

Autonomic dysfunction in patients with central serous chorioretinopathy

Disfunção autonômica em pacientes com coriorretinopatia serosa central

Fernanda Machado Bezerra¹, Emerson Fernandes de Sousa e Castro¹, Fábio Mendonça Xavier Andrade¹, Maria Cláudia Costa Irigoyen²

ABSTRACT

Objective: To evaluate the association between sympathetic nervous system activity and blood pressure variability with central serous chorioretinopathy (CSC). **Methods:** We performed an individual, observational, and cross-sectional study involving 11 patients with CSC and 16 healthy individuals in similar age range. Participants underwent spectral power analysis of heart rate variability (HRV) at the Hypertension Department of Heart Institute at the University of São Paulo. **Results:** We demonstrated sympathetic activity predominance in CSC group and found that the LF (low frequency) of heart rate variability was significantly higher in this group ($p = 0.04$) when compared to control group. The CSC group's mean LF / HF (high frequency) ratio was higher than the control group but was not statistically significant ($p = 0.2$). Blood pressure variability was higher in CSC patients than in normal patients ($p = 0.055$), whereas heart rate variability was lower in these patients when compared to normal patients, although no statistical significance was found ($p = 0.2$). Spontaneous baroreflex function was significantly reduced in patients with CSC when compared to healthy individuals ($p = 0.04$). **Conclusion:** Autonomic dysfunction and a predominance of sympathetic modulation were observed in CSC patients.

Keywords: Autonomic nervous system; Central serous chorioretinopathy; Retina/physiopathology.

RESUMO

Objetivo: Avaliar a associação entre a atividade do sistema nervoso simpático e a variabilidade da pressão arterial com a coriorretinopatia serosa central (CSC). **Métodos:** Estudo individuado, observacional e transversal envolvendo 11 pacientes com CSC e 16 indivíduos saudáveis de idade semelhante. Os participantes foram submetidos à análise de poder espectral da variabilidade da frequência cardíaca no Departamento de Hipertensão do Instituto do Coração da Universidade de São Paulo. **Resultados:** Observamos o predomínio da atividade simpática no grupo com CSC, evidenciado pelo LF da variabilidade da frequência cardíaca significativamente maior neste grupo ($P = 0.04$) quando comparado ao grupo controle. A média da relação LF / HF e a variabilidade da pressão arterial foram maiores nos pacientes com CSC do que nos pacientes normais ($P = 0,2$ e $P = 0,055$, respectivamente), enquanto a variabilidade da frequência cardíaca foi menor nesses pacientes quando comparados aos pacientes normais ($P = 0,2$), embora não tenha sido encontrada significância estatística. A função barorreflexa espontânea também foi significativamente reduzida nos pacientes com CSC quando comparados aos indivíduos saudáveis ($P = 0,04$). **Conclusão:** Concluímos que há sinais de disfunção autonômica e predomínio da modulação simpática nos pacientes com CSC.

Keywords: Sistema nervoso autônomo; Coriorretinopatia serosa central; Retina/fisiopatologia.

¹ Departamento de Oftalmologia, Hospital do Servidor Público Estadual de São Paulo "Francisco Morato de Oliveira", São Paulo, SP, Brazil.

² Laboratório de Hipertensão Experimental do InCor, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

The authors declare no conflict of interests.

Received for publication 24/04/2018 - Accepted for publication 12/11/2018.

INTRODUCTION

Central serous chorioretinopathy (CSC) is a condition characterized by serous detachment of the neurosensory retina and can be associated with retinal pigment epithelium (RPE) detachment. This condition is usually restricted to the macular area and caused by the leakage of fluids through RPE into the subretinal space due to increased choroidal permeability.⁽¹⁾

Many studies have reported a higher incidence of this pathology in patients with competitive personalities, high levels of stress and anxiety, and the onset of symptoms associated with episodes of emotional stress. A CSC-like condition has been produced experimentally.^(2,3)

Because stress response and choroidal circulation are regulated by the autonomic nervous system (ANS), it has been suggested that ANS stimulation is associated to choroidal hyperpermeability and consequent onset of this disease. However, there are only a few studies showing this association.

In this context, the aim of this study is to evaluate the association between sympathetic nervous system activity and CSC.

METHODS

Study design

This is a unicentric, observational, and cross-sectional study. Participants were selected from the Ophthalmology Department of the Hospital do Servidor Público Estadual de São Paulo (HSPE). Their medical records were reviewed, and data from ophthalmologic exams were collected, including visual acuity, anterior and posterior biomicroscopy, as well as results of complementary tests. Patients were then asked about their medical history and, after signing an informed consent form, underwent spectral power analysis of heart rate variability (HRV) at the Hypertension Department of the Heart Institute at the University of São Paulo. The study began after evaluation and receiving approval from the HSPE's Research Ethics Committee.

Patient selection

Inclusion criteria were as follows: patients diagnosed with acute or chronic central serous chorioretinopathy, confirmed by biomicroscopy, fluorescence angiography (FA), and optical coherence tomography (OCT). We excluded patients with systemic arterial hypertension, diabetes mellitus, and/or cardiomyopathy, who underwent intravitreal injection of anti-angiogenic and did not have a confirmed diagnosis or did not undergo all the complementary tests.

Heart rate variability analysis

Spectral power analysis of heart rate variability (HRV) is a noninvasive exam that measures the sympathetic and parasympathetic nervous system activity from RR interval variation. This method observes that the heart rate's (HR) RR interval variation is not a random occurrence but has a periodicity with two main peaks: low frequency (LF) band (around 0.1 Hz), which reflects sympathetic activity, and high frequency (HF) band (between 0.15 Hz and 0.4 Hz), which mainly reflects vagal activity. Another important parameter analyzed is the LF/HF ratio, as any alteration would indicate an unbalance in sympathetic nervous system. In normal individuals, this ratio should not be higher than 1.5 at rest.^(4,5)

To measure heart rate and systolic blood pressure (SBP) variability, blood pressure curves were obtained by the Finometer®

pressure monitor. As a basic principle, the equipment uses the digital photoplethysmography technique, as described by Penaz and developed by Wesseling et al.,⁽⁶⁻⁸⁾ to provide blood pressure curves in a noninvasive and continuous manner. For these curves acquisition, a small sensor was placed surrounding the middle phalange of one hand finger.

Blood pressure curves obtained with Finometer® were simultaneously recorded on another computer equipped with a PowerLab/16 SP biological signal acquisition system. The signal sampling frequency was 1000 Hz, and the stored signals were subjected to a routine analysis to provide HR and SBP variability.

For autonomic modulation evaluation, measurement analyses of HRV and SBPV in both frequency and time domains were performed.

Variability in Frequency Domain (Spectral Analysis):

Initially, pressure curves recorded were edited by detecting occurrences of beat-to-beat blood pressure systolic events to obtain time-series blood pressure (BP) and pulse interval (PI) data. After we obtained visual inspection of the series, we generated a spreadsheet in Microsoft Excel format with BP and PI data and analyzed data using CardioSeries version 2 software. The frequencies of interest were

- LF, which is between 0.15 Hz and 0.01 Hz, for sympathetic modulation and
- HF, which is between 0.4 Hz and 0.15 Hz, for parasympathetic modulation.

The ratio between both LF/HF was calculated to evaluate the autonomic balance.

- Autonomic balance: LF/HF

• Variability in Time Domain

The time series of heart rate was obtained by determining pulse interval of blood pressure signal and was analyzed in time domain by measuring variation in normal beat intervals.

Statistics

We summarized baseline characteristics for all patients as percentages for categorical variables and as means with standard deviations for continuous variables. Comparisons between the means of the groups used Student's t test for parametric and the Mann-Whitney test for nonparametric variables.

The means of three or more groups were compared by a one-way ANOVA, followed by the Bonferroni multiple comparison test for parametric variables. For nonparametric variables, we used the Kruskal-Wallis test, followed by multiple comparisons based on Dunn's test.

Tests were two-sided. Values of $P < .05$ were considered statistically significant. Statistical analyses were performed with SPSS 21.0 for Mac.

RESULTS

For the study, 27 patients were selected, 11 with CSC and 16 healthy controls. Among CSC patients, 8 (72.7%) were male and 3 (27.3%) were female, while in control group, 10 (62.5%) were male and 6 (37.5%) were female. The mean age was 54.3 years (+ 7.22, case group) and 51.9 years (+ 7.44, control group). Among patients with central serosa, 3 had an acute episode with remission, 3 had recurrent acute episodes, and 5 had chronic CSC.

The group of patients with CSC presented higher blood pressure and HRV when compared to control group; however, there was no statistically significant difference between both groups, as shown in Figure 1 and 2. Regarding autonomic heart

rate modulation, CSC patients showed greater LF fraction ($p = 0.04$), and worse baroreflex function when compared to controls ($p = 0.04$), as shown in Figure 3 and 5. The mean LF/HF ratio, which represents the autonomic balance, was also higher in CSC group but without statistical significance ($p = 0.2$).

Table 1
Baseline clinical characteristics of patients enrolled in this study.

	Cases	Controls
Gender (male) n(%)	8 (72.7)	10 (62.5)
Age (years)	54.3 (+7,22)	51.9 (+7,44)
BMI (kg/m ²)	26,44 (+5,43)	26,46 (+4,13)

Table 2
Comparison of autonomous activity mean values between CSC and control groups

Parameters	Cases	Controls	p-value
SBPV (mmHg ²)	63,65	37,84	0,055
HRV (ms ²)	1997,96	3243,02	0,2
Heart Rate LF (ms ²)	5014,72	761,25	0,04
Sympathetic-vagal Balance (LF/HF)	3,315	2,078	0,2
Baroreflex effectiveness index (BEI)	0,474	0,609	0,04

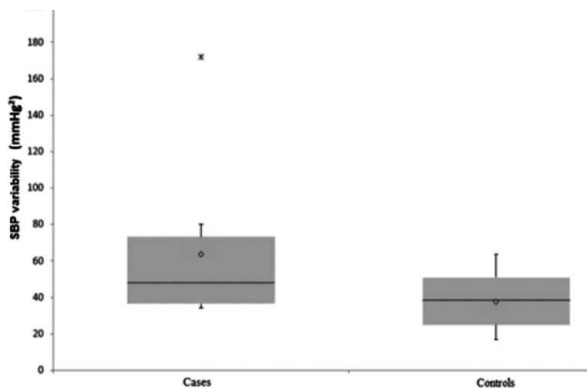


Figure 1: Systolic blood pressure variability values

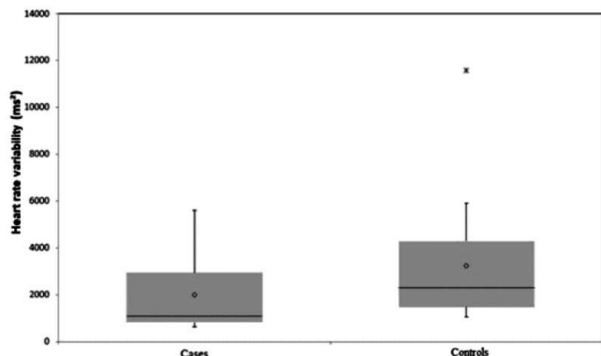


Figure 2: Heart rate variability values

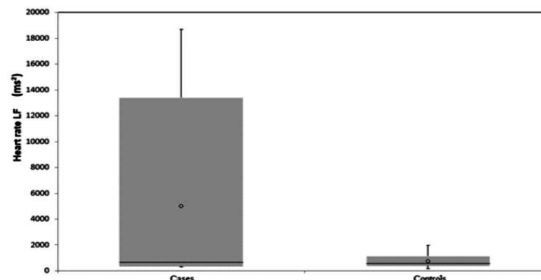


Figure 3: Heart rate sympathetic activity (LF) values

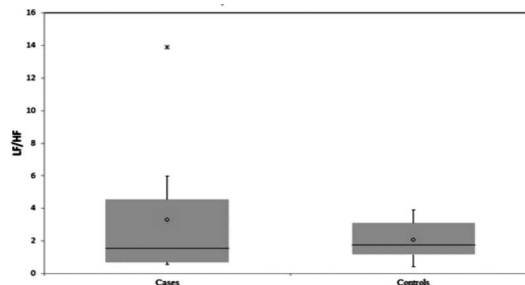


Figure 4: LF / HF ratio values

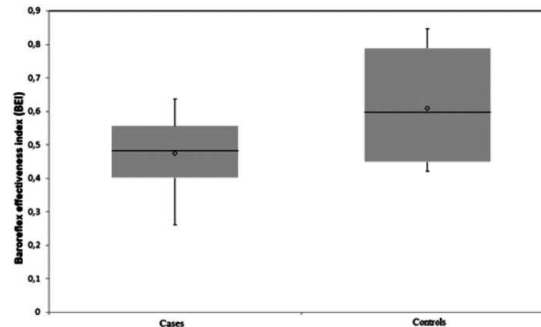


Figure 5: Baroreflex effectiveness values

DISCUSSION

CSC pathophysiology remains unclear. Recent studies have demonstrated the involvement of mineralocorticoid pathway in central serous chorioretinopathy pathogenesis. They suggest that the mineralocorticoid receptors activation in choroidal endothelium by aldosterone or glucocorticoids leads to vasodilation and relaxation of the choroidal vasculature muscle cells and frequently to choroidal thickening (pachychoroid).⁽⁹⁾ Pachychoroid-related macular disorders are characterized by choroidal thickening and choriocapillaris attenuation, which is often associated with dilated choroidal veins, progressive RPE dysfunction, and neovascularization. CSC is only one on the pachychoroid disease spectrum, which also includes pachychoroid pigment epitheliopathy, pachychoroid neovascularization, polypoidal choroidal vasculopathy, focal choroidal excavation, and peripapillary pachychoroid syndrome.^(10,11)

Several risk factors for CSC have been reported, but the most consistent is associated with glucocorticoids use. Increased cortisol levels, pregnancy, type A personality, systemic arterial hypertension, gastroesophageal reflux disease, H. pylori infection, sympathomimetics, and alcohol use are also mentioned in literature as risk factors but remain controversial.⁽¹²⁻¹⁴⁾

Its specific treatment is not yet well established. However, acute CSC is typically a self-limited condition, with spontaneous resolution and visual acuity recovery generally taking place within 1 to 4 months. Close observation, therefore, would be the best option for such cases. Treatment would be reserved for chronic cases, characterized by subretinal fluid accumulation for more than 3 months, low persistent visual acuity, bilateral involvement, and multiple recurrences. Treatment options involve glucocorticoids discontinuation, laser photocoagulation, photodynamic therapy, intravitreal antiangiogenic drugs, and oral spironolactone.^(13,15-18)

In our study, we demonstrated a predominance of sympathetic activity in CSC group, as we found that the LF of HRV was significantly higher in this group when compared to control group. The LF/HF ratio was also numerically higher but without statistical significance, which may be attributed to our small sample.

Some studies have already demonstrated this association. Berasconi et al.⁴ have measured autonomic balance using spectral power analysis in central serous chorioretinopathy patients and found a significant increase in LF/HF ratio of CSC patients when compared to healthy individuals.

Tewari et al.⁽¹⁹⁾ also detected, in CSC group, a higher LF/HF ratio and high sympathetic activity demonstrated by the high LF of HRV in spectral power analysis.

Other parameters analyzed in our study were blood pressure variability (BPV), heart rate variability, and spontaneous baroreflex function. BPV was higher in patients with CSC than in normal patients. Elevated BPV is well established as a strong predictor of mortality, acute myocardial infarction, stroke, and other cardiovascular events.^(20,21) Recently, Castro et al.⁽²²⁾ observed that increased BPV is associated with greater retinal oxidative stress in rats, corroborating that this variability may be involved in ocular vascular diseases pathogenesis and confer a higher cardiovascular risk to these patients.

We also observed lower heart rate variability and significantly reduced spontaneous baroreflex function in CSC patients when compared to controls. Changes in heart rate variability patterns are sensitive and early indicators of health impairments. This decreased variability indicates abnormal and inadequate adaptation of the autonomic nervous system.⁽²³⁾ Spontaneous baroreflex function is also an effective measure of autonomic function.⁽²⁴⁾ Its decrease demonstrated inefficient autonomic mechanisms in this group.

Thus, our results indicate that there are signs of autonomic dysfunction and predominance of sympathetic modulation in CSC patients, which may be associated with increased cardiovascular risk and morbidity. However, the small number of participants is a limitation of our study, and more studies with larger samples are needed to support our findings.

REFERENCES

- Lin D, Chen W, Zhang G, Huang H, Zhou Z, Cen L, et al. Comparison of the optical coherence tomographic characters between acute Vogt-Koyanagi-Harada disease and acute central serous chorioretinopathy. *BMC Ophthalmol*. 2014;14(1):87.
- Watanabe S, Ohtsuki K. [Experimental serous choroidopathy (author's transl)]. *Nippon Ganka Gakkai Zasshi*. 1979;83(7):808-17.
- Yoshioka H, Katsume Y, Akune H. Experimental central serous chorioretinopathy in monkey eyes: fluorescein angiographic findings. *Ophthalmologica*. 1982;185(3):168-78.
- Bernasconi P, Messmer E, Bernasconi A, Thölen A. Assessment of the sympatho-vagal interaction in central serous chorioretinopathy measured by power spectral analysis of heart rate variability. *Graefes Arch Clin Exp Ophthalmol*. 1998;236(8):571-6.

- Cambri LT, Fronchetti L, De-Oliveira FR, Gevaerd MS, Oliveira FR. Variabilidade da frequência cardíaca e controle metabólico. *Arq Sanny Pesq Saúde*. 2008;1(1):72-82.
- Peñáz J. Photoelectric measurement of blood pressure, volume and flow in the finger. 10th international conference on Medical and Biological Engineering, Dresden; 1973. p. 104.
- Wesseling KH. Finapres, continuous noninvasive finger arterial pressure based on the method of Peñáz. *Blood Pressure Measurements*; 1990. p. 161-72. https://doi.org/10.1007/978-3-642-72423-7_18
- Wesseling KH, Wit B, Hoeven GM, Goudoever J, Settels JJ. Physiological, calibrating finger vascular physiology for Finapres. *Homeostasis Health Dis*. 1995;36(2-3):67-82.
- Daruich A, Matet A, Dirani A, Gallice M, Nicholson L, Sivaprasad S, et al. Oral mineralocorticoid-receptor antagonists: real-life experience in clinical subtypes of nonresolving central serous chorioretinopathy with chronic epitheliopathy. *Transl Vis Sci Technol*. 2016 Mar;5(2):2.
- Gallego-Pinazo R, Dolz-Marco R, Gómez-Ulla F, Mrejen S, Freund KB. Pachychoroid diseases of the macula. *Med Hypothesis Discov Innov Ophthalmol*. 2014;3(4):111-5.
- Cheung CMG, Lee WK, Koizumi H, Dansingani K, Lai TYY, Freund KB. Pachychoroid disease. *Eye (Lond)*. 2018; Jul 11. <https://doi.org/10.1038/s41433-018-0158-4>.
- Conrad R, Geiser F, Kleiman A, Zur B, Karpawitz-Godt A. Temperament and character personality profile and illness-related stress in central serous chorioretinopathy. *ScientificWorldJournal*. 2014;2014:631687.
- Nicholson B, Noble J, Forooghian F, Meyerle C. Central serous chorioretinopathy: update on pathophysiology and treatment. *Surv Ophthalmol*. 2013;58(2):103-26.
- Liegl R, Ulbig MW. Central serous chorioretinopathy. *Ophthalmol J Int d'ophtalmologie Int J Ophthalmol. Z Augenheilkd*. 2014;232(2):65-76.
- Serracarbassa PD. Coroidoretinopatia central serosa. *Arq Bras Oftalmol* 2002;65:385-9
- Putnam CM, Vang SS. Modified Photodynamic Therapy Treatment of Central Serous Chorioretinopathy. *Optom Vis Sci*. 2016 93(7):760-771,
- Iacono P, Battaglia Parodi M, Falcomatà B, Bandello F. Central serous chorioretinopathy treatments: a mini review. *Ophthalmic Res*. 2015;55(2):76-83.
- Abouammoh MA. Advances in the treatment of central serous chorioretinopathy. *Saudi J Ophthalmol*. 2015; ;29(4):278-86.
- Tewari HK, Gadia R, Kumar D, Venkatesh P, Garg SP. Sympathetic-parasympathetic activity and reactivity in central serous chorioretinopathy: a case-control study. *Invest Ophthalmol Vis Sci*. 2006;47(8):3474-8.
- Carlberg B, Lindholm LH. Stroke and blood-pressure variation: new permutations on an old theme. *Lancet*. 2010;375(9718):867-9.
- Suchy-Dacey AM, Wallace ER, Mitchell SV, Aguilar M, Gottesman RF, Rice K, et al. Blood pressure variability and the risk of all-cause mortality, incident myocardial infarction, and incident stroke in the cardiovascular health study. *Am J Hypertens*. 2013;26(10):1210-7.
- Castro EF. Avaliação dos efeitos da variabilidade da pressão arterial sistêmica sobre a pressão de perfusão ocular e suas repercussões sobre o estresse oxidativo em retinas de ratos [tese]. São Paulo: Faculdade de Medicina da Universidade de São Paulo; 2014.
- Vanderlei LC, Patre CM, Hoshi RA, de Carvalho TD, de Godoy MF. Noções básicas de variabilidade da frequência cardíaca e sua aplicabilidade clínica. *Rev Bras Cir Cardiovasc*. 2009;24(2):205-17.
- De Angelis K, Do M, Brasileiro S, Irigoyen MC, Humano M, São U, et al. Sistema nervoso autônomo e doença cardiovascular. *Rev Soc Cardiol do Rio Grande do Sul*; 2004;13(3):1-7.

Corresponding author:

Fernanda Bezerra
Hospital do Servidor Público Estadual de São Paulo
Department of Ophthalmology
Rua Pedro de Toledo 1800, São Paulo, SP-Brazil.
E-mail: fernandamb1901@gmail.com