

Alteration in autonomic reactivity from hypothyroid to euthyroid status

Anjali Nadir Bhat^{1,*}, Sabita Yograj², Rakesh Bahl³¹Professor, Dept. of Physiology, ³Associate Professor, Dept. of Community Medicine, GMC, Jammu, ²Associate Professor, Dept. of Physiology, ASCOMS, Jammu***Corresponding Author:****Anjali Nadir Bhat**

Professor, Dept. of Physiology, GMC, Jammu

Email: anjalinadirbhat@hotmail.com

Abstract

This study was carried out on 25 hypothyroid patients attending the OPD of Govt. Medical College Jammu before their treatment started and after treatment when they attained euthyroid status. The parameters recorded and the tests used were pulse rate, blood pressure, orthostasis, cold pressor test, mental arithmetic and corrected QT interval [QTc] for assessment of sympathetic reactivity 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 reactivity. Our findings show significant improvement in parasympathetic reactivity after a hypothyroid subject became euthyroid with L₄ thyroxine treatment. For sympathetic reactivity only some parameters recorded significant improvement.

Keywords: Autonomic nervous system, Sympathetic reactivity, Parasympathetic reactivity, Hypothyroidism.

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-2126.2016.00086.4

Introduction

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 parts that maintain body homeostasis.

Dysautonomia is when abnormal autonomic function negatively affects a person's health. Among dysautonomias featuring altered sympathetic noradrenergic function are hyperthyroidism [noradrenergic inhibition] and hypothyroidism [noradrenergic activation].^[1]

Clinical characteristics of hypothyroidism are essentially diametrically opposed to those associated with hyperthyroidism.

The clinical picture of hyperthyroidism is suggestive of increased sympathetic activity^[2,3], but assessments of sympathetic activity suggests that sympathetic outflow is either unchanged or reduced.^[4,5,6,7]

In contrast — whereas several clinical features of hypothyroidism are consistent with reduced sympathetic activity — indirect techniques suggest that sympathetic activity is elevated.^[8,9]

But in both hypothyroidism and hyperthyroidism — the influence of parasympathetic nervous system on heart arte seems to be reduced.^[10,11,12]

The mechanism for the change in resting levels of sympathetic and parasympathetic outflow are unknown. Could be due to a variety of mechanisms— including direct effects [excess or depletion] of thyroid hormone in central regions involved in autonomic regulation or changes in cardiovascular reflex systems that control the autonomic nervous system.

Thyroid hormone replacement therapy is generally effective and beneficial in relieving symptoms and signs. This evidence supports the hypothesis that thyroid hormone deficiency causes decreased sympatho-adrenergic activity.

Data about the recovery of autonomic reactivity following treatment of hypothyroids with hormone replacement is scarce.

This study was undertaken to evaluate autonomic reactivity in hypothyroids after they attained a euthyroid state following thyroid hormone replacement and compare this with their autonomic status before replacement therapy began.

Material and Methods

This study was carried out on patients attending endocrinology OPD of Government Medical College Jammu.

Twenty five patients who had just been diagnosed as hypothyroids were selected and their autonomic reactivity assessed before they began replacement therapy.

These patients were selected on the basis of clinical features suggestive of decreased thyroid function and

laboratory findings of decreased T₃ and T₄ and TSH more than 5 mIU/L.

Patients with diseases known to affect autonomic function — like diabetes mellitus, renal diseases, psychiatric disorders or cardio-vascular disorders — were excluded from the study.

None of the patients was on any medication.

The procedure was explained to the patients in their own language and their consent obtained. Then autonomic function tests were carried out on these patients.

Subsequently thyroxine was prescribed to these patients by the treating clinician and they were told to get T₃, T₄ and TSH estimation done every fortnight and come to the OPD again with the test reports so that the dose of thyroxine required for replacement could be titrated.

When these patients attained a euthyroid state - autonomic function tests were again carried out on them.

Autonomic function testing

Standardized procedure was adopted for autonomic testing.

ECG was recorded by a simple compact electrocardiograph [BPL-cardiart] unit. All the ECG recordings were carried out with Lead-II.

The battery of tests done were:

For assessing Sympathetic reactivity:

1. Basal pulse rate by the 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.⁽¹³⁾
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.⁽¹⁴⁾
5. Mental arithmetic - Blood pressure is recorded after the subject is made to solve some mathematical problem.⁽¹⁵⁾
6. Corrected QT interval [QTc] - QT interval was measured from the ECG and then standardized by converting it to QTc. For this Bazett's formula was used.⁽¹⁶⁾

$$QTc \text{ (seconds)} = \frac{QT \text{ interval (in seconds)}}{R-R \text{ interval (in seconds)}}$$

For assessing parasympathetic reactivity parameters used were:

1. Pulse rate - It can be used for assessing both parasympathetic and sympathetic reactivity because of the 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.⁽¹⁷⁾
3. Heart rate response - The response being taken as the difference in heart rate in supine and erect positions.⁽¹⁸⁾
4. Expiratory-Inspiratory ratio - Taken as the ratio of longest R-R interval during expiration to shortest R-R interval during inspiration.^(19,20)
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.⁽²¹⁾
7. 30:15 ratio - Being the ratio of R-R interval at beat 30 to R-R interval at beat 15 after standing up from supine position.

Statistical analysis

Statistical analysis was carried out using student "t" test - where the mean values of all parameters tested were compared between the hypothyroid subjects before treatment and after they attained euthyroid state following replacement therapy.

Results

Table 1 shows values of parameters reflecting sympathetic activity in hypothyroid patients before and after L-thyroxine therapy.

Of these parameters significant difference was observed in the subjects in their blood pressure - both systolic and diastolic - in their hypothyroid state and after they became euthyroid with replacement therapy.

Similar significant difference in the pre-medication phase and post-medication phase was also observed in the subjects when blood pressure was recorded on change in posture.

This shows an improvement in autonomic reactivity and better cardiovascular compliance in these subjects after they became euthyroid with treatment.

And in our study other parameters reflecting sympathetic reactivity- i.e. pulse rate, the change in both systolic and diastolic blood pressures during cold pressor test and mental arithmetic, as well as QTc did show difference in the hypothyroid phase and euthyroid phase - but it was not statistically significant.

Table 1: Comparison of sympathetic reactivity

Parameters		Pre-medication	Post-medication	t-value	p-value
Pulse		76.35±8.93	81.35±11.92	-1.678	> 0.05
Blood Pressure	Systolic	136.7±24.26	117.8±27.40	2.58221	< 0.05 [S]
	Diastolic	90.8±9.62	84.3±10.99	2.22517	< 0.05 [S]
Orthostasis	Systolic	10.0±5.46	2.4±7.02	4.27285	< 0.05 [S]
	Diastolic	7.3±3.38	1.0±0.10	8.11586	< 0.05 [S]
Cold pressor test	Systolic	9.9±7.55	5.5±8.96	1.877	> 0.05
	Diastolic	8.1±6.34	5±8.06	1.5115	> 0.05
Mental arithmetic	Systolic	6.8±6.64	3.2±8.35	1.68725	> 0.05
	Diastolic	4.6±5.72	2±6.89	1.45172	> 0.05
QTc		0.412±0.024	0.372±0.029	1.45172	> 0.05

Table 2 shows values of parameters reflecting parasympathetic activity in subjects before and after treatment.

Most of these parameters recorded an improvement in parasympathetic reactivity in the subjects after they received L-thyroxine and attained a euthyroid status.

Table 2: Comparison of parasympathetic reactivity

Parameters	Pre-medication	Post-medication	t-value	p-value
Valsalva ratio	1.48±0.147	1.739±0.18	-5.5723	< 0.05 [S]
Heart rate response	15.45±9.79	9.75±6.97	2.3715	< 0.05 [S]
Expiratory inspiratory ratio	1.13±0.07	1.283±0.108	-4.1957	< 0.05 [S]
Heart rate variability	11.10±5.31	17.25±6.36	-3.7114	< 0.05 [S]
Sitting lying ratio	1.03±0.10	0.886±0.10	5.0911	< 0.05 [S]
30:15 Ratio	1.003±0.37	1.126±0.06	-1.6407	> 0.05

Table 3 shows serum free T₃ and T₄ levels and TSH values of patients in their hypothyroid state and when they became euthyroid after treatment.

Table 3: Thyroid hormone profile

Parameter	Pre-medication	Post-medication	t-value	p-value
fT ₃	1.32±0.46	3.04±1.02	-7.6859	< 0.001 [HS]
fT ₄	1.62±1.09	4.20±3.26	-3.7528	< 0.001 [HS]
TSH	32.40±26.32	2.04±1.59	5.7569	< 0.001 [HS]

Serum levels of fT₃ and fT₄ of the subjects were increased in their euthyroid state as compared to their hypothyroid state; whereas the TSH levels of subjects decreased when after treatment they achieved euthyroid state. The difference before and after treatment in these parameters was statistically highly significant.

Discussion

Variations from euthyroid status affect virtually all physiological systems and effects on cardiovascular system are particularly pronounced. Changes in thyroid status are associated with changes not only in cardiac and vascular function - but also in autonomic regulation of cardiovascular system.

Thyroid hormones have prominent effects on the heart and peripheral vascular system by direct action on these tissues and by indirect influences - at least in part

due to changes at the autonomic nervous system level.^(22,23)

The mechanisms suggested for autonomic disturbances in thyroid disorders include a high level of plasma adrenaline with a post-receptor sensitization^(2,9), a decreased chronotropic response to β -adrenergic stimulation or adrenergic sensitivity⁽²⁴⁾, increase in thyrotropin releasing hormone which directly influences the sympathetic outflow and direct effect of thyroid hormone on heart⁽²³⁾.

In the present study - we found that there was significant increase in parasympathetic reactivity on achieving euthyroid state. The sympathetic reactivity also improved after L-thyroxine supplementation. These findings are consistent with the findings of Inukai et al.⁽¹¹⁾ and Kahaly⁽²⁵⁾ as well as with the findings of Lakshmi et al.⁽²⁶⁾

Thyroxine therapy appears to restore vagal activity and alters the relative contribution of systems that maintain resting B.P and heart rate [cardiovascular function].

Foley et al.⁽²⁷⁾ in their study observed that hypothyroid rats have depressed arterial baroreflex function and elevated dependence on resting sympathetic tone to both the heart and vasculature.

Mahajan et al. in their study reported autonomic dysfunction in both subclinical hypothyroids and hypothyroid patients. Sympathetic function abnormality was more prominent and there was also selective parasympathetic dysfunction.⁽²⁸⁾

Some studies have reported a hypofunctional parasympathetic system based on analysis of heart rate recovery and R-R variations in ECG.^(25,29)

Inukai et al. referred to a group of patients as masked hypothyroids [normal T₃, T₄ and high TSH] and found no change in parasympathetic function.⁽¹¹⁾

Galetta et al. found a decrease in sympathetic vagal balance characterized by decreased cardiovascular sympathetic and vagal modulation in hypothyroid patients.⁽³⁰⁾

However an increase in sympathetic and decrease in parasympathetic activity has also been suggested.⁽³¹⁾

Some authors have even reported that the decrease in parasympathetic activity normalizes following restoration to euthyroid state.^(25,26,32)

Cacciatore et al. found that thyroid deficiency is associated with increased sympathetic influence on heart-but said that hypothyroids and controls may not differ when evaluated by traditional autonomic function tests. They suggested that power spectral analysis was more sensitive.⁽¹⁰⁾

Reviewing many studies Heemstra et al. postulated that heterogeneity in the study population and cause and duration of disease may be responsible for the varied response observed in all these cases.⁽³³⁾

Our study is a small group study with 25 subjects only and we believe that a study on larger number of subjects may further clarify the contradictory trend observed by different studies.

Conclusion

On basis of the findings of our study - we suggest that replacement therapy with L-thyroxine in hypothyroids causes significant improvement of cardiovascular autonomic reactivity and maintains resting blood pressure and heart rate - thereby decreasing risk of cardiovascular disease.

References

1. Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer G. Dysautonomias: Clinical disorders of autonomic nervous system. *Ann Intern Med* 2002;137:754-760.
2. Bilezikian JP and Loeb JN. The influence of hyperthyroidism and hypothyroidism on α - and β -

- adrenergic receptor systems and adrenergic responsiveness. *Endocrine reviews*. 1983;4:378-385.
3. Levey GS and Klein I. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. *Am J Med* 1990;88:642-646.
4. Matsukawa T, Mano T, Gotoh E, Minamisawa K and Ishi M. Altered muscle sympathetic nerve activity in hyperthyroids and hypothyroids. *Journal of the Autonomic Nervous System*. 1993;42:171-175.
5. Fagius J, Westermark K and Karlsson A. Baroreflex governed sympathetic outflow to muscle vasculature is increased in hypothyroidism. *Clinical Endocrinology*. 1990;33:177-185.
6. Harrison TS, Siegel JH, Wilson WS and Weber WJ. Adrenergic reactivity in hyperthyroidism. *Arch Surg* 1967;94:396-402.
7. Landsberg, I. Catecholamines and hyperthyroidism. *Clin Endocrinol Metab*. 1977;6:697-718.
8. Christensen NJ. Plasma noradrenaline and adrenaline in patients with thyrotoxicosis and myxoedema. *Clinical Science* 1973;45:163-166.
9. Manhem P, Brammert M and Hallengren B. Increased arterial and venous plasma noradrenaline levels in patients with primary hypothyroidism during hypothyroid as compared with euthyroid state. *Journal of Endocrinol Investig* 1992;15:763-765.
10. Cacciatore V, Gemma ML, Bellavere F, Castello R, De Gregori ME, Zoppini G, et. al. Power spectral analysis of heart rate in hypothyroidism. *Eur J Endocrinol*. 2000;143:327-33.
11. Inukai T, Kobayashi I, Kobayashi T, Ishu A, Yamaguchi Y, et al. Parasympathetic nervous system in hypothyroidism determined by R-R interval variation on electrocardiogram. *J Intern Med* 1990;228:431-4.
12. Inukai T, Takanashi K, Kobayashi H, Fujiwara Y, Tayama K, Aso Y and Takemura Y. Power spectral analysis of variations in heart rate in patients with hyperthyroidism and hypothyroidism. *Horm Metab Res* 1998;30:531-535.
13. Heidebrede E, Schafferhans K, Heidland A. Autonomic neuropathy in chronic renal insufficiency. *Nephron*. 1995;41:50-56.
14. Mines E A, Brown G E. The cold pressor test for measuring the reactivity of blood pressure. *Ameri heart J*. 1936;11:1-9.
15. Ludbrook J, Vincent A, Walsh J A. Effect of mental arithmetic on arterial pressure and hand blood flow. *Clin Exp Pharmacol Physiol* 1975 [Suppl 2];67-70.
16. Schamroth I. An introduction of electrocardiography. 7th edition, revised by Schamroth C. Oxford University press. New Delhi. 1991 pp5-33.
17. Levin A B.A simple test of cardiac function based upon the heart rate changes induced by Valsalva manoeuvre. *Am J Cardiol*. 1996;18:90-99.
18. Ewing D J, Campbell J W, Murray A et al. Immediate heart rate response to standing. Simple test for autonomic neuropathy in diabetes. *Br Med JR*. 1978;1:145-47.
19. Hilstead J. Autonomic neuropathy, The diagnosis. *Acta Neural Scan*. 1983;67:193-201.
20. Mcleod J G, Tuck R R. Disorders of ANS, Part-2- Investigation and treatment. *Ann Neurol*. 1987;21:579-89.
21. Rodrigues E A and Ewing D J. Immediate heart rate response to lying down. Simple test for cardiac parasympathetic damage in diabetes. *Br Med J*. 1983;287:800-02.

22. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system: from theory to practice. *Journal of Clin. Endocrinol and Metabol.* 1994;78:1026-1027.
23. Polikar R, Burger AG, Scherrer U and Nico DP. The thyroid and the heart. *Circulation.* 1993;87:1435-1441.
24. Polikar R, Kennedy B, Maisei A, Ziegler M, Smith J, Dittrich H, et al. Decreased adrenergic sensitivity in patients with hypothyroidism. *J Am Coll Cardiol* 1990;15:94-8.
25. Kahaly GJ. Cardiovascular and atherogenic aspect of subclinical hypothyroidism. *Thyroid.* 2000;10:665-79.
26. Laxmi V, Vaney N, Madhu SV. Effect of thyroxine therapy on autonomic status in hypothyroid patients. *Indian J Physiol Pharmacol.* 2009;53:219-26.
27. Foley CM, McAllister RM, Hasser EM. Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate. *Am J Physiol Heart Circ Physiol.* 2001;280:H-2061-H2068.
28. Mahajan A S, Lal R, Dhanwal D K, Jain AK, Chowdhury V.
29. Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients. *Indian J Endocr Metab* 2013;17:460-4.
30. Akcakoyun M, Emiroglu Y, Pala S, Kargin R, Guler GB, Esen O. Heart rate recovery and chronotropic incompetence in patients of subclinical hypothyroidism. *Pacing Clin Electrophysiol.* 2010;33:2-5.
31. Galetta F, Franzoni F, Fallani P, Tocchini L, Braccini L, Santoro G. Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. *Eur. J. Endocrinol.* 2008;158:85-90.
32. Carvalho MJ, vander Meiracker AH, Boomsma F, Lima M, Freitas J, Veld AJ et al. Diurnal blood pressure variations in progressive autonomic failure [Scientific contribution]. *Hypertension* 2000;35:892-7.
33. Osman F, Gammage MD, Franklyn JA. Thyroid disease and its treatment. Short term and long term cardiovascular consequences. *Curr Opin Pharmacol* 2001;1:626-31.
34. Heemstra KA, Burggraaf J, vander Klaann AA, Romijn JA, Smit JW, Corssmit EP. Short term overt hypothyroidism induces sympathovagal imbalance in thyroidectomised differentiated thyroid carcinoma patients. *Clin. Endocrinol.* 2010;72:417-21.