

## ALTERED AUTONOMIC BALANCE IN NORMAL TENSION GLAUCOMA

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Received: 01 September 2016, Revised and Accepted: 18 October 2016

## ABSTRACT

**Objective:** To study autonomic imbalance if any in normal tension glaucoma (NTG) patients by heart rate variability (HRV) and head-up tilt (HUT) test.

**Methods:** The study subjects of age between 45 and 65 years of either sex comprised 20 patients with NTG (Group II) and 20 age- and sex-matched healthy controls (Group I). Different variables of time and frequency domain of HRV were analyzed at rest, during HUT and the recovery period.

**Results:** Highly significant decrease in value of root mean square successive difference observed in Group II ( $p < 0.000$ ) in comparison to controls. The high-frequency variables (HF [nu] and HF [ms<sup>2</sup>]) were significantly less ( $p < 0.000$ ) and low frequency (LF)/HF ratio was significantly high ( $p < 0.000$ ) in Group II.

**Conclusion:** During stress test, i.e., HUT there was the greater withdrawal of parasympathetic input to heart; hence, there was relatively over sympathetic activity due to sympatho-vagal imbalance.

**Keywords:** Stress test, Sympatho-vagal imbalance, Autonomic function test.

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## INTRODUCTION

Glaucoma is broadly divided into two subcategories, namely, high tension or primary open angle glaucoma (POAG), 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. With regard to vascular risk, stronger associations between the presence of vascular factors such as vasospasm, vascular dysregulation, and hypotension have been made with NTG in comparison to POAG, and rather NTG patients have also been found to show a more frequency of migraine and Raynaud's phenomenon [1-3].

The possibility that POAG and NTG representing two distinct clinical entities can, therefore, not be ruled out, however, much of the literature is conflicting making it difficult to draw any firm conclusions. The disturbed vascular function has been recognized with regard to glaucoma, with authors as early as 1925 proposing an alternative vascular theory of glaucoma development along with the involvement of circulatory disturbances and vascular dysregulation. Autoregulation of ocular blood flow is a complex process involving the autonomic control, systemic blood pressure (myogenic control), circulating hormones (humoral control), and the endothelium. Abnormalities such as endothelial dysfunction, vasospastic syndrome, and autonomic dysfunctions have been implicated in the development of autoregulatory abnormalities in glaucoma. Indeed, few studies have provided evidence of disturbed autoregulation in glaucoma patients not only at the ocular level but also at the systemic level seen in those with progressive glaucoma [4-8].

Assessment of heart rate variability (HRV) can provide an indirect assessment of the autonomic control of the heart, commonly used for the investigation of normal physiology and pathological conditions. Heart rate response to head-up tilt (HUT) is a useful tool in the diagnosis of autonomic dysfunctions. Heart rate rises immediately due to withdrawal of parasympathetic activity. The hemodynamic response to postural challenge during HUT table test has emerged as an index test for cardiovascular autonomic activity. The HUT test produces

predictable set of circulatory adjustments on change of posture (lying to standing) to overpower the effect of gravity. The immediate cardiovascular response resulting due to passive HUT signifies the function of cardiopulmonary and arterial baroreceptors [9-12].

Therefore, in the present study, we aimed to assess the sympatho-vagal imbalance using HUT with HRV in patients with NTG.

## METHODS

The study sample of age between 45 and 65 years of either sex comprised two groups: Group I - 20 age- and sex-matched healthy controls and Group II - 20 patients with NTG. The study was approved by the Institutional Ethics Committee. Written consent was taken and the whole procedure was explained in detail to each subject in his/her own language. Each subject had undergone a complete ophthalmological examination in glaucoma clinic, IOP measurement with Goldmann applanation tonometer.

## Inclusion criteria for Group II (NTG)

IOP 10-21 mmHg without treatment, optic disc changes suggestive of glaucomatous damage including one or more of these signs: Neuroretinal rim notching, optic disc excavation, vertical or horizontal cup to disk ratio  $>0.5$  and peripapillary splinter hemorrhages, visual field outside normal limits on Humphrey automated perimetry on three perimetry readings, and all angles ( $360^\circ$ ) open on gonioscopy.

## Exclusion criteria

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

## Apparatus used

Powerlab 26T Polyrite D system was used for recording HRV. For HUT test, a wooden tilt table was used to avoid any electromagnetic disturbances. The table was prepared especially for manual tilting from horizontal position to  $90^\circ$  upright.

**Basal HRV**

The subject was asked to lie down on the tilt table. Then, three disposable pregelled electrodes were attached on left arm, right arm, and left leg. Basal recording of electrocardiogram (lead II) was taken for 5 minutes, and different variables of time and frequency domain were analyzed.

**Head-up tilt test**

Subjects were asked to comfortably restrain on a tilt table in horizontal position with foot plate support; then, the table was manually tilted to 70° head up position for 2 minutes. HRV was recorded during HUT. Then, tilt table was brought back to horizontal position and HRV was recorded after 5 minutes (recovery period).

The data obtained were statistically analyzed using SPSS (version 20). HRV of Group I (healthy controls) was compared with Group II (NTG) by unpaired Student's t-test. Two-tailed significance value was set at 0.05.

**RESULTS**

Basal HRV did not show any statistical differences between two groups. A highly significant decrease in root mean square successive difference (RMSSD) observed in Group II ( $p < 0.000$ ) as compared to control group. The decreased values of time domain variables signify decreased vagal activity due to greater withdrawal of vagal tone and relative increase in sympathetic activity (Fig. 1).

Highly significant decrease in values of both high and low frequency (LF) variables observed in both Group II as compared to Group I. However, a highly significant rise in LF/HF has been observed in Group II as compared to control group further indicating a greater withdrawal of vagal tone during HUT test (Table 1, Figs. 2 and 3).

Significant low values of LF and high frequency (HF) variables were observed in Group II. However, a highly significant difference has been observed in Group II (NTG) as compared to control group, and value of LF/HF ratio was significantly high in Group II.

The findings of frequency domain variables of HRV during the recovery phase of HUT were indication of delayed recovery from stress test due to sympatho-vagal imbalance mainly due to parasympathetic withdrawal (Fig. 4).

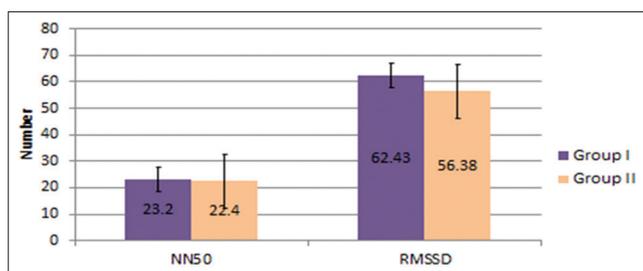
**DISCUSSION**

HUT test is an important autonomic function test to assess sympathetic activity. The normal response is increased sympathetic activity to overpower the effect of gravity. Highly significant decrease in value of RMSSD observed in NTG group ( $p < 0.000$ ) in comparison to controls. The above findings of time domain variables of HRV in the prospective study are in accordance with studies by Sharma *et al.* and Brown *et al.* [13,14]. Similarly, the HF variables (HF [nu] and HF [ms<sup>2</sup>]) were significantly less ( $p < 0.000$ ), and LF/HF ratio was significantly high ( $p < 0.000$ ) in Group II as compared to Group I. The HRV analysis of frequency domain variables was in accordance with the study. Kouakam *et al.* who analyzed the HRV response to orthostatic stress in patients with unexplained syncope during 60° HUT and observed LF/HF ratio was correlated with HUT. Since LF (nu) the marker of sympathetic activity, HF (nu) the marker of parasympathetic activity, therefore, during HUT significant less increase in LF band variables and less value of HF variables in glaucoma patients indicated less increase in sympathetic activity as well as decrease in parasympathetic activity [15].

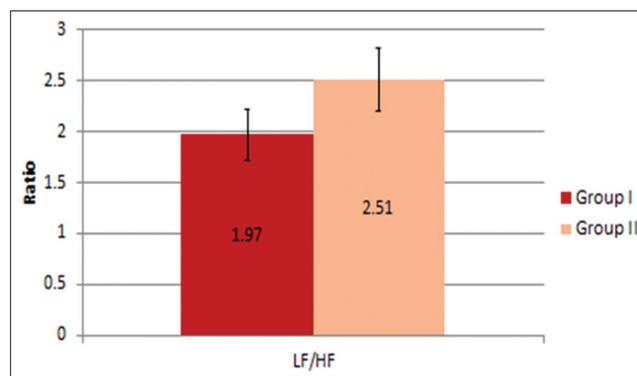
**Table 1: Frequency domain variables in Group I and II during HUT test**

Parameter	Group I Mean±SD	Group II Mean±SD	p value
LF (nu)	59.13±4.41	50.1±5.34	<0.000***
LF (ms <sup>2</sup> )	684.36±63.98	433.8±61.24	<0.000***
HF (nu)	30.26±2.79	20.16±2.53	<0.000***
HF (ms <sup>2</sup> )	345.45±4.38	175.94±34.48	<0.000***
LF/HF	1.97±0.25	2.51±0.31	<0.000***

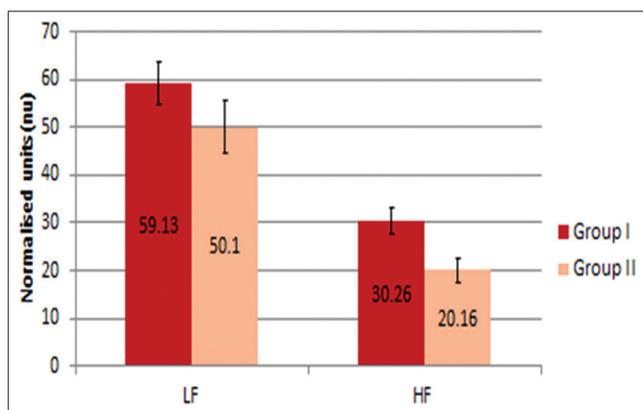
\*\*\* $p < 0.000$  very high significant. SD: Standard deviation, LF: Left frequency, HF: High frequency, HUT: Head-up tilt



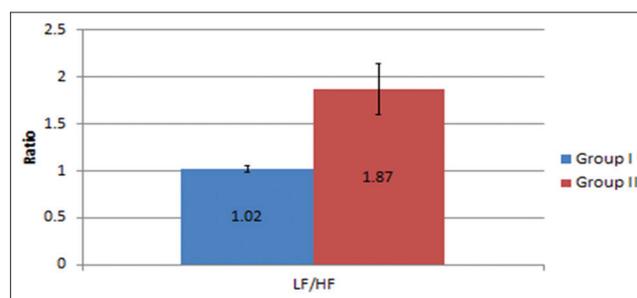
**Fig. 1: Comparison of time domain variables (NN50 and root mean square successive difference) during head-up tilt**



**Fig. 3: Comparison of left frequency/high frequency during head-up tilt**



**Fig. 2: Comparison of frequency domain variables left frequency and high frequency (nu) during head-up tilt**



**Fig. 4: Comparison of left frequency/high-frequency ratio during head-up tilt**

From these observations, during HUT, it can be concluded that in glaucoma patients, there is greater withdrawal of parasympathetic activity along with less increase in sympathetic activity. Significantly raised values of LF/HF ratio also suggestive of altered sympatho-vagal balance.

#### CONCLUSION

The above findings of HRV in this study further suggested greater withdrawal of vagal tone, and persistently overdrive of sympathetic activity due to sympatho-vagal imbalance, resulting delayed recovery from stress. The results and discussion of HRV analysis during provocative test concluded that autonomic imbalance was present in patients with NTG.

#### LIMITATIONS

As selection of glaucoma patients (NTG) was based on clinical levels of mean IOP above or below 21 mmHg, it is possible that certain degree of overlap may exist.

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