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Left Ventricular Diastolic Dysfunction in Patients with Subclinical Hypothyroidism

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ABSTRACT

Although subclinical hypothyroidism is frequently diagnosed, the decision to institute a substitutive therapy with L-T_4 remains controversial. Because the cardiovascular system is considered a main target for the action of thyroid hormone, we investigated whether subclinical hypothyroidism induces cardiovascular abnormalities.

Twenty-six patients (mean age, 36 ± 12 yr) were evaluated by Doppler-echocardiography, whereas a subgroup of 10 patients, randomly selected, were reevaluated after 6 months of L-T_4 substitutive therapy (mean dose, 68 μg daily). Thirty subjects (matched for age, sex, and body surface area) served as controls.

Mean plasma TSH was significantly higher in patients ($P < 0.001$), whereas mean serum free T_4 and free T_3 concentrations, although in the normal range, were significantly lower ($P < 0.001$ and $P < 0.005$, respectively). Blood pressure and heart rate did not differ from control values. Echocardiogram examination showed no abnormalities of the left ventricular morphology and a slight, but not significant, reduction in the systolic function in the patient group. In contrast, Doppler-derived indices of diastolic function showed significant prolongation of the isovolumic relaxation time (94 ± 13 *vs.* 84 ± 8 msec; $P < 0.001$), increased A wave (55 ± 13 *vs.* 48 ± 9 cm/sec; $P < 0.05$), and reduced early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio (1.4 ± 0.3 *vs.* 1.7 ± 0.3; $P < 0.001$). In the subgroup of 10 patients, thyroid hormone profile was normalized by 6 months of L-T_4 substitutive therapy, whereas no changes were observed in the left ventricular morphology. Systolic function was significantly enhanced, as compared with pretreatment values ($P < 0.01$) but did not differ from control values. Also, systemic vascular resistance was significantly decreased by L-T_4 replacement therapy. Assessment of diastolic function showed significant shortening of isovolumic relaxation time (77 ± 15 *vs.* 91 ± 8; $P < 0.05$), reduction of A wave (51 ± 13 *vs.* 60 ± 12; $P < 0.01$), and increase of early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio (1.7 ± 0.4 *vs.* 1.3 ± 0.3; $P < 0.001$). These indices, however, were comparable with those of control subjects.

These findings indicate that subclinical hypothyroidism affects diastolic function and that this abnormality may be reversed by L-T_4 substitutive therapy. (*J Clin Endocrinol Metab* **84:** 2064–2067, 1999)

SUBCLINICAL hypothyroidism (SHypo) is characterized by variably increased serum TSH concentration with apparently normal serum free T_4 (F-T_4) and free T_3 (F-T_3) levels. It occurs in 10–15% of the general population (1).

The clinical presentation of SHypo is nonspecific, and the symptoms are usually subtle, as compared with those of overt hypothyroidism, probably in relation to the intensity and the duration of thyroid hormone deficiency and the age of the patients.

The decision to treat the patients affected by SHypo with substitutive L-T_4 therapy remains controversial (1–3) and mainly dependent on the physician's attitude (to consider the disease as a mild form of tissue hypothyroidism or as a compensate state, in which the increase of TSH is required to maintain normal circulating thyroid hormone concentrations). Indeed, reports on the efficacy of replacement therapy with levothyroxine (L-T_4) on the lipid abnormalities in the patients with SHypo have shown conflicting results (4–10). However, although it is difficult to establish a cutoff for TSH values that clearly indicates the need to institute a substitutive therapy with L-T_4, the treatment is generally recommended in the presence of a serum TSH level of 10 mU/L or more (2, 11, 12). When the TSH level is less than 10 mU/L, the treatment may be indicated in relation to the presence of goiter or antithyroid antibodies to prevent the onset of overt hypothyroidism more than to tissue assessment of thyroid hormone deficiency (1).

Considering the high prevalence of SHypo and the well-established cardiac consequences of altered thyroid status, in the present study, we investigated whether SHypo causes cardiovascular abnormalities. To this aim, we assessed cardiac morphology and function, using noninvasive methods, in patients with SHypo before and after L-T_4 substitutive therapy.

Subjects and Methods

The study was performed by means of Doppler-echocardiography in 26 patients with SHypo and in 30 normal control subjects.

SHypo was diagnosed on the basis of TSH values above normal (see Table 1), associated with a supranormal response to TRH (ΔTSH above 30 mU/L), and FT_3 and FT_4 in the lower limit of the normal range. Only the patients with stable TSH and thyroid hormone levels for at least 6 months before the enrollment and with a positive test for serum antithyroid peroxidase antibodies were included in the study. TSH and thyroid hormone levels were considered stable if their variations were lower than 20% in three consecutive evaluations performed in the 6 months before study. Patients and normal volunteers had a sedentary life-style, none of them had a history of cardiovascular disease, and all were in sinus rhythm.

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TABLE 1. Characteristics of the study population

	Controls (n = 30)	SHypo patients (n = 26)
Age (yr)	36 ± 11	36 ± 12
Sex (M/F)	6/24	2/24
BSA (m^2)	1.67 ± 0.17	1.64 ± 0.12
HR (bpm)	71 ± 8	73 ± 9
SBP (mm Hg)	125 ± 12	120 ± 10
DBP (mm Hg)	77 ± 5	78 ± 7
FT_4 (7.7–23.2 pmol/L)	15.3 ± 2.6	9.4 ± 3.0[a]
FT_3 (3.9–8.8 pmol/L)	6.0 ± 1.2	5.1 ± 1.1[b]
TSH (0.2–3.0 mU/L)	1.6 ± 0.9	8.6 ± 4.8[a]

BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] $P < 0.001$.

[b] $P = 0.005$, *vs.* control subjects.

A subgroup of 10 patients, randomly selected, was reevaluated after 6 months of L-T_4 therapy, at substitutive doses ranging from 50–100 μg daily, with a mean dose of 68 μg. None of the subjects received any medication during the study, other than L-T_4 for the subgroup of 10 patients previously described.

All subjects gave informed consent before participating in the study, and the protocol was approved by the Ethics Committee of the University of Naples Federico II.

Assessment of thyroid status

Evaluation of plasma TSH levels was performed by an ultrasensitive immunoradiometric assay (Bouty, Milan, Italy) with a detection limit of 0.05 mU/L. The intra- and interassay variations were 3.1% and 3.8% at 0.25–50 mU/L. Serum FT_4 and FT_3 were measured using the Lisophase Kits (Bouty). The intra- and interassay variations and sensitivities were 2.9%, 4.7%, and 0.8 pmol/L for FT_3, respectively, and 4.1%, 5.9%, and 1.0 pmol/L for FT_4.

Doppler-echocardiography

Complete mono- and two-dimensional, and Doppler-echocardiographic analysis was performed by an ultrasound mechanical system equipped with a 3.5-MHz transducer (Apogee CX, Interspec, Inc., Ambler, PA), as previously described (13, 14). The examinations were performed by the same operator for all participants in the study. The investigator reading the echoes was blinded as to whether the recordings he was interpreting were of hypothyroid or normal subjects.

The parameters of systolic and diastolic function, derived by echocardiography and by Doppler examination, were assessed as previously reported (14, 15). Stroke volume was obtained using the method of Teichholz *et al.* (16). Cardiac output (CO) was measured as the product of stroke volume and heart rate. Systemic vascular resistance (SVR) was calculated as follows: SVR = [(mPAO-mPRA)/CO] × 80, where mPRA is the mean right atrial pressure, considered equal to zero mm Hg in each subject, and mPAO is the mean aortic pressure, derived by cuff-sphygmomanometer, as diastolic blood pressure + 1/3(systolic-diastolic blood pressure) (17). Furthermore, aortic peak flow velocity and mean aortic acceleration were obtained by the recording of the aortic flow velocimetry. In particular, mean aortic acceleration was obtained by dividing the peak flow velocity by the acceleration time (18).

Statistical analysis

All data in the text and tables are reported as the mean ± SD. Comparisons among control subjects and subclinical hypothyroid patients were performed by the two-tailed Student's *t* test for unpaired data, whereas comparisons among the subgroup of 10 subclinical hypothyroid patients, before and 6 months after L-T_4 treatment, were performed using the two-tailed Student's *t* test for paired data. A *P* value less than 0.05 was considered as significant.

Results

The clinical characteristics of the study population are shown in Table 1. Patients and normal controls were well matched for age, sex, and body surface area. Both heart rate and blood pressure were comparable in the two groups. As expected, TSH levels were significantly higher in patients than in controls. FT_3 and FT_4 levels, although in the normal range, were significantly lower in the patients than in control subjects.

As summarized in Table 2, no abnormalities were found in LV morphology and mass in the patients with SHypo.

Table 3 displays Doppler-echocardiographic resting indices of LV systolic and diastolic function. No clear evidence of systolic dysfunction was found in the patient group. The only abnormality was a significant, although mild, decrease in the mean aortic acceleration.

Doppler-derived indices of left ventricular (LV) diastolic filling showed clear abnormalities of myocardial relaxation, as indicated by significant prolongation of the isovolumic relaxation time (Fig. 1) and significant reduction of the early diastolic mitral flow velocity/late diastolic mitral flow velocity (E/A) ratio, mainly accounted for by increased A-wave of mitral flow velocity.

In the subgroup of SHypo patients receiving L-T_4 substitutive therapy for six months, TSH was normalized (from 9.2 ± 4.2 to 1.7 ± 1 mU/L, $P < 0.005$), whereas FT_3 and FT_4 increased (FT3: from 4.5 ± 1.2 to 5.6 ± 1.4 pmol/L, $P < 0.05$; FT4: from 9.3 ± 3.4 to 14.4 ± 3.8 pmol/L, $P < 0.005$) and were no longer different from the values of control subjects.

As summarized in Tables 4 and 5, L-T_4 substitutive therapy did not induce significant changes in LV morphology. In con-

TABLE 2. Echocardiographic parameters to left ventricular morphology in subclinical hypothyroid patients and in normal subjects

	Controls (n = 30)	SHypo patients (n = 26)
LVEDD (mm)	48 ± 3	47.5 ± 4
LVESD (mm)	30.5 ± 2	30.5 ± 4
Diastolic IVST (mm)	9.2 ± 1.5	9.8 ± 1.7
Diastolic LVPWT (mm)	8.5 ± 1.4	8.9 ± 1.1
LVMi (g)	83 ± 14	86 ± 17

LVEDD, left ventricular end diastolic diameter; LVESD, left ventricle end systolic diameter; IVST, interventricular septum thickness; LVPWT, left ventricle posterior wall thickness; LVMi, left ventricle mass corrected for body surface area.

TABLE 3. Doppler-echocardiographic parameters of left ventricular function in subclinical hypothyroid patients and in normal subjects

	Controls (n = 30)	SHypo patients (n = 26)
Systolic function		
FS (%)	36 ± 4.0	36 ± 4.5
mVCF (circ/sec)	1.3 ± 0.1	1.2 ± 0.2
Mean aortic acceleration (m/sec^2)	10.1 ± 1.1	9.3 ± 1.4[a]
Peak aortic flow velocity (cm/sec)	0.9 ± 0.1	0.9 ± 0.2
Cardiac output μL/min	5223 ± 959	5300 ± 1260
SVR (dynes/sec · cm^{-5})	1460 ± 343	1470 ± 372
Diastolic function		
E (cm/sec)	79 ± 11	74 ± 13
A (cm/sec)	48 ± 9	55 ± 13[a]
E/A ratio	1.7 ± 0.3	1.4 ± 0.3[b]
IRT (msec)	84 ± 8	94 ± 13[b]

FS, fractional shortening; mVCF, mean velocity of circumferential fiber shortening; IRT, isovolumetric relaxation time; SVR, systemic vascular resistance.

[a] $P < 0.05$, *vs.* control subjects.

[b] $P < 0.001$.

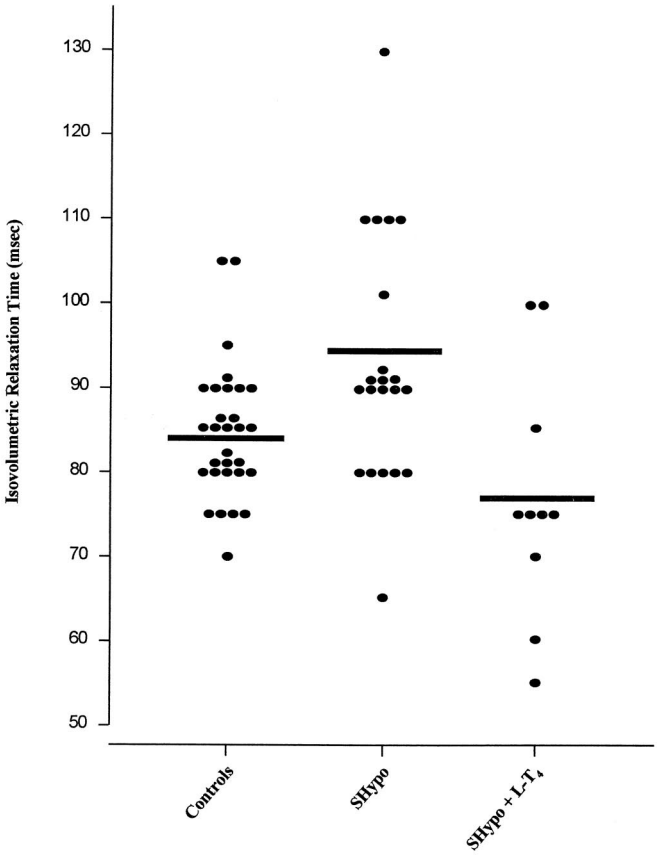

FIG. 1. Individual values of isovolumetric relaxation time (IRT) in controls and in patients with SHypo before (SHypo) and after (SHypo + L-T_4) L-T_4 replacement therapy.

TABLE 4. Echocardiographic parameters of left ventricular morphology in subclinical hypothyroid patients before and after L-T_4 replacement therapy

	SHypo patients (n = 10)	
	Before therapy	After therapy
LVEDD (mm)	47.5 ± 4	47 ± 3
LVESD (mm)	30 ± 4	28.5 ± 4
Diastolic IVST (mm)	9.8 ± 0.6	9.5 ± 1.1
Diastolic LVPWT (mm)	8.7 ± 0.9	8.4 ± 0.7
LVMi (g)	87 ± 20	82 ± 11

trast, Doppler indices of diastolic function were normalized by L-T_4 therapy, whereas systolic function improved. In particular, the isovolumic relaxation time shortened significantly to values comparable with those of normal subjects (Fig. 1), and the E/A ratio increased significantly. Fractional shortening, mean velocity of circumferential fiber shortening, and mean aortic acceleration were all enhanced by L-T_4 therapy, although they were still in the normal range. Moreover, CO increased slightly, but not significantly, whereas SVR was reduced by L-T_4 treatment, although it was not significantly different from the mean value of the control subjects.

Discussion

The results of the present study demonstrate that abnormal LV diastolic filling (suggestive of impaired LV relaxation) is a common finding in patients with SHypo and that this abnormality may be reversed by a short-term substitutive L-T_4 therapy.

TABLE 5. Doppler-echocardiographic parameters of left ventricular function in subclinical hypothyroid patients before and after L-T_4 replacement therapy

	SHypo patients (n = 10)	
	Before therapy	After therapy
Systolic function		
FS (%)	37 ± 5	39 ± 7[a]
mVCF (circ/sec)	1.2 ± 0.2	1.3 ± 0.2[a]
Mean aortic acceleration (m/sec^2)	9.3 ± 1.3	11.1 ± 2.3[a]
Peak aortic flow velocity (cm/sec)	0.9 ± 0.2	0.9 ± 0.1
Cardiac Output (mL)	5330 ± 1640	5806 ± 1758
SVR (dynes/sec · cm^{-5})	1497 ± 415	1361 ± 383[b]
Diastolic function		
E (cm/sec)	78 ± 12	85 ± 14[b]
A (cm/sec)	60 ± 12	51 ± 13[a]
E/A ratio	1.3 ± 0.3	1.7 ± 0.4[c]
IRT (msec)	91 ± 8	77 ± 15[b]

[a] $P < 0.01$ *vs.* before therapy.
[b] $P < 0.05$.
[c] $P < 0.001$.

Cardiac function has been previously evaluated in patients with SHypo, by systolic time intervals, with conflicting results (19–25). Some authors reported prolonged systolic time intervals in SHypo (19–21), which improved after L-T_4 therapy, particularly in those patients with more marked basal abnormalities (20). In contrast, Tseng *et al.* found that the isovolumic contraction time, the preejection period, and the ratio of preejection period to LV ejection time were normal in patients with SHypo (25), as assessed by simultaneous recording of aortic and mitral flow velocities.

Arem *et al.*, using Doppler echocardiography at rest and during exercise in eight patients with SHypo, found normal cardiac structure and function, and mild prolongation of the preejection period during exercise and slightly reduced LV diastolic dimensions at rest (26).

Bell *et al.* showed, by radionuclide ventriculography, that patients with SHypo have normal ejection fraction at rest, with a small (but significant) increase in LV ejection fraction during maximal exercise after L-T_4 therapy (27). Forfar *et al.* also reported a blunted increase in ejection fraction during exercise, with a clear improvement in this parameter after L-T_4 replacement therapy (28). Moreover, Foldes *et al.* found a lower ejection fraction, both at rest and during physical exercise, in patients with SHypo, as compared with normal subjects (29).

The discrepant results reported in previous studies of cardiac involvement in SHypo might be, in part, related to the different patient selection (age, inclusion of patients with previous hyperthyroidism, evaluation of patients with acute or unstable SHypo) and to the different diagnostic criteria (too-large range of TSH levels).

In the present study, we performed a strict selection of patients with stable SHypo, excluding patients with confounding factors particularly affecting the cardiovascular system. The impaired diastolic function in this group of patients suggests that SHypo is a condition of minimal tissue hypothyroidism rather than a compensated state. If this is the case, the patients with SHypo should all be considered as potential candidates for therapy with L-T_4.

The idea that SHypo should be treated is also supported by a recent study from Perk *et al.*, who found greater progression of left coronary angiographic lesions in hypothyroid patients with TSH levels in the range seen in SHypo, compared with patients whose TSH levels were assiduously maintained in the normal range (30).

An impairment of diastolic function is a common finding in many cardiac diseases, and it often precedes and causes systolic dysfunction (31). It has been documented that 30–40% of heart failure syndromes are secondary to impaired diastolic function (31). Therefore, the diastolic dysfunction observed in the current study could be the prelude to more serious limitations of cardiac function and physical performance. In this regard, our finding may be causally related to the blunted increase of LV ejection fraction during exercise observed in patients with SHypo (27, 28).

There is a seeming discrepancy between the results of the present study and our previous findings in subclinical hyperthyroidism (14). Specifically, both subclinical hyperthyroidism and hypothyroidism patients show similar diastolic abnormalities despite opposite hormonal patterns. However, subclinical hyperthyroidism is associated with mild LV hypertrophy, whose well-known deleterious consequences on diastolic function (31) may prevail over the enhanced relaxation induced by thyroid hormone excess (32). On the other hand, SHypo may impair directly diastolic function by reducing sarcoplasmatic calcium ATPase activity, with consequent impairment of ventricular diastolic function (33).

Among the indices of systolic function, only mean aortic acceleration was significantly reduced in the group of patients with SHypo. Therefore, this index seems to be the most susceptible to variations in thyroid hormone levels. Furthermore, in the groups of patients with SHypo treated with replacement L-T_4 therapy, SVR was significantly reduced, which confirms a direct vasodilatory effect of thyroid hormone (34).

Doppler-echocardiography represents a simple and reliable method for the evaluation of morphology and function in patients with SHypo. An additional advantage is its easy repeatability and, therefore, it could be used to serially evaluate the adequacy and efficacy of L-T_4 dose. To support this concept, in the subgroup of patients treated with substitutive doses of L-T_4, the echo-Doppler evaluation performed after 6 months demonstrated an improvement of cardiac function.

In conclusion, the results of this study show that diastolic function is impaired in patients with stable SHypo. This abnormality is reversible after 6 months of substitutive L-T_4 therapy. Doppler-echocardiography may be considered a reliable method for a cross-sectional and longitudinal assessment of left ventricular diastolic function in patients with SHypo.

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