A Simple Test of One Minute Heart Rate Variability during Deep Breathing for Evaluation of Sympatovagal Imbalance in Hyperthyroidism

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Abstract

Background: Heart rate variability is a sensitive marker of cardiac sympathetic activity.

Objectives: To determine whether long-term hyperthyroidism induced by thyroxine suppressive therapy affects HRV.

Methods: Nineteen patients treated with suppressive doses of thyroxin for thyroid cancer and 19 age-matched controls were enrolled. Thyroid function tests and 1 minute HRV were performed on all subjects and the results were compared between the groups. The 1 minute HRV was analyzed during deep breathing and defined as the difference in beats/minute between the shortest and the longest heart rate interval measured by eletrocardiographic recording during six cycles of deep breathing.

Results: One minute HRV during deep breathing was significantly lower among thyroxine-treated patients compared to healthy controls (25.6 ± 10.5 vs. 34.3 ± 12.6 beats/min, $P < 0.05$). There were no significant differences in mean, maximal and minimal heart rate between the groups

Conclusions: Thyroxine therapy administered for epithelial thyroid cancer resulted in subclinical hyperthyroidism and significantly decreased HRV due to autonomic dysfunction rather than basic elevated heart rate.

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The cardiovascular system is influenced by the autonomic nervous system and ANS abnormalities may increase cardiovascular morbidity and mortality [1]. The thyroid hormones affect the cardiovascular system through the ANS, especially the sympathetic tone. Hyperthyroid conditions are characterized by sympathetic features such as tachycardia and palpitation [2].

One of the most sensitive tools of ANS evaluation is heart rate variability. HRV is a physiological index that expresses the variation of the heart rate relative to the mean heart rate. The major fluctuations in heart rate are caused by respiration and are controlled by the peripheral and central nervous systems [3]. HRV reflects the balance between the sympathetic and the parasympathetic tone: when the sympathetic tone is dominant the HRV is low and vice versa. [3]. Decreased HRV has been demonstrated to be a marker of poor outcome in patients with diabetic autonomic neuropathy [4] and in patients with coronary artery disease [5].

Several studies examined the interaction between thyroid hormone and HRV, some of which found a decrease in HRV in patients with hyperthyroidism due to thyroid hormone-induced activation of sympathetic tone [6,7]. Others found no interaction [8].

A unique group comprises patients with well-differentiated thyroid carcinoma. These patients are treated with high doses of L-thyroxine for a long period in order to suppress the thyroid-stimulating hormone, which is a growth factor for the tumor [9,10]. In this study we examined HRV in patients receiving suppressive doses of thyroxine for thyroid carcinoma, which resulted in subclinical (biochemical) hyperthyroidism, in order to detect a subtle sign of autonomic dysfunction.

Patients and Methods

Twenty patients (age 21–61 years) being followed for differentiated thyroid carcinoma at the endocrine clinic of the Soroka University Medical Center were recruited for the study. All patients had recent TSH values below 0.4 mIU/mL. All were considered free of disease at the time of the study. Age and gender-matched euthyroid healthy control subjects were recruited from university personnel. The average age of the study and control groups was similar (41.9 ± 12.3 vs. 41.7 ± 12.2 respectively). If no TSH value was available from the control subjects in the 2 years preceding the study, one was drawn to verify euthyroidism. Upon review of the histopathology reports one patient was found to have had a benign hyperplastic nodule and, along with her age-matched control subject, was excluded from the final analysis. Thus the study included 19 patients and 19 controls. Individuals with diabetes mellitus, heart disease, or those taking medications affecting the heart (including beta-blockers and calcium channel blockers) were excluded from the study.

In order to evaluate the age effect on HRV, the two groups were divided into two subgroups, the first with 10 older subjects and the second with 9 younger subjects (median age 42 years old). The study was approved by the Soroka University Medical

HRV = heart rate variability
ANS = autonomic nervous system

TSH = thyroid-stimulating hormone

Figure 1. [A] Sample ECG recording of a patient with a low HRV. ECG was measured at paper speed of 25 mm/sec. The shortest and longest beat-to-beat interval was 1.7 and 2.0 sec respectively, 150/1.7 = 88, 150/2.0 = 75. The difference is 13 beats/min, hence the HRV of 13. **[B]** Sample ECG recording of a patient with a high HRV. ECG was measured at paper speed of 25 mm/sec. The shortest and longest beat-to-beat interval was 1.65 and 2.4 sec respectively, 150/1.65 = 90, 150/2.4 = 62. The difference is 28 beats/min, hence the HRV of 28.

Center Institutional Review Board and each patient signed an informed consent.

Heart rate variability

Heart rate variability was measured using the bedside test of 1 minute HRV during deep breathing as we described previously [11]. The test was performed with subjects in the supine position, connected to the limb leads of a standard electrocardiogram. All subjects lay supine for 10 minutes prior to testing. Before beginning the test, subjects were taught to breathe at a rate of six respiratory cycles per minute: 5 seconds for each inhalation and 5 seconds for each exhalation. All tests and measurements were performed by one examiner, who raised his hand to signal the start of each respiration and lowered his hand to signal the start of each exhalation. Lead II was then recorded continuously at a speed of 25 mm/second. The HRV interval (R-R intervals between adjacent QRS complexes resulting from sinus node depolarization) was measured manually with a scaled caliper. R-R intervals surrounding premature ventricular contractions were excluded from the analysis. The change in heart rate was calculated as the difference in beats per minutes between the shortest and the longest R-R interval [Figure 1]: HRV = short R-R interval (calculated as beats/min) – long R-R interval (calculated as beats/min)

Statistical analysis

Differences between groups were tested by the Students t-test. Associations between quantifiable variables were tested using the Pearson's coefficient.

Results

Thyroid function tests [Table 1]

The mean circulating TSH value for the thyroxine-treated patients was 0.09 ± 0.05 mIU/L (mean $\pm$ SD), and within normal limits for the healthy controls (1.77 ± 0.9 mIU/L, $P < 0.005$). The mean thyroxine dose for the study group was 156 ± 39 μg.

Minimal, maximal and mean heart rates [Table 2]

No differences were found when the minimal, maximal and mean heart rates were compared between the groups.

Table 1. TSH, thyroxine levels and daily thyroxine dosage in both groups

	Study group	Control group	P
TSH level (μIU/mL)	0.09 ± 0.05	1.38 ± 0.49	< 0.005
Thyroxine level (ng/dL)	1.62 ± 0.26	–	
Daily thyroxine dosage (mg/day)	156 ± 39	–	

Table 2. Minimal, maximal and mean heart rates of both groups

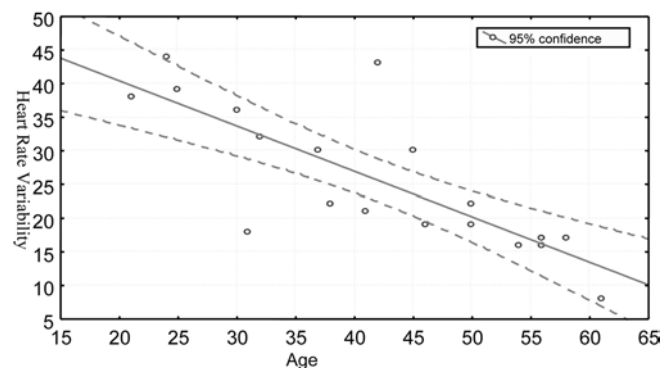|	Study group	Control group	P
Minimal heart rate	62.1 ± 9.96	59.8 ± 9.85	NS
Mean heart rate	74.5 ± 9.23	73.9 ± 12.6	NS
Maximal heart rate	87.7 ± 9.9	93.8 ± 14.6	NS

Figure 2. Anaylsis of the correlation between age and heart rate variation by Pearson correlation among subjects taking suppressive doses of thyroxine attested to a linear negative correlation between age and HRV: $r = -0.7932$ ($P < 0.05$). No correlation was found among control subjects: $r = -0.20$ ($P > 0.5$).

Heart rate variability

The mean HRV for all thyroxine-treated patients was 25 ± 10.5. This value was significantly lower than the mean heart rate variability for normal healthy subjects (34.2 ± 12.6, $P < 0.05$). Due to the wide variation in subjects' ages we examined the correlation between age and HRV for the group of thyroxine-treated patients and for the group of age-matched healthy control subjects. Though no correlation between age and HRV was found among the healthy controls, age was negatively and significantly related to HRV in thyroxine-treated patients [Figure 2]. The study and control groups were divided into two equal subgroups according to age. When thus analyzed, HRV differed between thyroxine-treated patients and healthy controls in the older age subgroup (20.7 ± 6.5 vs. 32.1 ± 16.8, $P < 0.05$). The difference between the thyroxine-treated younger subgroup and matched control subjects did not reach statistical significance (31.1 ± 9.07 vs. 36.6 ± 5.56 respectively, $P = 0.07$).

Discussion

Our study examined the influence of L-thyroxine treatment on the autonomic nervous system by the simple method of using HRV. We tested a group of patients with thyroid carcinoma treated

with high doses of L-thyroxine for a long period. We found a significantly lower HRV in these patients. Since there were no significant differences in mean, maximal and minimal heart rate between the groups, we concluded that the lower HRV is due to autonomic dysfunction rather than to a basic elevated heart rate.

Thyroid hormone is known to increase heart rate, velocity and force of contraction. Several theories have been proposed for these effects, one of which is decreased catecholamine metabolism in hyperthyroid conditions [12], while others proposed that thyroid hormones cause up-regulation of catecholamine receptor without any change in the catecholamine levels in the blood [13]. Various studies have investigated the influence of thyroid misbalance on ANS. Northcote et al. [6] found a significant increase in HRV after treating hyperthyroid patients with antithyroid drugs [6]. Caccatori et al. [7] noted that patients with Grave's disease showed decreased parasympathetic tone compared to the control group. Those studies were conducted on patients who suffered from thyroid dysfunction for a relatively short period.

Cardiovascular effects of long-term drug-induced hyperthyroidism are controversial: while several studies have found evidence for diastolic dysfunction and increased mean heart rate, others did not find any cardiovascular effect. Our study evaluated HRV in this subgroup of patients. We have shown that HRV level was significantly lower in the study group compared to healthy subjects. We used a simple bedside test to measure HRV; this test has been validated and used as a sensitive tool for HRV in several studies [14-16]. Previous studies have shown that time and frequency domain measurements of heart rate variability are excellent predictors of death or arrhythmic events after myocardial infarction and are equivalent for this purpose [17,18]. In a previous study we demonstrated that this method is a sensitive and independent predictor of all-cause mortality in patients after myocardial infarction [11].

The changes in heart rate associated with respiratory activity are mediated primarily by a combination of changing levels of efferent cardiac vagal and sympathetic activity and mechanically induced sinus node stretch with each respiration [19]. The contribution of each of these components is related to the frequency and amplitude of the respiratory signal, the mean level of vagal and sympathetic activity, and the mechanical state of the airways. There are no data on heart rate variability in patients with thyrotoxicosis assessed from short-term ECG recordings obtained during controlled respiration. One method of controlled respiration is to test the HRV during the breathing at a rate of six breaths/min, which expresses the maximal physiological sinus arrhythmia. Using this method, Bennet and co-workers [19] and Mackay et al. [4] demonstrated that heart rate variability during deep breathing proved to be a sensitive diagnostic test of autonomic nervous control of the heart in patients with diabetes mellitus. Patients with abnormally low vagal tone had reduced heart rate variability as measured during deep breathing [19] or quantitatively heart rate variability < 10 beats/min during six deep respirations [4]. In our study using similar methodology, we showed that this test is also useful for hyperthyroid patients.

An interesting result was the influence of age on HRV. Though no correlation between age and HRV was found among the healthy controls, age was negatively and significantly related to HRV in thyroxine-treated patients. Some previous studies suggested that HRV is affected by age and decreases in older people. A possible explanation for our findings is an additive effect of age and autonomic dysfunction in the older group, caused by L-thyroxine treatment.

Conclusions and clinical applications

Thyroxine therapy administered in clinically relevant doses for epithelial thyroid cancer significantly decreases HRV, with no significant differences in mean, maximal and minimal heart rate. HRV is a more sensitive marker for autonomic dysfunction than baseline heart rate; therefore, although those patients have normal baseline heart rate, they do have significant autonomic dysfunction. These findings suggest that thyroxine therapy in this subgroup may induce autonomic dysfunction, and stress the importance of the 1 minute HRV test. Further studies are needed to assess cardiovascular morbidity in these patients.

References

1. Task Force of the European Society and the North American Society of Pacing and Electrophysiology. Heart rate variability standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996;93:1043–56.
2. Burggraaf J, Tulen JH, Lalezari S, et al. Sympathovagal imbalance in hyperthyroidism. *Am J Physiol Endocrinol Metab* 2001;281:E190–5.
3. Van Ravenswaaij-Arts CM, Kollee LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. *Ann Intern Med* 1993;118:436–47.
4. Mackay JD, Page MM, Cambridge J, Watkins PJ. Diabetic autonomic neuropathy. The diagnostic value of heart rate monitoring. *Diabetologia* 1980;18:471–8.
5. Kliger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Circulation* 1987;59:256–62.
6. Northcote RJ, MacFarlane P, Kesson CM, Ballantyne D. Continuous 24-hour electrocardiography in thyrotoxicosis before and after treatment. *Am Heart J* 1986;112:339–44.
7. Cacciatori V, Bellavere F, Pezzarossa A, et al. Power spectral analysis of heart rate in hyperthyroidism. *J Clin Endocrinol Metab* 1996;81:2828–35.
8. Pitzalis MV, Mastropasqua F, Massari F, et al. Assessment of cardiac vagal activity in patients with hyperthyroidism. *Int J Cardiol* 1998;64:145–51.
9. Cooper DS, Specker B, Ho M. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from National Thyroid Cancer Treatment Cooperative Registry. *Thyroid* 1999;8:737–44.
10. Benbassat CA, Mechlis-Frish S, Guttmann H, Glaser B, Krausz Y. Current concepts in the follow up of patients with differentiated thyroid cancer. *IMAJ* 2007;9:540–5.
11. Katz A .Liberty IF, Porath A, Ovsysher I, Pryotovski EN. A simple bedside test of 1-minute heart rate variability during deep breathing as a prognostic index after myocardial infarction. *Am Heart* 1999;138:32–8.
12. Coulombe P. Dussalt JH, Walker P. Catecholamine metabolism in thyroid diseases. Norepinephrine secretion in hyperthyroidism and hypothyroidism. *J Clin Endocrinol Metab* 1977;44:1185–9.
13. Liggett SB, Shah SD, Cryer PE. Increased fat and skeletal muscle

beta adrenergic receptors but unaltered metabolic and hemodynamic sensitivity to epinephrine in vivo in experimental human thyrotoxicosis. J Clin Invest 1989;83:803–9.

14. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Glucose tolerance and other determinants of cardiovascular autonomic function: the Hoorn Study. Diabetologia 2000;43:561–70.

15. Naver HK, Blomstrand C, Wallin BG. Reduced heart rate variability after right-sided stroke. Stroke 1996;27:247–51.

16. Gutierrez J, Santiesteban R, Garcia H, Voustianiouk A, Freeman R, Kaufmann H. High blood pressure and decreased heart rate variability in the Cuban epidemic neuropathy. J Neurol Neurosurg Psychiatry 2002;73:71–2.

17. Malik M, Farrell T, Cripps TR, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction, selection of optimal processing techniques. Eur Heart J 1989;10:1060–74.

18. Bigger JT, Fleiss JL, Steinman RC, Rolinitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992;85:164–71.

19. Bennett T, Hosking DJ, Hampton JR. Baroreflex sensitivity and responses to the valsalva maneuver in patients with diabetes mellitus. J Neurol Neurosurg Psychiatry 1976;39:178–83.

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