Sympathetic–Parasympathetic Activity and Reactivity in Central Serous Chorioretinopathy: A Case–Control Study

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PURPOSE. This case–control study was conducted to evaluate autonomic function activity and reactivity in patients with central serous chorioretinopathy (CSCR), because stress and type A personality, known risk factors, are also related to autonomic nervous system activity.

METHODS. Patients with CSCR were selected from the outpatient department and medical retina services in one center. Control subjects were chosen from the healthy subjects of the same age group. The autonomic activity (both sympathetic and parasympathetic) was evaluated in 45 patients with CSCR and compared with that in 28 healthy control subjects, by using heart rate variability (heart rate variability) analysis according to the guidelines laid down by the Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). Autonomic reactivity (both sympathetic and parasympathetic) was also evaluated in 32 patients with CSCR and compared with that in 28 healthy control subjects, by using standard autonomic function tests: HRV, as a measure of the resting sympathetic and parasympathetic activity (tone), and changes in blood pressure and heart rate changes during various stressor stimuli in the tests as a measure of sympathetic and parasympathetic reactivity.

RESULTS. Patients with CSCR showed significantly decreased parasympathetic activity (P = 0.002), significantly increased sympathetic activity (P = 0.005), and significantly increased sympathetic-parasympathetic balance (P = 0.004) as measured from different measures of beat-to-beat heart rate variability. The patients also showed significantly decreased parasympathetic reactivity (P = 0.03). Sympathetic reactivity showed a trend toward lessening.

CONCLUSIONS. Autonomic function, both activity and reactivity components of sympathetic and parasympathetic system, is impaired in patients with CSCR. Because autonomic supply modulates the choroidal blood flow, there may be a correlation between measures of autonomic function and the presence of CSCR. (Invest Ophthalmol Vis Sci. 2006;47:3474–3478) DOI: 10.1167/iovs.05-1246

Central serous chorioretinopathy (CSCR) is an idiopathic detachment of macula due to accumulation of serous fluid at the posterior pole causing a circumscribed area of retinal detachment. Concurrent detachment of the retinal pigment epithelium may or may not be present. The etiology of the disease is unknown, and it is hence considered idiopathic. It is generally considered to be multifactorial in origin. Risk factors and systemic associations reported with central serous chorioretinopathy are many. Psychic stress and behavioral traits as potential contributing factors in the development of this disorder were emphasized as early as 1927. It is also known to be associated with stress, type A behavior pattern, hypercortisolemia, and pregnancy.1–6 Experimentally, a picture similar to CSCR has been produced by repeated intravenous administration of epinephrine in rabbits and monkeys.7–8

Recent observations in indocyanine green angiography and multifocal electroretinography have confirmed the earlier belief that patients with CSCR have diffuse retinchoroidal dysfunction, even when the disease is active in only one eye,9–12 indicating that the causative factor is a systemic event and possibly produces its effects by affecting the choroidal vasculature, which is under control of the autonomic nervous system (ANS). Because stress response is related to the ANS response, it is possible that CSCR is also related to abnormal responsiveness of the ANS to various stressor stimuli leading to imbalance of choroidal blood flow. With this postulate we evaluated autonomic function in patients with CSCR.

MATERIALS AND METHODS

The study was conducted at Dr. Rajendra Prasad Centre for Ophthalmic Sciences and the physiology department of the All India Institute of Medical Sciences, from October 2002 to September 2004. Patients with CSCR were recruited from the outpatient department and medical retina services at the center. Only patients with angiographic evidence of active leakage were included in the study. Control subjects were chosen from the healthy subjects presenting with refractive errors and nonspecific ocular complaints. They were selected randomly from the broad age group 25 to 40 years, to ensure that the age distribution of the subjects in the two groups was similar. Detailed history and complete physical examination of every candidate was recorded, to rule out any significant systemic disorder. Each candidate was subjected to autonomic function tests. Consent for undertaking the study was obtained from all participants (cases and controls), in accordance with the Declaration of Helsinki. Our institutional review board reviewed the protocol of the study.

Patients older than 50 years were not included in the study. Other exclusion criteria were the presence of high myopia; age-related macular degeneration; or a history of retinal laser treatment, hypertension, coronary artery disease, or diabetes mellitus. Patients with a history of smoking or alcohol dependence and those taking systemic medications such as cholinergic or adrenergic drugs or steroids were also excluded from the study.
All the subjects underwent a battery of tests aimed at assessing their autonomic function. The subjects were given proper instructions about the tests and recording procedure before starting the actual tests. The temperature of the laboratory was comfortable (22°C ± 2°C), and the laboratory was kept free of noise to the extent possible. Patients were advised to refrain from consuming food, tea, coffee, or any other beverages 2 hours before the test. EKG electrodes were applied for standard limb leads. All the tests were designed to evaluate autonomic activity and autonomic reactivity in the subjects.

Test for Autonomic Activity
Heart rate variability (HRV) was taken as a measure of autonomic activity (tone) and was measured according to the guidelines laid down by the Task force of European Society of Cardiology and North American Society of Pacing and Electrophysiology (1996). The subject was asked to lie down comfortably and the electrocardiogram (EKG) recordings were made under standardized conditions after the patient had rested for 10 minutes. Recordings were made in lead II. A signal sequence was recorded for 300 seconds, which was amplified for optimal detection of the QRS peaks, and a notch filter of 50 Hz was used. The sampling rate was kept at 500 Hz. The signal was processed using an HRV analysis system (Nevrokard, ver. 6.4; MediaStar, Lubljana, Slovenia), which consisted of A/D converter hardware apparatus (PCI 2045P DASport; Intelligent Instrumentation, Tucson, AZ) that acquired and recorded the EKG, which was fed into the software system in a computer. The software first automatically detected the QRS complexes using the fuzzy-logic–based peak detection algorithm, incorporated by Nevrokard software. A careful manual editing was then performed by visual inspection to mark any missing or false peaks. Recording was made for a minimum duration of 5 minutes for each subject.

HRV was then analyzed by time domain, frequency domain, and nonlinear (Poincare) measures. Time domain analysis determines parasympathetic activity while frequency domain analysis determines both sympathetic and parasympathetic activity. Poincare analysis provides data on the vagosympathetic balance.

For time domain analysis, either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous EKG record, each QRS complex is detected, and the instantaneous heart rate is calculated. Simple time–domain variables are then calculated: mean, the mean duration of the NN interval in milliseconds. The standard deviation of the RR interval (SDNN) is the square root of variance. It is mathematically equal to the total power of spectral analysis and reflects all the cyclic components responsible for variability in the period of recording in milliseconds; SDSD, standard deviation of differences between adjacent NN intervals in milliseconds; NN50 count, the number of interval difference of successive NN intervals greater than 50 ms of NN intervals; pNN50 count, the proportion derived by dividing NN50 by the total number of NN intervals. All the above parameters are measures of parasympathetic activity.

Frequency Domain Analysis
To provide deeper insight into the dynamics and components of HRV’s more advanced, higher-order statistics, such as power spectral density (PSD) analysis, are applied. By definition, this analysis decomposes the heart rate signal into its frequency components and quantifies them in terms of their relative intensity, termed “power.” It provides estimates of the power spectrum density function of heart rate—that is, information on how overall HRV (variance of NN intervals or heart rates) is distributed as a function of frequency into different components. The algorithm used for this analysis is the fast Fourier transformation (FFT). The nonparametric approach of estimating frequency is used in the FFT algorithm. The window-based power spectrum density is calculated using the Hamming window, and the power spectrum is subsequently divided into three frequency bands: very low frequency (VLF, 0.001–0.04 Hz), low frequency (LF, 0.40–0.15 Hz), and high frequency (HF, 0.15–0.4). The FFT was calculated in the three preset frequencies, which were measured and calculated in square milliseconds and also in normalized units (NU). The total power spectral density was also calculated. These frequencies of the heart rhythm have the following physiological correlates: LF is mediated by sympathetic nervous system activity predominantly, whereas HF is mediated by parasympathetic nervous system activity predominantly.

Poincare Analysis
Poincare analysis is a nonlinear method used to interpret HRV. It is a geometric plot of heart rate, a graphic representation of correlation between successive NN intervals. NNj,j+1 is plotted against NNj. The shape of the plot is its essential feature. A common method to parameterize the shape is to fit an ellipse into the plot, which is oriented according to the line of identity. The standard deviation of the points perpendicular to the line of identity, denoted by SD1, describes short-term variability (parasympathetic activity). The SD of the points along the line of identity denoted by SD2, describe long-term variability (sympathetic activity). SD1/SD2 denotes vagosympathetic balance.

The software used for the analyses is the HRV analysis system (Nevrokard, ver. 6.4; MediaStar). This software is registered to the Autonomic Function Laboratory, at the All India Institute Medical Sciences (AIIMS).

Tests for Autonomic Reactivity
Tests for autonomic function reactivity were conducted with a standard battery of tests, according to methodology reported earlier in literature. Sympathetic reactivity was assessed with the cold pressor test (CPT), hand-grip test (HGT), and head-up tilt test (HUT). Parasympathetic reactivity was assessed with a deep-breathing test (DBT), cold face test (CFT), and the HUT. These tests were performed as indicated in Table 1.

The following equipment was used for performing the autonomic reactivity tests: a polygraph (Polywrite; Recorders and Medicare Systems, Chandigarh, India) and a handgrip dynamometer, a light and small handgrip dynamometer (Jetter and Scheerer, Tuttingen, Germany), which was used for the isometric exercise test. It could comfortably be held in the hand. It had a scale of 0 to 250 kg and a needle that showed the grip strength. For blood pressure, a standard mercury sphygmomanometer was used to measure the blood pressure.

Statistical Analysis
Data were recorded in a predesigned proforma and were managed on a spreadsheet (Excel; Microsoft, Redmond, WA). All the entries were checked for any possible keyboard error. For the purpose of summarizing, all the quantitative variables were assessed for normality. Because most of the variables were of non-normal distribution, we used median and range as measures of descriptive statistics. A two-group Wilcoxon rank-sum test was applied to compare the difference in median values for each of the parameters at different time points on computer (Stata 8.0 statistical software; Stata, College Station, TX) was used for analysis. In this study, \( p < 0.05 \) was considered statistically significant.

RESULTS
For the purpose of the study, 77 subjects were selected, including 45 patients with CSCR and 32 control subjects. An activity test (HRV) was performed in 45 patients and reactivity tests were performed in 28. Because HRV data show a larger variation and are not distributed normally, a larger number of study participants were included for HRV. The mean age in the CSCR group was 35.7 ± 4.97 years and in the control group was 32.9 ± 6.68 years. The sex distribution between the two...
groups (male and female, respectively) was 42 and 3 in the CSCR group and 30 and 2 in control group.

**Autonomic Activity**

**Time Domain Measurements of HRV.** The result of time domain measures of HRV showed statistically significant decreased parasympathetic activity. Comparative median values and range (minimum-maximum), including the probabilities for different important parameters of CSCR group versus control group are given in Table 2.

**Frequency Domain Measurements of HRV.** The results of frequency domain measures of HRV showed increased sympathovagal balance, decreased parasympathetic activity, and increased sympathovagal balance. Increased sympathovagal activity was evident from significantly increased LF NUs in the CSCR group compared with the control group ($P = 0.02$; Table 2). Decreased parasympathetic activity was evident from significantly decreased HF NUs in the CSCR group compared with the control group, $P = 0.005$ (Table 2).

Increased sympathovagal balance was evident from the significantly increased LF/HF ratio in the CSCR group compared with the control group ($P = 0.004$; Table 2).

**Poincare Measurement of HRV.** The results of Poincare measures from HRV showed a trend toward decreased vagosympathetic balance, as seen by the decreased SD1-SD2 ratio (Table 2).

**Autonomic Reactivity Tests**

**Sympathetic Reactivity.** The diastolic blood pressure (DBP) response to the CPT was found to be lower in the CSCR group than in the control group but not the response to the HUT test and HGT. The change in blood pressure during the HGT showed a trend toward lower increase in systolic and DBP in the CSCR group than in the control group, although the difference was not statistically significant.

The change in systolic blood pressure (SBP) in the CSCR group during the HUT test was not significantly different from that in control subjects.

The change in blood pressure during the CPT showed a lower increase in DBP in the CSCR group than in control subjects. The increase in DBP is an indicator of sympathetic reactivity. The ΔDBP at 1 minute was significantly lower in the CSCR group than in the control group ($P = 0.005$; Table 3).

### Table 1. Tests for Autonomic Reactivity

1. Cold pressor test (CPT): The subject was directed to immerse his hand (up to the wrist) in water at 10°C for 1 minute. The increases in BP and HR over the baseline were monitored. An increase of DBP of ≥10 mm Hg is considered normal.

2. Isometric exercise test (hand-grip test HGT): The subject was directed to grip the hand-grip dynamometer with his dominant hand and contract to the maximum extent possible. The maximum reading was taken as the maximum volumetric contraction (MVC). The subject was then asked to contract the dynamometer continually at 30% of the MVC up to 4 minutes. The increase in blood pressure was measured in the contralateral arm at 1, 2, and 4 minutes during the procedure, and the HR changes were monitored during the procedure via polygraph tracings. An increase in DBP of ≥10 mm Hg is considered normal.

3. Head-up tilt test (HUT): The subject was placed on a tilt table, tilted at 70° for a period of 15 seconds and was maintained at that position for 5 minutes. The BP and HR changes were monitored before, during, and after the procedure. Intermittent BP was measured at baseline and at 0.5, 1, 2.5, and 5 minutes during the tilting procedure. The decrease in SBP is a measure of sympathetic reactivity. A decrease in SBP ≥10 mm Hg is considered normal.

4. Deep-breathing test (DBT): The subject was advised to inspire six breaths in 1 minute, comprising 5 seconds of inspiration and 5 seconds of expiration. The average of the maximum RR interval during expiration divided by the average minimum RR interval during inspiration gave the E:1 ratio. The difference between the maximum and minimum RR gave the ΔHR. An E:1 ratio of ≥1.21 and ΔHR of ≥15 beats per minute is considered normal.

5. Cold face test (CFT): An ice bag was placed over the forehead of the supine subject for 1 minute. The ΔHR was calculated as the CFT ratio, which is the ratio of the heart rate during the test and before the test.

6. Head up-tilt test (HUT): The subject was placed on a tilt table, tilted at 70° within 15 seconds, and maintained at that position for 5 minutes. The BP and HR changes were monitored before, during, and after the procedure. Intermittent BP was measured at baseline and at 0.5, 1, 2.5, and 5 minutes during the tilting procedure.

### Table 2. Comparison of Autonomic Activity from HRV between CSCR and Control Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSCR ($n = 45$) Median (Range)</th>
<th>Controls ($n = 32$) Median (Range)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ms)</td>
<td>757 (58-1005)</td>
<td>826.7 (625.2-1032)</td>
<td>0.03</td>
</tr>
<tr>
<td>SD SDNN (ms)</td>
<td>55 (8-75)</td>
<td>46 (20-4762)</td>
<td>0.003</td>
</tr>
<tr>
<td>SE SENN (ms)</td>
<td>1.7 (0.36-4.4)</td>
<td>2.4 (0.9-7.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>SDS (ms)</td>
<td>21.6 (6.4-68.6)</td>
<td>32 (13-155)</td>
<td>0.002</td>
</tr>
<tr>
<td>nn50</td>
<td>7 (0-118)</td>
<td>16 (1-120)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pnn50 (%)</td>
<td>1.66 (0-23.5)</td>
<td>4.6 (0.2-41)</td>
<td>0.009</td>
</tr>
<tr>
<td>TP (ms2)</td>
<td>1062 (51-7435)</td>
<td>1671 (190-17808)</td>
<td>0.009</td>
</tr>
<tr>
<td>HF (NU)</td>
<td>36 (9-79)</td>
<td>49 (23-84)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (NU)</td>
<td>56 (19-87)</td>
<td>43 (8-74)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sympathovagal balance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.593 (0.24-9.176)</td>
<td>0.866 (0.173-3.18)</td>
<td>0.004</td>
</tr>
<tr>
<td>Vago-sympathetic balance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD1/SD2</td>
<td>0.403 (0.45-0.722)</td>
<td>0.458 (0.2-1.09)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Sympathetic reactivity in CPT was significantly lower in patients with CSCR than in the control group. Thus, we found that patients with CSCR did not show lower sympathetic reactivity in two tests. Blood pressure response to the CPT was significantly lower in the CSCR group. Therefore, sympathetic reactivity showed a trend toward lower reactivity, but it did not reach statistical significance.

**Parasympathetic Reactivity.** A statistically significant difference was found in the parasympathetic reactivity parameters tested by the DBT and HUT. Although statistically nonsignificant, a lower trend was also noted with the CFT. The heart rate response to the DBT showed a lower response in the CSCR group. Therefore, sympathetic reactivity was also significantly decreased, as seen by the decreased value of all variables between CSCR and normal individuals. The change in heart rate during the HUT test showed a significantly lower (40:16) ratio in CSCR with the control group, though not significantly.

The change in heart rate during the HUT test showed a significantly lower (30:15) ratio in CSCR with the control group, but the difference was not statistically significant.

**DISCUSSION**

A significant relationship between the ANS and cardiovascular diseases, including essential hypertension, has been recognized over the past three decades. Unlike earlier guidelines for standards of measurement, physiological interpretation and clinical use of autonomic function tests are reported in the literature. As per Ewing’s criteria, a single test is not sufficient for evaluation of autonomic function; a battery of tests is always used for determination. Results from the various tests evaluated are considered together, they provide useful information regarding the status of the sympathetic and parasympathetic activity at rest and in response to a stimulus. Because the choroidal vasculature is under control of the ANS, results from these tests could indicate whether there are any deviations from normal in patients, wherein choroidal hyperpermeability is reported to be a causative factor in disease pathogenesis.

Harrington published a thesis in 1945, that concluded that ocular manifestations of autonomic dysfunction are present in central angiospastic retinopathy, ocular changes in Raynaud’s disease, amaurosis fugax, and commotio retinae. He analyzed 40 cases of CSCR and found that all patients had two findings in common: a clinical picture of vasoneurotic diathesis and exposure to one or more known ANS stimulants—for example, emotional or psychic trauma or exposure to extremes of temperature. However, there has been only one study, to the best of our knowledge, in which the autonomic function has been evaluated objectively by autonomic function tests in patients with CSCR. Bernasconi et al. measured the autonomic activity in the patients with CSCR in terms of sympathetic activity by measuring the sympathovagal balance. They performed only a power spectral density analysis of HRV and found a significant increase in the mean LF/HF ratio between CSCR and normal individuals.

In our study, we determined HRV as a measure of activity and analyzed it by time domain, power spectral density, and Poincare methods. Our results also revealed a high LF/HF ratio between CSCR and normal individuals in power spectral density analysis. In addition, we also found significantly high sympathetic activity in these patients, as indicated by high LF power spectral density of HRV. Parasympathetic activity was significantly low, as seen by the decreased value of all variables in time domain measures and decreased HF in a power spectral density measure. Sympathovagal balance was significantly high, as seen by the increased LF/HF ratio in power spectral density and decreased SD1/SD2 ratio in the Poincare measure.

This is the first study, to the best of our knowledge, in which the autonomic reactivity was evaluated in the patients of central serous retinopathy. Unlike our study, only autonomic activity was evaluated in the sole earlier study. In our study, sympathetic reactivity showed trends toward lower reactivity but did not reach statistical significance. The parasympathetic reactivity was also significantly decreased, as seen by the decreased heart rate response to the DBT and HUT.

From our observations, we suggest the following model as a possible mechanism in at least some patients developing...
CSCR: During situations of acute stress, blood pressure of an individual increases and tends to cause overperfusion of the vascular beds. In normal individuals, vasoconstriction induced by sympathetic stimulation, keeps the blood flow constant at a physiologic range, despite the stress-induced increase in blood pressure. In contrast, in patients with CSCR, there is high sympathetic activity and a trend toward lower sympathetic reactivity. Therefore, at the time of stress in patients with CSCR, sympathetic neuronal stimulus to the choroidal blood vessels is unable to maintain homeostasis and probably results in choroidal hyperperfusion and secondary dysfunction of the retinal pigment epithelium, leading to development of neurosensory retinal detachment involving the macula.

In conclusion, autonomic dysfunction is present in patients with CSCR in the form of higher sympathetic tone and poor reactivity. Improper sympathetic response during stressor stimuli may be an important factor in the pathogenesis of CSCR.

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References


