Association of slow coronary flow phenomenon with abnormal heart rate recovery

Yavaş koroner akım fenomeninin bozulmuş kalp hızı toparlanması ile ilişkisi

Göknur Tekin, M.D., Abdullah Tekin, M.D., Alpay Turan Sezgin, M.D., Fatma Yiğit, M.D., Şenol Demircan, M.D., Tansel Erol, M.D., Haldun Müderrisoğlu, M.D.

Department of Cardiology, Faculty of Medicine, Başkent University, Adana

Objectives: Heart rate recovery (HRR) at 1 minute after peak exercise is a measure of vagal reactivation and is considered a marker of parasympathetic activity. Blood pressure recovery index at 3 minutes (BPRI3) might reflect sympathetic activity. We aimed to assess HRR at 1 minute and BPRI3 in an attempt to determine parasympathetic and sympathetic activity in patients with slow coronary flow (SCF).

Study design: The study included 24 patients (19 males, 5 females; mean age 51±7 years) with angiographically diagnosed SCF using the Thrombolysis in Myocardial Infarction (TIMI) frame-count method. Heart rate recovery was calculated as the difference between the heart rate at peak exercise and heart rate at the relevant minute of recovery. Blood pressure recovery indexes were defined as the ratios of recovery systolic blood pressures at 1, 2, and 3 minutes to the systolic blood pressure at peak exercise. The results were compared with those of 26 age- and sex-matched subjects (19 males, 7 females; mean age 52±8 years) with normal flow.

Results: Patients with SCF had significantly lower HRRs at 1 minute (19±4 *vs* 25±6 beats/min; p<0.001) and 2 minutes (36±9 *vs* 44±13 beats/min; p=0.042) compared to controls with normal coronary flow. Blood pressure recovery index at 3 minutes was not significantly different between the two groups (0.81±0.07 *vs* 0.84±0.12; p=0.440).

Conclusion: Attenuation in HRR at 1 minute suggests the presence of reduced vagal tone in patients with SCF. Decreased vagal activity may contribute to the mechanisms responsible for SCF.

Key words: Blood flow velocity; coronary circulation; exercise test; heart rate/physiology; vagus nerve/physiology.

Amaç: Egzersiz sonrası birinci dakikadaki kalp hızı toparlanması (KHT) büyük ölçüde vagal reaktivasyonun bir göstergesidir ve parasempatik sistemin bir belirteci olarak kabul edilmektedir. Üçüncü dakika kan basıncı toparlanma indeksi (KBTİ3) ise sempatik aktiviteyi yansıtabilir. Bu çalışmada, yavaş koroner akımlı hastalarda birinci dakikadaki KHT ve KBTİ3 saptanarak hastaların parasempatik ve sempatik aktiviteleri belirlenmeye çalışıldı.

Çalışma planı: Çalışmada anjiyografik olarak TIMI (Thrombolysis in Myocardial Infarction) kare sayısı yöntemiyle yavaş koroner akım tanısı konan 24 hasta (19 erkek, 5 kadın; ort. yaş 51±7) incelendi. Kalp hızı toparlanması, pik egzersizdeki kalp hızından toparlanma döneminde ilgili dakikadaki kalp hızı çıkartılarak hesaplandı. Kan basıncı toparlanma indeksleri, toparlanma süresinin 1, 2 ve 3. dakikalarındaki sistolik kan basıncının pik egzersizdeki sistolik kan basıncına bölünmesiyle elde edildi. Sonuçlar koroner akımı normal bulunan, yaş ve cinsiyet uyumlu 26 olgunun (19 erkek, 7 kadın; ort. yaş 52±8) sonuçlarıyla karşılaştırıldı.

Bulgular: Yavaş koroner akımlı hasta grubunda birinci (19±4 ve 25±6 vuru/dakika; p<0.001) ve ikinci dakika (36±9 ve 44±13 vuru/dakika; p=0.042) KHT değerleri normal akımlı kontrol grubuna göre anlamlı derecede düşük bulundu. İki grubun KBTİ3 değerleri arasındaki farklılık ise anlamlı değildi (0.81±0.07 ve 0.84±0.12; p=0.440).

Sonuç: Birinci dakikadaki KHT'de gözlenen düşüş, yavaş koroner akımlı hastalarda vagal tonusun zayıfladığına işaret etmektedir. Azalmış vagal aktivite yavaş koroner akımdan sorumlu mekanizmada rol oynayabilir.

Anahtar sözcükler: Kan akım hızı; koroner dolaşım; egzersiz testi; kalp hızı/fizyoloji; vagus siniri/fizyoloji.

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Correspondence: Dr. Göknur Tekin. Dadaloğlu Mahallesi, 39. Sok., No. 6, 01250 Adana.
Tel: 0322 - 327 27 27 Faks: 0322 - 327 12 76 e-mail: goknurtek@yahoo.com

Slow coronary flow (SCF) characterized by slow antegrade progression of a dye to the distal branch of a coronary artery in the absence of obstructive coronary disease is not an infrequent finding during routine coronary arteriography. Slow flow of dye in epicardial coronary arteries was first defined by Tambe et al.,[1] and since then, a number of studies regarding the etiology, clinical manifestations, and treatment of this phenomenon have been published. Although histopathologic studies have shown capillary and endothelial damage in these patients,[2] the precise pathophysiological mechanism of slow coronary phenomenon remains uncertain. Beltrame et al.[3] showed increased resting coronary vasomotor tone in coronary resistance vessels in patients with SCF. Coronary vasomotor tone is under the regulation of mechanical forces, metabolic factors, and is also significantly modulated by autonomic nervous system.[4]

Heart rate recovery (HRR) at 1 minute after peak exercise is mainly a measure of vagal reactivation that occurs in response to cessation of exercise and is considered a marker of parasympathetic activity.[5] Blood pressure recovery index at 3 minutes (BPRI3) might reflect sympathetic activity.[6]

This study was designed to assess HRR at 1 minute and BPRI3 in an attempt to determine parasympathetic and sympathetic activity in patients with SCF.

PATIENTS AND METHODS

Study population. For this prospective study, 24 patients (19 males, 5 females; mean age 51±7 years) with angiographically diagnosed SCF were enrolled. All patients underwent coronary angiography for the evaluation of chest pain. Exclusion criteria included one or more of the following diseases or associated conditions: evidence for obstructive coronary artery disease, coronary ectasia, myocardial bridge, major coronary spasm, myocardial and/or valvular heart disease, atrial fibrillation, bundle branch block, connective tissue disorder, uncontrolled hypertension, or any other systemic disease except for diabetes mellitus. A negative result on the exercise test was required in order to distinguish SCF from cardiac syndrome X. A control group was comprised of 26 age- and sex-matched subjects (19 males, 7 females; mean age 52±8 years) with normal coronary flow. All the participants gave written informed consent.

Exercise testing. All the subjects underwent a symptom-limited exercise tolerance test according to the modified Bruce protocol (Quinton Treadmill system, Quinton, Inc., Bothell, WA, USA). The subjects were encouraged to continue exercise until they experienced limiting symptoms. During each exercise stage and at every minute within three minutes after recovery, blood pressure, heart rate, and cardiac rhythm were recorded. Following peak exercise, the subjects were asked to walk for a 2-minute cool-down period at 1.5 mph on a 2.5% grade. Heart rate recovery was calculated as the difference between the heart rates at peak exercise and at the relevant minute of recovery. For instance, HRR at 1 minute was defined as the difference between the heart rates at peak exercise and at 1 minute of the recovery cool-down period. Metabolic equivalents were calculated from the treadmill speed and the grade at peak exercise according to a standard nomogram.[7] A mercury sphygmomanometer was used to measure blood pressure. Blood pressure recovery indexes were defined as the ratios of the systolic blood pressure at 1, 2, and 3 minutes of recovery to the systolic blood pressure at peak exercise. Subjects receiving anti-ischemic drugs were instructed to discontinue these medications for 72 hours before the test.

Documentation of slow coronary flow. Selective coronary angiography was routinely performed without the use of nitroglycerin in all the subjects using the Judkins technique. Left ventriculography was performed and ejection fraction was calculated. Slow coronary flow was diagnosed using the Thrombolysis in Myocardial Infarction (TIMI) frame-count method.[8] The TIMI frame-count (TFC) method is a simple, reproducible, objective, quantitative index of coronary flow velocity. Coronary flow was quantified objectively by two independent observers using the corrected TFC (CTFC) method. These examiners were blinded to the clinical details of each subject. Any disagreement was resolved by a third observer. The first frame used for counting was the first frame in which the dye fully entered the artery. The last frames used for the left anterior descending artery (LAD), circumflex artery (Cx), and right coronary artery (RCA) were the frames in which the dye first entered the mustache segment, distal bifurcation segment, and the first branch of the posterolateral artery, respectively. Specifically, to identify the last frame we first ran the cine film past the point of initial opacification of the endpoint branch, and then reversed it frame by frame until the endpoint branch disappeared. Once this location was identified on the film, the frame count for each artery was determined by subtracting the

Table 1. Baseline characteristic of the patients with slow coronary flow (SCF) and the control group

	Patients with SCF (n=24)			Controls (n=26)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			51±7			52±8	0.53
Female	5	20.8		7	26.9		0.23
Hypertension	8	33.3		12	46.2		0.24
Hyperlipidemia	14	58.3		14	53.9		0.78
Diabetes mellitus	6	25.0		5	19.2		>0.99
Smoking	8	33.3		7	26.9		0.76
Body mass index (kg/m^2)			31±5			30±4	0.70

number of the first frame from the number of the last frame.

The normal frame counts for LAD are 1.7 times greater than the mean values for Cx and RCA. Hence, the longer LAD frame counts were divided by 1.7 to derive the corrected CTFC as described previously.[8] We calculated the mean CTFC for each patient and control subject by adding the CTFCs for the LAD, Cx and RCA, and then dividing the sum by 3. Frame counts greater than 2 standard deviations of the overall CTFC for the control group were considered to indicate SCF. All CTFCs were determined from matched projections using Medcon Telemedicine Technology (version 1.900, Tel Aviv, Israel).

Statistical analyses. The variables were expressed as means ± standard deviation (SD) for continuous data, and as proportions for categorical data. Continuous variables with and without normal distribution were analysed by the unpaired t-test and Mann-Whitney U-test, respectively. The Kolmogorov-Smirnov test was used to identify whether continuous variables were normally distributed. Categorical parameters were analysed by the chi-square test or Fischer's exact test whichever appropriate. Two-sided *p* values of less than 0.05 were considered significant. Multiple logistic regression analysis was performed using a forward stepwise procedure. All statistical analyses were performed using SPSS 9.0 for Windows.

RESULTS

Baseline clinical characteristics of the study population are presented in Table 1. There were no statistically significant differences between the two groups with respect to clinical characteristics.

In all the patients, slow flow was detected in three major epicardial vessels, and the CTFCs for three major epicardial coronary arteries were significantly greater than 2 standard deviations of the corresponding means of the control group (p<0.001; Table 2). The mean coronary artery diameters in the SCF group were significantly greater than the corresponding means of the control group (p=0.041 for LAD; p=0.01 for Cx; p<0.001 for RCA). Multiple logistic regression analyses showed a significant association between the mean coronary artery diameter and the mean TIMI frame count (p=0.004, 95% CI 1.61-11.87). No complications developed during coronary angiography, and all the subjects had an ejection fraction within the normal range.

Exercise test findings are presented in Table 3. Patients with SCF had significantly lower HRRs at 1 minute (19±4 *vs* 25±6 beats/min; p<0.001) and 2 minutes (36±9 *vs* 44±13 beats/min; p=0.042) compared to controls with normal coronary flow. Blood pressure recovery indexes at 1, 2, and 3 minutes were not significantly different between the two groups.

Table 2. Coronary artery diameters and TIMI frame counts (mean±SD)

	Patients with SCF	Controls	*p*
Corrected TIMI frame count			
Left anterior descending artery	23±7	8±3	<0.001
Left circumflex artery	18±8	10±3	<0.001
Right coronary artery	20±8	10±5	<0.001
Mean	20±6	9±2	<0.001
Diameters (mm)			
Left anterior descending artery	4.2±1.0	3.7±0.7	0.041
Left circumflex artery	3.8±0.8	3.2±0.6	0.011
Right coronary artery	3.7±0.6	3.0±0.7	<0.001

Table 3. Exercise test findings (mean±SD)

	Patients with SCF	Controls	*p*
Resting heart rate (beat/min)	89±16	88±17	0.799
Peak heart rate (beat/min)	164±11	163±11	0.634
Heart rate (beat/min)			
at 1min of recovery	145±11	138±12	0.104
at 2 min of recovery	129±12	119±15	0.046
at 3 min of recovery	117±10	108±16	0.075
at 5 min of recovery	106±9	98±15	0.129
Heart rate recovery (beat/min)			
at 1 min	19±4	25±6	<0.001
at 2 min	36±9	44±13	0.042
at 3 min	48±9	54±13	0.223
at 5 min	58±12	64±15	0.195
Resting systolic blood pressure (mmHg)	124±15	128±15	0.444
Peak systolic blood pressure (mmHg)	177±18	173±15	0.642
Systolic blood pressure			
at 1 min of recovery (mmHg)	173±20	174±24	0.853
at 2 min of recovery (mmHg)	159±17	161±26	0.423
at 3 min of recovery (mmHg)	144±15	146±26	0.796
Blood pressure recovery index			
at 1 minute	0.97±0.05	1.00±0.09	0.539
at 2 minute	0.89±0.05	0.92±0.11	0.420
at 3 minute	0.81±0.07	0.84±0.12	0.440
Metabolic equivalents	11.2±1.9	11.8±1.4	0.381

DISCUSSION

The demonstration of attenuated HRR at 1 minute suggests the presence of reduced vagal tone in patients with SCF. This study has found normal blood pressure recovery index at 3 minutes, implying normal sympathetic activity in these patients.

Proper control of coronary blood flow is very important for the maintenance of cardiac pump function, cardiac output, and arterial pressure. Myocardial perfusion depends on control of coronary resistance in both healthy subjects and those with coronary artery disease. If a coronary stenosis is critical, resistance is regulated at the site of the stenotic segment rather than in the downstream resistance vessels, since the narrowed arterial segment is the dominant resistance in the coronary circuit.[4] However, under normal conditions or under conditions where a stenosis is not appreciated as in SCF, coronary flow is regulated by the tone of coronary arterioles.[4] The tone of coronary arterioles is regulated by some factors in which autonomic nervous system plays a significant role. Parasympathetic stimulation or its neurotransmitter acetylcholine increase coronary blood flow in arteries with no or minimal lesion.[4,9,10] Sympathetic neural stimulation and the release of epinephrine and norepinephrine, on the other hand, can produce modest coronary constriction under normal physiological conditions.[4,11] Thus, reduced cardiac vagal tone demonstrated by this study may contribute to the pathogenesis of SCF.

The mechanism of an imbalance between vasoconstrictor and vasodilatatory factors was previously proposed for slow coronary flow phenomenon.[12-14] Studies showed an imbalance between endothelin-1 and nitric oxide release in patients with SCF as compared to controls with normal flow.[12] In the early phase of atherosclerosis or in the presence of intensive coronary disease risk factors, vasodilatation capacity of coronary resistance arterioles to pharmacological and physical stress has been shown to be disturbed before development of angiographic atherosclerotic disease.[15] Pekdemir et al.[16] showed diffuse calcification and intimal thickening in all segments of the vessels despite the absence of focal stenosis or plaques in these patients. Sezgin et al.[17] also demonstrated impaired vascular endothelial function in patients with SCF. Thus, in some patients, SCF may be an early sign of atherosclerosis, leading to imbalances between vasoconstriction and vasodilatation properties of arterioles.

The exact cellular mechanism of our observation of reduced vagal tone in SCF is not known. However, there is a plausible hypothesis that this might be due

to an insulin-resistant state in SCF. In a recently published article, Binak et al.[18] examined the relationship between impaired glucose tolerance and SCF. They suggested that impaired glucose tolerance might be an independent etiological factor for SCF. In addition, Turhan et al.[19] detected higher TIMI frame counts, indicating impaired coronary blood flow in patients with metabolic syndrome, the condition in which the insulin-resistant state prevails. Lind and Andren[20] showed that insulin sensitivity was correlated with HRR. Rissanen et al.[21] also showed that cardiac vagal tone was negatively associated with insulin resistance. Thus, insulin-resistant state might have a role in attenuation of HRR at 1 minute in patients with SCF.

Our findings may have some clinical implications. We previously showed in diabetic patients that attenuated HRR at 1 minute could be improved by a statin and an angiotensin converting enzyme inhibitor.[22,23] Hence, the role of insulin sensitizers, statins, and angiotensin converting enzyme inhibitors may be further appraised in future studies evaluating medical treatment of these patients.

Study limitations. Although there is ample evidence supporting HRR at 1 minute as a marker of parasympathetic activity, data suggesting BPRI3 as an indicator of sympathetic activity are scarce.[6] Moreover, there is no technique that can be viewed as a 'gold standard' in assessing human adrenergic function.[24] Nevertheless, we have shown that HRR values are significantly lower only at 1 and 2 minutes in patients with SCF. Since early decrease in heart rate after cessation of exercise is mainly due to vagal reactivation and late decrease occurs by sympathetic withdrawal,[5] our findings suggest that only the parasympathetic system is abnormal in patients with SCF. Several tests are available for the assessment of autonomic function. Heart rate variability with deep inspiration, heart rate response to a Valsalva maneuver or to a postural change, and power spectral analysis are some examples of tests of cardiovagal function.[25] The use of these tests along with HRR could have provided us with further evidence to support our findings. Blood pressures were measured using an indirect arm-cuff sphygmomanometer, which might have yielded inaccurate results, particularly during exercise.[26] Physical activity may increase parasympathetic tone. A standardized assessment of physical activity was not utilized in this study, though both groups exhibited similar exercise capacity and physical activity.

In conclusion, this is the first report that suggests diminished vagal activity, as assessed by HRR at 1 minute in patients with SCF. Further research is needed to support our findings and clarify the responsible mechanisms.

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