VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2012, Vol. 19, No. 4, pp. 374–380
10.5603/CJ.2012.0068

ISSN 1897–5593

Evaluation of left ventricular systolic asynchrony in patients with subclinical hypothyroidism

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Abstract

Background: *The heart was very sensitive to fluctuating thyroid hormone levels. To assess intra-left ventricular (LV) systolic asynchrony in patients with subclinical thyroid dysfunction.*

Methods: *Fifty patients with subclinical hypothyroidism and 40 controls were included. A diagnosis of subclinical hypothyroidism was reached with increased TSH and normal free T4. All subjects were evaluated by echocardiography. Evaluation of intra-LV systolic asynchrony was performed by tissue synchronization imaging (TSI), and four TSI parameters of systolic asynchrony were calculated. LV asynchrony was defined by these parameters.*

Results: *All of the groups were similar in terms of demographic findings and conventional and Doppler echocardiograpic parameters except peak systolic velocity and early diastolic velocity. LV systolic asynchrony parameters of TSI including; standard deviation of Ts of the 12 LV segments (Ts-SD-12), maximal difference in Ts between any 2 of the 12 LV segments (Ts-12), standard deviation of TS of the 6 basal LV segments (Ts-SD-6), maximal difference in Ts between any of the 6 basal LV segments (Ts-6) were significantly lengthened in patients with subclinical hypothyroidism than controls ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). The prevalence of LV asynchrony was significantly higher in patients with subclinical hypothyroidism than control.*

Conclusions: *Patients with subclinical hypothyroidism present evidence of LV asynchrony by TSI. LV systolic asynchrony could be a warning sign of the early stage in cardiac systolic dysfunction in subclinical hypothyroid patients.* (Cardiol J 2012; 19, 4: 374–380)

Key words: left ventricular asynchrony, thyroid stimulating hormone, tissue synchronization imaging

Introduction

Thyroid hormone receptors are abundant in the myocardium, so the heart is extremely sensitive to the thyroid hormones [1]. There are many regulatory effects of thyroid hormones, such as cardiac protein transcription, gene expression, [2] impaired myocardial contractility, decreased cardiac output, variability of heart rate, increased systemic vascular resistance, [3] cardiomyocyte atrophy, endothe-

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Received: 14.03.2012 Accepted: 10.04.2012

lial dysfunctions, [4, 5] higher prevalence of atherosclerosis and development of heart failure [6, 7]. Some clinical studies have shown that even in the form of subclinical hyperthyroidism and subclinical hypothyroidism were associated with changes in various cardiac parameters [8–10]. Subclinical hypothyroidism is associated with left ventricular (LV) diastolic dysfunction qualified by slowed myocardial relaxation and disabled rapid ventricular filling, both at rest and with exercise. Frequently this is related with a changeable impairment in LV systolic function even at the very early stage [11, 12].

LV asynchrony is defined as deterioration of the simultaneous contraction of corresponding cardiac segments. Because of this, delayed activation of some ventricular segments leads to uncoordinated contraction. LV asynchrony may affect the diastolic and systolic function, exercise capacity, prognosis, quality of life and symptoms of heart failure, so, it may lead to deterioration of heart failure. Previous studies commonly used QRS duration for the definition of LV asynchrony and decision of resynchronization therapy [13]. But, the developments in echocardiographic methods enabled the direct assessment of mechanical asynchrony [14, 15]. Recently, it has been shown that overt hypothyroidism [16] and clinical hyperthyroidism [17] were impaired LV synchronicity. However subclinical thyroid dysfunction causes LV asynchrony has not been evaluated. In this way, the aim of the present study was to evaluate intra-LV systolic asynchrony in patients with subclinical thyroid disorders.

Methods

Study population

We studied 50 patients (37 female and 13 male with mean age of 38.6 ± 11.5 years) with subclinical hypothyroidism who were newly or untreated, previously diagnosed patients in endocrine clinic. The study patients had normal sinus rhythm and narrow QRS complex on electrocardiography (ECG). In addition, 40 healthy control subjects (30 female and 10 male with mean age of 39.0 ± 10.1 years) were included. The diagnosis of subclinical hypothyroid was reached with increased serum TSH (> 4.0 mU/L) and normal free T4 (fT4) levels in fasting blood samples (normal values in our laboratory were; 0.4–4.0 mU/L for TSH and 0.9–1.9 ng/ /mL for fT4). All subjects' triiodothyronine (fT3) level was found normal. The entire study population's demographic characteristics, biochemical parameters, lipid values and ECGs were obtained. Exclusion criteria were as follows: overt hypothyroidism or hyperthyroidism, acute coronary syndrome, prior myocardial infarction and coronary artery disease, congestive heart failure, LV hypertrophy, prolonged QRS duration (≥ 120 ms), reduced LV ejection fraction (LVEF < 55%), chronic obstructive pulmonary disease, significant valvular heart disease, pacemaker implantation, atrial flutter or fibrillation, frequent ventricular pre-excitation and atrio-ventricular conduction abnormalities, hypertension (resting blood pressure ≥ 140/90 mm Hg), diabetes mellitus, medications known to alter cardiac conduction, peripheral vascular diseases, pulmonary or neurological disease, pericarditis, congenital heart disease, alcohol abuse, renal or hepatic disease and poor echocardiographic imaging. Approval for the study was obtained by the local ethics committee. All subjects included in the study singed upon inform consent with careful explanation of the study procedures.

Standard echocardiography

All patients were evaluated by transthoracic M- mode, two dimensional (2D), pulsed-wave (PW), continuous wave (CW), color flow and tissue Doppler imaging (TDI). All examinations were performed with the GE-Vivid-7 system (GE Vingmed, Horten, Norway) with a 2–4 MHz transducer at a dept of 16 cm. During echocardiography, continuous single-lead ECG recording was obtained. All patients were imaged in the left lateral decubitus position. 2D and conventional Doppler examinations were obtained in the parasternal and apical views according to the guidelines of the American Society of Echocardiography [18]. LV diameters and wall thickness was measured by M-mode echocardiography. LVEF was calculated using the apical 2- and 4-chamber views by Simpson's method, according to American Society of Echocardiography guidelines [18]. The mitral valve inflow pattern [E-wave, A-wave, E-wave deceleration time (Dt), E/A ratio and isovolumic relaxation time (IVRT)] were measured using pulsed wave Doppler. LV mass index was calculated using the formula with the Deveraux equation [19, 20].

Tissue Doppler echocardiography

TDI was performed by transducer frequencies of 3.5 to 4.0 MHz, adjusting the spectral pulsed Doppler signal filters to acquire the Nyquist limit of 15 to 20 cm/s was reached and using the minimal optimal gain. Myocardial TDI velocities (peak systolic [Sm], early diastolic [Em] and late diastolic velocities [Am]) were measured via spectral pulsed Doppler as of the LV-free wall from the apical

4-chamber view [18]. TDI was performed using apical 4-chamber, apical 2-chamber and apical long-axis views for motion of the ventricle.

Evaluation of intra-LV systolic asynchrony was performed by tissue synchronization images (TSI) [21]. It was a parametric imaging tool derived by 2D TDI images. TSI exhibits regional asynchrony on 2D echocardiography and enables the evaluation of regional delay in systole. TSI is calculated automatically and color-codes for the time to peak tissue velocity (Ts) in each position in the image with reference to the QRS signal [22, 23]. The algorithm of TSI defines positive velocity peaks within a specified time period and the color coding ranges from green (first), yellow, orange and red (latest) within this period. Initially, the event timing tool was measured manually the time from the onset of the QRS to the aortic valve opening and closure and separately recorded pulsed Doppler spectrum. The event timing tool allows the start and end times of TSI. Then it adjusted manually to align with the corresponding aortic valve opening and closure markers on ECG. Therefore, peak systolic velocities outside the ejection phase will be measured. In addition, for qualitative measurement of the wall with most severe delay was identified on the basis of TSI at the three apical views. A quantitative measurement device allowed numerical calculation of the median time to peak velocity within a 6-mm sample volume manually positioned within the 2D TSI image for 12 LV. At least three consecutive beats were stored and the images were analyzed offline for TSI by a customized software package (EchoPac for PC, GE Vingmed Ultrasond) [21]. The six-basal and six mid-segmental model was used [21–23]. Four parameters of intra-LV asynchrony were recorded only ejection phase included:

— standard deviation of Ts of the 12 LV segments (Ts-SD-12);
— maximal difference in Ts between any 2 of the 12 LV segments (Ts-12);
— standard deviation of Ts of the 6 basal LV segments (Ts-SD-6);
— maximal difference in Ts between any of the 6 basal LV segments (Ts-6) [16].

Ts-SD-12 is the most widely used parameter of intra-LV asynchrony [21–23]. Ts-SD-12 more than 31.4 ms is defined that intra-LV systolic asynchrony by TSI [19]. All measurements were performed by two experienced investigators, who were unaware of the subject's clinical status. If a difference of > 5% in any of the variables measured by both investigators was found, the patient was not included, whereas if the difference was < 5%, the measurements were averaged.

Statistical analysis

All analyses were performed using the SPSS (SPSS for Windows 15.0) software package. Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as the percentage. Fisher exact test and continuity correction were used for categorical variables and unpaired t-test was used for continuous variables if appropriate. Pearson's and Spearmen correlation exponents were used to force of relationship between continuous variables. Linear multivariate regression analysis was used to recognize the significant determinants intra-LV asynchrony. A value of $p < 0.05$ was considered statistically significant.

Results

Patients characteristics

The baseline demographic and biochemical parameters of the groups are demonstrated in Table 1. Both of groups had similar demographic findings such as age, sex, body mass index (BMI), smoking, heart rate, systolic and diastolic blood pressure and lipid levels ($p > 0.05$). Unsurprisingly, patients with subclinical hypothyroidism had significantly higher TSH and significantly lower fT4 ($p < 0.001$ and $p < 0.001$, respectively).

Echochardiographic parameters and asynchrony

Both of groups were similar in terms of conventional and Doppler echocardiograpic parameters (Table 1). Peak systolic velocity (Sm) and early diastolic velocity (Em) were significantly lower in patients with subclinical hypothyroid patients on TDI compared with controls ($p = 0.027$ and $p = 0.021$, respectively). Additionally, Although, left atrial diameter and late diastolic mitral annular velocity (Am) were higher in patients with subclinical hypothyroidism but these did not reach statistical significance (Table 2). Intra-LV systolic asynchrony parameters of TSI including Ts-SD-12, Ts-12, Ts-SD-6 and Ts-6 were significantly lengthened in patients with subclinical hypothyroid than controls ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$). The frequency of intra-LV systolic asynchrony defined as Ts-SD-12-ejection more than 31.4 ms was significantly higher in patients with subclinical hypothyroid than controls (73.3% and 9.3%, $p < 0.001$, respectively).

Table 1. Baseline demographic and biochemical characteristics of the groups.

	Subclinic hypothyroid (n = 50)	Control (n = 40)	P
Age	38.6 ± 11.5	39.0 ± 10.1	0.726
Gender (female)	37 (74.0%)	30 (75.0%)	0.901
Smoking	10 (20.0%)	9 (22.5%)	0.586
BMI [kg/m^2]	27.4 ± 4.6	28.3 ± 5.1	0.517
Heart rate [bpm]	74.6 ± 10.6	74.6 ± 9.0	0.869
SBP [mm Hg]	117.8 ± 18.3	119.1 ± 19.3	0.436
DBP [mm Hg]	77.8 ± 7.0	78.1 ± 8.3	0.572
Total cholesterol [mg/dL]	186.0 ± 26.7	186 ± 28.3	0.805
LDL [mg/dL]	114.7 ± 16.4	111.0 ± 18.3	0.588
HDL [mg/dL]	42.3 ± 7.1	42.5 ± 5.8	0.701
Triglyceride [mg/dL]	151 ± 28.2	152 ± 29.1	0.964
Glucose	95.6 ± 7.1	97.9 ± 14.2	0.547
Hemoglobin [g/dL]	13.4 ± 3.2	13.1 ± 2.8	0.692
Creatinine [mg/dL]	0.79 ± 0.18	0.77 ± 0.16	0.217
TSH	**8.6 ± 4.9**	**2.0 ± 0.8**	**< 0.001**
Free T3	2.9 ± 0.71	3.4 ± 0.83	0.492
Free T4	**0.97 ± 0.12**	**1.25 ± 0.20**	**0.010**

BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; LDL — low density lipoprotein; HDL — high density lipoprotein; TSH — thyroid stimulant hormone

Table 2. Standard and tissue Doppler echocardiographic charactheristics of subjects.

	Subclinic hypothyroid (n = 50)	Control (n = 40)	P
LVESD [mm]	30.0 ± 3.5	30.1 ± 4.1	0.930
LVEDD [mm]	48.2 ± 5.5	47.2 ± 4.2	0.341
LVESV [mL]	27.7 ± 8.0	27.1 ± 5.3	0.868
LVEDV [mL]	82.7 ± 16.2	85.4 ± 18.0	0.177
IVS [mm]	10.1 ± 1.7	9.5 ± 1.5	0.216
PW [mm]	9.5 ± 1.2	9.2 ± 1.0	0.709
LA [mm]	35.0 ± 8.7	32.3 ± 6.1	0.180
E [cm/s]	77.8 ± 27.0	78.1 ± 18.3	0.572
A [cm/s]	66.0 ± 26.7	59.6 ± 22.3	0.305
DT [ms]	216.7 ± 36.4	211.0 ± 38.3	0.788
IVRT [ms]	90.3 ± 27.1	87.5 ± 25.8	0.701
LVMI	84.4 ± 18.2	83.2 ± 19.1	0.461
LVEF [%]	64.0 ± 18.2	64.4 ± 19.1	0.811
Sm [cm/s]	**10.8 ± 2.2**	**12.3 ± 2.2**	**0.027**
Em [cm/s]	**11.4 ± 2.2**	**13.4 ± 1.9**	**0.021**
Am [cm/s]	13.6 ± 3.1	12.8 ± 2.4	0.653

LVESD — left ventricular end systolic diameter; LVEDD — left ventricular end diastolic diameter; LVESV — left ventricular end systolic volume; LVEDV — left ventricular end diastolic volume; IVS — interventricular septum; PW — posterior wall; LA — left atrium; E — early diastolic mitral inflow velocity; A — late diastolic mitral inflow velocity; DT — deceleration time; IVRT — isovolumetric relaxation time; LVMI — left ventricular mass index; LVEF — left ventricular ejection fraction; Sm — peak systolic mitral annular velocity; EM — early diastolic mitral annular velocity; Am — late diastolic mitral annular velocity

Correlation between intra-LV asynchrony and other parameters

Positive correlation was found between Ts-SD--12 and TSH in patients with subclinical hypothyroidism (r = 0.24, p = 0.047, Fig. 1). There was negative correlation between Ts-SD-12 and Em in patients with subclinical hypothyroid. In addition Sm and Am was not correlated with intra-LV asynchrony.

Linear multivariate regression analysis (included age, gender, BMI, TSH, fT4, Em, Sm, Am, systolic

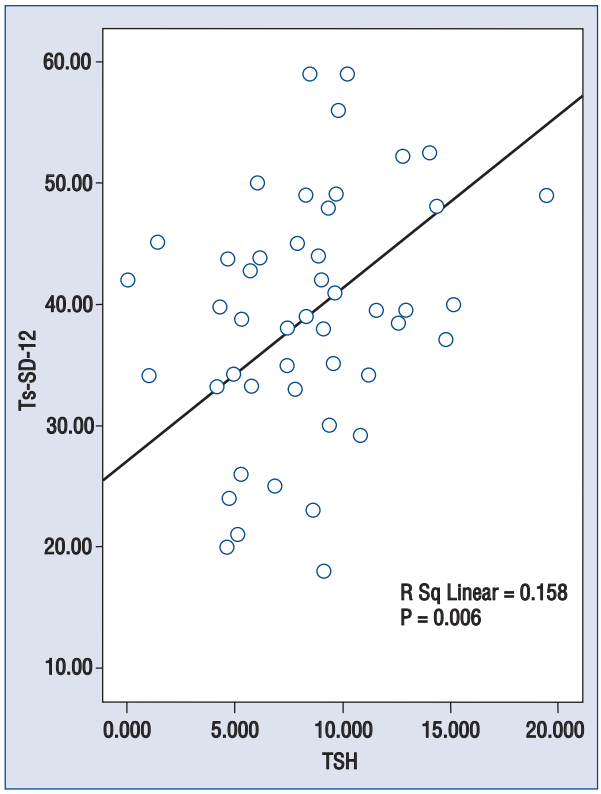

Figure 1. The correlation of standard deviation of time to peak tissue velocity of the 12 left ventricular segments (Ts-SD-12) and thyroid stimulant hormone (TSH) in patients with subclinical hypothyroidism.

and diastolic blood pressure) demonstrated that, TSH was the only independent factor of intra-LV systolic asynchrony in patients with subclinical hypothyroid ($R^2 = 0.459$, $\beta = 0.411$; $p = 0.017$).

Discussion

The objective of this study was to analyze the changes of intra-LV asynchrony in patients with subclinical hypothyroidism by TSI. Asynchrony parameters obtained by TSI (including Ts-SD-12, Ts-12, Ts-SD-6 and Ts-6) significantly prolonged in patients with subclinical hypothyroidism compared with the control group. Additionally TSH was the only independent factor of intra-LV asynchrony in patients with subclinical hypothyroidism. Also, Sm and Em velocities of mitral lateral-basal segment of LV were lower in patients with subclinical hypothyroidism than control as concordant with previous studies [24, 25].

The myocardium is well-known among tissues that include thyroid hormone receptors [10]. Thyroid hormone deficiency can alter cardiac muscle

Table 3. Comparison of parameters of tissue synchronization imaging between the groups.

	Subclinic hypothyroid (n = 50)	Control (n = 40)	P
Ts-SD-12	38.8 ± 14.9	23.8 ± 12.4	< 0.001
Ts-12	119.0 ± 33.2	70.2 ± 32.2	< 0.001
Ts-SD-6	33.6 ± 14.0	20.1 ± 15.3	< 0.001
Ts-6	102.7 ± 25.4	55.4 ± 18.0	< 0.001

Ts — time to peak tissue velocity; Ts-SD-12 — standard deviation of Ts of the 12 LV segments; Ts-12 — maximal difference in Ts between any 2 of the 12 LV segments; Ts-6 — maximal difference in Ts between any 2 of the 6 basal LV segments; Ts-SD-6 — standard deviation of Ts of the 6 basal LV segments

function by decreasing the activity of several enzymes involved in the regulation of myocyte calcium fluxes [10] and the expression of several contractile proteins [26]. In addition, thyroid hormone has been shown to affect calcium uptake by the sarcoplasmic reticulum, to stimulate plasma membrane Ca-ATPase activity and to increase voltage-dependent channels in animal ventricular cells [10, 26, 27]. The subclinical hypothyroidism is defined as an asymptomatic state characterized by normal serum concentration of fT4 and increased serum concentrations of TSH. Thus, it may seem surprising to find cardiac alterations similar to those observed in overt thyroid disorders. However, minute decrements in hormone synthesis may over time leading to biochemical and functional signs that are qualitatively similar to those of thyroid disorders [28].

The relationship between thyroid gland and the heart has been known for a long time. Accordingly, the alterations in thyroid status may affect both the LV diastolic and systolic function. Di Bello et al. [29] investigated and reported that early systolic hyperdeformability and hypercontractility together with impaired diastolic function by strain echocardiography in patients with subclinical hyperthyroidism. They speculated that the direct effect of thyroid hormones on the heart may cause of these results. Our results suggested that intra-LV systolic asynchrony in subclinical hypothyroid patients. Also, in our study we do not know disease duration and our patients were younger age group. Therefore, thyroid hormones may have a direct action on ventricular synchronization.

On the other way, thyroid hormones are also effect transcriptions of structural and regulatory proteins on the cardiovascular system [2]. Also, mildly changes in blood levels of thyroid hormones have many adverse effects on both function and

structure of the heart. These effects are decreased cardiac contractility and cardiac output, cardiomyocyte atrophy, [1–4] myocardial fibrosis and development of heart failure [30, 31]. The most consistent cardiac abnormality defined in subclinical hypothyroid patients is LV diastolic dysfunction [11]. Aghini-Lombardi et al. [32] demonstrated that early functional and textural alterations in subclinical hypothyroid patients using intra-myocardial ultrasonic video-densitometry analysis. Similarly, in our study suggests that intra-LV asynchrony in patients with subclinical thyroid disorders. Impaired diastolic function is a common finding in many cardiac diseases, and it often precedes and results in systolic dysfunction. Additionally, myocardial fibrosis and cardiomyocyte atrophy may cause LV systolic asynchrony in patients with subclinical hypothyroid.

LV asynchrony may be assessing by different echocardiographic techniques such as M-Mode, TDI, TSI, and strain imaging. Previous studies suggested that measuring Ts from myocardial velocity curves of TDI was very useful for quantitative assessment of systolic asynchrony [19, 22, 23]. Therefore, Yu et al. [21] reported that TSI was a good technique for assessing synchronization, so we used TSI method in this study.

Limitations of the study

The major limitation the size of our study population was relatively small. Secondly strain or strain rate was not performed for LV asynchrony. Nevertheless, strain and strain rate analysis are not applicable for routine clinical use and difficult to interpret strain images. In this study used TSI method which is reliable, practical and less time consuming.

Conclusions

The current study demonstrated that impaired ventricular systolic synchronization in patients with subclinical hypothyroidism by TSI. LV systolic asynchrony could be a warning sign of the early period in cardiac systolic dysfunction and heart failure in patients with subclinical hypothyroidism. In addition, TSI is a useful method to determined intra-LV asynchrony.

Conflict of interest: none declared

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