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Relationship between the Coronary Slow Flow Phenomenon and the Vertebrobasilar Insufficiency

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Abstract

Background: Coronary slow flow phenomenon (CSFP) and vertebrobasilar insufficiency (VBI) may have common pathophysiological mechanism.

Aim: Our aim was to investigate whether there is an association between vertebrobasilar flow assessed by Doppler sonography and CSFP assessed by Thrombolysis in Myocardial Infarction (TIMI) frame count.

Methods: We included 241 patients who had CSFP and underwent vertebrobasilar Doppler sonography. Patients with vertebral artery blood flow volumes greater than 200 ml/min and equal to or less than 200 ml/min were classified into the normal flow and low flow groups, respectively. Hospital records were used to determine the biochemical and demographic characteristics of the patients.

Results: The mean age of the study population was 58.75±9.34 years. We found no differences between patients with normal and low vertebral blood flow in terms of age, sex, body mass index, smoking habit, presence of hypertension, hyperlipidemia, diabetes mellitus or medication use. Patients with low vertebral blood flow were found to have greater mean platelet volume. The mean TIMI frame count and LAD, Cx, and RCA TIMI frame counts were significantly greater in patients with low vertebral blood flow and were negatively correlated with the vertebral artery blood flow volume ($p<0.001$ for all). A mean TIMI frame count of 24.5 predicted VBI, with a sensitivity and specificity of 61.2% and 86.8%, respectively. The only predictor of VBI was the mean TIMI frame count (OR: 1.066, 95% confidence interval: 1.043–1.091, $P<0.001$).

Conclusion: Our findings suggest that a common pathophysiological mechanism may underlie both CSFP and VBI.

Keywords: Coronary, slow flow, vertebrobasilar, flow.

Introduction

The term vertebrobasilar insufficiency (VBI) is used to describe a clinical syndrome in which there is decreased blood flow in one or more vessels of the vertebrobasilar circulation. The vertebral and basilar arteries supply blood to the posterior part of the brain, including the cerebellum, spinal cord, occipital cortex, and midbrain. Reduced blood flow to these arteries results in a variety of symptoms, including dizziness, syncope, drop attacks, confusion, and visual, auditory and cardiac problems [1]. Symptoms vary depending on the part of the brain affected. Elderly and diabetic patients are particularly affected by reduced perfusion, resulting in ischemia. The main cause of VBI is atherosclerosis, and the progression of atherosclerotic plaques over time can cause ischemic events [2]. Risk factors involved in the pathogenesis of atherosclerosis may predispose patients to VBI. Patients diagnosed with coronary or peripheral arterial disease are at risk for VBI. Like atherosclerotic disease, its prevalence increases with age and tends to affect men. In addition to atherosclerosis, embolic events and compressive effects of cervical spondylosis are other factors that cause VBI [3].

The coronary slow flow phenomenon (CSFP) is an angiographically described entity associated with the sluggish passage of contrast agent within coronary arteries without significant obstruction. It is found in 1 to 7% of patients undergoing coronary angiography and has been reported in up to one-third of patients with anatomically normal coronary arteries [4]. Since it may be the cause of ischemic symptoms, it may have a negative impact on the patient's life. Although the pathophysiological abnormalities underlying coronary slow flow are not well understood, an imbalance between the vasoconstrictive and vasodilator effects of substances secreted by the endothelium is among the suggested possible mechanisms of this phenomenon [5]. CSFP tend to occur in males, smokers, and those with characteristics of metabolic syndrome [6]. Caiati et al. reported that CSFP does not occur without atherosclerotic involvement of the coronary microvasculature, suggesting that it may be an early stage of atherosclerosis [7].

On the basis of the hypothesis that CSFP and VBI may have a common pathogenesis, we investigated the connection between vertebrobasilar flow assessed by Doppler sonography and CSFP assessed by Thrombolysis in Myocardial Infarction (TIMI) frame count.

Materials and methods

The study was retrospective in design. Five thousand seven hundred and twelve patients who underwent coronary angiographic examination at a tertiary hospital clinic between July 2016 and March 2022 were screened. Among these patients, 603 patients with CSFP were selected. Patients were considered acceptable for the study if they underwent vertebrobasilar Doppler sonography within six months prior to or following an angiography procedure. Patients with heart failure, subclavian steel syndrome, a hypoplastic vertebral artery, more than 50% occlusion in either the vertebral or coronary artery or vertebral artery stenosis, valvular heart disease, a history of cerebrovascular accidents, or acute infection were not included in the study. Two hundred forty-one patients remained and were included in the study. The study protocol complied with the ethical standards of the 1964 Declaration of Helsinki and was approved by the hospital ethics committee. Informed consent was obtained from patients prior to enrollment.

Blood samples for biochemical and complete blood count analyses were obtained from each patient after a 12-hour fast.

Doppler sonographic examinations of the patients were performed from the C4 and C5 intertransverse segments at an angle of less than 60 degrees via a Samsung RS80 EVO (Samsung Medison, Seoul, Korea) with a 3–12 MHz transducer. All measurements were performed with the patients at rest for ten minutes and in the supine position. Both vertebral arteries were evaluated from the level of the orifice to the base of the skull, and flow sampling was performed. The average of three measurements of blood flow volume (ml/min) was obtained from the right and left vertebral arteries of each patient. The net vertebral artery blood flow volume was obtained by averaging the right and left vertebral artery blood flow volumes. Patients were split into two groups according to their vertebral artery blood flow volumes. Patients with vertebral artery blood flow volumes greater than 200 ml/min or equal to or less than 200 ml/min were classified into the normal-flow or low-flow group, respectively.

The coronary angiograms of the study patients were interpreted by an interventional cardiologist who was aware of the patients' clinical information. The epicardial blood flow of the patients was classified into four groups according to the TIMI system [8]. The diagnosis of CSFP was made via the TIMI frame count method, in which the first frame is considered the moment when the coronary artery ostium is fully stained with a dying agent, and the last frame is considered the moment when the distal point of the relevant artery is filled with the dying agent [9]. The distal reference points of the left anterior descending artery (LAD), circumflex artery (Cx), and right coronary artery (RCA) are accepted as the terminal bifurcations of the LAD and Cx and the first branch of the posterolateral artery of the RCA, respectively. The corrected LAD TIMI frame count was calculated by dividing the TIMI frame count by 1.7. The mean TIMI frame count was calculated by adding the LAD, Cx, and RCA TIMI frame counts and dividing the result by three.

Statistical analysis

The normality of the data was assessed by analyzing the skewness and kurtosis of the data. Quantitative data from the two groups were examined via independent samples t tests or Mann–Whitney U tests. The differences in the qualitative data were determined via the chi-square test. The correlations of vertebral artery blood flow volume with TIMI frame counts were determined via Spearman correlation analysis. The cutoff value of the mean TIMI frame count for the VBI was calculated via receiver operating characteristic (ROC) curve analysis. Univariate logistic regression analysis was performed to evaluate the independent predictors of the VBI. Significantly different variables were included in the multivariate logistic regression analysis. A p value less than 0.05 was considered significant.

Results

The average age of the study population was 58.75±9.34 years, and the mean body mass index was 29.21±5.88 kg/m2. Among these patients, 126 (52.3%) were male, 65 (27%) had diabetes mellitus, 148 (61.4%) had hypertension, and 87 (36.1%) had hyperlipidemia. We found no differences between patients with normal and low vertebral blood flow with respect to age, sex, body mass index, smoking habit, or the presence of hypertension, hyperlipidemia, or diabetes mellitus. In addition, there were no differences between medication use and biochemical variables, except for the mean platelet volume, which was greater in patients with low vertebral blood flow. The mean TIMI frame count and LAD, Cx, and RCA TIMI frame counts were significantly greater in subjects with low vertebral blood flow. Table 1 and Figure 1 show the biochemical and clinical variables and the mean TIMI frame counts of the two groups.

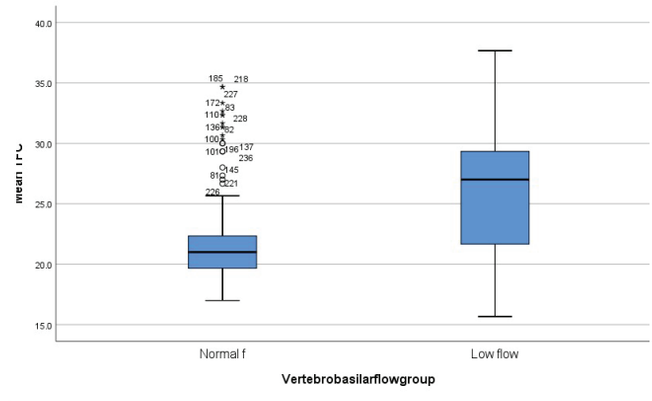

Figure 1 – TIMI frame counts of the two groups

Table 1 Clinical and biochemical variables of the two groups.

	Normal flow group (n=174)	Low flow group (n=67)	p
Age (years)	58.02±9.51	60.63±8.68	0.053
BMI (kg/m2)	28.68 (27.78-33.37)	29.38 (26.44-35.54)	0.231
Gender (n, %)			0.253
Male	87 (50)	28 (41.8)	
Female	87 (50)	39 (58.2)	
Smoking (n, %)	83 (47.7)	34 (50.7)	0.672
COPD (n, %)	31 (17.8)	18 (26.9)	0.125
Diabetes mellitus (n, %)	50 (28.7)	15 (22.4)	0.320
Hypertension (n, %)	103 (59.2)	45 (67.2)	0.255
Hyperlipidemia (n, %)	60 (34.5)	27 (40.3)	0.400
HbA1C (%)	5.8 (5.50-6.50)	5.70 (5.40—6.80)	0.501
Fasting glucose (mg/dl)	104 (96-126.25)	105 (91-125)	0.703
Creatinine (mg/dl)	0.74 (0.65-0.92)	0.79 (0.68-0.97)	0.215
GFR (mL/min/1.73m2)	93 (82-104.25)	92 (78-100)	0.115
LDL-C (mg/dl)	128.28±44.15	121.91±38.40	0.211
Triglyceride (mg/ml)	132(96-188.25)	142 (107-184)	0.428
HDL-C (mg/dl)	46.5 (38-55)	45 (38-57)	0.901
Albumin (g/l)	4.38 (4.16-4.54)	4.4 (4.1-4.60)	0.681
CRP (mg/l)	0.26 (0.16-0.42)	0.33 (0.21-0.45)	0.128
Hemoglobin (g/dL)	13.49±1.60	13.83±.55	0.136
Neutrophil count(10e3/Ul)	4.33 (3.58-5.04)	4.43 (3.58-5.58)	0.333
Platelet count (10e3/Ul)	259.61±61.69	253.53±75.53	0.507
Lymphocyte count (10e3/Ul)	2.42±0.74	2.24±0.77	0.110
Monocyte count (10e3/Ul)	0.56 (0.47-0.70)	0.60 (0.47-0.75)	0.240
MPV (fL)	10.25±0.89	10.61±1.07	**0.009**
ACE /ARB (n, %)	80 (46)	38 (56.7)	0.135
Beta blocker (n, %)	89 (51.1)	33 (49.3)	0.792
Ca channel blocker (n, %)	56 (32.2)	27 (40.3)	0.235
Diuretic (n, %)	57 (32.8)	27 (40.3)	0.271
Statin (n, %)	61 (35.1)	28 (41.8)	0.332
ASA (n, %)	57 (32.9)	29 (43.3)	0.134
Vertebral artery blood flow volume (ml/min)	270 (230-320)	180 (153-200)	**<0.001**
Mean TIMI frame count	21 (19.6-22.3)	27 (21.6-29.3)	**<0.001**
LAD TIMI frame count	22 (20-23)	24 (21-34)	**<0.001**
CX TIMI frame count	21 (18-22.25)	24 (21-26)	**<0.001**
RCA TIMI frame count	21 (19-23)	25 (21-33)	**<0.001**

ACE/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, ASA: Acetyl salicylic acid, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, Cx: Circumflex artery, GFR: Glomerular filtration rate, HDL-C: High density lipoprotein cholesterol, LAD: Left anterior descending artery, LDL-C: Low density lipoprotein cholesterol, MPV: Mean platelet volume, RCA: Right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

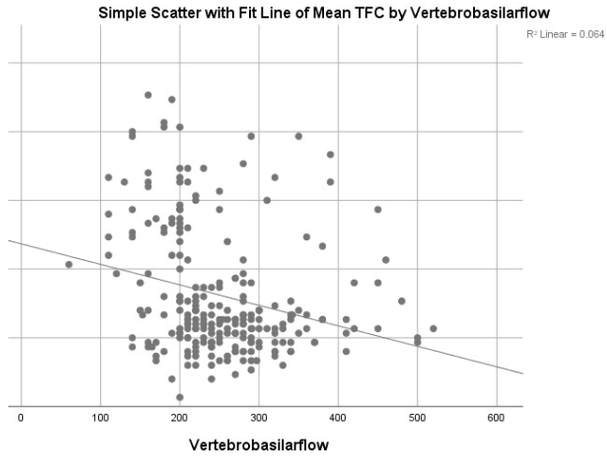

Figure 2 – Correlation of the TIMI frame count with the vertebral artery blood flow volume

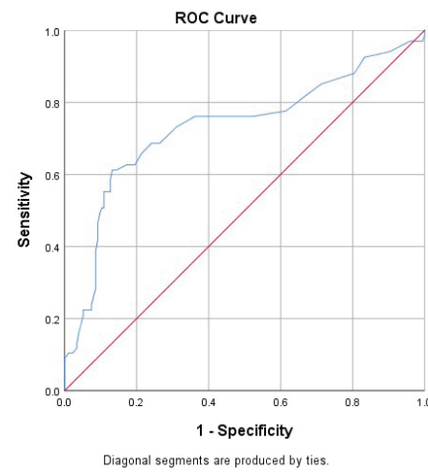

Figure 3 – ROC curve analysis of the TIMI frame count for the prediction of VBI

Table 2 Correlation of vertebral artery blood flow volume with mean TIMI frame count, LAD, Cx and RCA TIMI frame counts.

	r	p
Mean TIMI frame count	-0.278	<0.001
LAD TIMI frame count	-0.250	<0.001
CX TIMI frame count	-0.249	<0.001
RCA TIMI frame count	-0.234	<0.001

Cx: Circumflex artery, LAD: Left anterior descending artery, RCA: Right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Table 3 Univariate logistic regression analysis for the prediction of vertebrobasilar insufficiency.

	p	OR	95% CI
Age	0.054	1.013	0.999-1.064
BMI	0.341	1.023	0.976-1.073
Smoking	0.672	1.130	0.643-1.985
Diabetes mellitus	0.321	0.715	0.359-1.396
HbA1C	0.442	0.998	0.993-1.004
Fasting glucose	0.573	1.000	0.994-1.006
Creatinine	0.599	0.950	0.784-1.150
LDL-C	0.221	0.995	0.987-1.003
Triglyceride	0.465	1.001	0.998-1.004
HDL -C	0.604	1.005	0.985-1.025
Albumin	0.641	1.202	0.555-2.599
CRP	0.954	1.019	0.543-1.911
Hemoglobin	0.137	1.145	0.958-1.368
Neutrophil count	0.114	1.175	0.962-1.434
Platelet count	0.505	0.999	0.994-1.003
Lymphocyte count	0.111	0.731	0.498-1.074
Monocyte count	0.163	3.008	0.641-14.116
MPV	0.010	1.476	1.096-1.990
Mean TIMI frame count	<0.001	1.069	1.046-1.094
LAD TIMI frame count	<0.001	1.138	1.083-1.195
CX TIMI frame count	<0.001	1.138	1.071-1.209
RCA TIMI frame count	<0.001	1.142	1.085-1.201

ACE/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, ASA: Acetyl salicylic acid, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, Cx: Circumflex artery, GFR: Glomerular filtration rate, HDL-C: High density lipoprotein cholesterol, LAD: Left anterior descending artery, LDL-C: Low density lipoprotein cholesterol, MPV: Mean platelet volume, RCA: Right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Table 4 Multivariate logistic regression analysis for the prediction of vertebrobasilar insufficiency.

	p	OR	95% CI
Mean TIMI frame count	<0.001	1.066	1.043-1.091
MPV	0.123	1.303	0.931-1.825

MPV: Mean platelet volume, TIMI: Thrombolysis in Myocardial Infarction.

Our results revealed that 148 (84.6%) patients who did not have CSFP also did not have VBI, whereas 40 (60.6%) patients who had CSFP also had VBI. The mean TIMI frame count and LAD, Cx, and RCA TIMI frame counts were negatively correlated with the vertebral artery blood flow volume ($p<0.001$ for all). Table 2 and Figure 2 show the correlations among the variables. A mean TIMI frame count of 24.5 predicted VBI, with a sensitivity and specificity of 61.2% and 86.8%, respectively (area under the curve: 0.732, 95% confidence interval 65.2%-81.1%, $p<0.001$) (Figure 3).

The results of univariate logistic regression analysis revealed that the mean platelet volume and mean TIMI frame count were absolute predictors of VBI. The only predictor of VBI was the mean TIMI frame count (OR: 1.066, 95% confidence interval: 1.043–1.091, $P<0.001$). (Tables 3 and 4).

Discussion

Our results revealed that CSFP was associated with decreased vertebrobasilar blood flow volume and was an independent predictor of VBI, suggesting a common pathophysiological mechanism underlying both disorders.

Posterior circulation remains an important source of ischemic stroke, accounting for approximately 20% of cases [10]. Compared with patients who do not have vertebrobasilar occlusion, patients who have a transient ischemic attack or stroke and who have verebrobasilar occlusion are at substantial risk of recurrent stroke [11]. One study showed that a stenosis of more than 50% of the vertebral or basilar arteries was linked to a greater risk of stroke than a similar occlusion of the carotid arteries [12]. Subjects with symptomatic vertebrobasilar disease have one-year and five-year stroke-free survival rates of 67% and 48%, respectively [13]. As such, vertebrobasilar disease is a major cause of disability. Similarly, subjects with VBI tend to have high long-term morbidity and mortality, and because VBI is associated with nonspecific symptoms, it is usually an underdiagnosed condition [14].

Several pathophysiological mechanisms have been proposed for the development of CSFP. The coronary endothelium acts as a barrier between vascular tissue and plasma; in addition to vasodilation and contraction, it plays several important roles in regulating vascular tone, homeostasis and cellular adhesion [15]. In patients with CSFP, endothelium-dependent flow-mediated dilation is impaired, suggesting a role for endothelial dysfunction in the development of CSFP [16]. Vascular endothelial cells help maintain vascular tone by secreting vasoactive substances [17]. Nitric oxide, produced by endothelial nitric oxide synthase, is a potent vasodilator that regulates platelet activity, leukocyte adhesion and angiogenesis [18]. Studies have shown that patients with CSFP have significantly lower levels of plasma nitric oxide synthase, suggesting a link between endothelial dysfunction and CSFP [19, 20]. Inflammatory cytokines such as interleukins, tumor necrosis factor-α, C-reactive protein, and inflammatory biomarkers such as platelet-to-lymphocyte ratios and fibrinogen-to-albumin ratios were found to be increased in CSFP patients, suggesting that inflammation is involved in the pathogenesis of CSFP [21, 22]. These patients have elevated levels of inflammatory markers and abnormal hemorheologic properties, predisposing them to CSFP [23–26]. Beltrame et al. reported that CSFP is associated with increased coronary microvascular tone, confirming the role of microvascular abnormalities in this group of patients [27]. Patients with CSFP had coronary arteries with a normal appearance on coronary angiographic examination, but histopathologic examination of coronary arteries revealed small vessel abnormalities, including medial hypertrophy, endothelial degeneration and capillary damage [28]. In addition, functional abnormalities such as increased resistance of small coronary vessels have been reported [27, 29]. A combination of these mechanisms could lead to reduced myocardial blood flow and anginal symptoms. Several studies have demonstrated subclinical atherosclerotic involvement of the coronary arteries in this group of patients. Intravascular ultrasound of the coronary arteries revealed both epicardial atherosclerotic involvement and microvascular abnormalities [30, 31].

The evaluation of vertebral blood flow/velocity via Doppler sonography is a widely available and commonly used technique that provides important information regarding the hemodynamics of the vertebral arteries. It allows physicians to perform initial and serial assessments of the vertebral arteries. Acar et al. investigated Doppler vertebral artery blood flow volume to diagnose VBI. In their study, patients were divided

into three groups according to vertebral artery blood flow—severely attenuated flow volume, moderately attenuated flow volume, and normal flow volume—and vertebral artery blood flow volume measurements were more valuable than velocity measurements for the diagnosis of VBI [32]. In the present study, we evaluated vertebral blood flow via Doppler sonography and reported that TIMI frame counts were negatively correlated with vertebral artery blood flow volume. Our study highlights a common mechanism that affects more than just one vascular bed. Patients should therefore be followed up regularly, their risk factors should be treated, and emphasis should be placed on lifestyle changes.

Conclusion

Our results showed that patients who had CSFP had a greater incidence of VBI and that CSFP had good specificity for predicting VBI. Moreover, it was an absolute predictor of VBI. The TIMI frame count and vertebral artery blood flow volume were negatively correlated with each other. These findings suggest a common pathophysiological mechanism underlying both clinical conditions. Our results also revealed that the presence of CSFP indicates a more generalized phenomenon.

Limitations: We enrolled patients from a single center, and our study population was small. Patients were not followed longitudinally.

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References

1. Neto ACL, Bittar R, Gattas GS, Bor-Seng-Shu E, Oliverira ML, Monsanto RC, et al. Pathophysiology and Diagnosis of Vertebrobasilar Insufficiency: A Review of the Literature. *Int Arch Otorhinolaryngol.* 2017; 21(3): 302–307. https://doi.org/10.1055/s-0036-1593448.
2. Pirau L, Lui F. Vertebrobasilar Insufficiency. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing.* 2024.
3. Strek P, Reron E, Maga P, Modrzejewski M, Szybist N. A possible correlation between vertebral artery insufficiency and degenerative changes in the cervical spine. *Eur Arch Otorhinolaryngol*. 1998; 255:437–340. https://doi.org/10.1007/s004050050094.
4. Alvarez C, Siu H. Coronary slow-flow phenomenon as an underrecognized and treatable source of chest pain: case series and literature review. *J Investig Med High Impact Case Rep.* 2018; 6:1–5. Https://doi.org/10.1177/2324709618789194
5. Chalikias G, Tziakas D. Slow Coronary Flow: Pathophysiology, Clinical Implications, and Therapeutic Management. *Angiology*. 2021; 72(9): 808–818. https://doi.org/10.1177/00033197211004390.
6. Zhu Q, Wang S, Huang X, Zhao C, Wang Y, Li X, Jia D, Ma C. Understanding the pathogenesis of coronary slow flow: Recent advances. *Trends Cardiovasc Med.* 2024; 34(3): 137–144. https://doi.org/10.1016/j.tcm.2022.12.001.
7. Caiati C, Lacovelli F, Mancini G, Lepera ME. Hidden Coronary Atherosclerosis Assessment but Not Coronary Flow Reserve Helps to Explain the Slow Coronary Flow Phenomenon in Patients with Angiographically Normal Coronary Arteries. *Diagnostics (Basel)*. 2022; 12(9): 2173. https://doi.org/10.3390/diagnostics12092173.
8. Kern MJ, Moore JA, Aguirre FV, Bach RG, Caracciolo EA, Wolford T, Khoury AF, Mechem C, Donohue TJ. Determination of angiographic (TIMI grade) blood flow by intracoronary Doppler flow velocity during acute myocardial infarction. *Circulation*. 1996; 94(7): 1545–1552. https://doi.org/10.1161/01.cir.94.7.1545.
9. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. TIMI frame count: aquantitative method of assessing coronary artery flow. *Circulation*. 1996; 93: 879–888. https://doi.org/10.1161/01.cir.93.5.879.
10. Savits SI, Caplan LR. Vertebrobasilar disease. N Engl J Med. 2005; 352(25): 2618-2626. https://doi.org/10.1056/NEJMra041544.
11. Gulli G, Khan S, Markus HS. Vertebrobasilar stenosis predicts high early recurrent stroke risk in posterior circulation stroke and TIA. *Stroke*. 2009; 40 (8): 2732–2737. https://doi.org/10.1161/STROKEAHA.109.553859.
12. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. *Stroke*. 1998; 29(7): 1389–1392. https://doi.org/10.1161/01.str.29.7.1389.
13. Qureshi AI, Suri MFK, Ziai WC, Yahia AM, Mohammad Y, Sen S, Agarwal P, Zaidat OO, Suarez JI, Wityk RJ. Stroke-free survival and its determinants in patients with symptomatic vertebrobasilar stenosis: a multicenter study. *Neurosurgery*. 2003; 52(5): 1033–1040. https://doi.org/10.1227/01.NEU.0000057744.96295.9F.
14. Doss A, Phatouros CC. Vertebrobasilar insufficiency. *Curr Treat Options Cardio Med.* 2006; 8: 111–119. https://doi.org/10.1007/s11936-006-0003-0.
15. Zhang Q, Liu J, Duan H, Li R, Peng W, Wu C. Activation of Nrf2/HO-1 signaling: an important molecular mechanism of herbal medicine in the treatment of atherosclerosis via the protection of vascular endothelial cells from oxidative stress. *J Adv Res.* 2021; 34: 43–63. https://doi.org/10.1016/j.jare.2021.06.023.
16. Camsarl A, Pekdemir H, Cicek D, Polat G, Akkus MN, Doven O, et al.Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. *Circ J.* 2003; 67: 1022–1028. https://doi.org/10.1253/circj.67.1022.
17. Fleming I, Bauersachs J, Busse R. Paracrine functions of the coronary vascular endothelium. *Mol Cell Biochem.* 1996; 157: 137–145. https://doi.org/10.1007/BF00227892.
18. Ahmad A, Dempsey SK, Daneva Z, Azam M, Li N, Li PL, Ritter JK. Role of nitric oxide in the cardiovascular and renal systems. *Int J Mol Sci.* 2018; 19(9): 2605. https://doi.org/10.3390/ijms19092605.

19. Beltrame JF, Cutri N, Kopetz V, Tavella R. The role of nitric oxide in the coronary slow flow phenomenon. *Coron Artery Dis.* 2014; 25: 187–189. https://doi.org/10.1097/MCA.0000000000000112.
20. Sezgin N, Barutcu I, Sezgin AT, Gullu H, Turkmen M, Esen AM, Karakaya O. Plasma nitric oxide level and its role in slow coronary flow phenomenon. *Int Heart J.* 2005; 46(3): 373–382. https://doi.org/10.1536/ihj.46.373.
21. Kopetz V, Kennedy J, Heresztyn T, Stafford I, Willoughby SR, Beltrame JF. Endothelial function, oxidative stress and inflammatory studies in chronic coronary slow flow phenomenon patients. *Cardiology*. 2012; 121: 197–203. https://doi.org/10.1159/000336948.
22. Kayapinar O, Ozde C, Kaya A. Relationship between the reciprocal change in inflammation-related biomarkers (Fibrinogen-to-albumin and hsCRP-to-albumin ratios) and the presence and severity of coronary slow flow. *Clin Appl Thromb Hemost.* 2019; 25: 1076029619835383. https://doi.org/10.1177/1076029619835383.
23. Li JJ, Qin XW, Li ZC, Zeng HS, Gao Z, Xu B, Zhang CY, Li J. Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. *Clin Chim Acta.* 2007; 385: 43–47. https://doi.org/10.1016/j.cca.2007.05.024.
24. Turhan H, Saydam GS, Erbay AR, Ayaz S, Yasar AS, Aksoy Y, Basarc N, Yetkin E. Increased plasma soluble adhesion molecules; ICAM-1, VCAM-1, and E-selectin levels in patients with slow coronary flow. *Int J Cardiol.* 2006; 108: 224–230. https://doi.org/10.1016/j.ijcard.2005.05.008.
25. Gökçe M, Kaplan S, Tekelioğlu Y, Erdoğan T, Küçükosmanoğlu M. Platelet function disorder in patients with coronary slow flow. *Clin Cardiol.* 2005; 28: 145–148. https://doi.org/10.1002/clc.4960280310.
26. Cetin MS, Ozcan Cetin EH, Canpolat U, Aydın S, Temizhan A, Topaloglu S, Aras D, Aydogdu S. An overlooked parameter in coronary slow flow phenomenon: whole blood viscosity. *Biomark Med.* 2015; 9: 1311–1321. https://doi.org/10.2217/bmm.15.92.
27. Beltrame JF, Limaye SB, Wuttke RD, Horowitz JD. Coronary hemodynamic and metabolic studies of the coronary slow flow phenomenon. Am Heart J. 2003; 146: 84–90. https://doi.org/10.1016/S0002-8703(03)00124-8.
28. 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: 964–972. https://doi.org/10.1161/01.cir.74.5.964.
29. Fineschi M, Bravi A, Gori T. The “slow coronary flow” phenomenon: evidence of preserved coronary flow reserve despite increased resting microvascular resistances. *Int J Cardiol.* 2008; 127: 358–361. https://doi.org/10.1016/j.ijcard.2007.06.010.
30. Cin VG, Pekdemir H, Camsar A, Ciçek D, Akkus MN, Parmaksız T, Katýrcýbaºý T, Döven O. Diffuse intimal thickening of coronary arteries in slow coronary flow. *Jpn Heart J.* 2003; 44: 907–919. https://doi.org/10.1536/jhj.44.907.
31. Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus N, Döven O, Parmaksiz HT. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. *Acta Cardiol.* 2004; 59: 127–133. https://pubmed.ncbi.nlm.nih.gov/15139652/. https://doi.org/10.2143/AC.59.2.2005166.
32. Acar M, Degirmenci B, Yucel A, Albayrak R, Haktanır A, Yaman M. Comparison of vertebral artery velocity and flow volume measurements for diagnosis of vertebrobasilar insufficiency using color duplex sonography. *Eur J Radiol.* 2005; 54(2): 221–224. https://doi.org/10.1016/j.ejrad.2004.06.017.