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Echocardiography

Cardiac Autonomic Function and Global Left Ventricular Performance in Autoimmune Eauthyroid Chronic Thyroiditis: Is Treatment Necessary at the Euthyroid Stage?

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Objective: Autoimmune chronic thyroiditis (ACT) is characterized by lymphocyte infiltration in the thyroid gland and the presence of antithyroid antibodies in serum. Medical treatment does not affect antibody levels and treatment decision is not definite yet for the euthyroid patients. We aimed to evaluate cardiac autonomic function and global left ventricular performance in autoimmune euthyroid chronic thyroiditis and determine the need for medical treatment. Method: We studied 30 ACT patients and 25 healthy control subjects. Cardiac autonomic function is evaluated by heart rate recovery (HRR). Global left ventricular performance is evaluated by two-dimensional echocardiography and pulsed-wave tissue Doppler echocardiography. Results: There was no difference between patients and controls with respect to clinical and biochemical parameters except hemoglobin (13.67 $\pm$ 1.25 g/dL, 14.51 $\pm$ 1.35 g/dL, p:0.047) and low density lipoprotein (120.71 $\pm$ 24.91 mg/dL, 100.55 $\pm$ 14.73 mg/dL, p: 0.003). Tei index was significantly higher in ACT group (0.521 $\pm$ 0.074, 0.434 $\pm$ 0.034, $P < 0.0001$). E′/A′ was found to be significantly lower (1.234 $\pm$ 0.42, 1.750 $\pm$ 0.291, $P < 0.0001$) and E/E′ was found to be higher than the controls (8.482 $\pm$ 0.449, 6.039 $\pm$ 0.209, $P < 0.0001$). HRR was significantly lower than the controls (20 $\pm$ 4 BPM, 30 $\pm$ 8 BPM, $P < 0.0001$). Conclusion: Although left ventricular performance is found to be normal by conventional echocardiographic methods, it is found to be impaired when Tei index and tissue Doppler parameters are used. Cardiac autonomic function is also impaired in ACT patients. As a result of these cardiac changes, medical treatment may be considered earlier, even at the euthyroid stage. (Echocardiography 2011;28:15-21)

Key words: autoimmune chronic thyroiditis, cardiac autonomic function, heart rate recovery (HRR), myocardial performance index, pulsed-wave tissue Doppler

Autoimmune chronic thyroiditis (ACT), also called chronic lymphocytic thyroiditis or Hashimoto's thyroiditis, is the most common and extensively studied organ specific autoimmune disorder. ACT is characterized by diffuse lymphocytic infiltration of the thyroid gland, presence of antithyroid antibodies (ATA) in serum, clinical evidence of goitrous or atrophic gland and frequent thyroid dysfunction of varying degrees.[1,2] The two primary antigens to which autoantibodies develop are thyroglobulin (Tg) and thyroperoxidase (TPO). The clinical diagnosis of ACT depends on both physical and biochemical abnormalities as well as serological demonstration of autoantibodies to these major thyroid antigens.[3]

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Thyroid hormone has many effects on the heart and vascular system.[4] Many of the clinical manifestations of hyperthyroidism are due to the effects of thyroid hormone on cardiovascular hemodynamics.[5] Hypothyroidism is also associated with cardiovascular disorders and has been shown to affect both left and right ventricular function.[6] Alterations in cardiac hemodynamics have been reported even in patients with subclinical hyper- and hypothyroidism although they are less marked than overt thyroid dysfunctions.[7,8] The effect of L-thyroxine which has been proven to modulate the immune process in animal models of spontaneous lymphocytic thyroiditis, is not clear when it comes to clinical studies especially for euthyroid patients for whom indication of L-thyroxine therapy is controversial.[9–13]

The aim of this study was to evaluate the cardiac autonomic function and left ventricular performance of patients with euthyroid ACT and

determine the need for medical treatment at the euthyroid stage.

Subjects and Methods:

Patients:

We studied 30 patients (5 male and 25 female, mean age 37.14 $\pm$ 12.56) with ACT. All patients were euthyroid (thyroid hormone measurements were made on two consecutive visits at least 2 months apart; all their hormone levels were within normal ranges), without symptoms related to coronary artery disease, cerebrovascular disease or peripheral arterial disease. None of the patients had any systemic illness (including renal, pulmonary and liver disease) and were on any drug regimen. Patients who had anemia (hemoglobin $<$10 g/dL), an implanted pacemaker, congenital or severe organic valvular disease, chronic obstructive pulmonary disease, atrial fibrillation, left bundle branch block or Wolff-Parkinson-White on their resting electrocardiogram were excluded from the study. The diagnosis of ACT was based on laboratory criteria [thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), anti thyroglobulin (Tg-Ab), and antithyroid peroxidase (TPO-Ab) antibodies] supported by ultrasonographic findings of thyroid parenchymal heterogenity.

The control group consisted of 25 asymptomatic subjects (5 male and 20 female, mean age 32.60 $\pm$ 8.28) without history of coronary artery disease and any systemic illness and also had no evidence of heart disease. Exclusion criteria used for the patient group were applied for the control group as well. None of them were smoking and under any medical treatment. All the participants were given written informed consent to participate in the study.

Thyroid Hormone and Thyroid Autoantibody Measurements:

After 12 hours of fasting, blood samples were taken from antecubital vein. Thyroid hormones, Tg-Ab, TPO-Ab were measured by Elecsys Analyzer (Roche, Mannheim, Germany) through electrochemiluminescense immunoassay (ECLIA) method. Reference levels of our biochemistry laboratory for thyroid hormones were as follows; FT3: 0.18–0.44 ng/dL, FT4: 0.93–1.80 ng/dL, TSH: 0.27–4.2 μIU/mL.

Tg-Ab and TPO-Ab were also measured by Elecsys Analyzer (Roche) through ECLIA method (within-run precision 4.9%, between-run precision 5.9% for Tg-Ab; within-run precision 2.5%, between-run precision 7.1% for TPO-Ab). Tg-Ab levels up to 115 IU/mL and TPO-Ab levels up to 34 IU/mL were accepted as normal.

Thyroid Ultrasonography:

Thyroid ultrasonography was performed by using a 10 MHz lineer transducer (General Electric, Logic 7, Horten, Norway) by two different specialized radiologists.

Echocardiographic Examination:

Echocardiographic images were obtained by using 3.75 MHz standard probe (General Electric, Vivid 7) according to the guidelines of American Society of Echocardiography.[14] All echocardiographic examinations were carried out by an experienced operator blinded to the patient's clinical profile and all the measurements were performed on-line. Resting heart rate of the patients and the controls were within normal ranges during the echocardiographic examination. Peak velocity of early (E) and late (A) filling, deceleration time and isovolumetric relaxation time (IRT) were measured from Doppler scan of the mitral inflow and the aortic outflow. Tei index was introduced by Tei and is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET).[15] It provides useful information in many disease states before routine echocardiographic methods detect any problem.[16,17]

Pulsed-wave tissue Doppler imaging (TDI) was performed by using TDI function of the same echocardiography machine. From the apical four-chamber view, peak systolic velocity (S′), early diastolic (E′), and late diastolic velocity (A′) were measured using a 5 mm sample volume of the pulsed-wave Doppler placed at the septal side of the mitral annulus. E′/A′ and septal E/E′ were calculated thereafter.

Treadmill Exercise Stress Testing:

Tests were performed on Tepa-TM-Pro 2000 Model according to the Bruce protocol. Predicted peak heart rate was calculated as 220-age. Individuals were encouraged to exercise until they experience limiting symptoms, even if 85% of maximum predicted heart rate was achieved. Exercise was terminated when maximum heart rate greater than the age-predicted maximum was achieved or in the presence of physical exhaustion. During each exercise stage and recovery stage, symptoms, blood pressure, heart rate, and exercise workload in metabolic equivalents (METS) were recorded.

Following peak exercise, individuals walked for a 2-minutes cool-down period at 1.5 mph and 2.5% grade. Heart rate was measured during each minute of exercise, at maximum exercise and during recovery at 1, 2, 3, 4, and 5 minutes in the standing position. The exercise tests were performed, analyzed and reported with a standard protocol by way of a computerized database.

TABLE I

Clinical and Biochemical Parameters

	CAT	Control	P
Age (year)	37.14 ± 12.56	32.60 ± 8.28	0.182
Body mass index (kg/m^2)	23.82 ± 3.93	24.70 ± 2.39	0.394
Glucose (mg/dL)	94.64 ± 5.66	91.73 ± 4.86	0.674
Hemoglobin (g/dL)	13.67 ± 1.25	14.51 ± 1.35	0.047
C-reactive protein (mg/L)	2.43 ± 1.25	2.19 ± 1.13	0.516
Creatinin (mg/dL)	0.71 ± 0.08	0.69 ± 0.09	0.435
T. cholesterol (mg/dL)	205.71 ± 32.12	180.90 ± 18.48	0.064
Low-density lipoprotein (mg/dL)	120.71 ± 24.91	100.55 ± 14.73	0.003
High-density lipoprotein (mg/dL)	56.47 ± 15.02	51.80 ± 7.67	0.220
Triglyseride (mg/dL)	116.57 ± 48.67	149.70 ± 36.58	0.261

Heart rate recovery (HRR) was defined as the change from peak heart rate to the heart rate at the first minute of recovery. Abnormal HRR was defined as a decrease of $\leq$12 beats/min from peak exercise heart rate at 1 minute to recovery.[18]

Statistical Analysis:
Data are expressed as the mean ± standard deviation. Kolmogorof-Smirnov test was used for distribution of continous variables between groups. Mean values in different groups were compared with either Student's *t*-test or Mann-Whithey U test. A difference was considered significant at a P value of $<$0.05. SPSS for Windows Version 18 program (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis.

Results:
The ACT group and the control group did not show any difference with respect to clinical and biochemical parameters except hemoglobin and low density lipoprotein (LDL) values. Hemoglobin was found to be slightly decreased in the ACT group (13.67 ± 1.25 g/dL, 14.51 ± 1.35 g/dL, P: 0.047). LDL was significantly increased in ACT group (120. 71 ± 24.91 mg/dL, 100.55 ± 14.73 mg/dL, P: 0.003), however both of the groups had LDL levels that did not require to be treated medically. C-reactive protein (CRP) did not differ between the groups (Table I).

TABLE II

Hormonal and Autoantibody Parameters

	ACT	Control	P
TSH (μIu/mL)	2.21 ± 1.03	2.40 ± 0.62	0.489
sT3 (ng/dL)	0.39 ± 0.05	0.25 ± 0.06	0.083
sT4 (ng/dL)	1.45 ± 0.30	1.58 ± 0.22	0.467
ANTİ-TG (IU/mL)	391.48 ± 79.98	7.66 ± 2.44	$<$0.0001
ANTİ-TPO (IU/mL)	109.38 ± 31.10	2.87 ± 0.98	0.002

According to the hormonal parameters: TSH, FT3, and FT4 did not show significant difference between ACT group and the controls. All the patients in the ACT group were positive for Tg-Ab and TPO-Ab (391.48 ± 79.98 IU/mL, 109.38 31.10 IU/mL, respectively) (Table II).

Two-dimensional (2D) and Doppler Echocardiography Parameters:
The ACT group and the control group did not show any significant difference with respect to conventional systolic parameters. Mitral inflow Doppler parameters; peak E velocity and peak A velocity were both significantly increased in the ACT group than the controls; however E/A ratio did not show significant difference between the groups. Tei index was markedly increased in the ACT group (0.521 ± 0.074, 0.434 ± 0.034, P $<$ 0.0001) (Table III).

TDI Analysis:
The myocardial systolic velocity (Sm) measured from the septal mitral annulus was significantly decreased in the ACT group (0.080 ± 0.010, 0.109 ± 0.017, P $<$ 0.0001). Though late

TABLE III

2D/Doppler Echocardiography Parameters

	ACT	Control	P
EF (%)	67.42 ± 4.28	69.05 ± 3.11	0.176
FS (%)	37.28 ± 4.12	37.00 ± 3.40	0.811
LVEDD (cm)	45.61 ± 2.69	44.40 ± 2.45	0.139
LVESD (cm)	26.70 ± 5.95	23.15 ± 2.20	0.016
E (m/sec)	0.867 ± 0.144	0.708 ± 0.066	$<$0.0001
A (m/sec)	0.614 ± 0.185	0.491 ± 0.142	0.023
E/A ratio	1.47 ± 0.39	1.53 ± 0.37	0.642
ET (ms)	281.66 ± 31.35	306.00 ± 13.07	0.003
IRT (ms)	91.19 ± 12.91	83.50 ± 9.66	0.038
ICT (ms)	57.04 ± 9.66	48.55 ± 3.92	0.001
Tei index	0.521 ± 0.074	0.434 ± 0.034	$<$0.0001

TABLE IV

TDI Analysis Parameters (Septal Mitral Annulus)

	ACT	Control	P
E′m (cm/sec)	0.106 ± 0.023	0.141 ± 0.023	<0.0001
A′m (cm/sec)	0.092 ± 0.029	0.082 ± 0.018	0.184
Sm (cm/sec)	0.080 ± 0.010	0.109 ± 0.017	<0.0001
E′/A′	1.234 ± 0.420	1.750 ± 0.291	<0.0001
E/E′	8.482 ± 0.449	6.039 ± 0.209	<0.0001

diastolic velocity (A′m) did not differ between the groups; early diastolic velocity (E′m) was significantly lower than the controls (0.106 ± 0.023 cm/sn, 0.141 ± 0.023 cm/sn, $P < 0.0001$). The ratio of early and late diastolic velocities (E′/A′), was, however significantly decreased in the ACT group (1.234 ± 0.420, 1.750 ± 0.291, $P < 0.0001$). Septal E/E′ was found to be significantly increased in the ACT group than the controls (8.482 ± 0.449, 6.039 ± 0.209, $P < 0.0001$) (Table IV).

Exercise Stress Testing:

Resting heart rate and heart rate at peak exercise in the ACT group were similar to that of controls. Likewise resting systolic blood pressure values were not different than that of controls. Systolic blood pressure at peak exercise was significantly elevated in the ACT group when compared to the control group (172 ± 8 mmHg, 156 ± 10 mmHg, $P < 0.0001$). Exercise workload in metabolic equivalents (METS) in the ACT group was not statistically different from that of controls. However, HRR at 1 minute in the ACT group was significantly lower than that of the control group (20 ± 4 BPM, 30 ± 8 BPM, $P < 0.0001$) (Fig. 1), which was largely attributable to higher heart rate at the first minute of recovery in the ACT group (Table V).

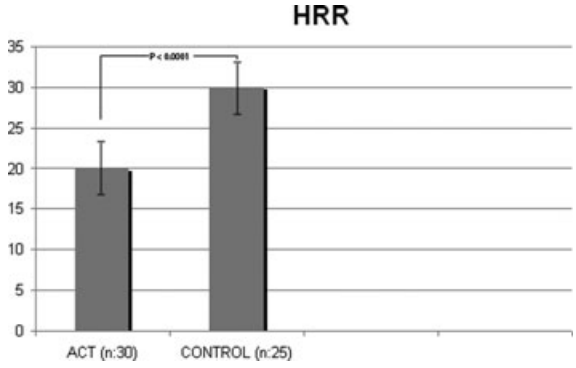

Figure 1. HRR results of ACT and the control groups.

TABLE V

Exercise Stress Testing Parameters

	ACT	Control	P
Resting HR (BPM)	90 ± 13	91 ± 17	0.665
Peak HR (BPM)	177 ± 8	177 ± 12	0.940
HR at 1 min of rec (BPM)	157 ± 9	132 ± 10	0.008
HRR at 1 min of rec (BPM)	20 ± 4	30 ± 8	<0.0001
Resting Sys BP (mm Hg)	117 ± 5	116 ± 8	0.623
Peak Sys BP (mm Hg)	172 ± 8	156 ± 10	<0.0001
METS	11.2 ± 1.5	10.7 ± 1.3	0.146

BPM = beat per minute; METS = metabolic equivalents.

Discussion:

ACT is the most common autoimmune disorder characterized by the presence of thyroid autoantibodies with a spectrum of clinical presentation changing from a large goiter to atrophy of the gland, hyperthyroidism to hypothyroidism.[1,19] Early clinical and autopsy studies had suggested an association between subclinical hypothyroidism and coronary heart disease, which has been subsequently confirmed by some, but not all, large cross-sectional and prospective studies.[20] Several mechanisms could explain why even subclinical thyroid abnormality has a greater adverse affect on cardiovascular system. According to one mechanism, the thyroid autoimmunity found in subclinical disease causes local inflammation and a pathological immune reactivity that induces coronary vascular stenoses.[21] However, the medical literature is controversial; some studies suggest the association of autoimmune thyroiditis with coronary heart disease[22,23] and other studies do not.[24,25] Meanwhile, when patients with subclinical hypothyroidism are treated with L-thyroxine, they improve clinically and systolic and diastolic contractility increase.[26,27]

Although we know much about cardiovascular effects of subclinical thyroid disorders, to the best of our knowledge, little is known about the impact of autoimmune euthyroid chronic thyroiditis on cardiovascular system. Recently, Sahin et al. concluded that pulmonary arterial pressure is higher in these patients.[28] As another interesting finding, Stamatelopoulos et al. showed that autoimmune euthyroid chronic thyroiditis is associated with increased pulsed-wave velocity independent of arterial atheromatosis, indicating a direct impact of this disorder on arterial stiffening.[29]

L-thyroxine has been shown to decrease the incidence of lymphocytic thyroiditis and the amount of lymphocyte infiltration in animal models.[30,31] Although it is mandatory in hypothyroid autoimmune thyroiditis, L-thyroxine

treatment which is shown to inhibit autoimmune process in animal models, is still controversial in autoimmune euthyroid chronic thyroiditis where the inflammatory process has not destroyed the gland enough to cause hypothyroidism.[32]

In our study, global cardiac performance was evaluated with TDI analysis of mitral annulus and Tei index as well as conventional 2D/Doppler scan measurements. Conventional methods were incapabable of demonstrating early functional impairment in ACT patients. The ratio of early and late diastolic filling, E/A did not differ from the controls in ACT group. According to this Doppler derived parameter, left ventricular diastolic function was considered to be normal. Tei index was significantly elevated in ACT group when compared with controls, as a result of prolongation of IVC and shortening of ET. Although conventional systolic and diastolic parameters were not different between the two groups, as a marker of early impairment of systolic function, Tei index was a useful parameter to demonstrate cardiac functional changes in the disease process.[15] The main technical limitation of Tei index is load dependancy especially in critically ill patients who may have changes in preload and afterload. However in our study, all the patients were hemodynamically stable without any changes in loading conditions.

TDI analysis has evolved as a new quantitative tool for the assesment of cardiac systolic and diastolic function and the hemodynamics of left ventricular filling. From tissue Doppler velocity analysis, a number of parameters have been shown to be useful to predict long-term prognosis, in particular, Sm, E′m, and E/E′. In our study, the ratio of early and late diastolic velocities measured from the septal mitral annulus, E′/A′ was significantly lower in the ACT group than the controls. Left ventricular transmitral filling pattern can be altered by changes in preload or left atrial pressure, therefore TDI parameters are considered more sensitive than conventional mitral Doppler indexes in the assesment of left ventricular relaxation.[33] TDI derived systolic velocities were markedly reduced in ACT patients when compared to controls. With regard to left ventricular systolic function, several investigators reported that Sm was well related to LV ejection fraction[34] and to peak positive dp/dt.[35] In our study, left ventricular systolic function measured by conventional echocardiographic methods was found to be normal but acccording to the TDI derived Sm, left ventricular systolic impairment was demonstrated at the euthyroid stage in ACT. Similarly, conventional diastolic parameters were insufficient to demonstrate impairment of left ventricular diastolic function. TDI derived E′/A′ is found to be a more sensitive parameter that shows ventricular relaxation and is significantly decreased early in the disease process in our study. Therefore, conventional echocardiographic methods are insufficient to detect early systolic and diastolic impairment and TDI should be a part of routine clinical evaluation of patients with ACT to show cardiac functional changes earlier, even at the euthyroid stage.

E/E′ ratio which is a combination of pulsed Doppler early mitral inflow velocity (E) and tissue Doppler-derived diastolic mitral annular velocity (E′), is well correlated with invasively measured LV filling pressure.[36] It has been known to be a strong prognostic factor in various cardiac diseases.[37,38] $E/E' > 15$ reflects elevated filling pressure while $E/E' < 8$ suggests normal filling pressure.[39] In our study, although E/E′ was found to be <15, it was still significantly higher than the controls in ACT group. This may reflect that LV filling pressure has a tendency to increase even at the euthyroid stage as a result of both systolic and diastolic impairment demonstrated by novel echocardiographic methods when routine methods fail to demonstrate any change.

The increase in heart rate that accompanies exercise is due in part to a reduction in vagal tone. Recovery of the heart rate immediately after exercise, especially during the 1 minute, however, is a function of vagal reactivation.[40] HRR appears to measure the autonomic response to exercise, abnormality of which have been demonstrated to independently predict adverse cardiac outcomes.[41] Abnormal HRR is associated with mortality in asymptomatic patients, patients undergoing coronary angiography, and patients undergoing nuclear perfusion imaging. The association is independent of left ventricular systolic function, functional capacity and coronary artery disease severity.[42] A recent study of asymptomatic patients demonstrated that abnormal HRR was a stronger predictor of sudden cardiac death, as compared to other modes of death.[43] In our study, we demonstrated that HRR is significantly reduced than the controls in ACT group as a result of cardiac autonomic dysfunction at the euthyroid stage. The underlying mechanism of reduced HRR reflecting alterations in autonome neural system in ACT is not known. Further prospective studies are needed to reveal the pathopysiology of abnormal HRR that represents abnormal autonomic response to exercise.

Small sample size is the main restriction of our study that limits the generalization of our findings. The changes observed may be the results of metabolic abnormalities occuring outside a quiscent period most likely owing to the intermittent presence of thyroid stimulating and throid blocking antibodies. Absence of pathological evaluation of the thyroid gland is another limitation and blood pressures were measured by using

indirect arm sphygmomanometry during exercise that may be considered as an inaccurate method.

Our study points out the role or effects of thyroid autoantibodies even in the presence of normal thyroid functions on echocardiographic parameters which are important in prediction of cardiac adverse outcomes. It is well known that even subclinical abnormalities of thyroid function affects heart and echocardiographic findings adversely, but up to our study the chronic thyroiditis patients with euthyroidism were not examined with regard to nonconventional echocardiographic parameters. Probable mechanisms that may explain the link between cardiac autonomic and functional changes and euthyroid chronic thyroiditis are probably related with autoimmunity; but the molecular, physiologic and clinical evidence is still missing.

In conclusion, impairment of global cardiac performance is present in ACT patients who are euthyroid and conventional echocardiography is insufficient to determine these changes. Tei index and TDI analysis of septal mitral annulus are novel echocardiographic methods to demonstrate early impairment of systolic and diastolic function even at the euthyroid stage and should be considered in the echocardiographic evaluation of these patients. Besides these cardiac functional changes, HRR is found to be decreased indicating an abnormality in autonomic neural control of the cardiovascular system. Therefore, these cardiac changes that are present early in the disease process may be considered as a reason to start medical treatment earlier, even at the euthyroid stage to prevent cardiac functional and autonomic impairment. However, underlying mechanisms for abnormalities despite normal thyroid hormone levels, criteria for selection of patients for medical treatment, duration of therapy and doses still need to be answered by further research.

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