Systemic Vascular Endothelial Function in Patients with Central Retinal Vein Occlusion

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ABSTRACT

Purpose: The aim of our study was to evaluate peripheral vascular endothelial function in patients with central retinal vein occlusion (CRVO) by measuring flow-mediated dilatation (FMD).

Materials and Methods: Our sample included 28 patients with CRVO (Group 1), 31 patients with systemic hypertension (Group 2) but no other systemic or ocular disease, and 29 age- and sex-matched healthy volunteers (Group 3). We excluded participants with diabetes mellitus, cardiovascular disease, dyslipidemia, renal dysfunction, or a smoking habit. A cardiologist assessed the responses of endothelial function in all participants by measuring the FMD following brachial artery occlusion.

Results: In Doppler measurements of the brachial artery, the brachial artery FMD value was 5.7±2.2 % in Group 1, 7.9±3.1 % in Group 2, and 15.6±7.9 % in Group 3. The arterial FMD values were significantly lower in patients with CRVO compared with healthy and hypertensive groups ($p < 0.001$ and $p = 0.004$, respectively).

Conclusion: Our findings indicate that systemic endothelial dysfunction may be associated with CRVO.

Keywords: Central retinal vein occlusion, Flow-mediated dilatation, Endothelial dysfunction.

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy in prevalence among retinal vascular diseases.[1] In fact, approximately 2.5 million people suffer from central retinal vein occlusion (CRVO), and this number will continue to increase as the global population ages.[1-3] Previous studies have documented the systemic risk factors of CRVO, including hypertension, hyperlipidemia, renal dysfunction, coagulation disorders, arterial emboli, and diabetes mellitus.[4-12] Anatomical factors such as crowding and compression at the level of the lamina cribrosa (LC) might additionally contribute to turbulent flow in the area, as well as the narrowing of the central venous lumen and the occlusion at the lamina cribrosa.[13] However, the exact mechanism of CRVO remains unclear.

Vascular endothelium is the largest organ that regulates the endothelium, vascular structure and functions, and vasomotor tonus, each by synthesizing and secreting various hormones.[14] Endothelial dysfunction is characterized by reduced nitric oxide (NO) bioavailability, that resulting in an increase in oxidation, development of vasoconstriction, leukocyte adhesion, impaired coagulation, platelet activation and thrombosis, leading to vascular inflammation.[15] Different invasive and non-invasive methods are used to measure vascular endothelial function. Of these, measuring the endothelium-dependent flow-mediated dilatation (FMD) of the brachial artery with two-dimensional Doppler ultrasonography is the most useful technique, given its high correlation with angiographic results.[16] During reperfusion after brachial artery occlusion hyperemia-induced transient ischemia leads increased stress in arterial wall and it causes vasodilation by promoting endothelial NO release.[17] To date, the FMD measurements have been used to evaluate peripheral endothelial function in patients with cardiovascular risk factors, including diabetes mellitus, hypertension, hyperlipidemia and smoking.[16-18] In this study, we evaluated the FMD in patients with CRVO in

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Received: 13.04.2021
Accepted: 08.10.2021

Ret-Vit 2021; 31: 9-14

DOİ:10.37845/ret.vit.2022.31.3

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order to determine whether systemic vascular endothelial dysfunction is associated with CRVO.

MATERIAL AND METHODS

This prospective study was performed according to principles of the Declaration of Helsinki and approved by the local ethics committee. All participants provided written informed consent for the collection and publication of their clinical data. The 28 patients with CRVO, 31 patients with systemic hypertension but no other systemic or ocular diseases, and 29 healthy volunteers were included in this study. All patients received a thorough ophthalmologic examination, including slit-lamp microscopy, retinoscopy, an examination of the fundus using a 90-diopter lens, and an assessment of best-corrected visual acuity (BCVA) and intraocular pressure. Diagnosis of the CRVO was verified based on results of fundus examination, optical coherence tomography images, and fundus fluorescein angiography findings by an experienced retina specialist. All patients of demographic and medical clinical data, including body mass index (BMI), inflammatory marker (CRP) levels, hypertension, and hypercholesterolemia were collected. Hypertension was diagnosed in all subjects who had antihypertensive medication or systemic blood pressure exceeded 140/90 mmHg. In our routine clinical practice, all patients were referred to internal medicine and cardiology clinics to investigate the presence of any systemic disease that may cause CRVO. Also, the medical data records of healthy participants were retrospectively reviewed in this study.

We excluded from our sample all patients with congestive cardiac failure, coronary heart disease, renal failure, liver dysfunction, hyperlipidemia, diabetes mellitus, chronic systemic disease including autoimmune disease, glaucoma, age-related macular degeneration, intraocular inflammatory disease, or any history of previous cerebrovascular events etc., as well as those who had undergone ocular surgery in the previous 6 months. We also excluded patients who had a sedentary lifestyle, patients with obese, alcohol and smoking consumption habits, use of any medication, except antihypertensive drugs. Before of FMD measurement, all participants fasted for at least 6 hours and avoided all exercise for at least 8 hours, along with all food and drink containing caffeine or alcohol.

We referred all participants to the cardiology clinic for FMD measurement. A cardiologist blinded to the clinical characteristics of patients measured all patients' FMD in the brachial artery by way of a two-dimensional, high-resolution ultrasound device (7.0-13.0 MHz, Siemens Medical Sol, Mountain View, CA, USA). In a dark, silent room with a temperature of 22-25 °C, we also performed an imaging study in the morning from 9:00 to 10:00 am. Prior to all measurements, participants received 10 min of rest in the supine position, and we applied electrocardiogram (ECG) monitoring throughout our measurements. We measured the brachial artery at a point 3-5 cm superior to the antecubital fossa. Transition zone was set at a depth between area at 3 cm depth and closer wall. By magnifying the image, we marked the intermediate zone between the tunica media and adventitia. We assessed blood flow velocity and volume with pulse Doppler sonography by way of two-dimensional images generated by a signal obtained from the center of the artery with a sampling angle of 65-70° and sampling distance of 1 mm. We obtained an occlusion of 5 min by inflating the cuff up to 250 mmHg in the area of the brachial artery, two-dimensional images of which we recorded 60 s after deflation and measurements of which we recorded in terms of the R wave on the ECG (i.e., end-diastole). We accepted the flow-mediated vasodilatation value as the percent change of the vessel width (i.e., response of the brachial artery diameter to hyperemia) compared to the basal value. We calculated flow-mediated dilatation using the following formula: [(post-occlusion diameter - basal diameter) / basal diameter] × 100 (Figure 1).

Statistical analysis

All analyses were performed using the SPSS for Windows V.21.0 software package (SPSS Inc., Chicago, Illinois). The variables were presented as mean±standard deviation (SD). The normal distribution of all variables was determined with Kolmogrov-Smirnov test. Categorical variables between groups were compared using the chi square test. Differences in measured parameters between the all groups were analyzed with a one-way ANOVA analysis of variance followed by post hoc comparison with the Tukey procedure. Pearson's correlation was used to examine the relationship between the continuous variables. A p value less than 0.05 was accepted as significant.

RESULTS

Our sample included 28 patients (12 male and 16 female) with CRVO in Group 1, 31 patients with systemic hypertension (14 male and 17 female) but no other systemic or ocular disease in Group 2, and 29 healthy volunteers (13 male and 16 female) in Group 3. The mean age of Group 1, 2 and 3 were 63.5±8.1 (57-72), 62.7±5.6 (55-74) and 61.9±6.2 (54-71) years, respectively. The average duration from onset of CRVO to measurement was 1.7±0.8 months (range 1-3 months). A total of 28 patients were diagnosed with unilateral CRVO. Of these, 5 patients were ischemic type and 23 of them were non-ischemic type CRVO. The demographic characteristics and laboratory findings of the patients were summarized in Table 1. There was no statistically significant difference in terms of demographic

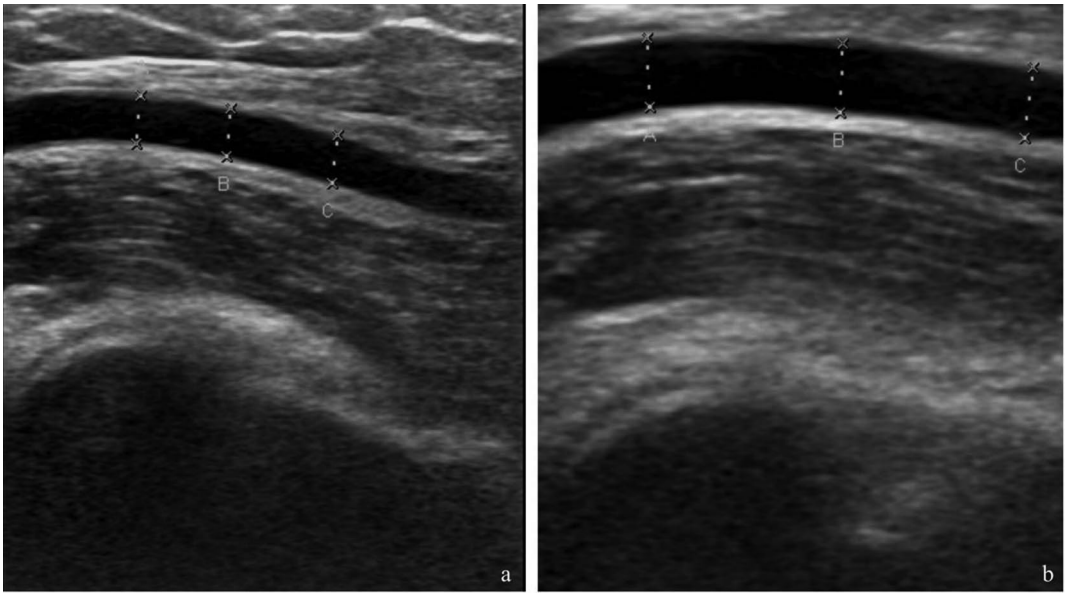

Figure 1: *High resolution ultrasound measurement of brachial artery diameter a) before occlusion (baseline), b) 60 s after post-occlusion.*

Table 1: *Demographic, clinical characteristics and vessel diameters values of the subjects*

	CRVO Group (n=28)	Hypertension Group (n=31)	Healthy group (n=29)	p*
Age (years)	63.5±8.1	62.7±5.6	61.9±6.2	0.614
Men/women	12/16	14/17	13/16	0.341
SBP (mmHg)	125.7±9.5	131.2±11.3	117.5±6.9	**0.04****
DBP (mmHg)	83.2±7.6	87.1±10.8	77.3±7.5	0.06
BMI kg/m^2	24.1±2.4	25.3±2.8	23.1±2.6	0.127
Cholesterol, mg/dL	184.2±25.1	191.6±28.4	185.7±31.6	0.114
Fasting glucose	84.5±9.8	88.1±10.7	79.5±7.3	0.09
CRP, mg/dL	1.9±1.2	1.9±1.5	1.8±0.9	0.461
Baseline vessel diameter (mm)	3.90±0.67	3.86±0.62	3.68±0.52	0.376
Post-occlusion vessel diameter (mm)	4.14±0.67	4.16±0.59	4.25±0.60	0.800
FMD (%)	5.7±2.2	7.9±3.1	15.6±7.9	**<0.001**

CRVO, central retinal vein occlusion; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; *, One way ANOVA test; **, chi square test

characteristics, clinical data and laboratory findings between the groups (p>0.05 for all). In Group 1, 4 of 28 patients (14.2%) exhibited systemic hypertension, all of whom were taking antihypertensive drugs. There were no significant differences between the CRVO patients and healthy individuals for systolic and diastolic blood pressure (p>0.05).

Figure 1 shows two-dimensional images of the brachial artery at baseline (a) and 60 s after deflation of cuff (b). The baseline vessel diameter was 3.90±0.67 mm in the Group 1, 3.86±0.62 mm in the Group 2 and 3.68±0.52 mm in the Group 3. There was no significant difference in baseline vessel diameters between the groups (p=376). After cuff release, the post-occlusion vessel diameter was 4.14±0.67 mm in the Group 1, 4.16±0.59 mm in the Group 2 and 4.25±0.60 mm in the Group 3. The change in vascular diameters of the group 1 was lower than those of the Group 2 and 3 (p=0.001 and p<0.001). After calculating flow-mediated dilatation values, brachial arterial FMD value was 5.7±2.2% in Group 1, 7.9±3.1% in Group 2, and 15.6±7.9% in Group 3. Arterial FMD values in Group 1 were significantly lower than that of the Group 3 (p<0.001). Also, there was a significant difference in terms of FMD values between the Groups 1 and 2 (p=0.004).

No significant relationship was found between the FMD values and the laboratory parameters in groups (p>0.05 for all).

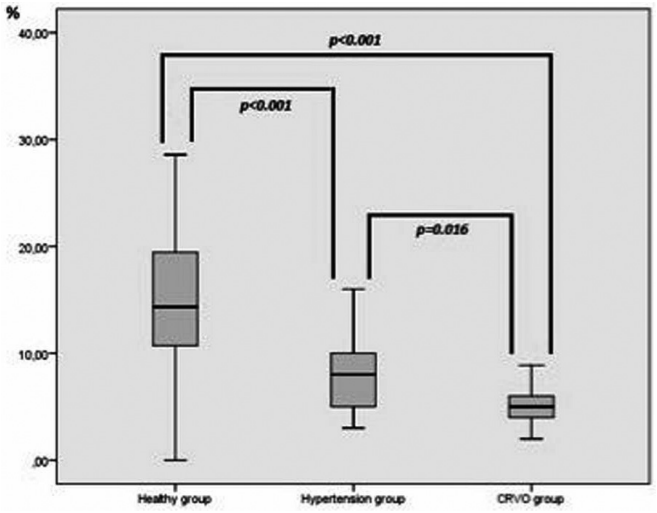

Figure 2: *The mean FMD value significantly lower in the CRVO group (5.7±2.2%) compared with the hypertension group (7.9±3.1%, p=0.004) and the healthy group (15.6±7.9%, p<0.001). The mean FMD value of hypertension group decreased significantly compared with healthy group (p<0.001)*

DISCUSSION

Previous studies have used FMD measurements to report systemic endothelial function in patients with ocular diseases such as glaucoma,[19-21] diabetic retinopathy,[22,23] branch retinal vein occlusion (BRVO),[24] and wet-type age-related macular degeneration.[25] To our knowledge, however, ours is the first study to demonstrate peripheral vascular endothelial dysfunction in patients with CRVO by using FMD. In the present study, the FMD value in patients with CRVO was significantly lower than that of age- and sex-matched hypertensive patients and healthy controls. We show that peripheral endothelial function was impaired in patients with CRVO compared with healthy controls. Our findings suggest that peripheral vascular endothelial dysfunction may be associated with the pathogenesis of CRVO as an independent risk factor.

Endothelium plays a major role in the regulating blood flow and vascular function by secreting relaxation and constriction inducing substances such as nitric oxide and endothelin-1 (ET-1) in the vessels' smooth muscles in addition to responses to several vasoactive agents and hormones. Hyperemia-induced transient ischemia causes increased stress in the brachial artery wall, which in turn causes vasodilation by promoting endothelial NO release.[26-28] Indeed, disequilibrium between NO and ET-1 prompts ischemia and vascular dysregulation.[29] Leoncini et al. reported that patients with RVO exhibited a lower basal level of nitric oxide compared with healthy patients, both in resting and stimulated platelets.[26] Meanwhile, Iannaccone et al.[30] reported that the plasma level of ET-1 increased in patients with retinal vein occlusion, whereas Flammer et al. posited that a local increase of ET-1 in patients with RVO could result from high plasma levels, since ET-1 can diffuse from the fenestrated capillaries of the choroid into the optic nerve head by bypassing the blood retinal barrier.[31]

This hormonal response of the vascular structure can be evaluated with FMD as an index of vasomotor function. FMD is a feasible, readily available diagnostic method of measuring arterial endothelial function in clinical trials.[26] It offers a high-frequency sonographic visualization of any brachial artery, exhibiting endothelial-dependent and flow-mediated vasodilation. Furthermore, the technique has noninvasive nature and allows the reproducibility of measurements and improved patient adherence.[28] Although no definite cutoff value exists, many researchers consider any FMD value of less than 7% to signify endothelial dysfunction.[26,28]

Numerous previous studies have reported that systemic endothelial dysfunction is implicated in the pathogenesis of several retinal vascular disorders, including diabetic retinopathy[22,23] and BRVO.[24] Tanano et al. reported significant impairment of the FMD in the brachial arteries in patients with BRVO and suggested that peripheral vascular endothelial dysfunction might be associated with the pathogenesis of BRVO.[24] Another study reported that systemic endothelial dysfunction appears to be related with diabetic retinopathy in patients with type 2 DM. Also, they found that there were no significant differences in term of arterial FMD values between the BRVO group and DM groups (4.6 ± 0.4% vs. 4.7 ± 1.4%, p = 0.18). In our study, we observed that arterial FMD values in patients with CRVO were significantly lower than that of the healthy groups (5.7±2.2% and 15.6±7.9% p<0.001). Also, after post-occlusion phase, the increase in vascular diameters of the CRVO groups was lower than those of the hypertension and healthy groups (p=0.001 and p<0.001). These results suggest that there was an impairment systemic vascular endothelial function in patients with CRVO. Considering the relationship between the underlying mechanism of CRVO development and vascular endothelial dysfunction, it has been suggested that CRVO is the consequence of the damage on the vein vascular endothelium and venous velocity changes in the region of the lamina cribrosa. The velocity of the blood flow increases due to narrowing vein in the region of the LC in comparison with other parts of the vein. Hemodynamic shear stress is occurred on the venous wall due to increased blood flow velocity and turbulant flow in the region of posterior LC. Hemodynamic shear stress could cause venous endothelial damage and explain the presence of endothelial proliferation with or

without thrombus formation in CRVO.[13] Nevertheless, it is still unclear whether and to which extend impaired FMD values could reflect retinal vessel endothelial dysfunction. Considering our study results, our findings indicate that the impaired FMD values may reflect the endothelial dysfunction in the retinal microvasculature in patients with CRVO. Thus, we suggest that peripheral vascular endothelial dysfunction could be associated with CRVO pathophysiology.

Although BRVO and CRVO have similar risk factors, previous studies have noted that systemic hypertension was a greater risk factor for the development of BRVO than CRVO.[32,33] Important factors that signify a relationship between BRVO and hypertension are degenerative changes in the vessel wall and the compression of the vein at the arteriovenous crossing site.[34] Tanano et al. reported that the FMD values in patients with BRVO decreased significantly compared with the hypertension group.[24] Similarly, in our study, the FMD values in the CRVO group were significantly lower than that of the hypertension group (5.7±2.2% and 7.9±3.1% p=0.004). Recent a study was documented an increase in arterial stiffness in patients with RVO, suggesting an important role for systemic arterial stiffness in the disease onset.[35] The central retinal artery and vein pass through the lamina cribrosa region in the same adventitial sheath. It is considered that the more rigid arterial wall compresses the vein, increasing thus the likelihood of central vein occlusion. This finding may indicate that arterial stiffness plays an important role in the pathophysiology of CRVO.

Our study has several limitations. First, this study was conducted with a small number of participants due to strict exclusion criteria. Second, a small number of patients in the CRVO group had hypertension. This may have affected the FMD values in CRVO patients. However, FMD values in the hypertension group were significantly greater than those in the CRVO group. Third, we did not evaluate the endothelium-independent vasodilatation with nitroglycerin given the risk-benefit considerations of using nitroglycerin in elderly patients. As such, we could not exclude the possible effect of smooth muscle dysfunction in patients with CRVO.

In conclusion, we observed that arterial FMD values in patients with CRVO were significantly lower than that of the healthy groups. Our findings suggest that systemic endothelial dysfunction may be associated with CRVO, providing further insights in the pathophysiology of the disease.

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