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Inverse correlation between coronary and retinal blood flows in patients with normal coronary arteries and slow coronary blood flow

Yaron Arbel [a,*], Amir Sternfeld [a], Adiel Barak [b], Zvia Burgansky-Eliash [e], Amir Halkin [a], Shlomo Berliner [c], Itzhak Herz [a], Gad Keren [a], Ardon Rubinstein [d], Shmuel Banai [a], Ariel Finkelstein [a]

[a] Department of Cardiology, Tel Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[b] Department of Ophthalmology, Tel Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] Department of Internal Medicine "D" and "E", Tel Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[d] Department of Metabolic Clinic, Tel Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[e] Department of Ophthalmology, The Edith Wolfson Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Background: The "Slow Coronary Flow" (SCF) phenomenon in the presence of angiographically normal coronaries is attributed to microvascular and endothelial dysfunction. The microcirculation can be non-invasively assessed by measuring retinal blood flow velocity.
The aim of the present study was to evaluate the efficacy of the "Retinal Functional Imager" (RFI) device as a noninvasive method of diagnosing patients with slow coronary flow.
Methods: Coronary blood flow velocity assessed by corrected TIMI Frame Count and retinal arterioles blood flow assessed by RFI were measured in 28 consecutive patients with normal coronary arteries. The patients were divided into 2 groups: a slow coronary flow (SCF) and a normal coronary flow (NCF) groups.
Results: Inverse correlation was found between retinal and coronary blood flows so that higher retinal arterial flow velocity was observed in the SCF group (3.8 ± 1.1 mm/s vs. 2.9 ± 0.61 mm/s, respectively, $p = 0.022$). RFI provided 73% sensitivity and 77% specificity for diagnosing SCF using ROC analysis. Additionally, patients with SCF had higher values of serum LDL cholesterol (104.7 ± 18.93 mg/dl vs. 81.55 ± 14.62 mg/dl in NCF, $p = 0.005$), Glucose (96.9 ± 23.0 mg/dl vs. 83.55 ± 9.7 mg/dl in NCF, $p = 0.024$), and lower percentage of statin consumption (40.0% vs. 76.9% in NCF, $p = 0.049$).
Conclusions: Slow coronary blood flow can be non-invasively diagnosed with Retinal Functional Imager. Patients with normal coronary arteries and slow coronary blood flow have high retinal arteriolar blood flow. Early non-invasive diagnosis of SCF might help detect individuals who are at higher risk to develop coronary atherosclerosis, and to provide them with early preventive measures.

1. Introduction

Approximately 20% of patients undergoing clinically driven coronary angiography are reported to have angiographically normal epicardial coronary arteries that are devoid of hemodynamically significant luminal stenosis [1]. Angina pectoris in patients with angiographically normal coronary arteries (ANCA) is related to endothelial dysfunction [2–6].

Endothelial dysfunction is characterized by an imbalance of vasodilation factors (e.g. Nitric Oxide) and vasoconstrictive factors (e.g. Endothelin-1), and it is considered an early stage of atherosclerosis which precedes any anatomical obstruction that can be seen during coronary angiography [7–9].

The phenomenon of slow coronary flow in patients presenting with chest pain and ANCA has important prognostic implications [10]. Moreover, treatment of endothelial dysfunction by various modalities has been shown to improve symptoms and outcome [11–13].

The current gold standard to assess the coronary microcirculation is by invasive coronary angiography (TIMI Frame count, Blush Score, Coronary clearance) [14].

* Corresponding author. Department of Cardiology, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 62439, Israel. Tel.: +972 3 6973313; fax: +972 3 6973259.
E-mail addresses: yarona@tlvmc.gov.il, yaronarbel@gmail.com (Y. Arbel).

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There is a growing need to develop non-invasive methods to assess the microcirculation for early diagnosis and treatment of patients with coronary endothelial dysfunction.

Evaluating the retina enables physicians to non-invasively assess the microcirculation in a patient. Past studies have evaluated retinal microcirculation by evaluating morphological changes such as arterial diameter [15]. To the best of our knowledge, there is no study that compared the coronary blood flow to the retinal blood flow. If exists, such correlation might offer physician a non-invasive and readily available method to evaluate and conduct follow up on patients with microvascular dysfunction who might be at increased risk to develop coronary atherosclerosis.

The aim of the present study was to evaluate the correlation between retinal blood flow velocities assessed non-invasively using the "Retinal Functional Imager" (RFI) and coronary blood flow measured during coronary angiography in patients with angiographically normal coronaries.

2. Methods

2.1. Study design and patients selection

We prospectively recruited patients who were referred for cardiac catheterization because of chest pain and were found to have angiographically normal epicardial coronary arteries. After their coronary angiography, their retinal microcirculation was evaluated with the "Retinal Functional Imager" (RFI) device (see below).

We excluded patients with ST segment elevation myocardial infarction, significant valvular heart disease, hypertrophic or dilated cardiomyopathy, and those with either heart failure or known left ventricular dysfunction. Patients with abnormal retina (diabetic retinopathy, age related macular degeneration, etc.), refractive error larger than 6 ± diopters, past retinal operation, or technical difficulties limiting full evaluation of the retina were also excluded.

All patients signed a written informed consent for participation in the current study which has the approval of the local institutional ethics committee.

2.2. Definition of risk factors

Diabetes Mellitus (DM) was defined if the patient have been informed of having DM by a physician or was receiving hypoglycemic treatments (dietary, oral anti-diabetic agents, or insulin) [16]. Hypertension was defined according to a medical records of elevated blood pressure on at least two separate occasions or the use of anti-hypertensive medications [17]. Dyslipidemia was defined by medical records, the use of lipid-lowering medications or low-density lipoprotein (LDL) concentrations >160 mg/dl in the fasting state. Past and current smoking status was established from the patient's self-reporting and medical records.

2.3. Angiographic evaluation

Each angiogram was evaluated and coronary blood flow velocity was graded by the consensus of 2 cardiologists who used a validated scoring system, the Corrected TIMI Frame Count (CTFC) [14]. Both cardiologists were blinded to all clinical characteristics of the patients.

2.4. Corrected TIMI Frame Count (CTFC) [18]

This is an objective evaluation of coronary blood flow as a continuous and quantitative variable. The angiography is performed at 30 frames/s. The number of frames required for contrast material to reach a distal coronary landmark from the second it first appears in the ostium of the related artery is counted and recorded.

2.5. Slow coronary flow (SCF)

SCF was defined as a CTFC above the mean + 2 standard deviations for each of the relevant arteries [15,18]. Thus, any TIMI Frame Count above 41 frames in the left anterior descending artery (LAD), above 26 frames in the right coronary artery (RCA), or above 30 frames in the left circumflex (LCX) was considered as SCF.

2.6. Ophthalmic evaluation

All participants underwent a comprehensive ophthalmic evaluation that included medical history, assessments of best-corrected visual acuity and refraction, and slit-lamp examination before and after pupillary dilation. Finally, 3 sets of RFI images of 20° centered on the fovea were obtained. Pupils were dilated with 1% tropicamide and 2.5% phenylephrine. When eligible, both eyes of a subject were included.

2.7. The imaging system

The RFI (Optical Imaging Ltd, Rehovot, Israel) is using standard fundus camera optics with the addition of a stroboscopic flash lamp system and a fast high-resolution digital camera. The system produces 8 flashes of illumination at 17.5 ms intervals. For the blood flow velocity operating mode, the illumination filter was centered at 548 nm and a bandwidth of 17 nm. To control the effect of heart pulsation phase on flow velocity measurements, a probe is attached to the subject's finger or earlobe, allowing image acquisition to be synchronized to a selected phase of the patient's pulse pattern (67% after the beginning of the systole). Differential imaging processing directly detects moving erythrocytes in retinal vessels and provides the measured velocity in secondary and tertiary branches of arteries and veins (Fig. 1) [19].

Each RFI session was repeated three times at the same area; the coefficient of variation (standard deviation/mean) of the measured velocity was calculated for each segment. Segments for which the coefficient of variation exceeded 45% were excluded from the

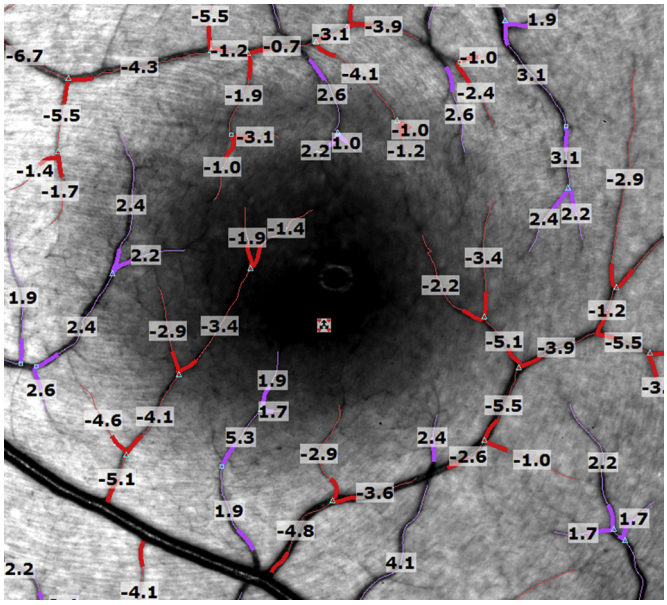

Fig. 1. Representative picture from the RFI analysis program. The figure demonstrates the different velocities measured in the retinal arteries.

analysis. Images were excluded if >33% of the segments were removed from the analysis. Images were also assessed subjectively for quality, focus and visibility of flow movement by one investigator (A.B.). The blood flow velocity measurements were found to have high repeatability with average coefficient of variation of 8.5 ± 4.9% in 114 eyes of 67 healthy [20]. Some experience with this instrument was accumulated by now showing significant abnormalities in different patient populations [19–21].

2.8. Statistical analysis

All data were summarized and displayed as mean ± standard deviation (SD) for the continuous variables (age, Body Mass Index [BMI], etc.), and as number of patients plus the percentage in each group for categorical variables (medication, cardiovascular risk factors, etc). Categorical variables were compared using Chi-square test and continuous variables Mann Whitney test (medians with interquartile range, IQR). We used Spearman's and Pearson's correlation tests as needed. The two groups that we used for our analysis (i.e., SCF and non-SCF patients) were formed according to their mean CTFC scores. Next, we applied Univariate analysis to examine the effect of the variables that were found to be different between the groups, and created a multivariate stepwise logistic regression model using the slow flow as the dependent variable and the variables that were found to be significant in the Univariate analysis. We evaluated the utility of the RFI in diagnosing SCF by using the ROC function. Statistical significance was assumed at $p < 0.05$. SPSS/WIN (version 20.0, SPSS Inc, Chicago, Il, USA) software was used to carry out all statistical analyses.

3. Results

A total of 28 patients with angiographically normal coronaries were prospectively recruited into the study. Clinical characteristics are presented in Table 1. The mean age was 59 ± 11 years (range: 35–76 years). Fifteen patients (54%) were males. The clinical indication for angiography (Table 2) was evenly divided between urgent and stable conditions.

Sixteen (57%) patients had at least one abnormal non-invasive test suggesting myocardial ischemia. Seven (25%) patients had a positive cardiac scan, 7 (25%) patients had a positive treadmill test, 3 (11%) patients had abnormal stress echocardiogram and 1 patient had both abnormal treadmill and stress echocardiogram test.

Table 3 summarizes the mean values of coronary flow and RFI. There was an inverse correlation between retinal blood flow velocities and coronary blood flow velocities ($r = -0.405$, $p = 0.03$) (Fig. 2).

Next, the cohort was divided into 2 groups: normal coronary flow (NCF)–13 patients and slow coronary flow (SCF)–15 patients. Retinal arterial flow velocity was higher in the SCF group compared to the NCF group (3.8 ± 1.1 mm/s vs. 2.92 ± 0.61 mm/s, respectively, $p = 0.022$, Fig. 3). In addition, the SCF group had higher values of serum LDL cholesterol (104.7 ± 18.9 mg/dl vs. 81.6 ± 14.6 mg/dl in NCF, $p = 0.005$), glucose (96.9 ± 23.0 mg/dl vs. 83.6 ± 9.74 mg/dl in NCF, $p = 0.024$), and lower percentage of patients using statins (40.0% vs. 76.9% in NCF, $p = 0.049$) (Table 1).

In the binary logistic regression model, LDL-C levels were significantly associated with SCF (odds ratio–2.59, CI 95% 1.2–13.8, $p = 0.03$) for every 10 mg/dl increase, while statins demonstrated a protective trend (odds ratio–0.2, CI 95% 0.04–1, $p = 0.056$).

We re-divided our cohort into 2 groups according to their median (3.01 mm/s) retinal artery flow velocity: fast retinal flow (FRF) and slow retinal flow (SRF). The mean retinal flow in the SRF was 2.7 ± 0.3 mm/s while in the FRF the average flow was 4.2 ± 0.9 mm/s. Coronary blood flow was slower (24.8 ± 6.4 frames) in the fast retinal flow (FRF) group and Faster (19.5 ± 6.4 frames) in the slow retinal flow (SRF) group, ($p = 0.035$). Similarly, there were significant differences between the FRF and SRF groups in regard to serum

Table 1
Comparison of clinical and laboratory variables between the slow coronary flow (SCF) group, patients with normal coronary flow (NCF) and the entire cohort.

Entire cohort $n = 28$		SCF $n = 15$	NCF $n = 13$	p value
		Number (%) of patients	Number (%) of patients	
22.1 ± 13.7	Mean CTFC (frames)	26.8 ± 5.2	16.7 ± 3.9	<0.0001
3.4 ± 1	Mean RFI (mm/sec)	3.8 ± 1.1	2.9 ± 0.6	0.022
59 ± 11	Age	58.3 ± 10.4	60.0 ± 12.4	0.65
27.6 ± 4.6	Body mass index (kg/m^2)	28.5 ± 5	26.6 ± 4	0.33
3 (11%)	Current smokers	2 (13%)	1 (8%)	0.63
11 (39%)	Past smokers	6 (40%)	5 (39%)	0.0.96
14 (50%)	Hypertension	8 (53%)	6 (46%)	0.71
7 (25%)	Diabetes mellitus	5 (33%)	2 (15%)	0.27
Medications				
9 (32%)	ACE inhibitors	6 (40%)	3 (23%)	0.34
9 (32%)	Aspirin	5 (33%)	4 (31%)	0.89
8 (29%)	β-blockers	5 (33%)	3 (23%)	0.55
1 (1%)	Clopidogrel	0 (0%)	1 (8%)	0.27
3 (11%)	Angiotensin receptor blockers	2 (13%)	1 (8%)	0.63
5 (18%)	Calcium blockers	3 (20%)	2 (16%)	0.75
16 (49%)	Statins	6 (40%)	10 (77%)	0.049
Laboratory results				
0.29 ± 0.01	Ultra-sensitive troponin ng/dl	0.20 ± 1.65	0.04 ± 0.09	0.32
91 ± 19	Glucose (mg/dl)	98 ± 22	85 ± 12	0.03
40 ± 3	Albumin (mg/dl)	40.9 ± 2.4	39.7 ± 3.5	0.56
4.5 ± 8	Hs-CRP (mg/l)	5.1 ± 8.7	2.4 ± 2.5	0.863
101 ± 42	Triglycerides (mg/dl)	104.7 ± 27.8	97.7 ± 52.3	0.370
47 ± 14	HDL-c (mg/dl)	44.5 ± 10.5	50.7 ± 17.2	0.387
93 ± 20	LDL-c (mg/dl)	104.7 ± 18.9	81.6 ± 14.6	0.005
5.6 ± 0.6	HBA1c %	5.6 ± 0.5	5.5 ± 0.8	0.58
39 ± 4	Hematocrit %	39.9 ± 3.9	38.1 ± 3.8	0.225
8.1 ± 2.2	WBC (n/mm^3)	7.6 ± 2.1	8.5 ± 2.2	0.25

NCF: Normal coronary flow, SCF: Slow coronary flow, CTFC: Corrected TIMI frame count, LDL-c: Low density lipoprotein cholesterol, HDL-c: High density lipoprotein cholesterol, Hs-CRP: High sensitive C- reactive protein, WBC: white blood cells.

Table 2
Indications for angiography by our study population.

Indication	Number (%)
Unstable angina	16 (57%)
Stable angina	5 (18%)
Non-specific chest pain	3 (11%)
NSTEMI	1 (4%)
Positive stress test	3 (10%)

NSTEMI: non-ST-segment elevation myocardial infarction.

cholesterol levels (175 ± 124 mg/dl vs. 149 ± 20 mg/dl, respectively, $p = 0.012$) and serum LDL-C levels (103 ± 21 mg/dl vs. 83 ± 14 mg/dl, respectively, $p = 0.02$). There were no differences in risk factors or other laboratory variables between the groups.

In order to evaluate the ability of the RFI system to diagnose SCF non-invasively, we created a receiver operator curve (ROC). The area under the curve was 0.754 ($p = 0.02$). Retinal arterial flow above 3.015 mm/s provided 73% sensitivity and 77% specificity for diagnosing SCF, similar to stress testing for diagnosing ischemia [22] (Fig. 4).

4. Discussion

In the present study, we demonstrate, for the first time, an inverse correlation between retinal and coronary artery blood flow velocities. Retinal blood flow velocity was higher in patients with SCF compared with patients with NCF. SCF could be identified by measuring retinal blood flow with a sensitivity of 73% and specificity of 77%. These results are similar to the capabilities of noninvasive testing such as stress testing for detection of ischemic heart disease [22]. Therefore, RFI testing might help signal out patients with slow coronary flow as opposed to patients with chest pain not related to cardiac causes. It might also offer a simpler method of evaluating endothelial function.

While in this study we evaluated the functional correlation between retinal and coronary blood velocities, other investigators have focused more on the vascular morphology. They demonstrated a correlation between retinal morphological abnormalities and endothelial dysfunction, ventricular remodeling, end organ damage and clinical outcomes [15,23,24]. These changes appear at a later stage of the vascular disease and therefore, RFI might help diagnose patients at an earlier stage.

Using myocardial perfusion cardiac MRI Wang et al. demonstrated that in patients without a history of cardiac disease individuals with lower cardiac perfusion have constricted diameter of the retinal arteries [15].

Wu et al. [25] evaluated patients with coronary artery disease per coronary angiography and used patient with normal coronaries per angiography as controls. They compared central retinal blood flow by Doppler measurements with flow mediated vasodilatation (FMD) of the brachial artery by ultrasound measurements. They found slower retinal artery velocity in the central retinal artery in patients with CAD and lower FMD in that group. It is possible that since they chose patients with known CAD, these patients exhibit more progressive atherosclerosis disease. Furthermore, we evaluated the microcirculation while they evaluated a blood vessel that was significantly larger than the ones we evaluated (160 μm compared to 5–10 μm).

In another study by Burgansky-Eliash et al. [19] it was shown that patients with type 2 diabetes mellitus without morphological changes in the retinal arteries ($n = 14$), exhibit increased retinal blood flow velocities as measured by the RFI device compared to non-diabetic patients ($n = 31$). They demonstrated a significant correlation between diabetic status and increased retinal blood flow velocity after adjustment for cardiac risk factors. Recently, another study using the RFI device also discovered increased retinal blood flow velocity in patients with metabolic syndrome [26]. It may be, that similar to our study, endothelial dysfunction causes

Table 3
Baseline imaging values for the study cohort.

Imaging modality	Measurement
Mean RFI (mm/s)	3.4 ± 1 (1.6–6.4)
TFC LAD (frames)	37.1 ± 12.7 (17–66)
TFC LCx (frames)	21.4 ± 10.2 (7–44)
TFC RCA (frames)	23.3 ± 9.8 (9–48)
Mean CTFC (frames)	22.1 ± 6.9 (10.9–35.8)

CTFC: Corrected TIMI frame count, LAD: Left anterior descending, LCx: Left circumflex, RCA: Right coronary artery.

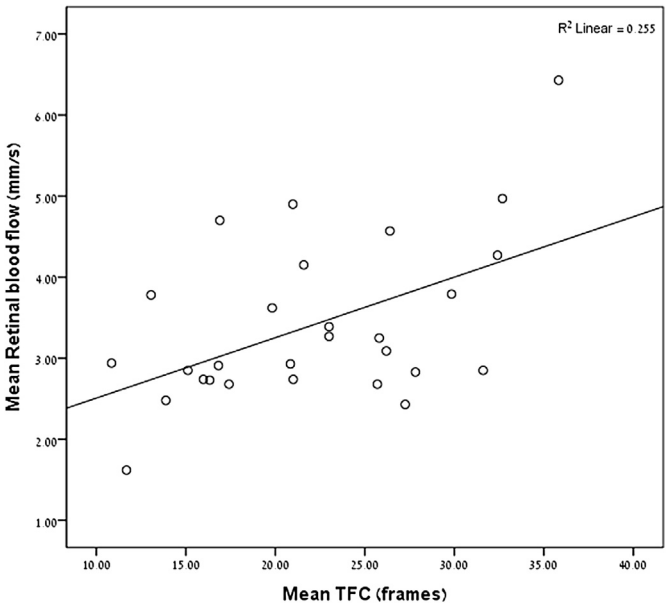

Fig. 2. Representation of the correlation between mean coronary and retinal arterial velocities.

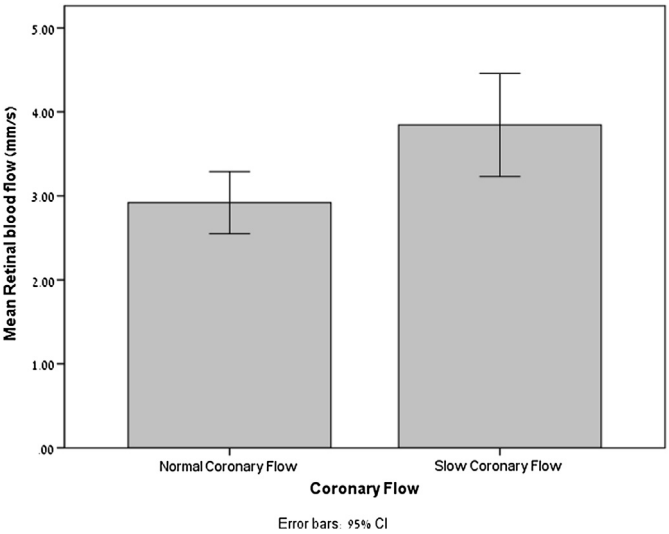

Fig. 3. Comparison of RFI between the slow coronary flow group and normal coronary flow group.

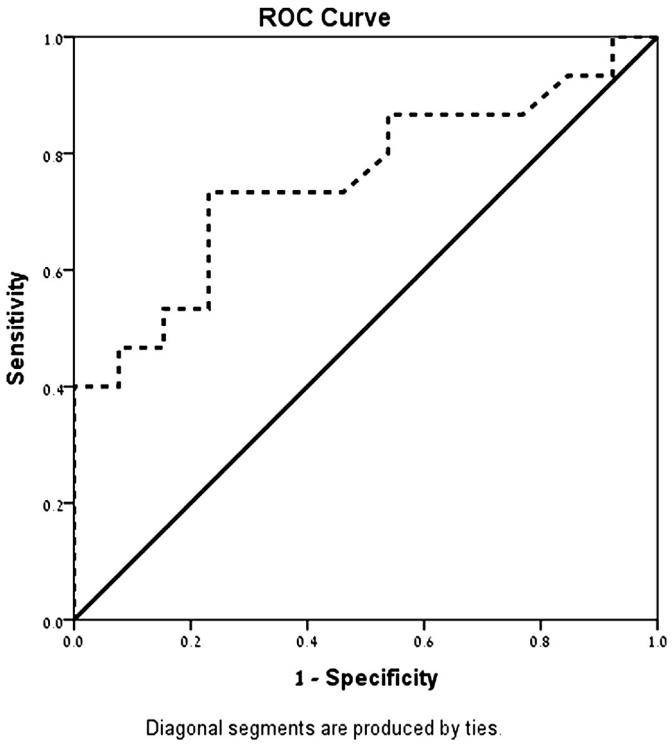

Fig. 4. ROC analysis of RFI as a predictive tool for SCF diagnosis.

increased retinal arterial blood flow velocity in diabetics and patients with the metabolic syndrome.

Indeed increased Intima–Media Thickness in the common carotid artery in patients with CAD, which is recognized as a marker of early atherosclerosis, was also correlated with increased retinal blood flow velocity measured with laser Doppler velocimetry [27].

The inverse correlation of blood velocities between the coronary and retinal vessels can be explained by the differences in the diameters of the blood vessels. Larger vessels (coronaries and central retinal) exhibit reduced velocities due to endothelial dysfunction while smaller vessels (microcirculation) exhibit increased velocities due to hardening of the blood vessels and their relative incompetence in vasodilatation [19]. In addition, a reduction in vessel density is caused by closure of some retinal capillaries leading to further in reduction in total vascular bed diameter [19]. Therefore, the same volume of blood has to be distributed through smaller blood vessels in the microcirculation causing an increase in velocity (Bernoulli Effect). This may impair retinal auto regulation where the retinal microcirculation is attempting to maintain retinal blood flow over a range of systemic blood pressures [28].

Slow coronary flow has been associated with endothelial dysfunction in various studies, most of which have used brachial flow mediated vasodilatation (FMD) as their method of assessing endothelial dysfunction [29]. FMD is a well-accepted method of assessing endothelial dysfunction. FMD evaluates the brachial artery (a relatively large artery) compared the arterioles assessed by the RFI system. However, it is costly, requires expertise to conduct and requires an hour for a full examination. Therefore, RFI might offer an easier and cheaper method of assessing endothelial function in this patient population.

5. Conclusions

In conclusion, in this pilot study, we demonstrated that the RFI device might be able to diagnose patients with SCF non-invasively. Furthermore, we found an inverse correlation between the coronary and retinal arteries in regard to blood velocities.

6. Limitations

The main limitation of the study is the relatively small number of patients. In order to overcome this limitation, we first used Univariate analysis and next, we used the significant variables in the multivariate analysis. Future studies will evaluate the prognostic value of the RFI device in addition to validation of our results.

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References

[1] Panza JA. Myocardial ischemia and the pains of the heart. N Engl J Med 2002;346:1934–5.
[2] Przybojewski JZ, Becker PH. Angina pectoris and acute myocardial infarction due to “slow-flow phenomenon” in nonatherosclerotic coronary arteries: a case report. Angiology 1986;37:751–61.
[3] Kapoor A, Goel PK, Gupta S. Slow coronary flow—a cause for angina with ST segment elevation and normal coronary arteries. A case report. Int J Cardiol 1998;67:257–61.
[4] Chauhan A, Mullins PA, Taylor G, et al. Both endothelium-dependent and endothelium-independent function is impaired in patients with angina pectoris and normal coronary angiograms. Eur Heart J 1997;18:60–8.
[5] Crea F, Lanza GA. Angina pectoris and normal coronary arteries: cardiac syndrome X. Heart 2004;90:457–63.
[6] Egashira K, Inou T, Hirooka Y, et al. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. N Engl J Med 1993;328:1659–64.
[7] Sakr SA, Abbas TM, Amer MZ, et al. Microvascular angina. The possible role of inflammation, uric acid, and endothelial dysfunction. Int Heart J 2009;50:407–19.
[8] Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). Circulation 2004;109:568–72.
[9] Geisler T, Bhatt DL. The role of inflammation in atherothrombosis: current and future strategies of medical treatment. Med Sci Monit 2004;10:RA308–16.
[10] Phan A, Shufelt C, Merz CN. Persistent chest pain and no obstructive coronary artery disease. J Am Med Assoc 2009;301:1468–74.
[11] McGowan CL, Murai H, Millar PJ, et al. Simvastatin reduces sympathetic outflow and augments endothelium-independent dilation in non-hyperlipidaemic primary hypertension. Heart 2013;99:240–6.
[12] Kiernan TJ, Boilson BA, Tesmer L, et al. Effect of enhanced external counterpulsation on circulating CD34+ progenitor cell subsets. Int J Cardiol 2011;153:202–6.
[13] Beck EB, Erbs S, Mobius-Winkler S, et al. Exercise training restores the endothelial response to vascular growth factors in patients with stable coronary artery disease. Eur J Preventive Cardiol 2012;19:412–8.
[14] Rind E, Arbel Y, Finkelstein A, et al. Angiographic evaluation of epicardial and microvascular coronary flow. Isr Med Assoc J 2009;11:173–7.
[15] Wang L, Wong TY, Sharrett AR, et al. Relationship between retinal arteriolar narrowing and myocardial perfusion: multi-ethnic study of atherosclerosis. Hypertension 2008;51:119–26.
[16] American Diabetes A. Standards of medical care in diabetes–2007. Diabetes Care 2007;30:S4–41.
[17] Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. J Am Med Assoc 2003;289:2560–72.
[18] Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
[19] Burgansky-Eliash Z, Barak A, Barash H, et al. Increased retinal blood flow velocity in patients with early diabetes mellitus. Retina (Philadelphia, Pa.) 2012;32:112–9.
[20] Burgansky-Eliash Z, Lowenstein A, Neuderfer M, et al. The correlation between retinal blood flow velocity measured by the retinal function imager and various physiological parameters. Ophthalmic Surg Lasers Imaging Retina 2013;44:51–8.
[21] Chhablani J, Bartsch DU, Cheng L, et al. Segmental reproducibility of retinal blood flow velocity measurements using retinal function imager. Graefe's Arch Clin Exp Ophthalmol = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2013 May 23 [Epub ahead of print].

[22] Fox K, Garcia MAA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341–81.
[23] Witt N, Wong TY, Hughes AD, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. Hypertension 2006;47:975–81.
[24] McClintic BR, McClintic JI, Bisognano JD, et al. The relationship between retinal microvascular abnormalities and coronary heart disease: a review. Am J Med 2010;123(374):e371–377.
[25] Wu Y, Li S, Zu X, et al. Changes of central retinal artery blood flow and endothelial function in patients with coronary artery disease. Curr Eye Res 2007;32:813–7.
[26] Gutfreund S, Izkhakov E, Pokroy R, et al. Retinal blood flow velocity in metabolic syndrome. Graefe's Arch Clin Exp Ophthalmol = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2013;251:1507–13.
[27] Nagaoka T, Ishii Y, Takeuchi T, et al. Relationship between the parameters of retinal circulation measured by laser Doppler velocimetry and a marker of early systemic atherosclerosis. Invest Ophthalmol Vis Sci 2005;46:720–5.
[28] Patton N, Aslam T, Macgillivray T, et al. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 2005;206:319–48.
[29] Sezgin AT, Sigirci A, Barutcu I, et al. Vascular endothelial function in patients with slow coronary flow. Coron Artery Dis 2003;14:155–61.