

## Echocardiographic left ventricular functional changes in acute hypothyroidism vs. subclinical hyperthyroidism in patients with differentiated thyroid carcinoma

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### ABSTRACT

**Introduction:** In order to assess echocardiographic left ventricular functional indices in patients with differentiated thyroid carcinoma (DTC), after L-T<sub>4</sub> withdrawal (short-term overt hypothyroidism) and during TSH suppressive therapy, we have evaluated cardiac hemodynamics in a single cohort study.

**Methods:** 24 patients with DTC were studied in two phases: 1: at least 4 weeks after L-T<sub>4</sub> withdrawal, 2: at least 8 weeks after beginning TSH suppressive therapy. All patients underwent conventional, Doppler and tissue Doppler echocardiography.

**Results:** Although early diastolic mitral inflow velocity (E wave) ( $p=0.033$ ), and early diastolic velocity of mitral annulus [E(m)] ( $p < 0.001$ ), were lower in overt hypothyroidism, there were no differences among left ventricular (LV) Dimensions, LV mass and LV mass index, LV Ejection fraction, late diastolic mitral inflow velocity (A wave), E/A ratio, deceleration time(DT), peak systolic velocity of mitral annulus [S(m)], late diastolic velocity of mitral annulus [A(m)], E(m)/A(m) ratio between the two phases. Pulse rate ( $p < 0.001$ ), LV end diastolic volume ( $p=0.011$ ) and LV end systolic volume ( $p=0.003$ ) were higher, while QTc Interval was shorter ( $p < 0.001$ ) during TSH suppressive therapy. E/E(m) ratio and pulmonary capillary wedge pressure ( $p=0.042$ ) were higher in hypothyroidism phase. Three patients developed mild pulmonary artery hypertension and 2 of the patients had mild pericardial effusion during TSH suppressive therapy.

**Conclusion:** Short-term overt hypothyroidism or L-T<sub>4</sub> suppressive therapy in patients with DTC may have undesirable cardiovascular effects. So in patients with known history of cardiovascular abnormalities, the caring physician should be aware of the cardiovascular complications during hypothyroidism or suppressive therapy.

**Keywords:** Hyperthyroidism, Hypothyroidism, Differentiated thyroid carcinoma, Echocardiography, Tissue doppler imaging.

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## INTRODUCTION

The most popular management of patients with differentiated thyroid carcinoma (DTC) consists of total or near total thyroidectomy and then radioiodine ablation of thyroid remnant (1). In long term follow-up; suppression of endogenous TSH secretion by administration of thyroid hormone is routinely performed (2) as well as assessment of the thyroglobulin (Tg), neck ultrasonography and radioiodine whole body scan (1). To stimulate TSH production and thereby increased radioiodine uptake in tumor cells in diagnostic radioiodine whole body scan or radioiodine therapy, thyroid hormone replacement therapy is withheld (3). This approach is useful to improve the sensitivity of Tg monitoring as well (1). Because of limitations in availability of recombinant human TSH (rhTSH), induced hypothyroidism by levothyroxine (L-T4) withdrawal is necessary for measurement of stimulated thyroglobulin and performing diagnostic radioiodine whole body scan (4-6), L-T4 withdrawal is still choice approach for radioiodine ablation therapy (7).

As the cardiovascular system is a major target for thyroid hormone action (4) by direct influence at cellular level and indirect mechanisms, thyroid dysfunction (both hyper- and hypothyroidism) can cause remarkable changes in left ventricular structure and function (8-10). Long-standing hypothyroidism as well as overt hyperthyroidism has profound effects on cardiovascular system (1). However, there are little data on the cardiac effects of short-term hypothyroidism induced by LT4-withdrawal or sub-clinical hyperthyroidism by TSH suppressive therapy in patients with DTC (1). In contrast to long-term hypothyroidism or hyperthyroidism, athyrotic patients in the follow-up of DTC develop a hypothyroid state quickly which is

readily reversible by reinstatement of thyroid hormone replacement (3).

Demonstration of cardiovascular dysfunction in patients with hypothyroidism or subclinical hyperthyroidism would favor consideration in patients with DTC which have a history of cardiovascular disease (11). On the other hand; there is no overall agreement on the clinical significance of these findings (12).

We have evaluated echocardiographic left ventricular functional indices in patients with DTC, after L-T4 withdrawal (short-term overt hypothyroidism) and during TSH suppressive therapy (sub-clinical hyperthyroidism) in order to assess and better clarify the cardiovascular impact of these situations. In addition to M-mode, two dimensional echocardiography, we used pulse-wave Doppler examinations as well as Tissue Doppler Imaging (TDI) for detailed and quantitative assessment of systolic and diastolic function of the left ventricle (13).

## METHODS

**Subjects:** Twenty four patients aged 29-76 years ( $46.79 \pm 14.09$ ) with history of DTC were studied. All patients were athyrotic with previous total or near total-thyroidectomy and radioiodine ablative therapy. The patients had no history of any cardiovascular abnormality, hypertension, known coronary artery disease, myocardial infarction, rheumatic fever, endocarditis, diabetes mellitus, or connective tissue disease as well as they were not taking any drug known to affect cardiovascular parameters or thyroid hormone metabolism. The study was approved by the ethics committees, and written informed consent was obtained from all patients.

**Study Protocol:** All patients were studied at two phases:

1- At least 4 weeks after L-T<sub>4</sub> withdrawal (2 weeks on liothyronin, and 2 weeks on no any

thyroid hormones) for their  $^{131}\text{I}$  whole body scan.

2- At least 8 weeks after beginning L-T<sub>4</sub> suppressive therapy.

At both visits, TSH levels were measured, a standard 12-lead electrocardiogram (ECG) was recorded and echocardiography was performed. Height and weight were measured for the calculation of body mass index: BMI= weight (kg)/height<sup>2</sup> (m).

**Echocardiography:** All patients underwent transthoracic echocardiography and ECG recording during two phases mentioned above. An independent Echo cardiologist blinded for treatment modalities performed M-mode, two dimensional, and pulse-wave Doppler examinations as well as Tissue Doppler Imaging (TDI). Patients in the left lateral decubitus position underwent echocardiography using a Vivid 3, GE system with 2.5-3.5 MHTZ probe according to the last ASE/AHA guidelines. Conventional parasternal long- and short-axis standard views as well as two and four-chamber apical views were obtained. Quantitative assessment of LV dimensions, and LV ejection fraction (LVEF) were analyzed using M-mode images from the parasternal long-axis views. Left ventricular mass (LVM) was calculated using the formula proposed by Devereux:  $\{0.8(1.04([\text{LVEDD} + \text{LVPWd} + \text{IVSd}]^3 - [\text{LVEDD}]^3) + 0.6$ , where LVEDD is the left ventricular end diastolic diameter, LVPWd is diastolic posterior wall thickness, IVSd is diastolic interventricular septal thickness(13,14). Using correction of LVM for body surface area LVM index (LVMI) was calculated. LV hypertrophy was defined as LVMI > 150 g/m<sup>2</sup> for men and > 120 g/m<sup>2</sup> for women (15-17). The following parameters were measured in Doppler studies: indices of ventricular filling derived from the mitral valve flow velocity at early phase (E wave: cm/s) as well as at the maximal late flow (A wave: cm/s), the E/A ratio, and the E wave deceleration time (DT). Using TDI, analysis was performed

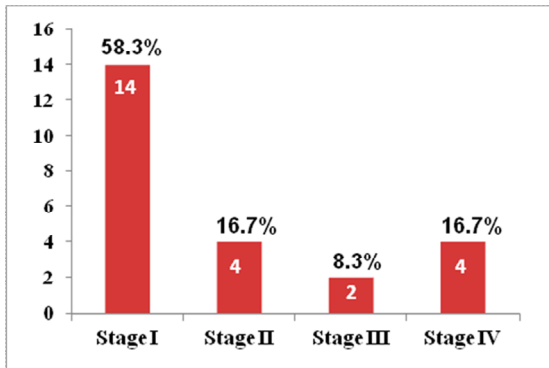
for the Systolic velocity [S(m)], the early[E(m)] and late [A(m)] diastolic peak velocity of mitral annulus(average of septal and lateral aspect). ECG and heart rate (HR) were recorded.

Based on guidelines of American Society of Echocardiography, grade of diastolic dysfunction as well as classification of pulmonary artery pressure was determined in each patient (16-17).

**Statistical analysis:** Data are expressed as mean  $\pm$  SD. Two-tailed Student's paired sample t test was used to compare continuous variables between two phases of the study, if they had a normal distribution, as assessed by kolmogorov smirnov test; Otherwise, noparametric Wilcoxon signed rank test was exploited. Differences were considered statistically significant at P value<0.05. The calculations were performed using SPSS 11.5.

## RESULTS

From the 24 patients, 5 (20.8%) were male and 19(79.2%) were female. Twenty one (87.5%) and 3 (12.5%) of patients had papillary and follicular thyroid carcinoma respectively while 6 (25%) of the cases had metastasis during the experiment. Treatment duration from time of diagnosis was  $6\pm 5.25$  (1-25) years. Stages of their cancer are shown in Figure 1 [American Joint Commission on Cancer staging classification (TNM) : Definition of TNM: T, primary tumor; TX, cannot be assessed; T0, no evidence of primary tumor; T1, ,1 cm; T2, 1- 4 cm; T3,>.4 cm; T4, tumor of any size beyond thyroid capsule; N, regional lymph node; NX, cannot be assessed; N0, not present; N1, present; M, distant metastases; M0, none; M1, present. Patients under age 45 with any T, any N, and M0 are stage 1; and M1 are stage 2. Patients>45-year with T1 are stage 1, T2-3 are stage 2, T4 or N1 are stage 3, and M1 are stage 4.](18, 19)



**Figure 1.** Frequency of stages of patients with differentiated thyroid carcinoma.

Table 1 showed conventional echocardiography findings. Only one patient had LV hypertrophy during L-T4 suppressive therapy. LV mass and LV mass index were remained unchanged statistically. There were no significant differences among LVEDD, LVESD, IVSd, LVPWd between the two statuses. The differences in LVEDV ( $p=0.011$ ), and LVESV ( $p=0.003$ ) between the two conditions were statistically significant. Both of them were higher during L-T4 suppressive therapy. LVEF was not significantly different between the 2 phases.

**Table 1.** Conventional echocardiographic findings in two phases: during withdrawal of L-T4 and L-T4 suppressive therapy.

Variable	Hypothyroidism	L-T4 Suppressive Therapy	P value
LV Mass	147.81±65.00	141.84±60.84	0.43
LV Mass Index	83.21±24.11	80.38±25.15	0.14
LVEDD	4.48±0.69	4.58±0.63	0.44
LVESD	2.80±0.63	2.95±0.60	0.08
LAD	3.31±0.61	3.38±0.74	0.59
IVSd	0.96±0.21	0.89±0.23	0.12
LVPWd	0.94±0.16	0.91±0.20	0.54
LVESV	21.79±6.84	27.04±8.18	0.003
LVEDV	63.12±14.82	72.42±16.90	0.01
LVEF	64.71±5.69	63.48±5.07	0.28

Doppler echocardiography variables were seen on the Table 2. A wave was not changed between both phases. In short-term overt hypothyroidism E wave was significantly less than during L-T4 suppressive therapy but there was no difference in the E/A ratio between the two phases. DT was longer in hypothyroidism, but it wasn't statistically significant.

**Table 2.** Doppler echocardiographic findings in two phases: during withdrawal of L-T4 and L-T4 suppressive therapy.

Variable	L-T4		P value
	Hypothyroidism	Suppressive Therapy	
E	75.75±19.77	85.50±22.98	0.03
A	68.42±23.37	69.58±21.51	0.71
E/A ratio	1.24±0.53	1.34±0.55	0.16
DT	200.17±37.06	188.33±48.04	0.16

In Tissue Doppler Imaging (Table 3), S(m), A(m), E(m)/A(m) ratio wasn't significantly changed between the two phases, although E(m) was lower in short-term overt hypothyroidism significantly.

All 24 patients had normal Pulmonary artery pressure (PAP) in short-term overt hypothyroidism, but 3 of them (12.5%) developed mild Pulmonary artery hypertension (PAP=30-45 mmhg) during L-T4 suppressive therapy, but it wasn't significant (Wilcoxon: P=0.08). No significant difference was noticed in PAP in two phases (Table 3). Both E/E(m) ratio and PCWP were higher in short-term overt hypothyroid state (both: P=0.04, Table 3).

During L-T4 suppressive therapy, 9(37.5%) patients had grade I, one (4.2%) had a grade

II of diastolic dysfunction and 14(58.3%) patients had normal diastolic function. 15(62.5%) patients had normal diastolic function and 9(37.5%) patients had grade I diastolic dysfunction in the withdrawal phase. There were no significant changes between diastolic function grades between the 2 conditions (Wilcoxon: P=0.41). Only during hypothyroid state, 2(8.33%) of the patients had mild pericardial effusion, but it wasn't significant (Wilcoxon: P=0.15).

All patients have sinus rhythm. HR was notably higher during L-T4 suppressive therapy than hypothyroid state (83.54±13.63 vs. 74.54±11.69 respectively; p<0.001). QTc was meaningfully shorter (p<0.001) during L-T4 suppressive therapy as compared to the hypothyroid state (0.43±0.03 vs. 0.45±0.34 respectively).

## DISCUSSION

We have evaluated left ventricular systolic and diastolic functional indices, HR and QTc interval in patients with DTC, during L-T4 suppressive therapy and during L-T4 withdrawal hypothyroid state. In our study statistically significant differences between two phases in following LV functional parameters were noticed: 1) E; 2) E(m); 3) E/E(m) ratio 4) PCWP. Previous studies mentioned that both subclinical and overt hypothyroidism might be associated with abnormal systolic or diastolic LV functional indices, increase in peripheral vascular resistance as well as systolic and diastolic cardiac dysfunction during exercise. Longtime hypothyroidism is one of the coronary artery disease risk factors (12). It is suggested that there is a continuum in cardiovascular effects related to thyroid hormone deficiency. Also hyperthyroidism has overt and striking cardiovascular effects that may cause arrhythmias, cardiomyopathy and hypertension, resulting increase in mortality (20).

**Table 3.** Tissue Doppler Imaging findings in two phases: during withdrawal of L-T4 and L-T4 suppressive therapy.

Variable	Hypothyroidism	L-T4 Suppressive Therapy	P value
S(m)	7.31±1.56	7.52±1.20	0.51
E(m)	8.02±2.74	10.43±2.82	<0.001
A(m)	8.21±2.34	8.62±2.38	0.43
E(m)/A(m) ratio	1.09±0.57	1.35±0.67	0.055
E/E(m) ratio	10.38±3.77	8.65±3.50	0.04
PAP	24.56±3.47	26.94±6.75	0.13
PCWP	14.77±4.67	12.62±4.15	0.04

Subclinical hyperthyroidism has been reported to induce cardiac dysfunction as well, and treatment with suppressive doses of L-T4 has also been associated with premature atrial beats, hyper-contractility, myocardial hypertrophy and diastolic dysfunction (2, 15, 21, 22). Elevated cardiac output is seen in overt hyperthyroidism due to increased heart rate and myocardial contractility and decreased peripheral vascular resistance. Increase in myocardial contractility may lead to stimuli of myocardial hypertrophy (2). In patients with DTC, however, it should be underlined that it is difficult to extrapolate these data to the effects of short-term hypothyroidism due L-T4 withdrawal on the cardiovascular system, or effects of suppressive L-T4 therapy (1).

Although some previous studies showed that chronic TSH-suppressive therapy can induce cardiac structural abnormalities such as increase in IVSd, LVPWd, and LV mass index (2,4,22) and some cardiac enlargement during hypothyroidism

(2,21,22); in our study, there was no significant cardiac structural changes (LVEDD, LVESD, IVSd, LVPWd, LV mass, LV mass Index). Most of the cardiovascular effects of thyroid hormones are measurable mainly in patients with overt hyperthyroidism. In subclinical hyperthyroidism, some of these alterations have also been described, but the findings have not always been consistent and are still controversial. Dörr et al (15) revealed an association between thyroid function status, cardiac mass, and LVH in a population based sample of subjects aged 45–79 yr. Hyperthyroidism was independently associated with determinants of cardiac morphology such as LVM, LVMI, and LVH. In contrast, no association was found between decreased serum TSH levels and these parameters. Overt hyperthyroidism was identified as an independent predictor for LVMI (15). One reason for our findings may be related to the shorter duration of TSH-suppressive therapy in our patients (a mean of approximately 6.5 years). On the



other hand short period hypothyroidism may not have been enough to produce changes in LV mass. In contrast, it is reported that LV mass was higher in DTC patients after 5 weeks of LT4-withdrawal than during L-T4 suppressive therapy which may be due to early interstitial myxedema (1).

In the present study, LVESV and LVEDV have declined during acute hypothyroidism while Wieshammer et al. (23) with radionuclide angiography showed that LVEDV had been higher in L-T4 replacement therapy but LVESV remained almost the same. In different studies, either by radionuclide angiography or echocardiography LVEF was not changed (4,10, 23, 24), although in some studies cardiac output was higher during hyperthyroid phase, basically because of higher PR (4, 23).

Pericardial effusion (PE) even cardiac tamponade have been reported in hypothyroidism (21). We found that 2 of our patients developed mild PE during the withdrawal phase. Although there was not statistically significant difference between two phases, but possibility of PE during overt and prolonged hypothyroidism should be taken into consideration.

Three of our patients had possessed mild pulmonary artery hypertension during the overt hypothyroidism. So the caring physician should be more cautious in patients with existing pulmonary artery hypertension.

In our Doppler study, while peak velocity of early diastolic filling (E) diminished meaningfully in the hypothyroid phase, peak velocity of late diastolic filling (A), E/A ratio and DT (although insignificantly decreased in hypothyroidism) remained almost the same in both conditions.

The findings in previous studies are not similar. Di paola et al. (24) reported no difference between E, A, E/A ratio, but reported an increased DT; whereas Grossman et al. have noticed a decrease in E

and A and also a decrease in DT, both in the same phase (10). Smith et al reported that after T4 dose reduction in patients with DTC, a significant and profound increase in the E/A ratio was observed (13). Botella-Carretero reported that in DTC during L-T4 withdrawal, the E and A waves decreased, and the E/A ratio increased. In contrast, no changes were observed in M-mode measurements and in the two-dimensional study specially LVM, LVMI and LVEF (4).

Previous studies described the effect of long-time hypothyroidism and subclinical hypothyroidism, where A(m), E(m) and S(m) were impaired (25, 26). But there is not enough data about short-time hypothyroidism. In our patients E(m) decreased during short-term overt hypothyroidism, while S(m), A(m), E(m)/A(m) weren't altered significantly. E/E(m) ratio, and LV end diastolic pressure(LVEDP) equal to PWCP in our patients were increased during the short-term overt hypothyroidism indicating the beginning of diastolic dysfunction in withdrawal phase.

In our patients diastolic dysfunction grade didn't changed significantly, but the early signs of diastolic dysfunction had appeared. E wave, E(m) were decreased and E/E(m) ratio and also LVEDP were increased. All of our patients didn't have any cardiovascular diseases, and they were relatively young (mean  $46 \pm 13.5$  years). Therefore, the effect of acute hypothyroidism on the diastolic function should be studied in older population, because their cardiovascular system is more susceptible to dysfunction. Short-term hypothyroidism may worsen diastolic function as a result of altered calcium handling induced by thyroid hormone deficiency (1).

QTc interval is traditionally used for assessment of ventricular repolarization. A prolonged QT interval is a risk factor for life-threatening ventricular arrhythmias and cardiovascular mortality (25).

Hypothyroidism makes the pulse rate (PR) decline and QTc interval increase (26-28). We also observed a significant decrease in PR, and notable increase in QTc interval during short-term overt hypothyroidism. Other studies found the same data (4, 9, 10, 29). Dörr et al reported that Serum TSH levels were positively correlated with the QTc interval (23). Changes in HR are due to direct effects of thyroid hormone on sinoatrial node function (2). Tachycardia is a well known feature of hyperthyroidism (2).

These findings suggest a plausible explanation for the worsening of symptoms, signs and complications of previous cardiovascular diseases during short-term hypothyroidism or during L-T4 suppressive therapy especially in elderly patients (1). Therefore, when there is a higher risk of adverse cardiovascular effects, rhTSH can preferably be ordered for diagnostic procedures (1). Furthermore, alterations of cardiovascular function in short-term hypothyroidism may not be well tolerated because they occur in patients that are almost on more than normal dose of thyroid hormones (1). rhTSH instead of L-T4 withdrawal is particularly recommended for older patients with previous cardiovascular diseases (1).

**Limitations:** We studied cardiac hemodynamics in a single cohort of patients with DTC, during L-T4 suppressive therapy and during withdrawal: short-term overt hypothyroidism. But it was better to include a healthy euthyroid control group in order to compare these patients with normal volunteers. Further prospective studies conducted on larger series of patients are needed to clarify the prognostic implications of the described abnormalities.

## CONCLUSION

Because of some differences in cardiac functional status in short-term overt hypothyroidism and thyroxine suppressive

therapy, undesirable cardiovascular effects in patients with DTC may be observed especially in these patients with previous cardiovascular abnormalities.

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