Editöre Mektup — Letter to the Editor

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

Sayın Editör,

Derginizin Nisan 2009 tarihli 3. sayısında Sayın Şen ve ark'nın "Yüksek serum gama-glutamiltransferaz aktivitesi ile yavaş koroner akım arasındaki ilişki"[1] başlıklı makaleleri ve bu makale ile ilişkili olarak Sayın Ağırbaşlı tarafından kaleme alınan "Yavaş koroner akım"[2] başlıklı editöryal yorum yer almaktadır. Şen ve ark. tipik anginası olan veya noninvaziv testlerde iskemi gösterilmiş bir hasta grubunda artmış gama-glutamiltransferaz aktivitesi ile yavaş koroner akım (YKA) arasındaki ilişkiyi incelemişlerdir. Editöryal yorumunda da, Sayın Ağırbaşlı ağırlıklı olarak perkütan girişimler sonrası gelişen YKA ile ilgili değerli güncel bilgileri okuyuculara aktarmıştır. Ancak, Şen ve ark'nın makalesi ile Sayın Ağırbaşlı'nın editöryal yorumu arka arkaya okunduğunda YKA'nın tanımı ile ilgili kardiyoloji terminolojisinde var olan karışıklığın etkisini gösterdiği anlaşılmaktadır. Şöyle ki, Şen ve ark. çalışmalarında, artık "primer YKA" ya da "YKA fenomeni" olarak isimlendirilen klinik tabloyu taşıyan hastaları incelemişler ve bu klinik tablonun etyopatogenezi ile ilgili geliştirdikleri hipotezi sınamışlardır. Sayın Ağırbaşlı da editöryal yorumuna "sekonder YKA" ya da "no-reflow fenomeni" olarak bilinen klinik tabloyu ve önemini tanımlayarak başlamış ve ağırlıklı olarak bu tablonun kliniği, tedavisi ve alternatif değerlendirme yöntemleri ile ilgili çok değerli bilgiler vermiştir. Hem okuyucularda olası bir kafa karışıklığını gidermek, hem de her ikisi de YKA olarak adlandırılmış olan iki farklı tabloyu yeni isimleriyle hatırlatmak için aşağıdaki bilgileri okuyucuların dikkatine sunuyorum.

Yavaş koroner akım tanımı Gibson'un önerdiği TIMI kare sayısı ölçümüne dayanır ve opak maddenin vasküler yapılarda ilerlemesinin gecikmesi şeklinde kendini gösterir.[3] Bu durum, primer YKA ve sekonder YKA olmak üzere iki ana başlık altında incelenir. Primer YKA için literatürde kullanılan ve daha yaygın olan diğer isim YKA fenomenidir. Yavaş koroner akım fenomeni artık yeni ve ayrı bir hastalık olarak kabul edilmektedir.[4] Tüm anjiyografilerde %4 sıklıkta görülmektedir.[5] Bu fenomenin yeni bir klinik tablo olarak tanımlanması, hastaların bir takım ortak özelliklerine dayandırılmaktadır. Bu hastalar sıklıkla kararsız anjina pektoris klinik tablosuna benzer bir şekilde istirahat anjinası ile acil servislere başvurmaktadırlar. Ayrıca, istirahat EKG'lerinde dinamik iskemik ST ve T değişiklikleri bulunmaktadır. Bu hastaların büyük çoğunluğu erkek olup sigara içiciliğine yüksek oranda rastlanmaktadır. Koroner arterlerinde tıkayıcı bir darlık bulunmamasına rağmen hastaların %80'inde göğüs ağrısı atakları tekrarlamakta ve 1/3'ünde hastaneye tekrar yatışlar gözlenmektedir.[6] Patogenezinde koroner akım rezervinin korunmuş olmasına rağmen istirahat mikrovasküler direncinin artmasının olduğu düşünülmektedir.[7] Bu klinik tablo için literatürde son önerilen isim "kardiyak sendrom Y"dir.[8]

Sekonder YKA ise belirgin bir nedene bağlanabilen YKA'dır. En sık olan ve en iyi bilinen şekli akut koroner sendromlarda primer perkütan girişim sonrası görülen YKA'dır. "No reflow" fenomeni olarak da adlandırılır. Girişim yapılan bölgede herhangi bir rezidüel darlık kalmamasına rağmen antegrat akımda azalma olmasıdır; %1-2 oranında görülür. Daha çok aterosklerotik plak veya trombüsün damarın mekanik manipülasyonu sırasında distale embolizasyonu sonucu oluşur. Devam eden anjina ve sürekli ST yüksekliği ile birliktedir. Altı yıllık mortaliteyi dört kat artırır. Diğer sekonder YKA nedenleri ise koroner ektazilerdeki YKA, iyatrojenik hava embolisine bağlı YKA ve bazı bağ dokusu hastalıklarında görülen YKA'dır.

Yavaş koroner akım konusundaki kavram karışıklığı olasılığını azaltmak için ilgili yazılarda sadece "YKA" terimi yerine, sözü geçen tablonun niteliğine göre "primer YKA ya da YKA fenomeni" ile "sekonder YKA ya da no-reflow fenomeni" tanımlamalarının kullanılmasının daha yararlı olacağı kanaatindeyim.

Saygılarımla,

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

Dear Editor,

Coronary slow flow (CSF) is a frequent phenomenon encountered during coronary angiographic procedures, whose precise physiopathological mechanisms have yet to be defined. It has come into prominence as well, partly because of the intensive research contribution of Turkish investigators. Gibson et al.'s paper[1] defining the quantification of coronary artery flow -so called as TIMI frame count (TFC)- has been a cornerstone in this research area. This pioneering paper not only provided evidence for normal reference values and reproducibility of the method, but also explained anatomic landmarks and fundamentals of the method in detail, with an extensive discussion on pitfalls and limitations of the TFC method. I have quite often noted that the methodological aspects of this method are overlooked, rendering the findings of some studies subject to major drawbacks. On the occasion of an article published in another journal, I previously underlined the importance of CSF definition and image acquisition rates.[2]

Şen et al.'s paper, recently published in the Archives of the Turkish Society of Cardiology,[3] is interesting in that it points out a different aspect of the CSF phenomenon by indicating a relationship with serum gamma-glutamyltransferase activity. Frankly, I appreciate the authors for their study and their efforts to avoid most of the methodological errors by exclusion of patients receiving intracoronary nitrate injection and utilization of similar contrast media, same-sized catheters, and automatic coronary injection system. However, the definition of CSF without consideration of variations in image acquisition rates makes their study prone to methodological bias. The authors used a recording speed of 25 frames/sec which resulted in considerably low TFC values compared to those reported by Gibson et al. whose image acquisition rate was 30 frames/sec. The resulting TFC values for their control group in comparison with those of Gibson et al. were as follows: 27.1 *vs*. 36.2 for the left anterior descending (LAD) coronary artery; 16.6 *vs*. 21.1 for the mean corrected TFC of the LAD; 16.3 *vs*. 22.2 for the left circumflex coronary artery; and 15.5 *vs*. 20.4 for the right coronary artery. If the authors had considered this difference in image acquisition rate and adjusted their TFCs for an acquisition speed of 30 fps (by multiplying each TFC by a conversion factor of 1.2) as described by Gibson et al.[1] and Vijayalakshmi et al.,[4] they would have had more comparable TFCs similar to reference values given by Gibson et al.

Actually, this lack of adjustment (as it was valid for each group of patients) would have no effect on the comparisons of the three groups in their study. However, the authors defined CSF according to the criteria based on the reference values of Gibson et al. (a TFC greater than two standard deviations from the normal range for a particular coronary artery). Thus, it is clear that their mean values represent some degree of underestimation and do not reflect the actual TFCs seen in CSF patients. This may well require re-analysis of their data with adjusted TFCs.

Of note, the authors defined CSF for individual coronary arteries. Therefore, the CSF group was somewhat "heterogenous" with a combination of patients having slow flow in "different" coronary arteries and varying CSF severity. From this point of view, I believe that a more "standardized and homogenous" classification of patients may require a CSF definition based on the average TFC derived from the sum of three coronary arteries compared to reference values

or a general definition of CSF in all coronary arteries. Indeed, I wonder how the presence of CSF in only one, two, and three coronary arteries would affect their results, as classification of patients based on the number of arteries with CSF would throw more light on the relationship of CSF and its severity with serum gamma-glutamyltransferase activity.

Depending on their methodology and database, the authors may find these issues worthy of consideration to improve and reinforce their impressive findings.

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Author's reply

Dear Editor,

First of all, we would like to express our appreciation to Dr. Başarıcı for his valuable comments on, and contribution to our article published in your journal.[1]

The images obtained by cineangiography in the study of Gibson et al.[2] were recorded at the rate of 30 frame/sec. In accordance with the remark of Dr. Başarıcı, we adjusted the TIMI frame counts (TFC) obtained at a speed of 25 frame/sec for an acquisition speed of 30 frame/sec as recommended by Vijayalakshmi et al.[3] After this adjustment, five patients in the control group shifted to the coronary slow flow (CSF) group, but this change made no difference in the comparison of the two groups (Table 1).

Table 1. TIMI frame counts (TFC) in patients with coronary slow flow (CSF) and in subjects with normal coronary flow

	CSF group (n=95) (Mean±SD)	Control group (n=81) (Mean±SD)	*p*
LAD	53.3±6.5	32.2±4.8	<0.01
cTFC of LAD	35.5±3.9	21.5±3.1	<0.01
Lcx	26.7±3.6	19.5±3.3	<0.01
RCA	25.4±6.2	18.6±2.9	<0.01
Mean TFC	29.2±2.5	19.8±2.3	<0.01
GGT (U/l)	30.4±7.2	22.2±5.2	<0.01

LAD: Left anterior descending artery; cTFC: Corrected TIMI frame count; Lcx: Left circumflex artery; RCA: Right coronary artery; GGT: Gamma-glutamyltransferase.

When we re-evaluated our findings and grouped the patients according to the number of the arteries showing CSF, we observed that serum gamma-glutamyltransferase (GGT) levels showed a slight elevation as the number of coronary arteries with CSF increased, but these elevations in serum GGT levels were not statistically significant. There were 55 (58%), 26 (27%), and 14 (15%) patients having CSF in one, two, and three coronary arteries, respectively, and the corresponding GGT levels in these groups were 30.2, 30.5, and 30.9 (U/l) (p=0.34). One possible reason for this insignificance might be the fact that the majority of patients with CSF had slow flow in one coronary artery. Nonetheless, our findings did not suggest a link between serum GGT levels and the severity of CSF.

It is clear that further studies are needed to understand the role of serum GGT levels in the pathophysiology and prevalence of CSF.

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The relationship between nonalcoholic fatty liver disease and the severity of coronary artery disease in patients with metabolic syndrome

Dear Editor,

We have read the article entitled "The relationship between nonalcoholic fatty liver disease and the severity of coronary artery disease in patients with metabolic disease" by Alper et al.[1] with great interest. We congratulate the authors for making an important but frequently neglected manifestation of metabolic syndrome, a current issue. In their study, they compared the patients with and without nonalcoholic fatty liver disease (NAFLD). The angiographic severity of the coronary artery disease was found to be higher in patients with NAFLD, suggesting that these patients need a more vigorous treatment against cardiovascular risk factors. Actually, NAFLD is a hepatic manifestation of metabolic syndrome, in which serum transaminase levels are increased in the majority of patients.[2] It is an increasingly recognized condition that has potential to progress to end-stage liver disease. It is well known that statins may sometimes be associated with hepatotoxicity, which is manifested by increased transaminase levels. For this reason, statins should be used with caution when the ALT level is three times higher than the upper limit of normal values.[3] However, we have observed that some of our colleagues hesitate about the prescription of lipid lowering drugs, especially the statins, in patients with transaminase levels lower than three times the upper limit. Statins are valuable agents that not only lower the cholesterol levels, but also have pleiotropic effects through their molecular properties. Deprivation from statin makes many coronary artery disease patients expose to substantially increased risk for future events. As shown by Alper et al., this exposure is more severe if the patient also has NAFLD. At this point, the question is "Is it really risky to use statins in patients with NAFLD in the presence of elevated transaminase levels?". To address this question, some studies have been performed and beneficial effects have been observed.[4,5]

We used atorvastatin in a 44-year-old male patient with grade II hepatosteatosis. His body mass index was 29 kg/m^2, LDL-cholesterol was 167 mg/dl (it progressively increased from 136 mg/dl in 6 months), HDL-cholesterol was 27 mg/dl, and serum ALT was 82 U/l (N=5-40 U/l). The patient had been on low-fat diet for the past month. We prescribed atorvastatin 20 mg/day and the patient was called for control after one month. He stated that he could not comply with the diet because of the bayram of sacrifice. The biochemical markers and lipid profile were as follows: LDL-cholesterol 51 mg/dl, HDL-cholesterol 42 mg/dl, and serum ALT 28 U/l. Ultrasonographic examination performed after an additional one month showed that hepatosteatosis had regressed to grade I. Atorvastatin-induced changes were striking in this patient.

In conclusion, patients with NAFLD may have great benefits from statin therapy. Statins may have paradoxical effects on serum transaminase levels in such patients. We suggest that the use of statins should be encouraged in NAFLD patients despite elevated transaminase levels, especially if the patient also has hyperlipidemia.

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Author's reply

Dear Editor,

We would like to thank the authors for their valuable comments on our article. Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and also an independent risk factor for another manifestation of metabolic syndrome-cardiovascular disease.[1] Primary and secondary prevention trials have shown that use of statins to lower an elevated low-density lipoprotein cholesterol level can substantially reduce death from cardiovascular disease. Occasionally, statin usage may cause increased serum ALT levels and many patients with NAFLD may already have elevated serum ALT levels. Previous studies suggest that it is safe to use statins to treat dyslipidemia in patients with NAFLD but, in these patients, larger follow-up studies are needed to prove that serum ALT level is decreased by the use of statins.[2]

Our study was designed mainly to assess the relationship between NAFLD and the severity of coronary artery disease. The issue of statin use is to be further investigated in this subgroup of patients. Dr. Uzun mentions some hesitations among physicians about the prescription of statins, but data on this issue are limited, requiring further studies in larger groups of patients.

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