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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

A high-normal thyrotropin level is associated with the severity of left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy

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Abstract

Background: Impaired left ventricular (LV) diastolic function is a common pathophysiological feature of patients with hypertrophic cardiomyopathy (HCM). High-normal thyrotropin (thyroid-stimulating hormone, TSH) levels may alter the performance of the left ventricle.

Aim: To ascertain whether the severity of impaired LV diastolic function in HCM patients might worsen with elevating TSH levels within the reference range.

Methods: This study included 152 HCM patients and 119 healthy controls with euthyroidism. Blood samples were taken to test for serum TSH, free triiodothyronine (FT3) and free thyroxine (FT4) levels. LV diastolic function was quantified by determining the ratio of the transmitral early LV filling velocity to the early diastolic mitral annulus velocity (E/Ea ratio).

Results: The E/Ea ratio was significantly higher in patients with high-normal TSH levels (25.7 ± 5.6 vs. 17.7 ± 4.9, $p < 0.001$). There was a significant correlation between the E/Ea ratio and the TSH levels within the high reference range ($\beta = 0.268$, $p = 0.021$). Univariate logistic regression showed that high-normal TSH levels were predictors of severe heart failure. However, after adjusting for the effect of LV diastolic dysfunction, high-normal TSH levels were no longer independent predictors of severe heart failure.

Conclusions: The HCM patients with high-normal TSH levels had a higher degree of LV diastolic dysfunction. Mild TSH level changes within the high reference range can influence the severity of impaired LV diastolic function. In HCM patients, high-normal TSH levels may affect the development of heart failure through their association with LV diastolic impairment.

Key words: hypertrophic cardiomyopathy, thyrotropin, left ventricular diastolic dysfunction, heart failure

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterised by varying degrees of myocardial hypertrophy. Left ventricular (LV) diastolic dysfunction is an important pathophysiological feature of HCM [1]. In HCM patients, heart failure (HF)-related symptoms appear to be largely attributed to diastolic dysfunction [2]. Furthermore, severe LV diastolic dysfunction is a marker of unfavourable HCM prognosis [3]. It is well known that both overt hypothyroidism and subclinical hypothyroidism are associated with impaired LV diastolic function [4–8]. Moreover, a previous study showed that thyroiditis patients with high-normal thyroid-stimulating hormone (TSH) levels have marked abnormalities in LV diastolic function compared to healthy controls with low-normal TSH levels [9]. Therefore, it is reasonable to determine whether LV diastolic function is correlated with TSH levels within

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the clinically accepted reference range, especially within the high-reference range, in HCM patients. To the best of our knowledge, no study has focused on the association between LV diastolic function and serum TSH concentration changes within the reference range among HCM patients. Thus, the aim of this study was to ascertain whether mild changes in TSH levels within the reference range could affect the severity of impaired diastolic function in a group of HCM subjects.

METHODS

Study population

We retrospectively studied HCM patients who underwent clinical and echocardiographic evaluation between June 2005 and December 2011 in the Fuwai Hospital. The patients were diagnosed with HCM based on a two-dimensional echocardiogram identifying LV hypertrophy (wall thickness of at least 15 mm and a ratio of septal to posterior wall thickness ≥ 1.3) not associated with another cardiac or systemic disease capable of producing hypertrophy of a similar magnitude. The patients were selected using the following criteria: an LV ejection fraction (LVEF) of ≥ 50% and normal TSH, free triiodothyronine (FT3) and free thyroxine (FT4) levels. We excluded patients with systemic hypertension, coronary artery disease, primary valvular heart disease, electronic ventricular pacing, prior cardiac surgery, prior septal ethanol ablation and renal failure. Patients with previously diagnosed thyroid dysfunction were also excluded. The control group consisted of age- and gender-matched healthy subjects who visited our hospital for annual routine medical examinations. This study was approved by the ethics committee of the Fuwai Hospital, China.

Echocardiography

Each subject underwent an echocardiographic evaluation using a commercially available ultrasound system (iE33; Philips Medical Systems, Best, The Netherlands) equipped with an S5-1 transducer (frequency transmitted, 1.7 MHz; frequency received, 3.4 MHz). Two-dimensional and M-mode echocardiographic evaluations were performed to measure the LV end-diastolic dimension (LVEDD), the left atrial end-systolic dimension (LAESD) and the thicknesses of the interventricular septum (IVS) and the LV posterior wall (LVPW) from the parasternal long-axis acoustic window. The ventricle was then divided into four regions: the anterior septum, the posterior septum, the lateral wall, and the posterior walls. The wall thickness was measured at the level of the mitral valve and papillary muscles in each of the four myocardial segments and at the apical level in the anterior and posterior segments using the parasternal short-axis views. The maximum LV wall thickness was defined as the greatest thickness in any single segment. The LVEF was calculated using the LV volumes by the modified biplane Simpson's rule. The LV outflow tract (LVOT) gradient was measured using a continuous-wave Doppler in the apical five-chamber view. An LVOT obstruction was defined as a gradient ≥ 30 mm Hg. The mitral inflow Doppler was measured in the standard fashion to determine peak E- and A-wave velocities. The tissue Doppler imaging (TDI) of the mitral annulus movement was obtained from the apical four-chamber view. A 1.5-mm sample volume was placed at the inferoseptal side of the mitral annulus. Analysis was performed for the early (Ea), and late (Aa) diastolic peak velocities. The E/Ea ratio was calculated and used as a surrogate for the LV filling pressure.

Biochemical analysis

Blood samples were drawn in the early morning from the antecubital vein of each subject after an overnight fasting. Once drawn, the serum samples were centrifuged and immediately stored at –20°C prior to the analysis. Serum TSH, FT3 and FT4 levels were tested using commercial kits (Immulite 2000 chemiluminescent immunoassay; Diagnostic Products Corp, Los Angeles, CA, USA). The intra-assay coefficients of variation (CV) for the concentrations of serum TSH, FT4, and FT3 levels were 1.23–1.38%, 3.44–5.82%, and 1.78––7.22%, respectively; the inter-assay CVs were 1.57–4.93%, 6.55–9.38%, and 4.74–9.35%, respectively. The reference ranges of TSH, FT3 and FT4 levels were 0.35–5.50 mIU/L, 1.76–4.06 pg/mL and 0.80–1.88 ng/dL, respectively. The patients were further divided into a low normal TSH group (TSH 0.35–2.50 mIU/L) and a high normal TSH group (TSH 2.51–5.50 mIU/L). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured by ELISA (Biomedica, Austria) using an automated ELISA assay system (Elx800, Bio-Tek, USA). The normal range was < 400 fmol/mL, and the intra-assay and inter-assay CVs were 5% and 10%, respectively.

Statistical analysis

The data is presented as mean ± standard deviation (SD) for continuous variables or percentages for categorical variables. Clinical characteristics were compared using the t-test for continuous variables and the χ^2 test for categorical variables. The relationships between E/Ea ratio and other clinical variables were first examined by Pearson's correlation. To evaluate the independent relationship between the E/Ea ratio and the levels of TSH, multiple regression analysis was performed using the E/Ea ratio as a dependent variable and the factors that may influence the E/Ea ratio as independent variables. Univariate and multivariate logistic regression analyses were used to examine the effects of sex, atrial fibrillation (AF), TSH levels and echocardiographic variables on the risk of severe HF (NYHA classes III/IV). For the t-tests, correlations and regression analysis, the NT-proBNP values were logarithmically transformed. The TSH values were analysed after extracting the square root. All probability values were for two-tailed tests. A value of $p < 0.05$ indicated a statistically significant result. Data processing and statistical analyses were performed using SPSS v 17.0 software (SPSS, Chicago, IL, USA).

Table 1. Clinical and echocardiographic characteristics of the study subjects

	Patients with HCM (n = 152)	Control subjects (n = 119)	P
Age [years]	47.6 ± 11.4	46.9 ± 8.8	0.571
Male	110 (72.4%)	79 (66.4%)	0.291
Height [m]	1.67 ± 0.08	1.67 ± 0.07	0.800
Weight [kg]	71.3 ± 10.8	69.7 ± 9.6	0.206
BMI [kg/m^2]	25.4 ± 2.8	24.9 ± 2.5	0.125
Heart rate [bpm]	68.3 ± 9.9	68.9 ± 11.0	0.636
SBP [mm Hg]	117.8 ± 16	116.8 ± 12.6	0.609
DBP [mm Hg]	73.4 ± 11.0	75.5 ± 8.1	0.082
Atrial fibrillation	16 (10.5%)	0 (0%)	—
NYHA classification III or IV	33 (21.7%)	0 (0%)	—
Medical treatment			
Beta-blocker	113 (74.3%)	0 (0%)	—
Ca channel blocker	23 (15.1%)	0 (0%)	—
ACEI/ARB	30 (19.7%)	0 (0%)	—
Diuretics	23 (15.1%)	0 (0%)	—
Echocardiographic parameters			
LAESD [(mm]	40.2 ± 6.6	32.8 ± 3.3	< 0.001
LVEDD [mm]	41.5 ± 5.1	46.2 ± 3.5	< 0.001
IVS thickness [mm]	21 ± 5.6	9.1 ± 1.1	< 0.001
LVPW thickness [mm]	11.8 ± 2.6	9.0 ± 1.0	< 0.001
Maximal wall thickness [mm]	23.2 ± 5.0	9.3 ± 1.0	< 0.001
LVEF [%]	72.2 ± 7.0	66.2 ± 4.7	< 0.001
LVOT gradients [mm Hg]	66.6 ± 36.2	0	—
Mitral E velocity [cm/s]	84.3 ± 22.5	78.0 ± 10.4	0.005
Mitral A velocity [cm/s]	77.0 ± 26.3	68.2 ± 12.6	0.001
Medial Ea [cm/s]	4.5 ± 1.5	9.8 ± 2.2	< 0.001
Medial Aa [cm/s]	6.4 ± 1.8	8.8 ± 2.5	< 0.001
E/Ea ratio	20.2 ± 6.3	8.2 ± 1.5	< 0.001
Moderate to severe MR	31 (20.4%	0 (0%)	—
NT-proBNP [fmol/mL]	1,466.3 ± 1,036.2	547.2 ± 204.9	< 0.001
TSH [mIU/L]	2.31 ± 2.25	2.13 ± 1.13	0.733
FT3 [pg/mL]	3.00 ± 0.42	3.02 ± 0.51	0.696
FT4 [ng/dL]	1.21 ± 0.22	1.19 ± 0.21	0.397

HCM — hypertrophic cardiomyopathy; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; NYHA — New York Heart Association; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker LAESD — left atrial end-systolic dimension; LVEDD — left ventricular end-diastolic dimension; IVS — interventricular septum; LVPW — left ventricular posterior wall; LVEF — left ventricular ejection fraction; LVOT — left ventricular outflow tract; E/Ea — the ratio of transmitral early LV filling velocity to early diastolic mitral annulus velocity; MR — mitral regurgitation; NT-proBNP — N-terminal pro B-type natriuretic peptide; TSH —thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

RESULTS

This study included 152 HCM patients and 119 control subjects. The clinical and echocardiographic characteristics of the patients and the controls are described in Table 1. There was no significant difference between the patients and the healthy controls in age or gender. The patients were predominantly male. Most of the patients experienced mild symptoms of HF, and only 21.7% of the patients experienced severe HF symptoms (NYHA classes III/IV). AF was paroxysmal in eight patients and chronic in eight patients. The LAESD, the IVS and the LVPW thickness and the maximal left ventricular thickness (LVT) were significantly higher in the HCM patients, whereas the LVEDD was lower in the patients with HCM. Furthermore, the E/Ea ratio and the plasma NT-proBNP concentration were much higher in

Table 2. Correlations of E/Ea ratio with demographic, echocardiographic and biochemical variables in patients with HCM

	Univariate analysis		Multivariate analysis	
	r-value	p-value	β-value	p-value
Age	0.171	0.036	0.163	0.025
BMI	0.248	0.003	0.14	0.043
HR	0.031	0.703	NI	—
SBP	–0.037	0.652	NI	—
DBP	–0.092	0.258	NI	—
LAESD	0.197	0.015	0.007	0.918
LVEDD	0.033	0.686	NI	—
Maximal LVT	0.249	0.002	0.054	0.500
LVEF	0.060	0.461	NI	—
LVOT gradient	0.318	<0.001	0.183	0.007
NT-proBNP	0.533	<0.001	0.313	< 0.001
TSH	0.523	<0.001	0.350	< 0.001

HCM — hypertrophic cardiomyopathy; NI — indicates not included in the multivariate analysis; BMI — body mass index; HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure; LAESD — left atrial end-systolic dimension; LVEDD — left ventricular end-diastolic dimension; LVT — left ventricular thickness; LVEF — left ventricular ejection fraction; LVOT — left ventricular outflow tract; NT-proBNP — N-terminal pro B-type natriuretic peptide; TSH — thyroid-stimulating hormone

the HCM patients. Compared to the healthy controls, the TSH, FT3 and FT4 levels were not different in the HCM patient group.

As shown in Table 2, age, body mass index (BMI), LAESD, maximal LVT, LVOT gradient and the level of TSH and NT-proBNP were significantly correlated with the E/Ea ratio in the HCM patients. In multiple regression analysis, both the level of TSH and the level of NT-proBNP were the strongest independent determinants of the E/Ea ratio (Table 2). However, in the control subjects, we did not find a significant relationship between the level of TSH and the E/Ea ratio ($r = 0.105$, $p = 0.257$).

We divided the participants into a low-normal TSH level group and a high-normal TSH level group; 105 HCM patients and 82 healthy controls had low-normal TSH levels, and 47 HCM patients and 37 healthy controls had high-normal TSH levels. The clinical characteristics of the four groups are presented in Table 3. In both the HCM and the control groups, the high-normal TSH level group had a higher proportion of female participants and contained subjects with higher BMI values. In the HCM patients, the subjects with high-normal TSH levels had significantly higher E/Ea ratios and NT-proBNP levels. However in the control group, there were no differences in the E/Ea ratios and the level of NT-proBNP between the subjects with low-normal TSH levels and the subjects with high-normal TSH levels. There was no difference in age, gender, BMI value or TSH, FT3 and FT4 levels between the controls with low-normal TSH levels and the HCM patients with low-normal TSH levels. Additionally, age, gender, BMI value and TSH, FT3 and FT4 levels were not different between the controls with high-normal TSH levels and the HCM patients with high-normal TSH levels. For the control subjects with either low-normal TSH levels or with high-normal TSH levels, the levels of TSH were not significantly correlated with the E/Ea ratios ($r = 0.114$, $p = 0.308$ and $r = 0.307$, $p = 0.065$). In addition, for the HCM patients with low-normal TSH levels, the levels of TSH were also not correlated with the E/Ea ratios ($r = –0.122$, $p = 0.217$). However, in the HCM patients with high-normal TSH levels, the TSH levels were significantly associated with the E/Ea ratios (Table 4). Multiple regression analysis showed that the correlation between the TSH levels and the E/Ea ratios remained after adjusting for possible confounding variables (Table 4).

Compared to HCM patients with low-normal TSH levels, HCM patients with high-normal TSH levels suffered from more severe HF, as shown by the larger proportion of patients with NYHA classes III/IV (Table 3) and with a significantly higher NT-proBNP level (Table 3).

The univariate logistic regression analysis (Table 5) indicated that AF, high-normal TSH levels and severely impaired LV diastolic function were significant determinants of severe HF (NYHA classes III/IV). HCM patients with high-normal TSH levels were three times more likely to suffer severe HF than HCM patients with low-normal TSH levels. However, in multivariate logistic regression analysis, high-normal TSH levels were no longer an independent determinant of severe HF. Severely impaired LV diastolic function (E/Ea ratio ≥ 20) was the strongest determinant of severe HF (Table 5).

DISCUSSION

HCM is a complex primary and genetically transmitted cardiac disease. Impaired LV diastolic function is a prominent feature of HCM [1]. Abnormal LV diastolic function has been impli-

Table 3. Clinical and echocardiographic characteristics of the different subgroups of the study subjects

	Control subjects		Patients with HCM	
	With low-normal TSH level (n = 82)	With high-normal TSH level (n = 37)	With low-normal TSH level (n = 105)	With high-normal TSH level (n = 47)
Age [years]	45.1 ± 8.1	50.7 ± 9.2[a]	46.4 ± 10.3	50.2 ± 13.2
Gender:				
Male	60 (73.2%)	19 (51.4%)[a]	87 (82.9%)	23 (48.9%)[§]
Female	22 (26.8%)	18 (48.6%)[a]	18 (17.1%)	24 (51.1%)[§]
BMI [kg/m^2]	24.6 ± 2.6	25.5 ± 1.9[a]	25.0 ± 2.9	26.2 ± 2.4[*]
LAESD [mm]	32.9 ± 3.3	32.6 ± 3.2	39.8 ± 6.5[b]	41.1 ± 6.8[#]
LVEDD [mm]	46.4 ± 3.3	45.8 ± 3.8	41.4 ± 5.2[b]	41.5 ± 5.0[#]
IVS thickness [mm]	9.2 ± 1.1	9.1 ± 1.3	20.5 ± 5.3[b]	22.1 ± 6.2[#]
LVPW thickness [mm]	9.0 ± 1.0	8.9 ± 1.0	11.6 ± 2.1[b]	12.3 ± 3.4[#]
Maximal LVT [mm]	9.3 ± 1.0	9.4 ± 1.1	22.8 ± 4.1[b]	24.2 ± 6.5[#]
LVEF [(%]	66.1 ± 4.5	66.5 ± 5.0	72.7 ± 6.8[b]	71.0 ± 7.3[Δ]
LVOT gradient [mm Hg]	—	—	65.0 ± 35.2	70.0 ± 38.6
E/Ea ratio	8.2 ± 1.3	8.2 ± 2.0	17.7 ± 4.9[b]	25.7 ± 5.6[§#]
NT-proBNP [fmol/mL]	545.3 ± 209.1	552.1 ± 198.1	1,244.9 ± 793.1[b]	1,961.0 ± 1,319.3[§#]
TSH [mIU/L]	1.5 ± 0.6	3.5 ± 0.8[b]	1.4 ± 0.6	4.4 ± 3.1[§]
FT3 [pg/mL]	3.06 ± 0.53	2.93 ± 0.46	3.10 ± 0.39	2.78 ± 0.41[§]
FT4 [ng/dL]	1.20 ± 0.20	1.17 ± 0.23	1.23 ± 0.21	1.17 ± 0.24

[a]$p < 0.05$ vs. control subjects with low-normal TSH level; [b]$p < 0.001$ vs. control subjects with low-normal TSH level; *$p < 0.05$ vs. HCM patients with low-normal TSH level; [§]$p < 0.001$ vs. HCM patients with low-normal TSH level; [Δ]$p < 0.05$ vs. control subjects with high-normal TSH level; [#]$p < 0.001$ vs. control subjects with high-normal TSH level; HCM — hypertrophic cardiomyopathy; BMI — body mass index; LAESD — left atrial end-systolic dimension; LVEDD — left ventricular end-diastolic dimension; IVS — interventricular septum; LVPW — left ventricular posterior wall; LVT — left ventricular thickness; LVEF — left ventricular ejection fraction; LVOT — left ventricular outflow tract; NT-proBNP — N-terminal pro B-type natriuretic peptide; TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

Table 4. Correlations of E/Ea ratio with demographic, echocardiographic and biochemical variables in HCM patients with high--normal TSH levels

	HCM patients with high-normal TSH levels (n = 47)			
	Univariate analysis		Multivariate analysis	
	r-value	p-value	β-value	p-value
Age	–0.083	0.579	NI	—
BMI	0.183	0.234	NI	—
HR	–0.071	0.637	NI	—
SBP	–0.213	0.151	NI	—
DBP	-0.212	0.152	NI	—
LAESD	0.395	0.006	0.061	0.610
LVEDD	–0.030	0.839	NI	—
Maximal LVT	0.411	0.004	–0.702	0.486
LVEF	–0.153	0.304	NI	—
LVOT gradient	0.315	0.031	0.143	0.191
NT-proBNP	0.710	< 0.001	0.593	< 0.001
TSH	0.478	0.001	0.268	0.021

HCM — hypertrophic cardiomyopathy; NI — indicates not included in the multivariate analysis; BMI — body mass index; HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure; LAESD — left atrial end-systolic dimension; LVEDD — left ventricular end-diastolic dimension; LVT — left ventricular thickness; LVEF — left ventricular ejection fraction; LVOT — left ventricular outflow tract; NT-proBNP — N-terminal pro B-type natriuretic peptide; TSH — thyroid-stimulating hormone

Table 5. Determinants of severe heart failure in HCM patients

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P	OR (95%CI)	P
Female sex	1.70 (0.75–3.85)	0.208	1.05 (0.40–2.74)	0.925
Atrial fibrillation	3.29 (1.12–9.65)	0.030	3.89 (1.10–13.72)	0.035
LAESD ≥ 45 mm	1.70 (0.74–3.95)	0.215	1.60 (0.61–4.18)	0.347
IVS thickness ≥ 20 mm	1.00 (0.41–2.48)	0.988	0.70 (0.25–1.91)	0.484
LVOT gradient ≥ 30 mm Hg	1.42 (0.49–4.10)	0.518	2.26 (0.64–8.05)	0.207
Moderate to severe MR	1.07 (0.41–2.75)	0.895	0.82 (0.29–2.32)	0.709
TSH > 2.5 mIU/L	2.67 (1.21–5.92)	0.016	1.47 (0.55–3.94)	0.447
E/Ea ratio ≥ 20	4.17 (1.74–10.00)	0.001	3.36 (1.21–9.30)	0.020

HCM — hypertrophic cardiomyopathy; OR — odds ratio; CI — confidence interval; LAESD — left atrial end-systolic dimension; IVS — interventricular septum; LVOT — left ventricular outflow tract; MR — mitral regurgitation; TSH — thyroid stimulating hormone; E/Ea — the ratio of transmitral early LV filling velocity to early diastolic mitral annulus velocity

cated as the primary determinant of symptoms related to HF in patients with HCM [2]. Our study provides unprecedented data connecting the levels of TSH within the reference range and the LV diastolic function quantified by the E/Ea ratio in the HCM patients.

Our data indicated that patients with high-normal TSH levels showed more serious diastolic dysfunction, as shown by the higher E/Ea ratio, compared to patients with low-normal TSH levels. For HCM patients, the E/Ea ratio increased with elevating TSH levels within the reference range. This association was also significant in patients with high-normal TSH levels. However, in the low-normal TSH level group, it was less likely that a change in TSH level would affect the E/Ea ratio. These findings indicate that the correlation between the E/Ea ratio and the TSH levels within the normal reference range is primarily attributed to the subjects with high-normal TSH levels.

Our findings may be partially explained by the prevalence of mild subclinical hypothyroidism in subjects with high-normal TSH levels. The upper limit of TSH is still a matter of debate, although in most laboratories the established upper limit of the serum TSH reference range is between 3 and 6 mIU/L. However, accumulating evidence supports the notion that TSH levels within the high reference range are often associated with mild subclinical hypothyroidism. An increased prevalence of the anti-thyroid peroxidase antibodies in the high-normal group has been observed [10]. The patients with high-normal TSH levels have an increased risk for overt hypothyroidism [11]. Recently, it has been argued that the upper limit for the normal range of TSH should be set at 2.5 mIU/L [12]. Thus, subjects with high-normal TSH levels should be suspected as having subclinical hypothyroidism. Previous studies demonstrated that the TSH levels within the normal reference range, especially within the high-normal range, are linearly associated with the severity of metabolic disturbances [13, 14]. This data indicated that elevating TSH levels within the high-normal reference range may be associated with the severity of subclinical thyroid dysfunction.

The heart is an organ sensitive to the action of the thyroid hormone. Impairment of LV diastolic function is common in patients with overt hypothyroidism [5, 6]. The most consistent cardiac abnormality observed in patients with subclinical hypothyroidism is impaired LV diastolic function [7, 8]. Mariotti et al. [15] included two groups of mild subclinical hypothyroidism patients in his study. The mean TSH level in group A was 5.69 ± 2.16 mIU/L, and the mean TSH level in group B was 2.53 ± 0.35 mIU/L. Compared to the healthy controls with low-normal TSH levels (mean TSH 1.2 ± 0.5 mIU/L), the subclinical hypothyroidism patients with high-normal TSH levels presented with significantly abnormal LV diastolic function [15]. His results indirectly support our findings that high-normal TSH levels can exacerbate LV diastolic dysfunction in HCM patients. In contrast to our results, Mariotti et al. [15] did not observe a significant difference in LV diastolic function among patients with high-normal TSH levels. The relatively small sample size used in his study may be a possible reason for these conflicting results.

In contrast to the HCM patients in our study, the TSH levels were not associated with the E/Ea ratio in the healthy controls. One possible reason is that HCM patients usually present with obviously impaired LV diastolic function, and they are more susceptible to factors that may impair LV diastolic function. Thus, slightly elevated TSH levels, within the high reference range, may be associated with the progression of LV diastolic dysfunction in HCM patients.

TSH can be influenced by several factors including age and obesity. According to the NHANES III report, the prevalence of thyroglobulin antibodies and thyroid peroxidase antibodies increases with age [16]. A positive association between the BMI values and the levels of serum TSH was observed in a previous study [17]. In our study, age and BMI values were higher in the HCM patients and the healthy controls with

high-normal TSH levels, so our result was consistent with the previous studies. Moreover, both the age and the BMI value can influence the LV diastolic function [18, 19]. To evaluate the independent association between the TSH levels and the E/Ea ratio, we performed multiple regression analysis in the present study. After adjusting for age, BMI value and other factors that may affect the LV diastolic function, the association between the TSH level and the E/Ea ratio remained significant.

HF-related symptoms, such as exertional dyspnoea, orthopnoea and fatigue, are very common in HCM patients. HCM patients with HF-related symptoms usually present normal or supranormal LV contractility but impaired LV diastolic function. Thus, congestive symptoms and exertional limitations in HCM appear to be largely the consequence of diastolic dysfunction. It has been shown that the severity of impaired LV diastolic function correlates well with the NYHA function classification and peak oxygen consumption [2, 20, 21] and plays a significant role in determining the plasma NT-proBNP levels in the HCM patients [22]. In the present study, we observed that HF was more serious in the HCM patients with high-normal TSH levels. Compared to the HCM patients with low-normal TSH levels, patients with high-normal TSH levels were 2.67 times more likely to suffer severe HF (NYHA classes III/IV). However, this relationship was no longer significant after adjusting for the effect of impaired LV diastolic function. These findings imply that TSH levels within the high-normal range might aggravate the severity of HF by exacerbating LV diastolic dysfunction in HCM patients.

Whether to treat or not to treat subclinical hypothyroidism remains a dilemma. Recent epidemiological data suggests that mild thyroid failure may be the only reversible cause of LV diastolic dysfunction [23]. A study has demonstrated that treatment with L-thyroxine can reverse echocardiogram LV diastolic function abnormalities associated with even a mildly raised serum TSH level within 5–10 mIU/L [24]. Mariotti et al. [15] has shown that diastolic dysfunction is reversible with L-thyroxine replacement therapy in mild subclinical hypothyroidism patients with high-normal TSH levels. However, there is no data describing the effect of replacement therapy on cardiac function in patients with HCM. Therefore, whether L-thyroxine treatment is indeed relieving the burdens of HF by improving LV diastolic function in HCM patients with high-normal TSH remains to be examined in controlled intervention trials.

However, the results of our study indicated that the increased TSH concentration within the high-normal reference range may have detrimental effects on the diastolic function in HCM patients. Therefore, subjects with HCM should be carefully assessed for the TSH level; for patients with high-normal TSH levels, the dosage of drugs that may exacerbate the thyroid dysfunction, such as contrast agents and amiodarone, should be strictly controlled.

Limitations of the study

This study had several limitations. In addition to the relatively small sample size and the cross-sectional study design, ours was a retrospective study, so thyroid autoimmunity cannot be assessed. However, previous studies have reported that the prevalence of anti-thyroid antibody is high in subjects with high-normal TSH levels, whether in the West or in China [10, 25]. Finally, we checked TSH levels only once, and it is unknown whether a single TSH measurement reflects the average TSH level of an individual over time. Future studies should be designed using larger cohorts of HCM patients with a long-term follow up to validate what we observed in the present study.

CONCLUSIONS

HCM patients with high-normal TSH levels had a higher degree of LV diastolic dysfunction than patients with low-normal TSH levels. The severity of impaired LV diastolic function in the HCM patients is associated with elevating TSH levels that are slightly beyond the optimal upper limit. HCM patients with high-normal TSH levels suffered more severe HF compared to HCM patients with low-normal TSH levels. High-normal TSH levels can affect the development of HF in HCM patients through their association with LV diastolic impairment.

Conflict of interest: *none declared*

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Związek między wysokim prawidłowym stężeniem tyreotropiny a stopniem ciężkości dysfunkcji rozkurczowej lewej komory u chorych z kardiomiopatią przerostową

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Streszczenie

Wstęp: Upośledzenie czynności rozkurczowej lewej komory (LV) jest zaburzeniem często występującym u chorych z kardiomiopatią przerostową (HCM). Prawidłowe wysokie stężenie tyreotropiny (hormon stymulujący tarczycę, TSH) może wpływać na zmianę czynności LV.

Cel: Celem niniejszego badania było ustalenie, czy dysfunkcja rozkurczowa LV u chorych z HCM może się nasilać ze wzrostem stężenia TSH w zakresie wartości prawidłowych.

Metody: W badaniu uczestniczyło 152 pacjentów z HCM i 119 zdrowych osób z prawidłową czynnością tarczycy, stanowiących grupę kontrolną. Od wszystkich pobrano próbki krwi w celu oznaczenia surowiczych stężeń TSH, wolnej trijodotyroniny (FT3) i wolnej tyroksyny (FT4). Czynność rozkurczową LV oceniano na podstawie wartości współczynnika E/Ea (stosunek prędkości maksymalnej fali wczesnego napływu mitralnego do wczesnorozkurczowej prędkości ruchu pierścienia zastawki mitralnej).

Wyniki: Współczynnik E/Ea był istotnie wyższy u chorych z wysokimi prawidłowymi stężeniami TSH ($25,7 \pm 5,6$ *vs.* $17,7 \pm 4.9$; $p < 0,001$). Stwierdzono istotną korelację między wartościami współczynnika E/Ea i stężeniami TSH w zakresie wysokich wartości prawidłowych ($\beta = 0,268$; $p = 0,021$). W modelu regresji logistycznej dla jednej zmiennej wykazano, że wysokie prawidłowe stężenia TSH były predyktorami ciężkiej niewydolności serca. Jednak po skorygowaniu pod względem wpływu dysfunkcji skurczowej LV wysokie prawidłowe stężenia TSH nie zachowały wartości predykcyjnej w stosunku do ciężkiej niewydolności serca.

Wnioski: U chorych z HCM, u których stężenia TSH utrzymują się w zakresie wysokich wartości prawidłowych, zaobserwowano bardziej nasiloną dysfunkcję LV. Niewielkie zmiany stężenia TSH w zakresie wysokich wartości prawidłowych mogą wpływać na stopień ciężkości dysfunkcji rozkurczowej LV. U pacjentów z HCM wysokie prawidłowe stężenia TSH mogą przyczyniać się do rozwoju niewydolności serca poprzez ich związek z dysfunkcją rozkurczową LV.

Słowa kluczowe: kardiomiopatia przerostowa, tyreotropina, dysfunkcja skurczowa lewej komory, niewydolność serca

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