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ORIGINAL RESEARCH

The Effect of Autonomic Nervous System Dysfunction on the Progression of Primary Open-Angle Glaucoma

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Purpose: To study the effect of autonomic nervous system (ANS) dysfunction on glaucoma progression in patients with primary open angle glaucoma (POAG).

Patients and Methods: A retrospective study of 40 cases of POAG patients who underwent regular reexamination for more than 3 years was performed. All participants were subjected to heart-rate variability (HRV) assessment. Patients were divided equally into the lowest and highest HRV groups according to the standard deviation value of the qualified normal to normal intervals (SDNN), a representative indicator of HRV. The lower the HRV, the more severe the ANS dysfunction with sympathetic predominance. Visual field (VF) parameters and retinal nerve fiber layer (RNFL) thickness were used to evaluate and compare the progression of glaucoma damage between the two groups.

Results: There were 20 cases in the lowest HRV group and 20 cases in the highest HRV group. The thinning rate of RNFL in the lowest HRV group was significantly faster than that in the highest HRV group (1.44±1.58 vs 0.29±0.56 μm/year, P=0.00), accompanied by greater fluctuation of intraocular pressure (IOP) (P=0.04), lower diastolic blood pressure (P=0.01), mean blood pressure (P=0.04), and lower mean ocular perfusion pressure (P=0.04). Meanwhile, the incidence of central VF defects in the lowest HRV group was significantly higher than that in the highest HRV group (65.0% vs 30%, P=0.03). Linear regression analysis showed that there was a significant correlation between SDNN and the thickness loss rate of RNFL (P=0.01).

Conclusion: POAG patients with lower HRV, which reflects ANS dysfunction with sympathetic predominance, presented faster glaucoma progression than patients with higher HRV. The more rapid progression of POAG with lower HRV may be explained by IOP and vascular risk factors.

Keywords: primary open angle glaucoma, heart rate variability, autonomic nervous system, visual field, retinal nerve fiber layer

Introduction

Primary open-angle glaucoma (POAG), a major cause of irreversible blindness worldwide,[1] is a neurodegenerative disease characterized by retinal ganglion cell damage and visual field (VF) defect.[2,3] Currently, there is no effective treatment for ganglion cell degeneration, and the focus of glaucoma treatment is to prevent progression.[4] Increased intraocular pressure (IOP) is considered to be the greatest risk factor for glaucoma progression and lowering IOP can effectively prevent its progression.[5] However, although the IOP is well controlled, some patients still have persistent optic nerve injury and visual field defects,[6] suggesting that non-IOP factors are also involved in the development and progress of glaucoma.[7,8] Therefore, further investigation into potential risk factors for glaucoma progression may be helpful for individualized treatment of POAG patients.

In fact, many studies have investigated the risk factors of glaucoma progression. According to their results, the risk factors related to glaucoma progression can be divided into two categories: mechanical (IOP) and vascular.[9,10] Currently, the theory of autonomic nervous system (ANS) dysfunction is attracting researchers' attention. The ANS is composed of

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the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), which control many body functions, including the balance of IOP and blood flow.[11] Thus, any autonomic disorder may lead to abnormalities in IOP and ocular blood flow, leading to the occurrence and development of glaucoma. Many researchers have observed that patients with POAG suffer from ANS regulation disorder,[12–15] and the degree of ANS disorder is related to the severity of glaucoma.[14,16]

Following the publication of the Task Force document on heart rate variability (HRV) in 1996, HRV was applicated in different physiological and clinical studies.[17,18] HRV reflects the fluctuation in the time intervals between adjacent heartbeats, which is generated by dynamic ANS processes.[17] So measuring HRV is considered one of the standard methods to evaluate ANS function. Compared with other methods of assessing autonomic dysfunction, which include cardiovascular reflex tests, sudomotor tests, Valsalva manoeuvre, the tilting test, and so on,[19–21] HRV assessment is simpler and non-invasive.[22] Numerous studies have validated HRV as a reliable measure of ANS function in cardiac and non-cardiac diseases.[23–26] By analyzing HRV of POAG, the researchers found that patients with POAG had autonomic dysfunction and the ANS dysfunction in POAG was characterized by reduced HRV.[12–14] However, the study on how ANS dysfunction characterized by low HRV affected glaucoma progression in POAG was defective.

Therefore, this paper attempts to study the effect of ANS dysfunction on glaucoma progression in POAG and clarify this mechanism from its relationship with risk factors related to glaucoma progression (mechanical and vascular).

Materials and Methods

Recruitment of Participants

Patients with POAG who underwent regular re-examination (every 3–6 months) for more than 3 years at the Ophthalmology Clinic of Tongji Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, who had more than six reliable visual field (VF) and RNFL thickness examinations were enrolled continuously from November 2021 to February 2022. Then the medical records were selected for study retrospectively. The following inclusion and exclusion criteria were adopted.

Subjects with POAG were included if they had an established diagnosis made by a glaucoma specialist based on the presence of an IOP of >21 mmHg, a normal open anterior chamber angle in gonioscopy, glaucomatous optic disc damage, and repeatable VF defects consistent with a diagnosis of glaucoma. Typical glaucomatous optic disc damage included increased cupping and/or focal or diffuse loss of the neuroretinal rim. A glaucomatous VF defect was defined as the consistent presence of a cluster of three or more non-marginal points on the pattern deviation plot with a probability of occurring in fewer than 5% of the healthy population, with one of these points having the probability of occurring in fewer than 1% of the healthy population. A central VF defect was defined as the presence of a cluster of three or more spots with a probability of occurring in fewer than 5% of the healthy population or two or more spots having the probability of occurring in fewer than 2% of the healthy population in the 10° domain of VF of a pattern deviation map. The exclusion criteria were as follows: subjects with a history of anti-glaucoma surgery, any other intraocular or nervous system diseases that may lead to VF loss or optic atrophy, and patients with persistent unreliable VF results (false negative rate ≥15%, false positive rate ≥15%, or fixation losses ≥20%). When both eyes of the same patient met the inclusion and exclusion criteria, one eye was randomly selected for the study.

Systemic, Ophthalmic Measurements, and Medical Records Collection

Systemic, ophthalmic, and HRV measurements and medical records collection were taken on any given day. All patients were advised to avoid drinking caffeine or alcohol 1 day before the measurements.

Each subject underwent comprehensive systemic and ophthalmic examinations, including blood pressure (BP), heart rate (HR), visual acuity, IOP, slit-lamp examination, gonioscopy, fundus photography, central corneal thickness (CCT), eyeball axial length (AL), RNFL thickness, and VF examination. Then these results were recorded as the latest results.

IOPs were measured using a non-contact tonometer (NIDEK RT-2100; NIDEK, CO., LTD, Gamagori, Japan) throughout the follow-up period. The mean IOP was the average of all measurements obtained during the follow-up period. Peak IOP was the maximum of all IOP measurements obtained during the follow-up period. The fluctuation of

IOP was calculated by subtracting the minimum IOP value from the maximum IOP value of all measurements obtained during follow-up.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured with an Omron automatic sphygmomanometer. Mean arterial pressure (MBP) = 1/3 SBP + 2/3 DBP. If the patient has multiple measurements of blood pressure or heart rate, the average of multiple measurements is calculated and recorded. Mean ocular perfusion pressure (MOPP) was calculated using the following formula: MOPP = 2/3 MAP-IOP.

The VF examinations were carried out in the same mode, ie, 30–2 mode, using the same type of perimeter (HFAII740; Meditec, California), and in a standard dark room (about 3.5 lux), quiet environment. The measurement parameters included visual field index (VFI), mean deviation (MD), pattern standard deviation (PSD), and central VF defects. VF results obtained from the same perimeter and in the same model, ie, 30–2 model during follow-up, were collected. Unreliable results were excluded. The progression rate of VF measurements were the latest valid results minus the earliest valid results and then divided by the time between getting those two results. The incidence of central VF defects was recorded in the latest valid VF measurements.

Average thickness parameters of RNFL were obtained using OCT (Spectralis OCT; Heidelberg Engineering, Germany). An annular scan of 3.5mm diameter was performed with the optic disc as the center, and the average RNFL thickness was measured. The results were collected using the same type of OCT and measured in the same mode. Unreliable results were excluded. The RNFL thickness loss rate was the earliest valid result minus the latest valid result and then divided by the time between getting those two results.

The medical records were collected from the beginning of regular check-ups in our hospital and at least 2 weeks after treatment with IOP-lowering medication. The records of systemic complications and medication were based on the medical records of patients at each visit.

HRV Assessment

HRV assessment was taken simultaneously with the medical records collection and all other parameters measurements. All subjects were required to avoid activities that affect HR at least 2 hours before the HRV measurements, such as running and jumping. The electrocardiograms (ECG) of all subjects were collected with a HeaLink-R1A mini-ECG recorder for 5 minutes, then the RRI sequences were extracted with ECG Viewer software, and finally the HRV parameters were analyzed with Kubios HRV software (Kubios HRV premium v2.2; University of Eastern Finland). SDNN which means the standard deviation value of the qualified normal to normal intervals, is an index obtained in time domain analysis of HRV. Patients were divided into two groups according to their SDNN values. It was reported that the SDNN we chose to classify patients had lower variability than other parameters.[26] The lowest HRV group included the lower half of patients with SDNN measurements, and the highest HRV group included the higher half of patients with SDNN measurements. The lower SDNN, the lower HRV, indicating higher SNS activity and more severe ANS dysfunction.

Statistical Analysis

Statistical analysis was performed using the SPSS Statistical Package (version 26.0, SPSS, Chicago, IL). The difference between the high and lowest HRV groups was evaluated by independent *t*-test and Chi-square test. All data were expressed as mean ± standard deviation (SD). Linear regression analysis was used to find the correlation between RNFL thickness loss rate and various parameters, including age, sex, SDNN, AL, average IOP, IOP fluctuation, SBP, DBP, etc. $P<0.05$ was considered statistically significant.

Ethical Considerations

This study followed the Helsinki Declaration, and all the subjects signed informed consent and were approved by the Ethics Committee of Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science & Technology.

Results

Forty eyes in 40 POAG patients met the inclusion and exclusion criteria and were divided equally into the lowest HRV and highest HRV groups according to SDNN values. There were no significant differences in age, sex, axial length,

central corneal thickness, follow-up time (P=0.75), number of IOP-lowering medication per person, use of local β-blockers and antihypertensive drugs (P=1.00), and mean heart rate between the two groups. The mean IOP (P=0.48) and the maximum IOP (P=0.35) were not significantly different between the two groups. The IOP fluctuation in the lowest HRV group and the highest HRV group were significantly different (P=0.04). There was no significant difference in systolic blood pressure (P=0.64) between the two groups, but there were significant differences in diastolic blood pressure (P=0.01), mean arterial blood pressure (P=0.04), and mean ocular perfusion pressure (P=0.04) between the lowest HRV group and highest HRV group (Table 1).

Baseline VF parameters and RNLF thickness showed similar stages of glaucoma damage between the two groups (Table 2). The baseline VFI, baseline MD, PSD, and RNLF thickness in the lowest HRV group and the highest HRV group had no significant difference (P=0.38, 0.31, 0.35, 0.15). Although there was no difference in the progression rate of VF parameters between the two groups, there was a significant difference in the incidence of central VF defects between the two groups, which was 65.0% (13 cases) in the lowest HRV group and 30% (6 cases) in the highest HRV group. The thinning rate of RNLF was 1.44±1.58 μm/year in the lowest HRV group and 0.29±0.56 μm/year in the highest HRV group, with a significant difference between the two groups (P=0.00).

Parameters related to the rate of RNFL thinning were evaluated by linear regression analyses (Table 3). The SDNN values were significantly correlated with the RNLF thinning rates (P=0.01). The relationships between SDNN values and the RNLF thinning rates are shown in Figure 1 (P=0.01), and the slope of the linear fit was negative for the rate of RNFL loss against SDNN values.

Discussion

HRV assessment is a standard method to evaluate ANS function.[22] SDNN was a representative index of HRV. The lower HRV indicates enhanced SNS activity, which may be characterized by dysfunction of ANS. In the present study, the POAG patients with lower HRV (shown as lower SDNN), which reflects ANS dysfunction with sympathetic predominance, were at greater risk for RNFL progression than patients with higher HRV, accompanied by increased IOP fluctuation, decreased DBP, MBP, and decreased MOPP. Similar results were observed by Park et al.[27]

Table 1 Comparison of the Clinical Characteristics of POAG Patients Classified by Heart-Rate Variability (HRV) Assessment

	Lowest HRV Group	Highest HRV Group	*P*-value
Age, years	40.9±13.45	41.95±12.02	0.80*
Sex, male/female	10/10	11/9	0.75†
Follow-up period, year	5.36±2.03	5.32±1.48	0.95*
Use of systemic antihypertensive, n (%)	2 (10%)	2 (10%)	1.00†
Use of topical β-blockers, n (%)	11 (55%)	12 (60%)	0.75†
Average number of IOP drugs used	2.45±1.1	2.25±0.97	0.55*
SBP, mmHg	113.1±6.7	114.0±5.9	0.64*
DBP, mmHg	68.9±7.2	74.3±5.2	**0.01***
MBP, mmHg	83.6±6.2	87.5±5.0	**0.04***
Mean HR	76.6±8.2	79.5±12.9	0.42*
AL, mm	25.79±1.55	24.98±1.36	0.09*
CCT, μm	523.7±22.7	528.6±21.3	0.49*
Mean IOP, mm Hg	16.8±1.9	16.2±3.0	0.48*
Peak IOP, mm Hg	21.9±2.2	22.6±2.8	0.35*
IOP fluctuation, mm Hg	9.1±2.6	7.6±1.6	**0.04***
MOPP, mmHg	38.9±4.7	42.1±4.8	**0.04***
SDNN	24.93±8.07	56.09±11.08	**0.00***

Notes: *The comparison was performed using independent samples *t*-test. †The comparison was performed using a chi-squared test. Values are mean±SD, unless otherwise noted. P<0.05 was statistically significant. Statistically significant values appear in bold.
Abbreviations: HRV, heart rate variability; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; AL, axial length; CCT, central corneal thickness; MOPP, mean ocular perfusion pressure; SDNN, standard deviation value of the qualified normal to normal RR intervals of all sinus beats.

Table 2 Comparison of Visual Field (VF) and Retinal Nerve Fiber Layer (RNFL) Thickness Progression Between Two Study Groups

	Lowest HRV Group	Highest HRV Group	*P*-value
Baseline VFI, %	74.65±30.43	81.50±15.95	0.38*
Baseline VF MD, dB	−10.61±8.57	−8.22±5.67	0.31*
Baseline VF PSD, dB	6.48±4.57	7.87±4.67	0.35*
Incidence of central VF defects, n (%)	13 (65%)	6 (30%)	**0.03**†
VFI progression rate, dB/year	0.76±1.62	0.04±0.45	0.06*
VF MD progression rate, dB/year	0.11±0.36	0±0.12	0.22*
VF PSD progression rate, dB/year	0.19±0.31	0.04±0.15	0.66*
Baseline RNFL thickness, μm	75.5±20.5	66.3±19.4	0.15*
RNFL thickness loss rate, μm/year	1.44±1.58	0.29±0.56	**0.00***

Notes: *The comparison was performed using independent samples *t*-test. †The comparison was performed using a chi-squared test. Values are mean±SD, unless otherwise noted. *P*<0.05 was statistically significant. Statistically significant values appear in bold.
Abbreviations: HRV, heart rate variability; VFI, visual field index; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

Table 3 Regression Analysis of Factors Associated with the RNFL Thickness Loss Rate

	Coefficient Estimate, b	*P*-value
Age	−0.04	0.09
Sex	−0.23	0.66
SDNN value	−0.05	**0.01**
CCT	−0.01	0.46
AL	−0.07	0.24
Baseline VFI	0.31	0.19
Baseline VF MD	0.08	0.52
Baseline VF PSD	0.00	0.89
Baseline RNFL thickness	0.10	0.97
Mean IOP	−0.01	0.94
Peak IOP	−0.07	0.57
IOP fluctuation	−0.02	0.96
SBP	0.10	0.92
DBP	−0.01	0.63
HR	−0.09	0.97
MOPP	−0.13	0.54

Notes: *P*<0.05 was statistically significant. Statistically significant values appear in bold.
Abbreviations: SDNN, standard deviation value of the qualified normal to normal RR intervals of all sinus beats; AL, axial length; CCT, central corneal thickness; VFI, visual field index; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MOPP, mean ocular perfusion pressure.

The authors retrospectively analyzed VF tests of normal-tension glaucoma (NTG) patients and found that NTG patients with lower HRV presented a faster rate of central VF progression than patients with higher HRV. The new finding of this study was the thinning speed of RNLF was negatively correlated with SDNN. That means the higher ANS dysfunction with sympathetic predominance (shown as lower SDNN), the faster the thinning speed of RNLF.

IOP is considered as the most important risk factor in the development and progression of glaucoma. Increased IOP not only leads to mechanical compression of the optic nerve fiber bundle, which leads to interruption of axon transport,[28] but also limits the blood supply of the optic nerve when IOP is greater than MOPP.[29] However, it does not explain why most patients with high IOP do not develop glaucoma[30] and why many patients have glaucoma progression despite IOP

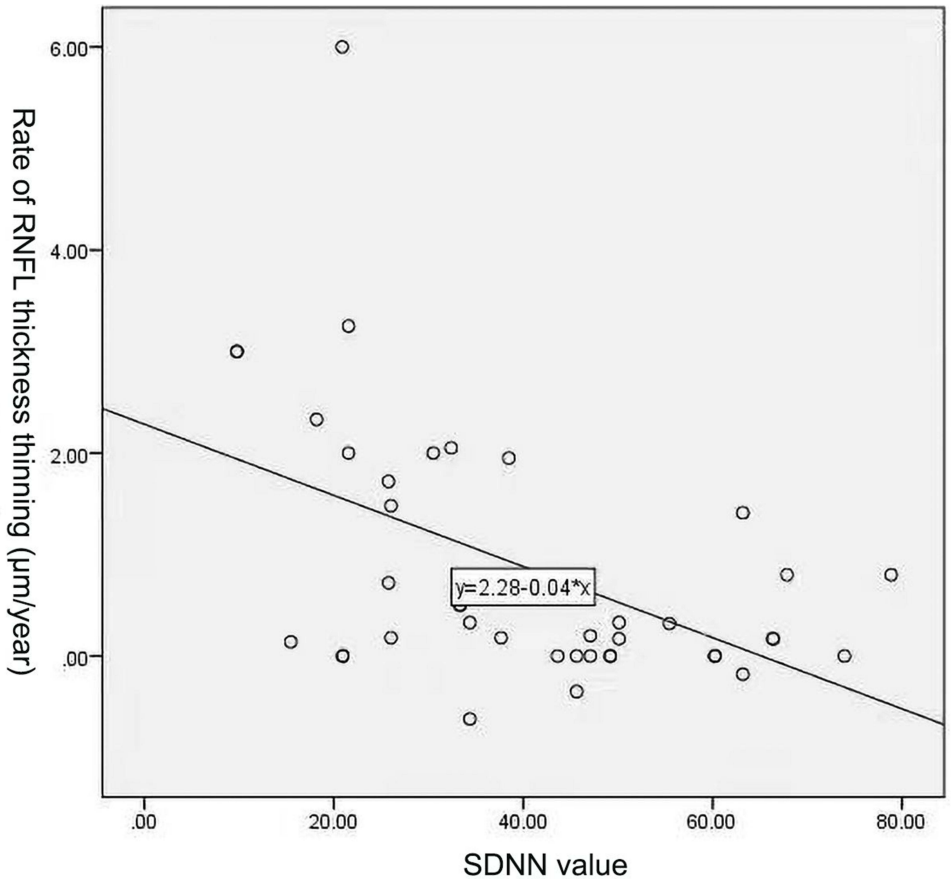

Figure 1 Scatter plot showing the relationship between RNFL thickness loss rate and SDNN values.

lowering therapy.[6] IOP is not static, but varies during the day.[31] Asrani et al[32] conducted IOP monitoring in 105 eyes of 64 patients with an average follow-up of 5 years, and found that in glaucoma patients with office IOP in the normal range, large fluctuations in IOP was a significant risk factor, independent of other parameters. Shin et al[33] found that there was a significant positive correlation between the thinning rate of RNLF and IOP fluctuations. These results indicated that large IOP fluctuation is also an important risk factor in glaucoma progression.

Other than IOP, there is growing evidence supporting the vascular risk factors, whereby glaucoma progression is caused by decreased MOPP, which affects ganglion cells at the optic nerve head. Large epidemiological studies have shown that low MOPP is a risk factor for the prevalence, incidence, and progression of glaucoma.[34,35] In addition, in glaucoma, decreased BP, which may lead to the decrease of MOPP, was reported to be highly correlated with the progression of glaucoma.[36–38] Furthermore, chronic increase of SNS activity can lead to arterial and cardiac remodeling, endothelial dysfunction, increased tissue oxygen demand, and decreased ischemic threshold of organs, including eyes.[39]

ANS participates in the regulation of production and outflow of aqueous humor and thus plays an important role in regulating the balance of IOP.[40,41] This suggested the fluctuation of IOP was closely related to ANS. ANS is thought to play a fundamental role in BP regulation.[14] HRV analysis results in previous studies have suggested that POAG patients have ANS dysfunction, with increased SNS activity as an obvious pattern.[12–14] Increased SNS activity (shown as a reduced SDNN) has been shown to be associated with orthostatic hypotension and decreased nocturnal BP, which are common in POAG patients.[42,43] Therefore, ANS dysfunction (decreased HRV) may fundamentally contribute to various risk factors that are associated with POAG. To sum up, in the present study, the more rapid progression of the lowest HRV group can be explained by these mechanical (increased IOP fluctuation) and vascular risk factors (decreased BP and MOPP).

There was no significant difference in the progression rate of VF test parameters (VFI, MD, PSD) between the low HRV and highest HRV groups, which may be due to the insufficient follow-up time. As structural damage (thinning of RNLF) occurs before functional defect (VF defect), the OCT-RNFL measurement is more sensitive than VF test to detect glaucoma progression.[44] Although there was no significant difference in the progression rate of VF test parameters between the two groups, the thinning rate of RNLF was enough to prove the progression of glaucoma. In this study, the incidence of central VF defects was higher in glaucoma patients with lower HRV. The result is consistent with Park et al.[27] A study which investigated the risk factors for VF defects in different areas found that the initial VF defects that present in the central 10° have been associated with disc hemorrhages and systemic vascular risk factors.[45]

Our research has several limitations that must be acknowledged. First of all, our sample size is limited. Secondly, glaucoma progresses slowly, so the observation period may not be long enough. In order to observe the progress of VF, it may take longer to follow up. Third, we did not measure the repeatability of HRV, though most studies have shown that it is a fairly good and reliable and repeatable measurement.[26] Fourth, the inclusion of patients who are using drugs to lower IOP or BP that may affect BP and HRV, such as β-blockers, may be another limitation of this study. However, the two groups were comparable in the use of these drugs of the study, which minimized the limitations.

Conclusion

Patients with POAG in the lowest HRV group showed a faster thinning rate of RNFL, accompanied by greater fluctuation of intraocular pressure and a decrease of blood pressure and ocular perfusion pressure. The faster progression of glaucoma patients with ANS dysfunction can be explained by these mechanical and vascular risk factors. And the thinning rate of RNLF was negatively correlated with SDNN values. That is, the more severe the ANS dysfunction is, characterized by enhanced activity of the sympathetic tone, the faster the glaucoma progression in POAG patients. Therefore, the treatment of ANS function may be conducive to the treatment of glaucoma.

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Disclosure

The authors report no conflicts of interest in this work.

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