase; heart catheterization.

Amaç: Çalışmamızda yavaş koroner kan akımı (YKA) olan hastalarda serum gama-glutamiltransferaz (GGT) aktivitesi ile koroner kan akımı arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya YKA saptanan 90 hasta (47 erkek, 43 kadın; ort. yaş 50.8±9.4) ve koroner arter hastalığı (KAH) olan 88 hasta (45 erkek, 43 kadın; ort. yaş 50.8±9.4) alındı. Yavaş koroner kan akımı ve KAH tanıları koroner anjiyografi ile kondu. Koroner arter hastalığı olan grupta normal koroner akım vardı. Tüm hastalarda koroner akım düzeltilmiş TIMI kare sayısı ile değerlendirildi ve serum GGT düzeyleri ölçüldü. Sonuçlar, yaş ve cinsiyet uyumlu ve koroner arterleri ve koroner akımı normal bulunan 86 hastadan oluşan kontrol grubuyla karşılaştırıldı.

Bulgular: Gruplar arasında beden kütle indeksi, hipertansiyon ve diyabet varlığı, lipit profili ve açlık kan şekeri açısından fark yoktu. Koroner arter hastalığı olan grupta ilaç kullanımı anlamlı derecede fazlaydı ($p<0.01$). Kontrol grubuyla karşılaştırıldığında, serum GGT aktivitesi YKA'lı ve KAH'li gruplarda anlamlı derecede yüksek bulundu ($p<0.01$); ancak, iki grup arasında bu açıdan fark yoktu ($p=0.71$). Epikardiyal koroner arterlerde ölçülen TIMI kare sayıları ve ortalama TIMI kare sayısı YKA grubunda anlamlı derecede yüksek bulundu ($p<0.01$). TIMI kare sayıları açısından KAH grubu ile kontrol grubu arasında fark yoktu. Ortalama TIMI kare sayısı serum GGT düzeyi ile orta düzeyde pozitif ilişki gösterdi ($r=0.326$; $p<0.001$). Regresyon analizinde, serum GGT aktivitesi ortalama TIMI kare sayısını öngörmede tek bağımsız değişken idi ($\beta=0.309$; $p<0.001$).

Sonuç: Çalışmamızda artmış serum GGT aktivitesi ile YKA arasındaki ilişki ilk kez gösterilmiş olmaktadır. Serum GGT aktivitesinin YKA'da tam patofizyolojik rolünü ortaya koymak için ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Kan akım hızı; koroner anjiyografi; koroner dolaşım; koroner hastalık; gama-glutamiltransferaz; kalp kateterizasyonu.

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The slow coronary flow (SCF) phenomenon is an angiographic finding characterized by delayed passage of angiographic contrast along the coronary arteries, in the absence of stenosis in the epicardial vessels. This phenomenon was first described in 1972 by Tambe et al.[1] Many etiological factors such as microvascular and endothelial dysfunction, small-vessel disease, and diffuse atherosclerosis are included among the causes of SCF,[2-4] but its etiopathogenesis is still unclear. Occlusive disease of small coronary arteries, which may be a form of early-phase atherosclerosis, has also been suggested as a cause.[5]

In the CARDIA study (Coronary Artery Risk Development in Young Adults), serum gamma-glutamyltransferase (GGT) values were demonstrated to be strongly and positively correlated with determinants of oxidative stress such as C-reactive protein (CRP), uric acid, and fibrinogen.[6] In addition, in patients with a history of myocardial infarction and documented coronary artery disease (CAD), it has been found that the level of GGT has an independent predictive value for mortality and non-fatal myocardial infarction.[7]

We hypothesized that serum GGT activity may be associated with coronary blood flow since it was also shown to be associated with atherosclerosis and oxidative stress. Therefore, we aimed to evaluate the relationship between coronary blood flow (expressed by means of thrombolysis in myocardial infarction -TIMI- frame count) and serum GGT activity in patients with SCF.

PATIENTS AND METHODS

Patient selection. The study included 90 patients (47 men, 43 women; mean age 50.8±9.4 years) with SCF and 88 patients (45 men, 43 women; mean age 51.4±8.8 years) with CAD whose diagnoses were made by coronary angiography. Diagnosis of SCF was based on TIMI frame count (TFC) and the presence of normal coronary arteries without luminal irregularities. All the patients in the CAD group had stenotic lesions of greater than 20% and normal coronary flow. The control group consisted of age- and gender-matched 86 patients who had normal coronary arteries and normal coronary flow on coronary angiography. In all the groups, the indication for coronary angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia.

Exclusion criteria were prior myocardial infarction, valvular heart disease, cardiac rhythm other than sinus, heart failure, peripheral vascular disease, severe systemic disease, active hepatobiliary disease, and alcohol consumption. The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Coronary angiography and documentation of TIMI frame count. Patients underwent selective coronary angiography using the standard Judkins technique. Coronary arteries were visualized in left and right oblique planes, and cranial and caudal angles. Left ventriculography was performed in left and right anterior oblique views. Injection of contrast medium (Iopromide, Ultravist-370; Schering AG, Berlin, Germany) was carried out by an automatic injector at a speed of 3-4 ml/sec for the left coronary artery and 2-3 ml/sec for the right coronary artery. Arteriographies were recorded at a speed of 25 frames/sec. Coronary flow was quantified objectively by two independent observers who were blinded to the clinical details of the individual participants, using the corrected TFC method. The first frame was defined by a column of contrast extending across more than 70% of the arterial lumen in an anterograde motion.[8] Since the normal frame counts for the left anterior descending (LAD) coronary artery are 1.7 times greater than the mean for the left circumflex coronary artery and the right coronary artery,[9] the TFCs for the LAD were divided by 1.7 to derive the corrected TFC as described earlier.[10]

Definition of slow coronary flow. All participants with a corrected TFC greater than two standard deviations from the normal range reported for the particular vessel were accepted as having SCF while those whose corrected TFC fell within two standard deviations were considered to have normal coronary flow.[8] After assessment of coronary flow using the corrected TFC method,[8] the mean corrected TFC was derived by averaging the sum of the corrected TFCs for the LAD, left circumflex coronary artery, and right coronary artery. Intra- and interobserver variabilities for TFC were 0.961 and 0.933, respectively.

Biochemical measurements. Blood samples were drawn without stasis at 7-8 AM after 20 minutes of supine rest following a fasting period of 12 hours. Glucose, creatinine, and lipid profiles were determined by standard methods. The activity of GGT was measured by using a Roche Modular P-800 autoanalyzer with original kits.

Statistical analysis. Continuous variables were given as mean±standard deviation (SD) and cat-

Table 1. Baseline clinical and laboratory characteristics of the three groups

	SCF group (n=90)			CAD group (n=88)			Control group (n=86)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			50.8±9.4			51.4±8.8			51.6±10.1	0.39
Sex										0.40
Males	47	52.2		45	51.1		44	51.2		
Female	43	47.8		43	48.9		42	48.8		
Systemic hypertension	21	23.3		21	23.9		20	23.3		0.32
Heart rate (beat/min)			75.3±8.8			77.6±9.1			74.1±7.9	0.27
Diabetes mellitus	12	13.3		11	12.5		11	12.8		0.58
Smoking	35	38.9		31	35.2		27	31.4		0.26
Body mass index (kg/m^2)			25.9±5.5			26.1±5.8			26.2±6.0	0.32
Laboratory findings										
Fasting glucose (mg/dl)			99.0±12.0			105.0±15.0			102.0±11.0	0.51
Gamma-glutamyltransferase (U/l)			30.5±7.2			30.0±7.4			22.1±5.2	**<0.01**
Aspartate aminotransferase (U/l)			22.7±6.7			21.9±6.5			21.9±6.2	0.84
Alanine aminotransferase (U/l)			22.9±5.7			22.9±5.8			22.6±5.8	0.81
Alkaline phosphatase (U/Ll)			155.4±55.8			155.6±52.9			154.2±51.2	0.77
Total bilirubin (mg/dl)			0.70±0.22			0.74±0.24			0.68±0.19	0.82
Direct bilirubin (mg/dl)			0.23±0.13			0.25±0.13			0.22±0.14	0.85
Hemoglobin (g/dl)			13.8±1.6			13.4±1.3			13.5±1.2	0.28
Total cholesterol (mg/dl)			195.8±50.9			196.5±43.7			198.0±39.5	0.82
LDL-cholesterol (mg/dl)			120.0± 26.2			122.0±24.6			117.0±28.7	0.80
HDL-cholesterol (mg/dl)			44.2±11.4			44.8±10.6			45.7±9.8	0.82
Triglycerides (mg/dl)			147.8±51.3			149.4±45.8			152.3±44.7	0.93
Creatinine (mg/dl)			0.94±0.18			0.92±0.13			0.93±0.15	0.80
Medications										
Beta-blocker	10	11.1		44	50.0		7	8.1		**<0.01**
ACE inhibitor	9	10.0		40	45.5		10	11.6		**<0.01**
Aspirin	25	27.8		80	90.9		6	7.0		**<0.01**
Statin	8	8.9		62	70.5		11	12.8		**<0.01**
Calcium channel blockers	4	4.4		4	4.6		5	5.8		0.34
TIMI frame count (TFC)										
Left anterior descending (LAD)			44.1±6.4			28.6±5.5			27.1±4.8	**<0.01**
Corrected TFC of LAD			26.0±3.8			17.2±3.2			16.6±3.1	**<0.01**
Left circumflex artery			22.2±3.7			16.7±3.1			16.3±3.3	**<0.01**
Right coronary artery			21.1±6.1			15.9±2.9			15.5±2.8	**<0.01**
Mean TFC			23.1±2.5			16.6±2.6			16.1±2.3	**<0.01**

SCF: Slow coronary flow; CAD: Coronary artery disease; ACE: Angiotensin-converting enzyme.

egorical variables were expressed as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Groups were compared with the Kruskal-Wallis test for multiple comparisons. When a significant difference between three groups was observed by using Kruskal-Wallis test, Mann-Whitney U-test was used for determination of difference between couples. Correlations between the mean TFC and clinical-laboratory parameters were assessed by the Pearson correlation test. Multiple linear regression analysis was performed to identify the independent predictors of the mean TFC. Statistical significance was defined as $p<0.05$. The SPSS statistical software (SPSS for windows 10.0) was used for all statistical calculations.

RESULTS

The clinical characteristics, laboratory parameters and TFC values of the SCF, CAD, and control groups are presented in Table 1. Age, body mass index, presence of hypertension and diabetes mellitus, lipid profiles, and fasting glucose levels were not different between the three groups. Laboratory characteristics of the groups were not statistically different (Table 1). The use of medications including angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, statin, and aspirin was significantly higher in the CAD group ($p<0.01$). Compared to the control group, serum GGT activity was significantly increased in both SCF and CAD groups ($p<0.01$), but the two groups did not differ significantly in this respect ($p=0.71$).

Table 2. Relationship between the mean TIMI frame count and clinical and laboratory parameters

	Pearson analysis		Regression analysis	
	r	*p*	β	*p*
Age	0.122	0.542		
Sex	0.237	0.168		
Body mass index	0.156	0.215		
Hypertension	0.044	0.875		
Diabetes mellitus	0.245	0.124		
Smoking	0.219	0.466		
Heart rate	-0.231	**0.017**	-0.098	0.174
Total cholesterol	-0.194	0.365		
LDL-cholesterol	-0.064	0.411		
HDL-cholesterol	-0.094	0.251		
Triglyceride	0.107	0.687		
Fasting glucose	0.156	0.569		
Creatinine	0.105	0.765		
Hemoglobin	0.187	0.654		
Serum GGT activity	0.326	**<0.001**	0.309	**<0.001**
Coronary artery disease	0.198	0.123		

Of the three groups, the TFCs for all the epicardial coronary arteries and the mean TFC were significantly higher in the SCF group ($p<0.01$; Table 1). Patients with CAD had similar TFC parameters compared to the controls.

Relationships between the mean TFC and clinical and laboratory data are presented in Table 2. The mean TFC showed a positive and moderate correlation with serum GGT activity. In linear regression analysis, serum GGT activity was found as the only independent predictor of the mean TFC ($\beta=0.309$; $p<0.001$).

DISCUSSION

In the present study, we found that *(i)* GGT activity was significantly increased in patients with SCF and in patients with CAD compared to subjects with angiographically normal coronary arteries and normal coronary flow, *(ii)* serum GGT activity was significantly and moderately correlated with the mean TFC, and *(iii)* GGT was an independent predictor of the mean TFC and the presence of SCF.

The precise pathophysiological mechanism of the SCF phenomenon still remains uncertain. Small vessel abnormality and dysfunction have been implicated in its pathogenesis.[1] Mangieri et al.[9] reported histopathological findings of left ventricular endomyocardial biopsy specimens in a group of 10 patients with SCF without any other cardiac or systemic diseases. They showed evidence for small vessel abnormality as endothelial thickening due to cell edema, capillary damage, and reduced luminal diameter of the small vessels. Additionally, inflammation,[11,12] platelet function disorder,[13,14] and imbalance of vasoactive substances[15,16] have also been implicated in the pathogenesis of the SCF phenomenon.

Serum paraoxonase (PON) is a high-density lipoprotein-bound antioxidant enzyme that inhibits atherosclerosis and endothelial dysfunction. Yıldız et al.[17] reported that serum PON activity was independently associated with the mean TFC, suggesting that reduced serum PON activity might represent a biochemical marker of SCF. Enli et al.[18] showed that patients with SCF had significantly increased serum malondialdehyde and erythrocyte superoxide dismutase levels and decreased erythrocyte-reduced glutathione levels compared to patients with normal coronary flow. These findings indicate that free radical damage may play a role in the pathogenesis of SCF.

Serum GGT activity has been used as a marker for alcohol consumption or hepatobiliary disease.[6] However, it has been shown in *in vitro* experiments that GGT activity is directly related to oxidative events, playing a role in the evolution of atheromatous plaque and induces LDL oxidation in the presence of iron ions.[19-22] Gamma-glutamyltransferase activity has been identified in human atheromatous plaques.[22] The prognostic significance of GGT has been studied extensively. A prospective research among CAD patients revealed that the prognostic significance of serum GGT activity was particularly evident in a subset of ischemic patients with multi-vessel CAD and previous myocardial infarction.[23] This finding suggests that the significance of serum GGT activity is more pronounced in patients having vulnerable plaques. *In vitro* studies showed that, in the presence of an iron source, such as transferrin, LDL oxidation catalyzed by GGT played an important role in plaque development.[19-22] All these findings point out to the possible role of GGT in the development of SCF.

Coronary microvasculature, with small-diameter and well-developed media, is the major vascular determinant of coronary vascular resistance[24] and atherosclerosis and dysfunction of coronary microvasculature are well-known pathophysiologic mechanisms of SCF.[5] In a recent article, Erdoğan et al.[25] reported that the coronary flow reserve, which reflects coronary microvascular function, was impaired in patients with SCF and corrected TFC was correlated with coronary flow reserve.

In our study, the TFCs for all the epicardial coronary arteries and the mean TFC were significantly

higher in the SCF group compared to patients with CAD and controls. On the other hand, serum GGT activity was significantly increased in both SCF and CAD groups. These findings were consistent with our expectations for the SCF group, but were unexpected for the CAD group with normal coronary flow. This may suggest a relationship between increased GGT levels and the pathogenesis of atherosclerosis. Furthermore, several studies have demonstrated that medications such as dipyridamol, ACE inhibitors, calcium channel blockers, and statins have positive effects on microvascular dysfunction and SCF.[9,26-30] The use of these medications was significantly more common in the CAD group, which may account for the presence of normal coronary flow and TFCs.

There are some limitations of our study that should be taken into account. Diagnosis of normal coronary arteries depends on contrast angiograms of the vessel lumen, which may underestimate the presence of atherosclerotic plaque.[31] Intravascular ultrasound (IVUS) provides a more precise assessment of the presence and distribution of atherosclerosis in vessel lumen and throughout the wall.[32] We did not have the opportunity to perform IVUS in this study. On the other hand, heart rate, nitrate use, and coronary catheter size may influence the frame count.[33] In this study, patients using nitrates were excluded and the catheters used in all the participants were of the same size. Heart rate was similar in the three groups and it was not an independent factor to affect the mean TFC in regression analysis. Thus, increased GGT levels in patients with CAD in the absence of SCF may have different mechanisms other than drug use. This can be better evaluated with the inclusion of another group of patients having both CAD and SCF. The absence of such a group is another limitation of our study.

To our knowledge, this is the first study to report an association between increased serum GGT activity and SCF. Further studies are needed to clarify the physiopathologic role of serum GGT activity in patients with SCF.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries-a new angiographic finding. Am Heart J 1972;84:66-71.
2. Pekdemir H, Cin VG, Çiçek D, Çamsarı A, Akkuş N, Döven O, et al. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. Acta Cardiol 2004;59:127-33.
3. Graham IM, Daly LE, Refsum HM, Robinson K, Brattström LE, Ueland PM, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA 1997;277:1775-81.
4. Tawakol A, Omland T, Gerhard M, Wu JT, Creager MA. Hyperhomocyst(e)inemia is associated with impaired endothelium-dependent vasodilation in humans. Circulation 1997;95:1119-21.
5. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation 1986;74:964-72.
6. Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003;49:1358-66.
7. Emdin M, Passino C, Michelassi C, Titta F, L'abbate A, Donato L, et al. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. Eur Heart J 2001;22:1802-7.
8. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879-88.
9. Mangieri E, Macchiarelli G, Ciavolella M, Barillà F, Avella A, Martinotti A, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn 1996;37:375-81.
10. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. Circulation 2001;104:2401-6.
11. Li JJ, Xu B, Li ZC, Qian J, Wei BQ. Is slow coronary flow associated with inflammation? Med Hypotheses 2006;66:504-8.
12. Turhan H, Saydam GS, Erbay AR, Ayaz S, Yaşar AS, Aksoy Y, et al. Increased plasma soluble adhesion molecules; ICAM-1, VCAM-1, and E-selectin levels in patients with slow coronary flow. Int J Cardiol 2006;108:224-30.
13. Lanza GA, Andreotti F, Sestito A, Sciahbasi A, Crea F, Maseri A. Platelet aggregability in cardiac syndrome X. Eur Heart J 2001;22:1924-30.
14. Gökçe M, Kaplan S, Tekelioğlu Y, Erdoğan T, Küçükosmanoğlu M. Platelet function disorder in patients with coronary slow flow. Clin Cardiol 2005;28:145-8.
15. Camsarl A, Pekdemir H, Çicek D, Polat G, Akkuş MN, Döven O, et al. Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. Circ J 2003;67:1022-8.
16. Pekdemir H, Polat G, Cin VG, Çamsarı A, Çiçek D, Akkuş MN, et al. Elevated plasma endothelin-1 levels in coronary sinus during rapid right atrial pacing in patients with slow coronary flow. Int J Cardiol 2004;97:35-41.
17. Yıldız A, Gür M, Yılmaz R, Demirbağ R, Polat M,

Selek S, et al. Association of paraoxonase activity and coronary blood flow. Atherosclerosis 2008;197:257-63.
18. Enli Y, Türk M, Akbay R, Evrengül H, Tanrıverdi H, Kuru O, et al. Oxidative stress parameters in patients with slow coronary flow. Adv Ther 2008;25:37-44.
19. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med 1999;340:115-26.
20. Lee RT, Libby P. The unstable atheroma. Arterioscler Thromb Vasc Biol 1997;17:1859-67.
21. Berliner JA, Heinecke JW. The role of oxidized lipoproteins in atherogenesis. Free Radic Biol Med 1996; 20:707-27.
22. Paolicchi A, Minotti G, Tonarelli P, Tongiani R, De Cesare D, Mezzetti A, et al. Gamma-glutamyl transpeptidase-dependent iron reduction and LDL oxidation-a potential mechanism in atherosclerosis. J Investig Med 1999;47:151-60.
23. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol 1995;142:699-708.
24. Epstein SE, Cannon RO 3rd, Talbot TL. Hemodynamic principles in the control of coronary blood flow. Am J Cardiol 1985;56:4E-10E.
25. Erdoğan D, Çalışkan M, Güllü H, Sezgin AT, Yıldırır A, Müderrisoğlu H. Coronary flow reserve is impaired in patients with slow coronary flow. Atherosclerosis 2007;191:168-74.
26. Beltrame JF, Turner SP, Leslie SL, Solomon P, Freedman SB, Horowitz JD. The angiographic and clinical benefits of mibefradil in the coronary slow flow phenomenon. J Am Coll Cardiol 2004;44:57-62.
27. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. Am J Cardiol 2002;90:974-82.
28. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. Circulation 2004; 109:53-8.
29. Li JJ, Zheng X, Li J. Statins may be beneficial for patients with slow coronary flow syndrome due to its anti-inflammatory property. Med Hypotheses 2007;69:333-7.
30. Çakmak M, Tanrıverdi H, Çakmak N, Evrengül H, Çetemen S, Kuru O. Simvastatin may improve myocardial perfusion abnormality in slow coronary flow. Cardiology 2008;110:39-44.
31. Roberts WC, Jones AA. Quantitation of coronary arterial narrowing at necropsy in sudden coronary death: analysis of 31 patients and comparison with 25 control subjects. Am J Cardiol 1979;44:39-45.
32. Ge J, Erbel R, Gerber T, Görge G, Koch L, Haude M, et al. Intravascular ultrasound imaging of angiographically normal coronary arteries: a prospective study in vivo. Br Heart J 1994;71:572-8.
33. Abacı A, Oğuzhan A, Eryol NK, Ergin A. Effect of potential confounding factors on the thrombolysis in myocardial infarction (TIMI) trial frame count and its reproducibility. Circulation 1999;100:2219-23.