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RESEARCH ARTICLE

COMPARATIVE STUDY ON SPECTRAL ANALYSIS OF HEART RATE VARIABILITY IN HYPERTHYROID PATIENTS AND EUTHYROIDS

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Background: Thyroid hormones exert effects on the heart and peripheral circulation. Heart rate variability (HRV) is a good marker for identifying the cardiovascular risk in patients with hyperthyroidism.
Aims and Objective: To evaluate the impact of hyperthyroidism on autonomic tone and to compare the HRV parameters in patients with hyperthyroidism and healthy volunteers.
Materials and Methods: This study was conducted at PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, on 30 hyperthyroid patients (cases) with average age 39.23 ± 6.91 years and 30 healthy volunteers (controls) with average age 42.13 ± 6.78 years. After obtaining the written consent from the subjects, ECG was recorded for 10 min in a computerized physiograph in lead II.
Results: Statistical analysis carried out by independent Student's *t*-test showed a significant difference ($P < 0.001$) in HRV parameters of patients with hyperthyroid and healthy volunteers. Among the frequency domain measures, a decrease in high frequency (HF) in normalized units and increase in low frequency (LF) in normalized units, and in the ratio of LF to HF (LF/HF) in hyperthyroid patients was observed. Among the time domain measures, decrease in RR intervals, SDNN, RMSSD, and NN50 was observed in patients with hyperthyroid compared to those with euthyroidism.
Conclusion: This study showed that individuals with hyperthyroidism had a higher sympathetic tone and a lower parasympathetic tone as compared to those with euthyroidism. Using HRV analysis, we can identify patients who are at risk for cardiac complications and early intervention can reduce mortality rates.

INTRODUCTION

Graves' disease is an autoimmune thyroid disorder. Thyroid-stimulating immunoglobulins are the antibodies that activate thyroid-stimulating hormone (TSH) receptor, thereby stimulating thyroid hormone synthesis and resulting in diffusely enlarged goiter. The most common cause of hyperthyroidism is Graves' disease.[1] Temporary viremia of thyroid gland, certain drugs, and toxic nodules can also cause hyperthyroidism.[2]

The prevalence of hyperthyroidism has been found to be 0.21% in men and 1.9% in women.[3] The total daily disposal of T_3 is disproportionately increased compared to that of T_4, which was due to increased secretion of triiodothyronine deiodinase-1, leading to increased peripheral conversion of T_4 to T_3.[4]

High levels of T_3 and T_4 affect anterior pituitary and rapidly suppress TSH production, leading to tachycardia, goiter, nervousness, amenorrhea, weight loss, palpitations, heat insensitivity, increased sweating, exophthalmos, and pretibial myxedema.[5] Complications of untreated hyperthyroidism are arrythmias, and atrial fibrillation.

Sleeping pulse rate more than 90 beats per minute distinguishes tachycardia of thyrotoxic origin from that of psychogenic causes.[6] Cardiovascular and extracardiovascular manifestations of hyperthyroidism are due to hyperadrenergic state. The increased sensitivity of atria to β-adrenergic

agonists is due to increased β-adrenoceptor density and sympathetic stimulation on β_1 receptors in the heart, which causes increase in the heart rate and cardiac output in patients with hyperthyroidism.[7]

In hyperthyroidism, circulatory T_3 enters cardiac myocytes, combines with its receptors, and enters the nucleus, causing enhanced transcription of genes for α-myosin heavy chain (α-MHC), β-adrenergic receptors, and Na^+/K^+ ATPase. Excessive thyroid hormone production increased utilization of oxygen, increased blood flow, increased cardiac contractility, and increased cardiac output and heart rate.[8] The present study tests the hypothesis that the sympathetic noradrenergic function alters with change in thyroid status of the subject.

Heart rate variability (HRV) analysis helps evaluate the equilibrium between the sympathetic and parasympathetic effects on heart rhythm by measuring the beat-to-beat variations of R-R interval.[9] The spectral variation of the heart rate in the lower (LF) and higher frequencies (HF) has a significant relationship with sympathetic activity and parasympathetic activity, respectively. An exaggeration of sympathetic tone in cardiac activity induces tachycardia and reduces cyclical beat-to-beat variations, whereas increased parasympathetic nerve activity reduces heart rate and increases HRV.[10] These autonomic nervous system derangements can be found out by HRV indices, which help us to assess the disease severity in hyperthyroid patients.

MATERIALS AND METHODS

This research study was carried out in Physiology Laboratory, PSG Hospitals, after getting approval from the institutional human ethics committee. Informed consent from both hyperthyroid and control groups was obtained. Physically active volunteers aged between 30 and 50 years were included. The study group consisted of 30 newly diagnosed hyperthyroid patients (before treatment) with TSH <0.27 μIU/ml (cases) and 30 normal healthy volunteers with TSH within normal range (controls).

Patients with hypertension, diabetes, on regular or irregular antithyroid treatment, or on drugs affecting autonomic nervous system such as anticholinergics and sympathomimetics were excluded from the study. The subjects who fulfilled the criteria for study underwent electrocardiogram (ECG) recording and HRV analysis.

Thyroid function test reports, age (in years), height (cm), weight (kg) of patients with hyperthyroidism and normal volunteers were collected. ECLIA was used for *in vitro* quantitative determination of T_3, FT_4, TSH, and FT_3. This method has been validated for determination of plasma thyroid hormones and is commonly used in medical diagnostic laboratories.

In the research laboratory, the subjects were asked to take rest (lying quietly in the supine position on a couch, awake, and not making any movements) for 5 min before the HRV procedure and the ECG procedures were explained.

ECG was recorded using the computerized physiograph (Niviqure digital ECG system) in lead II for 10 min by placing disposable adhesion electrodes on the pattern of the lead configuration and analyzing by Finland software. Baseline ECGs were obtained from all subjects and those with abnormal baseline ECGs were excluded.

HRV is a noninvasive procedure. RR intervals were obtained after clearance of noise and baseline fluctuations by digital filters. Resting heart rate was also recorded. The inbuilt software selected the RR peaks and these RR intervals, which were obtained as time points, were then fed into a Microsoft excel sheet and the RR intervals were copied to a notepad file.

The resting autonomic activity was assessed by measuring 10-min HRV, and time domain and the frequency domain parameters were determined.

Statistical Analysis

The statistical analysis was carried out using SPSS software (Statistical Package for the Social Science, version 19). Independent Student's *t*-test was used to compare the HRV indices of patients with hyperthyroidism and euthyroidism. Values were expressed as mean ± SD. *P*-value <0.05 was considered to be statistically significant.

RESULTS

The demographic characteristics such as age, basal heart rate, weight, height, and body mass index of

the patients with hyperthyroidism and euthyroidism are given in (Table 1). There is no statistically significant difference in the demographic characteristics between the two groups. The analysis of HRV by time domain measures (Table 2) showed statistically significant difference in mean R-R interval, SDNN (ms), RMSSD, NN50, and pNN50%. In the frequency domain measures LF power, HF power, VLF power, LF/HF ratio, LF nu, and HF nu are all statistically significant.

Table 1: Demographic characteristics of hyperthyroid (n=30) and euthyroid volunteers (n=30)

Parameter	Normal healthy volunteers (mean ± SD)	Hyperthyroid patients (mean ± SD)	*P*-value
Age (years)	42.13 ± 6.78	39.23 ± 6.91	0.140
Height (cm)	159.27 ±7.58	160.40 ± 6.52	0.551
Weight (kg)	59.03 ± 7.02	58.50 ± 6.22	0.781
BMI (kg/m^2)	22.86 ± 1.29	22.50 ± 1.64	0.671
Resting heart rate	74.47± 5.34	97.67 ±17.71	<0.005

Table 2: Comparison of HRV frequency domain measures of heart rate variability between hyperthyroids and euthyroids

Parameter	Normal healthy volunteers (mean ± SD)	Hyperthyroid patients (mean ± SD)	*P*-value
LF nu	50.993 ± 12.226	78.996 ± 10.383	<0.0001
HF nu	48.983 ± 12.240	21.466 ± 9.965	<0.0001
LF/HF Ratio	1.174 ± 0.5721	4.8150 ± 2.811	<0.0001
LF Power	26.21 ± 9.710	31.33 ± 12.683	<0.0001
HF Power	28.396 ± 13.985	8.496 ± 7.669	<0.0001
VLF Power	46.350 ± 18.356	59.114 ± 21.098	<0.0001

P < 0.0001 denotes statistical significance.

Table 3: Comparison of time domain measures of heart rate variability between hyperthyroids and euthyroids

Parameter	Normal healthy volunteers (mean ± SD)	Hyperthyroid patients (mean ± SD)	*P*-value
Mean RR (s)	0.769 ± 0.062	0.621 ± 0.106	<0.0001
SDNN (ms)	39.675 ± 8.63	24.297 ± 12.36	<0.0001
RMSSD	38.656 ± 7.66	14.196 ± 7.69	<0.0001
NN50 (count)	79.67 ± 17.35	8.67 ± 8.07	<0.0001
pNN50 (%)	21.46 ± 12.53	4.30 ± 4.0	<0.0001

P < 0.0001 denotes statistical significance.

DISCUSSION

Thyroid hormones modulate the development, growth, and metabolism of all systems in our body. Hyperthyroidism occurs due to hyperactive thyroid gland and increased production of thyroid hormones T_3 and T_4 and decreased serum TSH.

In patients with hyperthyroidism, cardiac contractility, cardiac output, and ejection fraction were found to be sharply elevated with a decrease in diastolic function. Sympathetic nervous system activation and thyrotoxicosis manifestations were mostly similar, especially with regard to ionotrophic effects.

Heart rate variability is a good marker for identifying cardiovascular risk and severity in individuals with hyperthyroidism. It denotes the individual's autonomic tone, and frequency domain measures indicate parasympathetic and sympathetic activities. A predominance of sympathetic tone in cardiac activity induces tachycardia and reduces beat-to-beat variations. Higher HRV is always desirable, and lower HRV is an established predictor of cardiac mortality and morbidity.

Recent studies show that thyroid hormones enhance gene transcription of calcium ATPase in sarcoplasmic reticulum and increase the pacemaker activity.[11] Thyroid hormone exerts its effect on the duration of cardiac pacemaker potential and repolarization currents. It alters both nongenomic and genomic actions, and the net effect is to alter the heart function toward increased contractility.[12]

It is possible that an interaction exists between the adrenergic system and the thyroid hormone system, which may also contribute to the cardiac actions of thyroid hormone.[13] A study by Williams et al.[14] showed that thyroid hormones increase sensitivity to β-adrenergic agonists by increasing the β-adrenoceptor density and G_s/G_i protein ratio with an excess activation of adenylate cyclase.

Of the HRV parameters, frequency domain measures HF power. HF nu was less among patients than controls, which shows less parasympathetic activity among patients with hyperthyroidism. LF nu, LF power, VLF, and LF/HF ratio were high among hyperthyroid patients than controls. This shows that sympathetic activity is high in hyperthyroid patients, and it is consistent with that reported by Chen et al.[15], who emphasized that hyperthyroidism is characterized by both increased sympathetic and decreased vagal modulation of the heart rate from spectral analysis of HRV.

As a result, sympathetic-to-parasympathetic ratio may increase in patients with hyperthyroidism. In few young euthyroid patients (with normal TFT), LF/HF ratio was more than 1, showing little sympathetic dominance, which can be due to stress in day-to-day life. However, it is negligent when compared with hyperthyroid patients with a sharp increase in LF/HF ratio.

Of the time variables, mean RR interval, SDNN,

RMSSD, pNN50, and NN50 values were less among the patients than controls, indicating parasympathetic withdrawal. This shows that HF variations in the heart rate are less and vagal modulation of the autonomic nervous system is decreased.

Supraventricular arrhythmias, atrial fibrillation, and cardiac failure are the known cardiovascular complications of thyrotoxicosis, and the same was proved to be the primary cause of death. There is an association between thyroid gland function, heart muscle mass, and ventricular hypertrophy. Hyperthyroidism is an independent risk factor for left ventricular hypertrophy, which has emerged as a powerful indicator of rapidly evolving lethal atherosclerotic disease.

TSH values were found to be significantly reduced in hyperthyroid patients. TSH has a linear relationship with parasympathetic activity. T3 and T4 values were found to be highly elevated, which is directly proportional with sympathetic activity and the degree of vagal withdrawal.

Our study presents strong evidence of increased cardiac autonomic activity, implicating sympathetic dominance in all cardiac morbidity and mortality. With the help of HRV, patients who are at risk for cardiac complications are identified using the time and frequency domains and early intervention can be initiated to prevent mortality.

β-Adrenergic blockers could be suggested as an initiative measure for high-risk cases. Tachyarrhythmias can be converted to sinus rhythm patterns and cardiac manifestations can be resolved. The results of our study show that there is reduced parasympathetic component and increased sympathetic component of HRV in hyperthyroid patients. Reduced HRV is most commonly associated with a risk of arrhythmic death and is an independent predictor of cardiac mortality and morbidity, but recent data suggest that any abnormal variability also predicts circulatory dysfunction, progression of coronary atherosclerosis, and death due to arrythmias.

One difficulty that we faced during the study was related to recruiting hyperthyroid patients before starting antithyroid treatment.

CONCLUSION

We conclude that decreased vagal modulation of heart rate may occur in hyperthyroidism, which may be restored following adequate treatment by blocking β-receptors and thereby inhibiting the adenyl cyclase–cyclic AMP pathway.

This provides an attractive future option for investigation and management of arrhythmias and other cardiovascular complications due to thyrotoxicosis. From our study, it is obvious that cardiovascular risk in thyrotoxicosis patients can be evaluated by HRV analysis before any appreciable change occurs in the heart rate itself. Prevention is better than cure. So even before the appearance of cardiac complications, they can be assessed and prevented. Further randomized control trials should be carried out to show the unexplored effects of autonomic dysfunction on cardiovascular system.

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