Retina

Pupillary Responses Reveal Autonomic Regulation Impairments in Patients With Central Serous Chorioretinopathy

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Purpose. This study assessed the autonomic nervous system in patients with central serous chorioretinopathy (CSC) by simultaneously measuring pupillary responses and heart rate variability (HRV).

Methods. We recruited 33 patients with CSC and 26 age- and sex-matched healthy controls. Using a pupillometry and acceleration plethysmography system, we measured the participants' pupillary light reflex and HRV simultaneously, and compared the following parameters between the two groups: the pupil diameters, diameter changes, and time and frequency domain HRV indices (high frequency power: HF; low frequency power: LF; log LF/HF ratio). Additional data from the Profile of Mood States (POMS) and pupillary responses during mental tasks were also analyzed.

Results. The CSC group had a significantly lower constriction amplitude and a higher redilation ratio compared with the control group, indicating parasympathetic inhibition and sympathetic activation. For the HRV measures, the CSC group demonstrated significantly lower HF and higher LF and log LF/HF ratio, indicative of higher sympathetic activity. The CSC group also showed significantly larger pupil dilation during tasks of moderate difficulty, and higher negative/lower positive POMS mood scores. Further analyses also revealed that the baseline pupil diameter was significantly larger in patients with active as opposed to chronic CSC.

Conclusions. Pupillary responses and HRV measures both revealed sympathetic activation and parasympathetic attenuation in patients with CSC. Larger pupil dilation during mental tasks in CSC could be a potential marker of psychophysiological stress.

Keywords: central serous chorioretinopathy (CSC), pupil light reflex, pupillary responses, heart rate variability (HRV), stress

Central serous chorioretinopathy (CSC) is a chorioretinal disorder that predominantly affects middle-aged men under chronic stress.[1,2] CSC is typically characterized by subretinal fluid at the posterior macula that occurs following a retinal pigment epithelial (RPE) defect detected upon morphological evaluation.[3] There is still no clear understanding concerning the pathogenesis of CSC. However, the disorder is currently thought to result from choroidal disturbances, such as a thickened choroid, hyperpermeable capillaries, and increased hydrostatic pressure.[1,4] Several risk factors may contribute to or precipitate the onset of the disorder, including high levels of endogenous cortisol, exposure to exogenous corticosteroids,[5,6] shift work,[7] pregnancy,[6] and personality traits or psychological disturbances, such as a type A personality,[8] anxiety, and chronic stress.[2]

The stress response is known to involve the autonomic nervous system (ANS), which has two primary branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS).[9] Some recent studies have found that patients with CSC have higher SNS activity, as assessed by power spectral analysis of heart rate variability (HRV).[10–12] It has been speculated that CSC may relate to an autonomic imbalance characterized by SNS arousal and PNS inhibition, which could be provoked by various stressors; this could lead to choroidal vascular stasis mediated by ANS, or epinephrine-induced damage to RPE cells.[2,10]

The PNS and SNS are responsible for pupil constriction and dilation, respectively. The pupillary response can therefore provide a sensitive, inexpensive, and noninvasive measure that reflects the ANS pathways. The response has been utilized to assess diseases, such as Parkinson's disease,[13] Alzheimer's disease,[14] schizophrenia[15], and depression.[16] It has also been measured during various cognitive tasks, because the increase in pupil size represents a psychophysiological index that reflects autonomic activation, which is influenced by levels of motivation, cognitive demands, and task-related effort.[15,17] Another measure that can be used clinically to detect autonomic dysfunction is HRV, which assesses the variations in instantaneous heart rate and RR intervals.[18]

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To date, the pupillary light reflex (PLR) and task-evoked pupillary responses have not been used to evaluate patients with CSC. In this study, we aimed to assess the autonomic activity in patients with CSC, compared with healthy controls, using pupillary responses combined with HRV; we also aimed to evaluate the association between the PLR and HRV.

Methods

Subjects

This prospective study was conducted at the Department of Ophthalmology at the Hyogo College of Medicine (Japan) between April 2020 and April 2022. The study adhered to the Declaration of Helsinki and was approved by the ethics committee of Hyogo College of Medicine. All of the study participants gave informed consent prior to participation in the study.

We recruited patients with unilateral CSC as well as age and sex-matched healthy controls without ocular diseases. The CSC was diagnosed based on the presence of subretinal fluid, as detected using optical coherence tomography, and leakage, as seen using fluorescein angiography. The patients with CSC were divided into two subgroups: an active group, where the first or recurrent symptomatic episode had occurred within the last 6 months (acute CSC and acute recurrent CSC), and a chronic group, where there had been visual symptoms or subretinal fluid for over 6 months.[4] The exclusion criteria for all subjects were the presence of other ocular diseases (age-related macular degeneration, optic neuritis, pathologic myopia, glaucoma, or a history of retinal disease), systemic diseases (diabetes mellitus, coronary artery disease, peripheral neuropathy, or atrial fibrillation), and taking substances that could affect the ANS measures (e.g. cholinergic/adrenergic drugs).

Each participant completed a questionnaire that covered their demographic information, medical history, drug usage, and lifestyle habits, such as smoking or drinking. In addition, their emotional functioning was evaluated using the Profile of Mood States (POMS) questionnaire, which contains 65 items that assess 7 different dimensions: Anger-Hostility (AH), Confusion-Bewilderment (CB), Depression-Dejection (DD), Fatigue-Inertia (FI), Tension-Anxiety (TA), Vigor-Activity (VA), and Friendliness (F), as well as the Total Mood Disturbance (TMD). Prior to the experimental tests, participants were given detailed instructions on how to perform the tasks and what they should pay attention to. During the tests, recordings of the pupillary response and HRV were obtained simultaneously.

Pupillary Light Reflex

The PLR was measured using the Tobii Pro Spectrum (Tobii Pro AB, Danderyd, Sweden), a screen-based eye-tracker that captures pupil data. In our study, we used a sampling frequency of 300 hertz (Hz). Visual stimuli were presented on a 23.8-inch monitor (EIZO FlexScan EV2451, EIZO Corporation, Japan) running at 60 Hz, with a resolution of 1920 × 1080 pixels (16:9 ratio). Tobii Pro Lab software was used to set up the experiment, to synchronize the stimulus presentation with the pupil recordings, and to enable the qualitative analysis and visualization of individual data.

The PLR test was performed in a dimly lit room. The participants were instructed to sit on a comfortable chair without wearing glasses and to stare at a red cross presented in the center of a screen against a black background. The monitor was positioned 60 cm away from the participants' eyes. A faint red light was used for the cross, because the long wavelength does not disrupt dark adaptation. A calibration was performed before the dark adaptation. The PLR test was carried out monocularly after the calibration; the right eye was tested in the healthy controls, and the healthy eye was tested in the patients with CSC. The contralateral eye was covered with an eye patch to avoid any interference effects.

Following 2 minutes of dark adaptation, the PLR was stimulated by a white light that covered the entire screen for 1 second at an intensity of 13 cd/m^2. The PLR was evaluated using a number of measures (Fig. 1): the baseline pupil diameter (BPD), 1 second before the light onset; the minimum pupil diameter (MIN) after pupil constriction; the constriction amplitude (AMP; BPD - MIN); the relative constriction amplitude (AMP%; ratio of AMP to BPD); the maximum constriction velocity (MCV); the maximum constriction acceleration (MCA); the re-dilation pupil diameter (D1) at 5.5 seconds; the ratio of D1 to BPD (D1%); the time from light onset to the minimum pupil diameter (T1); and the time from light onset to the maximum velocity (T2).

Task-Evoked Pupillary Response

Following the PLR test, the participants were asked to complete three different tasks. The first task was to solve a series of multiplication problems. This consisted of 4 math questions that were presented aurally (through the computer's speakers) in the same order for all participants: (i) 8 × 9; (ii) 9 × 14; (iii) 13 × 15; and (iv) 16 × 24.[19,20] Following each problem, the participants were prompted to give the answer after a delay of 5 seconds; following the response, another 5 to 10 seconds passed until the next problem was presented.[20] The pupil dilation was measured and averaged over the 5-second interval between the question and the response; this was determined relative to the baseline pupil diameter for each trial.

The second task involved a digit span test, with three (low difficulty), six (moderate difficulty), and nine (high difficulty) digits. These were presented acoustically using a computer-generated female voice at a rate of one digit per second. Following the presentation of the final digit, the word "repeat" prompted the participants to recall the digits in the correct order. The third task was similar, involving a digit span test with distraction. For this, a female voice was used to present four, five, or six digits; and a male voice presented irrelevant digits at the same time to distract the participants. The subjects were instructed to recall only the digits that were presented by the female voice. The main dependent variable was the average change in pupil diameter for the last digit relative to the first second of each trial.

For both the PLR test and the task-evoked pupillary responses, trials that contained more than 50% blinks or signal loss were discarded. Artifacts and blinks that occurred during the other trials were corrected using linear interpolation, and the data were smoothed by applying a 10-point moving average filter.

Heart Rate Variability

HRV was measured using an acceleration plethysmography (APG) system (ARTETT 2, U-MEDICA, Inc., Osaka, Japan)

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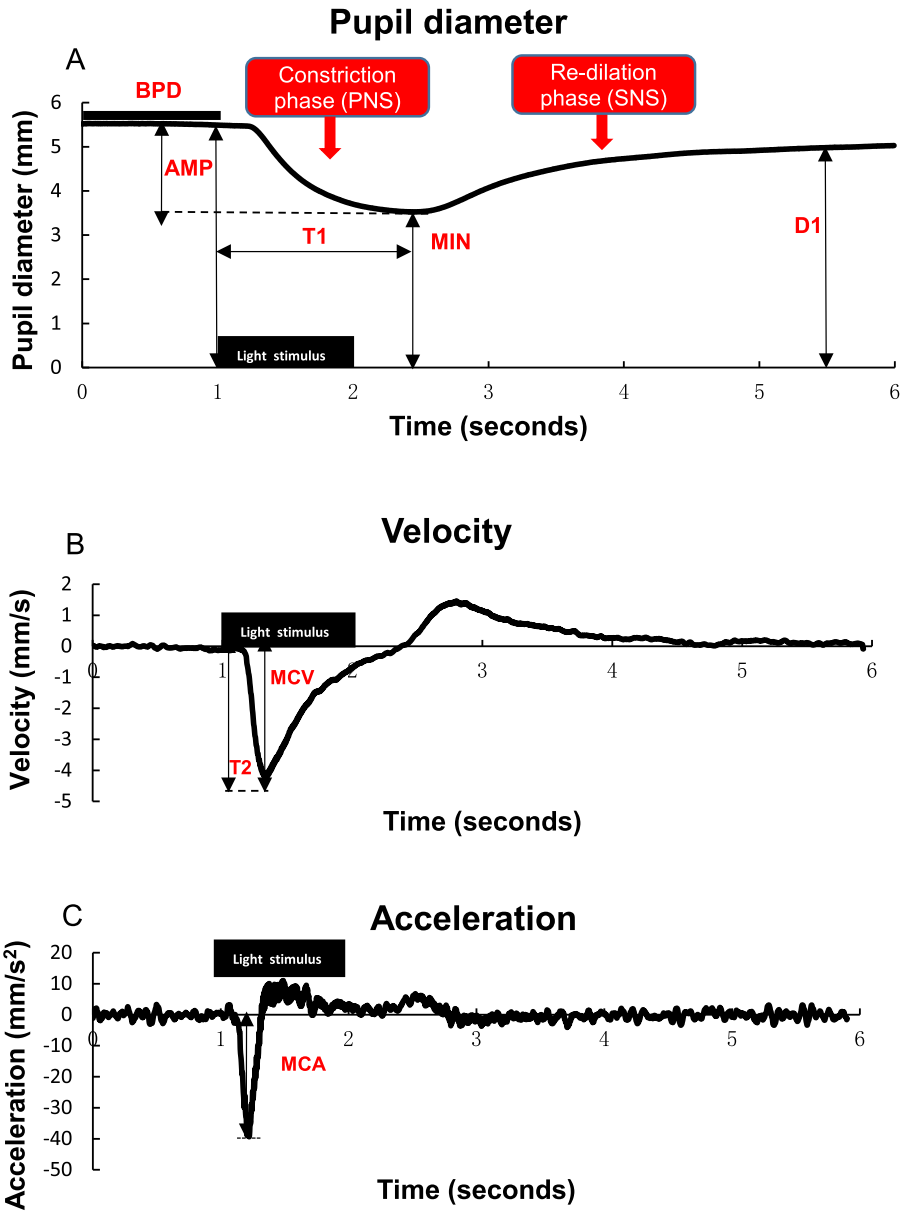

Figure 1. Changes over time in the pupil diameter (**A**), velocity (**B**), and acceleration (**C**) during the pupillary light reflex in one healthy subject. Abbreviations: BPD, baseline pupil diameter; AMP, constriction amplitude (BPD - MIN); MIN, minimum pupil diameter; T1, time from light onset to the minimum pupil diameter; D1, re-dilation pupil diameter at 5.5 seconds; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; T2, time from light onset to the maximum velocity; MCV, maximum constriction velocity; MCA, maximum constriction acceleration.

with an infrared reflective sensor (940 nm wavelength). Analog to digital conversion was carried out at a frequency of 1000 Hz, as is standard for an electrocardiogram (ECG).[21] The participants placed one finger on a sensor that was connected to a computer via a USB port. The APG waves were monitored continuously using software installed on the computer. The recordings began following the calibration, and the HRV was analyzed for the 2 minutes of dark adaptation.

Autonomic function was assessed using measures based on the time domain and the frequency domain. These included the coefficient of the variation of the a-a intervals (CVaa%), the low frequency power (LF; 0.04–0.15 Hz), the high frequency power (HF; 0.15–0.4 Hz), and the LF/HF ratio. The LF and HF measures reflect the sympathetic and parasympathetic (vagal) activity, respectively.

Statistical Analyses

The analyses were conducted using JMP Pro (version 15; SAS Institute Inc., Cary, NC, USA) and GraphPad Prism (version 7.0; GraphPad Software, San Diego, CA, USA). The *t*-tests were used for normally distributed continuous variables; and the Mann-Whitney *U* tests were run to compare measures that were not normally distributed (MCV and MCA). Chi-square or Fisher's exact test was adopted for categorical variables. Pearson's or Spearman's correlation coefficients were calculated between all of the PLR and HRV measures.

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Table 1. Demographic, Clinical, and Lifestyle Data for the Control Group and the Central Serous Chorioretinopathy Group

	Control Group (n = 26)	CSC Group (n = 33)	P Value
Age, y	49.2 ± 11.4	49.3 ± 8.5	0.945
Sex, male/female	23/3	30/3	0.758
Hypertension, n (%)	7 (26.9)	7 (21.2)	0.609
Migraine, n (%)	0	1 (3.0)	1.000
Medication, n (%)			0.823
Antihypertensives	4 (15.4)	5 (15.2)	
Anxiolytics	0	1 (3.0)	
Anticoagulants	1 (3.8)	2 (6.1)	
Hypnotics	0	1 (3.0)	
Tobacco smoker, n (%)			0.173
Current	5 (19.2)	9 (27.3)	
Past	3 (11.5)	9 (27.3)	
Daily alcohol drinker, n (%)	9 (34.6)	12 (36.4)	0.889
Sleep duration, h	6.4 ± 0.9	6.0 ± 1.1	0.239
Daily working time, h	8.8 ± 1.1	9.1 ± 1.9	0.483
Electronic device use, h	9.4 ± 3.6	9.0 ± 4.6	0.780

Abbreviation: CSC, central serous chorioretinopathy.

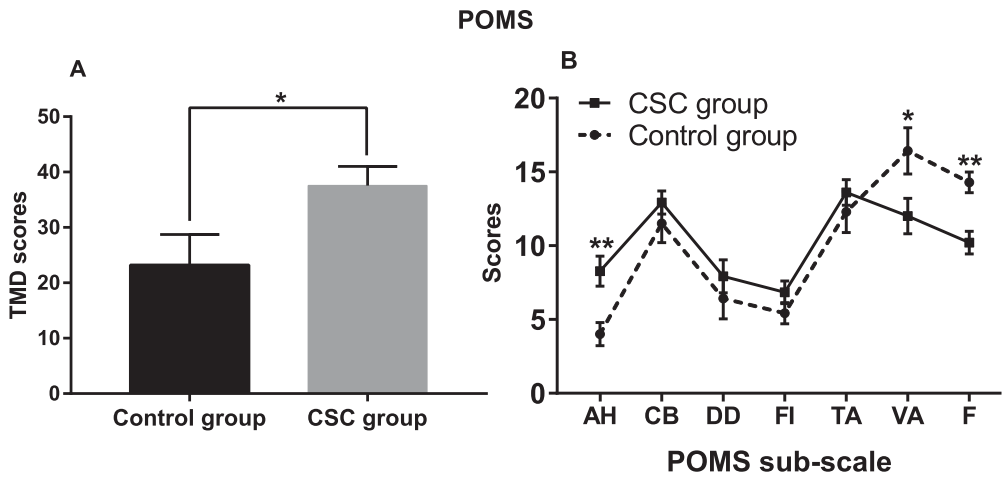

Figure 2. Profile of Mood States scores for the control group and the central serous chorioretinopathy group (n = 14 and n = 25, respectively). (**A**) The mean TMD scores are shown, demonstrating significantly higher scores in the CSC group (P = 0.026). (**B**) Mean scores for the seven subscales are shown, revealing significantly higher Anger-Hostility scores in the CSC group (P = 0.007), as well as significantly lower scores for Friendliness (P = 0.001) and Vigor-Activity (P = 0.033) compared with the control group. Statistical significance: * P < 0.05; ** P < 0.01; Error bars: ±1 standard error of the mean (SEM). Abbreviations: CSC, central serous chorioretinopathy; TMD, Total Mood Disturbance; AH, Anger-Hostility; CB, Confusion-Bewilderment; DD, Depression-Dejection; FI, Fatigue-Inertia; TA, Tension-Anxiety; VA, Vigor-Activity; F, Friendliness.

A 2-way repeated measures ANOVA (MANOVA) was run to analyze differences in the task-evoked pupillary responses between the control and CSC groups, followed by post hoc tests with Bonferroni correction. The CVaa% and LF/HF measures were log-transformed for the statistical analyses. A P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics and POMS Questionnaire

We recruited 26 healthy individuals (23 men and 3 women; mean age = 49.2 ± 11.4 years) and 33 patients diagnosed with CSC (30 men and 3 women; mean age = 49.3 ± 8.5 years) from the Japanese population. There were 22 patients in the active CSC group and 11 patients in the chronic CSC group. The mean best-corrected visual acuity of healthy eyes in the CSC group was 20/16 (range = 20/20-20/13) Snellen equivalent and the mean spherical equivalent was −1.00 ± 2.28 diopters (D). The demographic, clinical, and lifestyle characteristics are summarized in Table 1. There were 14 POMS records available for the control group and 25 for the CSC group. The POMS scores are shown in Figure 2. The mean TMD score was significantly higher in the CSC group (score = 37.6 ± 17.2) than in the control group (score = 23.2 ± 20.6, P = 0.026; see Fig. 2A). The Anger-Hostility score was also significantly higher in the CSC group (P = 0.007), whereas the Friendliness and Vigor-Activity scores were significantly lower (P = 0.001 and P = 0.033, respectively; see Fig. 2B).

Pupillary Light Reflex

The average pupil diameter changed over time in both the patient and control groups, as shown in Figure 3. Differences

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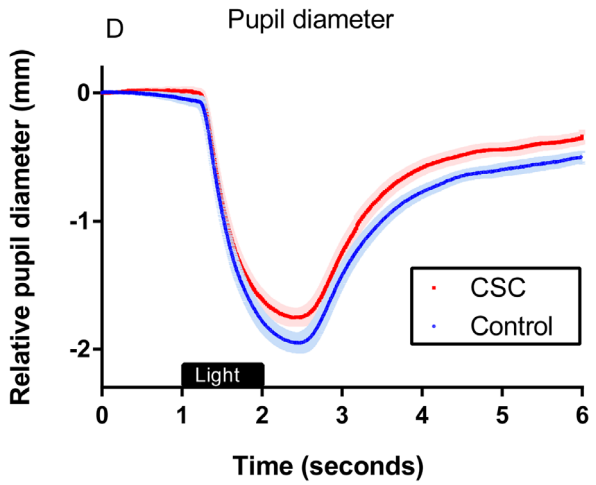

Figure 3. Average baseline-corrected pupil diameter during the pupillary light reflex in the control group and the central serous chorioretinopathy group. The blue line represents the control group and the red line represents the CSC group. The shaded area shows the standard error of the mean (SEM). Abbreviation: CSC, central serous chorioretinopathy.

in the PLR measures for the two groups were analyzed and are shown in Table 2. The CSC group had a significantly lower AMP and a significantly higher D1% compared with the control group ($P = 0.042$ and $P = 0.003$, respectively). The other PLR measures did not differ significantly between the two groups. Further analyses revealed that the BPD was larger in the active CSC group (5.46 ± 0.85 mm) than in the chronic group (4.80 ± 0.70 mm) after adjusting for sex and age ($P = 0.028$).

Task-Evoked Pupil Dilation

We examined whether there was a difference in the task-evoked pupil dilation between the CSC ($n = 29$) and control ($n = 25$) groups based on the available data. A 2 (group) × 4 (multiplication problem) MANOVA was run, and revealed a main effect of the multiplication problem [F (3, 156) = 12.47, $P < 0.001$], thus indicating that the pupils were larger for moderate difficulty. There was also a significant main effect of group [F (1, 52) = 5.33, $P = 0.025$], but the interaction between the group and the multiplication problem was not significant [F (3, 156) = 2.00, $P = 0.117$]. Between-group comparisons revealed that the pupil dilation was significantly larger in the CSC group for the second and third multiplication problems (9 × 14: mean = 0.41 ± 0.29, $P = 0.034$; 13 × 15: M = 0.39 ± 0.28, $P = 0.028$; Fig. 4A).

MANOVA analyses were also run for the digit span tasks with and without distraction. Similar to the multiplication task, it was found that the CSC group had a significantly larger pupil response for a moderately difficult task, namely the six-digit task with no distraction (mean = 0.18 ± 0.09, $P = 0.013$; Fig. 4B) and the five-digit task with distraction (mean = 0.25 ± 0.18, $P = 0.049$; Fig. 4C). For all of the tasks, the CSC group results followed a consistent pattern, with pupil dilation increasing as the task difficulty increased from low to moderate, and then declining for the high difficulty condition.

Autonomic Activity

The cardiovascular measurements showed that the patients with CSC had higher SNS activity, as indicated by significantly higher LF and log LF/HF values compared with the control group ($P = 0.006$ and $P = 0.011$, respectively; see Table 2). In contrast, the HF values were significantly lower in the CSC group, indicating that the PNS activity was inhibited ($P = 0.006$; see Table 2). The log CVaa% values did not differ significantly between the two groups ($P = 0.958$). Besides, the HRV parameters were not significantly different between active and chronic CSC groups.

To obviate the effects of nicotine intake, we compared the PLR and HRV in nonsmokers between the control ($n = 18$) and the CSC groups ($n = 15$), and found the main significant results (Supplementary Table S1) were consistent with the original data. Additionally, both POMS scores and

Table 2. Pupillary Light Reflex and Heart Rate Variability Measures for the Control Group and the Central Serous Chorioretinopathy Group

	Control Group ($n = 26$) *Mean* ± *SD*	CSC Group ($n = 33$) *Mean* ± *SD*	*P* Value*
PLR			
BPD, mm	5.38 ± 0.84	5.24 ± 0.86	0.536
MIN, mm	3.38 ± 0.68	3.42 ± 0.81	0.822
AMP, mm	2.00 ± 0.37	1.81 ± 0.31	0.042
AMP%	37.35 ± 5.67	35.14 ± 6.20	0.162
T1, s	1.41 ± 0.13	1.37 ± 0.19	0.334
D1%	89.28 ± 4.27	92.57 ± 3.85	0.003
T2, s	0.36 ± 0.04	0.37 ± 0.06	0.771
MCV, mm/s	4.40 ± 1.02	4.57 ± 1.56	0.849
MCA, mm/s^2	60.18 ± 23.11	69.24 ± 26.97	0.133
HRV			
Log CVaa, %	0.63 ± 0.20	0.63 ± 0.23	0.958
LF	58.18 ± 15.39	68.89 ± 13.39	0.006
HF	41.82 ± 15.39	31.14 ± 13.39	0.006
Log LF/HF	0.18 ± 0.29	0.37 ± 0.29	0.011

*Statistical analysis with the *T* test or Mann–Whitney *U* test.Abbreviations: CSC, central serous chorioretinopathy; PLR, pupillary light reflex; BPD, baseline pupil diameter; MIN, minimum pupil diameter; AMP, constriction amplitude; AMP%, relative constriction amplitude; T1, time from light onset to the minimum pupil diameter; D1%, ratio of the re-dilation pupil diameter at 5.5 seconds to the BPD; T2, time from light onset to the maximum velocity; MCV, maximum constriction velocity; MCA, maximum constriction acceleration; HRV, heart rate variability; Log CVaa, logarithm of variation coefficient of the a-a intervals; LF, low frequency power; HF, high frequency power; Log LF/HF, logarithm of the LF/HF ratio.

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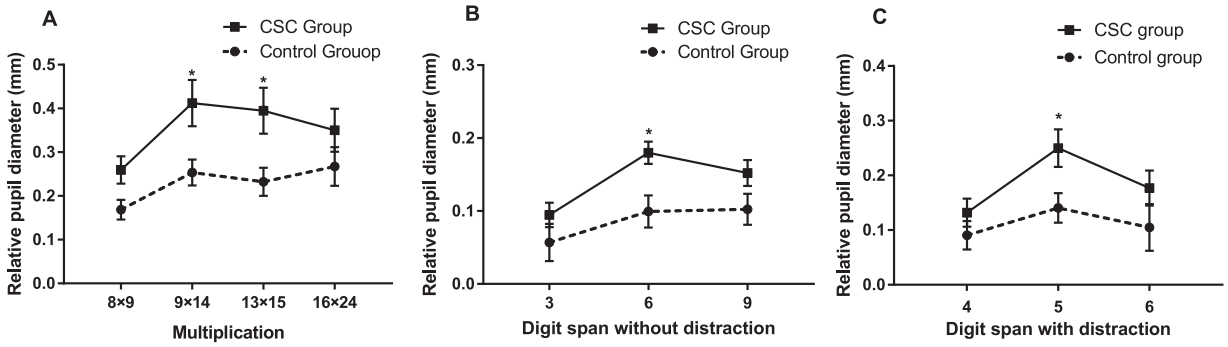

Figure 4. Baseline-corrected pupil dilation for the three mental tasks in the control group and the central serous chorioretinopathy group. (**A**) Baseline-corrected pupil diameter during the 5-second delay following the presentation of each multiplication problem. (**B**) Baseline-corrected pupil diameter at the time the last digit was presented in each digit-span item (with no distraction). (**C**) Baseline-corrected pupil diameter for the digit span task with distraction. Statistical significance: * $P < 0.05$; Error bars: ±1 standard error of the mean (SEM). Abbreviation: CSC, central serous chorioretinopathy.

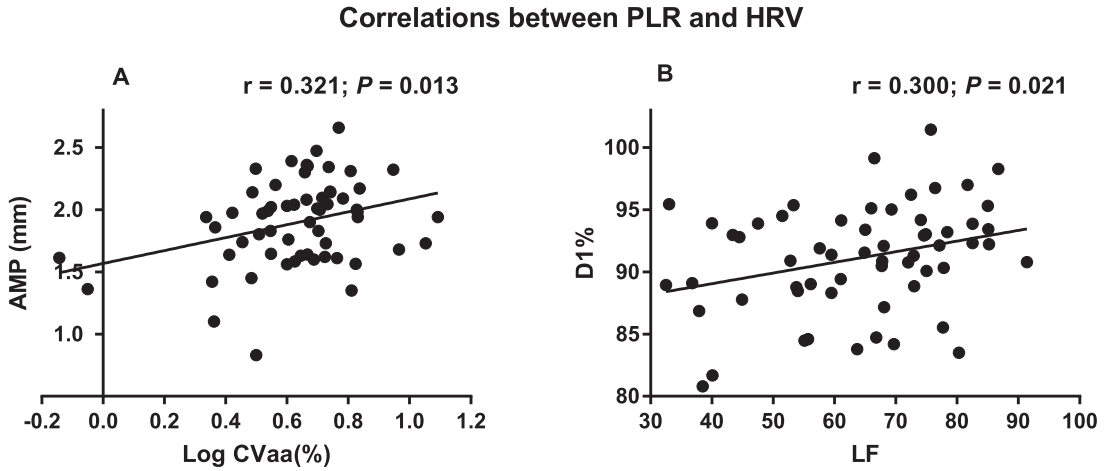

Figure 5. Correlations between the pupillary light reflex and heart rate variability measures for all subjects. (**A**) Correlation between the AMP and Log CVaa% measures (r = 0.321, $P = 0.013$; $n = 59$). (**B**) Correlation between the D1% (high values indicate high sympathetic activity) and LF measures (r = 0.300, $P = 0.021$; $n = 59$). Abbreviations: PLR, pupillary light reflex; HRV, heart rate variability; AMP, constriction amplitude; Log CVaa, logarithm of the variation coefficient of the a-a intervals; D1%, ratio of the re-dilation pupil diameter at 5.5 seconds to the baseline pupil diameter; LF, low frequency power.

task-evoked pupil dilation showed similar results to the total data, except for the digit span task without distraction.

Correlation Between the PLR and HRV Measures

Correlation analyses were run between the PLR and HRV measures using all of the subjects ($n = 59$). These revealed significant positive correlations between the AMP and log CVaa% (r = 0.321, $P = 0.013$; Fig. 5A), the D1% and LF (r = 0.300, $P = 0.021$; Fig. 5B), and the D1% and log LF/HF (r = 0.261, $P = 0.046$).

Discussion

In this study, patients with CSC were found to have a significant reduction in the AMP and a significant increase in pupil re-dilation (D1%). Similarly, there was substantially larger pupil dilation during tasks of moderate difficulty. These results can be taken to indicate increased SNS and decreased PNS activity in patients with CSC, as previous work has shown that the constriction phase of the pupillary light reflex reflects the PNS, while re-dilation reflects the SNS.[14,22] In our study, we simultaneously examined the HRV, and the results were found to indicate similar ANS alterations. Specifically, there was evidence for decreased parasympathetic regulation of the ANS in CSC, along with SNS activation.

Recently, pupillometry has been widely used to assess ANS activity, cognitive impairments, and psychological disorders, and it has been found to have high sensitivity and reproducibility.[13–16] It is known that a short light stimulus evokes a miotic response, which is predominantly mediated by parasympathetic nerves. The amplitude of the pupillary light reflex has been found to be reduced in patients with generalized anxiety disorder,[23,24] thus indicating inhibition of the PNS.[23] This mirrors the findings for patients with CSC in our study, where the AMP was significantly lower compared with the control group. It has previously been suggested that attenuation of the miotic amplitude, controlled by the PNS, may be reciprocally linked to

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enhanced SNS activity.[25] This would be in line with our finding that the D1% increased in patients with CSC, as this measure reflects the SNS.

We examined pupil dilation during the performance of three different tasks. We found that pupil dilation was larger in the CSC group, thus indicating higher autonomic activity. It is known that effortful or stressful tasks usually increase SNS activity, resulting in higher blood pressure, sweating, pupil dilation, and other symptoms.[26] Individuals with a type A personality have been found to have bigger pupils and a higher heart rate when performing a mental task, which indicates that they have higher epinephrine levels and increased sympathetic arousal.[27] CSC has also been associated with increased SNS activity following excessive treatment with sympathomimetic agents.[28] Stress-related psychological factors are generally considered to be risk factors for the development of CSC, especially in those with a type A personality.

The HRV was measured using an APG system. ARTETT was used to obtain measures of autonomic modulation,[29] such as the CVaa%, which is approximately equivalent to the CVRR% from an ECG.[21] We found that the LF and log LF/HF ratio were significantly higher in patients with CSC compared with controls. There is evidence that the LF mainly reflects SNS activity, whereas the LF/HF ratio reflects the autonomic balance.[11,18,30] Predominantly sympathetic ANS activity has been characterized by an increase in the LF and LF/HF ratio, and a decrease in HF.[11,18] This pattern was found for our patients with CSC, and is consistent with previous studies that found dysfunctional HRV in patients with CSC.[10,11]

We analyzed the association between the PLR and HRV measures and found that the pupil AMP was strongly associated with the log CVaa%. This was expected, as a decrease in the CVaa% has been linked to a decrease in parasympathetic activity,[21] as also found for the AMP measure. Positive correlations were also found between the D1% and LF, and the D1% and log LF/HF, all of which reflect SNS activity. Taken together, the correlations between the PLR and HRV measures suggest that both pupillary and cardiac functions are influenced by central autonomic networks, or peripheral autonomic pathways are substantially involved in both systems.[31] The findings also support the argument that the PLR could be used to detect ANS dysfunction as effectively as the HRV,[32] and that it could be used as a possible screening or diagnostic tool for psychosocial stress and stress-related diseases, such as CSC, psychotic disorders, and coronary heart disease.

We identified one measure that differed between the active and chronic CSC groups: the baseline pupil diameter. This was found to be larger in the active than the chronic group. This finding indicates that there is higher SNS activity in the acute episode of CSC. Bernasconi et al. found that mean LF/HF ratios correlated positively with CSC disease activity, with higher values in patients with acute and acute recurrent CSC than in those whose CSC had healed.[11] In our study, we did not find any HRV differences between the active and chronic CSC groups. This may be because the 2 minutes of measurement (during dark adaption) was not long enough to provide sufficient HRV information. Another possibility is that the ANS activity was higher than usual during the simultaneous recordings, which may have masked any subgroup differences.

Our study assessed the participants' mood using the POMS questionnaire. The patients with CSC had higher TMD and negative mood scores, and lower positive mood scores, in line with higher levels of stress. It is thought that CSC may be triggered by psychological states, such as emotional distress or hostility, which increase SNS stimulation.[33] Intense and persistent stress may lead to abnormal pupillary responses and HRV, as a result of high activity in the sympathetic adrenomedullary system.[2,34] In addition, stimulation of the cervical sympathetic nerves leading to arterioles vasoconstriction, may enhance choroidal blood flow as a passive net increase.[35] Dilation of the capillaries and venules may lead to choroidal hyperpermeability, which may contribute to the development of CSC.[1,36] In this way, stress could cause overaction of the sympathetic nervous system and suppress parasympathetic activity, which may lead to an increase in choroidal blood flow and dysfunction of the RPE and eventually lead to detachment of the neurosensory retina.[37]

The current study has some limitations that should be considered. First, we could not completely eliminate a possible influence of medication, nicotine and alcohol dependence, visual acuity, and refractive error on the results. However, we primarily used sound and light as stimuli for our experiment rather than over-relying on vision and previous studies have shown that visual acuity and refractive error have little effect on contraction amplitude and pupil diameter.[38,39] Second, the 2 minutes of dark adaptation may not have been long enough to ensure adequate pupil dilation. Third, it was difficult to determine whether the study measures differed between the active and chronic CSC groups because of the limited sample size. Future studies should be run with larger sample sizes, including patients at different disease stages and exploring the potential relationship between autonomic parameters and anatomic changes in CSC.

In conclusion, by measuring both pupillary responses and HRV we were able to confirm that there are ANS differences in patients with CSC, consistent with high levels of stress. The PLR and task-evoked pupillary responses could be used in clinical practice for screening and diagnostic purposes. An improved understanding of the mechanisms underlying autonomic dysfunction in patients with CSC could lead to the development of more effective treatments and preventive measures.

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