Usefulness of pulsed tissue Doppler for the assessment of left ventricular myocardial function in overt hypothyroidism

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Background. **The aim of this study was to assess the role of tissue Doppler (TD) in the identification of left ventricular (LV) myocardial regional abnormalities in overt hypothyroidism.**

Methods. **Fourteen women with newly diagnosed, never treated overt hypothyroidism and 14 healthy women, matched for age, underwent standard echocardiography and pulsed TD, by placing the sample volume at the basal posterior septum and lateral mitral annulus, in the apical 4-chamber view. The myocardial systolic (S_m) and diastolic velocities (E_m, A_m and their ratio) and time intervals (relaxation time [RT_m], pre-contraction time [PCT_m], contraction time) were measured.**

Results. **The two groups were comparable for body surface area, blood pressure and heart rate. At standard echocardiography, patients with overt hypothyroidism had a significantly greater septal thickness and LV mass index, a longer LV pre-ejection period (PEP), deceleration time and isovolumic relaxation time (IVRT) and a lower E peak velocity and E/A ratio. TD showed a significantly longer PCT_m and RT_m and a lower E_m and E_m/A_m ratio of both the septum and mitral annulus in overt hypothyroidism. The ratio of the standard Doppler E to E_m of the mitral annulus was 5.5 ± 1.2 in controls and 5.3 ± 1.7 in overt hypothyroidism (p = NS). In the overall population, PEP, IVRT, PCT_m and RT_m were correlated negatively with FT3 and FT4, and positively with thyroid-stimulating hormone. After adjusting for age, body surface area and heart rate in separate multivariate analyses, the associations of TD PCT_m with the thyroid hormones and thyroid-stimulating hormone were greater than the homologous associations of standard Doppler PEP.**

Conclusions. **Standard echocardiography confirms itself as a satisfactory diagnostic technique for the identification of LV global dysfunction in overt hypothyroidism. Pulsed TD may be useful to determine the severity of LV myocardial dysfunction in relation to the degree of hormonal impairment.**

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Introduction

Thyroid hormones influence several metabolic processes in almost all tissues and the cardiovascular system is particularly sensitive to their action. Basic studies have shown that the effects of thyroid hormones on the heart are exerted by their ability to regulate the transcription of myocyte specific genes, encoding important structural and regulatory proteins[1,2]. Thyroid hormones control heart beating and cardiac contractility directly and also by modifying tissue metabolism, extracellular fluid volume and distribution, and catecholamine effects[3,4]. Both deficiency and excess of thyroid hormones may be associated with clinical overt cardiovascular alterations[5-8].

Overt hypothyroidism is a common disease affecting about 1-2% of the adult population, in particular females. The most common cause is thyroid gland failure, due to chronic autoimmune lymphocytic thyroiditis[7,8]. Low serum concentrations of thyroid hormones are associated with a decrease in left ventricular (LV) cardiac output, myocardial contractility and relaxation, and an increase in systemic vascular resistance[8]. These findings are documented by several observations using noninvasive techniques such as radionuclide ventriculography and standard Doppler echocardiography[3-8].

Pulsed tissue Doppler (TD) is a tool which allows measurement of myocardial regional wall motion. Whereas standard echocardiography provides information on the global LV function, TD allows the measurement of the velocities and time intervals at multiple myocardial levels by placing a sample volume within a chosen myocardial wall[9-15]. This tool could be useful

in the clinical setting for the determination of the degree of LV myocardial involvement in overt hypothyroidism. In a recent study of ours, we have demonstrated the usefulness of TD for the detection of subclinical hypothyroidism[16].

On these grounds, the present study was designed to investigate the regional LV myocardial function in overt hypothyroidism by using pulsed TD, in relation to the hormonal profile and standard Doppler echocardiographic examination.

Methods

Study protocol. Fourteen women (mean age 38.9 ± 12.7 years) with newly diagnosed, never treated, autoimmune primary overt hypothyroidism and no previous history of thyrotoxicosis were included in the study after their informed consent and the approval of the Institutional Ethical Committee were obtained. Overt hypothyroidism was diagnosed on the basis of thyroid-stimulating hormone (TSH) values frankly above normal, associated with FT3 and FT4 serum levels less than the normal range. Fourteen healthy women, matched for age (SD ± 2 years) to the patients with overt hypothyroidism, recruited among the staff and relatives of our Departments, represented the control group. The exclusion criteria were: systemic arterial hypertension, diabetes mellitus, coronary artery disease, heart failure, valvular heart disease, primitive and congenital cardiomyopathies, respiratory, hematological, liver and/or kidney diseases, pregnancy, the administration of cardiac medications or any drug known to interfere with myocardial function, and echocardiograms of inadequate quality. At the time of admission, the demographic and anthropometric data of the patients were collected and blood sampling for serum FT3, FT4 and TSH as well as standard Doppler echocardiography and pulsed TD were performed on all participants.

Anthropometric and laboratory determinations. The body weight and height were measured and the body surface area (BSA) calculated using the standard formula. All blood samples for circulating serum FT3, FT4 and TSH were collected from the antecubital vein between 08:00 and 09:00 a.m. after an overnight fast. The serum levels of TSH, FT3 and FT4 were determined using chemiluminescent microparticle immunoassay kits, as previously described[16].

Procedures. Standard Doppler echocardiography and pulsed TD were performed using the Vingmed system Five (GE, Horten, Norway) equipped with TD capabilities. A variable frequency phased-array transducer (2.5-3.5-4.0 MHz) was used for Doppler echocardiography and TD. At the end of the study, the cuff blood pressure (mean of 3 measurements) was estimated by a physician who was blinded to the examination. Doppler-echo and TD tracings were recorded on super VHS videotapes and high-fidelity paper strip at a velocity of 50-100 mm/s. All measurements were analyzed by two experienced sonographers, unaware of the clinical and laboratory data, on an average of 3 to 5 cardiac cycles.

Doppler echocardiographic examination. M-mode quantitative analysis was performed in accordance with the recommendations of the American Society of Echocardiography in the parasternal long-axis view[17]. LV mass (in grams) was indexed for both the BSA[18] and height$^{2.7}$ [19]. Relative diastolic wall thickness was determined as the ratio between the sum of the septal thickness + posterior wall thickness and LV end-diastolic diameter. Fractional shortening was calculated as the percentage change in LV internal dimensions between systole and diastole. Pulsed Doppler of the LV systolic outflow tract was performed by placing the sample volume close to the aortic valve. The LV preejection period (PEP in ms, from ECG QRS to the beginning of systolic ejection), LV ejection time (LVET in ms, from the onset to the end of ejection) and the PEP/LVET ratio were determined as systolic time intervals. The stroke volume (SV, ml) was estimated in accordance with the outflow tract method using the following formula: SV = systolic time velocity integral × LV output diameter (in cm)[20]. The cardiac output (l/min) was calculated using the formula: CO = SV (ml) × heart rate (b/min). Pulsed Doppler LV inflow recording was performed in the apical 4-chamber view, by placing the sample volume at the level of the tips. The early (E) and atrial (A) peak velocities (m/s) and the E/A ratio, E velocity deceleration time (DT, ms) and isovolumic relaxation time (IVRT in ms, as the time interval between the end of systolic output flow and transmitral E velocity onset, by placing the sample volume between outflow tract and the mitral valve) were measured as indexes of the global LV diastolic function. Our methods and the reproducibility of LV Doppler indexes have been reported previously[21].

Tissue Doppler examination. Pulsed TD was performed at transducer frequencies of 3.5-4.0 MHz, adjusting the spectral pulsed Doppler signal filters until they reached a Nyquist limit of 15-20 cm/s, and using the minimum optimal gain. In the apical 4-chamber view, a 5 mm pulsed Doppler sample volume was subsequently placed at the level of the basal septum, taken as a regional myocardial wall, and at the basal LV lateral mitral annulus which reflects the global longitudinal motion of the left ventricle. The apical view was chosen to obtain a quantitative assessment of the regional wall motion almost simultaneously with the Doppler LV inflow and to minimize the incidence angle between the Doppler beam and the LV longitudinal wall motion. Pulsed TD of a chosen segment is characterized by a positive myocardial systolic velocity (S_m) and by two

negative diastolic velocities, the early (E_m) and the atrial (A_m). The S_m peak velocity (m/s), myocardial precontraction time (PCT_m, from the onset of the ECG QRS to the beginning of S_m), myocardial contraction time (CT_m, from the beginning to the end of the S_m wave) (both in ms) and the PCT_m/CT_m ratio were calculated as myocardial systolic indexes. The E_m and A_m peak velocities (m/s), E_m/A_m ratio and the myocardial relaxation time (RT_m in ms, as the time interval between the end of S_m and the onset of E_m) were determined as myocardial diastolic measurements. The ratio of the standard Doppler mitral E peak velocity to the E_m of the LV lateral mitral annulus (E/E_m ratio) was determined to unmask any possible increase in LV end-diastolic pressure[22-24]. The TD methods and reproducibility of our laboratory analyses have been described previously[10].

Statistical analysis. All the analyses were performed using SPSS for Windows, version 6.0 (Chicago, IL, USA). Variables are presented as mean ± SD. Analysis of variance (ANOVA) was used to estimate intergroup differences. Linear regression analyses and partial correlation test by Pearson's method were performed to assess univariate relations and stepwise, forward, multiple regression analyses to weigh the independent effects of potential determinants on a dependent variable. Differences were considered significant at $p < 0.05$.

Results

The demographic, clinical and laboratory characteristics of the study population are listed in table I. By selection, patients with overt hypothyroidism had significantly lower values of FT3 and FT4 and higher TSH serum levels. The two groups were comparable for age, BSA, blood pressure and heart rate.

No patients with overt hypothyroidism showed abnormalities of the regional LV wall motion (wall motion score index 1.0). Table II reports the results of M-mode echocardiographic analysis. The septal wall thickness and LV mass index (both for BSA and for height$^{2.7}$) were slightly greater in overt hypothyroidism than in the control group. The endocardial fractional shortening was similar between the two groups.

The analysis of standard Doppler measurements is presented in table III, where the time intervals are also analyzed adjusting for heart rate (measured time interval/$\sqrt{}$R-R). Patients with overt hypothyroidism had a longer PEP ($p < 0.0001$) and a higher PEP/LVET ratio ($p < 0.001$), DT ($p < 0.05$) and IVRT ($p < 0.005$), and a lower E peak velocity ($p < 0.01$) and E/A ratio ($p < 0.01$).

Table IV shows the TD measurements where the myocardial time intervals are also analyzed by adjusting for $\sqrt{}$R-R. In overt hypothyroidism, PCT_m and RT_m were significantly longer, the PCT_m/CT_m ratio higher and both the E_m peak velocity and E_m/A_m ratio lower than in controls, at the level of both the posterior septum and lateral annulus. Figure 1 shows the TD-derived PCT_m and RT_m in a normal subject and in a patient with overt hypothyroidism, where both these myocardial time intervals are prolonged.

Of note, the ratio of the standard Doppler transmitral inflow E to E_m of the mitral annulus (E/E_m ratio) was 5.5 ± 1.2 in controls and 5.3 ± 1.7 in overt hypothyroidism (p = NS) (data not shown).

Table I. Characteristics of the study population.

Variable	Hypothyroidism (n = 14)	Control group (n = 14)	p
Age (years)	38.9 ± 12.7	38.8 ± 11.9	NS
BSA (m^2)	1.75 ± 0.19	1.69 ± 0.21	NS
SBP (mmHg)	116.4 ± 11.5	118.6 ± 11.0	NS
DBP (mmHg)	72.1 ± 11.0	73.9 ± 7.9	NS
MBP (mmHg)	86.9 ± 10.6	88.8 ± 8.2	NS
HR (b/min)	68.1 ± 8.7	68.9 ± 6.2	NS
FT3 (pg/ml)	1.49 ± 0.61	2.46 ± 0.42	< 0.0001
FT4 (pg/ml)	3.76 ± 2.0	10.57 ± 1.51	< 0.0001
TSH (mIU/l)	104.0 ± 37.7	1.14 ± 0.63	< 0.0001

Data are expressed as mean ± SD. BSA = body surface area; DBP = diastolic blood pressure; HR = heart rate; MBP = mean blood pressure; SBP = systolic blood pressure; TSH = thyroid-stimulating hormone.

Table II. M-mode echocardiographic analysis.

Variable	Hypothyroidism	Control group	p
Septal wall thickness (mm)	9.4 ± 1.3	8.4 ± 1.2	< 0.05
Posterior wall thickness (mm)	7.7 ± 1.7	7.8 ± 2.9	NS
LV internal diastolic diameter (mm)	49.5 ± 3.2	48.7 ± 4.6	NS
LV internal systolic diameter (mm)	34.2 ± 2.6	33.3 ± 4.2	NS
Endocardial fractional shortening (%)	30.9 ± 5.0	31.7 ± 6.1	NS
Relative diastolic wall thickness	0.33 ± 0.08	0.33 ± 0.11	NS
LV mass (g)	153.6 ± 30.1	131.2 ± 27.1	< 0.05
LV mass/BSA (g/m^2)	88.6 ± 15.0	76.9 ± 14.9	< 0.05
LV mass/height$^{2.7}$ ($g/m^{2.7}$)	38.5 ± 8.3	31.8 ± 8.5	< 0.05

Data are expressed as mean ± SD. BSA = body surface area; LV = left ventricular.

Table III. Standard Doppler echocardiographic analysis of the study population.

Variable	Hypothyroidism	Control group	p
SV (ml)	61.6 ± 10.3	69.9 ± 10.9	< 0.05
CO (l/m)	4.67 ± 1.33	4.76 ± 1.33	NS
PEP (ms)	118.0 ± 21.4	90.0 ± 19.7	< 0.0001
Adjusted PEP* (ms/√R-R)	4.1 ± 0.81	2.98 ± 0.62	< 0.0001
PEP/LVET	0.53 ± 0.08	0.42 ± 0.07	< 0.001
Adjusted PEP/LVET ratio*	0.43 ± 0.09	0.31 ± 0.08	< 0.001
E peak velocity (m/s)	0.61 ± 0.13	0.74 ± 0.15	< 0.01
A peak velocity (m/s)	0.51 ± 0.15	0.56 ± 0.09	NS
Peak velocity E/A ratio	1.18 ± 0.21	1.34 ± 0.31	< 0.01
DT (ms)	175.7 ± 31.7	152.0 ± 27.1	< 0.05
Adjusted DT* (ms/√R-R)	5.90 ± 1.26	4.85 ± 0.96	< 0.02
IVRT (ms)	93.8 ± 17.6	75.3 ± 12.6	< 0.005
Adjusted IVRT* (ms/√R-R)	3.12 ± 0.43	2.50 ± 0.45	< 0.001

Data are expressed as mean ± SD. CO = cardiac output; DT = deceleration time; IVRT = isovolumic relaxation time; LVET = left ventricular ejection time; PEP = pre-ejection period; SV = stroke volume. * data adjusted for √R-R.

Table IV. Pulsed tissue Doppler analysis of the study population.

Variable	Hypothyroidism	Control group	p
Posterior septal wal			
S_m peak (m/s)	0.06 ± 0.01	0.06 ± 0.01	NS
PCT_m (ms)	167.1 ± 19.4	111.4 ± 16.6	< 0.0001
Adjusted PCT_m* (ms/√R-R)	5.76 ± 0.75	4.14 ± 0.63	< 0.0001
PCT_m/CT_m ratio	0.56 ± 0.07	0.35 ± 0.06	< 0.0001
Adjusted PCT_m/CT_m ratio*	0.57 ± 0.08	0.39 ± 0.07	< 0.0001
E_m peak velocity (m/s)	0.09 ± 0.02	0.11 ± 0.02	< 0.05
A_m peak velocity (m/s)	0.08 ± 0.02	0.08 ± 0.02	NS
Peak E_m/A_m ratio	1.12 ± 0.26	1.48 ± 0.28	< 0.01
RT_m (ms)	92.5 ± 17.0	68.1 ± 16.6	< 0.0001
Adjusted RT_m* (ms/√R-R)	3.15 ± 0.87	2.13 ± 0.40	< 0.0001
LV mitral lateral annulus			
S_m peak (m/s)	0.07 ± 0.02	0.08 ± 0.02	NS
PCT_m (ms)	161.4 ± 26.8	107.0 ± 15.2	< 0.0001
Adjusted PCT_m* (ms/√R-R)	5.57 ± 1.04	4.13 ± 0.69	< 0.0001
PCT_m/CT_m ratio	0.54 ± 0.12	0.34 ± 0.06	< 0.0001
Adjusted PCT_m/CT_m ratio*	0.55 ± 0.13	0.40 ± 0.08	< 0.0001
E_m peak velocity (m/s)	0.11 ± 0.04	0.14 ± 0.04	< 0.05
A_m peak velocity (m/s)	0.08 ± 0.02	0.08 ± 0.02	NS
Peak E_m/A_m ratio	1.36 ± 0.38	1.77 ± 0.71	< 0.005
RT_m (ms)	91.4 ± 21.8	64.9 ± 18.5	< 0.002
Adjusted RT_m* (ms/√R-R)	3.40 ± 0.74	2.21 ± 0.74	< 0.0001

Data are expressed as mean ± SD. A_m = myocardial atrial velocity; CT_m = myocardial contraction time; DT_m = myocardial deceleration time; E_m = myocardial early velocity; LV = left ventricular; PCT_m = myocardial pre-contraction time; RT_m = myocardial relaxation time; S_m = myocardial systolic velocity. * data adjusted for √R-R.

Univariate relations in the overall population. Among standard Doppler echocardiographic measurements, PEP and IVRT were related to FT3 (r = -0.47, p < 0.01 and r = -0.60, p < 0.001 respectively), FT4 (r = -0.55, p < 0.002 and r = -0.60, p < 0.001 respectively) and TSH (r = 0.46, p < 0.01 and r = 0.59, p < 0.001 respectively), the PEP/LVET ratio was negatively correlated with FT3 (r = -0.49, p < 0.01) and FT4 (r = -0.66, p < 0.0001) while the association with TSH did not reach statistical significance. The relations of the other standard Doppler and M-mode measurements with thyroid hormones and TSH were not significant.

Among TD measurements, at the septal wall PCT_m and RT_m were related to FT3 (r = -0.66, p < 0.0001 and r = -0.56, p < 0.002 respectively), FT4 (r = -0.76 and r = -0.67, both p < 0.0001) and TSH (r = 0.55, p < 0.002 and r = 0.54, p < 0.005 respectively). At the level of the LV mitral annulus, PCT_m and RT_m were related to FT3 (r = -0.50, p < 0.01 and r = -0.55, p < 0.002 respectively), FT4 (r = -0.75 and r = -0.68, both p < 0.0001) and TSH (r = 0.53 and r = 0.54, both p < 0.005). The PCT_m/CT_m ratio of both the septum and mitral annulus were negatively correlated with FT3 (r = -0.65, p < 0.0001 and r = -0.50, p < 0.01 respectively) and FT4

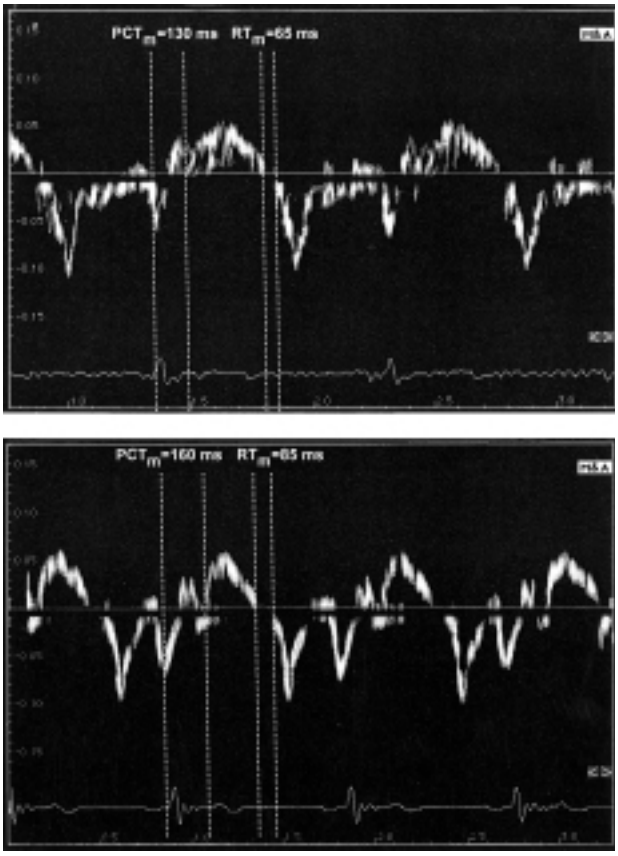

Figure 1. *Pulsed tissue Doppler pattern of the posterior septum in a healthy woman* (upper panel) *and in a woman with overt hypothyroidism* (lower panel*). The E_m/A_m ratio is > 1 in both cases, but the myocardial pre-contraction time (PCT_m) and relaxation time (RT_m) are longer in the patient with overt hypothyroidism.*

(r = -0.76, p < 0.0001 and r = -0.68, p < 0.0001) while the positive association with TSH was significant (r = 0.58, p < 0.001) only at the septal level. The other TD measurements of both the posterior septum and LV mitral annulus were not related to these hormones.

Figure 2 shows the negative relations of FT4 with standard Doppler PEP and TD-derived PCT_m of the septum and of the LV mitral annulus in the overall population. The scatterplots show how these associations involve a wide spectrum of thyroid functions.

Multiple linear regression analyses. The relations of FT3, FT4 and TSH with standard Doppler and TD indexes were tested in the pooled groups by adjusting for potential confounders such as age, heart rate and BSA in separate multilinear regression analyses (Table V). These analyses showed a greater association of thyroid hormones with the TD-derived (both septal and annular) PCT_m than with standard Doppler-derived LV PEP while the association of thyroid hormones with the septal and annular RT_m was greater than with IVRT, except for TSH whose associations were substantially similar. The associations of the PEP/LVET ratio with thyroid hormones (data not shown) were not independent of the BSA and heart rate. Homologous associations of the PCT_m/CT_m ratio with thyroid hormones were significant, after adjusting for age, BSA and heart rate, at the level of posterior septum (β = -0.65, p < 0.0001 with FT3; β = -0.76, p < 0.0001 with FT4; β = 0.58, p < 0.001 with TSH) but not at the level of LV mitral annulus (data not shown).

Discussion

Standard evaluation of the left ventricular global function in overt hypothyroidism. The first studies to assess cardiac function noninvasively in patients with overt hypothyroidism used LV systolic time intervals

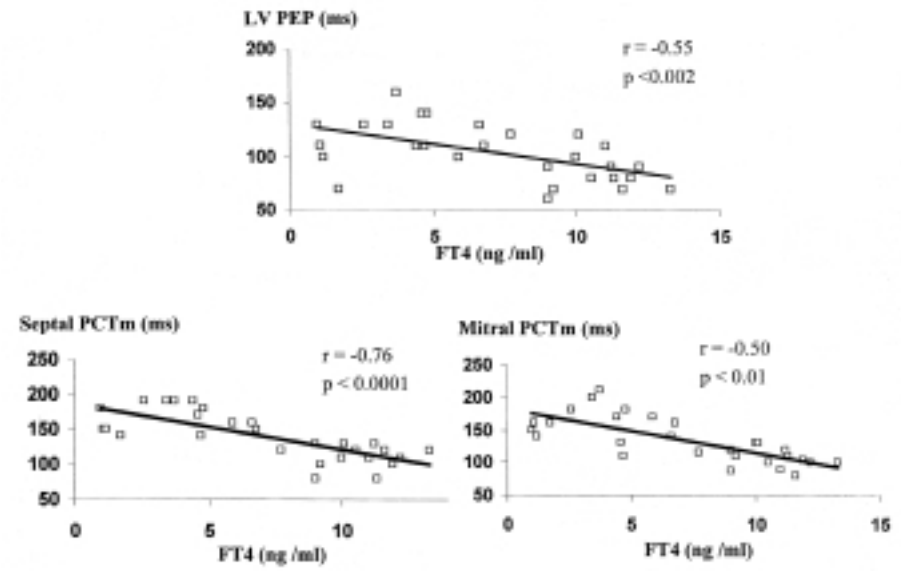

Figure 2. *Significant univariate relations of FT4 with the left ventricular pre-ejection period (LV PEP)* (upper panel) *and with the tissue Doppler-derived myocardial pre-contraction time (PCT_m) of both the septal wall and mitral annulus* (lower panel).

Table V. Multiple linear regression analysis with FT4 and thyroid-stimulating hormone (TSH) as independent variables and the pre-ejection period (PEP), isovolumic relaxation time (IVRT), myocardial pre-contraction time (PCT_m) and relaxation time (RT_m) of the posterior septal wall and left ventricular (LV) mitral lateral annulus as dependent variables, after adjusting for age, body surface area and heart rate.

Variable	FT3		FT4		TSH	
	β (t)	p	β (t)	p	β (t)	p
LV PEP	-0.47 (-2.32)	< 0.01	-0.56 (-3.27)	< 0.002	0.44 (2.44)	< 0.01
TD septal PCT_m	-0.66 (-4.06)	< 0.0001	-0.76 (-5.44)	< 0.0001	0.57 (-3.04)	< 0.002
TD annular PCT_m	-0.56 (-2.85)	< 0.002	-0.75 (-4.33)	< 0.0001	0.55 (3.01)	< 0.002
IVRT (ms)	-0.55 (-2.26)	< 0.002	-0.56 (-4.32)	< 0.002	0.60 (3.17)	< 0.001
TD septal RT_m (ms)	-0.60 (-2.35)	< 0.001	-0.68 (-5.03)	< 0.0001	0.56 (3.16)	< 0.002
TD annular RT_m (ms)	-0.60 (-2.52)	< 0.001	-0.67 (-5.34)	< 0.0001	0.59 (3.21)	< 0.001

TD = tissue Doppler.

measured by means of a polygraphic technique. This tool showed prolongation of PEP, shortening of LVET, and an increase of the PEP/LVET ratio[25-29], in relation to an impairment in LV myocardial contractility[30]. Subsequent reports in which M-mode and two-dimensional echocardiography were used described an asymmetric, disproportionate increase in septal thickness and in the ratio of the septal to posterior wall thickness[31] as well as an impairment of the regional septal wall motion and of the LV global function[32] in long-standing, untreated overt hypothyroidism. Simultaneous ECG, phonocardiographic and echocardiographic recordings allowed the identification of a prolonged IVRT[33]. These findings were confirmed at standard Doppler by means of which a pattern of impaired LV relaxation, characterized by a prolonged IVRT and a reduced E peak velocity[34], was demonstrated. More recently, prolongation of the systolic and early diastolic times and impairment of LV function were also detected at radionuclide ventriculography[35].

Among all these techniques, M-mode, two-dimensional and Doppler echo are simple and reliable methods but provide information only on LV global morphology and function. Pulsed TD has the peculiarity of providing quantitative analysis of myocardial wall motion, by measuring the regional (both systolic and diastolic) velocities and time intervals of multiple LV walls[10-12,22-25,36]. The reproducibility of TD has been tested[10] and the normal reference values of TD measurements have been reported[37,38].

Tissue Doppler evaluation of the left ventricular regional function in overt hypothyroidism. In a recent paper, we described the usefulness of pulsed TD for the identification of LV functional abnormalities in subclinical hypothyroidism[16]. In this setting, the septal and LV annular PCT_m, and RT_m were longer and the PCT_m/CT_m ratio higher than in controls. A similar behavior was observed even for the standard Doppler homologous indexes of LV global function (LV PEP, IVRT and PEP/LVET ratio). However, after adjusting for BSA and heart rate, IVRT was the only standard Doppler measurement correlated with FT4 and TSH, while TD-derived PCT_m and RT_m were negatively correlated with FT4 and RT_m was positively correlated with TSH.

In the present study, we investigated LV myocardial function in overt hypothyroidism again combining standard Doppler echocardiography and pulsed TD. Standard Doppler confirmed the prolongation of LV PEP, DT and IVRT as well as the increase in the PEP/LVET ratio and the reduction in E peak velocity and E/A ratio already found in overt hypothyroidism[25-29,33-35]. Even TD-derived PCT_m and RT_m were significantly longer, the PCT_m/CT_m ratio higher and the E_m peak velocity and E_m/A_m ratio lower than in controls at the level of the basal posterior septum. Worthy of note, TD of the posterior septum measures the functional properties which are directly dependent on the myocardial structure[39]. Although myocardial function should be sampled at numerous levels of the LV walls, the information provided by the posterior septum (where TD is particularly clear) may be extended to the other walls in the absence of regional wall motion abnormalities[9] which were not detected in the patients with overt hypothyroidism of the present study. The same TD measurements were altered even at the level of the LV mitral annulus, which provides information on the LV longitudinal global function[36]. Significant changes of the E/E_m ratio, a sensitive marker of the increase in LV end-diastolic pressure[22-24], could not be expected in our population sample, where patients with heart failure and thus with possibly elevated LV end-diastolic pressures were excluded by selection.

Among TD measurements, PCT_m and RT_m were very sensitive to LV myocardial involvement in overt hypothyroidism. PCT_m and RT_m, myocardial periods preceding LV contraction and filling respectively, when both the aortic and mitral valves are closed and LV volumes constant, are two different expressions of energy-dependent myocardial processes[40]. They depend on cytosolic calcium levels controlled by ATP-dependent calcium ion transport within the sarcoplasmic reticulum[41]. In turn, calcium-channel transport is modulated by the effect of circulating thyroid hormones[1].

Relation between the degree of hormone deficiency and extent of left ventricular involvement. In the present study, significant relations were found between standard Doppler and TD measurements and the hormone levels in the overall population. PEP and IVRT were negatively related to FT3 and FT4 and positively to TSH. Similarly, TD-derived PCT_m and RT_m were negatively correlated with FT3 and FT4 and positively with TSH. Even the Doppler standard PEP/LVET and TD septal and annular PCT_m/CT_m ratios were significantly correlated with hormones but, after adjusting for physiologic confounders[42,43], among these associations only that involving the septal PCT_m/CT_m ratio remained significant. Multiple regression analyses provided additional information since the magnitude of the associations of hormones with PCT_m and RT_m (except those with TSH) were substantially greater than the corresponding relations with standard Doppler LV PEP. TD appears, therefore, more effective than standard Doppler in determining the degree of LV systolic impairment in relation to the severity of hormone deficiency.

Study limitations. The first limitation is due to the performance of mitral annular TD only at the level of the lateral corner which can reflect the global, systolic and/or diastolic function only if the latter is normal or homogeneously depressed. In case of LV diastolic dysfunction involving one or two walls, the association between TD of a single corner and the global longitudinal function is not so good. Thus, the average of the velocities of at least 4 annular corners (lateral and septal, anterior and inferior) would have been more accurate. A similar criticism may be made regarding TD myocardial assessment which could have been more comprehensive if performed in LV regions other than the posterior septum alone. However, in the absence of wall motion abnormalities, septal TD may be considered representative of the myocardial muscle. In addition, our population sample was relatively small for correlation analyses and, by selection, included patients with no evidence of cardiac disease or wall motion abnormalities. The results obtained at standard Doppler and TD could be substantially different in patients with coexisting cardiac diseases.

In conclusion, the current study confirms that overt hypothyroidism is associated with LV dysfunction involving both the systolic and diastolic measurements. Standard Doppler echocardiography is satisfactory enough to determine the LV global involvement due to thyroid failure. However, on the grounds of independent associations found between the degree of TD myocardial impairment and the magnitude of hormonal deficiency, TD may constitute an additional tool to better assess the extent of LV myocardial damage in relation to the severity of disease. Subsequent studies should investigate the effect of L-thyroxine therapy on TD-derived myocardial abnormalities in patients affected by overt hypothyroidism.

References

1. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-9.
2. Dillmann WH. Biochemical basis of thyroid hormone action in the heart. Am J Med 1990; 88: 626-30.
3. Bengel FM, Nekolla SG, Ibrahim T, Weniger C, Ziegler SI, Schwaiger M. Effects of thyroid hormones on cardiac function, geometry and oxidative metabolism assessed non invasively by positron emission tomography and magnetic resonance imaging. J Clin Endocrinol Metab 2000; 85: 1822-7.
4. Gomberg-Maitland M, Frishman WH. Thyroid hormone and cardiovascular disease. Am Heart J 1998; 135: 187-96.
5. Klein I, Ojamaa K. Clinical review 36: cardiovascular manifestations of endocrine diseases. J Clin Endocrinol Metab 1992; 75: 339-42.
6. Landenson PW. Recognition and management of cardiovascular disease related to thyroid dysfunction. Am J Med 1999; 88: 638-41.
7. Klein I. Thyroid hormone and the cardiovascular system. Am J Med 1990; 88: 631-7.
8. Toft AD, Boon NA. Thyroid disease and the heart. Heart 2000; 84: 455-60.
9. Derumeaux G, Ovize M, Loufoua J, et al. Doppler tissue imaging quantitates regional wall motion during myocardial ischemia and reperfusion. Circulation 1998; 97: 1970-7.
10. Galderisi M, Caso P, Severino S, et al. Myocardial diastolic impairment due to left ventricular hypertrophy involves basal septum more than other walls: analysis by pulsed Doppler tissue imaging. J Hypertens 1999; 17: 685-93.
11. Severino S, Caso P, Galderisi M, et al. Use of pulsed Doppler tissue imaging to assess regional left ventricular diastolic dysfunction in hypertrophic cardiomyopathy. Am J Cardiol 1998; 82: 1394-8.
12. Caso P, D'Andrea A, Galderisi M, et al. Pulsed Doppler tissue imaging in endurance athletes: relation between left ventricular preload and myocardial regional diastolic function. Am J Cardiol 2000; 85: 1131-6.
13. Isaaz K, Thompson A, Ethevenot G, Cloez JL, Brembilla B, Pernot C. Doppler echocardiography measurement of low velocity motion of the left ventricular posterior wall. Am J Cardiol 1989; 64: 66-75.
14. McDicken WN, Sutherland GR, Gordon LN. Color Doppler velocity imaging of the myocardium. Ultrasound Med Biol 1992; 18: 651-4.
15. Sutherland GR, Stewart MJ, Groundstroem KW, et al. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. J Am Soc Echocardiogr 1994; 7: 441-58.
16. Vitale G, Galderisi M, Lupoli GA, et al. Left ventricular myocardial impairment in subclinical hypothyroidism assessed by a new ultrasound tool: pulsed tissue Doppler. J Clin Endocrinol Metab 2002; 87: 4350-5.
17. Sahn DJ, De Maris A, Kisslo J, Weyman A, for the Committee on M-mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiographic measurements. Circulation 1978; 58: 1072-83.
18. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol 1987; 59: 956-60.
19. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992; 20: 1251-60.

20. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984; 70: 425-31.
21. Galderisi M, Paolisso G, Tagliamonte MR, et al. Is insulin action a determinant of left ventricular relaxation in uncomplicated essential hypertension? J Hypertens 1997; 15: 745-50.
22. Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD. An index of early left ventricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. J Am Coll Cardiol 1997; 29: 448-54.
23. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997; 30: 1527-33.
24. Garcia MJ, Thomas JD. Tissue Doppler to assess diastolic left ventricular function. Echocardiography 1999; 16: 501-8.
25. Hillis WS, Bremner WF, Lawrie TD, Thomson JA. Systolic time intervals in thyroid disease. Clin Endocrinol 1975; 4: 617-24.
26. Bough EW, Crowley WF, Ridgway C, et al. Myocardial function in hypothyroidism. Relation to disease severity and response to treatment. Arch Intern Med 1978; 138: 1476-80.
27. Crowley WF Jr, Ridgway EC, Bough EW, et al. Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. N Engl J Med 1977; 296: 1-6.
28. Plotnick GD, Vassar DL, Parisi AF, Hamilton BP, Carliner NH, Fisher ML. Systolic time intervals in hypothyroidism: end organ function as a reflection of clinical status. Am J Med Sci 1979; 277: 263-8.
29. Lupoli G, Biondi B, Montedoro D, et al. Systolic time intervals (STI) in various thyroid diseases. Acta Cardiol 1991; 46: 87-91.
30. Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. Circulation 1968; 37: 149-52.
31. Santos AD, Miller RP, Mathew PK, Wallace WA, Cave WT Jr, Hinojosa L. Echocardiographic characterization of the reversible cardiomyopathy of hypothyroidism. Am J Med 1986; 68: 675-82.
32. Shenoy MM, Goldman JM. Hypothyroidism cardiomyopathy: echocardiographic documentation of reversibility. Am J Med Sci 1987; 294: 1-9.
33. Vora J, O'Malley BP, Petersen S, McCullough A, Rosenthal FD, Barnett DB. Reversible abnormalities of myocardial relaxation in hypothyroidism. J Clin Endocrinol Metab 1985; 61: 269-72.
34. Virtanen VK, Saha HH, Groundstroem KW, Salmi J, Pasternack AI. Thyroid hormone substitution therapy rapidly enhances left-ventricular diastolic function in hypothyroid patients. Cardiology 2001; 96: 59-64.
35. Tielens ET, Pillay M, Storm C, Berghout A. Cardiac function at rest in hypothyroidism evaluated by equilibrium radionuclide angiography. Clin Endocrinol 1999; 50: 497-502.
36. Garcia MJ, Rodriguez L, Ares M, Griffin BP, Thomas JD, Klein AL. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. J Am Coll Cardiol 1996; 27: 108-14.
37. Palka P, Lange A, Fleming AD, Sutherland GR, Fenn LN, McDicken WN. Doppler tissue imaging: myocardial wall motion velocities in normal subjects. J Am Soc Echocardiogr 1995; 8: 659-68.
38. Garcia MJ, Rodriguez L, Ares M, et al. Myocardial wall velocity assessment by pulsed Doppler tissue imaging: characteristic findings in normal subjects. Am Heart J 1996; 132: 648-56.
39. Shan K, Bick RJ, Poindexter BJ, et al. Relation of tissue Doppler derived myocardial velocities to myocardial structure and beta-adrenergic receptor density in humans. J Am Coll Cardiol 2000; 36: 891-6.
40. Gaasch WH, Le Winter MM. Physiology of left ventricular relaxation and filling. In: Gaasch WH, ed. Left ventricular diastolic dysfunction and heart failure. Malvern, PA: Lea & Febiger, 1994: 3-125.
41. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. J Am Coll Cardiol 1993; 22: 318-25.
42. Devereux RB, Savage DD, Sachs I, Laragh JH. Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. Am J Cardiol 1983; 51: 171-6.
43. Galderisi M, Benjamin EJ, Evans JC, et al. Impact of heart rate and PR interval of left ventricular diastolic filling in an elderly cohort (the Framingham Heart Study). Am J Cardiol 1993; 72: 1183-7.