*Research Article*

# Endothelial dysfunction impairs systemic, coronary and retinal blood flow.

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## Abstract

**Background and objectives—** endothelial dysfunction is a systemic process; assessment of endothelial function in the peripheral circulation may be used as a surrogate of coronary endothelial function. This approach is attractive as it is less invasive and being proposed as the primary etiology of atherosclerosis, endothelial dysfunction is the earliest identifiable event in the process of atherosclerotic cardiovascular disease, also proposed as etiology for CSF). Obstructive coronary artery diseases (OCAD) and coronary slow flow phenomenon (CSFP) are frequent angiographic findings for patients that have chest pain and required frequent hospital admission. The objective of this study is to asses if endothelial dysfunction in patients with CSFP and OCAD. **Methods—**A prospective study was conducted over ٣.٥ years, included a total of ١٠٥ patients were included in the study divided into ٤ groups: Group I (OCAD): Included ٣٠ patients with obstructive coronary artery disease, group II (CSF): Included ٣٠ patients with coronary slow-flow phenomenon and group III (Control group I"): (٣٠ patients) "No cardiac catheterization" No finding compatible with myocardial ischemia on diagnostic procedure , group IV "control group II" (١٥ patients) with normal coronary angiography. All participants were subjected to: Full history taking, full clinical examination, conventional resting Doppler-Echocardiography, stress electrocardiography, coronary angiography except (Control group I", ophthalmic artery Doppler for measuring Pulsatility index (PI) and resistance index (RI), flow mediated dilatation (FMD) for testing of peripheral endothelial function. **Results—** Patients with CSF and patients with OCAD showed decreased FMD and increased vascular resistance indices PI & RI in ophthalmic artery Doppler in comparison to control groups **(P=٠.٠٠١)** and without significant difference in between G١ (OCAD) & G٢ (CSF) **(P=٠.٤٤٨)**. There was significant positive correlation between TIMI frame count (TFC) in all subjects with indices of vascular resistance in ophthalmic artery Doppler (PI, RI) and BMI . Also, FMD was positively correlated with Duke Score and exercise duration, while, in contrary it was negatively correlated with PI and RI but no significant correlation between FMD and total TFC (P=٠.١٨٣). **Conclusion—**there is endothelial dysfunction in patients with coronary slow-flow phenomenon and OCAD in comparison to control groups.

**Keywords:** Coronary, Ocular, Circulations, Obstructive coronary artery disease, Coronary slow-flow phenomenon.

## Introduction

Endothelial dysfunction is a systemic process; assessment of endothelial function in the peripheral circulation may be used as a surrogate of coronary endothelial function. This approach is attractive as it is less invasive and good correlation has been demonstrated between responses to acetyl-choline in the coronary circulation and in the forearm vessels. to being proposed as the primary etiology of atherosclerosis, endothelial dysfunction is the earliest identifiable event in the process of atherosclerotic cardiovascular disease, also proposed as etiology for CSF [٦].

Coronary slow-flow phenomenon (CSFP) is a relatively rare angiographic finding observed in patients with normal or near-normal coronary arteries, it is characterized by delayed opacification of coronary arteries during angiography and it is initially reported in ١٩٧٢ by Tambe et al.,,[١]. The frequency of CSFP is approximately ١:٥٪ in patients undergoing coronary angiography. More than ٨٠٪ of patients with CSFP often experience recurrent chest pain, almost ٢٠٪ of whom require readmission following the same diagnosis, also CSF with poor prognostic outcomes, including fatal arrhythmias and sudden cardiac death[٢]. It is still not clear whether or not the coronary slow flow is a focal or a systemic disturbance of the vasculature that may occur simultaneously in other territories of the circulation[٣].

The aim of this study was to asses endothelial function in patients with CSFP and patients with obstructive coronary artery disease in comparison to control persons.

## Patients and methods

**Patients:**

The was a prospective study which carried out in the department of cardiology, Minia university hospital, Egypt during the period from October ٢٠١١ to May ٢٠١٥, ٩٠ subjects in this study were evaluated clinically and classified into three groups as follow:

**Group I (OCAD)**: Included ٣٠ patients with obstructive coronary artery disease.

**Group II (CSF)**: Included ٣٠ patients with coronary slow-flow phenomenon.

**Group III (Control -١)**: Included ٣٠ healthy control persons.

Group **IV** (**Control -II**): collected retrospectively included ١٥ persons with normal coronary angiography.

Patients of group (I) were included according to a specific criteria of typical anginal pain, Findings compatible with myocardial ischemia on diagnostic procedures and significant obstructive coronary arteries on angiography with ٥٠٪ stenosis or more. Patients of group (II) were included with a criteria of typical anginal pain, findings compatible with myocardial ischemia on diagnostic procedures and coronary slow flow on coronary angiography and diagnosed by TIMI Frame Count (TFC). However, persons in control group-١ were chosen by no history chest pain and no finding compatible with myocardial ischemia on diagnostic procedure, persons in control group – II were collected retrospectively with normal coronary angiography that done for diagnosis of CAD based on inconclusive results of noninvasive procedure. Persons with history of previous myocardial infarction, coronary intervention or CABG, moderate or severe valvular heart diseases, hypertrophic, dilated and restrictive cardiomyopathy, diabetes, hypertension, obese patients (BMI ≥ ٣٠ kg/m٢) and other coronary artery diseases as myocardial bridging or coronary were excluded from the study.

**Methods:**

***All subjects included in this study were subjected to the following:***

١. Full personal history and history of symptoms typical or atypical anginal chest pain.

٢. Full clinical examination including all vital signs, general examination and cardiac examination and BMI was calculated.

٣. Resting ١٢-leads ECG was performed by using Fukoda Denshi autocardiner No. FCP ٢/٥٥ and paper speed at ٢٥ mm/sec at standard ١٠ mm/mv.

٤. Conventional Resting Doppler-Echocardiography using GE Vivid-٣ Expert machine for assessment of the left ventricle (LV) dimensions, volumes, LV systolic function and diastolic function by Simpson's biplane method at apical views. Pulsed Doppler and color Doppler to evaluate all valves for exclusion of patient with moderate or severe valvular lesions.

٥. Stress electrocardiography was performed for all subjects. The exercise test was performed on a treadmill using protocol considered to be the most appropriate in each case (Bruce or modified Bruce) after full preparation of subject.

٦. Coronary Angiography study: All subjects underwent coronary angiography except control group- **I** after informed consent with mention of complications. TFC was calculated using the method of Gibson et al.,,[١٠].

٧. Ophthalmic artery Doppler study the right or left eye was evaluated by color Doppler imaging for all subjects with coupling gel applied to closed eye lids, and no pressure applied on the globe with the probe during measurement and Doppler study carried out with ٧.٥ MHz liner transducer and sample volume set at ١ mm and placed in the color Doppler images of the artery then peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI) and resistance index (RI) automatically calculated by the machine according to the following equations

Pulsatility index (PI)= (PSV-EDV) / TVI

Resistive index (RI)=(PSV-EDV) / PSV

٧. Testing of the peripheral endothelial function by flow mediated dilatation (FMD) of the brachial artery for all subjects in the study by using colored duplex ultrasound with ٧.٥ MHz linear array transducer with connection to electrocardiogram cables of the device in order to have the study ECG coupled and measurement of the brachial artery diameter ٣-٥ cm above the elbow ,measurement was applied from anterior to posterior interface between media and adventitia, mean diameter was calculated from ٦ cycles synchronized with the end-diastolic at the R wave peaks to avoid errors from arterial compliance with each scan

١st scan was taken to be the basic of the flow mediated dilatation

٢nd scan was taken after applying a pneumatic tourniquet of ٤٠ mmHg above systolic blood pressure ( using mercurial sphygmomanometer) for about ٥ min and the scan was taken after ٦٠ seconds after releasing the tourniquet. FMD percentage was calculated by the following equation:

FMD%= (٢nd scan – ١st scan)/ ١st scan x١٠٠

## Statistical analysis

Data was statistical analyzed by using SPSS_٢٠ software package. Categorical data was presented in the form of frequency and percentage. Quantitative data were expressed in the form of mean, SD. Kolmogorov- Smirnov for normality test was used to differentiate between parametric data and non-parametric data. One way ANOVA test was used to test the significance between groups for quantitative variables however, Chi - square ($x^٢$) was used for qualitative data. Duncan multi-comparison test was used. Person correlation coefficient was used to get the correlation between variables. Probability (p. value) was considered as non-significant if ≥ ٠.٠٥, Significant if < ٠.٠٥.

## Results

The results showed that there were no statistically significant difference regarding age, gender, DBP, SBP and FBS among studied groups. However, there was significant increase in BMI in CSF patients when compared to OCAD group and control groups, (Table, ١).

No significant difference among groups regarding ejection fraction. But regarding LV diastolic function, there was significant increase in grade ١ diastolic dysfunction in OCAD patients when compared to CSF group and control groups. Regarding the results revealed that Flow-mediated dilatetion (FMD) was significantly higher in control groups compared to CSF group and OCAD group with insignificant difference between group (I and II) (Table, ١).

Results of parameters of ophthalmic artery Doppler (RI & PI) are presented in table (١), the results showed that OCAD and CSF patients had significantly higher RI & PI as compared to control groups with no significant differences between OCAD and CSF groups. In respect of the results of TIMI frame count (TFC) of coronary arteries among groups, total, LAD, LCX & RCA TFC had the same trend of results among groups. The highest values were recorded in CSF patients with a significant difference when compared to the other groups, however there was no significant differences between OCAD and control groups in all TFC measurements (figure, ١).

There is negative significant correlation between FMD and duke score with (r= -٠.٨٦٥, p <٠.٠٠١), and also between FMD and exercise duration with (r = - ٠.٥٥٢, p < ٠.٠٠١), There was significant negative correlation between FMD and indices of vascular resistance of ophthalmic artery with PI (r = - ٠.٨٣٠, p < ٠.٠٠١) and RI (r = - ٠.٧٦٦, p < ٠.٠٠١).In our study no significant correlation between FMD and BMI (Table, ٢)

There is a weak negative insignificant correlation between TIMI frame count and Flow-mediated dilatation in all subjects (r=٠.١٥٦, p.=٠.١٨٣). There is significant positive correlation between TIMI frame count in all subjects and PI (r=٠.٤١٥, p.=<٠.٠٠١), RI (r=٠.٣٠٤, p.=٠.٠٠٨) and BMI (r=٠.٤١٨, p.=<٠.٠٠١), (Table, ٣).

## Discussion

Slow flow coronary phenomenon is sometimes considered as a new category of coronary disease with unknown etiology and indefinite outcome. Several surveys have investigated the relationship between CSFP and endothelial dysfunction as a probable etiology. In the present study we tried to ascertain whether there is a relationship between endothelial function and occurrence of CSF.

In the present study, patients with CSF had significant higher body mass index compared to other groups although it was within normal limits "٢٦.٣". These findings are in agreement with Signori et al.,,[١٢] who found that BMI was ٢٥.٤ ± ٣ (kg/m$^{٢}$) in control group versus ٢٩.٩ ± ٥ in CSF group with P < ٠.٠٤٤ and also, Gunes et al.,, found that BMI was (٢٦.٥ ± ٣.٣ in CSF patients versus ٢٣.٨ ± ٢.٨ in control group, p < ٠.٠٠١), although it was within normal limits also [١٣]. However, Mir Hossein et al., found that there was no significant differences between CSF and control group[١٤]. Our finding can be explained by the CSFP Patients tend to be obese and the metabolic syndrome was more frequent in CSFP in the presence with higher body mass index levels than controls[١٥].

In our study we confirmed that all subjects selected without traditional cardiovascular risk factors so all patients without any history of diabetes, hypertension, and smoking to avoid any cause can explain endothelial dysfunction. No significant difference between CSF group and control group regarding LV diastolic function, but patients with obstructive CAD displayed significant LV diastolic dysfunction when compared to control group. Hawkins et al., reported that ٥٢٪ of the normal population had diastolic dysfunction as compared to ٥٨٪ of the CSFP ones with no significant difference[١٦]. However, Baykan et al.,,[١٧] reported that diastolic function was impaired in patients with CSFP and Sezgin et al., reported impaired left ventricle filling in slow coronary flow phenomenon[١٨].Our study failed to show an association between coronary slow flow and diastolic dysfunction in comparison to control group may be due to the non-random sample of the total population.

Our results showed that patients with SCF as well as patients with obstructive CAD displayed arterial endothelial dysfunction with FMD less significantly in both groups in comparison to control group. These results with agreement with Signori et al.,,[١٢] study which showed that ٢١ subjects with nine (cases) were considered to be patients with SCF, and ١٢ (controls) had normal coronary flow, FMD was ١٣.٣ ± ٥ in control group and ٧.٥ ± ٥ in CSF group with P < ٠.٠٢٢. In a study by Sezgin et al., they showed that the flow mediated diameter increase in the SCF group was significantly smaller than that in the NCF group[١٨]. Also, Gunes et al., showed that brachial (FMD) was ٦.١ ± ٣.٩٪ in CSF group vs. ١٧.٦ ± ٤.٥٪ in control group with a significant difference [١٣]. But in Shapour et al., found that the response of the brachial artery to the cuff test was insignificantly different between the CSF group and control group may be because DM was significantly more common in the control (healthy) group ١٦ patients (١٩.٨٪) versus two patients (٤.٤ %) in SCF with a significant difference[٢١]. Also, Kuvin et al.,, found that Flow-mediated dilation was significantly lower in the subjects with CAD compared with subjects with no evidence of CAD [٢٢]. Furthermore, Gori et al.,, found that FMD was significantly blunted in patients with CAD than subjects with no evidence of CAD [٢٣].

But Corretti et al.,, reported no significant difference in FMD between patients with known CAD and a control group of healthy individuals [٢٤]. Similarly, in Frick et al., FMD most likely reflects "initial" risk and the earliest stage of the disease, so it is not surprising that FMD is reduced in adult patients with vascular risk factors and smooth coronary arteries, also similar FMD values between CAD and non-CAD patients may be due to the influence of medication[٢٥]. For example, statins and angiotensin converting enzyme inhibitors have been shown to improve endothelial function. So we concluded that endothelial dysfunction is a eature in our patients with CSF despite of no risk factors in comparison to control subjects and also a feature in patients with obstructive CAD, and thereby endothelial dysfunction is suggested to be a generalized process that affects coronary and peripheral vasculature and CSF might be a part of a systemic vascular disturbance rather than an isolated phenomenon.

In our study, the results showed that OCAD and CSF patients had significantly lower Pulsatility index & Resestive index "indices of vascular resistance of ophthalmic artery Doppler" as compared to control group with no significant differences between OCAD and CSF groups. In accordance with our findings, Maruyoshi et al.,, reported RI and PI were significantly higher in patients with CAD than in controls. Resistive index was ٠.٧ ± ٠.١ in control group versus ٠.٨ ± ٠.١ in CAD with P< ٠.٠٠١, pulsatility index ١.٥ ± ٠.٣ in control group versus ١.٧ ± ٠.٣ in CAD with P<٠.٠٠٠١[٢٦].

Hemodynamic Doppler flow changes of ophthalmic artery may reflect peripheral vascular resistance and seem to reflect diminished arterial compliance caused by systemic atherosclerosis. The relationship between OA Doppler findings and systemic atherosclerosis, however, remains unclear and the precise mechanisms underlying remain unknown, although several potential mechanisms are suggested. First, resulting from atherosclerotic changes in the ocular vessels accompanying systemic Atherosclerosis. Second, peripheral circulatory disturbance due to decreased aortic compliance because of impaired Windkessel function. In our study increase of indices of vascular resistance of ophthalmic artery Doppler in CSF and patients with obstructive CAD groups in comparison to control groups is a common feature and this means CSF may also associated with increase peripheral vascular resistance as patients with CAD and this can explained by as well as there is diffuse intimal thickening, widespread calcification along the coronary vessel wall and non-obstructive athermanous coronary changes that showed by using IVUS technique in CSF, also mostly other systemic vessels showed the same changes which suggests that coronary slow flow may be a form of early phase of atherosclerosis and it is a systemic phenomenon and not localized to coronary arteries .

our results indicated that there is significant positive correlation between TFC and indices of vascular resistance of ophthalmic artery Doppler PI (r = ٠.٤١٥, p < ٠.٠٠١) and RI (r = ٠.٣٠٤, p < ٠.٠٠٨) and that may reveal correlation between increase of coronary vascular resistance as suspected cause of prolonged TFC and increased peripheral vascular resistance. Also, there is significant positive correlation between TFC in whole study and BMI ( r = ٠.٤١٨, p < ٠.٠٠١) and these data with agreement of data that Patients with CSF had higher body mass index .

In our study there was no significant correlation between FMD and TFC (r = -٠.١٥٦, p < ٠.١٨٣) including all study subjects and this with agreement of Shapour et al., reported neither frame count nor mean frame count showed any significant correlation with FMD[٢١]. Negative significant correlation was found between FMD and duke score with (r = -٠.٨٦٥, p < ٠.٠٠١), and also between FMD and exercise duration with (r = - ٠.٥٥٢, p < ٠.٠٠١) , and these data with agreement of data of Kuvin et al., that showed a significant negative relationship between FMD and duration of exercise (r = - ٠.٢٨٠, p < ٠.٠١) [٢٢]. No significant correlation between FMD and BMI may be due to all subjects in our study were not obese and number of subjects in our study is few than other studies. However in a cross-sectional study, univariate regression analysis revealed that FMD correlated with Body Mass Index (r=-٠.١٤, p<٠.٠٠١)[٢٩].

**Table (١) : All studied variables among groups.**

| | ***Group I (OCAD) N= ٣٠*** | ***Group II (CSF) N= ٣٠*** | ***Group III (Control ١) N= ٣٠*** | ***Group IV (Control ٢) N= ١٥*** | ***P value*** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **I vs II** | **I vs III** | **I vs IV** | **II vs III** | **II vs IV** | **III vs IV** |
| **Sex:** Male. Female. | ١٩ (٦٣.٣٪) ١١ (٣٦.٧٪) | ١٧ (٥٦.٧٪) ١٣ (٤٣.٣٪) | ١٩(٦٣.٣٪) ١١(٣٦.٧٪) | ١٠(٦٦.٧٪) ٥ (٣٣.٣٪) | ٠.٥٩٨ | ١ | ٠.٨٢٦ | ٠.٥٩٨ | ٠.٥١٩ | ٠.٨٢٦ |
| **Age** | ٥٣.٤٦ ± ٥.٤٨ | ٥٠.٣٦ ±٧.٣٦ | ٥١.٤٣ ±٦.٥٣ | ٤٩.٤٦ ± ٧.٩٩ | ٠.٢٨٧ | ٠.٦٤٧ | ٠.٢٤٤ | ٠.٩٢٨ | ٠.٩٧٤ | ٠.٧٩٢ |
| **FBS** | ٩٠.٦٣ ± ٩.٣٤ | ٩١.١٣ ±٩.١٣ | ٩١.٤ ±٨.٦١ | ٩٤.١٣ ± ١٠.٨١ | ٠.٩٩٧ | ٠.٩٨٩ | ٠.٦٣٥ | ١ | ٠.٧٣٨ | ٠.٧٨٩ |
| **DBP** | ٧٧.٧٦ ± ٤.٩٤ | ٧٨.٣٣ ±٤.٢٢ | ٧٧.٩ ±٤.٣٢ | ٧٣ ± ٧.٢٧ | ٠.٩٦٢ | ٠.٩٩٩ | ٠.٧٤٥ | ٠.٩٨٢ | ٠.٤٩٨ | ٠.٦٨٩ |
| **SBP** | ١٢٩.٦٦ ± ٣.٤٥ | ١٢٩.٥ ±٣.٣١ | ١٢٩.٥٣ ±٣.٩١ | ١٣٠.٣٣ ± ٦.٦١ | ٠.٩٩٩ | ٠.٩٩٩ | ٠.٩٥٧ | ١ | ٠.٩٢١ | ٠.٩٢٩ |
| **BMI** | ٢٤.٦٩ ± ١.٥٥ | ٢٦.٣ ± ١.٤ | ٢٥.١ ± ١.٨٣ | ٢٤.٣٨ ± ١.٥٦ | ٠.٠٠١* | ٠.٧٥٩ | ٠.٩٢٤ | ٠.٠٢٤* | ٠.٠٠١* | ٠.٤٨٤ |
| **FMD** | ٩.٤٥±١.٥٥ | ١٠.٠٢±١.٥٥ | ١٦.٧±١.٣٧ | ١٤.٨٩±١.٣٨ | ٠.٤٤٨ | <٠.٠٠١* | <٠.٠٠١* | <٠.٠٠١* | <٠.٠٠١* | ٠.٠٠١* |
| **RI** | ٠.٧٧±٠.٠١ | ٠.٧٧±٠.٠٢ | ٠.٧ ± ٠.٠٢ | ٠.٧١±٠.٠١ | ٠.٩٦٩ | <٠.٠٠١* | <٠.٠٠١* | <٠.٠٠١* | <٠.٠٠١* | ٠.٢٥٥ |
| **PI** | ١.٧٦ ±٠.٠٢ | ١.٧٨ ± ٠.٠١ | ١.٥٧± ٠.٠٥ | ١.٥٩ ± ٠.٠٣ | ٠.١٦٠ | <٠.٠٠١* | <٠.٠٠١* | <٠.٠٠١* | <٠.٠٠١* | ٠.١٢٦ |
| **EF** | ٦٧.٤٦ ± ٣.٥٤ | ٦٦.٨٦ ± ٥.٠٦ | ٦٦.١ ± ٤.٣١ | ٦٦.٨ ± ٣.٧٤ | ٠.٩٨٤ | ٠.٦٠٣ | ٠.٩٦٠ | ٠.٨٩٩ | ١ | ٠.٩٥٥ |

**Table (٢): Correlation between FMD and other parameters in all subjects**

| **All groups** | **FMD** | |
|---|---|---|
| | **R** | **P value** |
| **PI** | -٠.٨٣٠ | <٠.٠٠١* |
| **RI** | -٠.٧٦٦ | <٠.٠٠١* |
| **Exercise duration** | ٠.٥٥٢ | <٠.٠٠١* |
| **Duke score** | ٠.٨٦٥ | <٠.٠٠١* |
| **BMI** | -٠.٠٨٦ | ٠.٣٨٤ |

**Table (٣) : Correlation between TFC and other parameters**

| **All groups** | **Total TFC** | |
|---|---|---|
| | **R** | **P value** |
| **PI** | ٠.٤١٥ | <٠.٠٠١* |
| **RI** | ٠.٣٠٤ | ٠.٠٠٨* |
| **FMD** | -٠.١٥٦ | ٠.١٨٣ |
| **BMI** | ٠.٤١٨ | <٠.٠٠١* |

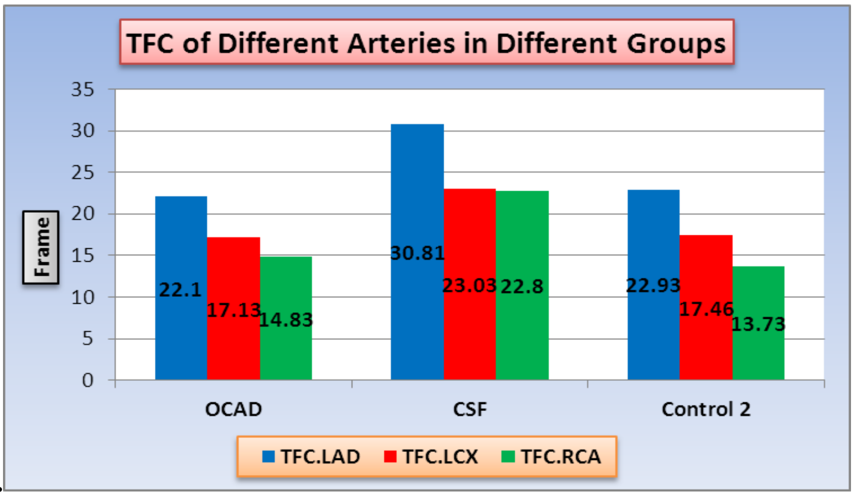


**Figure (١) showed significant high of TFC between (GII) and other groups, but no difference between group ١(OCAD) and group ١V and (control group -١١).**

## Conclusion

Based on the present results, we can conclude that patients with coronary slow-flow phenomenon and patient with OCAD displayed reduced FMD and increase indices of vascular resistance in ophthalmic artery Doppler, we can used peripheral endothelial function test (FMD) as surrogate for coronary endothelial function test in patient with CSF or CAD

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