

An appraisal on the time-domain parameters of short-term heart rate variability analysis in the study protocol: comparison between hypothyroid subjects and normal individuals

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Abstract

Introduction: Heart rate variability analysis is being widely used in the study of endocrine disorders such as hypothyroidism. It is well established that cardiac autonomic dysfunction occurs in hypothyroidism and is also confirmed in this study.

Aim: To find out the effectiveness of each time-domain parameters of short-term HRV analysis done in time-domain analysis method.

Materials and Methods: 25 Hypothyroid subjects are obtained (study group) from the department of endocrinology and metabolism, govt. Rajaji Hospital attached to Madurai Medical College, Madurai. And 25 normal subjects who are age and sex matched with the study group form the control group. All the persons are free from any other illness. Serum TSH levels are estimated in all the subjects. ECG recording in Lead II is performed in all the subjects using computerized ECG machine enabled with physio-pac software and time domain parameters are obtained by short term HRV analysis method. The results are tabulated and analysed by applying student- t test.

Results and Conclusion: Time domain parameters with increasing mathematical complexity (SDRR, RMSSD) yield good correlation between the two study groups.

Keywords: Hypothyroidism, Heart-rate variability, Time-domain analysis method, Serum TSH level.

Introduction

Hypothyroidism is associated with a decreased sympatho-vagal modulation of the heart rate. The assessment of heart-rate may represent an useful tool in monitoring cardiovascular risks. (Galetta F and Franzoni F in 2008).

In ECG, the duration of time between subsequent "R" wave peaks is called as the R-R interval. It is usually expressed in seconds (or) milliseconds. Among the limb leads, the R-R interval can be accurately determined in lead II. The R-R interval calculated in the ECG recording obtained from lead II is specific. The Heart rate is conventionally measured by noting the number of heart beats per minute. The duration of cardiac cycles of all the heart beats occurring in one minute, even under resting conditions, are not the same. The cardiac cycle length as noted from the duration of the R-R interval of the resting ECG vary from beat to beat, in the order of milliseconds. This spontaneous beat-to-beat variation of the heart rate is known as heart rate variability. The normal cardiac autonomic innervations and its activity is essential for normal heart rate variability. Heart rate variability is a measure of neuro-cardiac function that reflects heart-brain interactions and autonomic nervous system dynamics, (Mc Craty & Singer in 2002). And the assessment of heart rate variability by time domain parameters such as mean RR interval, SDRR and RMSSD has been

referred to as the heart rate variability analysis by the time domain method.

In 1966 – Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, recommended short-term HRV analysis to be done on a 5 minutes continuous recording of ECG.

Aim and Objectives

This study involves,

1. Estimation of serum TSH level in the study and control population.
2. Analysis of short term heart rate variability using the time domain parameters in the study and control population.
3. Tracing of R.R. intervals in the ECG of the above subjects.
4. Evaluation of heart rate variability with TSH levels.

Materials and Methods

This study was done in the Institute of Physiology, Madurai Medical College, Madurai in association with the Department of Endocrinology and Metabolism, Government Rajaji Hospital attached to the Madurai Medical College.

The study group consists of 25 subjects who were newly diagnosed hypothyroid individuals in the age group of 20–40 years, of which 20 were females and 5

were males, who were free from any other diseases. The control group consists of 25 subjects who were age and sex matched, normal and euthyroid, free from any other diseases. Written consent was obtained from the subjects before procedures.

Estimation of T₃, T₄ & TSH: Laboratory Evaluation: Serum levels of TSH, total circulating T₄ and total circulating T₃ are measured by radioimmunoassay. Radioimmunoassay technique is a type of antibody-based competitive immunoassay.

Blood Pressure: Blood pressure was recorded using sphygmomanometer and stethoscope.

Short- Term HRV Analysis: As per the recommendations of the Task force of the European Society of Cardiology and the North-American Society of Pacing and Electro-Physiology in 1996, the short-term HRV analysis is done on a Five(5) minutes recording of ECG.

Pretest instructions were given to the subjects as follows:

1. No heavy physical activity 24 hours prior to recordings. No smoking or drinking alcohol or caffeinated beverages after 9pm the previous day.
2. The recordings are taken 2 hours after a meal.
3. All recordings are taken in a temperature controlled and sound proof, well electrified room with the facility for continuous recording of ECG using the windows based computerized polygraph, installed with the physiopac computer software.

ECG Acquisition: The ECG electrodes are placed over suitable bony points on the torso such that noise-free signals with good amplitude upright R-waves are obtained.

Lead II of the standard bipolar limb leads is used to obtain the ECG recording. ECG signals are acquired with adjustable and reusable electrodes. The electrodes are firmly fixed to the skin of the subject after applying the ECG electrode-gel over the skin. The ECG signals which are acquired with the ECG leads and amplifiers are digitized by an analog – to – digital converter, (Physio-pac).

Operating Procedure of the PHYSIO-PAC Software

The following are the steps in operating the software

1. Double click on the icon of the “Physio-Pac” present on the Desktop.
2. Fill user ID and Password and click on the OK button to go to the next windows.
3. From this menu we can select what we want to do, either to record the data of a new subject or to view the old recorded data of a old subject.

If, we want to record the data of a new subject,

1. Click on the add new. Then it will display the windows.

Fill the details of the patient (ID No., Name, Age, Sex, Address).

After filling the details click on SAVE.

2. After saving the name of the patient click on the NEW TEST button. Following screen will display the channel selection options.
3. Select one particular channel among the total number of eight channels and select ECG test in that channel by clicking on the downward arrow on the channel.
4. Then click on the OK, now the main page will be displayed, which is utilized for the recording.
5. After checking the necessary settings and then select Lead II. Then click on the “Start button” to start the data acquisition.
6. If we are satisfied with data then click on the “Record button” to start recording the data, and the time will be displayed on the right corner top of the screen. We can record the data upto the desired time as required.
7. We have to set the sweep speed at 200ms/div. by clicking on the button provided for that.
8. After recording up to the desired time, first stop the recording by clicking on the recording button then stop the data by clicking on the “start data” button.
9. For closing this windows, click on the close button X presented on the right corner top of the screen. Recording is complete.
10. Then, for viewing the selected subject’s recorded data, click the “view test” button.

Arrangement of Settings

We have to do the necessary arrangements for proper recording of the ECG by clicking the “Settings” option, and the following are set.

1. Sensitivity - 1mv
2. Low cut filter - 0.5 Hz
3. Hi cut filter - 75 KHz
4. Notch - On

Test Conditions: All mobile phones should be switched off and recording should be done in a quiet room with controlled temperature. The subjects are instructed about the procedure. The ECG electrodes are the applied. Ensure that a clean, good recording is obtained. The subject is now made to rest quietly, without moving, in the supine positions with eyes closed for 15 minutes. Throughout this period ECG is acquired and at the end of the rest period from an average of the last 10 R – R intervals.

The procedure for off-line analysis of the recorded ECG is as follows:

1. Retrieval of recorded ECG – for this click the “view test” button to view selected subjects recorded data.
2. Click on the “Bookmark button” to place bookmark on the page from which we are going to trace the ECG waves continuously upto the end of 5 minutes.
3. Detection of ‘R’ Peaks: The ‘R’ peaks will be detected and marked with Time marker T₁, T₂, by clicking on the “markings” option.

4. Getting the R – R intervals: All the consecutive R – R intervals are noted in milliseconds in the continuous 5 minutes recording of ECG. This data is copied and transferred to a “Notepad” file and saved. This R – R interval data file can be fed into the software specialized for HRV analysis.
5. Analysis of Heart Rate Variability: The “Time domain analysis” of HRV can be done using the statistical methods available in the Microsoft excel spread sheet. On the time – domain analysis the following parameters are analysed.
 - a. Mean R – R interval
 - b. Standard deviation of the R – R interval (SDRR)
 - c. RMSSD (Root Mean Square of sum of Differences between successive R – R intervals)

In this same methodology, both the control and study group were analysed and results scrutinised.

Comparison between the Study Group and the Control Group: Applying the student ‘t’ test.

Table 1

	Mean Heart Rate	R-R Interval	SDRR	RMSSD	
Case	75.52	0.7981	0.0345	0.0331	Mean Value
	1.868	0.028	0.004	0.005	Standard Deviation
Control	73.12	0.8006	0.0346	0.0339	Mean Value
	0.875	0.017	0.003	0.003	Standard Deviation
t	0.8750	0.0556	0.0143	0.1000	
df	48	48	48	48	
p	0.3860	0.9559	0.9887	0.9208	

‘P’ value is > 0.05 not significant

Comparison between the Sub-group of Hypothyroid subjects with Serum TSH > 100µIU/ml and normal controls

Table 2

Serum TSH (µIU/ml)	Mean R – R interval	SDRR	
146	0.901	0.0295	
150	0.764	0.0205	
172	0.828	0.0218	
	0.8310	0.0239	Mean value
	0.069	0.005	Standard Deviation

Applying student ‘t’ test between the subgroup of hypothyroid subjects with serum TSH levels more than 100 µU/ml and the normal controls.

Table 3

	SDRR	
Case	0.0239	Mean value
	0.005	Standard Deviation
Control	0.0346	Mean value
	0.01	Standard Deviation
t	3.05	
df	26	
p	0.01	

‘p’ value is < 0.05 indicating significance.

Table 4

	RMSSD	
Case	0.0168	Mean value
	0.008	Standard Deviation
Control	0.0339	Mean value
	0.02	Standard Deviation
t	2.80	
df	26	
p	0.02	

‘p’ value is < 0.05 indicating significance.

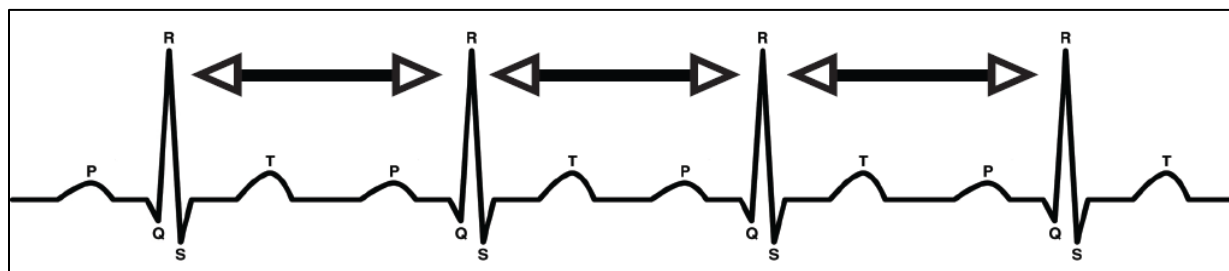


Fig. 1: Heart rate variability is measured by calculating the time between R spikes on an ECG trace

Observations

There is a mean value for mean RR interval of 0.8006 in the control group and 0.8310 in the study group of hypothyroid subjects with TSH levels more than 100 μ IU/ml. So it could be easily assumed that there is no statistical significance between the two groups. It is observed that the Mean value of the SDRR of the subgroup of hypothyroid subjects with TSH levels more than 100 μ IU/ml (Study group) and the standard deviation of the mean value of the SDRR of the study group subjects with normal TSH levels, by applying student 't' test, the 'p' value derived is 0.01, indicating that there is a significant difference in this parameter between these two groups. And it is also observed that the mean value of the RMSSD of the subgroup of hypothyroid subjects with TSH levels more than 100 μ IU/ml (study group) and the standard deviation of the mean value of the RMSSD of the study group when compared to these of the 25 control group subjects with normal TSH level, by applying student 't' test, the 'p' value derived is 0.02, indicating that there is a significant difference in this parameter between these two groups.

Discussion

The cardiac response to the autonomic nerve impulses depends on the distribution of specific receptors for both parasympathetic cholinergic discharge and sympathetic noradrenergic discharge in the different regions of the heart and the cardiac conduction system. In the myocardium, cholinergic receptors of muscarinic type (M_2 Subtype), and adrenergic receptor of beta₁ subtype are present.

The heart is supplied by both sympathetic and parasympathetic nerves. The parasympathetic nerves (the vagi) are distributed mainly to the SA node and AV node, to a lesser extent to the muscle of the two atria, and very little directly to the ventricular muscle. Vagal fibers are distributed on epicardial fat pads near SA node, AV node and Atria from where they travel intramurally (or) subendocardially and rise to the epicardium at the AV groove. (Schwartz PJ, 1999). Parasympathetic nerve impulses to heart result in momentary decrease of heart rate.

The sympathetic nerves, conversely, are distributed to all parts of the heart with strong representation to the ventricular muscle as well as to all the other areas. The intraventricular route of sympathetic nerves generally follows coronary arteries. Functional data suggest that afferent and efferent sympathetic nerves travel in the superficial layers of the epicardium forming an extensive epicardial plexus and dive to innervate the endocardium. (Douglas P Zipes, 1999). Sympathetic nerve impulses to heart result in momentary increase of heart rate and also increase in force of contraction. Molecular Mechanisms underlying the physiologic effects of thyroid hormones on the cardio – vascular system are as follows.

T_3 is not formed from T_4 in cardiac myocytes to any degree, but circulating T_3 enters the myocytes, combines with its receptors in the nucleus, where it promotes the expression of some genes and inhibits the expression of others. Those that are enhanced include the genes for α – myosin heavy chain, sarcoplasmic reticulum Ca^{++} ATPase, β – adrenergic receptors, G – proteins, $Na^+ - K^+$ ATPase and certain K^+ channels. (Klein I, and Qjamaa K, 2001).

Regulation of Thyroid function: The hypothalamic – Pituitary – Thyroid Axis

In normal serum, TSH is present at concentrations between 0.4 and 4.2 μ U/L. The level is increased in primary hypothyroidism. The plasma TSH half – life is about 30 minutes, and production rates in humans are 40 to 150 μ U/day. Circulation TSH displays both pulsatile and circadian variations. The former are characterized by fluctuations at 1 to 2 hour intervals. The circadian variation is characterized by a nocturnal surge that precedes the on set of sleep and appears to be independent of the cortisol rhythm and fluctuations in the serum T_4 and T_3 concentrations. (Adriaanse R, et al. 1993)

Both T_4 and T_3 mediates the feedback regulation of TSH secretion, and TRH determines its set-point. The serum TSH concentration is an exquisitely sensitive indicator of the thyroid state of patients with an intact hypothalamic – pituitary axis.

Heart rate variability - Increasing attention is being directed at the beat – to – beat changes in heart rate, termed heart rate variability, to gain insight into neuro-autonomic control mechanisms and their perturbations with aging, disease and drug effects. (Huikuri HV and Makikallio, et al. 1998).

Hypothyroidism is associated with a decreased sympathovagal modulation of the heart rate. The assessment of HRV in patients with overt - hypothyroidism may represent a useful tool in monitoring the cardiovascular – risks. (Galetta F & Franzoni F, 2008).

Even subclinical hypothyroidism can alter autonomic modulation of heart rate. (Cardiac autonomic modulation is evaluated by HRV), accordingly, early L-thyroxin treatment may be advised not only to prevent progression to overt hypothyroidism but also to improve abnormal cardiac – autonomic function. (Fallahi P, and Galetta F, 2006).

Among the hypothyroid subjects in the study group, those with TSH levels more than 100 μ IU/ml form a subgroup and it is clear that statistical significance begin to appear from SDRR in comparison of two groups and also present in RMSSD, but not in mean RR interval when both the two groups are compared.

Conclusion

From the present study, the results suggested that there is no significant difference between the hypothyroid subjects and the controls in the time domain measures of HRV such as mean R-R interval, SDRR and RMSSD. But there is a statistically significant difference observed only in the time domain measures of HRV such as SDRR and RMSSD between the sub group of hypothyroid subjects with TSH level more than 100 μ IU/ml and the control group comprising of normal subjects. The time domain parameters show statistical significance as the mathematical complexity increases further in the analysis of time domain parameters by HRV analysis method. This is in accordance with the proposition of scientists, Gundersen and Neubauer, who in 1981, proposed that a measure based on successive differences in the RR intervals, i.e., the actual difference between adjacent RR Intervals, would be more sensitive than the standard deviation to short-term fluctuations in Heart rate. The mean square successive difference (MSSD) is the average of the square of the differences between successive beats, the RMSSD is its square root.

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