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Original Article

Retinal fluorescein angiography: A sensitive and specific tool to predict coronary slow flow

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ABSTRACT

Background: Obstructive coronary artery disease (OCAD) and coronary slow flow (CSF) are frequent angiographic findings for patients that have chest pain and require frequent hospital admission. The retina provides a window for detecting changes in microvasculature relating to the development of cardiovascular diseases such as arterial hypertension or coronary heart disease.

Objectives: To assess the coronary and ocular circulations in patients with CSF and those with obstructive coronary artery disease.

Methods: A prospective study was conducted over 3.5 years, included a total of 105 subjects classified to 4 groups: *Group I (OCAD)*: Included 30 patients with obstructive coronary artery disease, *group II (CSF)*: Included 30 patients with coronary slow-flow, *group III (Control 1)*: Included 30 healthy control persons and *group IV (Control 2)*: Included 15 patients indicated for coronary angiography that proved normal. All participants were subjected to coronary angiography (except control group 1), ophthalmic artery Doppler for measuring Pulsatility index (PI) and resistivity index (RI) and Fluorescence angiography of retinal vessels.

Results: Patients with CSF showed slow flow retinal circulation (microcirculation) evidenced by prolonged fluorescein angiography (Arm-retina time [ART] & Arterio-venous Transit time [AVTT]). Ophthalmic artery Doppler measurements (RI & PI) were significantly delayed in OCAD and CSF patients. There was significant positive correlation between TIMI frame count in all subjects and ART, AVTT, PI, RI and Body Mass Index. Using ART cutoff value of >16 s predicted CSF with sensitivity and specificity of 100%, meanwhile AVTT of >2 s predicted CSF with a sensitivity 96.7% and specificity of 93.3.

Conclusion: Both delayed arm-retina time and retinal arterio-venous transit times can accurately predict coronary slow-flow.

1. Introduction

Coronary slow-flow (CSF) is an angiographic finding observed in patients with normal or near-normal coronary arteries. It is characterized by delayed opacification of coronary arteries during angiography and was initially reported in 1972 by Tambe et al.[1] The frequency of CSF is approximately 1–5% in patients undergoing coronary angiography. More than 80% of patients with CSF often experience recurrent chest pain; almost 20% require readmission following the same diagnosis.[2] Also, CSF has been linked to parameters of poor prognosis, including fatal arrhythmias and sudden cardiac death.[2] 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.[3]

Over the last 8–10 years, multiple large prospective cohort studies examining the relationship between retinal vascular changes and clinical endpoints of coronary disease, and there was strong positive correlation between the two, also an association between retinal microvascular abnormalities and markers of subclinical or microvascular coronary disease has been detected.[4] The retina is a unique site where the microcirculation can be imaged directly. Thus, it provides a window for detecting changes in microvasculature relating to the development of cardiovascular

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diseases such as arterial hypertension or coronary heart disease.[5] Retinal vascular imaging is explored in clinical settings as a risk stratification tool to aid clinicians in identifying patients with microvascular signs who are at high risk of future clinical cardiovascular and cerebrovascular events.[6]

The aim of this study is to assess if there is correlation between coronary and ocular circulations in patients with CSF and those with obstructive coronary artery disease in comparison to control persons.

2. Patients and methods

This is a prospective study which was carried out in the departments of cardiology and ophthalmology Minia University, Egypt during the period from October 2011 to May 2015. 105 subjects in this study were evaluated and classified into four groups as follow:

Group I (OCAD): Included 30 patients with obstructive coronary artery disease.
Group II (CSF): Included 30 patients with coronary slow-flow.
Group III (Control 1): Included 30 healthy control persons.
Group IV (Control 2): Included 15 patients with normal coronary angiogram.

Patients of group I were included with criteria of typical anginal pain, findings compatible with myocardial ischemia on diagnostic procedures and significant obstructive coronary arteries on angiography with 50% stenosis or more. Patients of group II were included with 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). As per group III (control 1), participants were chosen by being age and sex matching group I and II while having no history of chest pain and no findings compatible with myocardial ischemia on diagnostic procedure. Group IV (control 2) patients had chest pain, positive or equivocal diagnosis of ischemia on noninvasive procedure and normal coronary angiography.

Persons with history of previous myocardial infarction, coronary intervention or coronary artery bypass graft (CABG), moderate or severe valvular heart disease, hypertrophic, dilated and restrictive cardiomyopathy, diabetes; hypertension, obesity (BMI ≥ 30 kg/m^2) and other coronary artery diseases as myocardial bridging were excluded from the study.

All subjects included in this study were subjected to the following

1. Coronary Angiography study: All subjects in the study except group III underwent coronary angiography after informed consent with mention of possible complications. TFC was calculated using the method of Gibson et al.[7]
2. Ophthalmic artery Doppler study: For all subjects, the right or left eye was evaluated by color Doppler imaging with gel applied to closed eye lids, insuring no pressure applied on the globe with the probe during measurement. Doppler study was carried out with 7.5 MHz linear transducer and sample volume set at 1 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) were automatically calculated by the machine (Fig. 1).
3. Fluorescence angiography of retinal vessels: All subjects underwent fluorescence angiography of retinal circulation after exclusion of contraindications with adequate pupillary dilatation while the patient is seated in front of fundus camera. Red free images were captured after 5 ml of a 10% sodium fluorescein is administrated intravenously into an antecubital vein over 2–3 s. The images were taken at approximately one second intervals over 25 s after injection according to Prall et al.[8] We calculated two time intervals: 1- Arterial phase (arm- to retinal time ART): time from injection until the dye first appears in the central retinal artery. It can vary between 7 to 15 s and represents systemic venous and arterial circulation flow. 2-Retinal arteriovenous transit time AVTT: time from the first appearance of dye in the temporal retinal arteries of the arcades to the time when the corresponding veins are completely filled. It is considered to be 1–2 s after the arterial phase.

Statistical analysis was done using SPSS 20 software package. Categorical data were presented as frequencies and percentages. Quantitative data were expressed as mean and standard deviation. 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 meanwhile, Chi-square (x^2) was used for qualitative data. Duncan multi-comparison test was also used. Person correlation coefficient was used to get the correlation between variables. Sensitivity, specificity and accuracy were calculated. Probability (p. value) was considered significant if was <0.05.

3. Results

The results showed that there was no statistically significant difference regarding age, gender, diastolic blood pressure (DBP),

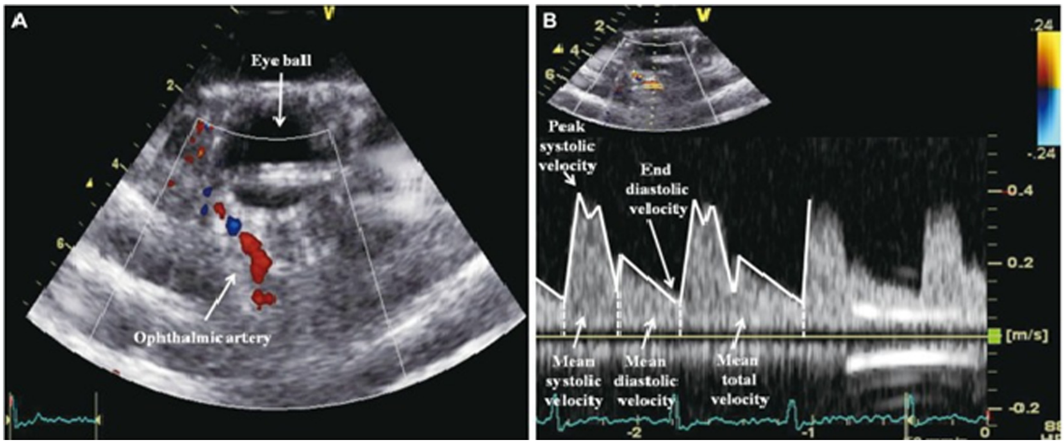

Fig. 1. Colour Doppler imaging measures velocity in ophthalmic artery.

systolic blood pressure (SBP) and fasting blood sugar (FBS) among studied groups. However, CSF patients (Group II) had a significantly higher BMI in when compared to the other three groups (Table 1).

No significant difference among groups was found regarding ejection fraction (LVEF). But grade 1 diastolic dysfunction was more prevalent among patients with OCAD patients (86.7%) when compared to the other three groups. Regarding stress ECG parameters Duke Risk Score had the significantly higher value in group (I) and was differed significantly among the other two groups. However, exercise duration was significantly higher in Group III (control group 1) than the other two groups (Table 2).

Results of ophthalmic artery Doppler parameters (RI & PI) showed that OCAD and CSF patients had significantly lower RI & PI as compared to the other two control groups with no significant differences between OCAD and CSF groups. Regarding parameters of fluorescein angiography (ART & AVTT), there was significantly increased in CSF patients (group, II) when compared to other groups, ART was significantly higher in CSF and OCAD patients compared to control groups with a significant difference between CSF and OCAD groups, however, AVTT was significantly higher in CSF patients compared to the other three groups (Table 3). Regarding the results of TIMI frame count (TFC) of coronary arteries among groups Left anterior descending artery (LAD), Left circumflex artery (LCX) & Right coronary artery (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 two groups; however there was no significant difference between OCAD and control group 2 in all TFC measurements (Fig. 2).

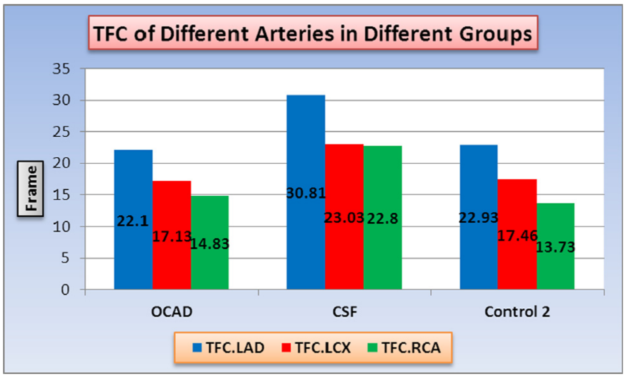

Fig. 2. TFC among different groups.

There is significant positive correlation between TIMI frame count in all subjects and ART AVTT, PI, RI and BMI (Table 4).

ROC curve analysis for the power of fluorescein angiography to predict coronary slow flow (Table 5 & Fig. 3), showed that at a cut-off value of ART and AVTT of >16 s and >2 s respectively, a high

Table 1
Age, fasting blood sugar, blood pressure and body mass index among groups.

Variable	Group I (OCAD) N = 30	Group II (CSF) N = 30	Group III (control 1) N = 30	Group IV (control 2) N = 15
Age (year)	53.5 ± 5.48	50.4 ± 7.36	51.4 ± 6.53	49.5 ± 7.99
FBS (g/dl)	90.6 ± 9.34	91.1 ± 9.13	91.4 ± 8.61	94.1 ± 10.83
DBP	77.8 ± 4.94	78.3 ± 4.22	77.9 ± 4.32	73.0 ± 7.27
SBP	129.7 ± 3.45	129.5 ± 3.31	129.5 ± 3.97	130.3 ± 6.67
BMI	24.7 ± 1.55	26.3 ± 1.4[a]	25.1 ± 1.83[b]	24.4 ± 1.56[b]

FBS (fasting blood sugar), DBP (diastolic blood pressure), SBP (systolic blood pressure), BM1 (body mass index).
[a] Significant versus I.
[b] Significant versus II.

Table 2
Ejection fraction, diastolic dysfunction, and stress ECG parameters among groups.

Variable		Group II (CSF) N = 30	Group I (OCAD) N = 30	Group III (control 1) N = 30	Group IV (control 2) N = 15
LV ejection fraction (EF)		67.5 ± 3.54	66.9 ± 5.06	66.1 ± 4.31	66.8 ± 3.74
LV diastolic dysfunction	Normal	4 (13.3%)	10 (33.3%)	13 (43.3%)	5 (33.3%)
	Grade I	26 (86.7%)	20 (66.7%)[a]	17 (56.7%)[a]	10 (66.7%)[a]
Stress ECG parameters	DUKE score	−5.28 ± 3.46	−1.06 ± 2.51[a]	10.65 ± 1.72[a]	–
	Exercise duration	8.46 ± 1.79[c]	9.21 ± 1.58[c]	10.65 ± 1.72	–

[a] Significant versus I.
[c] Significant versus III.

Table 3
Ophthalmic artery Doppler parameters, and Fluorescein angiography among groups.

Variable		Group I (OCAD) N = 30	Group II (CSF) N = 30	Group III (control 1) N = 30	Group IV (control 2) N = 15
Ophth. Art. Doppler	RI	0.77 ± 0.01	0.77 ± 0.02	0.70 ± 0.02[a,b]	0.71 ± 0.01[a,b]
	PI	1.76 ± 0.02	1.78 ± 0.01	1.57 ± 0.05[a,b]	1.59 ± 0.03 [a,b]
Fluorescein angio	ART	15.6 ± 1.09[b]	28.5 ± 4.66	12.4 ± 1.68[b]	12.9 ± 1.55[b]
	AVTT	1.82 ± 0.14[b]	2.86 ± 0.49	1.66 ± 0.15[b]	1.74 ± 0.18[b]

Resistance index (RI), pulsatility index (PI), ART (arm- to retinal time) AVTT (arteriovenous transit time).
[a] Significant versus I.
[b] Significant versus II.

Table 4
Correlations between TFC and other measurements in all studied subjects (3 groups).

TFC correlations	Correlation coefficient (*r*)	P. value (sig.)
ART	0.81	<0.001
AVTT	0.77	<0.001
PI	0.42	<0.001
RI	0.30	0.008
BMI	0.42	<0.001

TFC (TIMI frame count), ART (arm- to retinal time), AVTT (arteriovenous transit time).
PI (pulsatility index), RI (resistance index), BMI (body mass index).

sensitivity (100 and 96.7% respectively) and specificity (100 and 93.3%, respectively) were attained.

4. Discussion

Coronary Slow flow is sometimes considered as a new category of coronary disease with unknown etiology and indefinite outcome. Several surveys have investigated the relationship between CSF and ocular circulation. In the present study we tried to investigate whether there is a correlation between coronary and ocular circulations in patients with CSF and those with OCAD in comparison to control subjects.

In this study fluorescence angiography showed that there is a high arm-to-retina circulation time (ART) in patients with CSF with significant difference in comparison with other groups. This reflects the slower flow of blood in systemic circulation in patients with CSF similar to the coronary circulation. It actually includes two parts, firstly venous part from arm vein to heart and lastly from heart through carotid artery and ophthalmic artery to retina. In normal persons, Fluorescence dye is first detected in the retinal vasculature 12 to 15 s after dye is injected into the arm vein. Uncommonly, the dye may take up to 20 s to reach the retinal arteries in a normal person. We suspected that as ophthalmic artery is anatomically similar to coronary arteries as both are conductive arteries with the same structure less elastic tissue and more muscular tissue so slow flow that occurs in coronary arteries in CSF group may also occur in the ophthalmic artery. Similar to our results, Koç et al. found that ART was longer in CSF group compared to control group with $p < 0.001$.[9] The significant difference between obstructive CAD and control group in ART can be explained by peripheral endothelial dysfunction in group (I).

AVTT (arteriovenous phase transit time) is the shortest time of retinal microcirculation and it is described as the time period between the entrance of the opaque substance to the edge of the optic disc or to the retinal artery from a distance of 2 optic disc diameters and the appearance of the opaque substance in the vein at the same point.

This study reveals that retinal arterio-venous phase transit time, measured by fundus fluorescein angiography; is significantly higher in CSF patients in comparison to OCAD patients and controls. This agrees with a study of Koç et al. who reported that higher AVTT in CSF group than in control group with $p < 0.001$.[9] Retinal microcirculation similar to coronary microcirculation from anatomical and physiological view Kamran Ikram et al.[10] and Wang et al.[6] So, prolonged AVTT may reflect coronary slow flow and coronary microcirculation dysfunction.

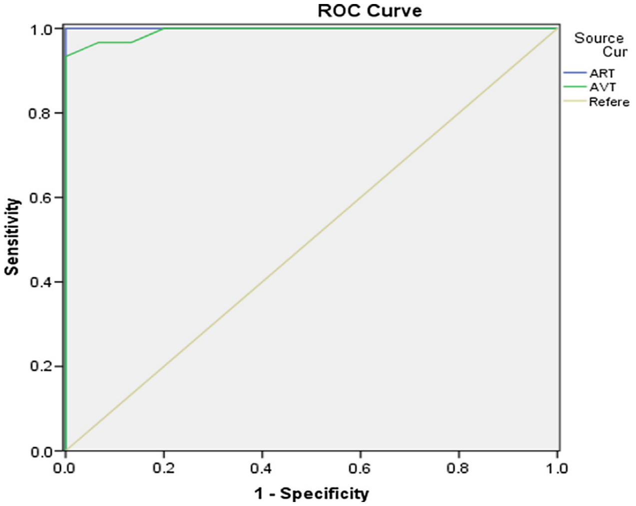

Fig. 3. ROC curve for prediction of coronary slow flow.

The result in this study showed that patients with CSF had prolonged TFC for each major coronary artery in comparison to both obstructive CAD and control groups. Also, Koç et al. reported significant differences in TFC for LAD, LCX, and RCA in CSF groups versus control one with $P < 0.001$.[9] Also, Signori et al.[11] reported that TFC was higher in patients with CSF than in controls for each major epicardial coronary artery. In addition, the average TIMI frame count was higher in patients with CSF than in control groups. In line with our findings, Ibrahim et al. reported that LAD, LCX and RCA corrected TFC was higher in CSF group when compared to control with $P < 0.001$.[12]

Also, there is a significant positive correlation between TFC and fluorescein angiography measurements including ART and AVTT. By the same way Koç et al. showed in the whole study group, mean TIMI Frame counts were positively correlated significantly with the measurements of ART, AVTT.[9]

The result of this study showed by using ROC curve, the optimal cut- off value of ART and AVTT for prediction of CSF is >16 and >2 respectively with a high sensitivity and specificity, so by using fluorescein angiography parameters (ART & AVTT) we can predict presence of CSF with high sensitivity and specificity. These findings are in line with those of Ghaffari et al. who studied clinical and laboratory predictors of coronary slow flow in coronary angiography.[13]

The result of this study showed that there is significant positive correlation between TFC and indices of vascular resistance of ophthalmic artery Doppler PI and RI 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 with $p < 0.001$ and these data with agreement of other data from different studies that patients with CSF had higher body mass index.

The result of this study showed that OCAD and CSF patients had significantly higher Pulsatility index & Resistive index “indices of vascular resistance of ophthalmic artery Doppler” as compared to

Table 5
ROC curve analysis of fluorescein angiography for prediction of coronary slow flow.

Variable	Optimal cut-off point	AUC	P value	Sensitivity	Specificity	PPV	NPV	Accuracy
ART	>16	1	<0.001*	100%	100%	100%	100%	100%
AVTT	>2	0.993	<0.001*	96.7%	93.3%	96.7%	93.3%	95.6%

ART (arm- to retinal time), AVTT (arteriovenous transit time).
* Highly significant value.

control groups with no significant differences between OCAD and CSF groups. In accordance with our findings, Maruyoshi et al. reported that RI and PI were significantly higher in patients with CAD than in controls with $p < 0.0001$.[14]

Hemodynamic Doppler flow changes of ophthalmic artery (OA) 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 the present 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 intra vascular ultra sound IVUS technique in CSF, also mostly other systemic vessels showed the same changes which suggests that slow coronary flow be a form of early phase of atherosclerosis and it is a systemic phenomenon and not localized to coronary arteries.

In the present study, patients with CSF had significant higher body mass index compared to other groups although it was within normal limits. These findings are in agreement with Signori et al.[11] who found that BMI was higher in CSF patients than in control groups with $p < 0.044$ and also, Gunes et al. found that BMI was higher in CSF patients compared to control group, although it was within normal limits also.[15] However, Mir Hossein et al. found that there were no significant differences between CSF and control group.[16] Our finding can be explained by that the CSF patients tend to have more metabolic syndrome than controls, a finding that may be associated with increased peripheral resistance.

5. Conclusion

- Patients with coronary slow-flow suffer from slow flow in retinal circulation that might lead to ischemic retinal complications.
- Retinal microcirculation may reflect coronary microcirculation and its flow velocity.
- CSF and OCAD patients displayed reduced FMD and increased indices of vascular resistance in ophthalmic artery Doppler.
- Retinal circulation can be used as mirror image for coronary circulation for diagnosis, risk stratification and follow up of changes in coronary circulation.
- ART > 16 s and AVTT > 2 s can predict presence of CSF with high sensitivity and specificity.

5.1. Study limitations

- Although this is a clinical trial with a relatively small cases number, yet statistical analysis was valid for the conclusions taken. However, a large number might be needed for firmer conclusions.

Conflict of interest

Affirm that they have no conflicts of interest to disclose.

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