Linear Analysis of Autonomic Activity and Its Correlation with Creatine Kinase-MB in Overt Thyroid Dysfunctions

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Abstract Autonomic activity may be deranged in thyroid dysfunctions and may lead to cardiovascular morbidity and mortality. Myopathy is a common manifestation in thyroid disorders and may be associated with raised serum creatine kinase (CK). We hypothesized that cardiovascular abnormality in thyroid dysfunction may manifest as raised CK-MB. This study was designed to investigate the correlation of CK and its isoform CK-MB with thyroid profile and linear parameters of heart rate variability (HRV). The study was conducted on 35 hypothyroid and hyperthyroid patients each, and 25 age-matched healthy controls. Autonomic activity was assessed by simple short term 5-min HRV. Biochemical evaluation of serum thyroid profile, CK-NAC and CK-MB were estimated in all the subjects. Our results demonstrated low HRV in hypo- as well as hyperthyroid patients. We observed significantly higher serum CK levels in hypothyroid patients when compared to hyperthyroids and controls. However, no significant differences were observed in CK-MB levels in the three groups. Significant positive correlation of CK with TSH and negative correlation with some HRV parameters (LF power, HF power, total power, SDNN, RMSSD) was observed in hypothyroid patients. Whereas correlation of CK-MB with thyroid profile as well as HRV parameters was non-significant in all the groups. Based on the CK and CK-MB findings and their correlation, we

conclude that the cardiovascular changes seen in thyroid dysfunctions may primarily be due to autonomic imbalance without apparent cardiac muscle involvement. Whereas, raised CK levels indicate predominantly skeletal muscle involvement in hypothyroid patients.

Keywords Heart rate variability · Hypothyroidism · Hyperthyroidism · Creatine kinase · Correlation

Introduction

Heart Rate Variability (HRV) is the temporal variation between sequences of consecutive heart beats. HRV analysis is a sensitive tool for detection of sympathetic and parasympathetic activity of the heart [1]. It detects the ability of the heart to respond to quick and unpredictable stimuli. High HRV is suggestive of adaptable and dynamically responsive autonomic nervous system (ANS), whereas attenuated HRV indicates an abnormal or restricted ability of the ANS in maintaining homeostasis [2]. Thyroid dysfunction may manifest as hyper- or hypothyroidism. Thyroid hormones affect cardiac systolic and diastolic function, peripheral vascular resistance and arrhythmogenesis [3]. Abnormal HRV has also been validated in thyroid dysfunctions [4, 5]. Patients with clinical hypothyroidism have sympatho-vagal imbalance and prolongation of repolarization duration predisposing them to potentially life threatening arrhythmias [6]. On the other hand, hyperthyroidism presents as hyper dynamic cardiovascular state may complicate pre-existing cardiac disease or may lead to cardiac complications in individuals with structurally normal hearts [7].

Creatine kinase, a dimeric enzyme found primarily in brain and muscle tissue exists in 3 isoforms: BB, MM and

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MB. BB is found primarily in the brain, MM isoform in skeletal muscles and MB primarily in cardiac muscles [8]. Rise in the amount of CK in the blood indicates muscle damage as muscle breakdown releases its contents into the blood [9]. Others have documented increased levels of CK in patients of thyroid dysfunction [10].

We hypothesized that cardiovascular abnormality in thyroid dysfunction may manifest as raised CK-MB and may co-relate with HRV findings. To prove the same, in this study, we correlated time and frequency domain parameters of HRV with CK and CK-MB in patients of hyper and hypothyroidism.

Methods

The present study was conducted in the department of Physiology with requisite inputs from the Department of Endocrinology of the Institute. The study was commenced after obtaining approval from Institutional Ethics Committee. Informed written consent was obtained from all the subjects included in the study.

Newly diagnosed confirmed hypo- and hyperthyroid patients (20–60 years of age) of either sex, never previously treated for any endocrine disease and ready to

participate were included in the study. Patients with any cardiac, hepatic or renal dysfunction, HIV/Immunodeficiency disorders, neurological disease, any other systemic disease that may affect autonomic activity i.e. diabetes, hypertension and those taking any drug which affects autonomic activity were excluded.

Patients were diagnosed on the basis of following clinical findings:

Hypothyroid—Patients presenting with 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 with following clinical features were considered as **Hyperthyroid**—Rapid Pulse rate, palpitation, tremor, weight loose, increase appetite, orbitopathy, anxiety, restlessness, diarrhea, intolerance to heat, hair loss, muscle aches, weakness, fatigue, dyspnea, hyperactivity, irritability and sweating.

Confirmation of clinical diagnosis was done by biochemical evaluation of FT₃, FT₄, TSH.

Based on the above mentioned criteria, the following recruitment/screening plan was charted:

Based on the finding of the screening, the patients were grouped as Hypothyroid patients (35), Hyperthyroid patients (35) and controls that included age matched 25 healthy subjects (asymptomatic with normal clinical examination and biochemical tests and not on any medication) randomly selected from general population.

Biochemical Assessment: Serum levels of FT3, FT4 and TSH were determined by chemiluminescent immunoassay with the IMMULITE 2000 Systems Analyzer, with reference ranges for FT3, FT4, TSH, 1.8–4.2 pg/mL, 0.89–1.76 ng/dL and 0.4–4.0 uIU/mL respectively.

Serum CK-NAC and serum creatine kinase-MB activity was measured by Fully Autoanalyzer Randox-imola (Diamond Diagnostics Inc. Holliston, MA) [11].

Assessment of HRV: Heart Rate Variability assessment was done by recording 5 min 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. Linear analysis of HRV for time domain (SDNN, RMSSD, pNN50%) and frequency domain (Total Power, LF (ms²), HF (ms²), HF in normalized unit (nu), LF (nu), LF/HF ratio) parameters was performed by Software Version 1.1.

Statistical analysis was done using SPSS version 21 (SPSS Software Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). All the data were presented as mean $\pm$ SD. Normality of data was tested by Kolmogorov–Smirnov test. For parametric data, the level of significance among the groups was tested by One-way ANOVA followed by post hoc Bonferroni test and for non-parametric data; Kruskal–Wallis One way ANOVA with post hoc Dunn's multiple comparison test was used. The correlation between various parameters was assessed by Spearman's rank's correlation test. *p* values < 0.05 were considered to be statistically significant.

Experimental Protocol:

1. The subjects were instructed to avoid food at least 2 h before the procedure, abstain from coffee, nicotine or

alcohol 24 h prior to testing and to wear loose and comfortable clothing. They were asked to report at 10.00 a.m. Their age, height, and body weight were recorded. Body Mass Index (BMI) was calculated by weight (kg) divided by the square of height (m) (Quetelet's Index). 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.

2. 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. Processing including R wave and RR interval detection was done by the software. Abnormal beats and areas of artifact were automatically identified and excluded from the recording.

Results

We measured short term HRV in normal healthy adults and compared it with the changes in hypothyroid and hyperthyroid patients. Table 1 shows the age, body mass index and thyroid hormone profile of the subjects in the three groups. BMI, free T3, free T4 and TSH showed significant differences between control and test groups.

A comparison between the time and frequency domain measures of HRV among three groups is depicted in Table 2. The spectral parameters of HRV TP, LF (ms²), HF (ms²), HF nu were significantly decreased in hyperthyroids and hypothyroids compared with the controls, however LFnu and LF/HF were significantly increased in both the study groups. The time domain indices of HRV (SDNN,

Table 1 Age, BMI and thyroid profile of hypothyroid, hyperthyroid and control groups

Parameter (mean $\pm$ SD)	Hypothyroid	Hyperthyroid	Control	<i>p</i> value	Intergroup comparison <i>p</i> value
Age (yrs.)	37.3 $\pm$ 9.3	34.37 $\pm$ 8.15	34.49 $\pm$ 10.07	0.34	ns
BMI (kg/m ²)	26.16 $\pm$ 3.47	17.47 $\pm$ 1.61	21.29 $\pm$ 1.11	0.000	<0.0001* ^{†‡}
Free T3 (pg/mL)	2.59 $\pm$ 0.47	1.69 $\pm$ 0.67	9.21 $\pm$ 6.31	<0.001	<0.0001* [†] , <0.05 [‡]
Free T4 (ng/dL)	1.29 $\pm$ 0.22	0.70 $\pm$ 0.29	13.57 $\pm$ 6.39	<0.001	<0.0001* ^{†‡}
TSH (uIU/mL)	2.41 $\pm$ 1.45	16.91 $\pm$ 7.38	0.06 $\pm$ 0.05	<0.001	<0.0001* ^{†‡}

p < 0.05 were considered statistically significant. *BMI* body mass index, *TSH* thyroid stimulating hormone. Intergroup comparison was done using one-way ANOVA followed by post hoc Bonferroni multiple comparison test (Age, BMI) and Kruskal–Wallis followed by Dunns multiple comparison test (Thyroid profile). * hypo versus hyperthyroids, [†] hyperthyroid versus control groups, [‡] hypothyroid versus controls, *ns* non significant

Table 2 Time and frequency domain (linear) measures of HRV of hypothyroid, hyperthyroid and control groups

Parameter (mean $\pm$ SD)	Hypothyroids	Hyperthyroids	Control	<i>p</i> value	Intergroup comparison <i>p</i> value
SDNN (ms)	30.46 $\pm$ 13.18	25.59 $\pm$ 10.57	54.29 $\pm$ 13.93	<0.0001	ns*, <0.0001 ^{†‡}
RMSSD (ms)	24.97 $\pm$ 16.82	17.27 $\pm$ 8.9	54.83 $\pm$ 22.43	<0.0001	ns*, <0.0001 ^{†‡}
pNN50 (%)	9.75 $\pm$ 2.61	2.54 $\pm$ 1.29	27.97 $\pm$ 13.58	<0.0001	<0.0001* ^{†‡}
TP	1364 $\pm$ 839.9	1052 $\pm$ 559.7	3564 $\pm$ 1246.7	<0.0001	ns*, <0.0001 ^{†‡}
LF (ms ²)	379.6 $\pm$ 305.6	324.4 $\pm$ 285.6	1094 $\pm$ 604	<0.0001	ns*, <0.0001 ^{†‡}
HF (ms ²)	453.41 $\pm$ 505.43	204.6 $\pm$ 173.7	1443 $\pm$ 710.9	<0.0001	ns*, <0.0001 ^{†‡}
LFnu	50.55 $\pm$ 16.48	59.43 $\pm$ 14.51	42.87 $\pm$ 15.60	<0.001	ns*, <0.0001 [†]
HFnu	49.21 $\pm$ 16.71	40.5 $\pm$ 14.39	56.93 $\pm$ 15.37	<0.001	ns*, <0.0001 [†]
LF/HF	1.29 $\pm$ 0.89	1.81 $\pm$ 1.09	0.91 $\pm$ 0.65	<0.001	ns*, <0.0001 [†]

$p < 0.05$ were considered statistically significant. *SDNN* standard deviation of normal to normal interval, *RMSSD* the square root of the mean of squares of the differences between adjacent NN intervals, *pNN50* the proportion derived by dividing NN50 by the total number of NN intervals, *TP* total power, *LF* low frequency power, *HF* high frequency power, *LFnu* normalized low frequency power, *HFnu* normalized high frequency power, *LF/HF* ratio of LF to HF. Intergroup comparison was done using Kruskal–Wallis followed by Dunns multiple comparison test. * hypo versus hyperthyroids, [†] hyperthyroid versus control groups, [‡] hypothyroid versus controls

Fig. 1 $p < 0.05$ were considered statistically significant. The figure depicts creatine kinase (CK in IU/L) in the control, hypothyroid and hyperthyroid group. *** shows statistically significant differences between control and the two test groups ($p < 0.0001$). ### signifies statistically significant difference between hypothyroid and hyperthyroid group ($p < 0.0001$)

RMSSD, pNN50) were significantly decreased in hyperthyroids and hypothyroids as compared to controls.

Creatine kinase (IU/L) in the hypothyroid, hyperthyroid and control groups were 231.9 ± 87.71 , 75.62 ± 25.01 and 110.8 ± 15.7 respectively (Fig. 1).

The Mean $\pm$ SD values of CK- MB (IU/L) in control, hypothyroid and hyperthyroid groups were 10.32 ± 1.84 , 14.50 ± 9.95 and 13.94 ± 5.58 respectively. Inter and intra group comparison showed nonsignificant differences ($p > 0.05$) among the groups (Fig. 2).

Our study demonstrated significant negative correlation between CK and LF (ms²), HF (ms²), TP (ms²), SDNN, RMSSD parameters. CK also showed significant positive correlation with TSH in hypothyroid subjects ($p < 0.05$, Table 3).

Fig. 2 Mean $\pm$ SD values of CK-MB (IU/L) in the control, hypothyroid and hyperthyroid group. No statistically significant differences in the three groups were observed on inter and between group comparisons using Kruskal–Wallis followed by post hoc Dunn's multiple comparison test ($p > 0.05$)

Our study failed to demonstrate any significant correlation of CK-MB with various parameters of HRV and thyroid profile in all the three groups ($p > 0.05$, Table 4).

Discussion

In this study, autonomic activity in hypothyroids and hyperthyroids was evaluated and compared with age and sex matched controls by measurement and analysis of time and frequency domain parameters of heart rate variability. As expected and as proved by other investigators, weight and BMI showed significant increase in hypothyroid and decrease in hyperthyroid patients when compared to controls [12].

Table 3 Correlation of CK-NAC with thyroid profile and HRV

Parameters	Controls (n = 25)		Hypothyroids (n = 35)		Hyperthyroids (n = 35)	
	r	p value	r	p value	R	p value
Free T3 (pg/mL)	0.002	0.99	−0.23	0.18	0.07	0.70
Free T4 (ng/dL)	0.18	0.39	−0.06	0.73	−0.06	0.72
TSH (uIU/mL)	0.10	0.62	0.58	0.002	−0.05	0.77
LF (ms ²)	−0.09	0.67	−0.34	0.04	−0.03	0.86
LF (nu)	0.20	0.37	0.24	0.16	−0.07	0.69
HF (ms ²)	−0.37	0.06	−0.34	0.04	0.09	0.61
HF (nu)	−0.20	0.37	−0.24	0.16	0.07	0.69
TP (ms ²)	−0.29	0.16	−0.34	0.04	−0.12	0.49
LF/HF	0.20	0.34	0.23	0.19	−0.07	0.69
SDNN	−0.23	0.27	−0.39	0.02	−0.07	0.69
RMSSD	−0.23	0.18	−0.36	0.03	−0.12	0.47
pNN50	−0.44	0.03	−0.02	0.89	−0.18	0.31

$p < 0.05$ were considered statistically significant are marked in bold. *CK-NAC* creatine kinase total, *TSH* thyroid stimulating hormone, *LF* low frequency power, *LF nu* normalized low frequency power, *HF* high frequency power, *HF nu* normalized high frequency power, *TP* total power, *LF/HF* ratio of LF to HF, *SDNN* standard deviation of normal to normal interval, *RMSSD* the square root of the mean of squares of the differences between adjacent NN intervals, *pNN50* The proportion derived by dividing NN50 by the total number of NN intervals

Table 4 Correlation of CK-MB with thyroid profile and HRV

Parameters	Control		Hypothyroids		Hyperthyroids	
	r	p value	r	p value	r	p value
Free T3 (pg/mL)	−0.08	0.71	0.003	0.99	−0.003	0.99
Free T4 (ng/dL)	−0.07	0.74	0.13	0.46	−0.32	0.06
TSH (uIU/mL)	−0.07	0.75	−0.02	0.90	−0.15	0.40
LF (ms ²)	−0.27	0.19	0.23	0.19	0.04	0.80
LF (nu)	−0.10	0.62	−0.01	0.95	−0.13	0.47
HF (ms ²)	−0.14	0.50	0.15	0.40	0.24	0.16
HF (nu)	0.11	0.62	−0.01	0.96	0.13	0.47
TP (ms ²)	−0.29	0.15	0.19	0.27	−0.17	0.33
LF/HF	−0.01	0.62	−0.01	0.99	−0.13	0.47
SDNN	0.06	0.79	0.23	0.17	−0.12	0.51
RMSSD	−0.02	0.91	0.09	0.60	0.02	0.89
pNN50	−0.15	0.47	0.13	0.45	−0.12	0.49

$p < 0.05$ were considered statistically significant. *CK-MB* creatine kinase MB isoform, *TSH* thyroid stimulating hormone, *LF* low frequency power, *LF nu* normalized low frequency power, *HF* high frequency power, *HF nu* normalized high frequency power, *TP* total power, *LF/HF* ratio of LF to HF, *SDNN* standard deviation of normal to normal interval, *RMSSD* the square root of the mean of squares of the differences between adjacent NN intervals, *pNN50* the proportion derived by dividing NN50 by the total number of NN intervals

We observed significant increase in the sympathetic activity as shown by increase in LF nu, LF/HF. More so, decreased HF nu, SDNN, RMSSD and pNN50 point towards low parasympathetic activity in hypo- and hyperthyroid patients when compared to controls. Sympathetic overactivity and parasympathetic withdrawal was to a greater extend in hyperthyroids then hypothyroids Similar to our observations, other workers also demonstrated

increased sympathetic activity in hypothyroid patients in their studies [13, 14].

Our results do not corroborate with the findings of some of the researchers in similar studies. Inukai et al. [15] observed significantly lower LF/HF ratio in hypothyroid patients than controls. Similarly, Xing et al. [16] also reported that autonomic imbalance in hypothyroid patients is due to a higher level of vagal tone, they observed higher

HF component in hypothyroid subjects than controls. These conflicting results in different studies may be partly expounded by the variations in the demographic profiles of the patients as well as differences in the type, severity and duration of the disease. LF-HF ratio is the most sensitive indicator of sympathovagal balance [1]. Increased sympathetic activity and poor vagal tone are predictor of increased cardiovascular morbidity. This fact should be taken into consideration while dealing with patients of thyroid dysfunction.

We demonstrated increased level of creatine kinase in hypothyroid patients in comparison to hyper thyroids and controls, though no significant differences were observed in CK-MB levels among the three groups. Similar to our findings, others have also observed significantly higher creatine kinase activity in hypothyroid patients than controls. [17–20]. Prakash et al. [21] reported average elevation of serum CK in 60% of hypothyroid subjects that is mostly due to increased CK-MM (muscle isoform).

Increased CK activity in patients with hypothyroidism points to skeletal muscle myopathy. Involvement of skeletal muscle is among the most prevalent clinical consequences of hypothyroidism. Evidence from a study by Sinclair and colleagues suggests that decreased muscle carnitine in patients with hypothyroidism and hyperthyroidism may contribute to thyroid myopathy [22]. The alteration in sarcolemmal membranes due to reduction in adenosine triphosphate (ATP) concentrations beyond a critical limit has been postulated as a possible mechanism for muscle involvement. Reduction in ATP is due to the hypometabolic state in hypothyroidism leading to altered cell permeability and the leakage of enzymes from cells [17]. Another possibility is increased concentration of the CK enzyme in skeletal muscle due to increased muscle mass and decreased clearance of enzymes because of hypothyroidism [23]. We observed significantly decreased creatine kinase activity in hyperthyroidism in comparison to controls and hypothyroids, this is in consistent with findings of other authors [24, 25]. It may be possibly due to increased enzyme degradation, muscle wasting or decreased muscle bulk in the hypermetabolic state in hyperthyroidism [24]. Our biochemical findings is corroborating with clinical and electrodiagnostic findings of Duyff et al. (2000). According to them weakness in hyperthyroidism, which completely resolves on treatment is suggestive of functional muscle disorder whereas in hypothyroidism where weakness is difficult to treat is suggestive of myopathy [25].

Our study demonstrated positive correlation of CK with TSH, suggesting skeletal muscle myopathy with increasing severity of hypothyroidism. We also observed a negative correlation of CK with HRV some parameters viz, LF (ms^2), HF (ms^2), TP, SDNN and RMSSD. All the above

parameters represent parasympathetic drive to the heart. Their negative correlation with CK suggests decreased parasympathetic tone and increased skeletal muscle myopathy.

However, heart specific isoform; CK-MB levels in the three groups did not vary significantly. There is paucity of literature describing relation between CK-MB and thyroid dysfunctions without pre-existing cardiac disease. Most of the studies on CK isoenzymes in hypothyroidism have shown CK-MM to be the predominant form [23–25], however a case report by Gunduz et al. [26] have demonstrated increased CK-MB levels without apparent myocardial damage. Comparable to our outcomes, Mush-taq et al. [18] also observed non-significant differences in the mean values CK-MB in hypothyroids as compared to control subjects.

Our study failed to demonstrate any significant correlation of CK-MB with various HRV parameters and thyroid hormone profile in hypothyroids, hyperthyroids and controls. It was assumed that increased cardiovascular morbidity in patients with altered autonomic activity may be associated with increased damage to cardiac muscles and consequently raised serum CK-MB levels, but no such correlation was observed by us. No other studies have looked for such correlation. We conclude that the cardiovascular morbidity seen in thyroid dysfunction may primarily be due to autonomic imbalance without apparent cardiac muscle involvement.

Our study was limited by small sample size, large cohort and follow up of patients could have led to more valid conclusion. Along with HRV, we could have performed battery of autonomic reactivity tests; emphasizing on latency and recovery time of autonomic responses. To strengthen our findings, we could plan a study with ECG recordings for longer duration to arrive at a better logical conclusion.

To explore the cardiac abnormalities associated with abnormal thyroid function, assessment of other cardiac specific enzymes and determination of corrected QT interval, QT dispersion and QT variability from ECG records are recommended. The patients may be advised to undergo Treadmill stress test and non-invasive assessment of endothelial dysfunction by flow mediated dilatation.

Compliance with Ethical standards

The study was commenced after obtaining ethical clearance from the Institutional Ethics Committee and has followed all Ethical standards.

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964

Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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