Comparing cardiac asymmetric septal hypertrophy in hypothyroid patients before and after Levothyroxine therapy

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Abstract

Asymmetrical septal hypertrophy (ASH) is the echocardiographic manifestation of hypertrophic cardiomyopathy (HCM). HCM is characterized by inappropriate left ventricle hypertrophy with preferential involvement of the interventricular symptom causing increased ventricular stiffness, which in turn results in diastolic dysfunction and dynamic left ventricular outflow tract pressure gradient. The study population included 65 newly diagnosed clinical hypothyroidism patients (52 female and 13 male with the mean age: 36.7±11.5), who were referred to endocrinology clinic of Shiraz University of Medical Sciences, Shiraz, Iran. All analyses were performed using SPSS for the window, version 15.0. Continuous variables are presented as mean±SD, while categorical variables are presented as percentage. The prevalence of ASH (IP ratio ≥1.3) was 20% (13 in 65 patients), which was statistically very significant (in relation to 0.2% seen in the total population). In the present study, we investigated the prevalence of ASH in clinical hypothyroidism and also myocardial systolic and diastolic parameter in these patients before and after the treatment. It is conceivable that hypothyroidism is associated with both global LV dysfunction and localized septal myocardial abnormality. Since the clinical significance of this reversible cardiomyopathy is unclear, routine echocardiograms are not indicated in hypothyroidism. However, any patient with hypothyroidism with symptoms of cardiovascular dysfunction (such as dyspnea, dizziness syncope, pericardial pain resembling angina pectoris) should undergo the echocardiographic examination to exclude HCM.

Keywords: Hypothyroid Patients, Levothyroxine Therapy, Hypertrophy

Resumen

La hipertrofia septal asimétrica (ASH) es la manifestación ecocardiográfica de la miocardiopatía hipertrófica (MCH). La HCM se caracteriza por una hipertrofia inadecuada del ventrículo izquierdo con afectación preferencial del síntoma interventricular que causa una mayor rigidez ventricular, que a su vez produce disfunción diastólica y un gradiente dinámico de presión del tracto de salida del ventrículo izquierdo. La población del estudio incluyó a 65 pacientes de hipotiroidismo clínico recién diagnosticados (52 mujeres y 13 hombres con una edad media: 36,7±11,5), que fueron remitidos a la clínica de endocrinología de la Universidad de Ciencias Médicas de Shiraz, Shiraz, Irán. Todos los análisis se realizaron con SPSS para la ventana, versión 15.0. Las variables continuas se presentan como media ± DE, mientras que las variables categóricas se presentan como porcentaje. La prevalencia de ASH (relación IP ≥1.3) fue del 20% (13 en 65 pacientes), que fue estadísticamente muy significativa (en relación con el 0.2% visto en la población total). En el presente estudio, investigamos la prevalencia de ASH en el hipotiroidismo clínico y también el parámetro sistólico y diastólico del miocardio en estos pacientes antes y después del tratamiento. Es concebible que el hipotiroidismo se asocie tanto a la disfunción global del VI como a la anormalidad del miocardio septal localizada. Dado que la importancia clínica de esta miocardiopatía reversible no está clara, los ecocardiogramas de rutina no están indicados en el hipotiroidismo. Sin embargo, cualquier paciente con hipotiroidismo con síntomas de disfunción cardiovascular (como disnea, mareo síncope, dolor pericárdico parecido a angina de pecho) debe someterse a un examen ecocardiográfico para excluir la MCH.

Palabras clave: Pacientes hipotiroideos, terapia con levotiroxina, hipertrofia.

Asymmetrical septal hypertrophy (ASH) is the echocardiographic manifestation of hypertrophic cardiomyopathy (HCM). HCM with a prevalence of 0.2% is the most common genetic cardiac disease[1,2] and has been reported in 0.5% of nonselective echocardiography[3]. It has a wide variety of clinical manifestations ranging from asymptomatic patients to sudden death without prior cardiac symptoms, especially after heavy exercise[4], with the latter reported in children and young adults.

HCM is characterized by inappropriate left ventricle hypertrophy with preferential involvement of the interventricular symptom causing increased ventricular stiffness, which in turn results in diastolic dysfunction and dynamic left ventricular outflow tract pressure gradient. The most common symptom is dyspnea, but chest pain, fatigue, and syncope may also be associated[5,6].

The cause of septal hypertrophy in this disease is of unknown origin, though in half of the patients, it is observed as an autosomal dominant trait[7-9].

Hypothyroidism is one of the most common endocrine diseases. Cardiac involvement is a significant complication of hypothyroidism, including decreased myocardial contraction and heart rate, diastolic hypertension, cardiomegaly, pericardial effusion, though myocardial derangement has rarely been reported[10].

During the past three decades, some studies have reported echocardiographic findings in favor of HCM in hypothyroid patients[11-15].

Moreover, the benefit of screening for ASH in hypothyroid cases echocardiographically has been emphasized, especially with regards to consumption of some medications (e.g digoxin, diuretics, vasodilators, and beta-agonist) which are contraindicated in HCM[12,16-18].

Considering the importance of cardiomyopathy in hypothyroid patients and its complications, in this study, we compared cardiac asymmetric septal hypertrophy in hypothyroid patients before and after levothyroxine therapy.

Study population

The study population included 65 newly diagnosed clinical hypothyroidism patients (52 female and 13 male with the mean age: 36.7±11.5), who were referred to endocrinology clinic of Shiraz University of Medical Sciences, Shiraz, Iran.

Patients who had valvular heart heart-valve disease, left ventricular hypertrophy, left and right bundle-branch block, atrial fibrillation, pericardial and chronic obstructive lung disease, documented coronary artery disease, and left ventricular dysfunction (EF<50%) were excluded from the study.

All patients had an elevated serum concentration of thyroid stimulation hormone (TSH), with levels of T3, T4 or both below the normal range. All of them were treated by with levothyroxine, and thyroid function test was obtained after 6mo. again.

The local ethics committee approved the study protocol, and informed consent was obtained from all patients prior to participation in the study.

Echocardiographic Examination

The complete echocardiographic study including tissue Doppler imaging was performed on all subjects in left lateral decubitus position using vivid GE machine, coupled with 2.5 MHz probes. Thirteen patients that had ASH finding were followed with echocardiogram until full correction of their hypothyroidism. Return to euthyroid state was assessed by clinical criteria and the return of TSH values to normal levels.

The following parameters were calculated: interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPWT), and ratio of IVST to LVPWT (IVST/PWT, IP ratio), for which a value equal to or above 1.3 was considered diagnostic of ASH, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF), Mitral early diastolic peak velocity (Em) and isovolumic relaxation time (IVRT), the time interval between the end of Sm and the onset of Em), systolic peak velocity of mitral valve (Sm) and isovolumic contraction time [IVCT, from the onset of electrocardiogram QRS or the end of A wave (late diastolic peak velocity) to the beginning of Sm].

Statistical Methods and Analysis: All analyses were performed using SPSS for the window, version 15.0. Continuous variables are presented as mean±SD, while categorical variables are presented as percentage. The paired t-test was used for comparing continuous variables before and after the treatment. On the other hand, categorical variables were compared using the chi-square test. Pearson correlation analysis was used for estimating the relationships between test parameters. A p-value < 0.05 was considered statistically significant.

Results

Table 1 summarizes the data, including the mean age, gender distribution, and average thyroid function test of all patients.

Table1: Data and echocardiographic parameters of all patients		
Parameters	**Patients**	**Normal values**
Mean age(year)	34.75±12.87	
Gender (F/M)	52/13	
TSH (mu/L)	60.3±26.81	0.5-5
T_4 (mg/dl)	2.41±1.79	5.4-11.7
T_3 (ng/dl)	72.44±44.96	75-195
S_m (cm/sec)	6.9±1.97	³ 7
$E_{m\ (cm/sec)}$	8.76±2.91	> 8
IVRT (ms)	94.72±20	60-80
IVST/PWT(IP ratio) ≥1.3	20%	0.2%
LVEDD(cm)	4.65±0.5	<5.3
LVESD(cm)	2.93±0.48	

TSH: thyroid-stimulating hormone; T_4: Thyroxine; T_3: Thyrotropin, Sm: systolic peak velocity of mitral value; Em: Mitral early diastolic peak velocity; IVRT: isovolumic relaxation time; IVST: interventricular septal thickness; PWT: posterior wall thickness; LVEDD: Left ventricular end diastolic dimension; LVESD: Left ventricular end systolic dimension; IVCT: isovolumic contraction time

The prevalence of ASH (IP ratio ≥1.3) was 20% (13 in 65 patients), which was statistically very significant (in relation to 0.2% seen in the total population). Further, the diastolic and systolic criteria of patients are provided in Table 1.

All subjects were divided into two groups according to an IP ratio (IVST/PWT). Group 1 included hypothyroid patients without ASH (IVST/PWT <1.3), while Group 2 had an IP ratio of 1.3 (IVST/PWT≥1.3) (Table 2).

Table 2: Age and gender parameters of patients			
Parameters	**Group I**	**Group II**	**P value**
Mean age (year)	36.3±12.55	42.85±14.57	0.327
Female ratio	80%	77%	1.000

The mean age of Group 1 was 36.33±12.55 and that of Group 2 was 42.85±14.57, which was not statistically significant.

The female ratio in the two groups was 80% for Group 1 and 77% for Group 2, which was not statistically significant.

After treating all subjects, TSH was measured, the mean level of which was 4.046±3.9, and in comparison with the TSH before the treatment (60.30±26.816), it statistically was significant (p-value < 0.001).

Table 3 presents the echocardiographic findings and TFT of Group 2 [IP ratio ()≥1.3] before and after the treatment, which were compared via paired t-test.

Table 3: TSH and echocardiographic findings of Group 2 before and after the treatment			
Parameters	**Before**	**After**	**P value**
TSH (mu/L)	62.68±33.29	3.75±2.9	0.001
Em (cm/ms)	6.33±2.23	8.55±1.94	0.001
Sm (cm/ms)	6.55±1.33	7.44±0.72	0.035
IVRT (ms)	105.04±17.88	86.66±13.16	0.001
IVCT (ms)	94.27±16.61	79.51±12.63	0.002
LVEDD (cm)	4.75±0.49	4.55±0.42	0.004
LVESD (cm)	2.97±0.51	2.5±0.29	0.001
IP ratio (IVST/PWT) ³ 1.3	100%	0	0.001

As can be seen, all patients with ASH developed normal IP ratio (IVST/PWT <1.3) after the treatment, and TSH also returned to the normal range. Further, diastolic (Em, IVRT) and systolic (Sm, IVCT) parameters changed to normal values, which is statistically significant, though diastolic parameter changes were more considerable.

LVEDD was in normal range (pretreatment), but its changes after the treatment were statistically significant.

Discussion

In the present study, we investigated the prevalence of ASH in clinical hypothyroidism and also myocardial systolic and diastolic parameter in these patients before and after the treatment.

Although some of the patients with ASH missed the follow-up, the investigators had the opportunity to treat 65 of them and repeated echocardiography study for nine patients with ASH. All of them had no criterion of ASH after the treatment. Diastolic and systolic parameters improved with treatment too.

Myocardial hypertrophy characterized by reversible asymmetric septal hypertrophy was first described by Santos et al. in 1980[19]. (Likely ref 11) Miller told JAMA medical news "the form of ASH that occurs with hypothyroidism has remained unrecognized probably because the thyroid disease is so easily treated. But one should raise the question of whether some patients previously described as having ASH or IHSS (previous name of HCM) may not have been hypothyroid as well"[12].

IHSS first recognized as a distinct syndrome in the late 1950s is sometimes misdiagnosed as the ventricular septal defect or mitral regurgitation, because of a systolic murmur that is associated with a fast carotid upstroke rather than the slow upstroke typical of aortic stenosis. The murmur, which is accentuated by the Valsalva manoeuver, is suggestive of the diagnosis. ASH in association with hypothyroidism is the first curable form of ASH, which is

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indistinguishable clinically and echocardiographically from other forms of ASH[12].

The septal myocardium is the most affected region of left ventricular in hypothyroidism, including subclinical cases[20-22].

During hypothyroid state, right ventricular wall thickness also increases. Further, myocardial involvement is not limited to the septum and more diffuse myocardial dysfunction is seen in hypothyroidism[13,23].

A model for muscular hypertrophy is the Kocher-Debre-semelaige or Hoffman's syndrome, in which hypothyroid patients develop skeletal muscle hypertrophy with profound weakness. Biopsies of hypothyroid myopathy have revealed hypertrophy of type I and atrophy of type II fibers, which improve with thyroid hormone therapy. This could occur in the cardiac muscle with a hypertrophic, but dysfunctional muscle. Although elevated TSH could act as growth factor stimulating muscle hypertrophy, in some hypopituitary patients with low TSH levels, it had the same cardiac abnormalities[13,24,25].

Several Some evidence suggests that certain abnormalities of cardiac function in patients with thyroid dysfunction directly reflect thyroid hormone on calcium-activated ATPase and phospholamban, which are involved primarily in the regulation of systodiastolic calcium concentrations in cardiomyocytes. Sarcoplasmic reticulum calcium-activated ATPase is responsible for the rate of calcium reuptake into the lumen of the sarcoplasmic reticulum during diastole which, in turn, is a major determinant of the velocity of myocardial relaxation after contraction[26-28].

However, the performance of sarcoplasmic reticulum calcium-activated ATPase is influenced by the level of expression of phospholamban: the higher the phospholamban expression, the lower the sarcoplasmic reticulum calcium-activated ATPase activity will be. In this regard, it has been extensively demonstrated that thyroid hormone upregulates the expression of the sarcoplasmic reticulum calcium-activated ATPase and downregulates the expression of phospholamban, thereby enhancing myocardial relaxation. Indeed, the improved calcium reuptake during diastole may favorably affect myocardial contractility. The greater reduction in the cytoplasmatic concentration of calcium at end-diastole increases the magnitude of the systolic calcium transient which, in turn, augments its availability to activate tropomyosin units. This finding strongly supports the key role of sarcoplasmic reticulum proteins and their effects on intracellular calcium involved in thyroid hormone-mediated changes in systodiastolic cardiac function among patients with thyroid dysfunction.

Furthermore, thyroid hormone also modifies the expression of other ion channels, such as Na_/K_-activated ATPase, Na_/Ca exchanger, and some voltage-gated K_ channels, thereby coordinating the electrochemical and mechanical responses of the myocardium.

In addition to these genomic effects, thyroid hormone develops changes in the cardiac inotropism and chronotropism more rapidly than would be expected from regulation of gene expression, which usually takes minutes to hours to be presented[29,30].

Some evidence suggests that thyroid hormone promotes acute phosphorylation of phospholamban, which attenuates the inhibitory effect of phospholamban on sarcoplasmic reticulum calcium-activated ATPase[31]. Interestingly, the fact that this process is mediated at least in part by the activation of intracellular kinase pathways involved in signal transduction of the adrenergic stimulus may help to explain the functional similarities between the cardiovascular effects of thyroid hormone and those promoted by the adrenergic system. Indeed, although most of the cardiovascular manifestations associated with hyperthyroidism and hypothyroidism mimic a condition of increased and reduced adrenergic activity, respectively, the sensitivity of the cardiovascular system to adrenergic stimulation does not seem to be substantially altered in these conditions[32].

Thyroid hormone also exerts an important effect on the vascular system. It acutely reduces the peripheral vascular resistance by promoting relaxation in vascular smooth muscle cells[26,33-35].

The observations here described suggest that asymmetric or disproportionate thickening of the interventricular septum is a common echocardiographic pattern in longstanding untreated hypothyroidism. We documented this finding, which appeared to be independent of age, in both male and female patients, It could not be correlated with the presence of pericardial effusion which commonly occurs in myxedema (and was excluded in our study).

Thirteen of 65 patients with more than six months (as assessed by history) hypothyroidism indicated this finding, suggesting that as further experience is gained, the echocardiographic evidence of asymmetric septal hypertrophy may become a common cardiovascular finding in this disorder.

On the other hand, hypothyroidism may also be involved in hypertrophic cardiomyopathy. In a group of 23 elderly patients with echocardiographic evidence of HCM reported by Krasnow and stein, one patient was thought to be hypothyroid[11,36-41].

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Conclusions

t is conceivable that hypothyroidism is associated with both global LV dysfunction and localized septal myocardial abnormality. Since the clinical significance of this reversible cardiomyopathy is unclear, routine echocardiograms are not indicated in hypothyroidism. However, any patient with hypothyroidism with symptoms of cardiovascular dysfunction (such as dyspnea, dizziness syncope, pericardial pain resembling angina pectoris) should undergo the echocardiographic examination to exclude HCM.

In other words, the physician who treats such hypothyroid patients should keep in mind the potential hazards of certain drugs known to aggravate left ventricular outflow tract obstruction, such as digitalis, diuretics, and vasodilators. Since the cardiac lesion is reversible, cautious hormone replacement therapy should be initiated for a symptomatic hypothyroid patient with evidence of outflow tract obstruction.

Finally, our demonstration of a reversible form of asymmetric septal hypertrophy in hypothyroidism, which at times may be indistinguishable by echocardiographic criteria from HCM, may provide a model to study this puzzling and often fatal condition.
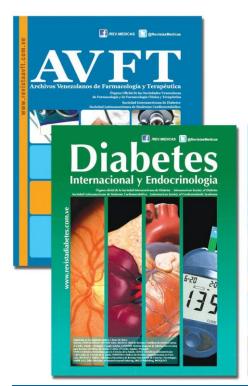
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