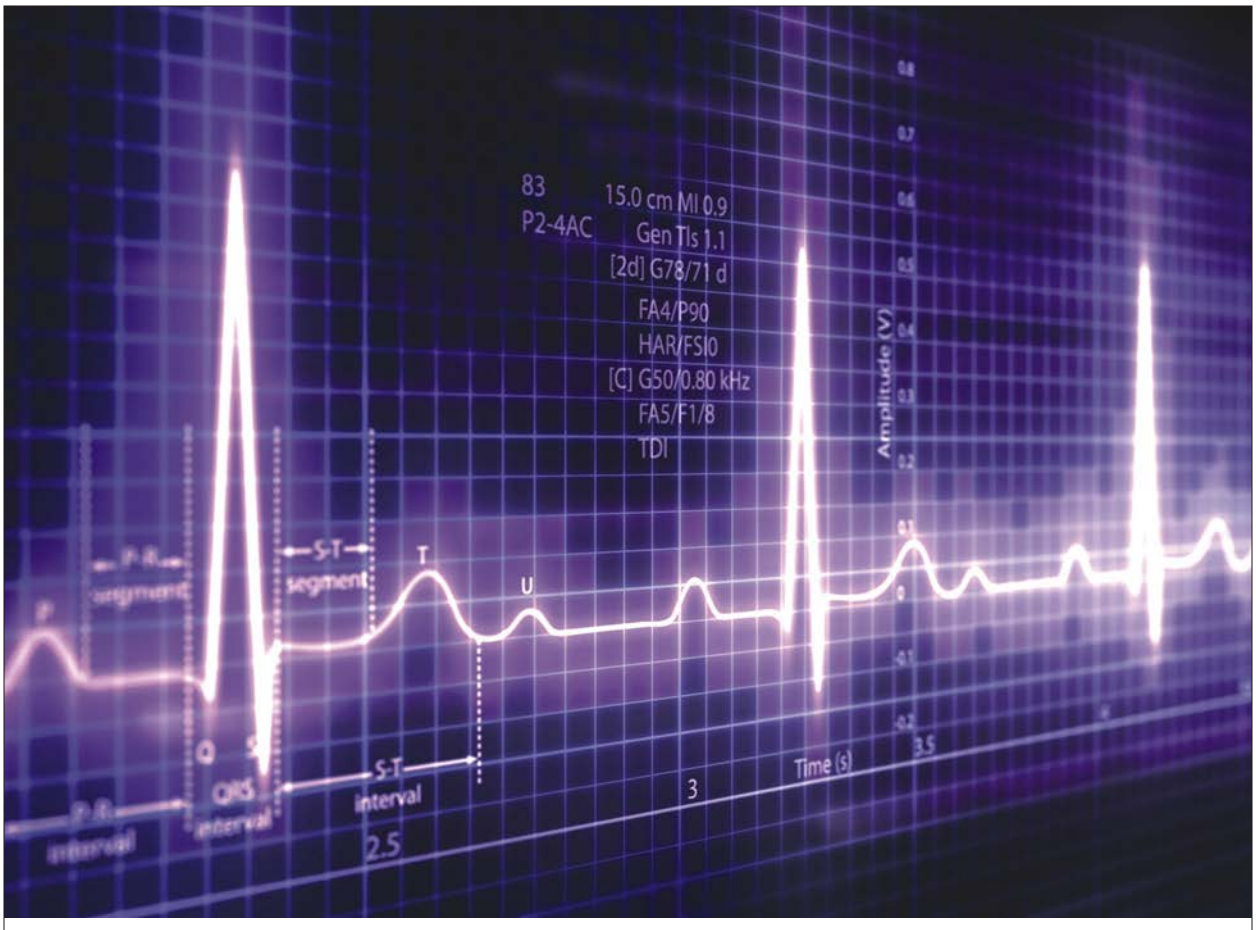

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Role of Tissue Doppler Echocardiography in the Diagnosis of Subclinical Left and Right Ventricular Dysfunctions in Patients with Subclinical Hypothyroidism

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ABSTRACT

Subclinical Hypothyroidism (SH) is a minor thyroid failure associated with subtle cardiac dysfunction and not all patients with SH need treatment. The main aim of study was to evaluate the role of tissue Doppler Imaging (TDI) indices such as Isovolumic Myocardial Acceleration (IVA), Myocardial Performance Index (MPI) and tissue velocity for diagnosing pre-clinical systolic and diastolic ventricular dysfunctions in patients with Subclinical Hypothyroidism (SH). Fifty five (55) patients were included in the study. Conventional echocardiography measuring Myocardial Performance Index (MPI) and Right Ventricular Fractional Area Change (RVFAC) were done. Patients with SH showed significantly higher E/E´ ratio (9.07±3.24 vs. 6.22±1.38 p = 0.0001) and prolonged isovolumic relaxation time [IVRT] (72.8±18.0 vs. 60.2±14.1 p = 0.005) as compared to control patients. The left and right ventricular MPI by TDI were higher in SH patients than the control (p = 0.0001), RVIVRT was prolonged (74.83±19.32 vs. 59.98±12.72 p = 0.04) while RV-FAC was similar in both groups. In conclusions, TDI proved to be a useful tool for diagnosing early LV and RV for systolic and diastolic dysfunction thus suggesting benefits from the early management of the SH in patients.

Key words: Subclinical hypothyroidism, myocardial performance index, tissue doppler imaging, left ventricular isovolumic acceleration

INTRODUCTION

The treatment of patients with subclinical hypothyroidism is controversial issue (Osman *et al*., 2001). The American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) recommended treatment for patients with TSH levels between the upper limits (usually around 4.0 mU L^{-1}) and 10 mU L^{-1} if the patient showed symptoms of hypothyroidism, positive thyroid perokidase antibodies, evidence of cardiovascular disease or risk factors for cardiovascular disease. When the serum thyrotropin is less than 10 mU L^{-1}, the decision to treat subclinical hypothyroidism should be tailored to individual patient (Garber *et al*., 2012). Previously, many studies demonstrated the cardiovascular effects of SH and the beneficial effects of thyroid hormone replacement in reversing all the cardiovascular abnormalities induced by Cooper *et al*. (1984), Nystrom *et al*. (1988), Erkan *et al*. (2011) and Martins *et al*. (2011).

Several studies reported that the Myocardial performance index (Tei index) is independent of arterial pressure, heart rate, ventricular geometry, atrioventricular valve regurgitation before and after load. The superiority of the Tei index is attributed to its ability to reflect combined systolic and diastolic performance (Tei *et al*., 1995; Bruch *et al*., 2000). Patients with SH had prolonged IVRT and diastolic dysfunction (Vitale *et al*., 2002; Turhan *et al*., 2006). The early detection of adverse cardiovascular effects of SH will help in recognizing the patient who need early levothyroxine treatment. Our hypothesis of this study was to assess the usefulness of TDI indices for early diagnosis of RV and LV dysfunction by measuring Myocardial Performance Index (MPI) and Myocardial Isovolumic Acceleration (IVA) of both ventricles (LV and RV) in patients with Subclinical Hypothyroidism (SH).

MATERIALS AND METHODS

Patients with newly diagnosed SH in the endocrinology clinic of King Saud Medical City were enrolled for the study. All the patients were not on hormone replacement with levothyroxine. Thirty age and sex-matched healthy subjects were enrolled as controls. Subclinical hypothyroidism was diagnosed based on increased level of TSH in serum (between 4.2-9.9 mU mL^{-1}) in the presence of normal FT3 and FT4 levels (Bemben *et al*., 1994). Furthermore, elderly patients having more than 60 years of age were excluded from the study. We also excluded patients having hypertension, diabetes mellitus, atrial fibrillation, history of coronary artery disease, valvular heart disease or previous use of anti-thyroid agents. Furthermore, well informed written consent was obtained from all the patients. A prior approval of study protocol was obtained from the local ethics committee.

All the patients including controls were tested for fasting blood glucose, urea, creatinine, liver function test, total cholesterol, low density lipoprotein LDL, High Density Lipoprotein (HDL) and triglyceride levels. Height and weight of patients were also recorded.

The serum-free T3, T4 and TSH were assessed using the microparticular enzyme immunoasssay method (Abbott, USA). Normal reference levels of the thyroid functions considered were TSH (0.27-4.20 mU mL^{-1}), FT3 (2.8-7.1 pmol L^{-1}) and FT4 (12-22 pmol L^{-1}).

Standard transthoracic two-dimensional, pulsed, color-flow and color M-mode Doppler, TDI, echocardiographic examinations were performed with a Vivid 7 System ultrasound machine (GE Medical Systems) equipped with a multi-frequency phased-array transducer. The LV end-systolic and end-diastolic dimensions, the LV ejection fraction and left atrial dimensions were measured according to the guidelines of the American Society of Echocardiography [ASE] (Lang *et al*., 2005). End-diastolic and end-systolic areas of the RV cavity were calculated using planimetry. The RV fractional area change (RV-FAC) was calculated [(end-diastolic area-end-systolic area)/end-diastolic area)×100)] from the apical 4-chamber view (Lang *et al*., 2005). The Tricuspid Annular Plane Systolic Excursion (TAPSE) was measured by M-mode placing the cursor in apical 4-chamber view at the junction of the tricuspid valve with the right ventricular free wall. Maximum displacement during systole was evaluated (Kaul *et al*., 1984).

Conventional transmitral flow Early (E), Atrial (A) transmitral peak flow velocities were measured with PW-Doppler. Isovolumic Contraction Time (ICT), Isovolumic Relaxation Time (IVRT) and aortic Ejection Time (ET) were measured by using continuous-wave Doppler tracings obtained at the apical five-chamber view. The Myocardial Performance Index (MPI) was calculated by dividing the sum of IVCT and IVRT by ET (Tei *et al*., 1995).

The tissue Doppler sample was placed on septal and lateral localizations of the mitral annulus and tricuspid annulus in the apical four-chamber view. Systolic (S) and diastolic (E' and A')

velocities of the annulus were measured. The ratio between pulsed wave Doppler-derived E wave mitral inflow velocity/tissue Doppler-derived mitral septal and lateral annular velocity E' (E/E' ratio an index of diastolic dysfunction) were estimated. The E/E' ratio was used to classify Left Ventricular Diastolic Dysfunction (LVDD). The LVDD was defined as E/E' ratio = 15, borderline diastolic function as E/E' between 8-14 and normal diastolic function as E/E´<8 according to the guidelines of ASE (Rivas-Gotz *et al*., 2003; Nagueh *et al*., 2009).

The Isovolumic Contraction Time (IVCT), Isovolumic Relaxation Time (IVRT) and Ejection Time (ET) were measured. Then the MPI was estimated both for the mitral and tricuspid annuli. In addition to TDI-derived systolic indices from both the mitral and tricuspid annuli. Peak myocardial velocity during isovolumic contraction (IVV) and the myocardial acceleration during isovolumic contraction (IVA) were also included. It is defined as the ratio of IVV divided by the acceleration time (Rivas-Gotz *et al*., 2003; Nagueh *et al*., 2009). All the measurements were calculated and averaged from three consecutive cycles.

Statistical analysis: Data were analyzed to Mean±Standard deviation. Quantitative data of the two groups patients with SH and controls were compared using the independent student´s t-test with SPSS software version 17 (SAS Institute, 2001). A p-value <0.05 considered to be significant.

RESULTS

Baseline demographic data were similar in both groups (Table 1). There were no significant differences between the 30 healthy individuals (control) and 22 patients with subclinical hypothyroidism SH. The thryotropin (TSH) level were significantly higher in patients with SH than the control group (7.18±1.78 vs. 2.29±0.99 p-value = 0.0001). By conventional echocardiography the IVCT and IVRT of the LV were significantly higher in SH as compared to healthy patients considered as controls (76.9±21.6 versus 65.9±13 p = 0.02 and 88.3±21.9 vs. 69.8±13.3 p = 0.001, respectively). Patients with SH showed significantly higher MPI (0.55±0.12 vs. 0.42±0.08 p = 0.001) (Table 2).

The Tissue Doppler Imaging (TDI) findings of both the groups showed that patients with SH have higher E/E´ ratio (Table 3). The lateral E/E´ ratio was 7.81±3.08 in patients with SH vs.

Table 1: Baseline clinical and demographic characteristics of the patients and controls

Parameters	Subclinical HT (22)	Control (30)	p-value
Age	41.32±12.62	35.36±13.44	0.490
Body mass index	29.55±6.45	25.51±4.8	0.456
Gender	19 female 3 male	16 females 14 male	
Systolic blood pressure	130±21.68	119.36±13.11	0.191
Diastolic blood pressure	76.18±12.01	73.75±10.02	0.673
Heart rate/min	79.68±13.6	73.75±10.02	0.536
Total cholesterol (mmol L^{-1})	5.012±1.06	4.46±0.76	0.127
LDL cholesterol (mmol L^{-1})	3.22±1.03	2.76±0.63	0.105
HDL cholesterol (mmol L^{-1})	1.12±0.2	1.13±0.31	0.889
Triglycerides (mmol L^{-1})	1.43±0.69	1.14±0.59	0.132
Free Triiodothyronine (pmol L^{-1})	4.54±0.79	4.58±0.69	0.973
Free Thyroxine (pmol L^{-1})	13.84±3.07	13.53±3.49	0.765
Thyrotropin (Uiu mL^{-1})	7.18±1.78	2.29±0.99	0.0001

Table 2: Echocardiographic left and right ventricular parameters of patients and controls

Parameters	Subclinical HT (22)	Control (30)	p-value
LVEDd (mm)	42.50±8.70	43.95±9.39	0.55
LVESd (mm)	26.21±5.83	27.02±5.66	0.60
IVS d	8.13±2.13	7.89±1.81	0.65
LVPW thickness (mm)	8.34±2.01	8.15±1.79	0.41
Ejection fraction EF (%)	60.40±12.9	61.20±11.4	0.81
Fractional shortening FS	36.45±8.00	37.93±7.30	0.83
LVd Mass (ASE) (g)	104.00±0.08	114.8±34.70	0.29
LVs Mass (ASE) (g)	126.00±45.2	126.2±41.60	0.98
RVAd (cm)	10.28±3.13	9.58±3.29	0.42
RVAs	5.43±2.20	5.94±2.27	0.29
RV FAC (%)	0.44±0.15	0.42±0.11	0.45
LA area	9.41±3.71	9.33±2.65	0.92
Tricuspid annular TAPSE	21.73±4.62	23.07±4.95	0.31
Pul valve AccT (msec)	125.70±31.0	132.50±26.0	0.38
MV E velocity (m sec^{-1})	0.81±0.23	0.82±0.19	0.91
MV A velocity (m sec^{-1})	0.65±0.14	0.54±0.16	0.57
E/A ratio	1.29±0.37	1.62±0.57	0.018
Deceleration Time (msec)	190.00±48.5	192.60±42.2	0.83
Ejection time ET (msec)	289.20±65.9	312.60±58.5	0.16
IVCT (msec)	76.90±21.6	65.9±13.0	0.02
IVRT (msec)	88.30±21.9	69.8±13.3	0.001
MPI	0.55±0.12	0.42±0.08	0.001

Table 3: Tissue doppler echocardiographic parameters of SH patients and controls

Parameters	Subclinical HT (22)	Control (30)	p-value
$S_{lateral}$ (m sec^{-1})	8.47±2.61	9.42±2.53	0.170
$E_{lateral}$ (m sec^{-1})	10.68±3.37	14.98±3.74	0.640
$A'_{lateral,}$	9.55±2.72	8.20±2.24	0.320
E'/A'	1.27±0.82	1.95±0.82	0.003
E/E'lateral	7.81±3.08	5.71±1.56	0.002
Isovolumic IVA m/sec2	2.79±0.80	3.16±0.91	0.100
IVRT lat	72.8±18.00	60.20±14.1	0.005
IVCT	70.63±13.90	59.33±8.85	0.013
ET	254.60±54.5	295.30±57.5	0.010
MPI	0.53±0.12	0.38±0.07	0.0001
S septal (m sec^{-1})	7.59±2.21	8.13±2.16	0.360
E' septal (m sec^{-1})	9.16±3.16	13.30±2.18	0.070
A' septal (m sec^{-1})	9.42±2.31	8.86±3.29	0.100
E/E'septal	9.07±3.24	6.22±1.38	0.0001
IVA	2.70±0.90	3.66±1.08	0.002
MPI	0.53±0.12	0.39±0.07	0.0001
S RV (m sec^{-1})	12.13±3.04	12.53±3.03	0.630
E' RV (m sec^{-1})	11.97±3.19	13.14±2.74	0.440
A'RV (m sec^{-1})	15.37±4.95	11.10±3.62	0.120
ET	246.90±56.3	280.80±52.6	0.024
IVA	4.41±2.46	4.59±1.39	0.850
MPI RV	0.52±0.12	0.39±0.07	0.0001
IVRT RV	74.83±19.32	59.98±12.72	0.006

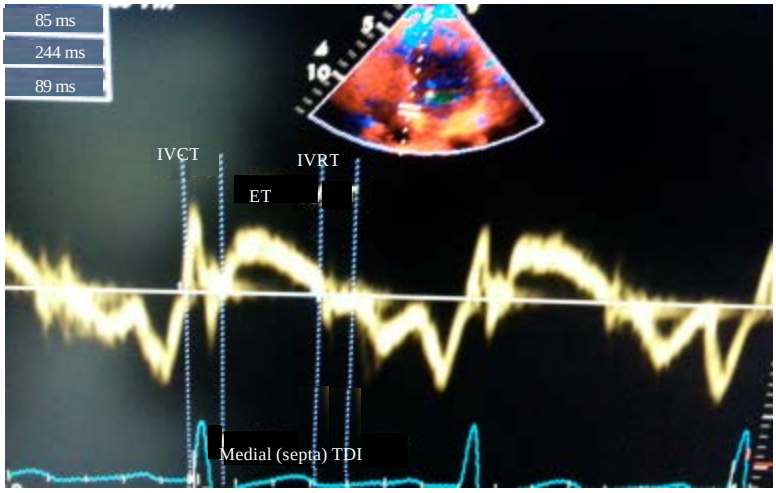

Fig. 1: Tissue Doppler imaging of the Medial (septal) mitral annulus with measurement of isovulmic contraction time, Ejection time and isovolumic relaxation time

5.71±1.56 in healthy control group p = 0.002. The Septal E/E´ratio was 9.07±3.24 vs. 6.22±1.38 p = 0.0001. In addition to that, the IVRT prolonged significantly in patients with SH as compared to the control patients (lateral IVRT by TDI was 72.8±18.0 vs. 60.2±14.1 p = 0.005) (Fig. 1).

Patients with SH showed lower isovolumic myocardial acceleration (IVA) of the LV and higher MPI than the control patients (IVA 2.7±0.9 vs. 3.66±1.08 p = 0.002 and MPI 0.53±0.12 vs. 0.32±0.07 p = 0.0001). The ejection time (ET) reduced significantly in SH patients as compared to healthy control patients (254.6±54.5 vs. 295.3±57.5 p = 0.01). However, these parameters indicated LV systolic and diastolic dysfunction in patients with SH.

The RV-FAC and TAPSE were similar in patients with SH and the controls (0.44±0.15 in SH vs. 0.42±0.11 in controls p = 0.45 and TAPSE 21.73±4.62 in SH vs. 23.07±4.95 p = 0.31). The TDI of RV and IVA and S velocity were similar in patients with SH and controls (p = 0.85 and 0.63, respectively) suggesting preserved RV systolic function in patients with SH. In the patient group, the RV IVRT prolonged as compared to controls (p = 0.006). The MPI increased in SH patients (0.52±0.12 in SH vs. 0.39±0.07 in controls p = 0.0001). Whereas, the ET reduced in SH patients (246.9±56.3 in SH vs. 280.8±52.6 in controls p = 0.024) thus suggesting a significant RV diastolic dysfunction.

DISCUSSION

Presently, treatment of patients with subclinical hypothyroidism is still controversial. But the generally accepted opinion is that treatment can be started to prevent progression to manifest hypothyroidism or to alleviate symptoms if present (Gharib *et al*., 2005). Previous studies showed that Subclinical Hypothyroidism (SH) was associated with cardiovascular disorders, such as endothelial dysfunction, atherosclerosis and myocardial dysfunction (Kosar *et al*., 2005).

In this study, the TDI findings were consistent with LV systolic and diastolic dysfunctions in patients with subclinical hypothyroidism as compared to controls. The RV systolic function was preserved as RV-FAC, TAPSE, RV S velocity and the IVA by TDI were similar in controls and SH patients but RV MPI significantly increased in patients with SH.

Data regarding the association between SH and cardiovascular disease outcomes are conflicting among large prospective cohort studies. Rodondi *et al.* (2010) analyzed the data of 7 prospective cohorts including 25,977 participants. They found that the risk of coronary heart disease events and coronary heart disease mortality increased with higher TSH concentration. In Whickham survey, an association was found between incident Ischemic Heart Disease (IHD) events and IHD-related mortality with SH over the last 20 years of follow-up. They also concluded that properly designed and controlled trials of treatment of SH are required to clarify this issue (Razvi *et al.*, 2010).

It was reported that Thyroid hormone deficiency leads to a decrease in heart rate and impairment of myocardial contraction and relaxation, as its deficiency alters cardiac muscle function by decreasing the activity of enzymes involved in the regulation of myocyte calcium intake and the expression of several contractile proteins (Osman *et al.*, 2001; Fazio *et al.*, 2004). In the present study, early diagnosis of impaired LV and RV function by using pulsed tissue Doppler echocardiography TDI in patients with SH proved useful to identify patients who need early treatment.

In the present study, MPI derived from TDI was used which indicates the systolic and diastolic functions of both ventricles (LV and RV). It was significantly higher in SH patients as compared to control. Some of the previous studies confirmed impaired LV diastolic function in SH using TDI-derived indices and are in agreement with the present study findings (Yazici *et al.*, 2004; Monzani *et al.*, 2001; Mishra *et al.*, 2005; Turhan *et al.*, 2006). In our study patients with SH exhibited higher E/E´ ratio which reflected LVDD. However, in parallel to this study findings, Oner *et al.* (2011) studied 27 patients with SH who were not on hormone replacement. They found lower E´ velocity and a higher E/E´ ratio thus suggesting significant LV diastolic dysfunction. The present study also used TDI-derived parameters such as peak myocardial velocity during isovolumic contraction (IVV) and IVA to evaluate LV systolic functions. It decreased significantly in patients with SH. In contrast to this, Oner *et al.* (2011) found significantly lower level of IVV and IVA in SH patients which suggested subclinical LV systolic dysfunction. It was also reported that IVA is an accurate, non-invasive measurement easy applicable for the evaluation of ventricular systolic function (Vogel *et al.*, 2002; Toyono *et al.*, 2004). Yazici *et al.* (2004) found a positive impact of L-thyroxin replacement in cardiac function with significant reduction in MPI after thyroid hormone replacement therapy. While it is generally agreed that therapy is considered for patients whom serum TSH levels are more than 10 mU mL^{-1}. The higher TSH levels suggest initiating thyroid hormone replacement therapy, but still for patients with TSH levels ranging between 4.2 and 10 mU mL^{-1} is controversial. Erkan *et al.* (2011) investigated the response of diastolic dysfunction to thyroid hormone replacement therapy in twenty two patients with SH. They found improvement of left ventricular diastolic function in SH with thyroid hormone replacement therapy using tissue Doppler. They also concluded that tissue Doppler echocardiography seems to be a useful tool for monitoring the response of diastolic dysfunction to thyroid hormone replacement therapy in patients having SH.

Met analysis of Chen *et al.* (2013) concluded that SH patients showed significantly lower LV mitral annular Ea peak velocity and significantly higher mitral annular Aa peak velocity. They also found that patients aged more than 60 years with SH showed significantly worse parameters of LV diastolic function than thyroid controls.

In this study, RV, MPI and IVRT increased significantly which suggested both the systolic and diastolic RV dysfunction in patients with SH. However, RV systolic parameters by conventional echocardiography and TDI were preserved in subjects with SH. The study findings were similar to those of Oner *et al.* (2011) and Kosar *et al.* (2005) who found that RV systolic functions were preserved but RV diastolic functions were impaired in patients with SH.

CONCLUSION

Patients with SH showed subclinical LV and RV dysfunction. The TDI proved to be a sensitive and useful tool in diagnosing subclinical RV and LV systolic and diastolic dysfunction in patients with SH. The early diagnosis of cardiac dysfunction might help in early treatment of patients with SH.

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