

# Evaluation of the coronary flow by the coronary clearance time in patients with cardiac syndrome X

Journal of International Medical Research

2018, Vol. 46(3) 1121–1129

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DOI: 10.1177/0300060517743671

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## Abstract

**Objective:** The vessels involved in the microcirculation are too small to be visualized by conventional angiography and no tools are currently available that can directly evaluate the coronary microcirculation. This study evaluated the coronary clearance frame count (CCFC) in patients with cardiac syndrome X (CSX).

**Methods:** The retrospective study enrolled patients with angina, who had a positive nuclear imaging test and normal coronary angiography; and a control group consisting of patients who underwent an angiogram to exclude coronary artery disease. Thrombosis in myocardial infarction frame count (TFC) and CCFC for each coronary artery (left anterior descending coronary artery [LAD], circumflex coronary artery [CFX] and right coronary artery [RCA]) were calculated offline.

**Results:** A total of 71 patients with CSX and 61 control patients were enrolled in the study. No significant differences were found between the two groups regarding the baseline demographic and clinical variables. The TFC of LAD, CFX and RCA were similar between the two groups. The mean CCFC-LAD, CCFC-CFX and CCFC-RCA were significantly longer in the CSX group compared with the control group.

**Conclusion:** CCFC is a simple, quantitative and highly reproducible method that might be used as a marker of coronary microvascular dysfunction.

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## Keywords

Coronary clearance frame count, microvascular disease, cardiac syndrome X

Date received: 6 May 2017; accepted: 31 October 2017

## Introduction

Normal coronary arteries are found in 20–30% of patients presenting with typical angina or angina-like chest discomfort.<sup>1</sup> Although noncardiac causes may be responsible for the chest-pain syndrome,<sup>2</sup> a considerable subset of these patients have true angina due to myocardial ischaemia in the absence of angiographically significant coronary stenosis.<sup>3,4</sup> The syndrome of angina with normal coronary arteries is still a controversial issue due to difficulties in defining the pathophysiology and a lack of robust diagnostic criteria.<sup>5,6</sup> The terms ‘microvascular angina’ or ‘cardiac syndrome X’ (CSX) are used to describe patients with typical angina pectoris and a positive stress test (exercise tolerance test or myocardial perfusion scan), in the absence of significant coronary stenosis on angiography and other cardiac diseases.<sup>7,8</sup> The vessels involved in the microcirculation are too small to be visualized by conventional angiography and there are no tools currently available that can directly evaluate the coronary microcirculation. Thrombosis in myocardial infarction (TIMI) frame count (TFC) was suggested as a simple, fast, inexpensive and reproducible method to detect microvascular dysfunction and was widely used previously.<sup>9,10</sup> Recently, several angiographic variables derived from TFC, such as coronary clearance frame count (CCFC) and coronary sinus filling time (CSFT), were evaluated to assess microvascular circulation.<sup>11,12</sup> CCFC has been reported to be a good predictor to assess the degree of myocardial reperfusion achieved following primary angioplasty in acute myocardial infarction.<sup>11</sup> To the best of our knowledge,

CCFC in patients with CSX has not been evaluated. The aim of this study was to assess the CCFC in patients with CSX.

## Patients and methods

### *Study design and population*

This retrospective study enrolled consecutive patients who were referred to the Department of Cardiology, Gulhane Training and Research Hospital, Ankara, Turkey for coronary angiography for typical angina between January 2008 and December 2016 and who had a positive nuclear imaging test with angiographically normal coronary arteries. Exclusion criteria included: (i) significant valvular heart disease; (ii) previous myocardial infarction; (iii) cardiomyopathy, left bundle branch block, or reduced left ventricular ejection fraction; (iv) anaemia; (v) malignancy or any evidence of infection; (vi) visually detectable minimal coronary stenosis at angiography; (vii) angiographic images that were inadequate for CCFC calculation.

The control group was recruited from patients who were referred to the same institution for coronary angiography with varying indications during the same time period as the main study population. The control group consisted of patients without ischaemic heart disease who had a coronary angiogram to exclude coronary artery disease due to administrative requirements for nonspecific electrocardiogram findings, arrhythmias such as ventricular tachycardia, atrial fibrillation or supraventricular tachycardias and before valvular surgery. Patients with angiographically

normal coronary arteries without typical angina were included in the control group. The exclusion criteria were the same as those for the CSX group.

The local ethics committee of Gulhane Training and Research Hospital, Ankara, Turkey (no. 50687469-1491-156-16/1648-414) approved the study protocol. Informed patient consent was not required because of the retrospective design of the study.

### *Clinical and angiographic measurements*

Baseline demographic variables, medical histories and clinical features were obtained from the electronic medical records. Two observers (E.Y. and S.G.) who were unaware of patients' clinical data and scintigraphic results reviewed the angiographic data.

Coronary angiograms were performed using two different angiography units (Allura Xper FD10-10, Philips Healthcare, Best, the Netherlands; Coroskop Milenium Edition, Siemens, Erlangen, Germany) and the standard Judkins' technique. Intracoronary administration of nitroglycerin was not performed before contrast injection. The angiographic images had different frame rates (either 15 frames/s or 25 frames/s) based on the discretion of the operator and were converted to 30 frames/s by using relevant conversion factors as described below. TFC and CCFC were obtained offline. On the basis of the angiographic images, TFCs for each coronary artery were calculated for each patient as described previously.<sup>9</sup> CCFC was defined previously as 'the opposite index of TIMI frame count'.<sup>11</sup> In a previous study, CCFC was defined as the number of angiographic frames elapsed from the first frame in which the contrast medium was seen to be cleared from the ostium of the examined artery (at least 70% of the width of the artery) to that in which the contrast begins to be cleared from the same distal artery landmark proposed by the TIMI Group.<sup>11</sup> A conversion

factor of 2 and 1.2 was used to convert the frame rate values filmed at 15 and 25 frames/s, respectively, to adjust for the 30 frames/s acquisition speed used in the original cine angiographic studies.<sup>9,10</sup>

### *Statistical analyses*

All statistical analyses were performed using the SPSS<sup>®</sup> statistical package, version 20.0 (SPSS Inc., Chicago, IL, USA) for Windows<sup>®</sup>. Continuous data are expressed as mean  $\pm$  SD and tested for normal distribution using the Kolmogorov–Smirnov test. Data with normal distribution were compared using Student's *t*-test, while not normally distributed data were compared using Mann–Whitney *U*-test. Categorical data are expressed as numbers and percentages and compared using  $\chi^2$ -test. Receiver operating characteristic (ROC) curves were used to analyse the sensitivity and specificity of CCFC in discriminating the presence of CSX. A *P*-value  $< 0.05$  was considered statistically significant.

## **Results**

The study enrolled 71 patients in the CSX group and 61 patients in the control group. There were no significant differences in baseline characteristics including age, sex, and cardiovascular risk factors including hypertension, smoking and hyperlipidaemia between the two groups (Table 1). A history of diabetes mellitus was significantly higher in the CSX group (*P* = 0.001). All baseline laboratory findings were similar in the two groups except mean platelet volume, which was significantly higher in patients with CSX compared with the control group (*P* = 0.013) (Table 2).

The CSX and control groups were compared with respect to TFC and CCFC for each coronary artery and the results are shown in Table 3. No significant differences were found between the two groups with

regard to TFC-left anterior descending coronary artery (LAD), TFC-circumflex coronary artery (CFX) and TFC-right coronary artery (RCA). The mean CCFC-LAD, CCFC-CFX and CCFC-RCA were significantly longer in patients with CSX compared with the control group ( $P=0.002$ ,

$P=0.001$  and  $P=0.005$ , respectively). The interobserver and intraobserver agreement in the CCFC evaluations were 92.5% and 94.0%, respectively. The ROC curve presented in Figure 1 shows area under the curves of 0.687, 0.694 and 0.663 for CCFC-LAD, CCFC-CFX and CCFC-RCA, respectively. To discriminate the presence of CSX, the optimal cut-off points of CCFC for LAD, CFX and RCA were 41 frames (sensitivity 0.63, specificity 0.74), 40 frames (sensitivity 0.60, specificity 0.76) and 34 frames (sensitivity 0.64, specificity 0.71), respectively.

**Table 1.** Baseline demographical and clinical data of patients with cardiac syndrome X (CSX) and control patients who participated in this study.

Characteristic	CSX group n = 71	Control group n = 61
Age, years	55.32 ± 15.11	53.66 ± 10.90
Male	33 (46.5%)	21 (34.4%)
Smoker	42 (59.2%)	29 (47.5%)
Diabetes mellitus	42 (59.2%)	15 (24.6%)*
Hypertension	36 (50.7%)	26 (42.6%)
Hyperlipidaemia	30 (42.3%)	19 (31.1%)

Data presented as mean ± SD or n of patients (%).

\* $P=0.001$  compared with the CSX group;  $\chi^2$ -test.

## Discussion

This present study demonstrated a delay in CCFC in patients with angina and normal coronary arteries. The findings of the present study suggest that CCFC may be a sign of microvascular dysfunction in patients

**Table 2.** Baseline laboratory findings of patients with cardiac syndrome X (CSX) and control patients who participated in this study.

Laboratory parameter	CSX group n = 71	Control group n = 61
Glucose, mg/dl	112.00 ± 34.91	104.91 ± 26.88
Urea, mg/dl	30.84 ± 8.96	29.85 ± 8.44
Creatinine, mg/dl	0.88 ± 0.15	0.91 ± 0.17
Uric acid, mg/dl	5.78 ± 1.19	5.37 ± 1.39
HDL-C, mg/dl	44.93 ± 10.97	46.52 ± 11.63
LDL-C, mg/dl	135.54 ± 37.07	134.52 ± 38.77
Triglycerides, mg/dl	185.01 ± 96.28	163.67 ± 77.23
White blood cell, 103/ $\mu$ l	6.54 ± 1.73	6.89 ± 1.40
Haemoglobin, g/dl	13.76 ± 1.41	13.93 ± 1.28
Haematocrit, %	41.68 ± 3.96	41.18 ± 3.50
Platelet count, 103/ $\mu$ l	263.14 ± 67.01	244.82 ± 52.03
Mean platelet volume, fl	8.88 ± 1.10	8.25 ± 0.75*
Neutrophil count, 103/ $\mu$ l	4.02 ± 1.42	4.05 ± 1.23
Lymphocyte count, 103/ $\mu$ l	2.17 ± 0.57	2.16 ± 0.56
N/L ratio	1.91 ± 0.65	2.02 ± 1.00

Data presented as mean ± SD.

\* $P=0.013$  compared with the CSX group; Student's *t*-test.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/L, neutrophil/lymphocyte ratio.

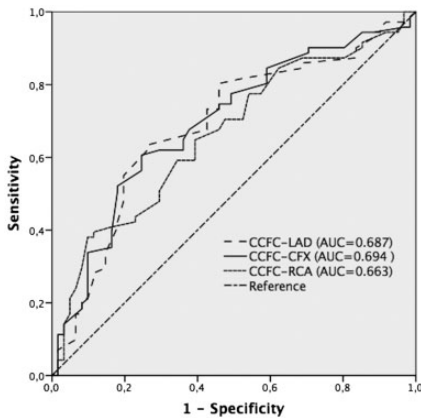
**Table 3.** Angiographic characteristics of patients with cardiac syndrome X (CSX) and control patients who participated in this study.

Characteristic		CSX group n = 71	Control group n = 61	Statistical significance <sup>a</sup>
TIMI frame count	LAD	40.69 ± 13.03	38.91 ± 8.61	NS
	CFX	29.71 ± 10.49	28.47 ± 6.64	NS
	RCA	25.13 ± 11.94	22.36 ± 5.71	NS
Coronary clearance frame count	LAD	43.82 ± 8.50	39.21 ± 7.95	P = 0.002
	CFX	40.87 ± 8.24	36.09 ± 7.83	P = 0.001
	RCA	37.24 ± 7.43	33.56 ± 7.49	P = 0.005

Data presented as mean ± SD.

<sup>a</sup>Compared with the CSX group; Student's *t*-test.

TIMI, thrombosis in myocardial infarction; LAD, left anterior descending coronary artery; CFX, circumflex coronary artery; RCA, right coronary artery; NS, no significant between-group difference ( $P \geq 0.05$ ).



**Figure 1.** Receiver-operator characteristic curves of coronary clearance frame count (CCFC) for the three coronary arteries: left anterior descending coronary artery (LAD), circumflex coronary artery (CFX) and right coronary artery (RCA). AUC, area under the curve.

with CSX. CSX is defined by typical angina pectoris with a positive noninvasive test (exercise tolerance test or myocardial perfusion scan) plus a normal coronary angiogram and absence of any other cardiac diseases.<sup>7,8</sup> Studies have reported an increased risk of myocardial infarction and cardiac death, especially in patients with a positive stress test.<sup>13,14</sup> Because of

controversies about its definition, a diagnosis of CSX is challenging and is primarily a diagnosis of exclusion. Since the vessels involved in the microcirculation are too small to be visualized by angiography, there is no simple diagnostic modality to assess the coronary microcirculation; and noninvasive as well as invasive methods have revealed inconsistent results.<sup>15,16</sup> TFC has been widely used in previous studies and demonstrated to be useful in detecting the coronary flow changes after coronary angioplasty or the impaired coronary microcirculation in patients who have severe coronary atherosclerosis and microvascular angina.<sup>17,18</sup> It has the advantage of being a quantitative index and avoids potential subjective bias. But an important limitation of TFC in CSX is that it is an epicardial flow-dependent parameter and gives limited information about transition of blood to the coronary microvasculature. Furthermore, TFC may be affected by the injection speed, which can vary due to the operators' technique. Since there is no available technique to visualize the coronary microvasculature, efforts are being made to investigate new noninvasive imaging indices to better diagnose this syndrome. It was previously reported that coronary flow reserve determined by

Doppler wire is a reliable method for the evaluation of microvascular dysfunction.<sup>19</sup> A less invasive diagnostic modality is to assess myocardial perfusion reserve index (MPRI) by cardiac magnetic resonance imaging in response to adenosine. A recent report revealed that lower MPRI values in women were related to previously confirmed microvascular dysfunction.<sup>20</sup> However, both of these techniques cannot be used widely because they require additional resources and technical expertise. Thus, angiographic parameters derived from TFC such as CCFC and CSFT have gained popularity in recent years. CCFC is defined as 'the opposite index of TIMI frame count' and has been demonstrated to have a good correlation between myocardial blush grade and TIMI myocardial perfusion grade in patients with myocardial infarction.<sup>11</sup> It has been demonstrated to be a valuable tool in assessing myocardial perfusion following primary angioplasty.<sup>11</sup> But to the best of our knowledge, CCFC in CSX has not been evaluated to date. This present study demonstrated that CCFC was significantly longer in patients with CSX compared with control patients, while TFCs were similar in the two groups. TFC is a well-validated technique to assess epicardial blood flow. However, the primary problem in CSX is microvascular dysfunction rather than macrovascular (epicardial) obstruction. Furthermore, coronary circulation comprises a physiologically complex functional anatomy in which development of intraventricular pressure compresses intramyocardial vessels, reduces intramural blood volume and causes a decrease in coronary arterial flow. In our opinion, CCFC is not affected by contrast injection speed because after two or three cardiac cycles following the contrast injection, the coronary arteries will reach their own flow physiology and then CCFC can be performed by native coronary flow speed. Therefore, CCFC may give valuable information about

angiographic tissue perfusion whilst taking into account this complex physiology. The results of the present study support this theory and showed that this quantitative and highly reproducible index is useful in assessing microvascular dysfunction in patients with CSX. CCFC can be easily calculated during conventional coronary angiography and provides an objective, reproducible and quantitative index of coronary flow to evaluate coronary microvascular function.

In contrast to most of the previous studies about CSX, in which a treadmill exercise test was used while assessing myocardial ischaemia, this present study used myocardial perfusion imaging for this purpose. The most important limitation of the treadmill exercise test is that it gives relatively frequent false positive results. Therefore, this present study chose to use nuclear imaging instead of a treadmill exercise test in the diagnosis of CSX to overcome this important limitation. Nuclear perfusion studies have been employed in the investigation of patients with CSX and regional defects are frequently seen after stress.<sup>21,22</sup>

Coronary sinus filling time is a recently reported index as a marker of coronary microvascular function and suggested as a predictor of prognosis in patients with microvascular angina.<sup>12,23</sup> CSFT was defined as the time required for the contrast agent in the epicardial coronary artery to traverse the coronary microvasculature and reach the coronary sinus.<sup>12</sup> Studies have shown that patients with angina and normal coronaries have prolonged coronary sinus filling time.<sup>12,23</sup> However, CSFT has some important drawbacks to use in routine practice. Since the contrast dye reaches to coronary sinus after six to eight cycles on average, assessing coronary sinus filling time leads to increased radiation exposure for both the operator and the patient. In contrast to CSFT, assessing



CCFC requires less frames, which results in less radiation exposure.

Consistent with previous research,<sup>24</sup> the current data showed that mean platelet volume was higher in patients with CSX than the control group. Platelets have a key role in atherothrombosis and inflammation. Mean platelet volume is a known marker of platelet activation and reflects the platelet production rate and platelet stimulation.<sup>25</sup> Therefore, recent studies have focused on mean platelet volume as a potential marker of platelet reactivity, to define their importance in cardiovascular diseases, including CSX.<sup>26,27</sup> The pathophysiology of CSX is still controversial; however, a reduced coronary microvascular vasodilatory response due to endothelial dysfunction and increased coronary resistance are thought to have important roles. Thus, higher mean platelet volumes that indicate increased platelet activation is not surprising in patients with CSX.

The current study had several limitations. First, the study had a single-centre design. Secondly, the study had a relatively small patient population. Thirdly, the study lacked a 'gold standard' of microvascular dysfunction such as myocardial blood flow measurement (dynamic single-photon emission computed tomography [SPECT] using a SPECT/computed tomography camera or positron-emission tomography). The study defined microvascular angina using the method of myocardial perfusion imaging. The sensitivity of SPECT in this regard is debatable.<sup>28</sup> Fourthly, because a stress test was not performed in the control group, this issue is also open to criticism. A control group without symptoms and with a negative stress and angiographically normal coronary arteries would have been ideal. However, it would be impossible to get approval from the ethics committee to perform coronary angiography in a patient group without symptoms and with a negative stress test in our country. Lastly,

intracoronary administration of nitroglycerin was not performed before contrast injection. Despite these limitations, these current findings support the need for further studies.

In conclusion, CCFC is a simple, quantitative and highly reproducible method that might be used as a marker of microvascular dysfunction in patients with CSX. Although the sensitivity and specificity of CCFC was not enough to promote its use in clinical practice, in our opinion, this index may provide further information on the overall rate of perfusion of the cardiac microcirculation.

#### Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

#### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

#### References

1. Melikian N, De Bruyne B, Fearon WF, et al. The pathophysiology and clinical course of the normal coronary angina syndrome (cardiac syndrome X). *Prog Cardiovasc Dis* 2008; 50: 294–310.
2. Phan A, Shufelt C and Merz CN. Persistent chest pain and no obstructive coronary artery disease. *JAMA* 2009; 301: 1468–1474.
3. Cannon RO and Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 1988; 61: 1338–1343.
4. Cannon RO, Watson RM, Rosing DR, et al. Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* 1983; 1: 1359–1373.
5. Cannon RO. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. *J Am Coll Cardiol* 2009; 54: 877–885.

6. Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation* 2004; 109: 568–572.
7. Lanza GA and Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation* 2010; 121: 2317–2325.
8. Ong P, Sivanathan R, Borgulya G, et al. Obesity, inflammation and brachial artery flow-mediated dilatation: therapeutic targets in patients with microvascular angina (cardiac syndrome X). *Cardiovasc Drugs Ther* 2012; 26: 239–244.
9. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996; 93: 879–888.
10. Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. *Circulation* 1999; 99: 1945–1950.
11. Perez de Prado A, Fernández-Vázquez F, Cuellas-Ramón JC, et al. Coronary clearance frame count: a new index of microvascular perfusion. *J Thromb Thrombolysis* 2005; 19: 97–100.
12. Haridasan V, Nandan D, Raju D, et al. Coronary sinus filling time: a novel method to assess microcirculatory function in patients with angina and normal coronaries. *Indian Heart J* 2013; 65: 142–146.
13. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institute of Health-National Heart, Lung, & Blood Institute-Sponsored Women Ischemic Syndrome Evaluation Trial (WISE). *Circulation* 2004; 109: 2993–2999.
14. Bugiardini R. Women, 'non-specific' chest pain, and normal or near-normal coronary angiograms are not synonymous with favourable outcome. *Eur Heart J* 2006; 27: 1387–1389.
15. Meller J, Goldsmith SJ, Rudin A, et al. Spectrum of exercise thallium-201 myocardial perfusion imaging in patients with chest pain and normal coronary angiograms. *Am J Cardiol* 1979; 43: 717–723.
16. Rossetti E, Fragasso G, Mellone R, et al. Magnetic resonance contrast enhancement with gadolinium-DTPA in patients with angina and angiographically normal coronary arteries: effect of chronic beta-blockade. *Cardiologia* 1999; 44: 653–659.
17. Bickel C, Rupprecht HJ, Maimaitiming A, et al. The superiority of TIMI frame count in detecting coronary flow changes after coronary stenting compared to TIMI Flow Classification. *J Invasive Cardiol* 2002; 14: 590–596.
18. Mega JL, Morrow DA, Sabatine MS, et al. Correlation between the TIMI risk score and high-risk angiographic findings in non-ST-elevation acute coronary syndromes: observations from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial. *Am Heart J* 2005; 149: 846–850.
19. Kothawade K and Bairey Merz CN. Microvascular coronary dysfunction in women: pathophysiology, diagnosis, and management. *Curr Probl Cardiol* 2011; 36: 291–318.
20. Shufelt CL, Thomson LE, Goykhman P, et al. Cardiac magnetic resonance imaging myocardial perfusion reserve index assessment in women with microvascular coronary dysfunction and reference controls. *Cardiovasc Diagn Ther* 2013; 3: 153–160.
21. Legrand V, Hodgson JM, Bates ER, et al. Abnormal coronary flow reserve and abnormal radionuclide exercise test results in patients with normal coronary angiograms. *J Am Coll Cardiol* 1985; 6: 1245–1253.
22. Tweddel AC, Martin W and Hutton I. Thallium scans in syndrome X. *Br Heart J* 1992; 68: 48–50.
23. Kadermuneer P, Vinod GV, Haridasan V, et al. Prognostic significance of coronary sinus filling time in patients with angina and normal coronaries at one year follow up. *Indian Heart J* 2015; 67: 245–249.
24. Demirkol S, Balta S, Unlu M, et al. Evaluation of the mean platelet volume in patients with cardiac syndrome X. *Clinics (Sao Paulo)* 2012; 67: 1019–1022.
25. Tsiara S, Elisaf M, Jagroop IA, et al. Platelets as predictors of vascular risk: is



- there a practical index of platelet activity? *Clinical and Applied Thrombosis/Hemostasis* 2003; 9: 177–190.
26. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost* 2010; 8: 148–156.
27. Gasparyan AY, Ayvazyan L, Mikhailidis DP, et al. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des* 2011; 17: 47–58.
28. Geltman EM, Henes CG, Senneff MJ, et al. Increased myocardial perfusion at rest and diminished perfusion reserve in patients with angina and angiographically normal coronary arteries. *J Am Coll Cardiol* 1990; 16: 586–595.