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CLINICAL STUDY

Cardiac function in borderline hypothyroidism: a study by pulsed wave tissue Doppler imaging

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Abstract

Objective: In subclinical hypothyroidism (SH), impaired diastolic function has been documented at rest and on effort, while systolic dysfunction has only been assessed on effort.
Design: The aim of the present study was: (a) to further assess systolic function at rest in SH; and (b) to ascertain whether cardiac dysfunction could precede TSH increase in euthyroid patients with a high risk of developing SH.
Methods: We studied 32 patients with classical Hashimoto's thyroiditis (22 with increased serum TSH (>3 mU/ml – group A), and 10 with normal serum TSH (<3 mU/ml – group B)); a third group (C), which included 13 healthy controls. All subjects underwent pulsed wave tissue Doppler imaging (PWTDI) to accurately quantify the global and regional left ventricular function.
Results: When compared with group C, PWTDI indices showed that in both groups A and B there was a significant impairment of systolic ejection ($P < 0.001$ and $P < 0.05$, respectively), a delay in diastolic relaxation ($P < 0.001$ and $P < 0.05$, respectively) and a decrease in the compliance to the ventricular filling ($P < 0.05$). Several significant correlations were found between PWTDI parameters and serum-free T_3 and T_4 and TSH concentrations.
Conclusion: PWTDI is a sensitive technique that allows detection of both diastolic and systolic abnormalities, not only in patients with SH, but also in euthyroid subjects with a high risk of developing thyroid failure. Futhermore, the significant correlations of several PWTDI indices with serum FT_3 and TSH concentrations strongly support the concept of a continuum spectrum of a slight thyroid failure in autoimmune thyroiditis extending to subjects with serum TSH still within the normal range.

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Introduction

Subclinical hypothyroidism (SH) is a frequent condition defined by elevated thyroid stimulating hormone (TSH) secretion in the presence of normal concentrations of circulating thyroid hormones (1–3). Most cases of SH are due to the slow progression of thyroid failure caused by autoimmune thyroiditis and it is generally believed that the majority of patients with SH will eventually become frankly hypothyroid (2). Clinical symptoms and signs are often non-specific, and diagnosis and monitoring of therapy depend crucially on measurements of thyroid hormones and TSH in the blood (3–5). On the other hand, patients with unequivocal evidence of autoimmune thyroiditis may report symptoms (mainly chronic fatigue) even in the presence of normal serum TSH concentrations; the term 'subchemical hypothyroidism' has been suggested for this condition (6), but this remains open to speculation (7).

The clinical relevance of SH is still unclear, in spite of several reports of an increased risk of low density lipoprotein (LDL)-cholesterol and negative influence on the hemostatic profile, and of increased occurrence of coronary and peripheral arterial disease and depression (1–4). Several mild cardiac abnormalities, such as impairment of left ventricular diastolic function at rest and of systolic function on effort have been described in SH (8–12). These anomalies are probably responsible for a wide spectrum of symptoms suggestive of thyroid failure observed in patients with SH (13).

In the present study, taking advantage of the peculiar sensitivity of the heart to the action of the thyroid hormone, we assessed diastolic and systolic function in patients with SH and in subjects with euthyroid

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autoimmune thyroiditis with normal serum TSH concentration, but at risk of developing thyroid failure. For this purpose, we used pulsed wave tissue Doppler imaging (PWTDI), a technique based on the Doppler principle, which is able to precisely assess the ventricular wall motion (14).

Subjects and methods

Study population

We studied 32 patients (31 females, one male) with documented classical Hashimoto's thyroiditis (see below for the diagnostic criteria), whose main features are reported in Table 1. Twenty-two of them had SH with increased serum TSH (>3 mU/ml: 5.40±2.08 mU/ml, range 3.31–10.7 mU/ml; group A), and 10 had normal serum TSH (<3 mU/ml: 2.27±0.52 mU/ml, range 1.20–2.89 mU/ml; group B). Serum-free T_3 (FT_3) concentration was within the normal range in both groups. A third group included 13 healthy euthyroid controls (12 females, one male; group C). These were subjects who came to our laboratory for a thyroid function test and were found within normal values. All groups were matched for age, sex and body mass index (BMI) (Table 1). No significant differences were observed among the groups in heart rate, blood pressure and serum FT_3 concentration. Mean serum-free T_4 (FT_4) concentration was significantly lower and mean serum TSH significantly higher in group A when compared with group B and C. Although individual serum TSH concentration in group B was within the normal range, its mean value was significantly higher in comparison with group C.

Table 1 Biophysical characteristics, cardiovascular measurements and hormonal data of patients and controls.

	Patients		
	Group A TSH > 3 mU/l ($n = 22$)	Group B TSH < 3 mU/l ($n = 10$)	**Group C** ($n = 13$)
Age (years)	42.5±9.9	40.9±11.9	39.0±8.2
Male/female	1/21	0/10	1/12
Weight (kg)	64.1±10.6	64.6±10.9	62.1±11.4
Height (cm)	158.2±5.4	160.1±4.4	162.6±10.5
BSA (m^2)	1.6±0.1	1.7±0.1	1.6±0.2
BMI (kg/m^2)	25.6±4.2	25.1±4.6	23.5±3.7
HR (bpm)	69.9±9.5	72.0±13.3	76.2±11.6
SBP (mmHg)	126.4±12.7	124.8±19.2	122.2±7.1
DBP (mmHg)	80.5±7.7	76.1±6.5	77.8±7.1
FT_3 (pg/ml)	3.2±0.5	3.2±0.4	3.5±0.2
FT_4 (pg/ml)	7.8±1.7**	10.2±1.4	10.2±1.7
TSH (mUI/l)	5.4±2.1* *f*	2.3±0.5*	1.2±0.5

*$P < 0.01$ vs Group C; *f* $P < 0.01$ vs Group B.
**$P < 0.001$ vs Group B and Group C.
BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure. Values are given as means±S.D.

Study protocol

The Ethical Committee of our University approved the present study, and informed written consent was obtained from all subjects. Participants were familiarized with instrumentation and medical environment of echocardiographic laboratory before testing. All subjects underwent physical examination, 12-lead electrocardiogram and M-mode, 2D and Doppler-echocardiography. Finally, subjects underwent PWTDI study, using an ultrasound system equipped with tissue Doppler imaging capabilities (SSA-380A; Toshiba Corp., Tochigi, Japan). A single experienced echocardiographer, who was unaware of the subjects' thyroid conditions, carried out all examinations with subjects in the left lateral decubitus position. A simultaneous electrocardiographic tracing was also obtained.

Doppler echocardiography

A complete M-Mode, 2D, spectral- and color-Doppler recordings were performed using a 2.5-MHz transducer. Left ventricular mass (LVM) was measured according to the Devereux method (15); LVM index (LVMI) was obtained by dividing LVM by body surface area. Ejection fraction (EF) was calculated using the Simpson method (16). Pulsed Doppler transmitral flow velocities were recorded from the 4-chamber apical view, with the sample volume placed at the level of the mitral valve leaflet tips. Early (E_m) and late (A_m) diastolic velocities of transmitral flow were measured and the E_m/A_m ratio was derived. Isovolumic relaxation time (IVRT) was measured as the time interval between the end of systolic output flow and transmitral E_m wave onset, by placing the sample volume between outflow tract and the mitral valve.

PWTDI

PWTDI uses the Doppler principle to assess the ventricular wall motion velocity by positioning the sample volume within the myocardium (14). In PWTDI, low-amplitude blood-flow signals are eliminated by gain adjustment to allow only high-amplitude Doppler signals from wall motion to enter the velocity calculation circuit. By means of a 4-chamber apical view, a 3 mm sample volume was placed both at the level of basal lateral and infero-septal mitral annulus, with the ultrasonic Doppler beam in a position as parallel as possible to the motion of the myocardial wall. Three distinct waves were obtained through PWTDI in each of the two mitral annular sites during the cardiac cycle: a systolic wave (S); an early diastolic wave (E) and a late diastolic wave (A). The following measurements were made from the PWTDI recordings: peak systolic velocity (S_a, cm/sec), acceleration time of S (ATS_a, sec), deceleration time of S (DTS_a, sec), peak early diastolic velocity (E_a, cm/sec), peak late diastolic velocity

(A_a, cm/sec), acceleration time of E (ATE_a, sec), and deceleration time of E (DTE_a, sec). The E_a/A_a ratio was then calculated. Mean acceleration and deceleration rates of S (ARS_a, cm/sec^2; DRS_a, cm/sec^2) and of E (ARE_a, cm/sec^2; DRE_a, cm/sec^2) were obtained as S_a and E_a divided by their respective time intervals. These measurements were repeated on recordings of three consecutive cardiac cycles and their mean value was obtained. Then, values of basal lateral and inferoseptal mitral annulus were averaged. Finally, we considered the peak early diastolic velocity of lateral mitral annulus (E_{al}, cm/sec) as a relaxation index. We then calculated the ratio between E_m and E_{al} (E_m/E_{al}), a parameter that takes into account the influence of cardiac relaxation on mitral flow (17). Reproducibility of PWTDI parameters in our laboratory had been previously documented (18).

Assessment of thyroid function

Serum TSH, FT_4 and FT_3, anti-thyroglobulin and anti-thyroid peroxidase antibodies (TgAb, TPOAb) were measured in all subjects. FT_4 and FT_3 were assayed by a direct method with chromatographic separation in Lisophase columns (Technogenetics, Milano, Italy). The normal ranges for FT_4 and FT_3 were 6.6–16 pg/ml and 2.8–5.6 pg/ml, respectively. Serum TSH was measured by immunochemiluminescent assay (Ortho-Clinical Diagnostic, Amersham, UK, normal range 0.3–3.0 mU/l). TPOAb were determined by RIA (ICN: normal range $<$ 10 UI/ml); TgAb by passive hemoagglutination (Fujirebio Inc. Pharmaceuticals, Tokyo, Japan: normal range $<$ 1/100). TPOAb ranged 64–3000 UI/ml (median 369) in group A, 134–3000 UI/ml (median 379) in group B, and were negative in controls. Thyroid ultrasound was performed in all cases using a 7.5 mHz linear electronic transducer, and thyroid echogenicity was subjectively evaluated by a conventional gray scale. The diagnosis of Hashimoto's thyroiditis was made on the basis of hypoechoic goiter (19) associated to high levels of TPOAb and/or TgAb (20, 21).

Statistical analysis

Data from all groups are reported as mean±S.D. Differences between control subjects and patients were assessed by the Student's 2-tailed *t*-test for unpaired observations. Correlations between echocardiographic parameters and PWTDI indices, and hormones (FT_3, FT_4 and TSH) were evaluated using Pearson's correlation coefficient. *P* values <0.05 were considered to be significant.

Results

Doppler echocardiography

In comparison with controls, E_m and E_m/A_m ratio showed a significant decrease ($P < 0.05$ and $P < 0.001$, respectively), and IVRT a significant prolongation ($P < 0.001$) in group A (Table 2). Conversely, these parameters remained unmodified in group B. On the other hand, none of the echocardiographic parameters showed relevant differences between patients of group A and B. No single parameter of conventional echocardiography was correlated to serum TSH or FT_3 concentration, with the exception of E_m/A_m ratio, which showed a significant inverse correlation ($r = -0.36$, $P < 0.01$) with serum TSH.

Table 2 Left ventricle morphological and functional echocardiographic indices.

	Patients		
	Group A TSH $>$ 3 mU/l ($n = 22$)	Group B TSH $<$ 3 mU/l ($n = 10$)	**Group C** ($n = 13$)
LVMI (g/m^2)	84.11±11.64	84.07±8.68	80.98±12.35
EF (%)	64.77±4.68	63.70±3.50	65.69±5.48
E_m (cm/sec)	61.05±11.23*	64.46±10.22	69.93±9.92
A_m (cm/sec)	57.02±9.45	57.54±18.75	52.79±10.58
E_m/A_m	1.09±0.26**	1.20±0.52	1.36±0.27
IVRT (msec)	95.00±10.91**	88.50±8.14	83.92±9.90

*$P < 0.05$, **$P < 0.001$ vs Group C.
A_m, mitral late diastolic peak velocity; EF, ejection fraction; E_m, mitral early diastolic peak velocity; IVRT, isovolumic relaxation time; LVMI, left ventricle mass index. Values are given as means±S.D.

PWTDI systolic function

PWTDI systolic indices analysis revealed a significant impairment of the systolic ejection in both groups A and B, in comparison with group C, as shown by a decreased S_a and DRS_a ($P < 0.001$ in group A, $P < 0.05$ in group B). Moreover, patients of group A showed an increase of TS_a and DTS_a ($P < 0.05$), and a decrease of ARS_a and DRS_a in respect to group C ($P < 0.001$). None of the systolic PWTDI indices showed significant differences between groups A and B. Table 3 shows PWTDI systolic indices in all the groups.

Table 4 details correlations between PWTDI systolic indices and serum FT_3, FT_4 and TSH when patients of groups A, B and C were analyzed together. Taken collectively, the results showed significant correlations between most systolic indices and serum FT_3 or TSH, whereas, with the exception of DRS_a, no correlation was found with serum FT_4. Some of these correlations are depicted in Fig. 1.

PWTDI diastolic function

PWTDI diastolic recordings analysis revealed a significant impairment of both diastolic relaxation (decreased E_a, ARE_a, DRE_a and E_{al}, $P < 0.001$) and compliance to the ventricular filling (decreased E_a/A_a ratio, $P < 0.001$, and increased E_m/E_{al} ratio, $P < 0.05$) in

Table 3 Systolic mitral annulus indices assessed by PWTDI.

	Patients		
	Group A TSH > 3 mU/l ($n = 22$)	Group B TSH < 3 mU/l ($n = 10$)	**Group C** ($n = 13$)
S_a (cm/sec)	8.68±1.08**	9.03±1.54*	10.65±1.37
TS_a (sec)	0.29±0.02*	0.28±0.01	0.27±0.02
ATS_a (sec)	0.06±0.01	0.05±0.01	0.05±0.01
DTS_a (sec)	0.23±0.03*	0.22±0.01	0.21±0.04
ARS_a (cm/sec^2)	155.74±41.35**	176.55±56.37	227.13±113.58
DRS_a (cm/sec^2)	37.85±5.67**	40.58±7.57*	53.62±19.26

*$P < 0.05$, **$P < 0.001$ vs Group C.
ARS_a: mean acceleration of S_a; ATS_a: acceleration time of S_a; DRS_a: mean deceleration of S_a; DTS_a: deceleration time of S_a; S_a: peak systolic velocity of mitral annulus; Ts_a: $ATS_a + DTS_a$. Values are given as means±S.D.

Table 4 Correlations between PWTDI systolic indices and thyroid hormones in all subjects of Groups A, B and C.

	FT_3		FT_4		TSH	
	r	*P*	r	*P*	r	*P*
S_a	0.37	<0.05	0.28	NS	−0.37	<0.05
TS_a	−0.49	<0.001	0.15	NS	0.44	<0.005
ATS_a	0.06	NS	−0.06	NS	0.13	NS
DTS_a	−0.47	<0.005	−0.20	NS	0.33	<0.05
ARS_a	0.12	NS	0.20	NS	−0.28	NS
DRS_a	0.53	<0.005	0.30	<0.05	−0.46	<0.005

For abbreviations see Table 3.

groups A and B as compared with group C. None of the diastolic PWTDI indices showed significant differences between Groups A and B. Table 5 displays PWTDI diastolic indices in all the three groups.

Table 6 shows correlations between PWTDI diastolic indices and serum FT_3, FT_4 and TSH when patients of groups A, B, and C were analyzed together. Again, in keeping with the important role of this hormone in determining cardiac function, most diastolic parameters were significantly associated to FT_3. Surprisingly, three diastolic indices (E_a/A_a, E_{al}, E_m/E_{al}) were strongly correlated to serum FT_4 and TSH but not to serum FT_3, thus suggesting a different sensitivity to circulating T_3 and T_4 concentrations. The correlations between serum TSH and selected PWTDI diastolic parameters are depicted in Fig. 2.

Discussion

In the present study we carried out an extensive investigation of cardiac function in patients with borderline or mild thyroid failure using PWTDI, a method of wall motion-velocity assessment for quantifying the dynamics of the cardiac cycle. The results obtained confirmed the presence of a diastolic dysfunction in patients with SH and provided further evidence that an impairment of systolic function is present in mild thyroid failure, and also at rest. Moreover, our results provided the first evidence that a subtle impairment in both

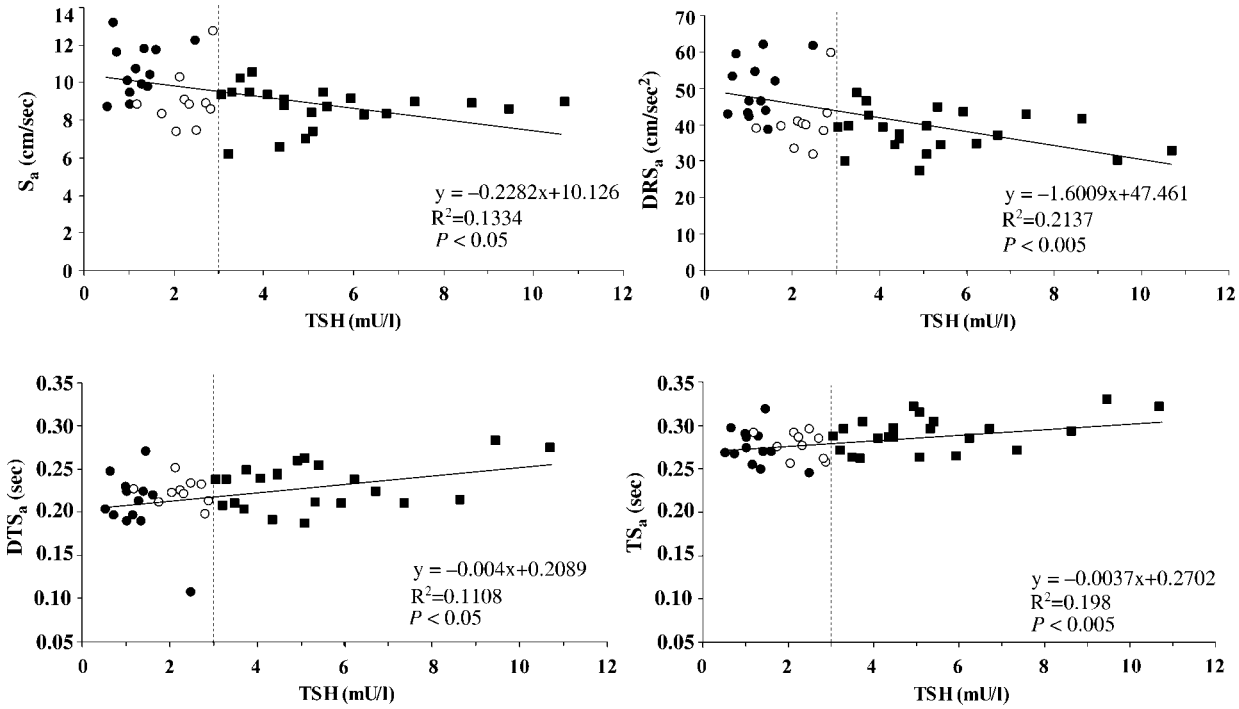

Figure 1 Selected correlations between plasma TSH concentrations and PWTDI systolic indices. ■ TSH > 3 mU/l patients (group A); ○ TSH < 3 mU/l patients (group B); ● control subjects (group C).

Table 5 Diastolic mitral annulus indexes assessed by PWTDI.

	Patients		
	Group A TSH > 3 mU/l ($n = 22$)	Group B TSH < 3 mU/l ($n = 10$)	**Group C** ($n = 13$)
E_a (cm/sec)	10.99±2.35**	12.10±2.58**	15.21±2.5
A_a (cm/sec)	10.84±1.94	11.34±2.15	10.38±1.72
E_a/A_a	1.04±0.28**	1.13±0.37**	1.53±0.47
ATE_a (sec)	0.05±0.00	0.05±0.01	0.05±0.01
DTE_a (sec)	0.08±0.01*	0.08±0.02	0.07±0.01
ARE_a (cm/sec^2)	226.19±57.83**	244.29±59.42**	336.25±71.15
DRE_a (cm/sec^2)	146.50±37.01**	166.45±44.45**	212.30±40.63
E_{al} (cm/sec)	12.65±3.30**	13.42±3.20**	17.94±3.36
E_m/E_{al}	5.00±1.28*	4.85±1.12*	4.03±0.95

*$P < 0.05$, **$P < 0.001$ vs Group C.
A_a: late diastolic velocity of mitral annulus; ARE_a: mean acceleration of E_a; ATE_a: acceleration time of E_a; DRE_a: mean deceleration of E_a; DTE_a: deceleration time of E_a; E_a: early diastolic peak velocity of mitral annulus; E_{al}: early diastolic peak velocity of lateral mitral annulus; E_m: mitral early peak velocity. Values are given as means±S.D.

Table 6 Correlations between PWTDI systolic indices and thyroid hormones in all subjects of Group A, B and C.

	FT_3		FT_4		TSH	
	r	*P*	r	*P*	r	*P*
E_a	0.31	<0.05	0.42	<0.005	−0.53	<0.0005
A_a	0.29	<0.05	−0.06	NS	0.21	NS
E_a/A_a	0.08	NS	0.36	<0.05	−0.46	<0.005
ATE_a	−0.38	<0.05	0.001	NS	0.11	NS
DTE_a	−0.44	<0.005	0.01	NS	0.05	NS
$ATE_a + DTE_a$	−0.44	<0.005	0.11	NS	0.09	NS
ARE_a	0.41	<0.01	0.38	<0.01	−0.50	<0.001
DRE_a	0.46	<0.005	0.36	<0.05	0.28	NS
E_{al} (cm/sec)	0.24	NS	0.40	<0.01	−0.53	<0.005
E_m/E_{al}	0.16	NS	−0.38	<0.01	0.41	<0.01

For abbreviations see Table 5.

systolic and diastolic function is also detected in patients with autoimmune thyroiditis with serum TSH concentration still comprised within the normal range.

As far as the diastolic function is concerned, our results with PWTDI are in keeping with several previous studies (for extensive reviews see (10, 11)) carried out by conventional echocardiography, documenting the presence of a significant diastolic impairment in patients with SH. With respect to conventional echocardiography, PWTDI allowed the use of E_{al}, a relaxation index independent from the preload, and of E_m/E_{al}, a filling index closely correlated with the wedge pressure (17). This approach avoided the potential confounding effects of conventional echocardiography indices of left ventricular filling assessed by Doppler transmitral flow, e.g. E_m/A_m, which are influenced by several confounding factors such as age, heart rate, preload and afterload (22).

In contrast with the consistent findings on diastolic function, the literature provided conflicting data on systolic function in patients with SH. Biondi *et al.* (8) reported a significant reduction of the mean aortic acceleration, whereas peak aortic flow velocity, cardiac output, fractional shortening, and mean velocity of circumferential fiber shortening remained unaltered (8). An impairment of systolic function was observed by means of the systolic time interval, which shows the limits of an indirect method, inferred by the integration of electrocardiographic and Doppler data (9, 12). Systolic abnormalities were detected with certainty in SH only in the course of physical exercise, when the evaluation of the cardiac performance is favored by the discrepancy between the energy request and the functional cardiac reserve (8, 9, 12). In this context, SH has been found to be associated with a deranged cardio-respiratory function, both at the level of anaerobic threshold and at peak exercise (23). Evidence suggesting systolic abnormalities in SH has recently been reported by other techniques such as ultrasonic myocardial textural analysis (24), impedance cardiography (25), and radionuclide ventriculography (26).

By means of recordings performed at several sites of the mitral annulus, the PWTDI technique produces an average figure of the structure displacement velocity, which represents a reliable index of global systolic function (27). This methodological approach allowed us to demonstrate that an impairment of the systolic phase is also present at rest in patients with SH.

On account of the assumption that PWTDI is the most sensitive technique to assess the effects of subtle thyroid failure on heart contractility, we decided to use it to test the possibility that patients with autoimmune thyroiditis and normal TSH levels (i.e. those with a high risk of developing SH or overt thyroid failure) may actually be slightly hypothyroid: this condition has been recently envisaged (6, 28) but, to our knowledge, no investigation (and particularly no studies on heart contractility) has been carried out to directly address the question.

Unlike conventional echocardiography, which did not show any significant alteration in both systolic and diastolic function of patients with 'euthyroid' autoimmune thyroiditis, PWTDI allowed us to detect a subtle but significant impairment in the whole cardiac function of these individuals. In detail, our findings were consistent in showing a significant impairment of left ventricular ejection (decreased S_a and DRS_a), diastolic relaxation (decreased E_a, ARE_a, DRE_a and E_{al}) and ventricular filling (decreased E_a/A_a ratio and increased E_m/E_{al}).

The degree of derangement of the above parameters found in patients with 'euthyroid' autoimmune thyroiditis was always intermediate between patients with SH and normal euthyroid controls.

These results, along with the significant correlations of a number of PWTDI indices with thyroid hormones

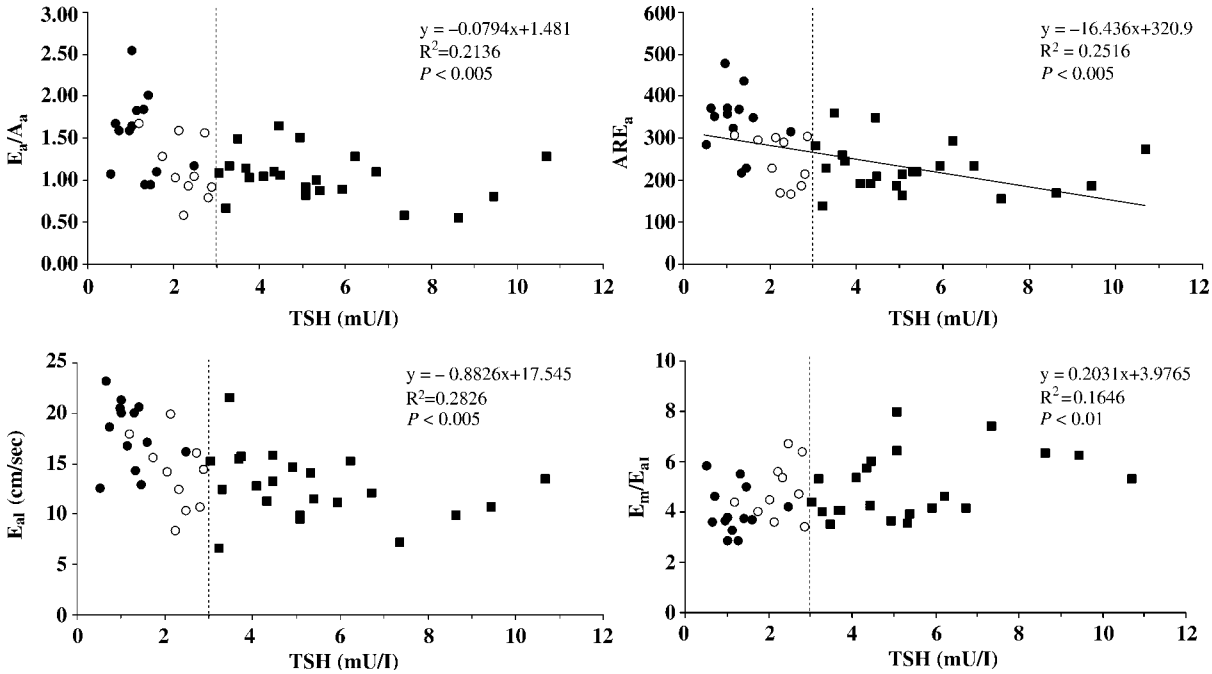

Figure 2 Selected correlations between plasma TSH concentrations and PWTDI diastolic indices. ■ TSH > 3 mU/l patients (Group A); ○ TSH < 3 mU/l patients (Group B); ● control subjects (Group C).

and TSH concentrations, strongly support the concept of a continuum spectrum of a slight thyroid failure in autoimmune thyroiditis extending to subjects with serum TSH still within the normal range. The majority of PWTDI indices were correlated to serum FT_3 rather than FT_4 concentrations. This proves the pivotal role of T_3 in cardiac function. Moreover, some diastolic indices such as E_a/A_a, E_{al} and E_m/E_{al} were significantly correlated to FT_4 but not to FT_3. The reason for such findings is unclear and cannot be derived from the present data. We are inclined to think that some indices may be more affected by local generation of T_3 (from circulating T_4) than by circulating T_3. Indeed, autoimmune thyroid disease is so common in the population (up to 40% of women with lymphocytic infiltration of the thyroid and 10–15% with thyroid autoantibodies) (1–4), that laboratory reference ranges derived from apparently healthy subjects could easily be affected by diseased individuals. In keeping with this concept, increased prevalence of TPOAb has been found in subjects with serum TSH concentrations outside the narrow range 0.2–1.9 mU/l, providing evidence that TSH in the upper reference range is often associated with abnormal pathology in the thyroid (7).

In conclusion, by showing an impaired systolic function in the basal condition of patients with SH, the tissue Doppler imaging has extended our knowledge of the cardiac involvement in this disease. However, the clinical relevance of this finding and the effects of L-thyroxine substitution therapy remain matters for further investigation.

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