Alterations In Left Ventricular Diastolic Function In Hypothyroidism

SA Deoke*, P Gowardhan**

*Associate Professor, ** Ex- Lecturer, Department of Medicine, N.K.P.Salve Institute of medical Sciences and Research Centre, Digdoh Hills, Hingna Road, Nagpur

Abstracts: **Background and Objectives:** Hypothyroidism decreases the heart rate, cardiac output and myocardial contractility. Altered intracellular Calcium handling results in left ventricular diastolic dysfunction in hypothyroidism. **Methods**: 33 cases of primary hypothyroidism and 33 age (+/_ 5 years) and sex matched healthy controls were studied. Thyroid profile and 2 D Echocardiography was done in all patients. Pulsed wave Doppler examination to study the diastolic transmitral flow velocities was done to assess the left ventricular diastolic function. **Results**: There was female preponderance (male to female ratio of 1:7.25), weight gain (60.60% cases) being the most frequent presenting symptom. The mean BMI and mean systolic and diastolic blood pressure were significantly increased in the cases ($p<0.05$). Hypothyroid patients had significant bradycardia ($p<0.05$). 7(21.21%) patients had pericardial effusion. Statistically significant difference was found in the IVST, PWT, IVRT and DT ($p<0.05$); the trans-mitral 'A' wave velocity was significantly increased in cases (72.13 +/-13.27 Vs 65.48 =/-9.345; $p=0.022$). The ratio of E: A was significantly decreased in the hypothyroid group (1.23 in cases and 1.38 in controls; $p=0.011$). **Interpretation and Conclusion**: Hypothyroidism results in left ventricular structural changes in the form of concentric remodelling, pericardial effusion and left ventricular diastolic dysfunction. [Deoke S NJIRM 2014; 5(2) :66-70]

Key Words: Hypothyroidism, Left ventricular, pericardial effusion, diastolic dysfunction

Author for correspondence: Dr. Shilpa Deoke, Asso.ate Professor, Department of Medicine, N .K.P.Salve Institute of medical Sciences and Research Centre, Digdoh Hills, Hingna Road, Nagpur
E mail: dr.shilpa_deoke@rediffmail.com

Introduction: The cardiovascular system is the major target for actions of the thyroid hormones and, as such, bears the maximum brunt of thyroid dysfunction. Both, hypothyroidism and hyperthyroidism can alter the left ventricular structure and function.

Changes in cardiac gene expression in the contractile apparatus, the sarcoplasmic reticulum, and the outer myocyte cell membrane bring about these changes [1]. Thus, an increase in thyroid hormone level enhances myocardial contractility, relaxation, cardiac output and heart rate, whereas hypothyroidism decreases these parameters [2, 3]. Pericardial effusion is seen in severe long standing hypothyroidism.

Hypothyroid patients have an increased risk of coronary artery disease probably due to dyslipidemia and endothelial dysfunction [4].

LV diastolic dysfunction is a consistent finding in subclinical as well as overt hypothyroidism. Altered intracellular Calcium handling is a major factor. An increase in body weight and blood pressure in hypothyroidism causes left ventricular hypertrophy (LVH) and contributes to diastolic dysfunction [5].

Further, increased intra-myocardial fibrosis may be the contributing factor in overt and not subclinical hypothyroidism [6]. Even before the onset of LVH, early altered myocardial texture detected by newer ultrasonic intra-myocardial tissue techniques has been described in subclinical hypothyroidism [7].

Thus LV structural and functional alterations are observed not only in overt hypothyroidism, but also in milder, subclinical cases; changes are also noted with acute hypothyroidism as seen in patients undergoing thyroidectomy for thyroid malignancy [8, 9]. Further, the diastolic dysfunction in hypothyroidism is amenable to reversal after treatment [10, 11]. Hence the present study was undertaken to study the left ventricular structural and functional alterations in hypothyroidism, with emphasis on LV diastolic dysfunction.

Material and Methods: The study was initiated after prior approval by the Institutional Ethics Committee. 33 cases of primary hypothyroidism and 33 age (+/_ 5 years) and sex matched controls attending OPD or admitted in the hospital were included in the study. Patients with Diabetes

mellitus, previous myocardial infarction, rheumatic heart disease, Endocarditis, renal failure and pregnancy were excluded. Detail history and clinical examination was done in all patients. Thyroid profile was done in all subjects. Left ventricular function was assessed echocardiographically. Standard M-mode, 2 D-Echo and Doppler Echocardiography was done on Toshiba Nemio XG SSA- 580A machine with 3 MHz probe by the same person to minimize inter-observer variation. To minimize intra-observer variation, an average of 3 readings was taken. Echocardiographic measurements were done as per the guidelines of the American Society of Echocardiography. The parameters studied were diastolic septal wall thickness (IVSTd) and diastolic posterior wall thickness (PWTd). Diastolic septal wall thickness (IVSTd) and diastolic posterior wall thickness were estimated during M mode examination. Pulsed wave Doppler was done by keeping a sample volume of 2 mm at the tip of mitral annulus in the left lateral position and transmitral flow velocities were measured. The left ventricular diastolic function was assessed by parameters like diastolic transmitral peak velocities (E and A) and the E: A ratio, the Isovolumic relaxation time (IVRT) (time interval between end of systolic outflow and the transmitral E wave onset) and Deceleration time (DT) of the E wave.

Statistical Analysis: All statistical analysis was done by EPI INFO version 6. Categorical variables (Gender, symptoms, pericardial effusion) were expressed as actual numbers and sssspercentages. Continuous variables were presented as Mean+/- SD and compared by performing unpaired t test where data was normal and Mann Whitney U test was used where data was not normal (IVRT and TSH).

Result: 33 cases (4 males, 29 females) of primary hypothyroidism were included in the study. The male to female ratio was 1:7.25. Most subjects were in the age group 31 to 45 years. As expected, there was a significant difference in the mean levels of T3, T4 and TSH in cases and controls (p< 0.05) (Table 2).

Table: 1 Showing mean T3, T4 and TSH levels

Hormone	Group	Mean +/-SD	'p' value
T3(pg/ml)	1	0.502 +/-0.24	<0.0001
	2	1.279 +/-0.46	
T4(ng/ml)	1	4.006 +/-2.10	<0.0001
	2	9.352 +/-2.38	
*TSH (uIU/ml)	1	46.07 +/37.62	<0.0001
	2	2.93 +/-1.90	

1 – case, 2 – control *Mann Whitney 'U' test

There was a statistically significant difference in the mean BMI (21.40 and 19.88 in cases and controls respectively; p=0.042) between the two groups. Similarly there was significant bradycardia in the hypothyroid patients (p<0.05). Significant difference was also observed in the systolic and diastolic blood pressure between the two groups (p<0.05) (Table 2).

Table: 2 Showing distribution of various clinical parameters

Parameter	Group	Mean +/-SD	'p'
BMI (kg/m2)	1	21.40+/-3.694	0.042
	2	19.88+/-2.039	
P(beats /min)	1	68.24+/-13.723	<0.001
	2	78.55+/-7.387	
SBP(mm Hg)	1	120.42+/-17.739	0.020
	2	112.00+/-9.657	
DBP(mm Hg)	1	77.82+/-12.190	0.004
	2	70.48+/-6.727	

1 – case, 2– control, BMI – Body mass Index, P – pulse, SBP – Systolic Blood Pressure, DBP – Diastolic Blood Pressure

Amongst the various 2 D Echo parameters, the septal (8.9 +/- 2.8317 mm in cases and 7.7 +/- 0.9961in controls; p= 0.019) and posterior wall thickness (9.688+/- 1.60 mm in cases and 8.194+/- 1.4355 mm in controls, p=0.00) in diastole were significantly increased (Table 3)

On analysis of the various parameters of Left ventricular diastolic function, statistically significant difference was found in the IVRT and DT (p<0.05). However the difference in the 'E' wave velocity was not found to be significant in the hypothyroid group (84.64+/-17.66 vs 88.57+/- 8.248; p=0.251). The trans-mitral 'A' wave velocity was significantly increased in cases as compared to

healthy individuals (72.13 +/-13.27 and 65.48 =/- 9.345; p=0.022). There was a significant difference in the ratio of E: A in the two groups (1.23 in cases and 1.38 in controls; p=0.011) (Table 3).

7 (21.21%) subjects were observed to have pericardial effusion; all had serum TSH above 20 mIU/L. On correlating the presence of pericardial effusion with serum TSH, most (n=5, 33.33%) had levels above 50 mIU/L (Table 4).

Table: 3 showing the Left Ventricular Echo-Cardiographic parameters

Parameter	Group	Mean+/-SD	'p'
IVSTd (mm)	1	8.990+/- 2.8317	0.019
	2	7.730+/- 0.9961	
PWTd (mm)	1	9.688+/- 1.6000	<0.0001
	2	8.194+/- 1.4355	
*IVRT (msec)	1	97.61+/- 6.562	<0.0001
	2	89.03+/- 9.671	
DT (msec)	1	179.79+/-23.480	0.011
	2	164.39 +/-24.46	
E (m/s)	1	84.64+/- 17.657	0.251
	2	88.57+/- 8.248	0.001
A (m/s)	1	72.13+/- 13.266	0.022
	2	65.48+/- 9.345	
E/A	1	1.2252 +/-0.263	0.011

*Mann Whitney 'U' test

IVST (d)- Interventricular septal thickness in diastole;PW (d)- Posterior wall thickness in diastole; LVEF – Left ventricular Ejection Fraction; IVRT –Isovolumic relaxation time; DT- Deceleration time; E – Transmitral early diastolic flow velocity; A – Transmitral late diastolic flow velocity.

Table : 4 showing the correlation of TSH with the presence of pericardial effusion

TSH level (mIU/L)	Number of patients (n = 33)	Patients with Pericardial Effusion (%)
0.5 - 20	10	0 (0%)
20 -50	8	2 (25%)
>50	15	5(33.33%)

Discussion: The present study had female preponderance with a male to female ratio of 1:7.25. This has been observed in various epidemiological studies. Symptomatic thyroid failure is present in 1 -2 % of the population and tends to affect women [12].

Amongst the various clinical parameters, patients with hypothyroidism had significant bradycardia and systolic and diastolic hypertension (p<0.05). Similarly the BMI was significantly increased in hypothyroid patients as compared to controls (p=0.042). These changes are well described in hypothyroidism. Bradycardia is generally thought to be due to hypoactive sympathetic system in hypothyroidism. However, though there is overall depression of adrenergic response at cardiac and peripheral level, enhanced sympathetic output [13] and increased plasma Norepinephrine concentrations [14] have been described. Further, power spectral analysis of heart rate suggests an increased sympathetic influence on the autonomic cardiovascular system with blunted cardiovascular responsiveness [15]. Though the exact mechanism of elevated diastolic blood pressure in hypothyroidism is not known, altered autonomic function and structural changes in vascular tissue or expansion of extracellular fluid volume are the postulated mechanisms [16].Impaired vascular function in the form of increased systemic vascular resistance, arterial stiffness and impaired endothelial function also contribute [4].

In the present study, the mean interventricular septal thickness and posterior wall thickness were significantly increased in the cases. Previous studies have reported left ventricular concentric remodelling in subclinical hypothyroidism [11] and mild concentric hypertrophy in overt hypothyroidism [17]. This LV concentric remodelling of subclinical hypothyroidism is reversible with treatment [11]; thus institution of early treatment may prevent the development of LV remodeling which in turn may prevent LV hypertrophy, a predictor of future adverse cardiovascular events.

The various pulsed wave derived Doppler indices of diastolic function were significantly different in the cases as compared to the controls.LV relaxation abnormalities in the form of prolonged DT, IVRT and reduced E/A ratio were observed in the present study. Similar findings have been noted in previous studies. LV diastolic dysfunction has

been described in subclinical [10, 11, 18, 19] as well as overt hypothyroidism [20]. Short term acute hypothyroidism also causes discrete diastolic dysfunction [8, 9]. Furthermore many of these changes are reversible with treatment [10, 11, 18, 19]. Application of newer intramyocardial ultrasonic techniques allows early detection of altered myocardial texture, intrinsic contractility and regional deformability even before gross features of diastolic dysfunction are detected by conventional 2 D- Doppler echocardiography [7]. Alteration in cardiac gene expression in the contractile apparatus, causing changes in the cytosolic Calcium concentration occurs in hypothyroidism. Hence diastolic dysfunction occurs in these patients.

In the present study, 7(21.21%) patients had pericardial effusion; presence of pericardial effusion correlated with the severity of disease. The incidence of pericardial effusion has been variably described between 30-45%[20]. Pericardial effusions are seen in severe, prolonged untreated hypothyroidism; cardiac tamponade is a rare feature. As in the present study, correlation of pericardial effusion with the severity of hypothyroidism has been described previously [21].

Conclusion: To conclude, hypothyroidism is associated with various structural and functional alterations in the form of concentric remodelling, pericardial effusion and diastolic dysfunction. Along with other concomitant risk factors like hypertension and dyslipidemia, these changes portend an increased cardiovascular risk in these patients.

References:-

1. Kiss E, Brittsan AG, Edes I, Grupp IL, Grupp G, Kranias EG. Thyroid hormone induced alterations in phospholamban-deficient mouse hearts. Circ Res 1998; 83: 608–613.
2. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res 2004; 59: 31-50.
3. Osman F, Gammage MD, Franklyn JA. Thyroid disease and its treatment: short-term and long-term cardiovascular consequences. Curr Opin Pharmacol 2001; 1: 626–631
4. Owen PJ, Sabit R, Lazarus JH. Thyroid disease and vascular function. Thyroid 2007. 17; 6: 519-24.
5. Iqbal A, Schirmer H, Lunde P, Figenschau Y, Rasmussen K, Jorde R. Thyroid Stimulating Hormone and Left Ventricular Function. The Journal of Clinical Endocrinology & Metabolism 2007; 92(9): 3504-3510.
6. Ciulla M, Paliotti R, Tortora R, Valentini P, Cortelazzi B, Beck-Peccoz P. Myocardial ultrasonic reflectivity in patients with thyroid dysfunction: a tissue characterization study. Cardiovascular Imaging 1997; 9: 75-77.
7. Fabrizio AL, Vitantonio DB, Enrica T, Andrea DC, Fabio M, Lucia A, et al. Early textural and functional alterations of left ventricular myocardium in mild hypothyroidism. European Journal of Endocrinology 2006; 155: 3-9.
8. Hoftijzer HC, Bax JJ, Heemstra KA, Bleeker GB, Delgado V, van der Klaauw AA, et al. Short-term overt hypothyroidism induces discrete diastolic dysfunction in patients treated for differentiated thyroid carcinoma. Eur J Clin Invest 2009; 39 (3): 204-210.
9. Kakhki VRD, Nezhad AF, Zakavi SR, Rahmani E, Sadeghi R, Ayati NK. Echocardiographic left ventricular functional changes in acute hypothyroidism vs subclinical hyperthyroidism in patients with differentiated thyroid carcinoma. Iran J Nucl Med 2011; 19 (2): 28-37.
10. Mishra TK, Routray SN, Das S, Behera M. Left ventricular dysfunction in patients with subclinical hypothyroidism and its reversibility after hormone therapy. JAPI 2005; 53: 943-946.
11. Erkan G, Erkan AF, Cemri M, Karaahmetoglu S, Cesur M, Cengel A. The Evaluation of Diastolic Dysfunction with Tissue Doppler Echocardiography in Women with Subclinical Hypothyroidism and the Effect of L-Thyroxine Treatment on Diastolic Dysfunction : A Pilot Study. Journal of Thyroid Research 2011; Article ID 654304, 7 pages, doi 10.4061/2011/654304.
12. Toft AD, Boon NA. Thyroid disease and the heart. Heart 2000; 84: 455-460.
13. Matsukawa T, Mano T, Gotoh E, Minamisawa K, Ishii M. Altered sympathetic nerve activity in hyperthyroidism and hypothyroidism. Journal of

the Autonomic Nervous System 1993; 42: 171-175
14. Manhem P, Bramnert M, Hallengren G. Increased arterial and venous plasma noradrenaline levels in patients with primary hypothyroidism during hypothyroid as ompared with euthyroid state. Journal of Endocrinological Investigation 1992; 15: 763-765.
15. Cacciatori V, Gemma ML, Bellavere F, Castello R, Gregori MED, Zoppini G, et al. Power spectral analysis of heart rate in hypothyroidism. European Journal of Endocrinology 2000; 143: 327-333.
16. Bing RF, Briggs RSJ, Burden AC, Russel AC, Swaks JD, Thurston H. Reversible hypertension and hypothyroidism. Clinical Endocrinology 1980; 13: 339-342.
17. Rodondi N, Bauer DC, Cappola AR et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. Journal of the American College of Cardiology 2008; 52, (14): 1152–1159.
18. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, et al. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 1999; 84 (6): 2064–2067.
19. Virtanen VK, Saha HHT, Groundstroem KWE, Salmi J, Pasternack AI. Thyroid hormone substitution therapy rapidly enhances left ventricular diastolic function in hypothyroid patients. Cardiology 2001; 96: 59-64.
20. Gupta A, Sinha RSK. Echocardiographic changes and alterations in lipid profile in cases of subclinical and overt hypothyroidism. JAPI 1996; 44 (8): 546-553.
21. Rawat B, Satyal A. An Echocardiographic study of cardiac changes in hypothyroidism and the response to treatment. Kathmandu University MedicalJournal 2003; 2 (3): 182-187.

Conflict of interest: None
Funding: None