



# Autonomic Reactivity With Altered Thyroid Status

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## Abstract

The study was carried out to test the effect of altered thyroid status on the autonomic reactivity in 60 subjects (age group 20-50 years). The parameters recorded and the tests used were pulse rate, blood pressure, orthostasis, cold pressor test, mental arithmetic and QTc interval for assessment of sympathetic activity and valsalva ratio, heart rate response, expiratory-inspiratory ratio (E.I. ratio), heart rate variability, standing-lying ratio (S.L. ratio) and 30:15 ratio for assessment of parasympathetic activity. Our findings show that the changes in thyroid hormone levels - in both hypothyroids and hyperthyroids are associated with altered sympathetic reactivity, with no significant difference in the parasympathetic activity - in either hypothyroids or hyperthyroids- as compared to euthyroid controls.

## Key Words

Autonomic Nervous System, Sympathetic reactivity, Parasympathetic reactivity, Hyperthyroidism, Hypothyroidism

## Introduction

Variations from euthyroid status affect virtually all physiological systems and effects on the cardio-vascular system are particularly pronounced. (1) Changes in thyroid status are associated with changes not only in cardiac and vascular function but are also believed to alter autonomic regulation of cardiovascular system. The clinical picture of hyperthyroidism is suggestive of increased sympathetic activity (2,3) but assessments of sympathetic activity suggest that sympathetic outflow is either unchanged or reduced (4-7). In contrast, whereas several clinical features of hypothyroidism are consistent with reduced sympathetic activity, indirect techniques suggest that sympathetic activity is elevated (8-10). Interestingly, in both hypothyroidism and hyperthyroidism- the influence of the parasympathetic nervous system on heart rate seems to be reduced. (11-14).

In view of the contradictions, the present study was undertaken to assess the autonomic reactivity, both sympathetic and parasympathetic- with alteration of the thyroid status of a subject.

## Material and Methods

The study was conducted on sixty subjects of both sexes with age ranging from 20 to 50 years. These sixty subjects were selected on basis of their thyroid hormone profile after exclusion of other diseases which could alter autonomic reactivity like diabetes, renal diseases, psychiatric disorders or cardio vascular disorders. None of the subjects were on any form of medication and they were divided into three groups-

(1) Twenty subjects were euthyroid- with normal thyroid hormone profile- (Values in Table-I)

(Electro chemiluminescence immunoassay (ECLIA) was used in all subjects to determine the  $T_3$ ,  $T_4$  and TSH levels.

(2) Twenty subjects were hypothyroid- just diagnosed with low thyroid hormone level and had not yet been put on any form of medication. The hormonal levels of these subjects are shown in Table-I.

(3) Twenty subjects were hyperthyroid, recently diagnosed with high thyroid hormone levels and not on any medication. Table 1 shows the  $T_3$ ,  $T_4$  & TSH levels of these subjects.

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**Table-I: Thyroid Hormone Profile (Range)**

Parameter	IN EUTHYROIDS	IN HYPOTHYROIDS	IN HYPERTHYROIDS
T <sub>3</sub> (ng/ml)	0.8-2	0.43 - 0.7	2.8-11.76
T <sub>4</sub> (µg/dl)	4-13	0.71 - 4	16.80-57.50
TSH (µIU/ml)	0.27-4.2	7.74 - 100	0.01-<0.002

Pulse and Blood pressure were recorded by palpatory and auscultatory method respectively.

E.C.G was recorded by a simple compact electro cardiograph (BPL- cardiart) unit. All the E.C.G recordings were carried out with lead II.

For assessing sympathetic system activity the parameters recorded and tests used were:-

1. Basal pulse rate by palpatory method;
2. Blood Pressure- by auscultatory method;
3. Orthostasis- change in B.P being determined as the difference between the reading while supine and standing. (15)
4. Cold- pressor test- the maximal B.P reading obtained with a hand in 4°C water being taken as the index of response. Blood Pressure is recorded at the end of thirty seconds of immersion and at the end of sixty seconds thereafter in the opposite arm. (16)
5. Mental arithmetic- with blood pressure being recorded after the subject is made to solve some mathematical problem.(17)
6. Corrected QT interval (QTc)- QT interval was measured from the ECG and then standardized by converting it to QTc. For this Bazetts formula was used. (18)

$$QTc = \frac{QT \text{ interval}}{\sqrt{R-R \text{ interval}}}$$

QT Interval and R-R interval and QTc were expressed in seconds.

For assessing parasympathetic activity parameters used were-

1. Pulse rate- It can be used for assessing both para sympathetic and sympathetic reactivity because of dual innervation of heart.
2. Valsalva ratio- calculated as ratio between maximal R-R interval after release of strain and maximal R-R interval during the strain. (19)

3. Heart rate response- the response being taken as the difference in heart rate in supine and erect positions. (20)

4. Expiratory- Inspiratory ratio- taken as the ratio of longest R-R interval during expiration to shortest R-R interval during inspiration. (21,22)

5. Heart rate variability- is the maximum and minimum heart rate during quiet breathing.

6. Standing-Lying ratio- being the ratio of longest R-R interval during five beats before lying down to shortest interval during ten beats after lying down. (23)

7. 30:15 ratio- being ratio of R-R interval at beat 30 to R-R interval at beat 15 after standing up from supine position.

Statistical analysis was carried out using paired student 't' test where the mean values of all parameters tested were compared between Euthyroid and Hypothyroid group, between Euthyroid and Hyperthyroid group and between Hypothyroid and Hyperthyroid group.

#### Results

##### 1. Comparison of Euthyroids with Hypothyroids (Table-II)

(a) Of the parameters reflecting sympathetic activity, only systolic and diastolic pressure were significantly different in the two groups, (P< 0.01). (b) Of the parameters reflecting parasympathetic activity, there was no difference in the autonomic reactivity in the two groups.

##### 2. Comparison of Euthyroids with Hyperthyroids (Table-III)

(a) Of the parameters reflecting sympathetic activity- pulse rate, systolic B.P and cold pressor test showed significant results with sympathetic reactivity being more in hyperthyroids. (b) Of the parameters reflecting parasympathetic activity, there was again no difference in the autonomic reactivity in the two groups.

##### 3. Comparison of hypothyroids with hyperthyroids (Table-IV)

(a) Of the parameters reflecting sympathetic activity, the difference in pulse rate, and systolic B.P on application of mental arithmetic test was significant in the two groups, with sympathetic reactivity being more in hyperthyroid subjects. (b) Of the parameters reflecting parasympathetic activity, there was no significant difference in the two groups.

**Table-II Euthyroid Vs Hypothyroid**

Parameter	Euthyroid Mean $\pm$ S.P	Hypothyroid Mean $\pm$ S.P	"t" value	"p" value	
Pulse	81.8 $\pm$ 6.87	81.35 $\pm$ 8.93	0.17	>0.10	
B.P	Sys	119.1 $\pm$ 12.55	134.7 $\pm$ 24.26	2.55	(s) < 0.01
	Dias	76.6 $\pm$ 7.5	83.8 $\pm$ 9.62	2.64	(c) < 0.01
Ortho stasis	Syst	2.2 $\pm$ 4.58	2.0 $\pm$ 5.46	0.12	>0.10
	Dias	0.8 $\pm$ 3.86	1.3 $\pm$ 3.38	0.43	>0.10
CPT	Syst	8.7 $\pm$ 9.4	5.9 $\pm$ 7.55	1.04	>0.10
	Dias	2.3 $\pm$ 4.11	6.1 $\pm$ 6.34	2.26	>0.01
MA	Syst	8.4 $\pm$ 9.6	3.8 $\pm$ 6.64	1.76	>0.01
	Dias	2.8 $\pm$ 3.9	3.8 $\pm$ 5.72	0.64	>0.10
QTc	0.421 $\pm$ 0.026	0.412 $\pm$ 0.024	1.13	>0.05	
Valsalva ratio	1.18 $\pm$ 0.147	1.22 $\pm$ 0.20	0.74	>0.10	
Heart rate response	15.45 $\pm$ 9.79	13 $\pm$ 8.479	0.84	>0.10	
Expi-Inspi ratio	1.13 $\pm$ 0.07	1.175 $\pm$ 0.08	1.93	>0.01	
Heart rate variability	11.10 $\pm$ 5.31	14.7 $\pm$ 5.32	2.14	>0.05	
Sitting lying ratio	1.03 $\pm$ 0.10	0.99 $\pm$ 0.10	1.34	>0.05	
30:15 ratio	1.003 $\pm$ 0.037	1.006 $\pm$ 0.056	0.2	>0.10	

**Table III Euthyroid Vs Hyperthyroid**

Parameter	Euthyroid	Hypothyroid	"t" value	"p" value	
Pulse	81.8 $\pm$ 6.87	94.1 $\pm$ 15.59	3.2	(s) < 0.05	
B.P	Sys	119.1 $\pm$ 12.55	127.5 $\pm$ 13.62	2.75	(s) < 0.05
	Dias	76.6 $\pm$ 7.5	79.1 $\pm$ 9.3	0.936	>0.01
Ortho stasis	Syst	2.2 $\pm$ 4.58	0.6 $\pm$ 4.68	1.09	>0.10
	Dias	0.8 $\pm$ 3.86	1.5 $\pm$ 5.38	0.47	>0.10
CPT	Syst	8.7 $\pm$ 9.4	9.9 $\pm$ 8.06	0.43	>0.10
	Dias	2.3 $\pm$ 4.11	7.9 $\pm$ 5.25	3.75	(s) < 0.005
MA	Syst	8.4 $\pm$ 9.6	9.6 $\pm$ 7.12	0.45	>0.01
	Dias	2.8 $\pm$ 3.9	6.0 $\pm$ 5.72	2.19	>0.05
QTc	0.421 $\pm$ 0.026	0.406 $\pm$ 0.036	1.15	>0.10	
Valsalva ratio	1.22 $\pm$ 0.20	1.175 $\pm$ 0.196	0.73	>0.10	
Heart rate response	13 $\pm$ 8.47	13.15 $\pm$ 7.76	0.058	>0.10	
Expi-Inspi ratio	1.175 $\pm$ 0.08	1.15 $\pm$ 0.09	0.91	>0.01	
Heart rate variability	14.7 $\pm$ 5.32	13.2 $\pm$ 0.25	0.81	>0.10	
Sitting lying ratio	0.99 $\pm$ 0.10	1.05 $\pm$ 0.102	1.94	>0.05	
30:15 ratio	1.006 $\pm$ 0.056	1.018 $\pm$ 0.046	0.75	>0.10	

**Table IV Hypothyroid Vs Hyperthyroid**

Parameter	Euthyroid	Hypothyroid	"t" value	"p" value	
Pulse	81.35 $\pm$ 8.93	94.1 $\pm$ 15.59	3.17	(s) < 0.005	
B.P	Sys	134.7 $\pm$ 24.76	127.5 $\pm$ 13.6	1.15	< 0.05
	Dias	83.8 $\pm$ 9.62	79.1 $\pm$ 9.3	1.57	>0.05
Ortho stasis	Syst	2.0 $\pm$ 5.46	0.6 $\pm$ 4.68	0.87	>0.10
	Dias	1.3 $\pm$ 3.38	1.5 $\pm$ 5.38	0.13	>0.10
CPT	Syst	5.9 $\pm$ 7.55	9.9 $\pm$ 8.06	1.61	>0.05
	Dias	6.1 $\pm$ 0.34	7.9 $\pm$ 5.25	0.97	(s) < 0.10
MA	Syst	3.8 $\pm$ 6.64	9.6 $\pm$ 7.12	2.67	(s) < 0.01
	Dias	3.8 $\pm$ 5.72	6.0 $\pm$ 5.27	1.26	>0.05
QTc	0.412 $\pm$ 0.024	0.406 $\pm$ 0.036	0.625	>0.101	
Valsalva ratio	1.18 $\pm$ 0.147	1.175 $\pm$ 0.196	0.09	>0.10	
Heart rate response	15.45 $\pm$ 9.79	13.15 $\pm$ 7.76	0.84	>0.101	
Expi-Inspi ratio	1.13 $\pm$ 0.07	1.15 $\pm$ 0.09	0.80	>0.101	
Heart rate variability	11.10 $\pm$ 5.31	13.2 $\pm$ 6.25	1.14	>0.10	
Sitting lying ratio	1.03 $\pm$ 0.10	1.05 $\pm$ 0.102	0.626	>0.10	
30:15 ratio	1.003 $\pm$ 0.037	1.018 $\pm$ 0.046	1.15	>0.10	

## Discussion

The autonomic system is the part of nervous system mainly responsible for involuntary unconscious functions- within the body's organs. The autonomic

system has sympathetic and parasympathetic portions that maintain body homeostasis.

Dysautonomia is a condition in which abnormal autonomic function negatively affects a patient's health. Amongst dysautonomias featuring altered sympathetic noradrenergic function are hyperthyroidism (noradrenergic inhibition) and hypothyroidism (noradrenergic activation). (24) The thyroid hormones exert effects on the heart and peripheral circulation, playing an important role in the regulation of the function of sino-atrial node, the systolic and diastolic function of the myocardium and the peripheral resistance. They act directly by influence on protein-synthesis, the properties of cell membranes and indirectly by interactions with autonomic nervous system, causing increase in cardiac output and decrease in systemic vascular resistance. (25)

The present study tested the hypothesis that the sympathetic noradrenergic function is altered with change in thyroid status of the subject.

Our results show an increased sympathetic reactivity with some of the recorded parameters in hyperthyroids as compared to normal euthyroid controls and significant alteration in blood pressure of hypothyroids as compared to normal euthyroid controls. Hyperthyroid subjects showed greater sympathetic activity as compared to hypothyroid subjects. The parasympathetic reactivity showed no change with change in thyroid status.

Foley *et al* (1) studied the effect of thyroid status on arterial baroreflex function and autonomic contributions to arterial pressure and heart rate in conscious rats. Their results showed that thyroid status alters the balance of sympathetic to parasympathetic tone in the heart. Hypothyroidism in rats blunts the arterial baroreflex and alters the relative contribution of systems that maintain resting blood pressure and heart rate with a predominant sympathetic influence at rest which compensated for the lower intrinsic heart rate of hypothyroid rats, and the blunted arterial baroreflex would reduce the capacity to maintain blood pressure in situations that require reflex activation of the sympathetic system like stress or exercise. In the hyperthyroid rats, they observed similar autonomic contributions to resting mean arterial pressure heart rate as the euthyroid rats and the arterial baroreflex



function was not altered. In our study we also observed a significant increase in B.P in hypothyroids as compared to euthyroids and this can be explained by the predominant sympathetic influence.

Inukai *et.al* (26) studied the relationship between hypothyroidism and parasympathetic nervous system and observed that in marked hypothyroidism there are hypofunctional abnormalities in the parasympathetic system in association with a reduction in the levels of serum  $T_4$  and  $T_3$ . In our study the parasympathetic activity was not altered with alteration in thyroid status.

Barczynski and Thor (27) showed that ANS dysfunction in hyperthyroidism is expressed in gastric myoelectrical activity disturbances and gastric emptying disorders and in addition they tried to search for a correlation between the severity of clinical manifestation and free thyroid hormone levels and the degree of ANS dysfunction. They concluded that ANS dysfunction in hyperthyroidism results not only in withdrawal of vagal inhibitory effect on S-A node-but also in impaired mutual neurohormonal regulation (decrease of vagal influence) of gastric myoelectrical activity followed by delay of gastric emptying. In our study gastric activity was not studied-but the significantly higher pulse rate in hyperthyroids can be attributed to withdrawal of vagal inhibition.

Gautam *et.al* (28) also studied autonomic indices in relation to thyroid status. They observed that, the mean values were not significantly different in hypothyroid and hyperthyroid patients- but the correlation between autonomic function and thyroid hormone levels indicated a statistically significant difference with S/L ratio- indicating a decreased parasympathetic activity with increased  $T_3$  and  $T_4$ . They found sympathetic activity to be unaffected. This is at variance with our results but the authors have had a significant result with only one parameter of parasympathetic activity and have determined only galvanic skin resistance to find out the sympathetic reactivity. Sahin *et.al* (29) have evaluated autonomic activity in patients of subclinical hypothyroidism using the heart rate variability method and they observed that subclinical hypothyroidism can affect cardiac autonomic activity in correlation with TSH levels. In our study the subjects were clinically diagnosed

cases of hypothyroidism in whom subsequently  $T_3$ ,  $T_4$  and TSH levels were determined and the increased BP is attributed to increased sympathetic tone.

McAllister *et. al* (30) studied effect of exercise on hypothyroid and hyperthyroid subjects and observed that both hypothyroidism and hyperthyroidism are associated with exercise intolerance. It has been suggested that alteration in baroreflex function may account for majority of exercise intolerance in hypothyroidism and in hyperthyroidism- altered energy metabolism within the exercising muscle accounts for the majority of reduced exercise tolerance. The sympathetic response to dynamic exercise is appropriate or potentially enhanced in hyperthyroidism.

In our study the hypothyroids did not show a significant alteration in baroreflex function with stress. Whereas the hyperthyroids showed a significant change in diastolic BP when subjected to cold pressor test. The change in resting levels of sympathetic outflow can be due to direct effect of thyroid hormone in central regions involved in autonomic regulation or changes in cardiovascular reflex systems that control the ANS.

The arterial baroreflex buffers changes in arterial pressure on a beat to beat basis. Changes in arterial baroreflex function during either hypothyroidism or hyperthyroidism could potentially account for some of the change in autonomic out flow at rest and for altered regulation of autonomic function in response to various stresses.

Further studies that evaluate baroreflex function during exercise in hyperthyroids and hypothyroids are necessary to test these ideas directly.

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