Arterial Elasticity in Obese Subjects with Coronary Slow Flow Phenomenon

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ABSTRACT: **Background:** Coronary slow flow phenomenon (CSFP) is a functional and structural disease that is diagnosed by coronary angiogram.

Objectives: To evaluate the possible association between CSFP and small artery elasticity in an effort to understand the pathogenesis of CSFP.

Methods: The study population comprised 12 patients with normal coronary arteries and CSFP and 12 with normal coronary arteries without CSFP. We measured conjugated diene formation at 234 nm during low density lipoprotein (LDL) oxidation, as well as platelet aggregation. We estimated, non-invasively, arterial elasticity parameters. Mann-Whitney non-parametric test was used to compare differences between the groups. Data are presented as mean ± standard deviation.

Results: Waist circumference was 99.2 ± 8.8 cm and 114.9 ± 10.5 cm in the normal flow and CSFP groups, respectively (P = 0.003). Four patients in the CSFP group and one in the normal flow group had type 2 diabetes. Area under the curve in the oral glucose tolerance test was 22% higher in the CSFP than in the normal group (P = 0.04). There was no difference in systolic and diastolic blood pressure, plasma concentrations of total cholesterol, triglycerides, high density lipoprotein, LDL and platelet aggregation parameters between the groups. Lag time required until initiation of LDL oxidation in the presence of $CuSO_4$ was 17% longer (P = 0.02) and homocysteine fasting plasma concentration was 81% lower (P = 0.05) in the normal flow group. Large artery elasticity was the same in both groups. Small artery elasticity was 5 ± 1.5 ml/mmHgx100 in normal flow subjects and 6.1 ± 1.9 ml/mmHgx100 in the CSFP patients (P = 0.02).

Conclusions: Patients with CSFP had more metabolic derangements. Arterial stiffness was not increased in CSFP.

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KEY WORDS: coronary slow flow phenomenon (CSFP), metabolic abnormalities, arterial elasticity, pulse wave contour

Coronary slow flow phenomenon is characterized by normal or minimal atherosclerotic coronary arteries with delayed opacification of the distal vasculature [1]. Ninety percent of patients complain of recurrent chest pain. Most patients are men who smoke. In myocardial biopsy studies, it was demonstrated that CSFP patients had microvascular disease [2].

Ischemia demonstrated by electrocardiography and/or scintigraphy during stress provocation is found in less than 50% of CSFP patients. However, many of them demonstrate ECG evidence of ischemia during spontaneous chest pain, typically during initial presentation with an acute coronary syndrome [1]. ST segment elevation in the absence of epicardial artery spasm was reported in association with CSFP [3].

CSFP patients show increased resting coronary vasomotor tone with low coronary sinus oxygen saturation, reflecting an increased myocardial oxygen extraction caused by delayed resting coronary perfusion. Some patients fail to show CSFP on repeated angiography, implying a significant dynamic component to the impaired coronary microvascular resistance [4] beyond the structural (fixed) microvascular disease demonstrated in previous biopsy studies [2]. Angiographic resolution of CSFP can be demonstrated with dipyridamole, but not with nitrates [2]. Exercise perfusion SPECT showed reversible perfusion defect in 17 of 60 CSFP patients and was normal in 43 of 60 patients. Myocardial perfusion was normalized in all 17 patients with RPD after dipyridamole infusion. No correlation was observed between the time needed to fill a native coronary artery and RPD of the myocardium [5].

Since coronary blood flow increases with pacing tachycardia to the same extent in control patients and CSFP patients, it was suggested that appropriate vasodilatory response is present in CSFP patients [4]. Maximal coronary flow velocity with adenosine was lower in CSFP patients compared with control subjects [6]. Some patients experienced chest pain and ST segment elevation during acetylcholine infusion in the absence of pericardial artery spasm or myocardial lactate production [4]. Thromboxane A2 release across the coronary vascular bed is increased in patients with CSFP, suggesting

RPD = reversible perfusion defect

both the presence of intracoronary platelet activation and the potential for coronary vasoconstriction [7].

As CSFP appears to have an abnormal systemic microvascular and metabolic component, we aimed to determine whether measurement of small vessel elasticity can help us understand and thus predict slow flow in the coronary arteries. In the present study we aimed to determine whether patients with CSFP have a higher incidence of systemic derangements of the components of metabolic syndrome, oxidative stress and a platelet tendency to aggregation, and whether CSFP is a general vascular abnormality that can be predicted by measuring peripheral arterial elasticity.

PATIENTS AND METHODS

The first consecutive 12 catheterized patients with normal coronary arteries and CSFP in the three arteries and the first consecutive 12 patients from the same period with normal coronary arteries but without CSFP were included in the study. Patients were not under the effect of nitrates and abstained from consuming caffeine. Angiographic criteria for CSFP include coronary angiography with normal or near-normal (< 40% stenosis) coronary arteries and Thrombolysis in Myocardial Infarction (TIMI) 0-1 flow, i.e., requiring three or more beats to opacify the distal vasculature [8]. Secondary causes of CSFP such as coronary emboli, no-reflow phenomenon or coronary ectasia were excluded. All patients signed an informed consent, and approval of the hospital internal review board was given.

TIMI frame counts were counted for each vessel in the left anterior descending, circumflex and right coronary arteries. Corrected TIMI frame counts were calculated as described by Gibson and co-researchers [9]. The sum of TIMI frame counts for the three arteries was divided by three. Coronary perfusion pressures in mmHg (diastolic aortic pressure minus left ventricle diastolic pressure) were available in six patients in the CSFP group and seven patients in the coronary normal flow group.

Four days after the coronary angiography, blood samples were drawn and oral glucose tolerance tests were done. Arterial elasticity determinations were performed over 2 days . Patients ingested 75 g glucose after an overnight fast. Serum glucose was measured before, and 1 hour and 2 hours after ingestion. Biochemical parameters including total cholesterol and low density lipoprotein cholesterol and triglycerides were measured by specific kits (Olympus system reagents for clinical chemistry analyzers, Olympus Diagnostic GmbH, Hamburg, Germany). Serum levels for homocysteine were measured by AxSYM homocysteine assay based on the Fluorescence Polarization Immunoassay technology (Abbott laboratories, IL, USA). Blood for LDL separation was drawn into sodium ethylene diamine tetra acetic acid (NaEDTA) (1 mM) and centrifuged at 1500 rpm for 10 minutes at 4°C. LDL was separated from plasma by discontinuous density-gradient ultracentrifugation [10] and dialyzed against saline-NaEDTA (1 mM). LDL protein concentration was determined by the method of Lowry et al. [11].

LDL oxidation studies were performed each time on fresh samples. Prior to oxidation, LDL was dialyzed against saline 1.006 with Na_2EDTA 1 mM, pH=7.4 and then dialyzed against phosphate-buffered saline at 4°C to remove Na_2EDTA. It was then diluted with PBS to 0.2 mg protein/ml. The lipoprotein was incubated in the presence of 5 μM $CuSO_4$ at 37°C. Measuring conjugated diene formation at 234 nm continuously monitored the kinetics of LDL oxidation. For each LDL sample we received a curve consisting of three consecutive phases: lag phase (lag time in minutes required for the initiation of $CuSO_4$-induced LDL oxidation), propagation phase, and a final plateau phase [12].

PLATELET SEPARATION

Washed platelets were chosen to measure isolated platelet reactivity with the influence of plasma components. For platelet studies, venous blood (30 ml) was collected using siliconized syringes into acid citrate dextrose solution (1.4% citric acid, 2.5% sodium citrate, and 2% dextrose) at a ratio of 9:1 (v:v) for washed platelets preparation. Washed platelets were prepared by centrifugation at 240 g for 20 min. The platelet ring was washed twice in 5 mmol HEPES buffer, pH 7.4 (140 mmol NaCl, 2 mmol KCL, 1 mmol $MgCl_2$, 5 mmol HEPES, 12 mmol NaHCO3 and 5.5 mmol glucose). For the preparation of washed platelets suspension, 15 μl of acetic acid (1 mmol) was added to 1 ml of platelet suspension throughout WP preparation in order to ensure acidic conditions required for platelet resuspension. This procedure reduces the medium pH to 6.5 and does not influence the aggregation response of the washed platelets.

PLATELET AGGREGATION

Collagen (Nycomed, Germany) was used as the aggregating agent at a concentration of 4 μg/ml (this concentration can cause up to 60% aggregation amplitude in washed platelets). Platelet aggregation was performed at 37°C in an aggregometer (PACKS-4, Platelet aggregation chromogenic kinetic system, Helena Laboratories, Beaumont, TX, USA) using HEPES as a reference system. Results were expressed as the extent of maximal aggregation (% of maximal amplitude) and also as the slope of the aggregation curve (cm/min) [13].

ARTERIAL ELASTICITY DETERMINATION

Diastolic pulse contour analysis (Windkessel model) demonstrates arterial elastic properties. The wave form can be decomposed to two main components: C_1 is the main slope of the diastolic decay function and is assumed to be related to the proximal compliance (aorta and proximal part of carotids). C_2 is the superimposed decaying sinusoid function that represents the distal arteries and is dependent on systemic vascular resistance [14].

PBS = phosphate-buffered saline

Measurements were performed in a quiet temperature-controlled environment after the patient rested in a supine position. Radial arterial waveforms were recorded for 30 seconds for each subject in the supine position. The pressure transducer amplifier system was connected to a specially designed device (Model CR-2000, Hypertension Diagnostics Inc. and Eagen, MN). The passive transient response of the arterial vasculature to the initial loading conditions was determined by analyzing the diastolic portion of the pressure pulse wave form. This technique, which has been used extensively by us and others [15], was performed with a simple non-invasive radial pulse wave recording and a computer analysis of diastolic decay, thus providing a separate assessment of the large artery or capacitive compliance (C_1) and small artery reflective or oscillatory elasticity (C_2).

This method evaluates the components of the arterial pulse by waveform analysis, enabling differentiation between small and large arterial elasticity parameters.

STATISTICAL ANALYSIS

Mann-Whitney non-parametric test was used to compare differences between normal and slow flow groups. Data are presented as mean ± standard deviation. Multiple linear regressions were performed to predict TIMI flow by metabolic parameters and arterial elasticity.

RESULTS

Table 1 presents the clinical characteristics of the subjects with coronary normal and slow flow phenomenon. The number of patients treated by statins, beta-blocker, angiotensin-converting enzyme inhibitor, nitrate, alpha-blocker or acetyl salicylic acid was 4, 5, 3, 2, 1 and 3 in the CSFP group and 5, 5, 3, 3, 1 and 3 in the normal flow group, respectively. The number of atherosclerotic plaques < 40% in LAD, Cx and RCA in the normal flow and CSFP groups were 2, 1, 1 and 2, 2, 1, respectively.

Table 2 describes the angiographic parameters including TIMI flow grade and corrected TIMI frame count as an average for three arteries. Corrected TIMI frame count was significantly higher in the CSFP group by 91% compared with the normal flow group. There were no differences in coronary perfusion pressures (which were available in 50% of the patients) between the two groups.

There was no difference in mean age, number of smokers or body mass index between the two groups. Waist circumference was significantly higher by 16% in the CSFP group compared with the normal flow group. Four patients in the CSFP group and one in the normal flow group had type 2 diabetes mellitus. The mean area under the curve in the oral glucose tolerance tests was significantly higher by 22% in the CSFP compared with the normal flow group. The systemic systolic and diastolic blood pressure measured before the coronary catheterization were not significantly different from the systolic and diastolic blood pressure measured in the aorta during the coronary catheterization,

LAD = left anterior descending artery
Cx = circumflex artery
RCA = right coronary artery

Table 1. Clinical presentations in subjects with coronary normal and slow flow phenomenon

Clinical presentation	Angina at rest	ST segment depression by ECG	Positive exercise stress test	Positive stress perfusion imaging
Normal flow subjects	8	2	2	1
Slow flow subjects	10	5	0	2

Table 2. Metabolic parameters and elasticity in subjects with coronary normal and slow flow phenomenon

	Normal flow (n=12)	Slow flow (n=12)	*P* value
TIMI flow grade	3.0 ± 0.00	1.9 ± 0.2	‹ 0.001
Gender (male)	8	9	
Corrected TIMI frame count (average for three arteries)	23.2 ± 2.7	44.2 ± 11.1	0.001
Age (yr)	49.5 ± 5.3	50.3 ± 8.6	NS
Smokers	3	3	
Body mass Index (kg/m2)	30.0 ± 3.8	31.8 ± 4.2	NS
Waist circumference (cm) (combined average)	99.2 ± 8.8	114.9 ± 9.3	‹ 0.001
Type 2 diabetes mellitus	1	4	
Arterial hypertension	6	7	NS
Hyperlipidemia or lipid modifying drugs	9	11	NS
Area under curve in oral glucose tolerance test (mmol/L/hr)	14.3 ± 2.4	17.5 ± 0.7	‹ 0.050
Systolic blood pressure mmHg (at enrolment)	132.3 ± 23.2	133.2 ± 15.4	NS
Diastolic blood pressure mmHg (at enrolment)	88.1 ± 12.7	86.1 ± 11.3	NS
Systolic blood pressure mmHg (before coronary catheterization)	126 ± 8	134 ± 10	NS
Diastolic blood pressure (mmHg) (before coronary catheterization)	77 ± 8	79 ± 9	NS
Systolic blood pressure mmHg (aorta, during angiography)	132 ± 8	128 ± 18	NS
Diastolic blood pressure (mmHg) (aorta, during angiography)	76 ± 9	77 ± 9	NS
Coronary perfusion pressure (mmHg)	56 ± 19 (n=7)	57 ± 4 (n=6)	NS
Plasma total cholesterol (mg/dl)	212 ± 36	213 ± 48	NS
Plasma LDL-cholesterol (mg/dl)	135 ± 22	134 ± 47	NS
Plasma triglycerides (mg/dl)	171 ± 125	189 ± 86	NS
Plasma HDL-cholesterol (mg/dl)	42 ± 10	41 ± 8	NS
Homocysteine plasma levels (µmol/L)	11.4 ± 3.1	20.6 ± 14.2	p‹.050
Lag time required to initiation of LDL oxidation (min)	41.1 ± 8.8	34.2 ± 7.4	NS
Maximal platelet aggregation (% of maximal amplitude) Slope of aggregation curve (cm/min)	89.8 ± 5.3 140.6 ± 21.4	90.8 ± 5.4 146.0 ± 35.8	NS NS
Large artery elasticity C_1 (ml/mmHgx10)	16.2 ± 6.0	15.7 ± 5.8	NS
Small artery elasticity C_2 (ml/mmHgx100)	4.5±1.5	6.1±1.3	P‹.050

nor from systolic and diastolic blood pressure measured during enrolment of the patients to the study, both within and between the two groups. Three patients in each group were under treatment with aspirin 75 mg/day. Excluding these patients did not alter the conclusion that there was no difference in maximal platelet aggregation as a percent of maximal amplitude or slope of aggregation curve between the two groups. There was no difference in the serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides between the two groups. Homocysteine serum level was 81% higher ($P = 0.05$) and lag time required until initiation of LDL oxidation was significantly shorter by 17% in the CSFP group compared to the normal flow group. There was no difference in large artery elasticity (C_1) between the two groups, but small artery elasticity (C_2) was 22% significantly higher in the CSFP group compared with the normal flow group. Both homocysteine and area under the curve in the oral glucose tolerance test predicted TIMI flow by multiple linear regressions [Table 3].

DISCUSSION

Patients with CSFP have more risk factors for atherosclerosis than patients with normal coronary flow, including obesity, increased homocysteine and increased tendency of LDL to oxidation. As anticipated, most of the patients were men [1] and presented because of angina at rest. For metabolic parameters in the present study, there were no differences in serum total cholesterol, LDL-C, HDL-C or triglyceride concentrations between the two groups. On the other hand, there was increased oxidative stress in the serum of the CSFP group, as demonstrated by shorter lag time to LDL peroxidation in comparison to the normal flow group. We did not find a difference in systolic or diastolic blood pressures that were measured before and during coronary catheterization and during patients' enrolment; therefore, corrected TIMI frame counts difference between the two groups cannot be explained by changes in blood pressure or coronary perfusion pressures during coronary catheterization.

Waist circumference as a measure for abdominal obesity was higher in the CSFP group. In the CSFP group, both men and women had a waist circumference that fit the criteria for metabolic syndrome (Adult Treatment Panel III: waist circumference > 102 cm for men and > 88 cm for women) [16]. Area under the curve of the glucose tolerance test was significantly high in the CSFP group. This is in line with other studies in which insulin resistance was an independent risk factor for CSFP [17].

HDL = high density lipoprotein

Table 3. Multiple regression to predict TIMI flow by homocysteine and area under the curve in the oral glucose tolerance test

	B	SEB	β
Homocysteine	-0.023	0.007	-0.443*
Area under the curve Glucose tolerance test	0.007	0.002	0.613**
R^2		0.585	
F		14.787**	

*$P < 0.01$, ** $P < 0.001$
SEB = standard error of B

For prothrombotic tendency, it has been postulated that there is increased intracoronary platelet activation in CSFP patients [7]. In the present study, no increase in systemic platelet activity was found in the CSFP group as compared to the normal flow group. It seems that the different results in other studies are due to different methods of measuring platelet activity. Platelet aggregation is still considered the gold standard for platelet activity. The increased thromboxane A2 release across the coronary vascular bed in patients with CSFP may be secondary to sluggish intracoronary flow [7]. The increased plasma levels of homocysteine in CSFP patients together with coronary slow blood flow may affect endothelial function in coronary arteries, thus activating intracoronary platelets.

In the present study, CSFP patients presented with more metabolic derangements than did the normal flow group, which may affect endothelial function in this group beyond the structural pathology [2]. In various studies humoral factors were explored to understand the pathogenesis of CSFP. Endothelin-1 plasma concentrations were higher and nitric oxide plasma concentrations lower at baseline and peak exercise in CSFP patients [18]. The metabolic abnormalities suggest that CSFP is a generalized endothelial dysfunction state. Patients with coronary heart disease may have abnormalities of remote systemic arterial function [19]. Indeed, it was demonstrated in CSFP patients that there is a close relation between coronary artery endothelium-dependent vasomotor responses to acetylcholine and flow-mediated dilatation of the brachial artery [20] and elevated ascending aortic pulse pressure and aortic pulsatility [21]. Despite these findings, it was demonstrated that large artery stiffness and arterial wave reflection characteristics are normal in CSFP patients between their acute episodes [22].

To evaluate the possibility that CSFP is caused by or is associated with generalized increased small artery stiffness we analyzed the pulse wave contour in the radial artery. Pulse wave contour analysis can detect preclinical vascular disease of both small and large arteries [23]. In the present study, small artery elasticity was lower in the normal flow group and unrelated to passive decrease in elasticity frequently associated with higher arterial pressure. In a previous study there was no difference in augmentation index between CSFP and controls in response to either salbutamol or glyceryl trinitrate [24]. Augmentation index is a measure of endothelial function in small arteries. Even close to the acute episode, small artery elasticity was not impaired in CSFP.

In contrast to the suggestion that CSFP is always a systemic abnormality, it can be both a systemic and a regional phenom-

enon. Heterogeneity of response in conduit arteries in different regions of the vascular tree [25] has been shown.

The present study found no correlation between small artery elasticity and CSFP, which may be explained by the differing hemodynamic parameters at various sites. Regional variations, such as low shear stress, oscillatory flow or turbulent flow, may prime the local vascular wall and gene-expression profile to interact differentially with systemic factors, thereby resulting in the potential for local variations in arterial elasticity. CSFP can be a heterogeneous condition, as a local vascular abnormality or as a part of generalized endothelial dysfunction.

STUDY LIMITATIONS

Arterial elasticity was determined by two technicians from another hospital (Wolfson Medical Center) and the laboratory workup was performed by laboratory personnel who were blinded to the results of the coronary arteries angiogram; the first author, however, was not blinded. Another limitation was the small number of patients. The ideal control group would be of healthy persons with no history of chest pain or cardiac disease and with normal cardiac angiogram and normal coronary flow, but they would not be candidates for cardiac angiogram. On the other hand, without cardiac angiography it would not be possible to exclude coronary artery disease or the CSFP.

CONCLUSIONS

Patients with CSFP show a higher incidence of metabolic abnormalities and oxidative stress but do not demonstrate increased platelet tendency to aggregation. On the other hand, the finding of normal elasticity in the small vessels excludes the possibility that small artery stiffness plays a pathogenetic role in the mechanism of the coronary slow flow phenomenon. The contribution of the study is that CSFP is not a homogenous syndrome and not every method of measurement in the peripheral arterial system can detect CSFP.

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