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Original Research Article

Comparison of Basal Heart Rate Variability in Patients of Primary Open Angle Glaucoma and Healthy Controls

Singh H[1], Singh I[2], Khurana I[3], Dhull CS[4]

[1]Senior Consultant, Government Regional Hospital, Rohtak
[2]Assistant Professor, Department of Physiology, World College of Medical Sciences Research and Hospital, Jhajjar
[3]SGT Medical College, Budhera
[4]Professor and HOD, Department of Ophthalmology World College of Medical Sciences Research And Hospital, Jhajjar

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Corresponding author: Dr. Itika Singh
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Abstract:

Introduction: Primary Open Angle Glaucoma (POAG) is diagnosed by characteristic pattern of visual field defects, morphological changes in optic disc and raised intraocular >21mm Hg. Autonomic dysfunction is contributory factor in pathophysiology POAG. Heart rate variability (HRV) refers beat to beat variation of heart rate and reflects the modulating effect of autonomic nervous system on intrinsic firing rate of cardiac pacemaker. Analysis of HRV was done by time and frequency domain variables.

Material and Methods: Study comprised of 30 POAG cases (group I) and 30 controls (group II). Basal HRV was recorded in Physiology department. Data was statistically analysed using student t-test.

Observations: Insignificant low values of time domain parameters of basal HRV were observed in group I. On comparison of frequency domain analysis of basal HRV, significant high values of LF(nu) in group I was observed. LF/HF ratio was insignificantly higher in group I.

Discussion: HRV reflects fluctuations of impulses as the heart rate reflects. Low values of time domain variables observed in the present study document reduced parasympathetic tone in patients of POAG. Higher LF/HF ratio of basal HRV among group I suggests higher degree of sympathetic tone and relatively less parasympathetic tone.

Conclusion: The cardiac sympathetic markers of HRV change parallel to autonomic challenges. High vagal tone is cardioprotective while high sympathetic activity increases the vulnerability of the heart for cardiovascular risks.

Keywords: Primary Open Angle Glaucoma, Heart Rate Variability.

Introduction

Glaucoma affects over 67 million people worldwide causing bilateral blindness in 6.8 millions.[1] Primary open angle glaucoma (POAG) is often called 'the silent thief of vision' because it is an asymptomatic disease that leads to blindness without manifesting warning signs until late stage.[2] POAG is diagnosed by the presence of "classical triad"; characteristic pattern of visual field defects, morphological changes in optic disc (cupping) and raised intraocular pressure (IOP) >21mm Hg.[3] Two major theories i.e mechanical and vascular have been suggested for optic nerve head damage (ONH) in POAG. [4] The elevation of IOP occurs due to reduction of aqueous outflow due to blockage at trabecular meshwork level.[5] The Autonomic nervous system (ANS) supervises and influences the haemodynamic situation of the body through its constant regulation of heart rate (HR) and blood pressure (BP), thus playing a vital role in blood flow physiology.[6] Autonomic dysfunction has been thought to be contributory factor due to autonomic neuropathy in pathophysiology of both open angle and normal pressure glaucoma.[7] Heart rate variability (HRV) refers beat to beat variation of heart rate and reflects the modulating effect of the ANS on intrinsic firing rate of cardiac pacemaker. The actual balance of sympathetic and parasympathetic impulses is constantly changing to achieve optimum activity. HRV is a simple noninvasive measure of the autonomic impulses, representing one of the most promising quantitative markers of the autonomic imbalance. The analysis

of beat-to-beat variation in the heart rate has been used to investigate sympathovagal imbalance within cardiovascular system i.e. the integrity of autonomic innervation and physiological status of cardiac autonomic activity. Therefore, modulating effects on heart can be inferred with analysis of HRV. For analysis of HRV there are two domains:

- **Time Domain Method:** In this method individual's ECG profile and subsequent determination of the QRS complex is detected in continuous ECG recording. Intervals between adjacent QRS complexes known as normal to normal (NN) interval is determined. Mean NN interval, the mean heart rate and the difference between the longest and the shortest NN interval are the few time domain variables that can be measured.
- **Frequency Domain Method:** This technique involves spectral analysis of HRV in order to evaluate predominance of sympathetic and parasympathetic divisions of ANS and their effect on heart rate. Three main spectral components are distinguished in a spectrum calculated from short term ECG recording (2-5minutes). Very low frequency (VLF), Low frequency (LF) and High frequency (HF). The distribution of power and central frequency of LF and HF are not fixed and keep on varying in relation to change in autonomic modulation of heart.[8-10]

Material and Methods

The prospective 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 sample was comprised of two groups:

Group I- Thirty newly diagnosed patients with POAG.
Groups II-Thirty age, and sex matched healthy controls.

Inclusion Criteria for group I (POAG)

- 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, peripapillary splinter haemorrhages.
- Visual field outside normal limits on Humphery automated perimetry on three perimetry readings.
- All angles (360^0) open on gonioscopy.
- Pupil diameter ≥ 3mm without mydriatic or miotic drugs.

Inclusion Criteria for group II (controls)

No suspicion of any form of glaucoma or any other eye disease.

Exclusion Criteria

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

Ophthalmological Work Up

A prior informed consent was taken. Complete ophthalmological examination of each patient with POAG was done in Glaucoma Clinic of R.I.O. including uncorrected and best corrected visual acuity, slit lamp examination, detailed fundus examination, IOP measurement with Goldmann applanation tonometer, gonioscopy and visual field analysis.

Basal heart rate variability (HRV) was assessed by time and frequency domain method in Physiology department.

Apparatus Used

POWERLAB 26T POLYRITE D system was used. It is a 32-channel multipurpose machine. HRV was recorded on two separate channels simultaneously. The following recommendations were followed to make the results reliable and interpretable.

Sampling Rate

1K/s (1000 samples/sec)

Filters

Appropriate filters were chosen for HRV since the baseline shifting may affect the spectrum analysis.

Main filter was selected to eliminate background noise and mechanical disturbance.

Digital filter Low pass: 2KHz

High pass: 0.5 KHz

Sensitivity set: 20 mV.

Preliminary Preparation

The whole procedure was explained in detail to each subject in his/her own language to allay any fear or apprehension. Consent was taken from every individual to undergo whole procedure. The tests were conducted during working hours (9am-1pm) to avoid diurnal variation. All the subjects were tested under similar laboratory conditions and allowed to acclimatize themselves to the experimental and environmental conditions.

Procedure

The subject was asked to lie down on the tilt table. Three disposable pre-gelled electrodes were attached to left arm, right arm and left leg for ECG recording to measure HRV. The basal recording of ECG (lead II) and HRV was assessed by time and frequency domain methods. The data obtained was stored in hard disc and analyzed offline. Printed report was generated.[8]

Statistical Analysis

The data obtained was compiled, tabulated and statistically analyzed. Observations of group I (patients with POAG) were compared with group II (controls) using student t-test.

Observations

Insignificant low values of time domain parameters of basal HRV (SDNN, RMSSD, NN50) were observed in group I as compared to group II (figure 1). SDNN was 33.42±22.13 ms and 38.54±22.06 ms in group I and II, respectively. The values of RMSSD were low in group I (20.03±13.03) as compared to control group (24.73±16.35). Similarly, POAG cases (8.83±17.40) have insignificantly low values of NN50 in comparison with group II (17.63±25.23). On comparison of frequency domain analysis of basal HRV (table I), significant high values (p 0.026) of LF(nu) in group I (64.41 ± 11.67) as compared to group II (56.48 ± 15.00) was observed. Whereas HF (nu) and HF(ms^2) VLF(ms^2) showed statistically insignificant low values in group I as compared to group II. The value of LF/HF ratio was insignificantly higher in group I (2.89 ± 2.36) than in group II(2.66 ± 1.81).

Table 1: Frequency domain variables of basal HRV in group I and group *I*

Parameter	Group I (Mean ± SD)	Group II (Mean ± SD)	p value
VLF (ms^2)	976.35 ± 1736.70	991.88 ± 1445.32	0.970
LF (nu)	64.41 ± 11.67	56.48 ± 15.00	**0.026***
LF (ms^2)	433.50 ± 598.87	379.32 ± 421.70	0.687
HF (nu)	27.26 ± 9.86	29.79 ± 11.68	0.369
HF (ms^2)	190.84 ± 236.68	213.89 ± 279.01	0.731
LF/HF ratio	2.89 ± 2.36	2.66 ± 1.81	0.311

*Statistical significance (p<0.05)

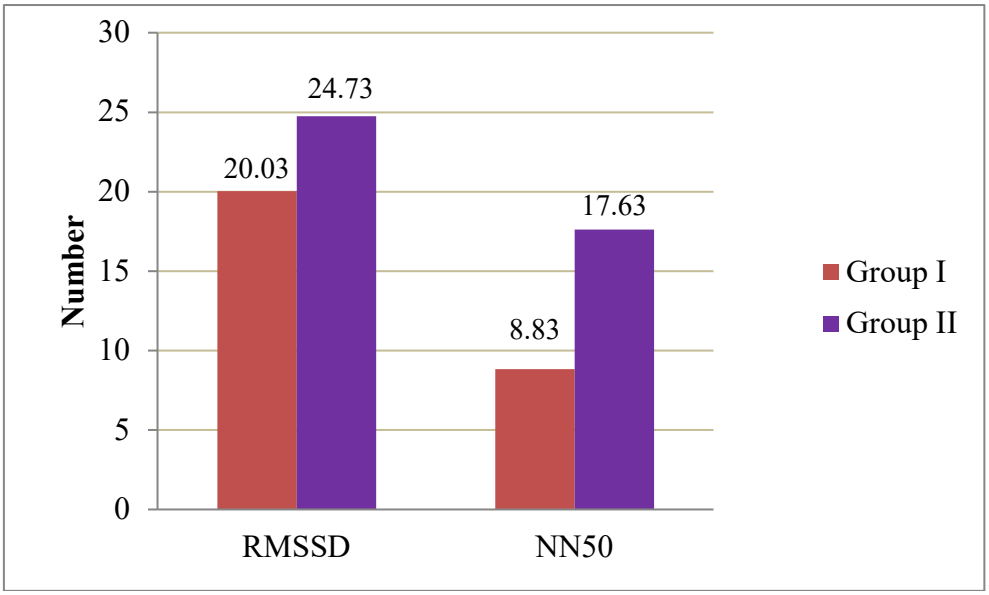

Figure 1: Comparison of time domain variables (RMSSD and NN50) of basal HRV in group I and group II

Discussion

The study was carried out on 30 patients with primary open angle glaucoma (group I) and 30 healthy age and sex matched controls (group II). Basal HRV was recorded in both the groups and the status of autonomic activity was studied and compared. Heart rate variability is primarily controlled by continuous interplay of activity of both the divisions of ANS. Therefore HRV reflects fluctuations rather than absolute values of impulses as the heart rate reflects.

In the present study HRV was assessed by analysis of both time domain and frequency domain variables. The values of RMSSD, SDNN and NN50

were insignificantly low in group I than in group II which is suggestive of low HRV.SDNN and RMSSD are qualitative markers of vagal activity. RMSSD and NN50 measure the short term variation in heart rate and thus are highly correlated. RMSSD is the most valuable time domain parameter for routine evaluation at rest as it provides highly reproducible results and is not influenced by mean resting heart rate.[8,11]Unlike SDNN which measures both short term as well as long term effects, RMSSD measures just the short term effects. Kleiger et al had documented that RMSSD and NN50 are correlated with SDNN and are markers of parasympathetic activity.[10-12] Low values of time domain variables observed in the present study document reduced parasympathetic tone in patients of POAG.A study by Menezes Jr et al in hypertensive individuals reported that on analysis of time domain variables, low value of SDNN, RMSSD and NN50 are indicative of reduced HRV, probably because of sympathetic hyperactivity.[13] The above statements corroborate with our findings. A reduced HRV has been identified as a strong indicator as a risk related to adverse events in healthy individuals and patients with large number of diseases, reflecting the vital role that ANS plays in maintaining health.[14] Power spectral analysis partitions total variability of heart rate into its components, which reflect autonomic influences on HR. The low frequency (LF) band is indicative of influence of both sympathetic and parasympathetic tone. The high frequency (HF) band estimates the cardiac vagal control.[10] Significant high values of LF ($p<0.05$) and LF/HF ratio were observed in group I. All these parameters of HRV denote decreased vagal tone and sympathetic predominance to the heart in patients with POAG. Akselord (1981) and Appel ML (1989) had reported that LF factor is influenced by sympathetic as well as parasympathetic activity.[15,16] However some studies indicate that LF is a better indicator of sympathetic activity. Malliani and associates have proposed that LF/HF ratio is better predictor of relative levels of sympathetic as well as parasympathetic activities as opposed to absolute values of either.[10,11,15,16] So, higher LF/HF ratio of basal HRV among group I in our study suggests higher degree of sympathetic tone and relatively less parasympathetic tone.

Conclusion

Basal HRV analysis showed low values of SDNN (time domain variable) and high value of LF/HF ratio (frequency domain variable) indicated reduced HRV, suggested decrease in vagal tone and relatively high overdrive of sympathetic activity in patient with POAG. The cardiac sympathetic markers of HRV change parallel to autonomic challenges. High vagal tone is cardioprotective while high sympathetic activity increases the vulnerability of the heart for cardiovascular risks. HRV has gained importance as a technique to explore the important role of ANS in maintaining homeostasis. The widest possible use, cost effectiveness and ease of data acquisition makes HRV is the most clinical tool to assess and identify health impairments. Heart rate variability is the most sensitive noninvasive and reliable tool to assess autonomic modulation in number of conditions.

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