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ORIGINAL ARTICLE

Intra-left ventricular systolic asynchrony in patients with overt hyperthyroidism

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Abstract Hyperthyroidism causes a variety of adverse effects on the cardiovascular system. Left ventricular (LV) asynchrony is defined as loss of the simultaneous peak contraction of corresponding cardiac segments. The aim of this study was to assess systolic asynchrony in patients with overt hyperthyroidism. Asynchrony was evaluated in 27 patients with overt hyperthyroidism and 21 controls. All the patients and controls were subjected to a tissue synchronization imaging (TSI). The time to regional peak systolic tissue velocity (Ts) in LV by the six-basal-six-mid-segmental model was measured on ejection phase TSI images and four TSI parameters of systolic asynchrony were computed. All TSI parameters of LV asynchrony increased in hyperthyroid patients compared to controls: the standard deviation (SD) of the 12 LV segments Ts (35.7 ± 14.4 vs 20.1 ± 10.1, $P < 0.0001$); the maximal difference in Ts between any 2 of the 12 LV segments (111.9 ± 40.7 vs 65.9 ± 30.7, $P < 0.0001$); the SD of the 6 basal LV segments (31.2 ± 18.2 vs 16.8 ± 9.7, $P = 0.01$); and the maximal difference in Ts between any 2 of the 6 basal LV segments (76.6 ± 42.0 vs 44.4 ± 25.7, $P = 0.005$). Patients with overt hyperthyroidism present evidence of LV asynchrony by TSI.

Keywords Hyperthyroidism · Left ventricular asynchrony · Tissue synchronization imaging

Introduction

Hyperthyroidism has a variety of effects on the cardiovascular system such as increased cardiac output and chronotropy [1], decreased systemic vascular resistance [2], impaired coronary perfusion, and cardiac relaxation [3, 4]. Also, in hyperthyroidism myocardial contractility increase but contractions are less efficient [4].

Left ventricular (LV) asynchrony may result from delayed activation of certain segments, which leads to uncoordinated contraction. In this situation, systolic and diastolic function indices, myocardial perfusion, exercise capacity, prognosis, and quality of life are impaired [5–7]. Previously, asynchrony was assessed by surface electrocardiography (ECG) using duration of the QRS complex in patients with heart failure [8]. Later, improved echocardiographic (ECHO) methods permitted direct measurements of mechanical asynchrony in patients with intraventricular conduction delay [9–11]. Recently, it has been shown that LV synchronicity may be impaired in patients with narrow QRS complexes in disorders such as acute myocardial infarction [12], diabetes mellitus [13], diastolic heart failure [14], and obesity [15]. However, LV asynchrony has never been studied in hyperthyroid patients. The purpose of this study is to evaluate the relationship between LV asynchrony and overt hyperthyroidism.

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Materials and Methods

Patients

The study population consisted of 27 newly diagnosed overt hyperthyroid patients (8 males and 19 females) who had narrow QRS complexes on ECG and normal LV ejection fractions (LVEF) on echocardiography. In addition, 21 healthy control subjects (8 males and 13 females) coming for routine check-up were included. Overt hyperthyroidism was defined as having increased serum thyroid hormone levels and a suppressed TSH concentration (< 0.1 μIU/ml). Full demographic data, biochemical blood tests including thyroid function tests and ECG were obtained from the entire study population. Clinical examination included height and body weight measurement. Body mass index was calculated as weight (kilograms) divided by the square of height (meters squared). Systolic and diastolic blood pressures were measured thrice in sitting position after 15 min of rest, and the mean was taken for all cases. Participants were advised to avoid cigarette smoking, alcohol, caffeinated beverages, and exercise for at least 30 min before their blood pressure measurements were taken. Exclusion criteria were subclinical hyperthyroidism or euthyroid status, diabetes mellitus, uncontrolled hypertension (resting blood pressure ≥140/90 mmHg), atrial flutter or fibrillation, cardiac pacing, prolonged QRS duration (≥120 msn), reduced LVEF (<60%), significant valvular heart disease, hypertrophic cardiomyopathy, chronic renal disease, heart failure, coronary artery disease including previous myocardial infarction, angina pectoris, percutaneous coronary intervention, and poor echocardiographic imaging. The study protocol was approved by the local ethical committee.

Laboratory analysis

Blood was collected in the morning between 08:00 and 09:00 h after an overnight fast to avoid the differences of diurnal variation, especially for hormonal and hemostatic parameters. Serum free T3 (FT3) and Free T4 (FT4) and TSH concentrations were measured by automated electrochemiluminescence system (Roche Diagnostics GmbH, Mannheim, Germany). The coefficient of variations of the thyroid studies is 2.5% for FT3, 2.6% for FT4, and 3.2% for TSH. Normal ranges are 1.8–4.6 pg/ml for FT3, 0.9–1.7 ng/dl for FT4, and 0.27–4.2 μIU/ml for TSH.

Echocardiography

Transthoracic two-dimensional (2D), Doppler, and Tissue Doppler echocardiography were performed according to the recommendations of the American Society of Echocardiography [16] using a commercially available system (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). Subjects were examined in the left lateral recumbent position using standard parasternal (short and long axis) and apical views (two chamber, four chamber, and long axis). LV dimensions were measured by two dimensional guided M mode echocardiography. Global LV function was assessed by LVEF using the modified biplane Simpson's rule. LV mass index (LVMI) was measured using the formula proposed by the Penn Convention [17]. Tissue Doppler imaging (TDI) was performed from the lateral mitral annulus.

The assessment of LV systolic asynchrony was performed by the tissue synchronization imaging (TSI) method as previously defined by Yu et al. [18]. TSI shows regional asynchrony on 2D echocardiography and allows immediate visual assessment of regional delay in systole. In addition, quantitative measurement of regional delay was derived from 2D-TDI images and automatically color-coded time to peak myocardial velocity (Ts) from green to red with reference to the QRS signal [18]. In other words, Ts suggests the time to reach regional peak systolic tissue velocity. A quantitative measurement device permits calculation of the median Ts within a 6-mm sample volume manually positioned within the 2D TSI image for 12 LV segments. Initially, to prevent the TSI system from measuring peak systolic velocities outside the ejection phase, the event-timing tool was used to manually adjust start and end times of the aort valve ejection. Later, at least three consecutive beats on TSI were stored, and the images were analyzed off line by a customized software package (EchoPac for PC, GE Vingmed Ultrasound). The six-basal-six-midsegmental model was used [18, 19]. Four parameters of systolic asynchrony were computed by the software. Parameters 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), SD of Ts of the 6 basal LV segments (Ts-SD-6), and maximal difference in Ts between any 2 of the 6 basal LV segments (Ts-6). Ts-SD-12 is the most widely used parameter for LV asynchrony [18, 19]. LV systolic asynchrony is defined as Ts-SD-12 > 31.4 ms assessed by TSI [20]. All echocardiographic analysis was performed by the same observer (K.A.)

Statistical analysis

Continuous variables were described as mean ± SD and analyzed unpaired *t* test and Mann-Whitney *U* test when appropriate. Chi-squared test was used for categoric variables. Pearson and Spearman correlation coefficients was used to assess the relationship between LV asynchrony and clinical and echocardiographic parameters.

A P value < 0.05 was considered statistically significant. SPSS software program (SPSS, 13.0, Inc., Chicago, IL) was used for statistical analysis.

Results

Patient characteristics

The baseline demographic and biochemical parameters of the patient and the control groups are demonstrated in Table 1. Both hyperthyroid and control groups had similar demographic findings including age, sex, hypertension rate, smoking, and QRS duration. Whereas, as expected, patients with hyperthyroidism had significantly lower TSH and higher thyroid hormone levels compared with the control subjects.

Echocardiographic parameters and asynchrony

The echocardiographic parameters of both groups are given in Table 2. Compared with the control subjects, early (E) and late (A) diastolic mitral inflow velocities and late diastolic mitral annuler velocity (Am) were significantly higher in hyperthyroid patients. LV systolic synchrony parameters of TSI including Ts-SD-12, Ts-12, Ts-SD-6, and Ts-6 significantly increased in patients with hyperthyroidism compared with controls ($P < 0.0001$, $P < 0.0001$, $P = 0.01$, $P = 0.005$, respectively, Table 3). The prevalence of LV systolic asynchrony defined as Ts-SD-12 > 31.40 ms was significantly higher in patients with hyperthyroidism compared with the controls (55.6% vs 14.3%, $P = 0.006$). In addition, a significant correlation was found between Ts-SD-12 and FT4 and TSH ($r = 0.436$ and $r = -0.425$, respectively, $P < 0.01$).

Table 1 Clinical and biochemical parameters of controls and patients with hyperthyroidism

	Hyperthyroidism ($n = 27$)	Control ($n = 21$)	P
Age, years	39.6 ± 12.5	44 ± 12.5	NS
Female, *n* (%)	19 (70.4)	13 (61.9)	NS
Body mass index	24.9 ± 4.4	27.9 ± 2.5	0.012
Smoking, *n* (%)	6 (22.2)	1 (4.8)	NS
Hypertension (%)	7 (25.9)	2 (9.5)	NS
TSH (μIU/ml)	0.01 ± 0.01	1.3 ± 1.1	<0.0001
FT3 (pg/ml)	11.1 ± 6.7	2.8 ± 0.5	<0.0001
FT4 (ng/dl)	3.6 ± 1.9	1.1 ± 0.1	<0.0001
Fasting glucose (mg/dl)	96.1 ± 25	94.8 ± 15	NS
QRS duration (ms)	94.9 ± 9.3	93.5 ± 7.5	NS
Heart rate (beats/min)	89.6 ± 10.5	78.2 ± 11	0.001

NS $P > 0.05$, *TSH* thyroid-stimulating hormone, *FT3* free tri-iyodotronin, *FT4* free thyroxine

Table 2 Echocardiographic parameters of study population

	Hyperthyroidism ($n = 27$)	Control ($n = 21$)	P
LVESD (mm)	28.4 ± 3.3	28.2 ± 3.9	NS
LVEDD (mm)	46.8 ± 5.0	47.2 ± 3.7	NS
LVESV (ml)	26.3 ± 9.5	24.2 ± 7.7	NS
LVEDV (ml)	80.8 ± 19.8	75.8 ± 16.4	NS
IVS (mm)	9.4 ± 1.3	9.1 ± 1.4	NS
PW (mm)	8.7 ± 1.7	8.7 ± 1.1	NS
LA (mm)	33.1 ± 4.3	32.3 ± 3.4	NS
E (cm/s)	87.1 ± 17	72.6 ± 17	0.008
A (cm/s)	73.8 ± 19.4	58.3 ± 20.6	0.015
E/A	1.25 ± 0.4	1.4 ± 0.6	NS
dT (ms)	185.9 ± 25.3	191.6 ± 25.6	NS
LV mass index	84 ± 22.6	78.3 ± 12	NS
Ejection fraction (%)	69.2 ± 4.5	66.5 ± 14.2	NS
Sm (cm/s)	12.8 ± 3.8	11.1 ± 2.9	NS
Em (cm/s)	15.5 ± 4.5	14.9 ± 5.1	NS
Am (cm/s)	11.9 ± 3.4	10 ± 2.7	0.046

A late diastolic mitral inflow, *Am* late diastolic mitral annular velocity, *DT* deceleration time, *E* early diastolic mitral inflow velocity, *Em* early diastolic mitral annular velocity, *IVS* interventricular septum, *LA* left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVEDV* left ventricular end-diastolic volume, *LVESD* left ventricular end-systolic diameter, *LVESV* left ventricular end-systolic volume, *PW* posterior wall, *Sm* peak systolic mitral annular velocity, *NS* $P > 0.05$

Table 3 Comparison of parameters of LV asynchrony between both groups

	Hyperthyroidism ($n = 31$)	Control ($n = 26$)	P
Ts-SD-12	35.7 ± 14.4	20.1 ± 10.1	<0.0001
Ts-12	111.9 ± 40.7	65.9 ± 30.7	<0.0001
Ts-SD-6	31.2 ± 18.2	16.8 ± 9.7	0.01
Ts-6	76.6 ± 42.0	44.4 ± 25.7	0.005

Ts time to reach regional peak systolic tissue velocity, *Ts-6* maximal difference in Ts between any two of the six basal LV segments, *Ts-12* maximal difference in Ts between any 2 of the 12 LV segments, *Ts-SD-6* standard deviation of Ts of the six basal LV segments, *Ts-SD-12* standard deviation of Ts of the 12 LV segments

Discussion

In this study, the presence of LV asynchrony was demonstrated by TSI method in patients with hyperthyroidism. Asynchrony parameters derived from TSI (including; Ts-SD-12, Ts-12, Ts-SD-6, and Ts-6) clearly increased in

patients with overt hyperthyroidism compared with the control group. Also, Ts-SD-12 was negatively correlated with TSH and positively correlated FT4. The baseline echocardiographic parameters of both groups such as EF, LV diameters, and volumes were similar. In the Doppler study, A wave velocity was significantly higher in hyperthyroid group as a compatible with previous study [21].

There is a close link between thyroid hormones and heart. Therefore, the abnormal thyroid hormone levels cause a variety of ECG and echocardiographic abnormalities. Hyperthyroidism may lead to decreased systemic vascular resistance [2], coronary spasm, myocardial ischemia and angina pectoris [4, 22], myocardial hypertrophy [23–25], prolonged QT dispersion [26], and abnormal echocardiographical findings. Donatelli et al. [27] determined reduced LV end-diastolic volume (LVEDV) and increased left atrium (LA) dimension. Smith et al. [21] reported conventional and tissue Doppler abnormalities such as decreased LVEF, E and Em velocity, E/A and Em/Am ratio whereas increased A velocities, deceleration time and isovolumic relaxation time in subclinical hyperthyroid patients. Di Bello et al. [28] performed a strain echocardiographic study in subclinical hyperthyroid patients and reported early systolic hyperdeformability and hypercontractility together with impaired diastolic function. Mercé et al. [29] showed that there was an increased prevalence of pulmonary hypertension in hyperthyroidism. Levick et al. [30] suggested increased calcium influx and cardiac stiffness in hyperthyroid rats. In addition, hyperthyroidism leads to increased but less efficient cardiac contraction and LVEF that significantly decreased during the exercise [4].

The causes and clinical importance of LV asynchrony have yet to be understood throughly. However, LV asynchrony may impair systolic and diastolic function indices, myocardial perfusion, exercise capacity, prognosis, and quality of life [5–7]. There are different echocardiographic techniques for assessment of LV asynchrony such as TDI, TSI, and strain imaging. In this study, we used TSI method because Yu et al. [18] reported that TSI was a good tool for assessing synchronization.

There are some possible mechanisms that have been proposed to explain the relation between asynchrony and hyperthyroidism. The myocardial hypertrophy might be considered as a cause of LV asynchrony because it may impair the coordination between regions of the ventricle resulting in ineffective contraction [31, 32]. However, in our study, LVMI was similar in both groups. Di Bello et al. [28] found regional systolic hyperdeformability and hypercontractility by strain echocardiography without increased LVM in subclinical hyperthyroid patients compared with control group. They speculated that their findings could be explained by a direct action of thyroid hormones on the heart. In this study, the hyperthyroidism was newly diagnosed, and our patients were of young age-group. Therefore, increased thyroid hormone levels may have a direct action on ventricular synchronization without increased LVMI.

Left ventricular asynchrony may contribute to some adverse cardiac effects of hyperthyroidism. For example, hyperthyroidism may produce myocardial ischemia and angina pectoris, even in patients with normal coronary arteries [4, 22]. This depends mainly on increased demands of myocardium, but coronary spasm may be an additional factor [3, 4]. Moreover, Bodlaj et al. [22] showed that hyperthyroidism decreased the subendocardial viability ratio, a surrogate measure of subendocardial perfusion, and this was connected to increased heart rates. Also, ventricular asynchronous contractions may lead to architectural changes in myocardium and induce LV remodeling. These changes impair homogenity of myocardial perfusion and coronary blood flow even in the absence of coronary artery disease [33, 34]. Thus, LV asynchrony may contribute to effects of hyperthyroidism on microvascular function.

Similarly, hyperthyroidism leads to increased but less efficient cardiac contractions and reduced exertional LVEF [4]. Recently, it has been shown that LV asynchrony may be related to the development of heart failure in patients with normal ejection fraction [35]. In addition, Vernooy et al. [36] demonstrated that ventricular asynchrony might induce ventricular remodeling and impaired LV systolic function. Therefore, LV asynchrony may be an additional factor for impaired ventricular contraction induced by hyperthyroidism.

Recently, we have reported the presence of LV asynchrony in overt hypothyroidism [37]. However, both hyperthyroidism and hypothyroidism leads to many changes in blood pressure, cardiac output and contractility, myocardial oxygen consumption [2, 38]. Also, there is increased systemic arterial stiffness in both hyperthyroidism and hypothyroidism [22, 39]. Consequently, adverse cardiovascular effects may be similar, but probable mechanisms are different in hypo- and hyperthyroidism.

Study limitations

First, our study population was relatively small. Second, no evaluation of asynchrony parameters after treatment of hyperthyroidism was made. Therefore, it is not clear that whether treatment of hyperthyroidism improves LV asynchrony. Third, in this study, there was a correlation between Ts-SD-12 and TSH and FT4. However, it should be kept in mind that our study had a small population, and there was an overlap of the values of control and treatment group. Thus, results of our correlation analysis should be confirmed by a larger study.

Conclusion

Patients with overt untreated hyperthyroidism show evidence of LV asynchrony by TSI. LV systolic asynchrony may contribute to the harmful cardiovascular effects of hyperthyroidism.

Conflicts of interest None.

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