



STUDY OF AUTONOMIC ACTIVITY IN PATIENTS WITH NORMAL TENSION GLAUCOMA (NTG) BY HEART RATE VARIABILITY (HRV) AND ISOMETRIC HANDGRIP TEST WITH HEALTHY CONTROLS

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ABSTRACT

Introduction Some local changes have been documented suggesting Glaucoma is related to activity of autonomic nervous system (ANS) but systemic association has not been established so far. The analysis of Heart rate variability (HRV) is used to investigate sympatho-vagal imbalance within cardiovascular system. Sustained handgrip is an important cardiac stress test to study the status of autonomic activity. **Material and method** The study subjects carried out on 20 patients with Normal Tension Glaucoma of age group between 45-65 years of either sex (group II) and 20 age & sex matched healthy controls (group I). Basal HRV and during Handgrip testing was analysed by frequency domain method and the data was compiled and statistically analysed using unpaired t test. **Observation and results** No statistical difference in baseline parameters of HRV found in both groups. However, Low frequency variables LF(nu) (58.94± 6.55), (p < 0.001) and LF/HF ratio (2.3±0.37), (p < 0.000) were significantly increased on immediate release of handgrip in patients with NTG as compared to controls [(LF 52.13±2.97), (LF/HF 1.47±0.29)] with a significant fall in high frequency variable HF(nu) (26.11±4.27) in group II (p < 0.000). During handgrip recovery there was a significant decrease in HF (nu) (36.82±4.59), (p < 0.000) and raised LF/HF (1.28±0.13), (p=0.001) in group II as compared to group I. **Conclusion** In patients with NTG the observed findings suggested sympathetic hyperactivity in response to stress (handgrip test) and reduced vagal activity during recovery period indicated of delayed recovery. These observations indicate sympatho-vagal imbalance in Normal Tension Glaucoma. Therefore, identification of such patients may be possible with the use of non-invasive technique i.e HRV.

KEYWORDS: Heart rate variability, isometric handgrip, handgrip recovery.

INTRODUCTION

Glaucoma is an optic neuropathy characterized by progressive retinal ganglion cell death and visual field loss. It is the most common cause of blindness in the world affecting over 66 million people world wide. Glaucoma is commonly divided into two subcategories namely high tension or primary open angle glaucoma (POAG), in which intraocular pressure (IOP) is elevated (>21mmHg) and normal tension glaucoma (NTG) in which IOP is within normal range (10-21mmHg) along with visual field defects and associated morphological changes in optic disc. While the clinical picture and features of GON are fairly well evidenced, the causes of the primary insults which trigger the cascade of events leading up to its development are less clear and have subsequently become a key focus of current glaucoma research.^[1,2]

Autonomic dysfunction has been thought to be contributory factor due to autonomic neuropathy to the pathophysiology of both OAG and NTG. Due to the important role that the ANS plays in the maintenance of blood flow physiology and the regulation of variables such as HR and BP, it is clear that a dysfunction of the ANS could have significant adverse hemodynamic effects. With regard to GON development both systemic parasympathetic and sympathetic neuropathies have been reported in those with POAG, and those with NTG using a variety of different assessment techniques. Heart rate is one of the important autonomic variables and heart rate variability refers beat to beat variation of heart rate. A change in HRV pattern is recognised as an early sensitive indicator of compromised health. Indeed a low HRV, suggestive of a poor adaptability of the ANS, has been correlated with increased mortality. The R-R tachogram is plotted using the RR intervals in the 5 minutes lead II ECG. The RR tachogram is considered

as a non periodic signal which is transformed to its frequency spectrum using fast-fourier transformation algorithm. Spectral components in frequency domain analysis are: LF (low-frequency) component regulated by sympathetic and parasympathetic nervous system and related with baroreceptor activity. HF (high frequency) component regulated by parasympathetic activity and related with respiratory and blood pressure changes. LF/HF ratio depicts absolute and relative variations between sympathetic and parasympathetic components of ANS. In hand grip test (a stress test) heart rate and blood pressure increase partly due to central motor command and partly by mechanical changes in response to contraction of the muscles that activate small fibres in the afferent limb of the reflex arch. The normal response is rise in diastolic pressure more than 15mmHg and rise in heart rate by 30%. BP rises due to sympathetic activity and HR rises due to decreased parasympathetic activity.^[3-5]

MATERIAL AND METHODS

The present study was conducted in the department of Physiology in collaboration with Regional Institute of Ophthalmology (R.I.O), Pt. B.D. Sharma, PGIMS Rohtak. The study subjects of age between 45-65 years of either sex comprised of two groups:

Group I- Twenty age and sex matched healthy controls.
Groups II-Twenty patients with NTG.

Inclusion Criteria for group III (POAG) are.

- Intraocular pressure >21 mm Hg 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 (C/D) ratio >0.5 or C/D asymmetry between 2 eyes greater than 0.2, and peripapillary splinter hemorrhages.
- Visual field outside normal limits on Humphery automated perimetry on three perimetry readings.
- All angles (360°) open on gonioscopy.
- Pupil diameter ≥ 3mm without mydriatic or miotic drugs.

Inclusion Criteria for group II (NTG) are same as of group III except

- Intraocular pressure ranging between 10-21 mmHg.

Exclusion Criteria

Table 1. Frequency domain variables of Basal HRV in group I and group II.

Parameter	Group I mean±SD	Group II mean±SD	P-val
LF (nu)	42.75±2.78	44.85±6.52	0.08
LF (ms2)	421.90±126.9	399.27±65.1	0.37
HF(nu)	44.96±3.89	46.55±3.34	0.09
HF(ms2)	445.97±130.65	424.96±80.89	0.37
LF/HF	0.98±0.08	0.96±0.13	0.41

- Patients with secondary causes of glaucoma, hazy media, optic neuritis, any disease involving the macula, retina, or visual pathway, high myopia (>6Dioptre), previous intraocular surgery and on drugs known to cause optic neuropathy.
- Patients with diabetes mellitus and hypertension. Each subject had undergone a complete ophthalmological examination in glaucoma clinic of R.I.O. followed by autonomic function tests. Consent was taken and the nature of the tests were explained to each subject.
- The subject was asked to lie down on the tilt table. Then three disposable pre-gel electrodes were attached on left arm, right arm and left leg. Basal recording of ECG lead II was taken for 5 minutes and different variables of time and frequency domain were analysed by POWERLAB 26T POLYRITE D system.
- The patient was asked to lie in supine position holding the handgrip dynamometer in the dominant hand and take a full grip on it. Maximal voluntary contraction (MVC) was noted. The subject was asked to maintain a tension of 30% of MVC for 2 minutes. HRV was measured immediately after the release of handgrip and then after 5minutes.

OBSERVATIONS

On comparison of time domain and frequency domain analysis of basal HRV, no statistical difference was observed in all the variables.

The table 1 showed that the values of low frequency variables [LF (nu) and LF (ms2) and LF/HF] were significantly raised and a significant fall in the values of high frequency variable [HF(nu), HF(ms2)] were observed in group II during handgrip testing.

The table 2 and 3 showed significantly raised values of low frequency variables [LF(nu)p<0.000 and LF (ms2) p =0.01] in group II. However the values of high frequency (HF nu) was significantly low in group II as compared to control group (p<0.000) and significant high value of LF/HF ratio in group II (p =.001) as compared to controls were observed during recovery phase of handgrip testing.

All the above findings were suggestive of delayed recovery due to sympatho-vagal imbalance in NTG (II).

Table 2. Frequency domain variables of HRV in group I and group II during handgrip testing.

Parameter	Group I mean±SD	Group II mean±SD	P-val
LF (nu)	52.13±2.97	58.94±6.556	0.001
LF (ms2)	524.84±96.5	537.58±87.92	0.21
HF (nu)	37.15±8.40	26.11±4.27	<0.000
HF (ms2)	371.59±101.33	237.01±41.24	0.07
LF/HF	1.47±0.29	2.30±0.37	<0.000

*** very high significant(p<0.000)

** high significant (p<0.001)

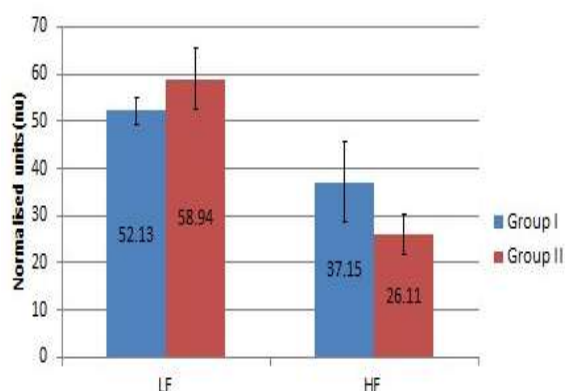
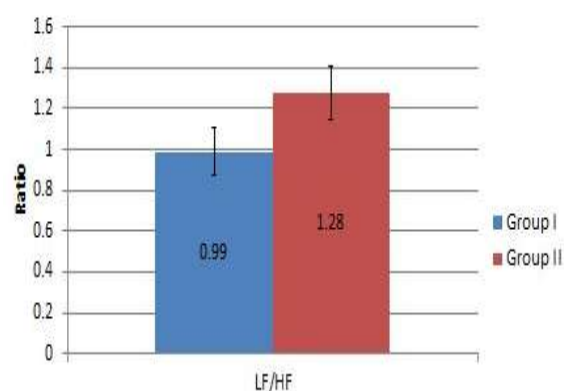
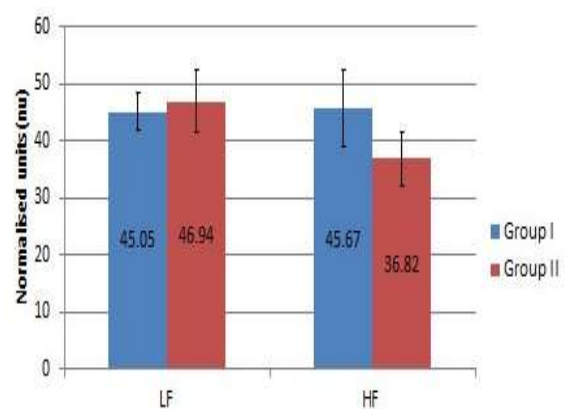
Table 3. Frequency domain variables of HRV in group I and group II during handgrip recovery.

Parameter	Group I mean±SD	Group II mean±SD	P-val
LF(nu)	45.05±3.31	46.94±5.41	0.1
LF (ms2)	440.39±100.71	420.85±52.68	0.44
HF(nu)	45.67±6.65	36.82±4.59	0.000
HF (ms2)	445.22±105.55	330.85±54.37	0.02
LF/HF	0.99±0.12	1.28±0.13	0.001

*p<0.05 significant

**p<0.001 highly significant

***p<0.000 highly significant

**Figure 1. Comparison of immediate effect of handgrip on LF & HF(nu) in group I and II****Figure 3. Comparison of LF/HF during handgrip recovery phase in group I and II****Figure 2. Comparison of LF & HF (nu) during handgrip recovery phase in group I and II**

DISCUSSION

In the present study on comparison of frequency domain variables of basal HRV of group II 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 two groups in resting condition. Askelord (1981) and Apple ML (1989) reported that LF band is influenced by both sympathetic and parasympathetic sympathetic activity. Mallani and associates proposed that LF/HF is better predictor of relative level of sympathetic and parasympathetic influence. Frequency domain analysis of HRV during HGT showed; highly significant raised values of Low frequency variables [LF (nu) {58.94±6.556, p=0.001} in NTG (group II). Decrease in high frequency variables [HF(nu){26.11 ± 4.27}, p<0.000] in group II. Highly significant rise in LF/HF

ratio in group II with p value <0.000 during handgrip testing.^[6-8]

Since LF (nu), the marker of sympathetic activity increased, and HF (nu), the marker of parasympathetic tone decreased significantly in the study. Therefore, from these observations of frequency domain analysis of HRV during stress test (HGT) it can be concluded that in NTG cases there was withdrawal of parasympathetic activity. A highly significant raised value of LF/HF ratio further suggestive of increased HRV due to altered sympatho-vagal balance.^[9,10]

As observed in table 3 and figure 2 and 3 a significant increase in LF (nu) { 57.8 ± 4.94 }, $p < 0.000$ in group II as compared to group I (45.05 ± 3.31), decrease in HF (nu) in group II [36.82 ± 4.59], $p = 0.000$ as compared to group I (45.67 ± 6.65) and significantly raised values of LF/HF ratio in group II ($p = 0.001$) suggested that the recovery from stress during HGT was not complete in glaucoma patients. A significant rise in LF/HF ratio further suggested persistently higher sympathetic overactivity even during recovery phase.

CONCLUSION

Increased value of frequency domain variables during handgrip suggests autonomic imbalance and inefficient compensatory mechanism during stress. During recovery period there is persistently high sympathetic tone, which did not touch the baseline values, may be due to altered autonomic activity in NTG patients. Sympathetic markers of HRV change parallel to autonomic challenges hence HRV is the most sensitive, noninvasive and reliable method to assess autonomic modulations. Therefore, in examination of glaucoma patients assessment of autonomic activity by HRV should be included.

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REFERENCES

1. Leske MC. Open-angle glaucoma-an epidemiologic overview. *Ophthalmic Epidemiol*, 2007; 14(4): 166-72.
2. Kumarswamy NA, Lam FS, Wang AL, Theoharides TC. Glaucoma: current and developing concepts for inflammation, pathogenesis and treatment. *European J Inflammation*, 2006; 4(3): 129-37.
3. Saul JP, Rea RF, Eckberg DL, Berger RD, Cohen RJ. Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *Am J Physiol*, 1990; 258: H713-21.
4. Malik M, Bigger JT, Camm AJ, Kleiger RE, Mallini A, Moss AJ. et al. Task force of European society of Cardiology and the North American Society of Pacing and Electrophysiology :Heart rate variability standards of measurement, physiological interpretation and clinical use. *Euro Heart J*, 1996; 17: 354-81.
5. Gherghel D, Hosking S, Armstrong R, Cunliffe I. Autonomic dysfunction in unselected and untreated primary open angle glaucoma patients: a pilot study. *Ophthalmic & physiological optics*, 2007; 27: 336-41.
6. Askelord S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectral analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. *Science*, 1981; 213: 220-2.
7. Appel ML, Berger RD, Saul JP, Smith JM, Cohen RJ. Beat to beat variability in cardiovascular variables : noise or music ? *J Am Coll Cardiol*, 1989; 14: 1139-48.
8. Malliani A. Cardiovascular sympathetic afferent fibres. *Rev Physiol Biochem Pharmacol*, 1982; 94: 11-74.
9. Gherghel D, Hosking S, Orgul S. Autonomic nervous system, circadian rhythms, and primary open-angle glaucoma. *Surv Ophthalmol*, 2004; 49: 491-508.
10. Kumar R, Ahuja VM. A study of changes in the status of autonomic nervous system in primary open angle glaucoma cases. *Indian Journal of Medical Sciences*, 1999; 53: 529-34.