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Original Article

Assessment of Heart Rate Recovery and Chronotropic incompetence in Subclinical Hypothyroid Adults

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Abstract

Overt hypothyroidism leads to altered cardiac functions due to hemodynamic and autonomic dysfunction, however, role of subclinical hypothyroidism (SCH) remains doubtful. A cross-sectional study was conducted on 30 adult subclinical hypothyroid subjects and equal number of euthyroid controls. Submaximal exercise was used for assessing the Heart Rate Recovery (HRR) in upright position at 1 min & 2 min and Chronotropic response (CR) was calculated. SCH subjects had decreased HRR2 (P=.012) and CR(P=.002) as compared to controls. Chronotropic incompetence (CI) was seen to be associated with SCH (P=.007). Stepwise regression analysis of Serum TSH with variables which are significantly different between cases & control, observed a negative relationship with peak heart rate (p=0.012). Slow HRR2 and decreased CR in SCH, indicates insidious subtle changes in cardiac responses in SCH before progression to overt hypothyroidism. HRR2 can be used as a preliminary test to make decisions regarding treatment at an early stage to prevent the further escalation of the derangement.

Introduction

Subclinical hypothyroidism (SCH) is usually an asymptomatic condition with a prevalence ranging from 9.4% to 21.5% across adult Indian population (1, 2) and is characterized by elevated level of serum thyrotropin (TSH) but normal free T3 and free T4 concentrations (3, 4).

Thyroid physiology plays an important role in regulating many organ systems of the body and metabolism (5). Parallel increase in levels of total lipids & cholesterol with increasing Serum TSH levels has been observed conferring to abnormal Lipid metabolism especially in SCH (6, 7). Changes in lipid profile leading to atherosclerosis along with alteration in cardiac functions due to hemodynamic & autonomic dysfunction (8) together has increased the risk of CAD and MI in SCH (9, 10). SCH persons more often presents with symptoms of fatigability, weakness and low exercise tolerance which is justified - among other factors - by the decrease in myocardial contractile force due to structural changes in the ATPase activity and down regulation of epinephrine activity. Impairment of cardiac autonomic activity in SCH is also evidenced by a hypo-functional parasympathetic system and an increase

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sympathetic tone as evaluated using heart rate variability (11, 12).

Exercise repeated at certain intervals causes pituitary thyroid reaction possibly elevating the requirement of thyroid hormone to fulfill exercise induced need of high oxidation fuel like fatty acids (13). With the cardiac tissue deriving most of the energy from fatty acids at rest exercise in hypothyroid cases may compromise the energy fuel and together with hypo-functional parasympathetic activity may cause intolerance to exercise. More over a recent study have observed a decrease in baseline heart rate with unchanged baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) in subclinical hypothyroid patients on levothyroxine treatment following sub minimal exercise indicating improvement in cardio pulmonary exercise performance (14).

Decrease in HR after exercise is considered to be due to decrease in sympathetic activity (15) & to reactivation of parasympathetic activity (16). Recently attenuated (HRR) has been demonstrated as a predictor of all – cause mortality (17, 18, 19). Asymptomatic SCH subjects may has a normal heart rate and cardiac structure & function at rest but exercise may bring out the subtle cardiovascular abnormality in them (11). Although impairment of cardiac autonomic activity in subclinical hypothyroidism has been studied (20) there is paucity of work onpost exercise HRR and chronotropic response (CR) in the SCH which is simple to administer and can help bring out latent abnormalities and may help identify apparently asymptomatic SCH cases who are at risk of developing coronary artery disease.

Materials & Methods

A cross sectional analytical study on adult SCH subjects was conducted in the department of physiology, Himalayan Institute of Medical Sciences (HIMS), SRH university, Dehradun after approval from the Institute ethical committee. Written informed consent was taken from the subjects for inclusion in the study.

Sample size and method

The study volunteers were selected by method of probability sampling. With the mean difference in HRR in 1 min of 8 (21) and pooled SD as 8.5 formula for difference in mean of two equal groups = $(r+1)(Z\alpha/2 + Z1-\beta)^2 / r(\Delta mean)^2$ a sample of 24 was calculated for each group which was increased to 30 in each group. An equal number of euthyroid control group with comparable age were also recruited (n=30).

Selection of subjects

Clinically healthy adults with history of weakness and lethargy reporting at medical OPD were followed for their thyroid status and 30 clinically healthy adults diagnosed with subclinical hypothyroidism in the age group of 20-40 years of both the sexes were recruited. The clinical diagnosis of SCH was established by a normal values of Serum FT3 and FT4 and a Serum TSH value of >5 micro IU/ml to 15 micro IU/ml (22). As per the hospital laboratory reference range the normal range of values of Serum FT3 and FT4 were 2-4.2 pg/ml & 0.6–1.7 ng/dl respectively. Equal number of clinically healthy euthyroid adults (normal FT3 & FT4 and TSH 0.34-5 micro IU/ml) were recruited from attendants of patients and residents in and around SRHU campus.

Common exclusion criteria were used to recruit the participants in both euthyroid and SCN group. The exclusion criteria assessed by detailed history, systemic examination & eye examination included, diabetes mellitus, hypertension, bipolar disorder, obesity (BMI >/=30 Kg/m2), recent delivery (</=9 months) tuberculosis, anemia, multiple endocrine syndromes, neuromuscular disorder, severe myopia, cataract, glaucoma and maculopathy, CNS dysfunction, smokers, alcoholics and those taking drugs affecting the thyroid status (Litium, NSAIDs) and acting on CNS. Basic investigations of fasting blood sugar, hemoglobin estimation, ECG and X ray chest were done along with other investigation as per specific exclusion criteria.

Study tools

Structured case reporting forms was used to generate

demographic, relevant history and anthropometric data. Treadmill (Company: JKEXERSno. A0047762) was used for submaximal exercise for assessing the Heart Rate Recovery after exercise. Bio Impedance Machine (Omeron KARADA SCAN Model HBF-375) was used to measure percentage of body fat and visceral fat. Fixed metered scale and weighing machine (Company: Krups) were used to measure height and weight. Non-invasive techniques were used to minimize the discomfort to the recruited subjects

Study protocol

Following written informed consent volunteers were asked to report to the Physiology department in morning hours on all working days. A standard case reporting form was administered by the investigator at the point of entry to collect information on demographic, anthropometric characteristics, personal medical history of past and present illness, and family history with detailed history of chronic medication, addiction and smoking. Volunteers were familiarized with the procedures to follow.

a) Demographic characteristics like age, gender and occupation were recorded. They were measure for standing height nearest to 1 cm, weight nearest to 100 grams using standard protocol and for body fat (% Body fat, Visceral fat) using the bio impedance method Blood was drawn to assess the serum levels of TSH, free T3 and T4. They were then subjected to sub-maximal exercise design using Ellestad Protocol using age predicted heart rate and Borg's scale for perceived excretion to assess heart rate recovery at 1 min & 2 min and chronotropic incompetence following exercise.

b) Experimental procedure: All subjects underwent "symptom-limited" treadmill exercise testing using the Ellestad protocol (23) for sub-maximal exercise designed to bring the subject up to a plateau at approximately 60-85% of age predicted Maximum HR. Age predicted maximum HR was calculated as 220—age. Prior to testing; all subjects were instructed not to eat, drink any beverages, or smoke for 3 hours before the test. After subjects were cleared for testing, they were fitted with a heart rate monitor and instructed to lie supine in a resting position for 5 minutes. At the end of this period, the subject's resting heart rate and blood pressure was recorded. Heart rate was recorded at the end of each stage. The subject was given a 5 minute warm-up on the treadmill at 4 miles per hour, as well as light stretching prior to beginning of sub maximal exercise. All subjects held on to the front rail of during the treadmill test and the polar ElctroInc HR monitor was tied around the chest. Subjects commenced walking at their comfortable pace on the treadmill and with a speed of 1.7 mph for 3 minute. Then the speed was increased to 3 mph for next 2 minutes and subsequently by 1 mph every 2 minutes for next 10 minutes until the criteria for test termination are achieved [60-85% age predicted maximum HR] but were instructed to stop exercise if they experienced any symptoms related to angina, light headedness, confusion, fatigue or subject had grade III level of exertion on Borg scale of exertion. When 60-85% of age predicted maximum HR was achieved on HR monitor the speed was held constant for 2 minutes and after recording of peak HR achieved during the exercises the procedure was stopped. Subject was made to immediately sitting on a chair and arm with arm rest. HR recovery was monitored following stoppage of the treadmill after 1 min and after 2 min into recovery. Chronotropic response was assessed by (peak HR–resting HR) / ((220–age)–resting HR); and a value of $\geq$0.80 was considered as Chronotrophic incompetence (CI) (24). HRR was defined as the difference between peak HR at sub-maximal exercise and 1 minute and 2 min into recovery in an upright position (25).

Data management & Statistical analysis

SPSS (Statistical Package for the Social Sciences, 17.0 version) was used to analyze the collected data. Mean and SD were used to represent the demographic, anthropometric and other measured variables in the two groups. χ^2 analysis was used to assess the differences between dichotomous variables. Differences in means of quantitative variables (eg HRR1, HRR2, CR, Relative decrease in

HR) in the groups were tested using unpaired "t" test. Correlation of the S.TSH with the measured variables for continuous variable eq BF%, HRR1, HRR2, CR, and relative decrease in HR was assessed by Pearson correlation. Level of significance was set at p<0.05.

Results

The study analyzed 30 cases of adults (20-40) clinically diagnosed subclinical hypothyroidism for cardio vascular variables, HRR and chronotropic response. An equal number of controls were taken for comparison.

The number and proportion of females were considerably more than males in SCH cases i.e., 26 (86.6%). As expected the difference of serum TSH levels among SCH cases and euthyroid controls in this study was statically significant (p=<0.001). No significant difference of FT3 levels and FT4 levels was observed between SCH case and control (Table I).

No significant difference was found in all the three parameters including PR, SBP and DBP of euthyroid control & SCH case (Table II).

A lower peak HR during exercise was observed in SCH cases and was statistically different from that achieved by euthyroid controls (P<0.001). HRR was less in SCH cases than in euthyroid controls but the difference was significant only at 2 second into recovery post exercise (p=0.002). Chronotropic response was also significantly lower in SCH than euthyroid controls following moderate exercise. Chi square test for association of CI (<0.08) with SCH established a significant positive association (p=0.005) (Table III & Fig. 1).

Serum TSH showed a negative relation to both Heart

TABLE I: Comparison of Anthropometric and Biochemical parameters among Euthyroid Controls and SCH Cases.

S. No.	*Parameter*	*Control (n=30)*	*Case (n=30)*	*P-value*
1	Age (years)	33.1±7.5	35.5±5.9	0.170
2	Height (cm)	159.3±9.7	155.9±6.9	0.116
3	Weight (kg)	65.8±12.9	64.1±9.8	0.568
4	BMI (kg/m²)	25.7±3.5	26.4±3.0	0.464
5	Body Fat (%)	28.6±7.5	32.4±4.1	0.015*
6	Visceral Fat (%)	9.3±3.6	10.5±5.0	0.257
7	Serum FT3 (pg/ml)	3.0±0.7	2.7±0.7	0.120
8	Serum FT4 (ng/dl)	1.1±0.6	1.1±1.0	0.875
9	Serum TSH (µIU/ml)	2.3±1.0	7.2±2.5	0.000***

Values in Mean±SD; Un-paired "t" test; P<0.05 is significant; FT3: Free T3; FT4: Free T4.

TABLE II: Cardiovascular parameters among Euthyroid control (n=30) & SCH cases (n=30).

S. No.	*Parameter*	*Control (n=30)*	*Case (n=30)*	*P-value*
1	PR (beats/min)	86.9±7.6	84.6±7.2	0.234
2	SBP (mmHg)	110.3±11.7	110.8±13.1	0.885
3	DBP (mmHg)	72.8±6.8	72.1±8.2	0.720

Values in mean±SD; Un-paired "t" test; P<0.05 is significant; PR: pulse rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

TABLE III: Exercise stress parameters among SCH case and Euthyroid control.

S.No.	*Parameter (mean±SD)*	*Euthyroid Control (n=30)*		*SCH Case (30)*		*p-value*
1	Resting HR(bpm)	88.0±9.3		85.3±7.9		0.231
2	Maximum HR(bpm)	186.9±7.5		184.5±5.9		0.170
3	Peak HR(bpm)	153.7±20.5		134.8±16.3		0.000***
4	HRR1(bmp)	30.3±11.8		27.0±10.6		0.269
5	HRR2(bpm)	47.1±0.4		38.6±11.9		0.012*
6	CR	0.6±0.2		0.5±0.2		0.002**
7	Cut off value=0.8 Chronotropic Incompetence	<0.8	≥0.8	<0.8	≥0.8	Yates: 7.12; p=0.007
	No. of subjects	20(66.6%)	10(33.3%)	29(96.6%)	1(3.3%)	Fischer p=0.005

Values in Mean±SD; HR: Heart Rate; HRR1: Heart Rate Recovery 1 min; HRR2: Heart Rate Recovery 2 min; CR: Chronotropic Response; CI: Chronotropic Incompetence. Values in mean±SD; Un-paired "t" test; P<0.05 is significant.

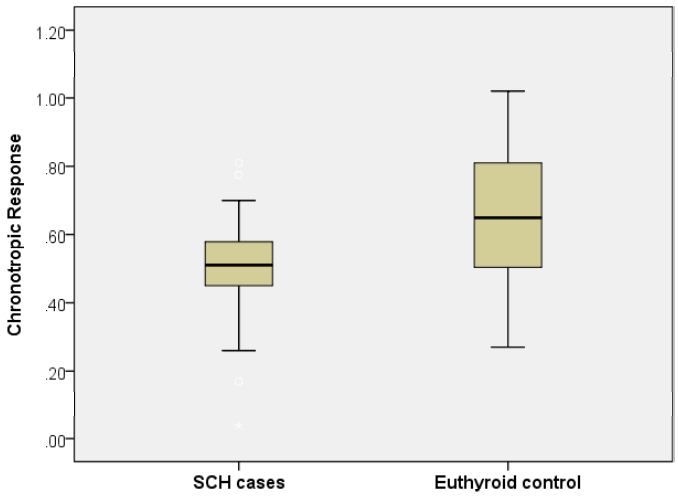

Fig. 1 : Boxplot showing chronotropic response among SCH cases (n=30) and Euthyroid controls (n=30).

rate recovery at 2 min and chronotropic response but was not statistically significant due to small sample size. Stepwise regression analysis of Serum TSH with variables like RHR, Peak MHR, %BF, %VF, HRR2 & CR which were significantly different among SCH & controls showed that peak MHR was the only factor showing a significant negative relationship to levels of Serum TSH ($\beta = -0.32$; p=0.012).

Discussion

The present study was carried out on 30 Subclinical hypothyroid case to assess the chronotropic response and HRR in comparison to euthyroid control.

Although asymptomatic SCH subjects having high serum TSH concentration in the setting of normal levels of serum T4 and T3 they are at risk for many cardiovascular manifestations due to altered lipid metabolism, structural and autonomic derangements (10). HRR following sub-minimal exercise is well correlated to vagal reactivation primarily in 1st minute after exercise (26) and have been suggested as an independent marker of cardiovascular risk factor (27, 28). The study investigated the evidence of impaired cardiac activity in SCH similar to that in overt hypothyroid (29). Chronotropic response and HRR2 were found to be significantly different between SCH and euthyroid control in our study. Study by Galetta et al observed an impaired cardiac autonomic function by reduced Heart rate variability in SCH patients (12). Study by Akcakoyun et al have also reported a reduced HRR and CR in SCH subjects (P<0.003; P<0.03, respectively) against similar gender and BMI controls (21). How ever they did not find any difference in RHR, Systolic and diastolic blood pressure. Our study observed a reduced HRR in both 1st & 2nd second but was statistically significant in only 2 min into recovery (p=0.012). HRR per se depends on the parasympathetic reactivity which may is attenuated in subclinical hypothyroid (30) however HRR in 2 min represents decrease in sympathetic activity along with reactivation of parasympathetic (31). A significantly lower HRR in two minute observed in the study may be related to altered activity of both sympathetic & parasympathetic nervous system. On the contrary Sunita et al found similar HRR (peak to 1-5 min of recovery) and percentage change in HRR (1 min recovery to 2-5 min of recovery) in SCH cases and euthyroid control (15).

The peak HR in SCH cases was significantly lower compared to the control (P<0.01) which may be due to decreased sympathetic tone and increased parasympathetic activity often a feature associated with increased TSH levels (32). Lower response to sympathetic activity during exercise could be the reason for lower peak HR reached during exercise in SCH cases.

An attenuated HR response to exercise called as CI is predictive of mortality and CAD even after adjustment for age, physical fitness and standard Cardio vascular risk factors (33, 34). Also it is unaffected by exercise protocol, and stage of exercise used for measurement (35). We observed a significantly decreased CR in SCH (p=0.002) as compared controls and definite association of Serum TSH levels with CI(<0.8) (p=0.005) in the SCH population. Akcakoyun M et al found similar impaired chronotropic response in their study on 25 patients of SCH indicating impaired cardiovascular autonomic function in SCH (21). However, Sunita et al found that CR was similar in both SCH cases and Euthyroid controls (15). The lower chronotropic responses in SCH cases in our study may be explained by deceased sympathetic reactivity (30), depressed systolic function at rest, left ventricular

diastolic dysfunction at rest and exercise (36). Although studies on effects of SCH on heart show conflicting results but SCH seems to be associated with increased cardiovascular risks of coronary heart disease and total mortality.

Conclusion

Slow HRR2 and decreased CR indicates insidious subtle changes in cardiac responses to exercise in SCH which in due course may cause alteration in cardiac contractility, myocardial oxygen consumption, cardiac output, blood pressure, and systemic vascular resistance. Negative association of HRR2 & CR with S TSH in SCH may suggest that abnormal TSH concentrations may be a novel cardiac risk factor not only for overt hypothyroid (37) but for SCH as well. Also HRR2 can be used as a preliminary test to make decisions regarding pharmacological treatment at an early stage to prevent progression to overt hypothyroidism but also to improve cardiac function & competence.

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References

1. Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. *J Indian Med Assoc* 2009; 107: 72–77.
2. Bashir H, Farooq R, Bhat MH, Majid S. Increased prevalence of subclinical hypothyroidism in females in mountainous valley of Kashmir, Indian Journey of Endocrinology and Metabolism. 2013; 17(2): 276–280.
3. Biondi B, Palmieri EA, Lombardi G, Fazio S. Subclinical hypothyroidism and cardiac function. *Thyroid* 2002; 12: 505–510.
4. Samuels MH. Subclinical thyroid disease in the elderly. *Thyroid* 1998; 8: 803–813.
5. Kim DW, Jung SL, Baek JH et al. The prevalence and features of thyroid pyramidal lobe, accessory thyroid, and ectopic thyroid as assessed by computed tomography: a multicenter study. *Thyroid* 2013; 23(1): 84–91.
6. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: Randomised, crossover trial. *J Clin Endocrinol Metab* 2007; 92: 1715–1723.
7. Duntas LH. Thyroid disease and lipids. *Thyroid* 2002; 12: 287–293.
8. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. *Indian J Endocrinol Metab* 2011; 15: S78–S81.
9. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam study. *Ann Intern Med* 2000; 132: 2708.
10. Duntas LH, Mantzou E, Koutras DA. Circulating levels of oxidized low density lipoprotein in overt and mild hypothyroidism. *Thyroid* 2002; 12: 10037.
11. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 2000; 10: 66579.
12. Galetta F, Franzoni F, Fallani P, Rossi M, Carpi A, Rubello D, et al. Heart rate variability and QT dispersion in patients with subclinical hypothyroidism. *Biomed Pharmacother* 2006; 60: 425–430.
13. Bogaard JM, Bush HFM, Sholte HR, Stam H, Versprille A. Exercise responses in patients with an enzyme deficiency in the mitochondrial respiratory chain. *J Eur Respir* 1988; 1: 445–452.
14. Mainenti MR, Vigario PS, Teixeira PF, Maia MD, Oliveira FP, Vaisman M. Effect of levothyroxine replacement on exercise performance in subclinical hypothyroidism. *J Endocrinol Invest* 2009; 32: 4703.
15. Sunita, Mahajan AS, Jain AK, Singh NP, Mishra TK. Exercise response of subclinical hypothyroid patient. *Int J Appl Basic Med Res* 2013; 3(2): 106–110.
16. Caraccio N, Natali A, Sironi A, Baldi S, Frascerra S, DardanoA, *et al*. Muscle metabolism and exercise tolerance in subclinical hypothyroidism: A controlled trial of levothyroxine. *J Clin Endocrinol Metab* 2005; 90: 405762.
17. Fletcher GF, Balady GJ, Amstrdam EA, Chaitman B, Eckel R, Fleg J, *et al*. Exercise standards for testing and training: A statement for health professionals from American Heart Association. *Circulation* 2001; 104: 1694740.
18. Mainenti MR, Teixeira PF, Oliveira FP, Vaisman M. Effect of hormone replacement on exercise cardiopulmonary reserve and recovery performance in subclinical hypothyroidism. *Braz J Med Biol Res* 2010; 43: 1095101.
19. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for health professionals from American Heart Association. *Circulation* 1990; 82: 2286322.
20. Galetta F, Franzoni F, Fallahi P, Rossi M, Carpi A, Rubello D, AntonelliA,et al. Heart rate variability and QT dispersion in patients with subclinical hypothyroidism. *Biomed Pharmacother* 2006 Sep; 60: 425–430.

21. Akcakoyun M, Emiroglu Y, Pala S, Kargin R, Guler GB, et al. Heart Rate Recovery and Chronotropic Incompetence in Patients with Subclinical Hypothyroidism Pacing. *Clin Electrophysiol* 2010; 33(1): 2–5.
22. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH etal. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004 Jan 14; 291(2): 228–238.
23. Ellestad MH. Exercise Testing Principles and Practice. 5th. 1,77. Oxford Press: 2003. pp. 82–322.
24. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA* 1999; 1999: 524–529.
25. Hattiwale HM, Hattiwale SH, Dhundasi SA, Das KK. Recovery Heart Rate Response in Sedentary and Physically Active Young Healthy Adults of Bijapur, Karnataka, India. *Basic Sciences of Medicine* 2012; 1(5): 30–33.
26. Arai Y, Saul JP, Albrecht P, Hartley LH, Lilly LS, Cohen RJ, ColucciWS.Modulation of cardiac autonomic activity during and immediately after exercise. *Am J Physiol* 1989; 256: H132–H141.
27. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer M. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999; 341: 1351–1357.
28. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005; 352: 1951–1958.
29. Cacciatori 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 Sep; 143: 327–333.
30. Mahajan AS, Lal R, Dhanwal DK, Jain AK, Chowdhury V. Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients. *Indian Journal of Endocrinology and Metabolism* 2013; 17(3): 460–464.
31. Buchheit M, Al Haddad H, Mendez-Villanueva A, Quod MJ, Bourdon PC. Effect of Maturation on Hemodynamic and Autonomic Control Recovery Following Maximal Running Exercise in Highly Trained Young Soccer Players. *Frontiers in Physiology* 2011; 2: 69.
32. Sahin I, Turan N, Kosar F, Taskatan C, Gunen H. Evaluation of autonomic activity in subclinical hypothyroidism. *J Endocrinol Invest* 2005; 28: 209–213.
33. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise: Prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation* 1996; 93: 1520–1526.
34. Ellestad MH. Chronotropic incompetence: The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?). *Circulation* 1996; 93: 1485–1487.
35. Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992; 10: 705–717. *Pacing Clin Electrophysiol* 2010; 33(1): 2–5.
36. Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. 1984 L-thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med* 101: 18–24.
37. Klein I, Danzi S. Cardiovascular involvement in general medical conditions, Thyroid disease and the heart. *Circulation* 2007; 116: 1725–1735.