Original Article

Increased cardio-ankle vascular index values in patients with acute branch retinal vein occlusion

Ibrahim Kocayigit, Mahmut Atum, Salih Sahinkus, Murat Aksoy, Yusuf Can

Purpose: Patients with retinal vein occlusions (RVOs) are at increased risk of cardiovascular disease. Arterial stiffness is an independent risk factor for cardiovascular events. Our aim is to evaluate the arterial stiffness in patients with acute branch retinal vein occlusion (BRVO) by using cardio-ankle vascular index (CAVI). **Methods:** This prospective study included 42 patients (18 male, mean age 57.5 ± 11.3) with acute BRVO and a matched control group (by age, sex, and presence of hypertension) with 70 (26 male, mean age 54.4 ± 9.4) patients. All patients and control subjects underwent complete ocular examination and CAVI measurement. BRVO was diagnosed based on clinical examination. **Results:** There were no significant differences between baseline clinical and demographic characteristics, echocardiographic measurements of left ventricular ejection fraction, systolic and diastolic blood pressure, and body mass index of the BRVO and control group. Both right and left CAVI values were found significantly higher in BRVO group (7.94 ± 1.53 vs 7.28 ± 1.25, $P < 0.05$ and 8.06 ± 1.41 vs 7.30 ± 1.26, $P < 0.05$, respectively). There were no significant difference in right and left ankle-brachial index values between the groups (1.05 ± 0.10 vs 1.06 ± 0.08, $P = 0.46$ and 1.04 ± 0.12 vs 1.05 ± 0.08, $P = 0.46$, respectively). **Conclusion:** Arterial stiffness is an important mediator of cardiovascular diseases. We found that CAVI which is a novel marker of the arterial stiffness is increased in patients with acute BRVO compared to controls.

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Branch retinal vein occlusion (BRVO) is a common vascular disorder of the retina and the second common cause of vision loss after diabetic retinopathy.[1] The pathogenesis of this disease still remains uncertain but the main cause is considered as the compression of retinal veins at the arteriovenous crossing by the branch retinal artery. Increased age, systemic hypertension, diabetes mellitus, smoking, and obesity are the known risk factors of this disorder.[2] It has been also reported that patients with BRVO have an increased risk of cardiovascular events.[3]

Arterial stiffness is a known risk factor for cardiovascular events.[4-6] Increased arterial stiffness may predict cardiovascular events in asymptomatic individuals without the overt cardiovascular disorder.[7] Systemic hypertension, diabetes mellitus, renal diseases, smoking, dyslipidemia, and increased age are associated with increased arterial stiffness.[8] These data were shown by using pulse wave velocity (PWV) as an index of arterial stiffness. But, PWV is well known to be dependent on the blood pressure at measuring time. Therefore, accurate assessment of aortic stiffness is not possible with PWV measurement. To overcome the blood pressure dependency, cardio-ankle vascular index (CAVI) was developed.[9] CAVI is an arterial stiffness index of arterial tree from the origin of the aorta to the ankle. One of its most important features is that CAVI is independent of blood pressure at measuring time.[10] And, it is established that CAVI reflected arteriosclerosis and also a predictor of cardiovascular events.[11,12] In this study, we aimed to evaluate arterial stiffness in patients with acute BRVO by using CAVI.

Methods

Patient characteristics

Informed consents were obtained from the patients and the local ethics committee approved the study. The study was performed in adherence to the Declaration of Helsinki. This study was performed prospectively in the departments of ophthalmology and cardiology of a tertiary center. The patients diagnosed with BRVO by the retina unit of our hospital between June 2018 and November 2018 were enrolled. All subjects underwent complete ophthalmic evaluation of both the eyes, including the best-corrected visual acuity, slit-lamp examination of the anterior segment, applanation tonometry, and slit-lamp examination of fundus with 90D Volk lens. We also performed color fundus photography, fundus fluorescein angiography, and optic coherence tomography in all patients. Based on ophthalmic fundus examination, cases with retinal venous dilation and tortuosity accompanied by flame-shaped and intraretinal hemorrhage wedge-shaped regions were diagnosed with BRVO. 42 patients (18 male, mean age 57.5 ± 11.3) with acute

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BRVO and a matched control group (by age, sex, and presence of hypertension) with 70 (26 male, mean age 54.4 ± 9.4) patients were enrolled in the study. The control subjects and patients did not differ with regard to age, sex, body mass index, presence of hypertension, diabetes mellitus, dyslipidemia, and smoking habits [Table 1]. The control group also underwent an ophthalmic examination to exclude occlusive vascular eye disease. Patients with BRVO secondary to inflammatory disease, patients with occlusive eye disease other than BRVO, and patients with thrombophilic disorders were excluded from the study. The patients with glaucoma or ocular hypertension which are known as risk factors for BRVO were excluded. Patients with known coronary and peripheral atherosclerotic diseases, uncontrolled diabetes mellitus, renal failure, heart failure, and moderate or severe valvular heart disease were also excluded. Hypertension was defined as systolic blood pressure (BP) of ≥140 mmHg, a diastolic BP of ≥90 mmHg on at least two separate occasions and off medication, or use of antihypertensive drugs. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥140 mg/dL, a high-density lipoprotein cholesterol level ≤40 mg/dL, a triglyceride level ≥150 mg/dL, or the use of antidyslipidemic medication. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL or the use of antidiabetic medication. All the measurements and echocardiographic examinations were performed by a cardiologist. The ejection fraction of left ventricle was calculated by using modified Simpson's method.

Cardio-ankle vascular index measurement

CAVI was measured noninvasively by using VaSera VS-1000 (Fukuda Denshi Co. Ltd, Tokyo, Japan) device. After a rest of 5 min, the cuffs were wrapped around both upper arms and ankles in a supine position to measure blood pressure and detect the brachial and ankle pulse waves. Electrocardiographic electrodes were attached to the upper arms, and a microphone was placed on the sternum to record an electrocardiogram and a phonocardiogram. PWV was calculated by dividing the directly measured length from the heart to the artery of the ankle joint by the sum of the arrival time interval of the brachial pulse wave and the pulse wave of the ankle joint and the time from the closing sound of the aortic valve to the notch of the brachial pulse wave. A problem in clinical use is that PWV itself is essentially dependent on blood pressure. For this reason, the values of the brachial systolic blood pressure and diastolic blood pressure were applied to the formula of the stiffness parameter β. CAVI, based on the formula of stiffness parameter β, reflects the stiffness of the aorta, femoral artery, and tibial artery and is not influenced by blood pressure.[9] VaSera device calculated the CAVI values automatically by using the following formula: CAVI = a{(2 ρ/Δ*P*) X ln (*P*s/*P*d) PWV2} + b, where *P*s is systolic BP, *P*d is diastolic BP, ΔP is *P*s–*P*d, ρ is blood density, and a and b are constants. The ankle-brachial index (ABI) was calculated by dividing the systolic BP at the ankle by that in the brachial artery. Subjects with ABIs <0.90 were excluded from the study because patients with severe peripheral arterial occlusive diseases may give false results of CAVI.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) statistical software version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as mean ± SD and categorical variables are expressed as a percentage. Kolmogorov-Smirnov test was used to test the normality of distribution of the continuous variables. Categorical variables between two groups were compared using the x^2-test. Continuous variables in each of the groups were compared using the independent sample *t*-test. $P < 0,05$ was regarded as statistically significant.

Results

The demographic and clinical characteristics of the groups are shown in Table 1. There were no significant differences between baseline clinical and demographic characteristics, echocardiographic measurements of left ventricular ejection fraction, and body mass index of the BRVO and control groups. Both right and left CAVI values were found significantly higher in BRVO group (7.94 ± 1.53, range 4.5–12 vs 7.28 ± 1.25, range 4.8–9.5; $P < 0.05$ and 8.06 ± 1.41, range 5.8–12.1 vs 7.30 ± 1.26, range 4.8–9.4; $P < 0.05$, respectively) [Table 2]. We also investigated the ABI values in the two groups. There was no significant difference in right and left ABI values between the groups (1.05 ± 0.10 vs 1.06 ± 0.08, $P = 0.46$ and 1.04 ± 0.12 vs 1.05 ± 0.08, $P = 0.46$, respectively).

Discussion

RVO is a common cause of marked or total loss of vision in the middle-aged and elderly population, and the second most common retinal vascular disease after diabetic retinopathy.[1] RVO can be classified as central and branch RVO according to the affected area on the retinal surface. In branch RVO, a branch of retinal venous system is occluded; while in central RVO, the occlusion is located in central retinal vein. Atherosclerosis, cardiovascular diseases, and hypertension are more common in branch RVO; hypercoagulable states, increased intraocular

Table 1: Baseline characteristics of the patients

	RVO group (*n*=42)	Control group (*n*=70)	*P*
Age (years)	57.5±11.3	54.4±9.4	0.12
Male sex (*n*,%)	18 (42.8)	26 (37.1)	0.55
Diabetes mellitus (*n*,%)	13 (30.9)	20 (28.5)	0.79
Hypertension (*n*,%)	30 (71.4)	50 (71.4)	1.00
Systolic BP (mmHg)	138.9±10.1	137.9±14.2	0.68
Diastolic BP (mmHg)	81.9±6.4	82.4±10.7	0.80
Dyslipidemia (*n*,%)	4 (9.5)	7 (10.0)	0.94
Smoking (*n*,%)	10 (23.8)	19 (27.1)	0.69
BMI (*n*, %)	30.4±6.2	29.6±6.0	0.50
LVEF (%)	64.1±5,9	62.7±4.1	0.13

RVO: Retinal vein occlusion, BP: Blood pressure, BMI: Body mass index, LVEF: Left ventricular ejection fraction

Table 2: CAVI values of the groups with and without branch retinal vein occlusion

	RVO group (*n*=42)	Control group (*n*=70)	*P*
R-CAVI	7.94±1.53	7.28±1.25	<0.05
L-CAVI	8.06±1.41	7.30±1.26	<0.05

RVO: Retinal vein occlusion, R-CAVI: Right cardio-ankle vascular index, L-CAVI: Left cardio-ankle vascular index

pressure, and erythrocyte sedimentation rates can be found in central RVO.[2] The major cause of branch RVO is considered as the compression of retinal veins at the arteriovenous crossing by the branch retinal artery.[13]

Increased age and systemic atherosclerosis are thought to be the most recognized risk factors for BRVO.[2] Stiffness of the artery depends on the vessel's elasticity and atherosclerosis has an important role in the development of arterial stiffness.[7] Thus, it is established that arterial stiffness is one of the indicators of the progression of cardiovascular diseases.[6] Several methods have been used for the evaluation of aortic stiffness such as PWV.[9] It has been reported that arterial stiffness is increased in patients with RVO by measuring brachial-ankle PWV.[14] But, measuring arterial stiffness using PWV had some limitations. The measured stiffness by using PWV depends on blood pressure at measuring time, then the effects of blood pressure as a risk factor on various diseases were overestimated.[10] It is also known that PWV is strongly influenced by several factors such as arteriosclerosis and autonomic nerve function.[15] CAVI was developed to evaluate proper arterial stiffness of the arterial tree from the origin of the aorta to the ankle. The most remarkable feature of CAVI is being independent of the blood pressure at measuring time. There are several reports that CAVI showed high values in arteriosclerotic diseases such as coronary artery diseases, cerebral infarction, and chronic kidney diseases, and also in patients with coronary risk factors such as hypertension, diabetes mellitus, and metabolic syndrome.[11] As far as ophthalmological region, Taniguchi reported that CAVI is high in patients with exudative age-related macular degeneration.[16] Shiba reported that arterial stiffness is an important contributor to optic nerve head microcirculation.[17] Shiba revealed that large arterial function shown by the CAVI contributes to smooth hemodynamics of microcirculation of the capillary area of optic nerve head which is shown by laser speckle flow graph.[17] Our present paper is the first to show that CAVI values of the patients with BRVO were high. And, high CAVI might be correlated with the retinal arterial sclerosis and could be involved in the onset of BRVO.

Recently, several studies showed the relationship between RVO and systemic atherosclerosis.[18] Systemic diseases such as hypertension, dyslipidemia, and diabetes mellitus are strongly associated with RVO.[19] Wong *et al*. reported the relationship between RVO and hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, and carotid artery plaques.[18] Ogawa *et al*. also reported that carotid artery intima-media thickness is greater in patients with RVO than in control subjects.[3] Ultrasonographically evaluated intima-media thickness is a parameter of arterial stiffness but it provides information about the vessel anatomy only, not functional data. Functional evaluation of the arterial stiffness can be provided by PWV measurement. Nakazato *et al*. showed increased arterial stiffness in patients with RVO by using brachial-ankle PWV measurement.[20] But it is known that PWV measurement can be affected by blood pressure. CAVI is a novel stiffness indicator of arteries independent of arterial blood pressure. CAVI reflects the state of smooth muscle contractions rather than changes in blood pressure so it represents both functional and organic stiffness.[21,22] We found higher CAVI values in the patients with branch RVO in our study compared to the control group.

Arterial stiffness is an important mediator of cardiovascular diseases. Clinical trials have shown the relationship between large artery stiffness and cardiovascular incidents.[6,23] However, the aortic stiffness measured by using CAVI especially reflects the stiffness of macrovessels. On the other hand, recent studies showed the role of increased large arterial stiffness on microvascular diseases, especially the damages of target organs such as the brain and kidney.[24] Retinal microcirculation was also related to arterial stiffness shown by CAVI.[25] The elasticity of large arteries provides a powerful, cushioning function, and steady flow in the small arteries despite the intermittent left ventricular ejection fraction. When the stiffness of the aorta increases, the cushioning function is impaired. Then, the stiff aorta promotes increased pulsability in the microvasculature instead of steady flow. Shiba reported that optic nerve head circulation determined by pulse wave analysis is significantly correlated with CAVI.[17] We claim that this increased pulsability in the retinal artery may have an important role in the development of RVO.

Previous studies have shown that arterial stiffness plays an important role in the onset and progression of BRVO.[14] PWV and carotid artery intima-media thickness measurements are well-known noninvasive methods to assess the arterial stiffness.[26,27] However, intima-media thickness provides information only about the vessel wall anatomy, not for vessel function. The PWV provides a simple evaluation of regional arterial stiffness but it can be affected by blood pressure changes. CAVI is a novel noninvasive method by which arterial stiffness can be evaluated and independent of blood pressure at the time of measurement. It is easy to measure with good reproducibility.[10,28] Recent studies showed that CAVI is superior as a prognostic indicator compared to other conventional methods.[29] Our study represents the first application of CAVI in patients with BRVO. CAVI measurement may be useful in evaluating future cardiovascular risk and help the management of patients with BRVO.

While increases in the CAVI values were associated with BRVO, there was no significant change in ABI in patients with BRVO in our study. The ABI is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery and used in clinical practice to evaluate the patency of the lower extremity arterial system and to screen for the presence of occlusive peripheral arterial disease. In our study, patients with ABI <0.90 were excluded because patients with severe peripheral arterial occlusive diseases may give false results of CAVI. Our results showed that arterial stiffness is increased in patients with BRVO which is measured by the CAVI, not by the ABI.

Conclusion

In summary, we evaluated CAVI, which reflects the arterial stiffness independent of blood pressure at measuring time, in patients with branch RVO. The results showed that the patient with RVO showed high CAVI compared to controls. High CAVI in RVO might not only reflect the progression of arteriosclerosis in retinal arteries but also be involved in the disturbance of microcirculation of retinal arteries. According to the results of our study, CAVI might be considered as a reliable biomarker for predicting patients who are more prone to RVO. Further studies are needed on this subject.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflicts of interest

There are no conflicts of interest.

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