

Retinal Vein Occlusion: A Form of Local Venous Thrombosis or a Result of Systemic Endothelial Dysfunction

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Research Article

Keywords: Retinal Vein Occlusion, Endothelial dysfunction, Flow-Mediated Dilation, Pulse Wave Velocity, Carotid Intima Media Thickness

Posted Date: March 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-258297/v1>

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Abstract

Background: To determine the condition of systemic endothelial function and carotid intima media thickness (CIMT) in patients with retinal vein occlusion (RVO) and to identify the risk factors associated with the disease.

Methods: Seventy-six patients who presented to the clinic with the diagnosis of RVO and 76 age- and gender-matched healthy individuals without a RVO history were included in the study. The patients' vision levels and central macular thickness were measured, and diabetes, hypertension, hyperlipidemia, carotid artery disease, body mass index and smoking histories were recorded. The endothelial function levels of the patients, pulse wave velocity (PWV), and CIMT were measured. Serum hematological parameters were evaluated.

Results: The most important risk factor in patients with RVO was found to be hypertension (OR 1.455, 95% CI 1.981-9.272; $p=0.001$) compared to the control group, and diabetes (OR 0.460, 95% CI 1.981-9.272; $p=0.001$) and hyperlipidemia (OR 0.124, 95% CI 0.371-3.456; $p=0.828$) were significantly more common among the patients.

There was a statistically significant difference between the RVO and control groups in terms of flow-mediated dilation (OR 0.050, 95% CI 0.020-0.080; $p=0.001$), PWV (OR 0.392, 95% CI 0.271-0.513; $p<0.001$), and the CIMT of both sides (OR 2.434, 95% CI 1.801-3.055 for the right CIMT and OR 2.284, 95% CI 1.646-2.922 for the left CIMT) ($p<0.001$ for all).

Conclusion: Considering that RVO is associated with systemic endothelial dysfunction and may also be accompanied by carotid artery stenosis, we think that additional systemic diseases should be questioned in this patient group.

Introduction

Retinal vein obstruction (RVO) is a retinal vascular disease that most commonly causes visual impairment after diabetic retinopathy and affects the middle age and elder population.¹ It is classified as central retinal vein occlusion (CRVO) and retinal vein branch occlusion (BRVO) according to the level of occlusion of the retinal vein. Although it is a disease that significantly affects vision, the etiology and pathogenesis of the disease have not yet been fully clarified.² The prevalence of BRVO is known to be 0.4% and that of CRVO is 0.08%.³ Many risk factors have been identified for the development of RVO, such as age, systemic hypertension, atherosclerosis, diabetes mellitus, hyperlipidemia, smoking, cardiovascular disease, increased body mass index ($>24 \text{ kg/m}^2$), hyperviscosity, and coagulation factors.⁴⁻⁵

Endothelial dysfunction is characterized by a decrease in endothelium-dependent vasodilation due to the reduced production of endothelial-associated nitric oxide (NO). Endothelial dysfunction is the first step of atherogenesis before atherosclerotic changes develop in vascular structures.⁶ On the other hand, in endothelial dysfunction the balance between vasodilation and vasoconstriction is impaired, creating a proinflammatory, proliferative and procoagulant environment. It is known to be associated with age, systemic hypertension, atherosclerosis, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease (CAD), and obesity, which are also risk factors for RVO.⁷ Endothelial dysfunction can be evaluated angiographically after stimulation with intraarterial pharmacological agents, as well as in a non-invasive manner. Vascular structures can change vasomotor tonus as a result of physical and chemical stimuli. Most vascular structures respond to the flow shear effect of vasodilation, called flow-mediated dilation (FMD). An FMD value below 2% is known to significantly increase the risk of cardiovascular events.⁸

Our aim in this study was to determine the role of endothelial dysfunction in the etiopathogenesis of RVO. In addition to risk factors in patients with RVO, internal carotid artery intima media thickness (CIMT) and hematological parameters will also be investigated.

Material- Method

Study design:

This is a single-center, prospective, and cross-sectional study.

Study Protocol:

The study was carried out in accordance with the principles of the Declaration of Helsinki after obtaining ethical consent from the Kafkas University, Medicine Faculty, Ethics Committee with the number 80576354-050-99/158. A total of 76 patients that presented to Kafkas University Faculty of Medicine Department of Ophthalmology between July 2019 and March 2020 and were diagnosed with RVO and 76 controls were included in the study. A consent form was received from all patients that they would participate in the study.

The detailed ophthalmological examinations of the patients with RVO were performed. The best-corrected visual acuity (BCVA) and the logarithmic equivalents of the minimum resolution angle (logMAR) were determined. In all cases, the anterior segment and fundus examination findings were recorded. The patients' RVO type (CRVO or RVBO) was recorded. The central macular thicknesses at the time of presentation were evaluated by optical coherence tomography (RTVue 100-2; Optovue, Fremont, CA, USA). In addition, the patients' body mass index (BMI) was calculated, and the presence of diabetes mellitus, hypertension, hyperlipidemia, CAD, and smoking was noted.

Biochemical analysis:

All venous blood samples were taken from the antecubital vein after 12 hours of fasting. Hemoglobin (Hgb), hematocrit (Htc), sodium (Na), potassium (K), AST, ALT, urea, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and some biochemical parameters, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and D-dimer level were evaluated.

Ultrasonic Evaluation of Endothelial Function

FMD and Pulse Wave Velocity (PWV) Measurement:

Brachial artery B-mode ultrasonography examinations were performed by a single radiologist (T.Ç.) blinded to the ocular examination findings and personal data of the patients, using an ultrasound system (Siemens Acuson S3000, Siemens Healthcare GmbH Henkestr. 127 91052 Erlangen/Germany). The images were digitally recorded and interpreted offline. Endothelial dysfunction was detected by applying the FMD technique to the brachial artery. The procedure was performed according to the guidelines published by Coretti et al., following a 12-hour fasting period in a quiet room at 22-25 °C.⁹

Alcoholic or caffeinated beverages were prohibited for 12 hours before the procedure. The patients were placed in a comfortable position on their back. The transducer was placed on the right brachial artery trace 4-5 cm above the elbow and longitudinally visualized in the region where there was no tortuosity, and the best image was taken during the course of the artery. In order to standardize the measurement site, the measurement was undertaken 5 cm above the antecubital fossa, covering a 5-7 cm artery segment. The brachial artery diameter (intima to intima) was measured three times, and the average of these three values was recorded as the basal diameter. The cuff of the sphygmomanometer was attached to the arm and inflated at an average pressure of 250 mmHg and held for five minutes before being suddenly lowered, and PWV was measured in 15 seconds. The brachial artery diameter was recorded at the first and second minutes after

the hyperemic response to evaluate FMD. The maximum diameter in these measurements was used in FMD calculations. FMD was calculated as a %increase compared to the basal vessel diameter using the formula, "FMD = [(MD - BD) / BD] x 100".

Ultrasonographic Evaluation of Carotid Arteries

Carotid artery B-mode ultrasonography examinations were performed by a single radiologist (T.Ç.) blinded to the patients' ocular examination findings and personal data, using an ultrasound system (Siemens Acuson S3000, Siemens Healthcare GmbH Henkestr. 127 91052 Erlangen/Germany) and a 9L4 linear transducer. The patients were placed on their back with their necks slightly extended, and the transducer was placed transversely in the midline of the neck. By shifting the transducer slightly to the right and left, the carotid arteries were viewed from the transverse section, and the carotid bulb was attempted to be localized. Longitudinal plane images were obtained from both internal carotid arteries (ICAs) of the patients. The lumen-intima and media-adventitia interfaces of the back wall of the carotid arteries were obtained by enhancing the images using the magnification-zoom function of the device. At least five measurements were made from the back wall in each segment, and the mean CIMT measurements of ICAs were taken. The average of these values was used in the statistical analysis.

Inclusion Criteria:

Aged 45-75 years, having undergone retinal vascular branch or root occlusion, and not having a history of surgical intervention that can affect the function of vascular structures in the neck and arm.

Exclusion Criteria:

Diabetic retinopathy, hypertensive retinopathy, presence of choroidal neovascular membrane, hepatic or renal insufficiency, history of systemic inflammatory disease (inflammatory connective tissue diseases), acute or chronic infectious (HIV, HBV, and HCV) disease, and pregnancy history.

Statistical analysis

Statistical evaluations were made using SPSS v. 21.0 (Statistical Package for the Social Sciences, Windows version Chicago, USA), and power analysis was undertaken using the ClinCalc program (Rosner B. Fundamentals of Biostatistics. 7th ed. Boston, MA: Brooks / Cole; 2011. <http://clincalc.com/stats/samplesize.aspx>). Type I error (alpha value) 0.05 and power 80% of the study were calculated. While evaluating the study data, descriptive statistics, including the mean, standard deviation, median, frequency, ratio, minimum and maximum values were used. The independent samples t-test and logistic regression analysis were used in the analysis of independent quantitative data. In the analysis of independent qualitative data, the chi-square and binary logistic regression tests were used. Using variables found to be significant in the univariate analysis, a multivariate logistic regression analysis was conducted to identify the independent determinants, which are risk factors for RVO. Statistical significance was accepted as $p < 0.05$.

Results

The study included a total of 76 patients with RVO, comprising 37 with CRVO and 39 with BRVO, and 76 controls without retinal vascular pathologies. There was no significant difference between the two groups in terms of age and gender ($p =$

0.161 and 0.061, respectively); however, a significant difference was found in BCVA and CMT ($p < 0.001$ and 0.001 , respectively) (Table 1).

Table 1
Hematological parameters and demographic characteristics of the groups

Variables	RVO	Control	p
Gender (f/M)	42/34	39/46	0.061
age (year)	62.04±10.28	59.84±8.91	0.161
BCVA (Logmar)	1.39±1.30	0.028±1.22	<.001
BMI (kg/m ²)	24.80±1.34	24.20±1.37	0.010
Diabetes n (%)	31 (40.8)	13 (17.1)	0.002
Hypertension n (%)	48 (63.2)	15 (19.7)	0.001
Hyperlipidemia n (%)	28 (36.8)	7 (9.2)	0.001
CAD n (%)	16 (21.1)	8 (10.5)	0.118
Smoking n (%)	26 (34.2)	15 (19.7)	0.067
CMT (µm)	588.76±104.02	265.20±45.11	0.001
TG (mg/dL)	166.1±58.3	155.9±76.6	0.360
TC (mg/dL)	188.2±28.6	178.3±45.6	0.114
HDL (mg/dL)	43.4±7.6	44.7±9.8	0.355
LDL (mg/dL)	115.5±39.1	107.3±39.4	0.201
ESR (mm/sa)	19.9±17.7	18.8±11.4	0.667
crp (mg/dL)	0.72±1.67	0.83±1.01	0.622
d-dimer (ng/mL)	481.8±421.6	309.4±161.6	0.012
Hgb (g/dL)	14.7±1.69	13.9±2.91	0.036
Htc (%)	46.1±6.2	42.0±8.5	0.011
K	4.26±0.41	4.23±0.65	0.713
Na	140.1±3,6	138.8±3.5	0.064
AST	18.6±6.9	17.4±6.7	0.290
ALT	18.7±11.1	16.7±7.8	0.198
Urea	42.6±15.1	38.4±22.9	0.185
Independent Sample t test, Chi-Square test			
CRVO: Central Retinal Vein Occlusion, BRVO: Branch Retinal Vein Occlusion, BCVA: Best Corrected Visual Acuity, BMI: Body Mass Index, CAD: Coronary Artery Disease, CMT: Central Macular Thickness, TG: Triglyceride, TC: Total Cholesterol, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, Hgb: Hemoglobin, Htc: Hemotocrit			

While there was a significant difference between the two groups in terms of the presence of diabetes, hypertension, and hyperlipidemia ($p = 0.002$, 0.001 , and 0.001 , respectively), no significant difference was observed in relation to smoking

status and CAD ($p = 0.118$ and 0.067 , respectively). The TG, TC, HDL, LDL, ESR, CRP, Na, K, AST, ALT and urea values did not statistically significantly differ between the RVO and control groups ($p = 0.360, 0.114, 0.355, 0.201, 0.667, 0.622, 0.064, 0.713, 0.290, 0.198, \text{ and } 0.185$ respectively), but there was a significant difference in D-dimer, Hgb, Htc ($p = 0.012, 0.036, \text{ and } 0.011$, respectively) (Table 1).

There was no significant difference between the RVO and control groups in the basal and maximum brachial artery diameters ($p = 0.676$ and 0.139 , respectively); however, a statistically significant difference was detected in FMD, PWV, and CIMT on both sides ($p < 0.001$ for all) (Table 2).

Table 2
FMD, PWV and CIMT values according to groups.

Variables	RVO	Control	p
Brachial artery Basal Diameter (mm)	5.08±0.62	5.12±0.57	0.676
Brachial Artery Maximum Diameter (mm)	5.42±0.65	5.58±0.63	0.139
FMD (%)	6.57±2.41	8.82±1.97	<.001
PWV (m/sn)	6.67±0.71	6.12±0.19	<.001
Right CIMT (mm)	0.76±0.08	0.64±0.09	<.001
Left CIMT (mm)	0.75±0.09	0.64±0.09	<.001
Independent Sample t test			
RVO: Retinal Vein Occlusion, FMD: Flow-mediated Dilation, CIMT: Carotid Intima Media Thickness, PWV: Pulse Wave Velocity			

The binary logistic regression analysis was performed for the parameters found to be significant risk factors for RVO using the chi-square test (diabetes, hypertension, and hyperlipidemia). The results were as follows: diabetes OR: 0.460, 95% CI: 0.704-3.567, $p = 0.266$; hypertension OR: 1.455, 95% CI: 1.981-9.272, $p = 0.001$, and hyperlipidemia OR: 0.124, 95% CI: 0.371-3.456, $p = 0.828$ (Table 3).

Table 3
Independent predictors of RVO with binary logistic regression analysis P-value, OR with 95% CI

Variable	p-value	Odd ratio	95% C.I.
Diabetes n (%)	0.266	0.460	0.704-3.567
Hypertension n (%)	0.001	1.455	1.981-9.272
Hyperlipidemia n (%)	0.828	0.124	0.371-3.456
Binary Logistic Regression Analysis			

A multivariate regression analysis was also conducted for the risk factors that were found to be related to RVO in the univariate analysis (BMI, D-Dimer, Hgb, Htc, FMD, PWV, and the right and left CIMT). The results of this analysis were: d-Dimer OR: 0.015, 95% CI: 0.000-0.001, $p < 0.001$; Htc OR: 0.021, 95% CI: 0.008-0.035, $p = 0.002$, FMD OR: 0.050, 95% CI: 0.020-0.080, $p = 0.001$; PWV OR 0.392, 95% CI: 0.271-0.513, $p < 0.001$, right CIMT OR: 2.434, 95% CI: 1.801-3.055, $p < 0.001$, and left CIMT OR: 2.284, 95% CI: 1.646-2.922, $p < 0.001$ (Table 4).

Table 4
Independent predictors of RVO with univariate and multivariate P-value, OR with 95% CI

Variable	Univariate analysis of RVO			Multivariate analysis of RVO		
	P-value	Odd ratio	95% C.I	P-value	Odd ratio	95% C.I.
BMI (kg/m ²)	0.010	0.076	0.019-0.133	0.130	0.036	0.011-0.083
D-dimer (ng/mL)	0.015	<.001	0.000-0.001	0.152	<.001	<.001-<.001
Hgb (g/dL)	0.145	0.034	0.012-0.080	0.599	0.015	0.041-0.071
Htc (%)	0.002	0.021	0.008-0.035	0.309	0.009	0.008-0.026
FMD (%)	<.001	0.093	0.122-0.064	0.001	0.050	0.020-0.080
PWV (m/sn)	<.001	0.392	0.271-0.513	0.842	0.015	0.136-0.167
Right CIMT (mm)	<.001	2.434	1.801-3.055	0.086	2.203	0.317-4.724
Left CIMT (mm)	<.001	2.284	1.646-2.922	0.613	0.647	1.898-3.173
Univariant and Multivariant Linear Logistic Regression						
RVO: Retinal Vein Occlusion, BMI: Body Mass Index, HGB: Hemoglobin, HTC: Hemotocrit, , FMD: Flow-mediated Dilation, PWV: Pulse Wave Velocity, CIMT: Carotid Intima Media Thickness,						

The PWV and CIMT values were significantly higher and the FMD values were significantly lower in patients with CRVO than those with BRVO, suggesting that systemic endothelial dysfunction was more severe in the former. (Figure 1)

Discussion

RVO is a disease that significantly affects vision, and the etiology and pathogenesis of the disease are unknown. The vast majority of patients with RVO have risk factors, such as hypertension, diabetes mellitus, and cardiovascular system diseases. Apart from these three main causes, various diseases and factors that cause stasis in the vascular system or activate coagulation mechanisms in the vascular system are also implicated in the RVO etiology.² In this study, the risk factors, CIMT, hematological parameters, and endothelial dysfunction were investigated in patients with RVO compared to the controls.

FMD is a commonly used non-invasive method to evaluate endothelial function from the brachial artery.¹⁰ The deterioration in vascular structures causes a decrease in NO production, leading to the dilatation and constriction responses of the vascular structures to decrease. This condition showing endothelial dysfunction occurs even in the earliest stages of atherosclerosis.¹¹ In our study, we found that the most important variable in patients with RVO was FMD. This indicates that systemic endothelial function is impaired in patients with RVO.

To date, the most important eye health problem associated with endothelial dysfunction has been considered as glaucoma. It is known that endothelial function is impaired in glaucoma patients, especially in those with pseudoexfoliative glaucoma. In these patients, PWV is reported to be significantly higher and FMD is significantly lower. It has also been shown that endothelial dysfunction and arterial vascular disorder play a role in the pathogenesis of pseudoexfoliative glaucoma.¹² It has also been shown that the intimal thickness of the internal carotid artery was significantly thicker in patients with ocular psodoexfoliation.¹³ It has been reported that endothelial dysfunction may play a role in normal pressure glaucoma pathogenesis with vascular dysfunction causing ischemia in the optic nerve head.¹⁴ In a study investigating endothelial dysfunction in patients with normal pressure glaucoma and primary open-angle glaucoma, the loss in the Humphrey visual field inferior areas was shown to be correlated with basal FMD.¹⁵

Although the state of endothelial dysfunction is not known in patients with RVO, it has been reported that the ejection fraction is significantly lower, and suboptimal cardiac functions are associated with larger systolic diameters in cardiac structures.¹⁶ It has been reported that patients with BRVO have myocardial dysfunction, and these patients may need monitoring in terms of CAD¹⁷. It has been shown that the severity of coronary diseases and myocardial performance can be estimated by a retinal vascular analysis.¹⁸

The incidence of findings, such as retinal venous stasis, Hollenhorst plaques and amaurosis fugax increases in carotid artery occlusive disorders.¹⁹ It is crucial to perform a carotid Doppler analysis in patients with retinal ischemic syndrome.
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According to Song et al., retinal vascular changes are a good indicator of carotid artery atherosclerosis, and both carotid arteries may be affected in patients with RVO. The authors stated that these patients should be screened for carotid artery atherosclerosis.²¹ In our study, we found that bilateral CIMT values in patients with RVO were significantly thicker, suggesting that patients with RVO should be evaluated using carotid Doppler ultrasound.

The risk of RVO is increased two times by hyperlipidemia and 3.5 times by hypertension.²² There are studies indicating that hyperlipidemia may play an important role in the RVO etiopathogenesis, as well as those suggesting the exact opposite.²³⁻²⁴ In our study, the presence of hyperlipidemia was seen as a significant risk factor in patients with RVO, but no significant difference was observed in the serum TG, TC, HDL and LDL values compared to the control group. We think that this is due to the patients using antihyperlipidemic drugs.

Dodson et al. stated that the CRP and ESR levels were much higher in hypertensive RVT patients than in those with normotensive RVT. Hypertensive patients with high serum CRP levels have a much higher risk of RVT.²⁵ Lee et al. noted that the high-sensitivity CRP level was high in patients with RVO, and therefore it could be an important parameter for ophthalmologists in the follow-up of vascular diseases.²⁶ In our study, we determined the most important risk factor for RVO as hypertension, while serum inflammation markers, such as CRP and ESR did not provide significant results.

The D-dimer level has been reported to be elevated in thromboembolic diseases of the retina.²⁷ Karska et al. stated that the serum D-dimer level was higher in patients with RVT.²⁸ Similarly, in our study, the serum D-dimer level was found to be significantly higher in the RVO group compared to the controls.

The limitations of the study include the absence of an evaluation of cardiac functions and echocardiographic findings of the patients. Furthermore, other serum biomarker levels, such as NO₃/ NO₂ ratio, NO₂, and citrulline that may play a role in endothelial dysfunction pathways, were not evaluated.

In conclusion, considering that RVO is associated with systemic endothelial dysfunction and may be accompanied by carotid artery stenosis, we think that these patients should be questioned in terms of the presence of any additional

systemic disease.

Declarations

Ethical approval:

This study was approved and monitored by Kafkas University Faculty of Medicine Ethic Committee, Kars, Turkey (Number: 80576354-050-99/158, Date: 09.07.2019)

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no conflict of interest. This sentence was added both on the title page and at the end of the article.

Funding:

The authors declared that this study has received no financial support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector. This sentence was added both on the title page and at the end of the article.

Authors' contributions:

E.B. designed the study. I.R. and T.C. performed the data analysis and investigation. E.B. wrote the main manuscript. T.C. and I.R. contributed to discussions of the results and reviewed the manuscript. All authors read and approved the final manuscript. T.C. and I.R. contributed equally to this work

Acknowledgements:

Not applicable.

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Figures

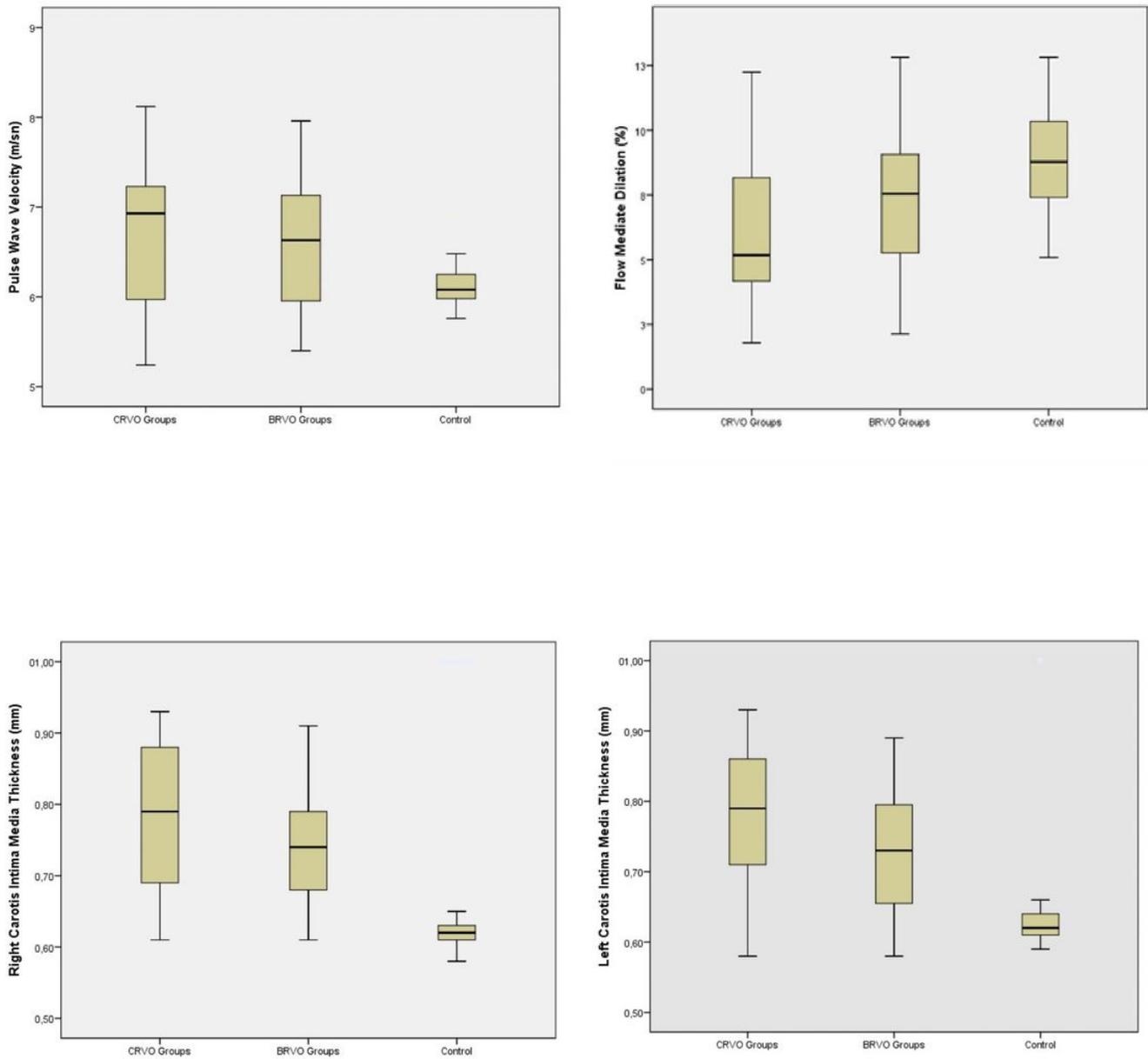


Figure 1

Comparison of FMD, PWV and CIMT levels by groups. CRVO: Central Retinal Vein Occlusion, BRVO: Branch Retinal Vein Occlusion, FMD: Flow-Mediated Dilatation, CIMT: Carotid Intima Media Thickness, PWV: Pulse Wave Velocity