Journal of Cardiology 61 (2013) 138–143

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Plasma homocysteine is associated with ischemic findings without organic stenosis in patients with slow coronary flow

Mustafa Yurtdaş (MD)[a,*], İsmail Turkay Özcan (MD)[b], Ali Sabri Seyis (MD)[c], Ahmet Çamsarı (MD)[b], Dilek Çiçek (MD)[b]

[a] Lokman Hekim Hospital, Department of Cardiology, Van, Turkey
[b] Mersin University, Department of Cardiology, Mersin, Turkey
[c] Medical Park Hospital, Department of Cardiology, Mersin, Turkey

ARTICLE INFO

Article history:
Received 25 May 2012
Received in revised form 5 August 2012
Accepted 10 October 2012
Available online 16 November 2012

Keywords:
Slow coronary flow
Exercise
Homocysteine
Angina
ST depression

ABSTRACT

Aim: To investigate the plasma concentrations of homocysteine (Hcy) in slow coronary flow (SCF) patients before and at the end of the exercise test and compare with the values of healthy controls.
Methods: Study population consisted of 41 patients with SCF [68% men, aged 49 ± 8 years], and 41 subjects with normal epicardial coronary arteries [56% men, aged 50 ± 9 years]. Exercise test was performed in all study participants. Blood samples were drawn at rest and immediately at the end of exercise testing after 12 h of overnight fasting.
Results: The baseline Hcy value of the SCF patients was higher than that of the control subjects ($p < 0.0001$), and this difference continued after exercise test between the groups ($p < 0.0001$). Median post-exercise increases in Hcy levels were higher in the SCF group than in the control group, without a significant difference ($p = 0.088$). In the SCF group after exercise, Hcy levels in 17 patients with angina and 18 patients with ST depression were higher than those without angina and ST depression ($p < 0.0001$ and $p < 0.0001$, respectively). In addition, Hcy values in patients with both angina and ST depression were greater than those with either angina ($p < 0.05$) or ST depression ($p < 0.05$).
Conclusion: The results of this study show that there is an important pathophysiologic link between the increased levels of plasma Hcy, the degree of ischemic findings, and the severity of slow flow in SCF patients.

Introduction

Slow coronary flow (SCF) is an angiographic finding characterized by the slow movement of contrast throughout the coronary lumen in the absence of epicardial coronary obstructive disease. Since its first description, although a number of factors such as endothelial, vasomotor, and microvascular dysfunction, and diffuse coronary atherosclerosis and increased platelet activity have been responsible for SCF [1–8], its etiopathogenesis is still not fully elucidated.

Homocysteine (Hcy) is a sulfhydryl-containing amino acid that might give rise to endothelial damage and generate free radicals that induce oxidative damage and stress. Hyperhomocysteinemia has been determined as emerging independent risk factor for cardiovascular system and related diseases [9–12].

In this study, we aimed to assess the plasma Hcy levels of SCF patients before and after very short time exercise, and compared with those of controls. As far as we know, there is no study investigating the plasma Hcy levels both at baseline and post-exercise in SCF patients.

Materials and methods

Study population

Among 2397 coronary angiograms performed between February 2011 and March 2012 at cardiology clinics of Lokman Hekim Hospital and Mersin University by reason of suspected coronary artery disease, 217 (9.1%) had normal epicardial coronary arteries, i.e. showing no evidence of any coronary stenosis, spasm, and ectasia. Physical examination and medical history were assessed. Echocardiographic and electrocardiographic analyses were performed on all 217 patients. Patients with valvular heart and/or myocardial disease, systolic and/or diastolic dysfunction, left ventricular hypertrophy and enlargement detected by the echocardiographic data were excluded from the study. Patients

* Corresponding author at: Lokman Hekim Van Hastanesi, Kardiyoloji Bölümü, 65200 Van, Turkey. Tel.: +90 432 214 68 68; fax: +90 432 212 10 08.
E-mail address: mustafayurtdas@yahoo.com (M. Yurtdaş).

0914-5087/$ – see front matter
http://dx.doi.org/10.1016/j.jjcc.2012.10.001

who suffered from one of the following diseases or related disorders were also excluded: those with a history of acute coronary syndrome, acute myocardial infarction, percutaneous coronary intervention, and coronary artery bypass graft surgery, arrhythmia, renal dysfunction, connective tissue disease, thyroid disorders, and other systemic diseases, and those contraindicated for exercise testing. SCF was determined in 41 of the 217 patients. The control group, consisting of 41 subjects matched for demographic characteristics, was selected in a consecutive manner from the catheterized patients without exclusion criteria during the same study period. All control subjects, who were proved to have normal epicardial coronary arteries without SCF, had normal exercise and echocardiographic parameters. After signed informed consent was obtained, all concomitant medications, which may affect both results of the exercise test and Hcy levels such as beta blockers and lipid-lowering drugs, were discontinued for at least 30 days before the test. The trial was performed according to the principles of the Declaration of Helsinki and approved by the Investigational Review Board of Mersin University, School of Medicine.

Thrombolysis in myocardial infarction frame count

Coronary flow rates of the all subjects were determined by the thrombolysis in myocardial infarction (TIMI) frame count (TFC) method. The coronary TFCs were calculated separately for each major coronary artery and their average was determined as the mean TFC for each subject according to the method described by Gibson et al. [13]. Due to different durations required for normal visualization of coronary arteries, the corrected cut-off values were 36.2 ± 2.6 frames for left anterior descending coronary artery, 22.2 ± 4.1 frames for left circumflex artery, and 20.4 ± 3 frames for right coronary artery, as has been reported in the literature. The subjects with a TFC greater than 2 standard deviations (SD) from these thresholds for the particular vessel were accepted as having SCF in the present study. All TFCs were measured in matched projections using Siemens Medical Solution (version Artis zee, Erlangen, Germany).

Exercise treadmill testing

The 12-leads maximal exercise test was carried out using standard graduated treadmill protocols consistent with American Heart Association (AHA) guidelines [14]. Patients were encouraged to give their maximal effort, but not to allow their angina to reach levels higher than previously experienced. The results were analyzed and reported using a computerized database (EXTRA; Mosby Publishers; Chicago, IL, USA) [15]. The ST segment response considered was the most horizontal or downsloping ST-segment depression in any lead, except aVR, during exercise or recovery. An abnormal response was defined as $\geq$0.1 mV at 0.08 s after the J point of horizontal or downsloping ST-segment depression and angina (pain felt as pressure, heaviness, and squeezing across the chest) during exercise or recovery.

Laboratory analysis

All blood samples were drawn after 12 h of overnight fasting for total cholesterol (TC), triglyceride (TG), high-density lipoprotein–cholesterol (HDL-C), complete blood count (CBC), and creatinine. Assays for TC, TG, HDL-C, and creatinine were performed using a Cobas Integra 800 automated analyzer (Roche Diagnostics, Mannheim, Germany). Assays for CBC were carried out using a Coulter LH 750 analyzer (Beckman Coulter, Galway, Ireland). The serum low-density lipoprotein–cholesterol (LDL-C) was calculated according to Friedewald's formula [16]. The glomerular filtration rate (GFR) was estimated as a function of age, serum creatinine, and race using the simplified Modified Diet in Renal Disease (MDRD) equation [eGFR ($mL/min/1.73\,m^2$) = $186.3 \times creatinine^{-1.154} \times age^{-0.203} \times (0.742$ if female)] [17].

Analysis of homocysteine levels

Blood samples for Hcy were drawn from the forearm vein at rest and immediately after the end of exercise testing. After centrifugation, the obtained plasma was stored at −20 °C. Plasma Hcy levels were determined by using reagent kit for high-performance liquid chromatography (HPLC) analysis of Hcy in serum/plasma (Chromosystems GmbH, Munich, Germany). Analyses were performed with isocratic HPLC system with fluorescence detector (HP 1100). The HPLC condition for Hcy: injection volume: 20 μl, flow rate: 1.7 mL/min, room temperature 25 °C, wavelength: EX 385, EM, 515. High plasma Hcy concentrations were accepted as >12 μmol/L [11].

Statistical analysis

Continuous variables were expressed as means ± SD. Categorical variables were expressed as percentage. The distribution of variables in both groups was assessed by the Kolmogorow–Smirnov test. To compare the two groups according to changes after the exercise in the variables that exhibit normal distribution and according to measurements before and after exercise, independent *t*-test was used. In contrast, for the variables that do not show normal distribution, Mann–Whitney *U* test was used. Also in the patients according to these measurements for comparison of that with angina and no angina; and also for comparison of those with ST segment depression and without ST depression, independent *t*-test was used. Paired *t*-test was used to determine the significance of changes observed before and after exercise in both patients and controls. ANOVA was used to compare more than two groups. Post hoc Tukey test was used when the ANOVA found a significant effect. Pearson and Sperman correlation analyses were used for the assessment of relation between variables in both groups. All hypothesis testing was 2-tailed. *p*-Values of <0.05 were regarded as significant. Statistical analysis was performed using SPSS software package (Version 15.0, SPSS Inc, Chicago, IL, USA).

Results

The clinical characteristics, risk factors, CBC, and TFC of both groups are delineated in Table 1. There were no statistically significant differences between the two groups in terms of clinical characteristics and risk factors. TFC was significantly higher in patients with SCF than in control subjects. SCF was detected to affect left anterior descending artery the most (82.9%), followed by right coronary artery (53.7%) and circumflex (51.2%). SCF was observed to have a tendency to affect two vessels (43.9%) or one vessel (34.1%), whereas three-vessel involvement was less common (22%) (Table 1). Plasma baseline Hcy levels of patients with SCF were found to be significantly higher than those of control subjects (14.9 ± 4.0 μmol/L vs 6.5 ± 4.8 μmol/L; $p < 0.0001$, respectively) (Table 2). Post-exercise plasma Hcy levels of SCF patients were also higher (16.4 ± 4.9 μmol/L vs 7.1 ± 5.2 μmol/L; $p < 0.0001$). The highest Hcy level was determined in patients with SCF in all of 3 coronary arteries both at baseline and post-exercise, when compared to that of the controls, one-vessel, and two-vessel SCF patients (Table 2) (ANOVA $p < 0.05$ vs control, $p < 0.05$ vs one-vessel SCF, and $p < 0.05$ vs two-vessel SCF, respectively). There was no significant difference for Hcy level between the one-vessel and two-vessels both at baseline and post-exercise in SCF patients ($p > 0.05$). Moreover, the number of vessels with slow flow was

Table 1
Baseline clinical characteristics, risk factors, laboratory findings, and TIMI frame counts of both groups.

	Controls ($n=41$)	SCF ($n=41$)	p
Age (year)	50 ± 9	49 ± 8	NS
Female gender, n (%)	18(44%)	13(32%)	NS
Hypercholesterolemia, n (%)	18(44%)	19(46%)	NS
Total cholesterol (mg/dL)	202 ± 15	203 ± 16	NS
HDL-cholesterol (mg/dL)	44 ± 8	43 ± 9	NS
LDL-cholesterol (mg/dL)	122 ± 16	123 ± 17	NS
Triglyceride (mg/dL)	179 ± 23	183 ± 28	NS
Hypertension, n (%)	16(39%)	16(39%)	NS
Systolic blood pressure (mmHg)	135 ± 17	132 ± 20	NS
Diastolic blood pressure (mmHg)	80 ± 10	82 ± 11	NS
BMI (kg/m^2)	26.1 ± 4.7	27.4 ± 5.4	NS
Cigarette smoking, n (%)	15(37%)	12(29%)	NS
Diabetes mellitus, n (%)	6(15%)	5(12%)	NS
Family history, n (%)	7(17%)	9(22%)	NS
Creatinine (mg/dL)	0.91 ± 0.19	0.87 ± 0.18	NS
eGFR (mL/min/1.73 m^2)	83.8 ± 31.9	92.0 ± 30.2	NS
Red blood cells (millions/mm^3)	5.4 ± 0.5	5.6 ± 0.6	NS
White blood cells (10^3/mm^3)	7.8 ± 1.2	8.2 ± 1.3	NS
Platelets (10^3/mm)	226 ± 53	244 ± 65	NS
Hemoglobin (g/dL)	13.6 ± 1.4	14.1 ± 1.6	NS
Hematocrit (%)	43.8 ± 4.8	44.9 ± 5.3	NS
TIMI frame count			
LAD	27 ± 4	50 ± 12	<0.0001
LCx	24 ± 3	38 ± 13	<0.0001
RCA	22 ± 3	37 ± 12	<0.0001
Mean TIMI frame count	24 ± 2	42 ± 7	<0.0001
Distribution of slow flow			
LAD, n (%)		34(82.9%)	
LCx, n (%)		21(51.2%)	
RCA, n (%)		22(53.7%)	
Number of slow flow arteries			
One vessel, n (%)		14(34.1%)	
Two vessels, n (%)		18(43.9%)	
Three vessels, n (%)		9(22.0%)	

SCF, slow coronary flow; NS, non-significant; TIMI, thrombolysis in myocardial infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; eGFR, estimated glomerular filtration rate; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

Table 2
Pre-exercise and post-exercise plasma homocysteine levels of both groups.

	Controls ($n=41$)	Slow coronary flow (SCF)			
		1-V ($n=14$)	2-V ($n=18$)	3-V ($n=9$)	Total ($n=41$)
Homocysteine (μmol/L)					
Pre-exercise	6.5 ± 4.8	13.1 ± 3.3*	13.9 ± 3.1*	19.4 ± 3.2*,†	14.9 ± 4.0¶,*
Post-exercise	7.1 ± 5.2	14.9 ± 4.0*	15.0 ± 4.7*	21.4 ± 4.1*,†,§	16.4 ± 4.9¶,*,§
Median increase (Δ)	0.6 ± 2.2	1.9 ± 3.5	1.1 ± 2.5	2.1 ± 2.4	1.5 ± 2.6

1-V, one-vessel involvement; 2-V, two-vessel involvement; 3-V, three-vessel involvement in SCF group.
¶ $p<0.0001$; SCF patients (total) vs controls (independent t-test).
* $p<0.05$; SCF patients (all subgroups and total) vs controls (ANOVA).
† $p<0.05$; SCF patients subgroup 3-V vs 1-V, and vs 2-V (ANOVA).
§ $p<0.05$; SCF patients (subgroup 3-V and total) vs pre-exercise (paired t-test).

positively correlated with both pre- and post-exercise plasma levels of Hcy in the SCF group ($r=0.489$, $p<0.01$; $r=0.419$, $p<0.01$, respectively). Median post-exercise increases (ΔHcy) in plasma Hcy level in the SCF group tended to be higher than those of the control group (ΔHcy: 1.5 ± 2.6 μmol/L vs 0.6 ± 2.2 μmol/L; $p=0.088$, respectively) (Table 2), but the result was not statistically significant. Exercise test was stopped because of only angina in 5 SCF patients, only ST segment depression in 6 SCF patients, and both angina and ST depression in 12 SCF patients. Control subjects completed the whole protocol and none showed

Table 3
Exercise parameters of both groups.

	Controls ($n=41$)	SCF ($n=41$)	p-Value
Baseline heart rate (beats/min)	75 ± 8	74 ± 10	NS
Peak exercise heart rate (beats/min)	177 ± 8	160 ± 13	<0.0001
Peak systolic blood pressure (mmHg)	188 ± 11	178 ± 12	=0.001
Rate–pressure product [(mmHg × beats/min)] × 10^2	332 ± 21	286 ± 30	<0.0001
Only angina, n (%)	–	5 (12%)	–
Only ST depression, n (%)	–	6 (15%)	–
Both angina and ST depression, n (%)	–	12 (29%)	–

SCF, slow coronary flow.

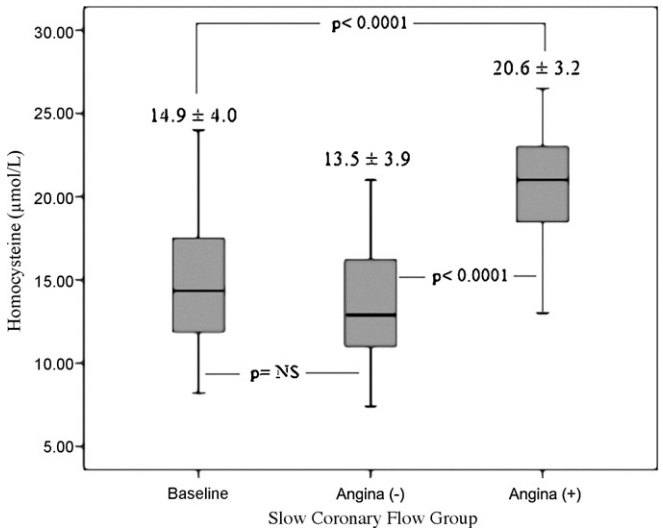

Fig. 1. Comparison of homocysteine levels at baseline, and after exercise in patients with and without angina in the slow coronary flow group.

ST-segment changes, tachyarrhythmias, or angina throughout the procedure. Peak exercise heart rate, peak exercise systolic blood pressure, and rate–pressure product were significantly higher in the control group than in the SCF group. The exercise parameters of the two groups are summarized in Table 3. In the SCF group, Hcy values in 17 patients with angina were higher than those without angina after exercise (Hcy: 20.6 ± 3.2 μmol/L vs 13.5 ± 3.9 μmol/L; $p < 0.0001$, respectively) (Fig. 1). Hcy values in 18 patients with ST segment depression were also higher than those without ST segment depression after exercise (Hcy: 20.9 ± 2.7 μmol/L vs 12.9 ± 3.2 μmol/L; $p < 0.0001$, respectively) (Fig. 2). In addition, Hcy values in 12 patients with both angina and ST depression (22.1 ± 2.2 μmol/L) were greater than those with only angina (16.9 ± 2.2 μmol/L), with only ST depression (18.7 ± 2.3 μmol/L), and with no symptoms (11.8 ± 2.5 μmol/L) (ANOVA, $p < 0.05$; $p < 0.05$; $p < 0.05$, respectively) (Table 4). Post-exercise Hcy levels were negatively correlated with the exercise rate–pressure product among exercise testing parameters in SCF patients group ($r = -0.334$, $p = 0.03$). The mean TFC was positively correlated with pre- and post-exercise Hcy concentrations in the SCF group (Fig. 3), whereas the mean TFC was not correlated with pre- and post-exercise Hcy concentrations in the control group ($p = 0.38$, $p = 0.21$; respectively).

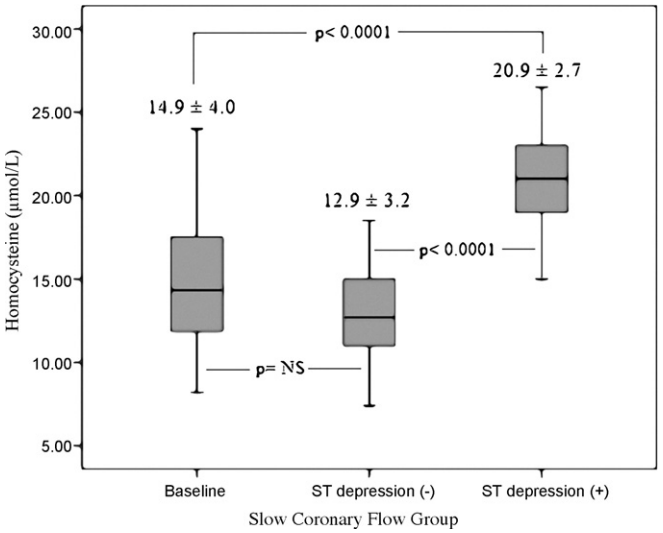

Fig. 2. Comparison of homocysteine levels at baseline, and after exercise in patients with and without ST depression in the slow coronary flow group.

Table 4
Comparison of plasma homocysteine levels at baseline, and after exercise in patients with and without symptoms in SCF group.

	Homocysteine levels (μmol/L)
SCF group ($n = 41$) at baseline	14.9 ± 4.0
SCF group ($n = 41$) after exercise	16.4 ± 5.0*
(1) No symptoms ($n = 18$)	11.8 ± 2.5
(2) Only angina ($n = 5$)	16.9 ± 2.2†
(3) Only ST depression ($n = 6$)	18.7 ± 2.3†,§
(4) Both angina and ST depression ($n = 12$)	22.1 ± 2.2†

SCF, slow coronary flow.
* $p = 0.001$; SCF group after exercise vs baseline (paired t-test).
† $p < 0.05$; sub-group 2 vs 1; sub-group 3 vs 1; sub-group 4 vs 1, sub-group 4 vs 2; sub-group 4 vs 3 (ANOVA).
§ $p > 0.05$; sub-group 3 vs 2 (ANOVA).

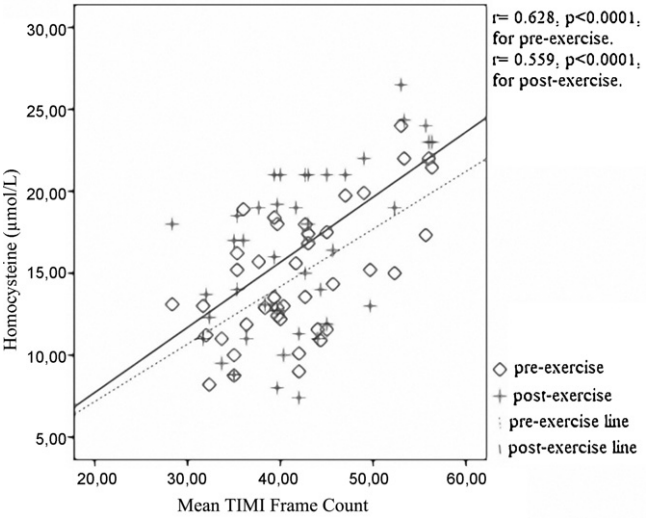

Fig. 3. Correlations between homocysteine levels and mean TIMI frame count pre- and post-exercise in the slow coronary flow group. TIMI, thrombolysis in myocardial infarction.

Discussion

The main findings of our study were the increased level of Hcy in patients with SCF compared with control subjects at baseline, and the elevated level of Hcy in patients with angina and ST segment depression compared to those without angina and ST segment depression in the SCF group after exercise testing.

Hcy is a potentially cytotoxic amino acid that is synthesized during methionine metabolism. Several studies have identified that even mild hyperhomocysteinemia is associated with an increased risk of cardiovascular, and related vascular diseases, independently of classic risk factors [9–12]. The main detrimental effects of Hcy are probably on vascular endothelium. The proposed mechanism by which endothelium is damaged by Hcy is impairment of the basal production of nitric-oxide (NO) in consequence of the emergence of some biochemically active products such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-) and hydroxyl radical (HO) [9,10,18–20]. In humans, reports demonstrated that elevated Hcy level was associated with impaired endothelium-dependent vasodilation and suggested that the bioavailability of NO was decreased in hyperhomocyst(e)inemic persons [18]. In non-human primates, data showed that a continuous Hcy infusion for 3 months gave rise to patchy endothelial desquamation of the

aortic surface, and moderately elevated Hcy induced by methionine loading resulted in abnormal arterial vasomotor activity [19,20]. All these human and non-human studies support a strong correlation between the increased plasma Hcy level and endothelial dysfunction. SCF is an angiographic finding associated with the slow dye progression throughout the coronary lumen in the absence of occlusive coronary artery disease. Some biopsy studies have shown that SCF is associated with microvascular pathology, including myointimal proliferation, medial hypertrophy, reduced luminal size, and endothelial degeneration [2,3]. Additionally, a few studies have demonstrated that SCF is not only a microvascular disease, but also, may be a marker of early stage of macrovascular disease or atherosclerosis [5,6]. Recently, Camsari et al. [6] reported a study in which patients with SCF had coronary intimal thickness and carotid intima-media thickness measured, and they concluded that SCF resulted from coronary atherosclerosis. To date, a few studies [21,22] have shown that SCF patients had elevated plasma levels of Hcy compared to control subjects, supporting the results of our study. Similar to previous trials, our findings revealed that mean TFC was significantly positively correlated with the plasma level of Hcy in SCF patients. Hence, all this evidence supports the possibility that impaired homocysteine metabolism in SCF patients has potentially toxic effects on endothelial barrier, as described above, culminating in micro- and/or macrovascular disease.

One of the findings of the current trial was that Hcy levels in SCF patients tend to be greater than those of control subjects after exercise test, but without a statistical significance. To the best of our knowledge, there is no report on homocysteine values in response to exercise in patients with SCF. The vast majority of current data are usually pertained to those of persons who are healthy and/or obese [23–25]. The data available in the literature demonstrate that different exercise protocols may cause considerable changes in plasma levels of Hcy. In the present study, a maximal exercise test that can be easily applied and found in almost all clinics was performed using standard graduated treadmill protocols in accordance with AHA guidelines. Acute exercise may lead to certain changes in plasma volume and content, including an increase in fluid osmolarity, circulating adiponectin, and/or arterial pressure, resulting in filtration of blood fluid into the interstitial area [26,27]. Thus, a decrease in plasma volume may cause hemoconcentration. Although the precise mechanism for these increases observed in our study remains unclear, hemoconcentration, which may be further aggravated owing to the underlying pathophysiology, may have contributed to slightly increased Hcy level in SCF patients compared to controls.

Another important point of the present study was that plasma levels of Hcy increased in parallel with the amount of ischemic findings observed after exercise test in the SCF group. Exercise may show both direct vasoconstrictor and vasodilator effects through α- and β-receptor stimulation, respectively [28]. Increased adrenergic stimulation may cause abnormal microvascular constriction and promote coronary flow indirectly through the metabolic vasodilation secondary to an elevation in heart rate and myocardial contractility and, in part, to endothelium-mediated vasodilation [28,29]. The net effect is intimately related to the underlying pathophysiologic state of the small coronary arteries. The formerly published reports exhibited that SCF patients were associated with impaired endothelium-mediated vasodilation, indicating endothelial dysfunction. Thus, the endothelial dysfunction and increased sympathetic activation during exercise in SCF patients may lead to elevated coronary resistance [30] and, as a result, may create a suitable territory for the myocardial ischemia in pre- and especially post-exercise period. Indeed, Yazici et al. [31] showed higher adrenaline and noradrenaline levels both at baseline and after exercise, and a significant correlation between TFC and ischemia in SCF patients, indicating that elevated adrenergic activity could be the manifestation of SCF. Moreover, Turkmen et al. [7] reported that SCF phenomenon may alone lead to myocardial ischemia even in the absence of obstructed major epicardial coronary arteries as detected by similar exercise QRS scores to those of significant coronary artery stenosis, a finding supporting the results of the current trial, and they concluded that microvascular disorders and vasomotor changes frequently observed in this group of patients could be the responsible mechanisms. Oudi et al. [32] have demonstrated that elevated levels of Hcy are associated with a greater number of diseased arteries and, consequently, the severity of coronary artery disease. In addition, Ankrah et al. [12] showed that there was a correlation between plasma Hcy level and the presence of myocardial perfusion defects in patients with coronary artery disease, especially those with multiple risk factors and multivessel infarction. In keeping with these findings, we detected that patients with SCF in all of three vessels had higher plasma levels of Hcy when compared to the controls and patients with SCF in one and two vessels. Tanriverdi et al. [22] showed that increased concentrations of Hcy were negatively correlated with endothelial function in SCF patients. We also found that post-exercise Hcy levels were negatively correlated with the exercise rate–pressure product among exercise testing parameters and, the mean TFC was positively correlated with post-exercise level of Hcy in the SCF group. Therefore, it can be concluded that increased levels of plasma Hcy may be closely related to the degree of possible endothelial dysfunction, the severity of slow flow in the affected vessels, and/or the presence of multivessel involvement that could make SCF patients more sensitive to ischemia during an adrenergic activation such as exercise through the discussed mechanisms above.

Study limitations

The small number of patients recruited for our study is the main limitation. Moreover, another limitation is that plasma levels of the folic acid, vitamin B12 were not able to be measured simultaneously with the plasma Hcy level to determine the possible disorder of Hcy metabolism. Hematocrit, fibrinogen, serum total protein or albumin, osmolarity, uric acid, and the density and viscosity of blood and plasma have been used as measures of dehydration and hemoconcentration. All these parameters were not assessed to detect whether acute exercise caused hemoconcentration. An inflammatory parameter, C-reactive protein, and single-photon emission computed tomography analysis, and flow-mediated vasodilatation, a marker of endothelial function, were not investigated. Further studies with larger samples are needed to confirm our results.

Conclusion

We found that patients with SCF had increased levels of Hcy pre- and, to a lesser extent, after exercise compared with control subjects. Our study also demonstrated that SCF patients with angina and ST segment depression during exercise test had higher Hcy values than those without angina and ST segment depression. These findings might suggest an important pathophysiologic link between the increased plasma Hcy levels, the number of slow flow coronary arteries, and exercise-related ischemic findings in SCF patients, in particular those with both angina and ST depression. The present trial is the first report to evaluate the relation between exercise and Hcy plasma levels in this patient group.

Conflict of interest

There is no potential conflict of interest.

Sources of funding

There were no external funding sources for this study.

References

[1] Tambe AA, Demany MA, Zimmermann 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] 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.
[3] Mangieri E, Macchiarelli G, Ciavolella M, Barillà F, Avella A, Martinotti A, Dell'Italia LJ, Scibilia G, Motta P, Campa PP. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn 1996;37:375–81.
[4] Sezgin AT, Sigirci A, Barutcu I, Topal E, Sezgin N, Ozdemir R, Yetkin E, Tandogan I, Kosar F, Ermis N, Yologlu S, Bariskaner E, Cehreli S. Vascular endothelial function in patients with slow coronary flow. Coron Artery Dis 2003;14:155–61.
[5] Cin VG, Pekdemir H, Camsar A, Çiçek D, Akkus MN, Parmaksýz T, Katýrcýbaý T, Döven O. Diffuse intimal thickening of coronary arteries in slow coronary artery flow. Jpn Heart J 2003;44:907–19.
[6] Camsari A, Ozcan T, Ozer C, Akcay B. Carotid artery intima-media thickness correlates with intravascular ultrasound parameters in patients with slow coronary flow. Atherosclerosis 2008;200:310–4.
[7] Turkmen M, Barutcu I, Esen AM, Karakaya O, Esen O, Basaran Y. Comparison of exercise QRS amplitude changes in patients with slow coronary flow versus significant coronary stenosis. Jpn Heart J 2004;45:419–28.
[8] Elsherbiny IA, Shoukry A, El Tahlawi MA. Mean platelet volume and its relation to insulin resistance in non-diabetic patients with slow coronary flow. J Cardiol 2012;59:176–81.
[9] Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, Graham I. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 1991;324:1149–55.
[10] Glueck CJ, Shaw P, Lang JE, Tracy T, Sieve-Smith L, Wang Y. Evidence that homocysteine is an independent risk factor for atherosclerosis in hyperlipidemic patients. Am J Cardiol 1995;75:132–6.
[11] Rasouli ML, Nasir K, Blumenthal RS, Park R, Aziz DC, Budoff MJ. Plasma homocysteine predicts progression of atherosclerosis. Atherosclerosis 2005;181:159–65.
[12] Ankrah A, Buscombe J, Sathekge MM. Association between plasma homocysteine and myocardial SPECT abnormalities in patients referred for suspected myocardial ischaemia. Cardiovasc J Afr 2012;23:313–7.
[13] Gibson CM, Cannon CP, Daley WL, Dodge Jr JT, Alexander Jr B, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
[14] Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for health professionals from the American Heart Association. Circulation 1990;82:2286–321 [revised Circulation 1995;91:580–632].
[15] Shue P, Froelicher V. Extra: an expert system for exercise reporting. J Noninvasive Test 1998;2:21–7.
[16] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[17] Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G, National Kidney Foundation. National kidney foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–47.
[18] Celermajer DS, Sorensen K, Ryalls M, Robinson J, Thomas O, Leonard JV, Deanfield JE. Impaired endothelial function occurs in the systemic arteries of children with homozygous homocystinuria but not in their heterozygous parents. J Am Coll Cardiol 1993;22:854–8.
[19] Harker LA, Ross R, Slichter SJ, Scott CR. Homocysteine-induced arteriosclerosis: the role of endothelial cell injury and platelet response in its genesis. J Clin Invest 1976;58:731–41.
[20] Lentz SR, Sobey CG, Piegors DJ, Bhopatkar MY, Faraci FM, Malinow MR, Heistad DD. Vascular dysfunction in monkeys with diet-induced hyperhomocyst(e)inemia. J Clin Invest 1996;98:24–9.
[21] Riza Erbay A, Turhan H, Yasar AS, Ayaz S, Sahin O, Senen K, Sasmaz H, Yetkin E. Elevated level of plasma homocysteine in patients with slow coronary flow. Int J Cardiol 2005;102:419–23.
[22] Tanrıverdi H, Evrengul H, Enli Y, Kuru O, Seleci D, Tanriverdi S, Tuzun N, Kaftan HA, Karabulut N. Effect of homocysteine-induced oxidative stress on endothelial function in coronary slow-flow. Cardiology 2007;107:313–20.
[23] Nygard O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, Ueland M, Kvåle G. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 1995;274:1526–33.
[24] De Cree C, Malinow MR, Van Kranenburg GP, Geurten PG, Longford NT, Keizer HA. Influence of exercise and menstrual cycle phase on plasma homocyst(e)ine levels in young women – a prospective study. Scand J Med Sci Sports 1999;9:272–8.
[25] Herrmann M, Wilkinson J, Schorr H, Obeid R, Georg T, Urhausen A, Scharhag J, Kindermann W, Herrmann W. Comparison of the influence of volume-oriented training and high-intensity interval training on serum homocysteine and its cofactors in young healthy swimmers. Clin Chem Lab Med 2003;4:1525–31.
[26] Sakaguchi M, Fukuda S, Shimada K, Izumi Y, Izumiya Y, Nakamura Y, Nakanishi K, Otsuka K, Ogawa H, Fujita M, Yoshikawa J, Yoshiyama M. Preliminary observations of passive exercise using whole body periodic acceleration on coronary microcirculation and glucose tolerance in patients with type 2 diabetes. J Cardiol 2012;June [Epub ahead of print].
[27] Ahmadizad S, El-Sayed MS. The acute effects of resistance exercise on the main determinants of blood reology. J Sports Sci 2005;23:243–9.
[28] Zehier AM, Drexler H, Wollschlaeger H, Saurbier B, Just H. Coronary vasomotion in response to sympathetic stimulation in humans: importance of the functional integrity of the endothelium. J Am Coll Cardiol 1989;14:1181–90.
[29] Cordero DL, Cagin NA, Natelson BH. Neurocardiology update: role of the nervous system in coronary vasomotion. Cardiovasc Res 1995;29:319–28.
[30] Pekdemir H, Polat G, Cin VG, Camsari A, Cicek D, Akkus MN, Doven O, Katircibasi MT, Muslu N. 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.
[31] Yazici M, Demircan S, Durna K, Sahin M. The role of adrenergic activity in slow coronary flow and its relationship to TIMI frame count. Angiology 2007;58:393–400.
[32] Oudi ME, Aouni Z, Mazigh C, Khochkar R, Gazoueni E, Haouela H, Machghoul S. Homocysteine and markers of inflammation in acute coronary syndrome. Exp Clin Cardiol 2010;15:e25–8.