Peripheral Vascular Endothelial Dysfunction in Central Serous Chorioretinopathy

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Purpose. To explore the pathophysiology of central serous chorioretinopathy (CSC) by comparing peripheral vascular endothelium function in patients with CSC and control subjects.

Methods. This study included 34 patients with CSC who attended the Department of Ophthalmology and 34 healthy age- and sex-matched healthy control subjects from a routine physical check-up population. Endothelium-dependent flow-mediated vasodilation (FMD) and endothelium-independent nitroglycerine-mediated vasodilation (NMD) were measured using high-resolution, two-dimensional ultrasonographic imaging of the brachial artery. Blood samples were taken to test serum glucose, cholesterol, triglyceride, alanine aminotransferase, uric acid, and high-sensitivity C-reactive protein (hs-CRP) levels.

Results. The mean age of patients with CSC was 44.0 years (SD ±8.1) and that of controls 46.1 years (±9.9) ($P = 0.352$). There were no significant differences between groups in serum biochemical data, including serum glucose, alanine aminotransferase, uric acid, cholesterol, triglyceride, and hs-CRP. FMD was significantly impaired in patients with CSC compared with control subjects (CSC: 4.62 ± 1.96, control: 7.52 ± 2.63, $P < 0.001$), whereas NMD did not differ significantly between the two groups (CSC: 16.31 ± 5.60, control: 16.22 ± 5.56, $P = 0.950$).

Conclusions. This study demonstrated impaired FMD in patients with CSC and the results have provided evidence of peripheral endothelium dysfunction associated with CSC in patients.

Keywords: central serous chorioretinopathy, endothelium, ultrasonography

Central serous chorioretinopathy (CSC) is typically characterized by accumulation of serous fluid under the neurosensory retina and neurosensory retinal detachment secondary to exudation of fluids from the choriocapillaris through one or more focal lesions of the RPE.[1–3] CSC affects predominantly men between the ages of 20 and 50 years.[4] Patients with CSC may present with blurred vision, relative central scotoma, metamorphopsia, dyschromatopsia, micropsia, hypermetropization, and reduced contrast sensitivity.[1]

The diagnosis of CSC is based on multimodal imaging. Spectral-domain optical coherence tomography (SD-OCT) reveals retinal detachment with subretinal fluid accumulation, subfoveal choroid thickening, and choroidal vessel dilation.[5–7] Fluorescein angiography identifies single or multiple points of leakage from the choroid near the site of retinal detachment,[7] and indocyanine green angiography shows choroidal vascular hyperpermeability.[8,9] Recently, a new noninvasive diagnostic imaging technique, OCT-angiography, has identified high signal intensity in the choriocapillaris layer and dilation of the choriocapillaris.[10] The results of OCT-angiography confirmed the previous reports of choroidal abnormalities in patients with CSC. All of the imaging findings indicate that CSC is associated with choroidal dysfunction. The choroid is primarily a vascular structure that consists mostly of blood vessels, and the blood vessel walls are lined with a single layer of endothelial cells. We hypothesized that endothelial impairment might be involved in choroidal dysfunction, which can be associated with the pathogenesis of CSC.

Currently, noninvasive two-dimensional (2D), high-resolution ultrasound imaging of the brachial artery is widely used to measure vascular endothelial function.[11,12] Reactive hyperemia induced by transient ischemia of the forearm may increase blood flow and shear stress on the vessel wall, resulting in release of endothelial nitric oxide (NO) and in vascular dilation, termed endothelium-dependent flow-mediated vasodilation (FMD).[13,14] In contrast, endothelium-independent nitroglycerine-mediated vasodilation (NMD) is the result of direct vasodilation by exogenous NO acting on vascular smooth muscle cells. Previous studies have shown that FMD can be considered a marker of vascular endothelial function.[15,16] In this study, we aimed to explore the pathophysiology of CSC by

comparing peripheral vascular endothelium function in patients with CSC and control subjects.

Materials and Methods

CSC Patients

We enrolled patients who had been diagnosed with acute CSC symptoms in the Department of Ophthalmology. All the patients provided informed consent to the study procedures, which were reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital (99–0510B). Acute CSC was defined in patients who first had symptoms of central visual loss or distortion within the past 3 months, and who had subretinal fluid in an SD-OCT scan. Fundus photography, fluorescence, and indocyanine green angiographies were performed in all patients to confirm the diagnosis. Patients with glaucoma, AMD (soft drusen of diameter >100 μm in the eye), other retinal diseases (such as diabetic retinopathy or hereditary maculopathy), systemic hypertension >160/110 mm Hg or history of hypertension >160/110 mm Hg, hypertensive retinopathy, or choroidopathy, were excluded. Patients with subretinal blood; RPE atrophy implying possible other etiologies, chronic or recurrent; symptoms of an unknown period (longer than 3 months); or previous symptoms that occurred before they were aware of the CSC also were excluded.

Control Subjects

The age- and sex-matched healthy control subjects were recruited from the health care center at Chang Gung Memorial Hospital. All had normal physical and ocular examinations and no history of cardiovascular disease and were not taking systemic medications. Ocular examination included best-corrected visual acuity, IOP, slit lamp examination, indirect ophthalmoscopy, and SD-OCT. Fluorescence and indocyanine green angiographies were not performed in these healthy subjects. We defined normal ocular examination as refractive error less than –6 diopter, with no abnormalities in IOP, slit lamp examination, indirect ophthalmoscopy, or SD-OCT.

Sample Size Estimation

The pretest effect size of the sample was estimated in our pilot study. Based on 10 CSC patients and 10 controls, the mean ± SD of the FMD were 3.89% ± 1.94% and 7.53% ± 2.93% in the CSC and control groups, respectively. Thirty cases were adequate sample numbers for each group with 80% power at a 5% significance level.

Data Collection

Demographic and other information, including age, sex, smoking history, body mass index (BMI), heart rate, and systolic and diastolic blood pressure were recorded. Systemic diseases, such as diabetes mellitus, hypertension, hyperlipidemia, hyperuricemia, and fatty liver, are associated with endothelial dysfunction. Therefore, we analyzed serum glucose, cholesterol, triglyceride, uric acid, and alanine aminotransferase (ALT) by biochemical tests. Venous blood samples were collected after 12 hours of overnight fasting. Serum glucose (normal range, 70–100), ALT (normal range, ≤36), cholesterol (normal range, < 200 mg/dL), triglyceride (normal range, < 150 mg/dL), and uric acid levels (normal range, < 8.0 mg/dL) were measured enzymatically. As a nonspecific marker of immune system activation, levels of the inflammation marker high-sensitivity C-reactive protein (hs-CRP) (<1 mg/L low risk, 1–3 mg/L average, >3 mg/L high risk) were determined using a high-sensitivity commercial assay kit (Daiichi Pure Chemicals Co. Ltd., Tokyo, Japan; analyzer: model 7600-210; Hitachi, City, Japan).

Vascular Endothelial Function Test

All study subjects were referred to the vascular laboratory in the morning after fasting overnight for at least 8 hours. Cigarette smoking, drinking coffee and tea, and taking medications were not allowed before the examination. Two-dimensional images of the left brachial artery and pulsed-Doppler flow velocity signals were obtained using a high-resolution linear-array transducer (13 MHz) on an ultrasound system (Aloka Prosound α10; Aloka Co., Tokyo, Japan). Examinations were performed in a dimly lit and quiet room with room temperature control. Patients rested in a supine position for at least 10 minutes before the first scan and remained supine until the final recording was acquired under continuous electrocardiogram (ECG) monitoring. Blood pressure was taken from the right arm before imaging. The left arm of each subject was fixed on an arm splint and a 7-cm-wide blood pressure cuff was placed around the forearm. The brachial artery was scanned longitudinally approximately 3 to 5 cm above the antecubital fossa. The transmit zone was set to the depth of the near wall so that the interface between media and the adventitia "m" line was clearly visible. When the optimal B-mode image of the anterior and posterior intimal interfaces between the lumen and vessel wall was obtained, the transducer was maintained in an identical position throughout the scan using a micrometer-adjustable stereotactic probe holder (probe-fixing unit: Aloka MP-PH0001; arm holder: Aloka MP-AH0001; Aloka Co.) to ensure consistency in the image. Pulsed-Doppler blood flow velocity was obtained with the signal at a 65° to 70° angle to the vessel lumen and a 1.0-mm-wide gate at the center of the artery to record flow velocity and volume. Then, baseline 2D images and pulse-Doppler blood flow velocity were acquired. To induce hyperemia, a 7-cm-wide blood pressure cuff was inflated at the forearm to 250 mm Hg. Arterial occlusion was kept for 5 minutes. The cuff was then rapidly deflated and pulsed-Doppler velocity signals were recorded for 15 seconds following deflation. Reactive hyperemia was determined by the mosaic change in color-flow imaging and increase in flow volume. At 60 seconds after cuff deflation, 2D images of the brachial artery were recorded for 15 seconds. To determine endothelium-independent NMD, sublingual nitroglycerin spray (400 μg) was administered following another 10 minutes of rest, ensuring the brachial artery diameter had returned to baseline. Brachial artery scans were performed at the same position 4 minutes after the nitroglycerin spray was administered.

Image Analysis

The brachial artery diameter was measured by a single observer unaware of clinical details. Special attention was paid to analyzing identical segments by identifying anatomic landmarks. Measurements were obtained from the anterior to posterior "m" line at the end diastole coinciding with the R-wave on the ECG. The vessel diameter (VD) of the brachial artery was calculated as the average of three end-diastolic frames. Moreover, FMD was calculated as the percentage change in brachial artery diameter in response to hyperemia ($FMD = [(VD_{hyperemia} - VD_{baseline})/VD_{baseline}] \times 100\%$). Similarly, NMD was calculated as the percentage change in

Table. Demographics, Biochemical, and Vascular Parameters in Patients With CSC and Control Groups

	CSC	Control	*P*
No. of cases	34	34	
Age, y	44.0 ± 8.1	46.0 ± 9.9	0.352
Sex, *n* (%)			
Male	29 (85.2)	28 (82.3)	0.500
Female	5 (14.8)	6 (17.7)	
Smoking, *n* (%)	8 (17.6)	6 (26.7)	0.765
BMI, kg/m^2	24.9 ± 2.6	25.9 ± 3.4	0.184
Heart rate, beats per min	69 ± 12	74 ± 10	0.062
Systolic blood pressure, mm Hg	118 ± 13	119 ± 14	0.713
Diastolic blood pressure, mm Hg	76 ± 10	77 ± 10	0.777
Fasting glucose	91 ± 7	92 ± 8	0.821
ALT	22 ± 8	21 ± 8	0.708
Uric acid, mg/dL	6.0 ± 1.6	6.3 ± 0.9	0.378
Cholesterol, mg/dL	188 ± 30	189 ± 26	0.859
Triglyceride, mg/dL	126 ± 74	117 ± 48	0.534
hs-CRP, mg/dL	1.27 ± 1.61	1.26 ± 1.00	0.983
Baseline vessel diameter, mm	4.21 ± 0.59	4.31 ± 0.55	0.478
Hyperemic VD, mm	4.40 ± 0.60	4.63 ± 0.54	0.113
Nitroglycerin VD, mm	4.87 ± 0.59	4.99 ± 0.52	0.370
FMD, %	4.62 ± 1.96	7.52 ± 2.63	<0.001*
NMD, %	16.31 ± 5.60	16.22 ± 5.56	0.950

Data are shown as mean ± SD.
* $P < 0.05$.

brachial artery diameter in response to nitroglycerin (NMD = $[(VD_{nitroglycerin} - VD_{baseline})/VD_{baseline}] \times 100\%$).

Reproducibility

To determine the reproducibility of imaging studies, 15 subjects were assessed. Intraobserver variability for measuring brachial artery diameter was assessed by comparing the two baseline arterial measurements in each of the 15 subjects. Mean difference between the two baseline arterial diameter determinations was 0.060 ± 0.062 mm. The coefficient of variation for baseline arterial diameter measurement was 1.7%.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 20.0; IBM Corp., Armonk, NY, USA). Data were reported as mean ± SD for continuous variables, such as age, BMI, heart rate, systolic blood pressure, diastolic blood pressure, serum glucose, cholesterol, triglyceride, uric acid, ALT, hs-CRP, baseline VD, FMD, and NMD. Data were reported as a percentage for categorical variables, such as proportions of male participants and smokers. Continuous covariates were assessed using an independent samples *t*-test. Categorical covariates were individually assessed using the χ^2 test. Fisher's exact test was used when the numbers were small. A *P* value < 0.05 was considered significant.

Results

The demographics and baseline characteristics of 34 patients in the CSC group and 34 in the control group are summarized in the Table. The mean age of the patients with CSC was 44.0 ± 8.1 years (mean ± SD) and that of the healthy controls was 46.1 ± 9.9 years. The mean proportions of male participants in the CSC group and in the healthy control group were 85.2% and 82.3%, respectively. In the CSC group, there were 18 right eyes and 16 left eyes. All the eyes with CSC showed subretinal fluid and three eyes showed RPE detachment in SD-OCT. Ten eyes (29%) had more than one leaking point in fluorescein angiography. Other associated factors, including smoking habits, BMI, heart rate, systolic and diastolic blood pressure, serum glucose, ALT, uric acid, cholesterol, triglyceride, and hs-CRP, are listed in the Table. There was no significant difference in hs-CRP between the CSC patients and controls, and other biochemical data for participants in this study were within the normal range. There were no significant differences between the CSC patients and controls for these variables.

Endothelial Function Test

Figure 1 shows representative 2D high-resolution ultrasound images of the brachial artery at baseline (Fig. 1A: control; Fig. 1D: CSC), 60 seconds after cuff release (Fig. 1B: control; Fig. 1E: CSC), and 4 minutes after nitroglycerin sublingual spray (Fig. 1C: control; Fig. 1F: CSC). The value of baseline VD was 4.31 ± 0.55 mm in the controls and 4.21 ± 0.59 mm in the CSC patients; hyperemic VD was 4.63 ± 0.54 mm in the controls and 4.40 ± 0.60 mm in the CSC patients; and nitroglycerin VD was 4.99 ± 0.52 mm in the controls and 4.87 ± 0.59 mm in the CSC patients. There was no significant difference in VD between the two groups. After calculating FMD and NMD using the equations above, FMD was 7.52 ± 2.63 in the controls and 4.62 ± 1.96 in the CSC patients; this difference was significant ($P < 0.001$). In contrast, there was no significant difference in NMD values between the two groups (Fig. 2).

Discussion

Previous studies have reported that CSC is associated with a nonspecific disturbance of the choroidal circulation, which might induce the development of choroidal ischemia because of hyperpermeability of the choroidal vessels.[3,8,9] Although many previous investigations have identified that CSC originates in a disorder of the choroid, its relationship with peripheral vascular endothelial function has not been investigated. The current study is the first to examine peripheral vascular endothelial function using the brachial FMD technique in patients with CSC. We found that FMD is impaired in CSC patients, which indicates an association between CSC and endothelial dysfunction.

Endothelial function plays an important role in many organs and tissues. Endothelial cells maintain vascular homeostasis by influencing smooth muscle cells, platelets, and peripheral leukocytes.[17,18] In addition, endothelial cells express numerous mediators, surface proteins, and cytokines that regulate vasomotor function, coagulation, and inflammation.[19] Endothelial dysfunction is defined as an imbalance between the vasodilating and vasoconstricting substances acting on endothelial cells.[20] The underlying cellular mechanisms of endothelial dysfunction are directly or indirectly associated with a reduction in NO bioavailability. NO, a major mediator in the regulation of endothelial function, exerts a variety of effects, including modulation of vascular dilation, regulation of local cell growth, and maintenance of antithrombotic, antioxidant, and anti-inflammatory effects.[21] Intact endothelium is crucial for vascular homeostasis and the balance of vascular mediators. Injury of the endothelium leads to impairment of NO production and contributes to the accumulation of the

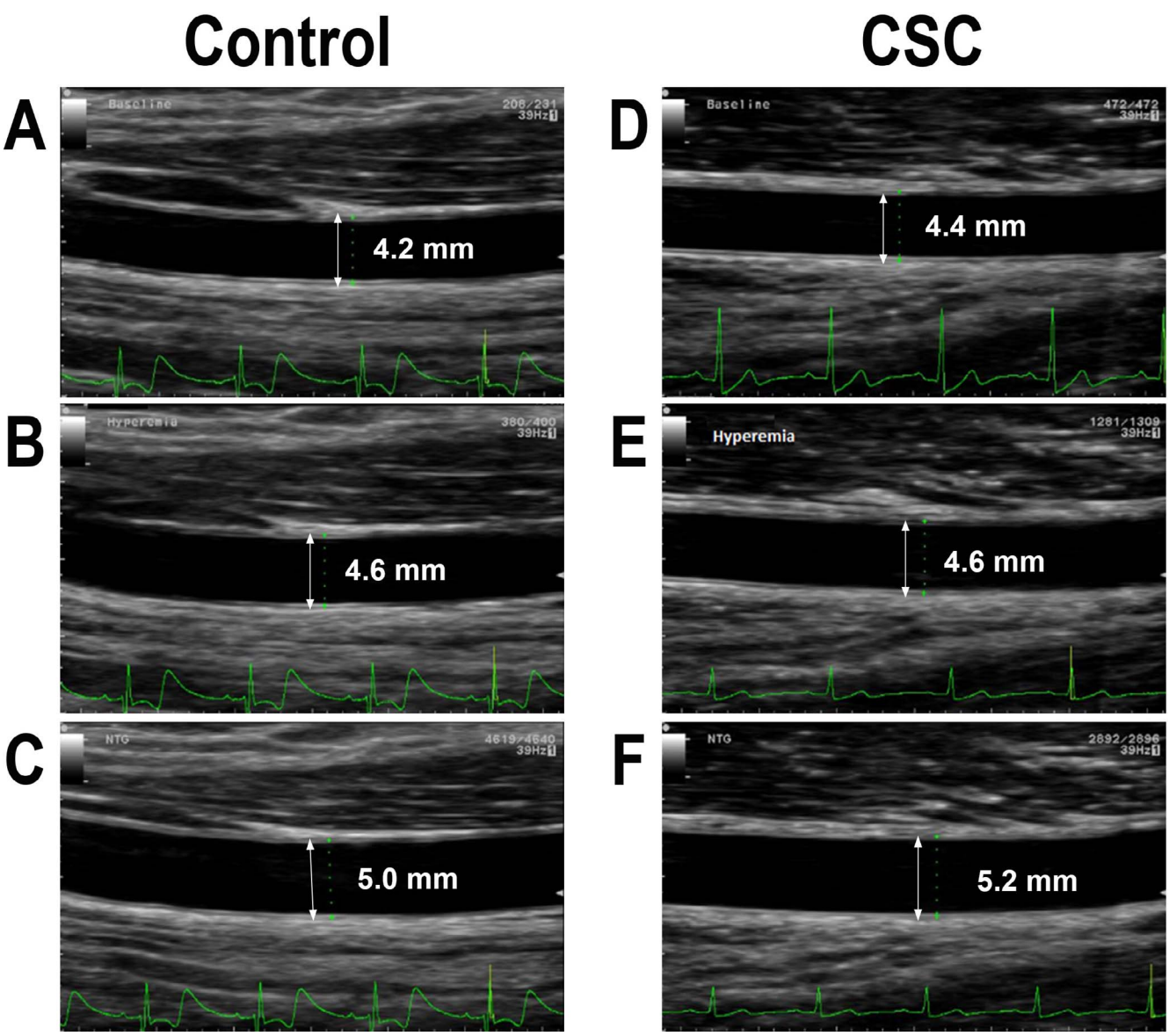

FIGURE 1. Two-dimensional high-resolution ultrasound images of the brachial artery at baseline (**A**), 60 seconds after cuff release (**B**), and 4 minutes after nitroglycerin sublingual spray (**C**) of a control subject, FMD = 9.52% and NMD = 19.05%; brachial artery at baseline (**D**), 60 seconds after cuff release (**E**), and 4 minutes after nitroglycerin sublingual spray (**F**) of a CSC patient, FMD = 4.55% and NMD = 18.18%, respectively.

mediators of oxidative stress, which can lead to inflammatory damage of tissues. With increasing inflammation, the activity of NO synthase can be disrupted, resulting in deterioration of endothelial function.[22] This vicious cycle then decreases NO bioavailability and subsequently results in endothelial dysfunction. However, in this study, we found no significant difference between the two study groups in the levels of the inflammatory marker hs-CRP.

The mechanism of FMD is an NO-mediated vasodilation in response to stimulation caused by shear stress.[23] Impaired FMD indicates an abnormality in NO release or a decrease in its bioavailability, which in turn indicates endothelial dysfunction. The advantage of brachial FMD is that it is a noninvasive and cheap technique that is applicable to testing the endothelial function of asymptomatic young subjects. Previous studies have used FMD as an important indicator of endothelial dysfunction in the etiology of erectile dysfunction[24] and numerous cardiovascular diseases, including atherosclerosis, atrial fibrillation, hypertension, variant angina, and coronary heart disease,[25–27] and have shown that all these cardiovascular diseases share the same feature of endothelial dysfunction. In CSC, although several ocular imaging modalities have localized the lesion to the choroidal layer, there is limited ability to measure choroidal endothelial function directly. Our results showing impaired peripheral endothelial function in patients with CSC reveal that CSC shares the feature of endothelial dysfunction that is common to many cardiovascular diseases. Consistent with this, accumulating evidence shows an association between CSC and cardiovascular diseases: for example, Tittl et al.[28] retrospectively compared 230 patients with CSC and 230 age- and sex-matched control subjects, and found that CSC patients were more likely to have hypertension. A recent meta-analysis also confirmed that hypertension was associated with CSC.[29] Several nationwide cohort studies have shown that CSC increases the risk of ischemic stroke (adjusted hazard ratio [AHR] = 1.56, 95% confidence interval [CI] = 1.11–2.18),[30] erectile dysfunction (AHR = 2.22, 95% CI = 1.42–3.46),[31] coronary heart disease (AHR = 16.1, 95% CI = 1.12–

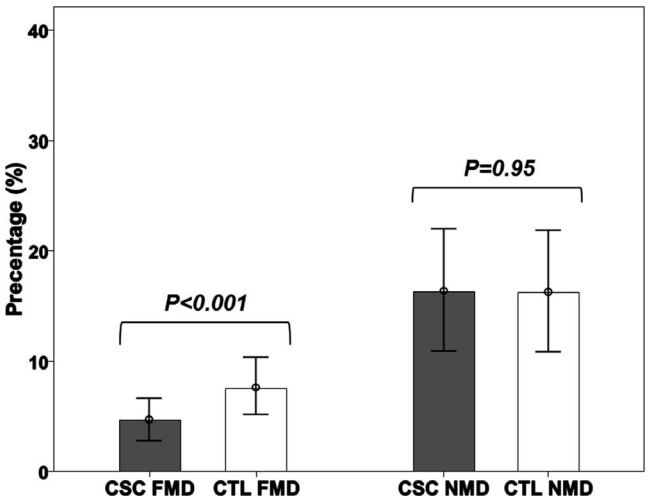

FIGURE 2. Endothelium-dependent FMD and endothelium-independent NMD in patients with CSC and in control subjects (CTL). Values are means ± SD.

2.30),[32] and retinal vein occlusion (AHR = 3.15, 95% CI = 1.91–5.21).[33] Although no adequate explanation of the relationship between CSC and these cardiovascular diseases was identified in these previous studies, the results of the current study provide a possible explanation.

The present study has several limitations that might impact the conclusions. First, the limited sample size might affect the reliability of this survey. Second, we excluded CSC patients with hypertension because of the impact of hypertension on FMD. Third, biomarkers of rheumatologic disease, such as antinuclear antibodies, were not recorded, although a recent study showed that patients with rheumatologic disease are at risk of CSC.[29] In addition, we did not compare the endothelial function in patients with active and nonactive CSC to examine whether active CSC is associated with temporary endothelial dysfunction. Finally, we did not follow these CSC patients long enough to evaluate other possible comorbidities of endothelial dysfunction, such as coronary artery disease, erectile dysfunction, and cerebrovascular disorders. Therefore, a long-term follow-up with a larger sample size is necessary to clarify the relationship between CSC and the other cardiovascular diseases associated with endothelial dysfunction.

In summary, the results of this study demonstrated significant impairment of FMD associated with CSC patients, indicating that CSC might be an ocular presentation of systemic disease associated with endothelial dysfunction. Patients with CSC should be informed about their increased risk of other manifestations of cardiovascular disease associated with endothelial dysfunction. Further surveys and testing for cardiovascular disease in patients with CSC are strongly recommended.

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