

RESEARCH ARTICLE

Normal tension glaucoma versus primary open-angle glaucoma – The autonomic perspective

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ABSTRACT

Background: Dissimilarities in the risk factors concerned with primary open angle glaucoma (POAG) and normal tension glaucoma (NTG) suggest these two forms of glaucoma to be separate clinical entities, each having their own pathogenesis, yet the relationship between them is not clear convincing. **Aims and Objectives:** The aim of the study was to compare the autonomic activity between healthy controls, POAG, and NTG patients by heart rate variability (HRV). **Materials and Methods:** The study was conducted on 30 age- and sex-matched healthy controls (Group I), 30 patients with NTG (Group II), and 30 patients with POAG (Group III) of age between 45 and 65 years. The basal HRV was analyzed at rest followed by stress tests, handgrip testing (HGT) and passive head-up tilt (HUT), and post recovery. Data obtained were statistically analyzed using SPSS 20. **Results:** Significant raised values of low frequency variables (LF [nu] [58.94 ± 6.556] and [73.39 ± 4.04]) in Group II and Group III, respectively, as compared to Group I (52.13 ± 2.97). LF/HF ratio was significantly rise in Groups II and III with $P < 0.000$ during HGT. LF/HF ratio was significantly high ($P < 0.006$) and ($P < 0.004$) in Groups II and III, respectively, as compared to Group I during HUT. **Conclusion:** The above findings of HRV suggested greater withdrawal of vagal tone and persistently overdrive of sympathetic activity due to sympathovagal imbalance indicated ocular vascular alterations more in NTG than in POAG as compared to normal healthy subjects.

KEY WORDS: Autonomic Dysfunction; Heart Rate Variability; Vascular Dysregulation

INTRODUCTION

Glaucoma is one of the leading causes of blindness in the world characterized by a progressive visual field loss and a distinctive excavation of the optic nerve.^[1] Primary open angle glaucoma (POAG) is broadly classified into two

subcategories, namely high tension, in which intraocular pressure (IOP) is elevated (>21 mmHg) and normal tension glaucoma (NTG) in which IOP is within normal range (10–21 mmHg) along with visual field defects and associated morphological changes in optic disc.^[2] At a systemic level; hypertension, hypotension leading to reduced ocular blood flow (OBF), vasospasm, oxidative stress, and cardiovascular disease history are associated with glaucoma.^[3,4]

With regard to NTG; the female gender, Japanese ethnicity, and optic disc hemorrhages are the provoking factors for its development.^[5] Furthermore, with regard to vascular risk, stronger associations between the vascular factors such as vasospasm, vascular dysregulation, and hypotension have been

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made with NTG in comparison to POAG, and furthermore, NTG patients have also been seen experimentally to present with a greater frequency of conditions such as migraine and Raynaud's phenomenon.^[6] However, the above literature is conflicting, and while some results have been identified by some studies, others have found no such relationships, making it difficult to draw any firm conclusions.

Autonomic dysfunction has been thought to be a contributory factor due to autonomic neuropathy to the pathophysiology of both OAG and NTG.^[7] Glaucoma therapeutics are based on manipulation of the ANS in the anterior segment of the eye; hence, autonomic nerve function is an important determinant of intraocular pressure.^[8,9] With regard to optic neuropathy development both parasympathetic and sympathetic neuropathies has been reported in those with POAG, and those with NTG using a variety of different assessment techniques. Besides, abnormalities suggestive of altered systemic ANS function have been linked to abnormal ocular blood flow regulation in POAG patients using cold pressor testing, and on this basis, it could be hypothesized that disturbed ANS function may contribute to the development of glaucomatous optic neuropathy.^[10,11]

The analysis of HRV provides an insight into the modulation of heart and been used to investigate sympathovagal imbalance within the cardiovascular system.^[12-14] Sustained handgrip testing (HGT) correlates autonomic activity through changes in HR, mean arterial pressure, and vascular resistance. The head-up tilt (HUT) test is an important autonomic cardiac function test mainly to assess the sympathetic activity.

MATERIALS AND METHODS

The study sample comprised of three groups: Group I - 30 age- and sex-matched healthy controls, Groups II - 30 patients with NTG, and Group III - 30 patients with POAG. The research followed the tenets of the Declaration of Helsinki and consent of the Ethical Committee was obtained for the study protocol. All patients provided written informed consent before participation.

Inclusion criteria for Group III (POAG) are: Intraocular pressure >21 mm Hg without treatment, optic disc changes with neuro-retinal rim notching, optic disc excavation, vertical

or horizontal cup to disk (C/D) ratio >0.5 or C/D asymmetry between 2 eyes >0.2, peripapillary splinter hemorrhages, visual field outside normal limits on Humphrey automated perimetry on three perimetry readings, all angles (360°) open on gonioscopy.

Inclusion criteria for Group II (NTG) are the same as for POAG except intraocular pressure ranging between 10 and 21 mmHg.

Exclusion criteria include patients with secondary causes of glaucoma, hazy media, optic neuritis, any disease involving the macula, retina, or visual pathway, high myopia (>6 diopters), previous intraocular surgery and on drugs known to cause optic neuropathy, patients with diabetes mellitus and hypertension.

Autonomic function tests include basal heart rate variability (HRV), HRV during sustained handgrip, and HRV during passive HUT followed by HRV during post recovery in both.

HRV-Powerlab26T polyrite D system was used for recording HRV. The basal recording of ECG (Lead II) was taken for 10 min and analyzed for HRV.

Sustained handgrip test-the patient was asked to lie in the supine position, fitted with a BP cuff on the upper aspect of the non-dominant arm. The patient was asked to hold the handgrip dynamometer in the other dominant hand and to maintain tension at 30% of maximal voluntary contraction for 2 min. During this procedure, BP and HRV were recorded. HUT-subjects were comfortably restrained on a tilt table with foot plate support, with BP cuff fitted on the non-dominant arm. ECG was used for continuous monitoring of heart rate and rhythm. Following the positioning of the non-invasive recorders, subjects were allowed to rest in the supine position for 10 min. After this period of equilibration and completion of baseline hemodynamic measurements, subjects were undergone passive HUT to 70° angle. HRV and BP were recorded. The statistical data analysis was performed using software SPSS version 20.0. The analysis of the quantitative variables included the calculation of the mean and standard deviation ($\times$). Unpaired student *t*-test was used to compare independent groups. The level of significance was $P < 0.05$.

Table 1: Frequency domain variables of basal HRV in Groups I, II, and III

Parameter	Group I mean $\pm$ SD	Group II mean $\pm$ SD	P	Group III mean $\pm$ SD	P-value
LF (nu)	42.75 $\pm$ 2.78	44.85 $\pm$ 6.52	0.10	44.72 $\pm$ 6.41	0.11
LF (ms ²)	421.90 $\pm$ 126.9	399.27 $\pm$ 65.1	0.37	403.09 $\pm$ 67.39	0.41
HF (nu)	44.96 $\pm$ 3.89	46.55 $\pm$ 3.34	0.09	46.99 $\pm$ 4.71	0.16
HF (ms ²)	445.97 $\pm$ 130.65	424.96 $\pm$ 81.15	0.37	427.13 $\pm$ 70.07	0.41
LF/HF	0.98 $\pm$ 0.08	0.96 $\pm$ 0.13	0.41	0.95 $\pm$ 0.13	0.19

SD: Standard deviation, HRV: Heart rate variability

RESULTS

Age Distribution

The mean age of Groups I, II, and III was 51.6 ± 5.25 , 53.45 ± 4.85 , and 51.75 ± 6.07 years, respectively. The mean age of all the three groups was comparable.

Sex Distribution

The Group I comprised 60% males and 40% females, in Group II 55% were males and 45% females, and in Group III 65% were males and 35% females.

Basal Heart Rate, R-R Interval, and HRV

Basal heart rate and R-R interval

In the present study, the mean basal heart rate in all the three groups was within normal range. The mean R-R interval was also within normal range and comparable. On comparison of frequency domain analysis of basal HRV, no statistical difference was observed in all the frequency domain variables Table 1.

HRV during HGT

Frequency domain analysis

Different frequency domain parameters of HRV during HGT of Group II and III were compared with Group I in Figures 1 and 2. The difference in the rise in the values of LF and LF/HF variables was highly significant in POAG group ($P < 0.000$) and in NTG group ($P < 0.001$) as compared to control (Group I).

Recovery phase of HGT

Frequency domain analysis

The frequency domain variables of HRV during the recovery phase of HGT of Group II and III were compared in Table 2.

HRV during HUT

Frequency domain analysis

It changes in frequency domain variables of HRV in Groups I, II, and III during HUT depicted in Figure 3. A highly significant rise in LF/HF has been observed in Group II than in Group III as compared to control group ($P = 0.004$) further indicating a greater withdrawal of vagal tone during HUT test.

Recovery phase of HUT Frequency domain analysis

The frequency domain variables of HRV in Groups I, II, and III during the recovery phase of HUT were compared in Figure 4.

Significant low values of low-frequency and high-frequency variables were observed in Groups II and III. However, a highly significant difference has been observed in Group II

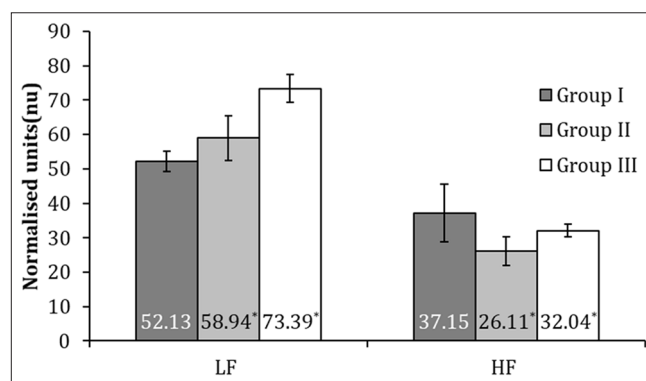


Figure 1: Different frequency domain parameters of heart rate variability during handgrip testing of Groups II and III were compared with Group I. * $P < 0.05$ significant

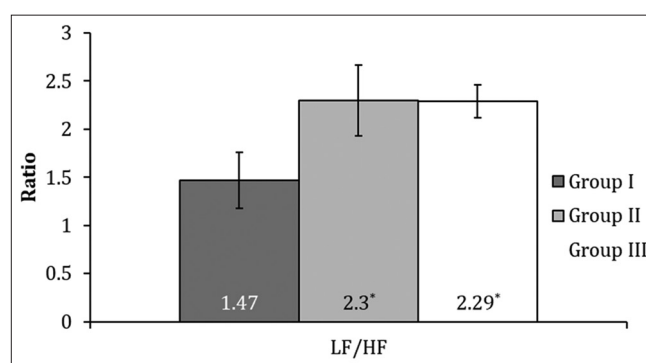


Figure 2: Comparison of the immediate effect of handgrip testing on LF/HF ratio. * $P < 0.05$ significant

(NTG) as compared to control group and value of LF/HF ratio was significantly high in Groups II and III.

DISCUSSION

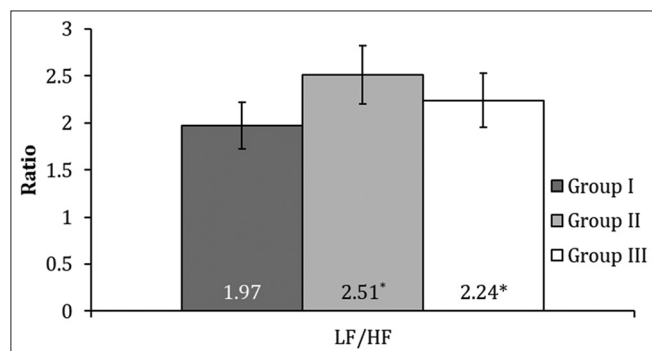
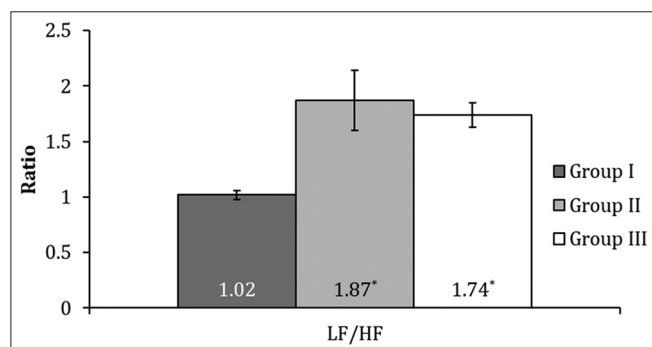
In the present study, HRV was assessed by analysis of both time and frequency domain variables. In the present study, on the comparison of frequency domain variables of basal HRV of Groups II and III with Group I no statistical difference in mean values of LF(nu), LF(ms²), HF(nu), HF(ms²), and LF/HF ratio was observed. These findings were suggestive of balance tone of both the divisions of ANS in all the three groups in resting condition. These observations were consistent with the studies by Askelord *et al.* (1981) and Apple (1989) who reported that LF band is influenced by both sympathetic and parasympathetic sympathetic activity and Mallani and associates proposed that LF/HF is a better predictor of the relative level of sympathetic and parasympathetic influence.^[15]

Sustained HGT is a provocative stress test to assess autonomic activity. The isometric handgrip test increases heart rate, arterial pressure due to increase in reflex sympathetic activity. In POAG group vagal withdrawal is greater, as root mean square of the successive differences value is significantly low in POAG ($P = 0.03$). These findings were consistent with the

Table 2: Comparison of frequency domain variables of HRV in Groups I, II, and III during recovery phase of handgrip testing

Parameter	Group I mean±SD	Group II mean±SD	P	Group III mean±SD	P
LF (nu)	45.05±3.31	46.94±5.41	0.1	57.8±4.94	<0.000***
LF (ms ²)	440.39±100.71	420.85±52.68	0.44	352.29±33.76	0.01**
HF (nu)	45.67±6.65	36.82±4.59	0.000***	38.4±8.07	<0.000***
HF (ms ²)	445.22±105.55	330.85±54.37	0.02*	237.44±65.93	<0.000***
LF/HF	0.99±0.12	1.28±0.13	0.001**	1.55±0.28	<0.000***

*P<0.05 significant, **P<0.001 highly significant, ***P<0.000 very high significant. SD: Standard deviation, HRV: Heart rate variability

**Figure 3:** Comparison of LF/HF during head-up tilt. *P<0.05 significant**Figure 4:** Comparison of LF/HF ratio during head-up tilt recovery. *P<0.05 significant

study conducted by Khurana and Setty.^[16] Highly significant raised value of LF/HF ratio further suggestive of increased HRV due to altered sympathovagal balance. Since LF (nu), the marker of sympathetic activity has increased, and HF (nu), the marker of parasympathetic tone has decreased significantly in the study; therefore, frequency domain analysis of HRV during the stress test (HGT) further suggested withdrawal of parasympathetic activity in both type of glaucoma cases. A significant rise in LF/HF ratio further suggested persistently higher sympathetic overactivity even during the recovery phase. These findings were consistent with the study by Khurana and Gasser *et al.*^[17]

HUT test is an important autonomic function test to assess sympathetic activity. It mainly assesses the baroreceptor activity in response to a fall in blood pressure due to change of posture (lying to standing). The above findings of HRV

in this study further suggested greater withdrawal of vagal tone, and persistently overdrive of sympathetic activity due to sympathovagal imbalance, resulting in delayed recovery from stress. These findings were in accordance with the studies of Kenny *et al.*^[18]

Strength of the Study

This is the first study so far in India to study the comparative analysis between NTG and POAG based on the perspective of autonomic functions.

Limitations

The study limitation was categorization of glaucoma patients into two groups (NTG and POAG) which was based on clinical levels of mean IOP above or below 21 mmHg. It is possible that a certain degree of overlap may exist, which perhaps accounted for comparable findings of HRV domains and MAP and MOPP between NTG and POAG patients in this study.

Future Prospects

- Both type of glaucoma patients (NTG and POAG) must be followed up to find out if the comparable findings in the early stage remain consistent as the disease progresses or become less consistent.
- Study regarding structural changes at the ocular level should be carried out to find out the correlation with the vascular changes.
- The available literature has provided enough evidence that HRV to be the most sensitive, noninvasive, and reliable method to assess autonomic modulations. Therefore, in the examination of glaucoma patients assessment of autonomic activity by HRV should be included.

CONCLUSION

The results and discussion of HRV analysis during provocative tests concluded that autonomic imbalance was present in both types of glaucoma patients, slightly greater in POAG patients, however keeping in mind the vascular risk factors in etiology of both conditions, the present study also

highlighted the need to become less rigid in separating two conditions.

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