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Original article

Effect of L-thyroxine treatment on left ventricular function in subclinical hypothyroidism

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Abstract

Aim of this study was to investigate the effects of thyroxine treatment on myocardial regional left ventricular (LV) systolic and diastolic function in patients with subclinical hypothyroidism (SH) by tissue Doppler imaging (TDI). Forty-two patients (29 women and 13 men; mean age 52.2 ± 15.1 years) with SH, as judged by elevated serum thyroid-stimulating hormone (TSH) levels (>3.6 mIU/l; range, 3.8–12.0) and free thyroid hormones (FT_4 and FT_3) within the normal range, and 30 euthyroid volunteers (21 women and nine men; mean age 50.4 ± 17.1 years) underwent standard echocardiography and TDI-derived early (E_m) and late (A_m) diastolic velocities, systolic (S_m) velocity, and isovolumetric relaxation time ($IVRT_m$). Patients were randomly assigned to receive or not L-thyroxine replacement therapy. All patients returned after 6 months to repeat thyroid function tests and the evaluation of all parameters. No significant differences were seen in the S_m peak between SH and control groups. Respect to controls, SH patients exhibited a lower E_m, a higher A_m, and, subsequently, a reduced E_m/A_m ratio of both lateral wall (LW) and interventricular septum (IVS) ($P < 0.001$ for both). The $IVRT_m$ was distinctly longer in SH patients, as compared to controls ($P < 0.001$). At 6 months, L-thyroxine-treated patients showed a significant increase of E_m ($P < 0.01$) and a subsequent increase of the E_m/A_m ratio ($P < 0.01$), whereas $IVRT_m$ significantly reduced ($P < 0.05$). No significant change in any of these parameters was observed in the untreated group. Our data suggest that SH is associated with a subtle, reversible impairment of myocardial function. TDI analysis detects and extends these functional defects by displaying alterations in regional myocardial function. L-T_4 replacement therapy should be advised for these patients with the aim to correct preclinical cardiac dysfunction and prevent the development of clinically significant myocardial dysfunction.

Keywords: Subclinical hypothyroidism; L-Thyroxine; Tissue Doppler imaging (TDI)

1. Introduction

Subclinical hypothyroidism (SH) is characterized by normal serum concentrations of free thyroxine and elevated serum concentrations of thyroid-stimulating hormone (TSH) [1]. SH has been shown to be an independent risk factor for atherosclerosis and myocardial infarction in elderly women [2]. Altered serum lipid levels and abnormal vascular reactivity in patients with SH, particularly in elderly women, may confer a higher risk for cardiovascular disease [3–6]. Moreover SH is associated with the risk of heart failure, other cardiovascular events, and death [7,8].

Clinical trials on cardiac function in SH patients have shown an impairment of left ventricular (LV) function, which may be reversible with L-thyroxine therapy [9–12]. These studies have been performed with standard echocardiography, which gives informations on the global function of the left ventricle and is influenced by heart rate and preload. More recently, new techniques for the assessment of myocardial regional wall motion have been applied for the evaluation of LV function [13–15]. Some authors [16–20] have demonstrated the usefulness of tissue Doppler imaging (TDI), a technique relatively not influenced by heart rate, preload, left atrial pressure, and aortic pressure, in the detection of cardiac func-

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tional abnormalities due to SH. Therefore, the aim of this study was to investigate the effects of thyroxine treatment on myocardial regional LV systolic and diastolic function in SH by TDI. While we write, Arinc et al. [18] have recently published results of a similar study.

2. Materials and methods

2.1. Participants

We studied 42 patients (29 women and 13 men; mean age 52.2 ± 15.1 years; body surface area 1.75 ± 0.14 m^2) with SH, as judged by elevated serum TSH levels (> 3.6 mIU/l; range, 3.8–12.0) and free thyroid hormones (FT_4 and FT_3) within the normal range.

The etiology of SH was Hashimoto's thyroiditis in all patients. Only the patients with stable elevated serum TSH and normal thyroid hormone levels for at least 3 months before enrollment in the study were included.

All the subjects were free from cardiovascular disease or other major medical disorders, as assessed by clinical history, physical examination, basal and stress electrocardiography, blood chemistry, hematology and urine analysis.

Major criteria for inclusion of subjects in the trial were as follows: body mass index lower than 30 kg/m^2, diastolic arterial blood pressure lower than 90 mmHg and systolic arterial blood pressure lower than 140 mmHg. Subjects were excluded if they had abnormal findings at physical examination, smoking habits, diabetes mellitus, or received any drug treatment within the previous 3 months.

Before inclusion in the protocol, a blood sample for the determination of FT_4, FT_3, antithyroglobulin, and antithyroid peroxidase antibodies (TPO-Ab), and TSH was obtained at 08:00 h after an overnight fast.

Additionally, 30 sex-, age-, and body surface area-matched healthy volunteers (21 women and nine men; mean age 50.4 ± 17.1 years; body surface area 1.68 ± 0.17 m^2) recruited among staff and relatives of patients attending the Department of Internal Medicine, were recruited to form the control group (Table 1).

Patients were randomly assigned to receive or not L-thyroxine (Eutirox, Bracco S.p.A., Milan, Italy) replacement therapy. All patients returned after 6 months for repeat thyroid function tests and the evaluation of all parameters.

The study protocol was approved by the institutional ethics committee; all patients gave their informed written consent to the study.

2.2. Standard echocardiography

The study was performed using an *HP Sonos 5500* (Hewlett-Packard Co., Andover, Mass) phased-array echocardiograph with M-mode, two-dimensional, equipped with pulsed, continuous and color-flow Doppler capabilities. The echocardiograms were evaluated according to the recommendations suggested by the American Society of Echocardiography [21]. LV mass was calculated according to the "Penn convention" [22] and normalized for height to the 2.7th power, based on results of a multicenter study [23]. A pulsed Doppler transmitral flow velocity profile was obtained from the apical four-chamber view, and the sample volume was positioned just below the mitral valve leaflets. The following parameters were evaluated: peak transmitral flow velocity in early diastole (peak *E*), peak transmitral flow velocity in late diastole (peak *A*) and *E*/*A* ratio. Furthermore, for the early diastolic inflow curve, the mitral deceleration (MD: from peak *E* wave to baseline) were measured. The isovolumetric relaxation time (IVRT) was quantify via a simultaneous pulsed Doppler recording of LV output flow and mitral valve inflow.

Table 1
Clinical and hormonal characteristics of the study groups (mean ± S.D.)

	SH $N = 32$	Controls $N = 26$	P
Age (years)	52.2 ± 15.1	50.4 ± 17.1	n.s
Sex (M/F)	12/19	9/22	n.s.
BSA (m^2)	1.75 ± 0.14	1.68 ± 0.17	n.s.
BMI (kg/m^2)	23.8 ± 1.2	23.6 ± 0.9	n.s.
HR (bpm)	70.4 ± 8.2	68.3 ± 7.4	n.s.
SBP (mmHg)	125.0 ± 11.3	122.8 ± 9.4	n.s.
DBP (mmHg)	75.7 ± 2.8	72.5 ± 3.1	n.s.
Glucose (mg/dl)	88 ± 6	89 ± 4	n.s.
Total cholesterol (mg/dl)	198.3 ± 25.0	185.0 ± 11.7	< 0.05
LDL-cholesterol (mg/dl)	113.3 ± 18.1	102.0 ± 13.0	< 0.05
HDL-cholesterol (mg/dl)	52.1 ± 12.5	55.2 ± 10.8	n.s.
Tryglicerides (mg/dl)	116.4 ± 20	112.6 ± 19.1	n.s.
TSH (mIU/l)	8.8 ± 1.7	1.9 ± 0.3	< 0.0001
Free T_3 (pmol/l)	4.29 ± 0.16	4.92 ± 0.15	n.s.
Free T_4 (pmol/l)	9.27 ± 1.10	9.88 ± 0.74	n.s.

BSA: body surface area; BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

2.3. Pulsed TDI

Pulsed wave TDI was performed using a special software package available on the *HP Sonos 5500* with a 3.5-MHz transducer. This method is capable of providing measurements of ventricular wall motion velocity by positioning the sample volume within the myocardium. TDI of diastolic velocities of the basal lateral segment and of the basal (VS in the apical four-chamber view were measured at the end of echocardiographic studies. The sample volumes were placed in the center of myocardial segments. The acoustic power and filter frequencies of the echocardiographic system were set to the lowest values possible to minimize noise. The pulsed TDI of a chosen segment is characterized by a myocardial systolic wave (S_m) and two diastolic waves, early (E_m) and atrial (A_m) (Fig. 1). In addition, the $IVRT_m$ of each segment was measured as the interval from the aortic component of the second heart sound to the peak of the early diastolic wave. All parameters were measured during three consecutive cardiac cycles and their mean value calculated. To assess intraobserver and interobserver variability, echocardiographic and Doppler measurements were made on the same tracing in duplicate by the same obser-