CLINICAL STUDY

Early textural and functional alterations of left ventricular myocardium in mild hypothyroidism

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Abstract

The aim of the present study was to evaluate cardiac function and texture in patients with subclinical hypothyroidism (sHT) both by conventional and new ultrasonic intramyocardial tissue techniques. sHT was characterized by normal serum free tetraiodotironine and free triiodotironine levels and slightly increased serum TSH level. Twenty-four patients affected by sHT and 24 sex- and age-matched healthy volunteers were studied. All subjects were submitted to conventional two-dimensional (2D)-color Doppler echocardiography, pulsed wave tissue Doppler imaging (PWTDI) for the analysis of the diastolic function, color Doppler myocardial imaging (CDMI) for the analysis of regional strain and strain-rate and integrated backscatter (IBS) for the evaluation of intrinsic contractility and tissue characterization. The results of the present study were: (a) the detection in sHT subjects of a lower cyclic variation index (CVI) indicating an altered myocardial intrinsic contractility; (b) a higher ultrasonic myocardial reflectivity indicating an altered myocardial texture; (c) the detection of lower systolic strain and strain-rate indicating an alteration of myocardial regional deformability; (d) an initial impairment of left ventricular diastolic function indicated by a decrease of peak E mitral flow velocity and an increase of peak A mitral flow velocity. All parameters studied with conventional 2D-echo in sHT patients were comparable with controls, except for a mild alteration in diastolic function. A significant correlation among systo-diastolic modifications detected by CDMI and IBS and serum TSH levels were found. The CVI at septum, the PWTDI S-peak wave and the systolic strain at septum were inversely related to the serum TSH levels. In conclusion, the new intramyocardial ultrasonic techniques confirm and extend the previous knowledge on the effect of the sHT on the heart, allowing the detection of early ultrastructural and regional functional systolic and diastolic abnormalities.

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Introduction

Subclinical hypothyroidism (sHT) is an apparently asymptomatic condition defined by slightly increased serum thyroid-stimulating hormone (TSH) concentrations and normal free thyroid hormone levels (1, 2). As reported, in iodine sufficient areas, sHT occurs in 4–9.5% of the general population, being more frequent in women and in the elderly (3–5). In view of the minimal hormonal impairment and the apparent failure of symptoms, the need of a life-long treatment with levothyroxine (L-T4) is a matter of controversy. Nevertheless, this condition may be clinically relevant at level of target organs over a period of several years. Cardiovascular system is very sensitive to minimal defects of circulating thyroid hormones, and cardiovascular disorders are usually associated with overt hypothyroidism (6–8). Furthermore, the abnormalities in myocardial contractility and the changes of the

lipoprotein profile that are frequently documented in hypothyroid patients have been reported (6, 8, 9). Therefore, sHT may be considered a true risk factor for the development of coronary heart disease (6–13). Indeed, a progression of coronary angiographic lesions in untreated sHT patients in comparison with L-T4-treated sHT patients has been reported (14).

Recently, it has been reported by an ultrasonic tissue characterization technique (videodensitometry) that sHT is associated with early abnormalities in both myocardial function and structure, which are reversible with replacement therapy (15, 16).

The aim of the present study was to evaluate heart function in patients with sHT, in otherwise cardiologically healthy subjects, by a new intramyocardial ultrasonic technique, such as integrated backscatter (IBS) (17) for the evaluation of intrinsic contractility and tissue characterization, and color Doppler myocardial imaging (CDMI) (18, 19) for the analysis of regional myocardial

strain and strain-rate. The advantage of both these methods is the independence of load condition and for strain also a relative independence from heart rotational and translational motions. Therefore, these techniques allow a very early diagnosis of systolic and diastolic dysfunction, when conventional echo-Doppler parameters of left ventricular function are still within normal range. In particular, both techniques correlate functional abnormalities with structural changes, such as the increased myocardial fibrosis, and left ventricular hypertrophy recently demonstrated in hypertension, in aortic stenosis and in acromegalic cardiomyopathy (20–22).

Patients and methods

Subjects

We studied 24 patients (19 women; mean age 34.8 ± 6.3 years) with newly untreated sHT. Mean serum-free thyroxine and free triiodothyronine were 8.9 ± 1.8 and 3.5 ± 0.7 pg/ml respectively. Mean serum TSH was 5.3 ± 1.1 mU/l (normal range 0.4–3.4 mU/l). In all patients, the etiology of sHT was chronic autoimmune thyroiditis, diagnosed by elevated circulating anti-peroxidase and/or anti-thyroglobulin autoantibodies and diffuse hypoechogenicity by thyroid ultrasound. The inclusion criteria were age less than 45 years and slightly high serum TSH level ranging between 3.5 and 7.5 mU/l. Patients with impairment of left ventricular systolic function (ejection fraction <50%), significant valvular heart disease, cardiomyopathy and diabetes mellitus were excluded. All sHT patients had normal blood pressure, normal level both of cholesterol (low- and high-density lipoprotein) and triglycerides and had a negative history for myocardial infarction or coronary artery disease. The control group included 24 sex- and age-matched healthy volunteers (19 women; mean age 30.8 ± 6.7 years). Cardiovascular and respiratory diseases were excluded in both patients and controls by a complete clinical work-up. Routine laboratory chemistry was normal in all, and none assumed any drug. Body mass index was 22.3 ± 2.6 in controls and 24.5 ± 3.0 in sHT patients.

Experimental procedure

Hormonal and metabolic profile. Blood samples for free tetraiodotironine (FT4), free triiodotironine (FT3) and TSH evaluation were collected between 0800 and 0900 h. Serum FT4 and FT3 levels were measured using a chemiluminescent method (Vitros Eci-Ortho-Clinical Diagnostic Spa). The normal range was 7.0–17.0 pg/ml for FT4 and 2.7–5.7 pg/ml for FT3. Serum TSH level was determined by an ultra-sensitive chemiluminescent method (IMMULITE 2000-Diagnostic Products

Corporation analyzer) with a normal range of 0.4–3.4 mU/l. Determination of serum anti-thyroglobulin (Tg-Ab), anti-thyroperoxidase (TPO-Ab) was measured using an immunofluorescent method (AIA 21 TOSOH-Italia). Diagnosis of sHT was based on the evidence of serum TSH level ranging between 3.5 and 7.5 mU/l and normal serum-free thyroid hormone levels.

Echocardiographic analysis. At the baseline, all the patients and controls were submitted to conventional echocardiography, pulsed wave tissue Doppler imaging (PWTDI), CDMI and acoustic densitometry. The operator was blinded of the subject's group.

Conventional 2D Doppler echocardiography.

Conventional echocardiographic evaluation was performed as previously reported in detail (15, 16).

Pulsed wave tissue Doppler imaging (PWTDI). In the apical four-chambers view, the pulsed wave Doppler sample volume was subsequently placed in two different places of mitral annulus: septum and lateral wall. The apical four-chambers view was chosen to obtain a quantitative assessment of the global diastolic left ventricular function, almost simultaneously to the Doppler left ventricular inflow and to minimize the incidence angle between the Doppler beam and the longitudinal motion of mitral annulus (23, 24). PWTDI of the septal annulus was used for the measurements of early peak diastolic mitral annulus velocity (Es). Left ventricular filling pressures were approximated from the relationship of E/Es (E being derived by mitral flow velocity) (23).

CDMI derived-indices: Mean regional velocities, strain-rate and strain. CDMI data were offline analysed using a dedicated software (AMID, Florence, Italy). Velocity and strain-rate profiles were averaged over three cardiac cycles to derive mean velocity (VEL) and strain-rate curve averaged a mean RR interval. Mean natural strain (ϵ) profiles and values were obtained integrating the mean strain profile by time using the AMID software. The frame rate ranged between 75 and 90 Hz. A region of interest (ROI) consists in a myocardial segment bounded by four segments, two of them across the tissue and the other two parallel to the segment in a way that the enclosed area always contains the entire tissue segment during its movement. The software automatically recognizes the moving tissue inside the outlined area and the analysis is performed on the myocardial wall segment contained inside the area. In this way, the ROI becomes a responsive area that continuously follows the wall. The strain (computed from time-integration of the strain-rate) and the strain-rate were calculated as reported (18, 19).

Regional motion and the deformation in the longitudinal direction, both at medium posterior septum and medium lateral wall, were described by the following parameters calculated by apical chamber view: isovolumic relaxation time (VEL_{IVRT}); isovolumic contraction time (VEL_{IVCT}); maximum systolic velocity (VEL_{sys}); early diastolic peak velocity (VEL_E); late diastolic peak velocity (VEL_A); maximum strain (ϵ_{sys}); maximum strain-rate (SR_{sys}); early diastolic peak strain-rate (SR_E); late diastolic peak strain-rate (SR_A). The intraclass correlation coefficient (r_i) was calculated according to Bland and Altman's procedure (25). Three values of the strain-rate and strain were sampled for each patient and for each segment: septal and lateral; the correlation coefficient (r_i) was 0.86 for septal and 0.89 for lateral segment, respectively.

Acoustic densitometry. High frame rate IBS imaging technology has been commercially applied to provide a more robust signal (calibrated in decibels, dB), with a substantial improvement of time-sequence of back-scattered signal, further optimized for tissue characterization research. Acoustic densitometry measurement is independent from non-linear compression and post-processing functions of the ultrasound imaging chain. The images were obtained using harmonic imaging mode. A detailed IBS methodology as previously described (21–23). Other important control settings of the imaging chain such as pre-processing, focus position, persistence, compression, high frame rate and post-processing were maintained constant for all patients, accurately avoiding the signal saturation (i.e. backscatter value sampled at the maximum value for the dynamic range of the system) at every level (pericardium, valve, myocardium) for possibility of estimation errors. End-diastolic IBS parameters (IBS_{ed}) were then indexed for IBS pericardial values both at septum ($IBS_{septumper}$) and at posterior wall ($IBS_{post-wallper}$). The measurements obtained for each cardiac cycle were intensity of IBS at end-diastole (IBS_{ed}), intensity of IBS at end-systole (IBS_{es}). Cyclic variation index at septum (CVI_{septum}) and posterior wall level ($CVI_{posteriorwall}$), which were computed using the following formula: $(IBS_{ed} - IBS_{es}) / IBS_{ed} \times 100$ (23).

Statistical analysis

Continuous variables were expressed as mean $\pm$ s.d. Student's *t*-test was used to quantitate variables among groups. The intraclass correlation coefficient (r_i) was calculated according to Bland and Altman's procedure (25), using a one-way ANOVA for repeated measurements. Relation between two-dimensional (2D) echocardiographic measurements and TSH level were

evaluated by terms of linear regression analysis. A *P*-value of <0.05 was considered significant.

Results

Clinical and hormonal data of sHT patients and controls are shown in Table 1. Systolic, diastolic mean blood pressure values, heart rate and body mass index (BMI) were comparable in both groups, remaining within the normal range. Serum TSH level was significantly higher in sHT patients than in controls ($P < 0.001$), while no differences were found in serum FT4 and FT3 levels. All patients with sHT had high level of Tg-Ab and/or TPO-Ab.

Conventional echo-Doppler parameters

Data derived from conventional echocardiographic analysis are summarized in Table 2. The septum and posterior wall thickness was significantly higher in sHT, while the left ventricular (LV) end-diastolic diameter was comparable. left ventricular mass (LVM_{bs}) was slightly but significantly higher in sHT, although still within the normal range. Cardiac output and systemic vascular resistances overlapped in both groups. With regard to LV systolic function, fractional shortening (FS) and ejection fraction (EF) values were within the normal range in both groups. Isovolumic contraction time was significantly higher ($P < 0.01$) in sHT patients than in controls. Pre-ejection period (PEP) was significantly higher in sHT patients in comparison with controls ($P < 0.05$); as a consequence PEP/left ventricular ejection time (LVET) was significantly higher in sHT than in controls ($P < 0.05$). Left ventricular diastolic function showed a significant difference between sHT patients and controls due to decreased peak E ($P < 0.05$) and increased peak A flow velocity, which was higher in sHT as compared with controls ($P < 0.05$). As a consequence, E/A ratio was significantly lower ($P < 0.01$) in sHT patients than in controls (Fig. 1, panel A). Isovolumic relaxation time (IVRT) was significantly higher in sHT compared with controls ($P < 0.01$).

Table 1 Clinical and hormone parameters in sHT patients and in controls.

	sHT (n=24), mean $\pm$ s.d.	Controls (n=24), mean $\pm$ s.d.	P
Age	34.8 $\pm$ 6.2	33.9 $\pm$ 6.4	NS
BMI	22.33 $\pm$ 2.6	24.5 $\pm$ 3.0	NS
SBP (mmHg)	117.2 $\pm$ 9.9	119.9 $\pm$ 8.2	NS
DBP (mmHg)	73.2 $\pm$ 5.6	74.8 $\pm$ 7.4	NS
MBP (mmHg)	90.3 $\pm$ 5.9	92.9 $\pm$ 10.5	NS
HR (b/min)	78.9 $\pm$ 12.4	75.9 $\pm$ 11.7	NS
FT4 (pg/ml)	8.9 $\pm$ 1.8	12.2 $\pm$ 2.7	NS
FT3 (pg/ml)	3.5 $\pm$ 0.7	3.9 $\pm$ 3.4	NS
TSH (μ U/ml)	5.3 $\pm$ 1.1	1.4 $\pm$ 0.8	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP diastolic blood pressure; MBP, mean blood pressure; HR, heart rate.

Table 2 Echo-Doppler conventional parameters in sHT patients and in controls.

	sHT (n=24) mean $\pm$ s.d.	Controls (n=24) mean $\pm$ s.d.	P
EDD (cm)	46.2 $\pm$ 4.8	48.2 $\pm$ 4.7	NS
FS (%)	42.8 $\pm$ 5.3	39.5 $\pm$ 8.2	NS
EF (%)	65.4 $\pm$ 8.2	62.5 $\pm$ 9.5	NS
DSth (mm)	8.2 $\pm$ 1.3	9.8 $\pm$ 1.4	0.05
DPWth (mm)	8.3 $\pm$ 1.1	9.5 $\pm$ 1.6	0.05
LVM bs (g/m ²)	88.2 $\pm$ 11.7	98.5 $\pm$ 12.1	0.01
EDV (cm ³)	83.6 $\pm$ 4.3	86.3 $\pm$ 6.5	NS
CO (l/min)	5.2 $\pm$ 1.2	5.3 $\pm$ 1.3	NS
SPR	1364.6 $\pm$ 331.2	1382.2 $\pm$ 312.6	NS
Peak E (cm/sec)	81.2 $\pm$ 13.0	71.2 $\pm$ 15.7	0.05
Peak A (cm/sec)	52.4 $\pm$ 9.6	67.5 $\pm$ 10.7	0.01
E/A ratio	1.5 $\pm$ 0.3	1.1 $\pm$ 0.2	0.02
Mitral Dec time (msec)	170.6 $\pm$ 23.9	143.6 $\pm$ 34.6	0.05
IVRT (msec)	71.3 $\pm$ 10.5	86.2 $\pm$ 16.3	0.01
IVCT (msec)	53.6 $\pm$ 8.3	63.5 $\pm$ 12.5	0.05
LVET (msec)	276.6 $\pm$ 25.5	279.6 $\pm$ 25.9	NS
PEP (msec)	80.6 $\pm$ 10.8	88.2 $\pm$ 11.6	0.05
PEP/LVET	0.28 $\pm$ 0.05	0.35 $\pm$ 0.06	0.02

EDD, end diastolic diameter; FS, fractional shortening; EF, ejection fraction; DPW, diastolic posterior wall; LVM, left ventricular mass; EDV, end diastolic volume; CO, cardiac output; SPR, systemic peripheral resistance; IVRT, isovolumetric relaxation time; IVCT, isovolumic contraction time; LVET, left ventricular ejection time; PEP, pre-ejection period.

Pulsed wave tissue Doppler imaging (PWTDI)

Data derived from PWTDI are summarized in Table 3. The mean early diastolic peak velocity (PWTDI E_s and E_L) was lower in sHT patients than in controls ($P < 0.01$ and < 0.03 respectively); the late diastolic peak velocity (PWTDI A_s and A_L) was higher in sHT patients than in controls ($P < 0.03$). The ratio between E and A velocities

(PWTDI E/A_s and E/A_L), expression of global diastolic left ventricular longitudinal function, was significantly lower in sHT patients than in controls ($P < 0.04$ and < 0.01 respectively). The PWTDI-IVRT both at septum and lateral wall annular level were significantly higher in sHT patients than in controls ($P < 0.03$ and < 0.02 respectively).

CDMI-derived indices: mean regional velocities, strain-rate and strain

The data of CDMI indices are also summarized in Table 4. The $VEL_{sys}(s)$ and $VEL_{sys}(L)$ were significantly lower in sHT patients in comparison with controls ($P < 0.05$ and < 0.02 respectively); the early mean diastolic regional velocity, both at medium septum and lateral wall level was lower in sHT patients than in controls ($P < 0.01$ and < 0.05 respectively); the late diastolic regional velocity, both at medium septum and lateral wall level was higher in sHT patients than in controls ($P < 0.01$ and < 0.05 respectively); the $VEL_{E/Aratio}$ was significantly lower in sHT patients than in controls ($P < 0.01$). The regional myocardial systolic strain findings evaluated both at medium septal and lateral wall level were significantly lower in sHT patients as compared with controls ($P < 0.05$ and < 0.02 respectively). The regional myocardial systolic strain-rate both at medium septal and lateral wall was significantly lower in sHT patients in comparison with controls ($P < 0.05$). When considering the diastolic SR, the late phase was compromised in sHT patients as compared with controls ($P < 0.05$ and < 0.02 respectively).

Figure 1 E/A ratio obtained by 2D conventional echocardiography (panel A) and cyclic variation index at septum level obtained by integrated backscatter (panel B) in patients with subclinical hypothyroidism and in controls.

Table 3 Pulsed wave tissue doppler imaging (PW-TDI) findings in sHT patients and in controls.

PWTDI parameters	sHT (n=24) mean $\pm$ s.d.	Controls (n=24) mean $\pm$ s.d.	P
PWTDI Ss	8.0 $\pm$ 1.1	7.9 $\pm$ 2.2	NS
PWTDI Es	11.4 $\pm$ 2.0	9.8 $\pm$ 2.7	0.01
PWTDI As	7.7 $\pm$ 1.7	8.9 $\pm$ 2.4	0.03
PWTDI E/As	1.5 $\pm$ 0.3	1.1 $\pm$ 0.2	0.04
PWTDI IVRTs	74.4 $\pm$ 9.2	85.5 $\pm$ 13.5	0.03
PWTDI SI	10.6 $\pm$ 2.1	9.9 $\pm$ 1.9	NS
PWTDI EL	15.7 $\pm$ 2.6	13.9 $\pm$ 3.5	0.03
PWTDI AL	8.1 $\pm$ 2.5	10.3 $\pm$ 4.3	0.03
PWTDI E/AL	1.6 $\pm$ 0.4	1.2 $\pm$ 0.5	0.01
PWTDI IVRTL	73.6 $\pm$ 10.3	87.4 $\pm$ 10.6	0.02
E/Es	5.2 $\pm$ 0.9	5.6 $\pm$ 2.1	NS

PWTDI Ss: peak of systolic velocity (S wave) at septal mitral annulus level; PWTDI Es, early diastolic longitudinal peak velocity of mitral annulus at septum level; PWTDI As, late diastolic longitudinal peak velocity of mitral annulus at septum level; PWTDI IVRTs, isovolumic relaxation time of mitral annulus at septum level. PWTDIL, the same above cited parameters of velocity or time of mitral annulus sampled at lateral wall level. E/Es ratio between peak E transmitral flow and PWTDI Es.

Acoustic densitometry

The main findings of backscatter parameters were also summarized in Table 4. CVI of both the septum (Fig. 1, panel B) and posterior wall level were significantly lower in sHT patients in comparison with controls

Table 4 Color Doppler Myocardial Imaging (CDMI) and Integrated Backscatter (IBS) findings in sHT patients and in controls.

CDMI parameters			
VEL sys (S)	3.1 $\pm$ 0.6	2.4 $\pm$ 0.8	0.05
VEL E (S)	-4.9 $\pm$ 1.2	-5.9 $\pm$ 1.0	0.05
VEL A (S)	-2.8 $\pm$ 1.0	-4.5 $\pm$ 1.8	0.01
VEL E/A (S)	1.8 $\pm$ 0.4	1.1 $\pm$ 0.4	0.01
ϵ sys (S)	-23.3 $\pm$ 5.4	-19.2 $\pm$ 4.2	0.05
SR sys (S)	-1.2 $\pm$ 0.4	-0.7 $\pm$ 0.2	0.05
SR E (S)	1.5 $\pm$ 0.6	1.0 $\pm$ 0.4	0.01
SR A (S)	0.6 $\pm$ 0.4	0.9 $\pm$ 0.3	0.05
VEL sys (L)	4.3 $\pm$ 1.5	3.0 $\pm$ 1.1	0.02
VEL E (L)	-5.4 $\pm$ 1.3	-4.2 $\pm$ 1.6	0.05
VEL A (L)	-2.5 $\pm$ 1.2	-3.4 $\pm$ 1.3	0.05
VEL E/A (L)	-2.1 $\pm$ 0.8	-1.6 $\pm$ 0.7	0.01
ϵ sys (L)	-23.1 $\pm$ 5.6	-18.4 $\pm$ 3.7	0.02
SR sys (L)	-1.25 $\pm$ 0.2	-1.05 $\pm$ 0.2	0.05
SR E (L)	1.17 $\pm$ 0.5	1.09 $\pm$ 0.4	NS
SR A (L)	0.5 $\pm$ 0.2	0.8 $\pm$ 0.3	0.02
IBS parameters			
CVI septum	37.2 $\pm$ 9.5	22.6 $\pm$ 10.2	0.0001
CVI post-wall	42.5 $\pm$ 8.6	32.2 $\pm$ 11.2	0.001
IBS septumper	45.5 $\pm$ 8.2	53.8 $\pm$ 7.3	0.05
IBS post-wallper	43.5 $\pm$ 6.9	48.8 $\pm$ 7.4	NS

CDMI parameters: VEL sys (S), peak of systolic regional velocity (S wave) at septum level; VEL E (S), early diastolic longitudinal regional peak velocity at septum level; VEL A (S), late diastolic longitudinal regional peak velocity at septum level; ϵ sys (S), regional systolic strain at septum level; SR sys (S), regional systolic strain-rate at septum level; SR E (S), early diastolic longitudinal regional systolic strain-rate at septum level; SR A (S), late diastolic longitudinal regional systolic strain-rate at septum level. (L), all the above cited parameters at regional lateral wall level. IBS parameters: CVI septum, cyclic variation index at septum level; CVI post-wall, cyclic variation index at posterior wall level; IBS septumper, ultrasonic reflectivity at septum level referred to pericardial interface reflectivity; IBS post-wall per, ultrasonic reflectivity at posterior wall level referred to pericardial interface reflectivity.

($P < 0.0001$). The IBS values of the septum, indexed by pericardial interface, were higher than in controls ($P < 0.05$). No difference in IBS values of the posterior wall between sHT patients and controls were found. CVI at septum level ($P < 0.001$), the systolic strain at septum ($P < 0.04$) and at lateral level ($P < 0.05$) were related to TSH levels. CVI_{posterior wall} was inversely related to TSH level ($P < 0.01$). In Fig. 2 is reported the correlation between CVI at septum and serum TSH level. In the present study, no relations among thyroid autoantibodies and CVI_{septum}-(%) and E/A ratio were found.

Discussion

The results of the present study indicate that backscatter ultrasonic non-invasive technique and CDMI allow to detect in sHT patients coexisting functional and textural abnormalities of the myocardium partially undetectable by conventional 2D-Doppler echocardiography. A large number of studies have been carried out to assess cardiac performance in sHT patients, but the results are conflicting (26–31), the question of whether sHT is related to risk for cardiovascular disease is controversial. These conflicting results may be explained by different selection of patients (number, age, type and length of sHT), different diagnostic criteria (range of TSH levels), different techniques and indexes used to assess cardiac performance. Our previous study showed that sHT is associated with early alterations in both myocardial function and structure as investigated by conventional echocardiography and videodensitometric analysis (15). Myocardial abnormalities were reversible by L-T4 replacement therapy (16).

Figure 2 Relationship between cyclic variation index (CVI) at septum level and serum TSH level in patients with subclinical hypothyroidism (sHT).

The present case-control study was carried out in a series of 24 young, otherwise healthy patients with untreated autoimmune sHT newly diagnosed and serum TSH ranging between 4.5 and 7.5 mU/l. The intramural function and myocardial texture were investigated by acoustic densitometry with IBS technique and CDMI. The IBS technique is an evolution of the videodensitometric analysis, which allows a stronger characterization of the intrinsic myocardial contractility and texture (17). The CDMI allows the analysis of regional myocardial strain and strain-rate (18, 19). The advantages of these methods are the independence of load condition and for CDMI, the independence from heart rotational and translational motion.

In the present series of sHT patients, the results confirm and extends the impairment of both systolic and diastolic myocardial function previously described (15, 16), a lower CVI indicating a decreased myocardial intrinsic contractility and a high ultrasonic myocardial reflectivity suggesting an altered myocardial texture. The detection in sHT patients of a lower systolic strain and strain-rate analysis in comparison with controls suggests an alteration of myocardial regional deformability. Conventional echocardiographic indexes of left ventricular systolic function such as ejection fraction and fractional shortening are partially unable to differentiate healthy from sHT myocardium, while new ultrasonic systolic functional indexes have a high discriminating power between the two study groups. Among all new ultrasound parameters, the CVI at septum level showed the higher discriminating power (86%) between groups, while conventional Doppler mitral flow E/A ratio showed a very low discriminating power (33%) (comparison between the two methods, $P < 0.001$). In our previous study carried out in sHT patients by videodensitometric approach, a significantly lower CVI was found in sHT than controls (14). These subtle myocardial alterations were reversible after replacement L-T4 therapy (15). The L-T4 reversible cyclic variations of the echo amplitude in the face of normal load-dependent functional indexes, suggested that changes in CVI amplitude may be a distinct, early index of impaired intrinsic myocardial contractility (15, 16). Present data suggest that myocardial dysfunction in sHT is also associated with modifications of both the acoustic properties (IBS) and the velocity of myocardial fibres motion (CDMI). Several components can influence both the acoustic properties and the velocities of myocardial fibres, such as collagen, ventricular muscle fibres orientation, tissue albumin and water content, and capillary blood flow distribution (6, 21). The microstructural arrangement of myocardial cells embedded in a collagen matrix may provide a sufficient local acoustic impedance mismatch to account for the scattering from normal myocardium (6, 20).

Pulse wave tissue Doppler, as expression of global longitudinal left ventricular function, has already been

used to identify left ventricular myocardial abnormalities in sHT. In fact, using PWTd, Vitale *et al.* (28) reported both an impairment of global longitudinal ventricular diastolic function and an alteration of myocardial time intervals, in patients with sHT. Zoncu *et al.* (29) demonstrated systolic and diastolic changes in patients with borderline hypothyroidism. Our study confirms the above-cited pioneering PWTd data and originally extends the observation of myocardial subclinical involvement in sHT status when studied by tissue characterization ultrasonic technique (IBS) and by CDMI, which allows the analysis of regional longitudinal strain and strain-rate. Previous tissue characterization study by videodensitometry documented high broad-band and higher volume collagen fraction – indicating increased intramyocardial fibrosis – only in overt, but not in subclinical hypothyroid patients (32). Minimal decrements in hormone activity at myocardial level may over time lead to biochemical and functional effects qualitatively similar to those of overt hypothyroidism, responsible for the functional myocardial alterations (6). These early alterations of myocardial function and texture, strengthen the opinion that sHT is strongly associated with risk for cardiovascular events (33). The role of thyroid autoimmunity in the development of cardiovascular events is still debated. In the present study, no relations among thyroid autoantibodies and CVI_{septum}-(%) and E/A ratio were found. These data suggest that the observed cardiac alterations were related to hypothyroidism, but independent from autoimmune phenomena (34).

In conclusion, present data confirm and extend the previous observation that both phases of heart cycle are early and contemporary involved in sHT causing the decrease of intramyocardial contractility and the impairment of both active and passive phases of diastole. The application of new sensible non-invasive techniques, which are more independent from load, rotational and translational heart motion, such as CDMI and IBS, allowed to detect subtle functional and textural alterations of intramural myocardium, partially undetectable by conventional 2D-Doppler echocardiography. Indeed, the high sensitivity of new ultrasonic intramyocardial indices of left ventricular global or regional function in comparison with conventional echo parameters may contribute to explain the different data of the literature regarding cardiac consequences of sHT.

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