**Evaluation of the QTc internal and QT dispersion in patients with newly detected clinical hypothyroidism**

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**ABSTRACT**

**Background:** Thyroid hormones play an important role in the orchestration of various metabolic functions in the body and thus thyroid dysfunction can produce dramatic cardiovascular effects. Electrocardiographic changes such as bradycardia, low voltage complexes, and varying degrees of heart block are commonly recognized in hypothyroid patients. Hypothyroidism has been found to be associated with increased cardiovascular morbidity and mortality. Hence, it is important to investigate the ECG profile in these patients. The present study aimed at evaluating the QTc interval and QT dispersion, an indicator of inhomogeneity of ventricular repolarisation and cardiac autonomic modulation in patients with newly detected clinical hypothyroidism.

**Methods:** 50 patients with newly detected clinical hypothyroidism and 50 healthy controls were included in the study. The ECG was recorded and the heart-rate, QTc interval and QT dispersion were calculated.

**Results:** The mean heart-rate was found to be significantly (p <0.05) reduced in hypothyroid patients when compared to healthy controls. The mean QTc interval and QT dispersion were significantly increased in hypothyroid patients when compared to controls. QTmin and QTmax of cases and controls also showed a statistically significant difference.

**Conclusion:** Thus, the present study confirms the role of thyroid hormones on the cardiovascular system, particularly on ventricular repolarisation and cardiac autonomic modulation. Hence, early and prompt therapy with levothyroxine may help to prevent the adverse events resulting from cardiovascular dysfunction.

**Keywords:** Hypothyroidism, Heart-rate, QTc interval, QT dispersion

**INTRODUCTION**

Hypothyroidism is characterized by the inability of the thyroid gland to synthesize and secrete adequate quantities of T3 and T4. Estimates of the incidence of hypothyroidism vary depending on the population studied. Among adult people in India, the prevalence of overt hypothyroidism, defined as an elevated serum TSH concentration and reduced free thyroxine concentration (FT4) is 3.9%. The prevalence of subclinical hypothyroidism was also high, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%.

Thyroid hormone plays an important role in regulating the cardiovascular system. The cardiac effects of hypothyroidism depend on the severity and duration of the abnormality and can range from subtle abnormalities to overt manifestations. It has long been recognized that hypothyroidism exerts major effect on the heart rate, rhythm, cardiac output, cardiac contractility and systemic vascular resistance.
Myocardial contractility and pulse rate are reduced, hence, leading to a reduced stroke volume and bradycardia. Increased peripheral resistance may be accompanied by hypertension, particularly diastolic hypertension. Blood flow is diverted from the skin, producing cool extremities. Pericardial effusions can occur in up to 30% of patients but rarely compromise cardiac function. Although alterations in myosin heavy chain isoform expression have been documented, cardiomyopathy is unusual. There are significant changes in modifiable atherosclerotic risk factors including hypercholesterolemia, diastolic hypertension, carotid intima media thickness, and endothelial derived relaxation factor (nitric oxide), which accompany overt hypothyroidism.

Electrocardiographic changes such as sinus bradycardia, prolonged AV conduction time, low voltage complexes and varying degrees of heart blocks are commonly recognized. It has also been reported that hypothyroidism is associated with prolongation of the heart–rate corrected QT interval (QTc), a measure of the duration of ventricular repolarisation. If undiagnosed or improperly treated, hypothyroid status can also lead to cardiac autonomic dysfunction and inhomogeneity of ventricular repolarisation (as measured by QT dispersion), which have been linked to the occurrence of malignant ventricular arrhythmias and sudden cardiac death.

This study was taken up to assess the cardiac changes in terms of cardiac autonomic modulation and ventricular repolarisation in patients with newly detected clinical hypothyroidism. The aim of the study was to evaluate the heart-rate corrected QT interval and QT dispersion in patients with newly detected clinical hypothyroidism.

METHODS

Out of 50 patients with newly detected clinical hypothyroidism presenting to the hospitals affiliated to Bangalore Medical College & Research Institute, during the study period from September 2018 to February 2019 and 50 healthy controls were included in this study.

Inclusion criteria

1. Age ≥18 years (of either sex).
2. Patients willing to give written informed consent.
3. Patients with newly detected clinical hypothyroidism.

Exclusion criteria

1. Age <18 years or patients not willing to give written informed consent.
2. Critically ill patients
3. Known cases of electrolyte abnormalities
4. Known hypertensive patients

5. Patients with established Ischemic heart disease, Post Myocardial infarction
6. History of intake of drugs known to influence QT interval in the past 3 months.

Experimental protocol

ECG recording

ECGs with a duration of 10s was recorded using 25mm/s paper speed and standardized at 0.1 V/mm.

Measurement of heart rate

Heart rate was calculated by “Box counting method” in rhythm strip of lead II, where the small boxes (n) which measures 1mm is counted in the R-R interval and is measured using the formula: 1500/n.

Measurement of QT interval

QT intervals were measured manually in all the leads in a blinded fashion from the onset of QRS complex to the end of T wave. When U waves were present, the QT interval was measured to the nadir of the trough between the T and U waves. If the end of the T wave couldn’t be identified, the lead was not included. With use of Bazett’s formula, QT interval was corrected (QTc) for heart rate (Figure 1).

Measurement of QT dispersion

A minimum of nine leads in which the QT interval can be measured will be used to determine QT dispersion. QT dispersion is defined as the difference between the longest and shortest QT intervals. With the use of Bazett’s formula, QT dispersion will be corrected for heart rate (Figure 1).

Figure 1: Measurement of QT interval and QT dispersion.
Statistical analysis

All data is expressed as Mean±SD (Standard Deviation) and analysed using student t-test. Confidence intervals at the 95% level were calculated for the QT indices. Differences were considered statistically significant when P <0.05.

RESULTS

50 patients with newly detected clinical hypothyroidism and 50 healthy controls were recruited for the study. The mean age of the patients and the controls in the study was 40.22 and 38.26 years respectively and there was no statistical difference between the two groups. The values are graphically represented below in figure 2. Among the patients and controls, the female to male ratio was 44:6 and 45:5 respectively. The gender distribution of the patients and controls are tabulated in Table 1.

Table 1: Distribution of the subjects based on gender.

| Groups | Gender | Frequency | Percent |
|--------|--------|-----------|---------|
| Cases  | Females| 44        | 88.0    |
|        | Males  | 6         | 12.0    |
|        | Total  | 50        | 100.0   |
| Controls| Females| 45        | 90.0    |
|        | Males  | 5         | 10.0    |
|        | Total  | 50        | 100.0   |

The mean TSH value of the hypothyroid group in the study was 44.38µIU/ml and those of the controls were 2.81 µIU/ml (Figure 3).

Table 2: Comparison of the groups based on heart rate.

| Groups | N    | Minimum | Maximum | Mean | Std. deviation | Mean difference | p value |
|--------|------|---------|---------|------|----------------|-----------------|---------|
| Cases  | 50   | 59      | 100     | 77.62| 9.868          | -11.32          | 0.00*   |
| Controls| 50   | 64      | 118     | 88.94| 13.338         |                 |         |

*significant

Table 3: Comparison of the groups based on QT avg.

| Groups | N    | Minimum | Maximum | Mean | Std. Deviation | Mean difference | p value |
|--------|------|---------|---------|------|----------------|----------------|---------|
| Cases  | 50   | 0.3280  | 0.5000  | 0.397560| 0.0403329     | 0.027          | 0.00*   |
| Controls| 50   | 0.3170  | 0.4210  | 0.369800| 0.0248045     |                 |         |

*significant

The mean heart rate of the hypothyroid patients was 77.62 bpm and that of the controls was 88.94 bpm (Table 2) and the difference was statistically significant (p <0.05).

The mean QTc of the cases (397.56 milliseconds) differed significantly (p <0.05) from the control group (369.8 milliseconds) as shown in Table 3. Both the QTmax and the QTmin of the cases and controls also showed a statistically significant difference.

The average QTmin of the patient group was 356 milliseconds when compared to 345 milliseconds in the control group (Figure 4). The average QTmax of the patients was 438 milliseconds whereas the average QTmax of the controls was 404 milliseconds (Figure 5).
Hypothyroid patients also showed a very significant increase in mean QT dispersion with respect to the control group, with mean QT dispersion being milliseconds and milliseconds respectively (Figure 6).

The findings are consistent with prior studies. A study done by Cacciatore et al, showed that there will be decreased responsiveness to endogenous catecholamines in patients with hypothyroidism due to a desensitisation at the receptor or post – receptor level. Manhem P et al, have shown that during hypothyroidism venous and arterial noradrenaline were significantly higher as compared to euthyroidism due to catecholaminergic desensitization. A study by Polikar et al, concluded that patients with untreated hypothyroidism showed a blunted cardiac chronotropic response to beta-adrenergic stimulation that was corrected by hormone replacement, which contributed to decreased basal and maximal daily heart rates in patients with hypothyroidism despite elevated plasma catecholamines. This is in correlation with our study which showed decreased heart rate in hypothyroid patients when compared to healthy controls.

Hypothyroidism can also affect structure of the heart. The predominant route by which triiodothyronine (T3) affects cardiac action is by exerting a direct effect in cardiac myocytes through binding to thyroid hormone nuclear receptor isoforms. Thyroid hormone influences the sinus node of the left atrium. Some of these ion channels, such as the IF channel, the sodium/calcium exchanger protein, the L-type and T-type calcium channel, and the ryanodine channel are targets for thyroid hormone action.

Conflicting results about HRV have been reported by Inukai et al, in marked hypothyroidism, where hypo functional abnormalities in the parasympathetic nervous system were found in association with a reduction in the levels of serum T₄ and T₂, as indicated by significant reductions in R-R interval variations. These conflicting results may be partially explained by the different selection of patients (number, age, gender, type, severity, and duration of hypothyroidism) in the study.

As shown by many studies, a significant association is present between the QTc interval, QTc dispersion, HRV and thyroid disorders. The cardiac effects of hypothyroidism depend on the severity and duration of the disease. The occurrence of malignant arrhythmias is higher in long standing and severe hypothyroidism and in myxoedema coma. The evaluation of markers of arrhythmic risk, such as QTc dispersion (which can be easily measured), can be helpful in evaluating the cardiac risk in these patients.

The correlation of serum TSH with QT dispersion, as shown by a study performed by Alton et al, confirms that the severity of hypothyroidism plays an important role in determining the arrhythmic risk. The increase in QT dispersion is closely associated life-threatening ventricular arrhythmias and has been shown to be an independent risk factor for sudden cardiac death. However, the factors which may act on QT dispersion such as age, gender, myocardial ischemia, cardiac failure,
diabetes, hypertension and electrolyte imbalance and some drugs, and the circadian pattern of QT dispersion, might make its clinical use challenging.

CONCLUSION

Patients with newly detected clinical hypothyroidism have a sympathovagal imbalance and increased inhomogeneity of ventricular repolarization, both of which predispose to potentially life threatening arrhythmias. QTc and QT dispersion can be used as simple, inexpensive indicators of myocyte functionality and cardiac autonomic modulation in patients with hypothyroidism and hence, may represent a useful tool in monitoring the cardiovascular risks in these patients.

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