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Endothelial dysfunction is related to central retinal artery occlusion

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Abstract

Aim: Central retinal artery occlusion (CRAO) leads to significant, non-painful loss of sight due to retinal infarction. Most CRAO patients have atherosclerotic risk factors. Pulse wave velocity (PWV) and Flow-mediated dilatation (FMD) can provide insights into the onset and development of atherosclerosis. This research aims to assess arterial stiffness measures and identify endothelial dysfunction in individuals with CRAO.

Materials and Methods: 33 consecutive CRAO patients (63 ± 7 years, 21 men (63.6%)) were recruited in the study. 35 age /sex-matched participants were included as a control group. FMD and PWV were measured from the brachial artery, as indicators of endothelial dysfunction and atherosclerosis in the arterial wall, respectively. Additionally, the transthoracic echocardiographic parameters of the patients were investigated.

Results: CRAO patients had significantly higher frequencies of hypertension, hyperlipidemia, and smoking status. Furthermore, the frequency of diabetes was also higher in the CRAO group, but this difference did not reach statistical significance. CRAO patients showed markedly elevated PWV and reduced FMD. However, no notable differences were observed between groups in terms of left ventricle systolic and diastolic functions.

Conclusion: Our study showed that CRAO patients may have increased arterial stiffness and endothelial dysfunction. Systemic endothelial dysfunction and atherosclerosis may be linked to the development of CRAO.

Introduction

Central retinal artery occlusion (CRAO) is one of the most severe ophthalmologic emergencies that cause rapid and severe vision loss [1]. CRAO is categorized into two types based on its fundamental pathophysiology [2]. More than 90% of cases are non-arteritic CRAO, typically caused by thromboembolism arising from the heart, carotid artery, or arcus aorta; while arteritic CRAO, which is less common, often develops secondary to vasculitis or autoimmune diseases [1,3]. Although the precise pathophysiology of CRAO is not fully understood, the prognosis is poor if prolonged retinal ischemia occurs [1].

Endothelial dysfunction plays a crucial role in atherosclerosis as endothelium is responsible for regulating vascular tonus, platelet function, and leukocyte adhesion [4]. Flow-mediated dilation (FMD) is a widely used method to evaluate the function of endothelium and to predict future cardiovascular disease (CVD) risk [5]. FMD has been associated with subclinical target organ damage and is one of the factors indicating the development of atherosclerosis [6].

Arterial stiffness denotes a reduction in the elasticity of the arterial wall and indicates actual damage to the artery [7,8]. Pulse wave velocity (PWV) which is a noninvasive evaluation method of arterial stiffness, can be used to detect both early and cumulative vascular damage [7]. It is a prognostic factor for cardiovascular (CV) events, including mortality [9]. Also, PWV is a superior predictor of CV outcomes in cases where baseline CV risk is high, such as the presence of hypertension, diabetes, or coronary artery disease [10].

CRAO patients have common risk factors with CVD [11]. However, the main mechanism connecting these two entities is still unclear. Mechanical properties of the arterial wall and endothelial function are major factors in CV pathophysiology [4,12]. Therefore, our study aimed to determine a possible relationship between the development of CRAO, endothelial function, and arterial wall properties.

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Materials and Methods

This investigation complied with the principles outlined in the Declaration of Helsinki. The local ethics committee approved the study (Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee, Decision No: 2024/010.99/6/8). Written informed consent was obtained from all participants before participating.

Study population

Forty-five consecutive patients aged 18 years or older, who were diagnosed with non-arteritic CRAO, were invited to take part in this research. The diagnosis of CRAO was determined by the ophthalmologist during a comprehensive ophthalmic examination based on the sudden onset of painless vision impairment, the presence of a relative afferent pupillary defect, ischemic retinal edema, segmentation of blood flow in the retinal arterioles, retinal arteriolar attenuation, and fundus biomicroscopic examination revealing normal optic disc. In selected cases, imaging techniques confirmed the diagnosis with early findings such as inner retinal hyperreflectivity on optical coherence tomography and reduced blood flow through the arterioles seen on fundus fluorescein angiography.

After excluding the 12 patients with exclusion criteria the remaining 33 patients were included. Exclusion criteria included arrhythmia, peripheral artery disease, connective tissue disease, and conduction abnormalities. Patients with a history of ocular diseases (glaucoma, diabetic retinopathy, any stages of hypertensive retinopathy, uveitis, age-related macular degeneration, high myopia, etc.) or previous ophthalmic surgeries that could impact the choroidal vascular network were also excluded. As a control group, the study included 35 volunteers matched for age and sex who had normal biomicroscopic examination and no prior history of thromboembolic events.

Intraocular pressure, LogMAR-converted visual acuity levels, and biomicroscopic findings of the anterior and posterior segments, as well as the severity of CRAO, were recorded at the presentation.

All study groups had a detailed cardiac examination including history, physical examination, and standard 12-lead electrocardiography. Comorbidities, including hypertension, hyperlipidemia, and diabetes were evaluated. Diabetes was stated as a fasting blood glucose level of $\geq$126 mg/dl in at least two consecutive measurements, a prior diagnosis of diabetes, or the use of anti-diabetic medications. Hyperlipidemia was considered as total cholesterol $\geq$200mg/dl, serum triglyceride $\geq$150mg/dl, or LDL cholesterol $\geq$130 mg/dl, prior diagnosis of hyperlipidemia or present use of lipid-lowering medication. Hypertension was stated as a blood pressure $\geq$140/ 90 mmHg or current use of antihypertensive drug therapy. Family history (first-degree relative) of cardiovascular disease and smoking status were recorded.

All patients received a comprehensive transthoracic echocardiographic examination using a Philips Epic echocardiography device (Philips Medical Systems, Andover, MA, USA) by an experienced cardiologist within the first three days after the onset of central retinal artery occlusion. Echocardiographic measurements were conducted in accordance with the recommendations of the American Society of Echocardiography guidelines [13]. The Biplane Simpson method was used to calculate LVEF.

Flow-mediated dilatation (FMD) assessment

The endothelial functions of the patients were evaluated in a room with a constant temperature of 22-24 °C in the morning after 8-12 hours of fasting by a single experienced cardiologist blinded to the clinical characteristics of the patients. It was assessed noninvasively via brachial artery ultrasonography using a Vivid 7 (GE Healthcare, Horten, Norway) ultrasound system equipped with a 10 MHz linear transducer, following established protocols [14]. Baseline measurements of resting end-diastolic lumen diameter and blood flow of the right brachial artery were taken initially. Following this, a sphygmomanometer cuff was positioned on the forearm and inflated to a supra-systolic level for 5 minutes to ensure arterial occlusion. Lumen diameter was estimated 1 minute after cuff deflation at the same site. FMD was calculated as the percentage increase in lumen diameter relative to baseline measurement during the first minute of reactive hyperemia. Three consecutive measurements were averaged. Intra-observer variability (mean of differences) for repeated measurements in our laboratory was 0.00$\pm$0.11 mm.

Arterial stiffness assessment

Arterial stiffness was evaluated early in the morning (between 08.00-10.00 am) in a quiet, temperature-controlled room while patients were in a supine position. This assessment was conducted after the patients had rested for 30 minutes and abstained from consuming alcohol, coffee, tea, or food for at least 12 hours before the study. Measurements were obtained from the brachial artery using a Mobil-O-Graph arteriography system (Mobil-O-Graph NG, Stolberg, Germany) by a single cardiologist blinded to patient clinical characteristics.

The cuff was inflated to a value 35 mmHg above the measured systolic blood pressure value, and blood flow from the brachial artery was interrupted for an average of 8 seconds. Despite this high pressure, the system can detect the signals coming from the brachial artery. This measurement method relies on the analysis of the formation and morphology of two systolic waves. The early systolic peak is the pulse wave formed by the spread of myocardial contraction downwards through the aorta in systole. The late systolic peak occurs by the reflection of the initial wave of the aortic wall at the distal branching site, and its shape is affected by the stiffness of the large artery. PWV was calculated as specified in the guideline [15].

Statistical analysis

Statistical analyses were conducted using SPSS 21.0 for Windows (Chicago, IL, USA). Continuous variables were assessed for normality using the one-sample Shapiro–Wilk test. Continuous variables displaying normal distribution were presented as the mean $\pm$ standard deviation, and values not displaying normal distribution were expressed as median, 25^{th}- 75^{th} percentiles, and interquartile range. Comparison of normally distributed data was compared

with the independent sample Student's t-test, and values not displaying normal distribution were analyzed using the Mann–Whitney U test. Categorical data were reported as numbers or percentages and the chi-square test was used to compare them. The threshold for statistical significance was chosen to be a p-value of <0.05.

Results

The study included sixty-eight patients and 33 of them (48.5%) had CRAO. In the CRAO group, loss of vision lasted between 2 hours and 8 days. At the baseline visit, the best-corrected visual acuity (BCVA) ranged from light perception to counting fingers at half a meter. The mean intraocular pressure was 18.2 mmHg (r:13-22 mmHg). All patients exhibited a significant relative afferent pupillary defect. Twenty-eight patients had pale fundus with the "cherry-red spot" and 5 patients had no cherry spot sign.

The demographic features and laboratory measurements of the patients are detailed in Table 1. The groups were matched for age and sex. The CRAO group had significantly higher rates of hypertension, hyperlipidemia, and smoking compared to the control group. While the frequency of diabetes was also higher in the CRAO group, this difference was not statistically significant. Moreover, the CRAO group had significantly elevated levels of hs-CRP compared to the control group.

Tablo 2 provides the arterial stiffness parameters and brachial artery measurements for groups. The CRAO patients showed significantly elevated peripheral systolic blood pressure, peripheral diastolic blood pressure, and PWV (p <0.001 for all parameters). The CRAO group exhibited a 25.8 % reduction in FMD % (p <0.001).

The conventional echocardiographic parameters are presented in Table 3. Although the CRAO group had slightly larger left atriums, thickened left ventricle walls, and larger left and right ventricles than the control group, these values were within the normal range. Furthermore, the left ventricular ejection fraction did not differ significantly among the patients. When echocardiographic diastolic function parameters were examined, the patient group showed septal e'<7 and lateral e'<10. However, diastolic functions were deemed normal due to left atrial volume index (LAVI) <34 mL/m^2, tricuspid regurgitation velocity <2.8 m/sn and E/e'<14.

Table 1. Demographic characteristics of the patients and controls.

	CRAO group (n=33)	Control (n=35)	p
Age (years)	63 ± 7	66 ± 8	0.66
Male sex (n – %)	21 (63.6%)	20 (57.1%)	0.12
Hypertension (n – %)	25 (75.7%)	13 (37.1%)	**<0.001**
Diabetes mellitus (n – %)	12 (36.3%)	10 (28.5%)	0.065
Hyperlipidemia (n – %)	14 (42.4%)	7 (20%)	**<0.001**
Family history of CVD (n – %)	24 (72.7%)	28 (80%)	0.059
Smoking (n – %)	23 (69.6%)	20 (57.1%)	**0.032**
Glucose (mg/dL)	93.25 ± 47.10	89.14 ± 50.24	0.35
hs-CRP (mg/L)	3.67 ± 1.5	2.77 ± 0.94	**0.014**

CRAO: Central retinal artery occlusion; CVD: Cardiovascular disease; hs-CRP: High sensitive C reactive protein.

Table 2. Comparison of brachial artery measurements among groups.

	CRAO group (n=33)	Control (n=35)	p
FMD percent (%)	6.18 ± 2.63	8.33 ± 1.97	**<0.001**
Peripheral systolic blood pressure (mmHg)	139.24 ± 40.75	124.60 ± 31.33	**<0.001**
Peripheral diastolic blood pressure (mmHg)	94.52 ± 25.56	86.33 ± 28.22	**<0.001**
Heart rate (beat/min)	84.25 ± 24.39	79.87 ± 27.65	0.058
PWV (m/sn)	6.90 ± 0.58	6.03 ± 0.21	**<0.001**

CRAO: Central retinal artery occlusion; FMD: Flow-mediated dilation; PWV: Pulse wave velocity.

Discussion

In this study, we evaluated the arterial stiffness parameters and endothelial function in CRAO patients. Our findings revealed significantly higher PWV and reduced FMD in these patients compared to controls. These results highlight the presence of atherosclerotic changes in arterial walls and endothelial dysfunction among CRAO patients.

The term endothelial dysfunction refers to the impairment of endothelium-mediated vasodilation, but it is used to refer to conditions that lead to endothelial activation, such as leukocyte adhesion and platelet aggregation. Endothelial dysfunction causes changes in the initial stages of the atherosclerotic process and plays a role in dynamic plaque control in the late period [16]. In addition, atherosclerosis itself appears as a factor that worsens endothelial dysfunction [17]. In other words, these two pathologies are both the cause and the result of each other.

Endothelial vasodilation is impaired in individuals with atherosclerotic risk factors such as hypercholesterolemia, hypertension, and diabetes, and may be an indicator of atherosclerotic disease activity [4]. Studies show that systemic microvascular dysfunction may contribute to the development of various retinal vascular disorders [18,19]. However, it remains unclear whether reduced FMD reflects locally impaired endothelial function in the retinal microvasculature. Furthermore, there are not many studies revealing the relationship between FMD and CRAO. Almost all previous research exploring the link between retinal vascular obstruction and endothelial dysfunction has focused on retinal veins [20,21]. In our study, we showed a decrease in FMD in the patient group by one-quarter. The only study on this subject recently showed that vascular endothelial damage characterized by a decrease in FMD was found in CRAO patients, which is consistent with our result [11]. Additionally, in a follow-up study, the progression of end-organ damage with FMD was predicted in the presence of known predisposing factors [22]. This could facilitate the use of FMD in the follow-up of asymptomatic patients with risk factors for developing CRAO.

Table 3. Echocardiographic parameters of study groups.

		CRAO group (n=33)	Control (n=35)	p
LVEDD (mm)	Median (25-75th percentile) (IQR)	46 (43–50) (7)	42 (41-46) (5)	**0.02**
LVESD (mm)	Median (25-75th percentile) (IQR)	30 (27-32) (5)	28 (27-29) (2)	0.38
LVEF (%)	Median (25-75th percentile) (IQR)	58 (54-63) (9)	60 (56-64) (8)	0.70
LA diameter (mm)	Median (25-75th percentile) (IQR)	36 (34–38) (4)	33 (30–35) (5)	**0.018**
LV mass index (g/m^2)	Median (25-75th percentile) (IQR)	94.6 (80.0-119.6) (39.6)	67.6 (54.5-76.3) (21.8)	**<0.001**
IVS thickness (mm)	Median (25-75th percentile) (IQR)	12 (10–14) (4)	8 (7–9) (1)	**<0.001**
PW thickness (mm)	Median (25-75th percentile) (IQR)	10 (9-11) (2)	8 (7-9) (2)	**<0.001**
LAVI (mL/m^2)	Median (25-75th percentile) (IQR)	32.4 (30.6-40.0) (9.4)	24.6 (20.2-27.4) (7.2)	**<0.001**
E (m/s)	Median (25-75th percentile) (IQR)	0.7 (0.6-0.9) (0.2)	0.7 (0.5-0.78) (0.28)	0.27
A (m/s)	Median (25-75th percentile) (IQR)	0.8 (0.7–0.88) (0.18)	0.7 (0.6–0.8) (0.2)	0.07
Deceleration time (ms)	Median (25-75th percentile) (IQR)	209 (170-237) (67)	175 (162-204) (42)	**0.03**
E/A ratio	Median (25-75th percentile) (IQR)	0.86 (0.76-1.2) (0.44)	0.82 (0.7-1.1) (0.4)	0.26
Lateral e' (cm/s)	Median (25-75th percentile) (IQR)	6.8 (6.0–8.7) (2.7)	8.9 (6.9–11.9) (5)	**0.02**
Lateral a' (cm/s)	Median (25-75th percentile) (IQR)	10.3 (8.4-11.6) (3.2)	10.1 (8.7-12.2) (3.5)	0.69
Lateral s' (cm/s)	Median (25-75th percentile) (IQR)	7.8 (6.4–8.9) (2.5)	8.1 (7.0–9.3) (2.3)	0.33
Septal e' (cm/s)	Median (25-75th percentile) (IQR)	5.8 (4.6-7.8) (3.2)	7.4 (5.8-8.7) (2.9)	**0.03**
Septal a' (cm/s)	Median (25-75th percentile) (IQR)	9.0 (7.9–10.4) (2.5)	8.9 (7.7–10.2) (2.5)	0.79
Septal s' (cm/s)	Median (25-75th percentile) (IQR)	6.6 (5.4-6.9) (1.5)	6.5 (5.6-7.3) (1.7)	0.42
E/e' ratio	Median (25-75th percentile) (IQR)	10.4 (9.7-11.8) (2.1)	7.9 (6.7-9.3) (2.6)	**<0.001**
RVMD (mm)	Median (25-75th percentile) (IQR)	22 (19-23) (4)	20 (19-21) (2)	**0.019**
sPAP (mm Hg)	Median (25-75th percentile) (IQR)	26 (21-34) (13)	24 (20-29) (9)	0.15

CRAO: Central retinal artery occlusion; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; LA: left atrial diameter; LV: left ventricle; IVS: interventricular septum wall; PW: posterior wall; LAVI: two-dimensional left atrial volume index; E: early diastolic mitral inflow velocity; A: late diastolic mitral inflow velocity; E/A: the ratio of early diastolic mitral inflow velocity to late diastolic mitral inflow velocity; e': early diastolic mitral annulus velocity; a': late diastolic mitral annulus velocity; s': systolic mitral annulus velocity E/e': the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; RVMD: Right ventricular mid diameter; sPAP: systolic pulmonary artery pressure.

Arterial stiffness is the change in the geometry and structural properties of the arterial wall, including intramural changes [23]. Changes in arterial wall properties and extracellular matrix proteins due to arterial stiffness can activate many pathways involved in atherosclerosis [24]. Various methods are available for assessing arterial stiffness, but PWV is the most widely used due to its non-invasive approach and ease of measurement [25]. We evaluated the PWV to assess arterial stiffness and identified a notable link between CRAO and elevated PWV.

As far as we are aware, no prior studies have examined the relationship between arterial stiffness and CRAO. Previous research on examining the association between retinal vascular structure and arterial stiffness has focused solely on branch retinal vein occlusion (RVO) [26,27]. In these studies, brachial PWV was measured and the effect of atherosclerotic risk factors on the relationship between retinal vein occlusion and arterial stiffness was not excluded. On the contrary, another recent study measured carotid-femoral PWV and showed an association of high PWV with RVO, independent of the influence of multiple risk factors [20]. Since the relationship between endothelial function assessed from the brachial artery and arterial stiffness has been previously demonstrated, endothelial dysfunction in CRAO patients may similarly be associated with arterial stiffness in these individuals [28].

We examined the echocardiographic diastolic function parameters in our study and found that septal e'<7, lateral e'<10, and E/e' were higher in the patient group. The presence of diastolic dysfunction has been demonstrated in CRAO patients [11]. However, diastolic functions were considered normal in our study because tricuspid regurgitation velocity <2.8 m/sec, E/e'<14, and the left atrial volume index (LAVI) <34 mL/m^2. Moreover, our study revealed that hypertension, hyperlipidemia, and smoking were significantly more common in the patient group.

The presence of at least one of the CV risk factors in CRAO patients is reported at a rate as high as 67% [29]. The most frequently identified atherosclerotic risk factors are hyperlipidemia and hypertension which is in line with our study [30]. The increased prevalence of these contributing factors could potentially raise the risk of CV events in these patients.

With future research on CRAO, we may be able to understand its relationship with CVD better and thus obtain better prognostic prediction. Additionally, perhaps we can identify asymptomatic patients at risk of CRAO with additional cardiological evaluations.

Limitations

A limitation of our study was its small sample size. Although comorbidities such as diabetes, hypertension, and dyslipidemia may affect endothelial function in CRAO patients, the most significant limitation of our study was that the impact of these factors could not be assessed through univariate or multivariate analysis due to the relatively small sample size. Large-scale prospective studies are necessary to validate our results.

Conclusion

Our study revealed the presence of endothelial dysfunction and increased arterial stiffness in CRAO patients. Our findings suggest that endothelial dysfunction and atherosclerosis might contribute to the pathophysiology of CRAO. It is important to evaluate the whole arterial system from a multidisciplinary perspective in the treatment of CRAO patients. This research may inspire future research with larger cohorts and follow-up periods to better understand the impact of endothelial dysfunction and arterial stiffness on the pathophysiology of CRAO.

Ethical approval

Approval was received for this study from the Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (Decision No: 2024/010.99/6/8).

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