

## Research article

**Assessment of cardiovascular autonomic dysfunction in untreated adult hypothyroid patients**Shuvojoyoti Rakshit<sup>1</sup>, Krishnachura Mitra<sup>2</sup>, Biswajit Sarkar<sup>3</sup>, Maumita Das<sup>4</sup><sup>1</sup>NRS Medical College and Hospital, Kolkata, West Bengal, India<sup>2</sup>Department of Physiology, R.G.Kar Medical College and Hospital, Kolkata, West Bengal, India<sup>3</sup>Department of Physiology, Midnapore Medical College, Paschim Midnapore, West Bengal, India<sup>4</sup>Department of Physiology, Bankura Sammilani Medical College, Kenduadihi, Bankura, West Bengal, India

(Received: November 2022

Revised: February 2023

Accepted: March 2023)

Corresponding author: **Maumita Das**. Email: moumitadasdr@gmail.com**ABSTRACT**

**Introduction and Aim:** Hypothyroidism is an endocrine disorder with a high prevalence worldwide in the adult population. Due to the thyroid hormone's widespread role in controlling metabolic processes to permissive action on the heart, patients with hypothyroidism suffer from a significant chance of acquiring cardiac autonomic dysfunction which further deteriorates the prognosis. Heart rate Variation analysis can be a possible way to detect this autonomic dysfunction early and may help in patient care. This study aims to assess Heart Rate Variability (HRV) parameters in untreated overt hypothyroid patients and compare the parameters of heart rate variability test with an age and sex-matched healthy control group.

**Materials and Methods:** With the permission from the institutional ethics committee, 50 untreated hypothyroid patients are collected from the endocrine outpatient department and 50 healthy age, sex, and matched individuals are taken, maintaining proper inclusion and exclusion criteria. HRV analysis data is collected in both time and frequency domains in both groups and compared using statistical tools.

**Results:** In our research, it is seen that compared to healthy control group, untreated hypothyroid patients have a significant alteration in the following parameters - SDNN ( $p < 0.005$ ) and RMSSD ( $p < 0.009$ ) in the time domain and LF (nu), LF (%), HF (%), LF/HF, HF (nu) [ $p < 0.05$ ] in the frequency domain.

**Conclusion:** Due to several alterations in HRV parameters indicating sympathovagal disbalance in the hypothyroid patients, it can be concluded that untreated hypothyroid patients are prone to develop cardiovascular autonomic dysfunction and HRV analysis can be a possible way to detect it early.

**Keywords:** Untreated hypothyroidism; cardiac autonomic dysfunction; heart rate variability; time domain.

**INTRODUCTION**

**H**ypothyroidism is an endocrine abnormality with a high prevalence in the adult population. It can be categorized into 1. Subclinical, where TSH level is elevated but free T<sub>3</sub>, T<sub>4</sub> levels in serum are normal or 2. Overt where TSH level is elevated but free T<sub>3</sub>, T<sub>4</sub> levels in serum are significantly low. Apart from that hypothyroidism can also occur in deficiency of TSH and TRH secretion causing secondary and tertiary hypothyroidism (1-3). Thyroid hormone has permissive action on the effect of the adrenergic system as it helps in increasing the number of Beta-adrenergic receptors in myocardial tissue. As thyroid hormone plays a role in increasing the expression of LDL receptors in the liver, a low level of this hormone predisposes to dyslipidemia (4). Due to its thermogenic action, thyroid hormone indirectly helps to lower diastolic blood pressure by cutaneous vasodilation. So, in hypothyroid patients due to deficiency of this hormone a wide range of cardiac abnormalities is seen including bradycardia, low cardiac output, coronary artery diseases, atherosclerosis, and heart failure (4).

There is a lot of research work regarding cardiovascular abnormalities in hypothyroidism like dyslipidemia, atherosclerosis, etc., but data regarding cardiac autonomic dysfunction in hypothyroidism is less overall. There are few research works on cardiac autonomic dysfunction in subclinical hypothyroidism but studies in untreated overt hypothyroidism patients regarding this is lacking, particularly in the eastern Indian region. So, the status of cardiac autonomic function in hypothyroidism needs to be explored.

In India, one in every 10 adults suffers from hypothyroidism with more prevalence in females and older people (5). Because of the profound effect of thyroid hormones on the heart, patients with hypothyroidism are already at great risk of cardiovascular dysfunction, so if cardiac autonomic dysfunction is also detected in these patients the prognosis will be poor.

Through the assessment of these cardiac autonomic abnormalities in untreated hypothyroid patients, cardiac autonomic dysfunction can be diagnosed early and if appropriate measures are taken on time, then the further progress of cardiac morbidity and mortality can be reduced (4).

## MATERIALS AND METHODS

A cross-sectional observational study involving clinical investigation was conducted for 6 months on the patients attending the Endocrinology Outpatient Department (OPD) of a tertiary care hospital. A group of healthy individuals within the same age group were also selected as a control group for the study. This hospital is situated in one of the metropolitan cities in India with a population of 1.49 crore. So, patients from all over Eastern India both from the rural and urban areas, of both sexes, and from diverse age groups come here. After taking informed consent Adult (Age > 18 years) Patients of both sexes diagnosed with hypothyroidism who have not yet received any treatment were selected. For determining Hypothyroidism, a thyroid function test was performed. The reference intervals for TSH and fT4 were taken as 0.35-5.5 mIU/L and 10.2-31 pmol /L respectively (6). Following patients are excluded 1. Patients who are either suffering from cardiac abnormalities or have a previous history of cardiac autonomic diseases 2. Patients with diabetes, hypertension, or any chronic disease which may lead to autonomic neuropathy 3. Patients with prior history of cerebrovascular accident or head injury 4. Patients who have taken prior medication for hypothyroidism.

Following the same inclusion and exclusion criteria, a control sample group of healthy individuals, without any thyroid dysfunction were also chosen for comparative analysis. The sample size of this study consisted of 50 untreated hypothyroid patients and 50 healthy age and sex-matched individuals following the inclusion and exclusion criteria. Complete confidentiality of the participants was maintained during the study and even after the study (7).

All the participants were instructed to refrain from smoking, caffeine intake for 2 hours, and alcohol intake for 36 hours prior to examination. They had

taken adequate rest, at least 8 hours of uninterrupted sleep on the night before the assessment of HRV and had a normal breakfast on the day of the assessment. All procedures were carried out in an acclimatized room, at ambient temperature (20 to 25° Celsius).

After explaining the procedure to the subject, heart rate variability was assessed using an ambulatory ECG system (iWorx TA- 220) in lead II for 5 minutes at the Department of Physiology. The machine was provided with LabScribe data acquisition software. The acquired data was stored and analyzed in Kubios HRV Standard 3.5.0 software.

The final data obtained from both the control group of healthy individuals and from the untreated hypothyroid patients were further statistically analyzed using the IBM SPSS tool. A comparative study of thyroid and HRV parameters of normal and affected individuals was done and a correlation was established between these two parameters. The research proposal was submitted to and reviewed by the institutional ethics committee.

## RESULTS

In the present study, 50 untreated hypothyroid patients and age and sex, matched 50 healthy individuals were taken as study subjects. Among the patient group, 32% were male and 68% were female (Fig. 1), and in the healthy controls, 48% were male, and 52% were female (Fig. 2).

Between both groups, demographic parameters (Age, Height, Weight, BMI) were compared and presented in Table 1. The values of HRV parameters both in time domain (Mean HR, Mean RR, SDNN,

RMSSD, NN50, pNN50) and frequency domain (LF (nu), HF (nu), LF (%), HF (%), LF/HF) are tabulated and compared in Table 2 and 3.

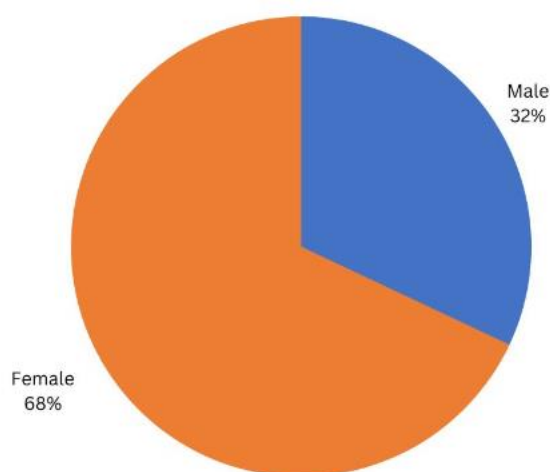


Fig. 1: Patients with hypothyroidism

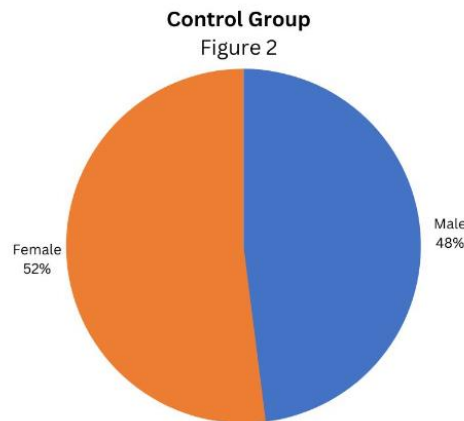


Fig. 2: Control group

Table 1: Demographic parameters between healthy controls and patients

Demographic Parameters (Mean $\pm$ SD)	Hypothyroid Patients	Healthy Control Group	P Value
Age (years)	31.8 $\pm$ 6.064	32.04 $\pm$ 6.064	0.84
Height (cm)	158.94 $\pm$ 6.37	32.04 $\pm$ 6.064	0.71
Weight(kg)	60.78 $\pm$ 11.55	67 $\pm$ 12.04	<b>0.01*</b>
BMI (kg/m <sup>2</sup> )	60.78 $\pm$ 11.55	67 $\pm$ 12.04	<b>0.01*</b>

Table 2: HRV parameters (time domain) between healthy controls and hypothyroid patients

HRV Parameters (Time Domain) (Mean $\pm$ SD)	Hypothyroid Patients	Healthy Control Group	P Value
Mean RR	872.66 $\pm$ 363.83	785.82 $\pm$ 143.18	0.12
Mean HR	78.58 $\pm$ 18.82	75.72 $\pm$ 13.10	0.38
SDNN	541.82 $\pm$ 673.11	171.06 $\pm$ 204.64	<b>0.0005*</b>
RMSSD	703.86 $\pm$ 889.56	232.44 $\pm$ 310.39	<b>0.0009*</b>
NN50	95.18 $\pm$ 85.35	113.06 $\pm$ 93.94	0.32
pNN50	30.34 $\pm$ 30.62	31.97 $\pm$ 25.07	0.77

Table 3: HRV parameters (frequency domain) between healthy controls and hypothyroid patients

HRV Parameters (Frequency Domain) (Mean $\pm$ SD)	Hypothyroid Patients	Healthy Control Group	P Value
LF (nu)	55.99 $\pm$ 20.79	38.42 $\pm$ 10.83	<b>0.005*</b>
HF (nu)	43.91 $\pm$ 20.76	61.48 $\pm$ 10.86	<b>0.0001*</b>
LF (%)	51.38 $\pm$ 17.13	36.93 $\pm$ 9.92	<b>0.003*</b>
HF (%)	439.03 $\pm$ 20.95	120.88 $\pm$ 10.99	<b>0.003*</b>
LF/HF	55.99 $\pm$ 1.69	38.41 $\pm$ 0.42	<b>0.005*</b>

In demographic parameters, only weight( $p=0.01$ ) and BMI( $p=0.03$ ) showed slight differences in statistical analysis (Table 1). In case of time domain of HRV parameters, though significant changes were seen in SDNN ( $p<0.005$ ) and RMSSD ( $p<0.009$ ), Other time domain parameters (Mean RR, Mean HR, NN50, pNN50) didn't show any statistically significant difference between the two groups. In the case of frequency domain parameters, LF (nu), LF (%), HF (%), and LF/HF ( $p<0.05$ ) were significantly increased in patients though HF (nu)[ $p<0.05$ ] values were lower compared to healthy control group (Table 2).

## DISCUSSION

In normal physiological conditions, heart rate increases during inspiration and decreases during expiration mediated by sympathetic and parasympathetic (vagal) discharge. This is called sinus arrhythmia (8). In the case of hypothyroid patients, as

the autonomic control on Heart rate is diminished this variability of heart rate is decreased and can be monitored in the collected data from the ambulatory ECG system using time-domain analysis. Mathematical parameters used in time-domain-dependent analysis are mean RR, mean HR, Standard Deviation of Normal Sinus RR Intervals (SDNN), Successive Normal Sinus RR intervals  $>50$  ms (NN50), the percentage of successive normal sinus RR intervals  $>50$  ms (pNN50), root mean square of successive heartbeat interval differences (RMSSDs). Values of SDNN can be used to measure short and long-term variation within the RR interval series and RMSSDs can be measured for short-term variation (9). Thus, this diminished HRV can indicate Cardiac Autonomic Dysfunctions. In case of frequency-domain analysis, for the RR interval series, a spectrum estimate is calculated and then it is divided into very low frequency (VLF), low frequency (LF), and high

frequency (HF) bands. For HRV analysis, from these bands, peak frequencies, absolute and relative powers, LF/HF ratio is calculated. LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) bands denote sympathetic and parasympathetic activity respectively. So, with the help of the LF/ HF ratio, the sympathovagal balance can be measured and if the sympathetic tone is more profound, the prognosis may be poor for these patients (10).

In the above data analysis, demographic parameters, as well as HRV parameters in time domain and frequency domain analysis, are compared. Except for the weight and BMI values, no significant difference is noticed between the two groups in the case of demographic parameters. In time domain analysis, though short-term HRV analysis does not record enough data to get a conclusive result (9), still SDNN( $p=0.005$ ) and RMSSD( $p=0.009$ ) are significantly altered in untreated hypothyroid patients. On the other hand, the parameters of frequency domains are significantly increased in the hypothyroid patients compared to the control group except for HF (nu) which shows a significantly lower value in patients ( $p<0.05$ ).

In our study, ambulatory HRV analysis is mainly a short-term measurement (5m recording), so the time domain parameters are inconclusive (9). But the frequency domain parameters show predictable changes in hypothyroid patients (7). Cardiac autonomic dysfunctions are characterized by an imbalance in sympathovagal tone in heart rate regulation. Through the application of the fourier method done in the data obtained by spectral analysis, LF, HF band frequency and its ratio (LF/HF) clearly indicate the sympathovagal balance in the heart.

Increase in the values of LF (nu), LF (%), and LF/HF ratio ( $p<0.05$ ) and decrease in HF (nu)[ $p<0.05$ ] indicate overactive sympathetic drive and diminished vagal tone (9). This autonomic imbalance predisposes hypothyroid patients to cardiac autonomic dysfunctions and various cardiovascular accidents (12). Similar findings are obtained in a few other studies too (7, 11).

### Strengths and limitations

In eastern India, there are very few studies that concern the assessment of cardiac autonomic anomaly in hypothyroid patients through HRV analysis. HRV analysis through ambulatory ECG can be a cost-effective and easier-to-use method for earlier detection of cardiac autonomic dysfunction in the concerned patient group. Furthermore, a routine study of HRV parameters along with ongoing treatment of hypothyroidism can help in a better prognosis of cardiac dysfunctions. The limitations concerned with this study are 1. Long Term HRV analysis could not be done which produced inconclusive time domain values, 2. The study sample was very small and thus

statistical trends might have been missed in the analysis, 3. Observer's bias cannot be removed 4. No blinding was done due to the short time frame of the study and extra complexities.

### CONCLUSION

In this study, we compared the Heart rate variability parameters between untreated hypothyroid patients and age and sex-matched healthy control groups. Our findings indicate the presence of cardiac autonomic dysfunctions in these patients which may predispose them to further cardiac complications in the background of already disturbed hormonal balance. HRV analysis provides a non-invasive, easy-to-use, and cost-effective method to measure the autonomic control of the heart in these patients and may help in earlier detection of further cardiac complications.

### CONFLICT OF INTEREST

No conflict of interest has arisen in this research.

### REFERENCES

1. Iervasi, G., Pingitore, A., Landi, P., Raciti, M., Ripoli, A., Scarlattina, M., *et al.*, Low-T3 Syndrome. *Circulation*. 2003;107: 708-713.
2. Khandelwal, D., Tandon, N. Overt and subclinical hypothyroidism: who to treat and how. *Drugs*. 2012; 72:17-33.
3. Gaitonde, D.Y., Rowley, K.D., Sweeney, L.B. Hypothyroidism: an update. *Am Fam Physician* 2012; 86: 244-251.
4. Udovcic, M., Pena, R. H., Patham, B., Tabatabai, L., Kansara, A. Hypothyroidism, and the Heart. *Methodist Deakey Cardiovasc J* 2017;13: 55-59.
5. Unnikrishnan, A.G., Kalra, S., Sahay, R. K., Bantwal, G., John, M., Tewari N. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. *Indian J Endocrinol Metab*. 2013;17: 647-652.
6. Abdu, F.A., Mohammed, A.Q., Liu, L., Zhang, W., Yin, G., Xu, B., *et al.*, Low Free Triiodothyronine as a Predictor of Poor Prognosis in Patients with Myocardial Infarction with Non-Obstructive Coronary Arteries. *Front Endocrinol (Lausanne)* 2021;12: 681978.
7. Kabir, R., Begum, N., Ferdousi, S., Begum, S., Ali, T. Relationship of Thyroid Hormones with Heart Rate Variability. *Journal of Bangladesh Society of Physiologist* 2010; 5:20-26.
8. Angelone, A., Coulter, NA. Respiratory sinus arrhythmia: a frequency dependent phenomenon. *Journal of Applied Physiology*. 1964;19: 479-482.
9. Tarvainen, M.P., Niskanen, J.P., Lipponen, J.A., Ranta-Aho, P.O., Karjalainen, P.A. Kubios HRV--heart rate variability analysis software. *Comput Methods Programs Biomed* 2014;113: 210-220.
10. Shaffer, F., Ginsberg, J.P. An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health*. 2017; 5: 258.
11. Mahajan, A.S., Lal, R., Dhanwal, D.K., Jain, A.K., Chowdhury, V. Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients. *Indian Journal of Endocrinology and Metabolism* 2013;17: 460-464.
12. Vinik, A.I., Maser, R. E., Ziegler, D. Autonomic imbalance: prophet of doom or scope for hope? *Diabetic Medicine*. 2011; 28:643-651.