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Research Article

Assessment of Autonomic Dysfunctions in Altered Thyroid Status by Time Domain Parameters of HRV

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Abstract: Thyroid hormone has important effects on the cardiovascular system. Many signs and symptoms recognized in patients with of thyroid disorders (hyperthyroidism and hypothyroidism) are due to the increased or reduced action of thyroid hormone on the cardiovascular system. The aim of the study was to assess the cardiac autonomic functions by time domain parameters of heart rate variability in patients with hypothyroidism, hyperthyroidism and to compare it with healthy controls. Autonomic functions were evaluated by measurement and analysis of time domain parameters of HRV by ECG method and scored in 50 hypothyroid, 50 hyperthyroid patients, 20-60 years and compared with 25 controls. The present study was conducted in the Dept. of Physiology, SMS Medical College, Jaipur with the collaboration of Dept. of Endocrinology of the Institute. Informed written consent was obtained from all the subjects included in the study. Biochemical estimation of TSH, fT_3, fT_4 was done. Results were presented as Mean ± SD. For statistical analysis, One Way ANOVA (Post Hoc Tukey) test was used. In hyperthyroids and hypothyroids the mean values of SDNN, RMSSD, pNN50 were found significantly lower ($p<0.001$) than controls. Thus our finding showed autonomic dysfunction with decrease parasympathetic activity in both hypothyroids and hyperthyroids than controls.
Keywords: Heart rate variability(HRV), Hypothyroidism, Hyperthyroidism, SDNN, RMSSD, pNN50.

INTRODUCTION

The autonomic nervous system have sympathetic and parasympathetic components[1]. Both the sympathetic and the parasympathetic limbs can be characterized by tonic levels of activity, which are modulated by, and respond reflexively to, physiological changes. Heart rate provides an index of the net effects of autonomic tone on the sinus node, and carries prognostic significance [2]. The rhythmic beating of the heart at rest was once believed to be monotonously regular, we now know that the rhythm of a healthy heart under resting condition is actually surprisingly irregular [3]. Variation in the beat to beat interval is a physiological phenomenon. Heart rate variability, though related to heart rate, assesses modulation of autonomic control of heart rate and carries additional prognostic information, which in some cases is more powerful than heart rate alone [2]. HRV predicts total mortality, sudden death, and cardiovascular disease risk, as well as other morbidities [4, 5].

Thyroid hormones are mandatory for various processes that are essential for human metabolism [6]. Increased or reduced action of thyroid hormone on certain molecular pathways in the heart and vasculature causes relevant cardiovascular derangements [7].The clinical features of hyperthyroidism and hypothyroidism are suggestive of sympathetic nervous system overactivity and hypoactivity respectively [8]. Similarly Bhat AN *et al.* [9] reported altered sympathetic activity, with no significant difference in the parasympathetic activity in either hypothyroid or hyperthyroid subjects.

In this study time domain methods were assessed. Time domain measures of HRV are assessed with calculations based on statistical operations on R-R intervals. Commonly used measures include standard deviation of normal R-R intervals (SDNN), the root mean square of successive R-R interval differences (RMSSD), and the percentage of normal R-R intervals that differ by >50 ms (pNN50). Although all these are measures of HRV, they are not interchangeable, nor do they necessarily reflect similar physiology. For example, the SDNN is related to the total power (variance) whereas both RMSSD and pNN50 detect high frequency oscillations [2]. This study was

therefore undertaken to evaluate autonomic functions in thyroid patients and to compare it with controls.

METHODOLOGY

The present study was conducted 125 subjects, age ranging between 20-60 years, in the Department of Physiology, SMS Medical College, Jaipur with the requisite inputs from the Department of Endocrinology of the Institute. The study was carried out after getting formal approval from Institutional Ethics Committee of SMS Medical College, Jaipur. Informed written consent was obtained from all the subjects included in the study.

Patients visiting Endocrinology Outdoor of the SMS Hospital were preliminary assessed clinically and biochemically to acertain whether the patient has any endocrine disorder and if so, whether he or she is hypothyroid, hyperthyroid or euthyroid. The clinical assessment for the thyroid disorders was done by Endocrinologist using standard clinical protocol and if the subjects were suspected to be having clinical manifestations of thyroid malfunction was further subjected to biochemical investigation for confirmation of diagnosis.

Inclusion Criteria

Patients readiness to participate in the study, confirmed thyroid patients by endocrinologist based on clinical, biochemical and laboratory findings in the age group of 20 to 60 years of either sex, never previously treated for endocrinal disease were included in this study.

Clinical parameters

Patients having history or complication of following symptoms were clinically considered as *Hypothyroid* - Heavy voice, bradycardia, puffiness of face, hair loss, constipation, lethargy, weight gain, decrease appetite, cold intolerance, snoring, muscle weakness, thin brittle fingernails, decreased sweating, muscle cramps, joint pain, dry, itchy skin.

Patients having history or complication of following symptoms were clinically considered as *Hyperthyroid* - Pulse rate, palpitation, tremor, weight loose, increase appetite, orbitopathy, anxiety, restlessness, diarrhoea, intolerance to heat, hair loss, muscle aches, weakness, fatigue, dyspnea, hyperactivity, irritability and sweating.

Biochemical Parameters

For confirmation of clinical diagnosis, the patients were further subjected to following biochemical parameter evaluation: FT_3, FT_4, TSH. The fasting venous blood samples were collected by standard aseptic techniques. Serum was separated and assays were performed. To evaluate thyroid functions serum free thyroxine (FT_4), free triiodothyronine (FT_3) and thyroid stimulating hormone (TSH) were measured. FT_3, FT_4 were measured because these are the active form of thyroid hormone and generally they are initially affected with TSH in thyroid disorders. Serum levels of FT_3, FT_4 and TSH were determined by chemiluminescent immunoassay with the IMMULITE 2000 Systems Analyzer. IMMULITE 2000 can be expected to have reference ranges for FT_3, FT_4, TSH were 1.8-4.2 pg/mL, 0.89-1.76 ng/dL and 0.4-4.0 uIU/mL respectively.

Exclusion Criteria

Subjects were excluded from the participation if they exhibited Cardiac Problems, liver diseases, renal dysfunction, HIV / Immunodeficiency disorders, neurological disease, any other systemic disease that can affect autonomic activity i.e. diabetes, hypertension, patients taking any drug which affects autonomic activity were excluded.

After screening, the newly diagnosed thyroid patients based on thyroid hormone profile, clinical manifestations and those who were not on any thyroid hormone replacement therapy was grouped as Group A (50 hypothyroid) and Group B (50 hyperthyroid). The age matching control subjects were grouped under group C. All the thyroid patient and control subjects were the subjected for assessment of HRV.

Assessment of HRV

Heart rate variability can be measured over any length of recorded ECG, as per the guidelines of Task Force (1996) at least 5 minutes of ECG must be recorded to quantify Sympathetic and Parasympathetic tone. HRV analysis was done by ECG method as the ECG method is more accurate than the PPG method in measuring heart rate variability [10]. One fact worth noting is that using the ECG signal allows for much more precision in the detection of beats than using BVP because the ECG wave has a sharper definition than the rounded pulse waveform [11].

- Heart Rate Variability assessment was done by recording 5 minutes ECG by RMS ECG (DECG 1/ 63041/ ADBXB).
- The analogue signals were converted to digital signals by National Instrument Software NI-DAQ Version 8.0.
- Heart rate Variability was analyzed in Time domain and Frequency domain measures by Software Version 1.1.

Procedure

Patient's preparation

All the subjects (thyroid patients and control subjects) included were instructed to avoid food preceding two hours of the testing, no coffee, nicotine or alcohol and smoking 24 hours prior to the testing and to wear loose and comfortable clothing to obtained accurate measurement and analysis for Heart Rate Variability.

Recording

For short term analysis of HRV, ECG was recorded in supine position for 5 min after 15 min of supine rest. Recording was done in noise free room and room temperature was maintained at 24-28°C. Subject was instructed to close the eyes and to avoid talking, moving hands, legs and body, coughing during test, sleeping

Acquisition

All standard limb leads were applied and the lead with upright R wave was selected for recording. The ECG signals were continuously amplified, digitized and stored in the computer for offline analysis. The detection of R wave was done by HRV Soft version 1.1 developed by AIIMS, New Delhi. The procedure calculated heart rate variability (HRV) in time domain measures.

Processing (R wave detection and RR intervals)

The detection of R wave was done by software. Different software use different algorithms to detect the R-wave and differ in the features. They all have basic similarity in that they all compute R-R intervals after the R wave detection. Abnormal beats and areas of artifact were automatically and manually identified and excluded from the recording.

Quantification of HRV

The analysis of HRV can be done by different methods like Time domain, frequency domain, nonlinear, periodic and non periodic oscillation pattern. In the present study HRV was done by Time domain measures.

A number of variables that describe either the heart rate at any time or determine the intervals between successive normal complexes were calculated during Time Domain analysis. The time domain measures are based on the amount of time, in milliseconds, in the beat-to-beat intervals of the heart or from the differences between the normal beat-to-beat intervals. The gold standard for time domain measures is to examine a 24 - hour assessment of HRV that has been recorded with a holter monitor. A brief 5 minute recording of HRV is also clinically valid and meaningful.

Selected Time domain measures of HRV: SDNN, RMSSD, pNN50

Most of the conventional time domain parameters (i.e. SDNN, RMSSD and pNN50) are markers of parasympathetic activity. The mean values of all variables were compared by using Oneway ANOVA (Post Hoc Tukey) test. Results were presented as Mean ± SD. All the statistical analysis was performed using SPSS Version 20 and Microsoft Excel 2007. A $p<0.05$ was considered statistically significant.

RESULTS

Values obtained from biochemical analysis for thyroid profile and HRV were expressed as mean ± SD and then statistical analysis were done by One way ANOVA and Post Hoc Tukey Test.

As depicted from Table 1 mean values of fT3, fT4 were decrease and increase significantly in hypothyroids and hyperthyroids than controls. Mean value of TSH was significantly high and low ($p<0.001$) in hypothyroid and hyperthyroid subjects respectively compared to controls.

Table 1: Thyroid Hormone Profile

Parameter	Group A	Group B	Group C	p value
fT3	1.95 ± 0.83	6.07 ± 5.27	2.59 ± 0.47	<0.001***
fT4	0.83 ± 0.34	7.55 ± 8.28	1.30 ± 0.22	<0.001***
TSH	13.96 ± 7.68	0.09 ± 0.9	2.41 ± 1.15	<0.001***

Note:-Group A: Hypothyroid; Group B: Hyperthyroid; Group C: Control. Values were expressed as mean ± SD.
p> 0.05 non-significant*, p<0.05 significant** and p<0.01 highly significant.***

Table 2: Time domain measures of HRV in three groups (n= 125)

Groups	SDNN (ms)	RMSSD (ms)	pNN50 (%)
A (n=50)	31.69 ± 13.25	26.86 ± 17.72	8.44 ± 15.14
B (n=50)	27.19 ± 10.45	17.45 ± 8.43	1.78 ± 2.70
C (n=25)	54.29 ± 13.93	54.83 ± 22.43	21.37 ± 19.03

Group A: Hypothyroids; Group B: Hyperthyroids; Group C : Controls. All values are expressed as Mean ± Standard deviation.

Table 3: Statistical Analysis

Groups	p value		
A vs B vs C	0.000***	0.000***	0.000***
A vs B	0.07*	0.004***	0.01**
A vs C	0.000***	0.000***	0.000***
B vs C	0.000***	0.000***	0.000***

Note-p > 0.05 non-significant*, p<0.05 significant** and p<0.01 highly significant***

The mean values of Time Domain measures of SDNN, RMSSD, pNN50 were reduced significantly ($p<0.001$) in study groups (A, B) when compared with Control group – C. Again statistically significant ($p<0.001$) differences were observed when all these parameters compared between group A & C, between group B & C. Similarly, when the comparison was done between Test Groups A & B difference was significant in all except SDNN (Table 2 and 3).

DISCUSSION

In last decade several investigators had assessed cardiac autonomic activity by time domain measure of HRV from the ECG recording in hypothyroid and hyperthyroid patients. The present study was undertaken to observe the heart rate variability (HRV) in hypothyroid and hyperthyroid patients in order to assess their cardiac autonomic nervous activity (CANA).Time domain measures which were assessed in this study included SDNN, RMSSD, pNN50. Statistically significant lower value of SDNN was observed in hyperthyroid patients and hypothyroids as compare to controls. However nonsignificant difference was observed between hypothyroids and hyperthyroids. In respect to other time domain measures RMSSD and pNN50 statistically significant lower values were found in hyperthyroids as compared to both hypothyroids and controls.

Time domain indices of HRV indicate mainly the parasympathetic functions [12]. Lower values of SDNN, RMSSD, pNN50 denote decreased high frequency component of HRV which is suggestive of decreased cardiac vagal modulation [10]. The region behind lower values of SDNN, RMSSD, pNN50 in thyroid patients may be due to poor vagal tone. Similar observations were also made by some other studies [6, 13-15]. Similarly, Syamsunder AN *et al*. [16] reported the time domain indices of HRV (RMSSD, SDNN, NN50, pNN50) were significantly decreased ($p=0.000$) in hypothyroid group compared with the control group whereas Bhat AN *et al*. [9] found no significant difference in the parasympathetic activity in either hypothyroid or hyperthyroid subject as compared to euthyroid controls. Therefore, present study reveals lower values of time domain measures in hypothyroids and hyperthyroids, however, values were grossly reduced in hyperthtroids, indicating severely decreased parasympathetic activity, especially, in subjects suffering from hyperthyroidism, predisposing hyperthyroid subject to more cardiovascular complications.

CONCLUSION

It can be concluded from this study that cardiac vagal modulation was reduced in both hypothyroids and hyperthyroids than controls, however hyperthyroids showed more impaired vagal cardiac autonomic activity.

Abbreviations: SDNN= Standard deviation of RR interval, RMSSD= the root mean square of successive differences between adjacent RR intervals, ms= millisecond. ms^2= millisecond square, %= percentage, n- number of subjects, T3: tri-iodothyronine, T4: thyroxine, TSH- thyroid stimulating hormone

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