European Review for Medical and Pharmacological Sciences 2022; 26: 3677-3685

Frequency of fragmented QRS on ECG and relationship with left ventricular dysfunction in patients with subclinical hypothyroidism

E. YILMAZ[1], E. AYDIN[1], S. ÇAMCI[1], E. AYDIN[2]

[1]Department of Cardiology, Giresun University Medical Faculty, Giresun, Turkey
[2]Department of Cardiology, Kanuni Medical Training and Research Hospital, Trabzon, Turkey

Abstract. – OBJECTIVE: Subclinical hypothyroidism (SH) is a biochemical definition that has been proven to be associated with cardiovascular diseases. Fragmented QRS (fQRS) is defined as an electrocardiographic (ECG) reflection of cardiac fibrosis. It is associated with increased cardiovascular mortality and morbidity. In this study, we aim to evaluate the presence and frequency of fQRS in SH patients and determine the relationship between fQRS presence and left ventricular dysfunction by using the myocardial performance index (MPI).

PATIENTS AND METHODS: Our study included 50 newly diagnosed SH and 50 healthy participants with similar demographic characteristics. We compared demographic characteristics, laboratory findings, electrocardiographic and echocardiographic measurements of the study population. SH patients were evaluated as two groups in the subgroup analysis: [fQRS(+) SH] with fQRS and [fQRS(-) SH] without fQRS. We analyzed the correlation of thyroidstimulating hormone (TSH) levels with demographic characteristics, electrocardiographic and echocardiographic data. Independent predictors of fQRS presence were evaluated by logistic regression analysis.

RESULTS: The mean age of SH patients was 44 ± 8 years, and 46% (n = 23) of the patients were women. In the control group, the mean age was 45 ± 11 years, and 52% (n = 26) of the participants were women. MPI was found to be significantly higher in the SH group compared to the control group (0.53 ± 0.07 *vs.* 0.41 ± 0.08, $p < 0.001$). fQRS was found to be significantly higher in the SH group compared to the control group ($p = 0.004$). In echocardiographic measurements, isovolumic relaxation time (IVRT) was found to be significantly longer in the fQRS(+) SH group (105.6 ± 21.8 ms *vs.* 91.1 ± 24.4 ms, $p < 0.001$), while isovolumic contraction time (IVCT) was not significantly different between the groups. Ejection time (ET) was significantly longer in the fQRS (-) SH group (286.9 ± 32.1 ms *vs.* 274.2 ± 30.6 ms; $p = 0.011$). MPI was 0.57 ± 0.12 in the fQRS (+) SH group and 0.48 ± 0.06 in the fQRS (-) SH group, which was significantly higher ($p = 0.001$). TSH was found to be 8.82 ± 4.58 in fQRS (+) SH group and 5.73 ± 3.10 in fQRS (-) SH group ($p = 0.003$). It was found that MPI (r = 0.302, $p < 0.001$) and fQRS (r = 0.321, $p < 0.001$) were significantly positively correlated with TSH. TSH levels [OR = 1,645, 95% CI = 1,322 to 2,067 ($p = 0.001$)], IVRT [OR = 1,502, 95% CI = 1,119 to 95% ($p = 0.003$)], and MPI [OR = 1,408, 95% CI = 0.989 - 1.806 ($p = 0.001$)] were found to be independent predictors of the presence of fQRS.

CONCLUSIONS: The frequency of fQRS in SH patients was found to be higher than in the healthy population. MPI values were higher in fQRS (+) SH patients compared to fQRS (-) SH patients, resulting indirectly having a higher risk of tendency to left ventricular systolic/diastolic dysfunction. MPI and fQRS had a significant positive correlation with TSH. TSH, IVRT, and MPI were found to be independent predictors of the presence of fQRS in SH patients.

Key Words:
Fragmented QRS, Left ventricular dysfunction, Myocardial performance index, Subclinical hypothyroidism.

Introduction

Subclinical hypothyroidism (SH) is a biochemical definition for normal free triiodothyronine (FT3) and free thyroxine (FT4) levels, with isolated elevated serum thyroid stimulating hormone (TSH) levels (>4 mIU/L). Patients do not have any clinical signs and symptoms of overt hypothyroidism[1,2]. Although subclinical hypothyroidism is more common in women around 60 years of age, its prevalence varies between 4% and 10% in the general population[3]. Many scholars[4] have found that SH is associated with cardiovascular diseases (CVD), and some studies have even re-

Corresponding Author: Ercan Aydın, MD; e-mail: ercanaydin112@yahoo.com

ported SH as an independent risk factor for CVD.

Global myocardial performance index (MPI) (Tei index) is an echocardiographic parameter used in the evaluation of left ventricular systolic and diastolic function. It is defined as the sum of isovolumic contraction (IVCT) and relaxation (IVRT) time divided by ejection time (ET)[5,6]. It has been previously revealed that MPI predicts morbidity and mortality in patients with cardiovascular pathologies[7-9]. Clinical studies have shown MPI is higher in SH patients compared to healthy participants in the control group, and MPI value can improve after medical treatment[10-13].

Fragmented QRS (fQRS) is defined as a variety of RSR patterns. There is an additional R wave (R'), notching in the R wave or in the nadir of the S wave in at least two consecutive leads corresponding a major coronary artery region[14]. Previous studies have shown that the presence of fQRS is associated with an increase in cardiovascular mortality and morbidity[15,16]. This relationship is thought to be due to regional myocardial fibrosis, ventricular arrhythmia, and structural heart defects. There is no previous study evaluating the frequency of fQRS in SH patients compared to the healthy population. In this study, we aimed at determining the presence and frequency of fQRS in SH patients and also at evaluating the relationship between fQRS presence and myocardial performance index and indirectly left ventricular dysfunction in SH patients.

Patients and Methods

Study Population

The Clinical Research Ethics Committee of Ordu University approved the study (Approval No: 2022/16). Our study was carried out in accordance with the principles of the Declaration of Helsinki, with the signed consent of the patients. Our study included newly diagnosed SH patients aged >18 years in endocrinology and internal medicine clinics, planned outpatient follow-up, and healthy participants with similar demographic characteristics. Inclusion criteria for the SH group were not receiving thyroid hormone replacement therapy. The exclusion criteria were history of coronary artery disease, cardiomyopathy, moderate/severe valve disease, any type of arrhythmia, hypertension, diabetes mellitus, chronic lung disease, liver or kidney failure, serum electrolyte abnormalities including hypocalcemia or hypercalcemia, a history of pacemaker or cardioverter defibrillator implantation, bundle branch block on the ECG, ST-T wave changes and the use of any drugs affecting the cardiac conduction system, including antiarrhythmics. The same exclusion criteria were applied to healthy participants. Cases over the age of 60 were excluded from the study because they are physiologically prone to left ventricular diastolic dysfunction. In addition, patients with significant hypothyroidism (TSH level equal to or higher than 10 mIU/L) were not included in the study because cardiovascular involvement, including diastolic dysfunction and heart failure, has been scientifically proven in patients with significant hypothyroidism[17]. Patients with SH were classified according to their etiology as follows: (1) Hashimoto's thyroiditis (n=42), (2) SH due to thyroidectomy (n=3), (3) SH with negative thyroid autoantibodies and not due to surgery (n=5). SH was defined as the detection of TSH level >4.0 mIU/L, FT3 and FT4 values within normal limits in 2 separate fasting blood samples taken 2 to 6 weeks apart[2]. Serum TSH, FT3 and FT4 levels were measured by electrochemiluminescence immunoassay (ECLIA) on a Cobos e601 analyzer (Roche HITACHI Germany).

The patients were rested in the supine position (Cardiofax GEM, model 9022 K, Nihon Kohden, Tokyo, Japan) for 10 minutes; electrodes were placed on standard anatomical regions and ECG recordings were taken at 25 mm/s speed and 10 mm/mV width. ECGs were recorded in our local online imaging program to increase the accuracy and reliability of our measurements. Manual ECG measurements were evaluated by two cardiologists using caliper and magnifying glass. ECG evaluators were blinded to the demographic data of the patients. Inter-observer coefficient of variation was 2.12%. Standard ECG measurements: heart rate (HR), PR interval, QRS interval, QT and QTc [calculated using Bazett's Formula ($QTc=QT\sqrt{(R-R\ interval)}$] intervals were calculated manually. Measurements were determined by averaging the values obtained separately from each lead of the 12-lead ECG. One measurement was taken from each lead, but in leads with poor image quality at least two consecutive measurements were averaged to improve accuracy. ECGs were included in the study data if at least 8 out of 12 leads could be measured. Das et al[14] defined fQRS as the presence of an additional R wave (R') corresponding a major coronary artery re-

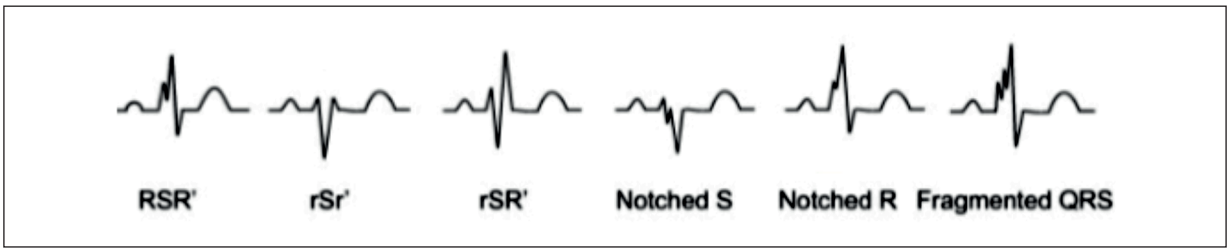

Figure 1. Classification of fragmented QRS (various RSR' patterns). Fragmented QRS was defined as an additional spike of QRS complexes without bundle branch block. Various RSR' patterns are present in the mid precordial lead or inferior lead.

gion or QRS complexes accompanied by a notch in the R wave or in the nadir of the S wave or the presence of >1 R' (fragmentation) in 2 consecutive leads (Figure 1).

Echocardiographic Examination

Two-dimensional (2D), M-mode, pulse and color flow Doppler transthoracic echocardiography (Vivid S5 Pro, GE, Horten, Norway, 2-4 MHz phased-array transducer) were performed on all study participants to exclude primary cardiac pathologies that could affect ECG measurements. All echocardiographic studies were performed by two cardiologists who were blinded to the clinical data of the study population and had no conflict of interest. Inter-observer coefficient of variation was 2.41%. Echocardiographic images were obtained using a standard 3.75 MHz probe in accordance with the guidelines of the American Society of Echocardiography[18]. Early (E) and late (A) peak velocity and deceleration time (DT) values were calculated from Doppler scanning. The E/A ratio was calculated manually. MPI is defined as the sum of IVCT and IVRT divided by ET[7] (Figure 2). In systolic dysfunction, IVCT is prolonged, and ET is shortened. Diastolic dysfunction causes prolongation of IVRT. MPI, calculated by dividing the sum of IVCT and IVRT by ET, is below 0.40 if overall ventricular function is normal. An MPI greater than 0.40 reflects diastolic and/or systolic dysfunction.

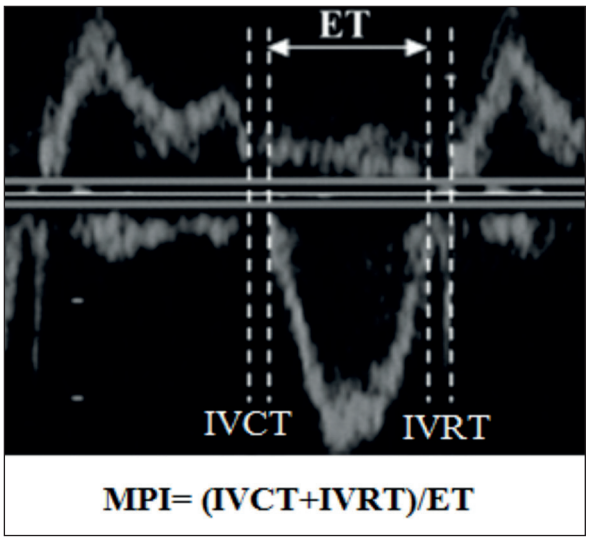

Figure 2. Doppler Echocardiographic display of MPI calculation. IVRT: isovolumic relaxation time, IVCT: isovolumic contraction time, ET: ejection time.

Statistical Analysis

Statistical analyses were performed using SPSS v. 22 (SPSS/IBM, IBM Corp., Armonk, NY, USA). Numerical variables were expressed as mean ± standard deviation (SD), categorical variables as number (n) and percentage (%). The conformity of the data to the normal distribution was determined by the Kolmogorov-Smirnov test. Student's *t*-test was used to compare normally distributed groups, and Mann-Whitney U-test was used for non-normally distributed groups. Chi-square test was used to compare qualitative variables between groups. Relationships between numerical variables were evaluated with Pearson Correlation analysis. Logistic regression analysis was performed to identify independent predictors of fragmented QRS. The hypotheses were two-sided and a p-value < 0.05 was considered statistically significant.

Results

Fifty SH patients were included in our study. The mean age was 44 ± 8 years, and 46% (n=23) of the patients were female. In the control group, the mean age was 45 ± 11 years, and 52% (n=26) of the participants were women. There was no significant difference between the two groups in terms of other demographic data, laboratory

tests, systolic and diastolic blood pressures. No significant difference was observed in the heart chamber measurements of the control and SH groups. In Doppler measurements: A wave was found to be 82.5 ± 11.7 cm/s in the SH group and 75.3 ± 12.4 cm/s in the control group ($p = 0.009$). On the other hand, E/A ratio was found to be significantly higher in the control group than in the SH group (1.33 ± 0.16 *vs.* 1.18 ± 0.16, $p < 0.001$).

IVRT was found to be significantly higher in the SH group than in the control group (98.3 ± 23.7 ms *vs.* 81.7 ± 14.7 ms, $p < 0.001$). While IVCT was not significantly different between groups, ET was observed to be significantly longer in the control group (291.8 ± 30.5 ms *vs.* 280.7 ± 31.2 ms, $p = 0.02$). MPI was found to be significantly higher in the SH group compared to the control group (0.53 ± 0.07 *vs.* 0.41 ± 0.08, $p <$ 0.001). Since it was our grouping criterion, TSH level was found to be 7.20 ± 5.58 mIU/L in the SH group and 2.17 ± 1.10 mIU/L in the control group, as expected ($p < 0.001$). It was observed that free FT3 and FT4 levels did not differ between the groups. No significant difference was observed between the groups in electrocardiographic measurements. The fQRS rate was found to be significantly higher in the SH group compared to the control group ($p = 0.004$) (Table I).

In the subgroup analysis, the SH group was evaluated as two groups as [fQRS(+) SH] with fQRS and [fQRS(-) SH] without fQRS (Table II). There was no significant difference between the groups in terms of demographic characteristics and laboratory tests. In echocardiographic measurements, it was determined that IVRT was significantly longer in the fQRS (+) SH group (105.6

Table I. Demographic characteristics, echocardiographic and electrocardiographic data of study participants.

Variables	SH (n = 50)	Controls (n = 50)	*p*-value
Age (years)	44 ± 8	45 ± 11	0.410
Gender, female (%)	23 (46%)	26 (52%)	0.162
BMI (kg/m^2)	27.4 ± 3.1	28.5 ± 3.5	0.087
SBP (mmHg)	116 ± 13	120 ± 12	0.509
DBP (mmHg)	71 ± 6	75 ± 5	0.522
Creatinine (mg/dL)	1.01 ± 0.4	1.04 ± 0.2	0.089
Hemoglobin (g/dL)	13.1 ± 2.5	13.2 ± 3.1	0.611
Glucose (mg/dL)	106 ± 10.9	110 ± 11.7	0.616
LVEF (%)	61.9 ± 5.3	63.2 ± 4.1	0.543
LVEDD (mm)	48.3 ± 5.8	47.5 ± 6.4	0.655
LVESD (mm)	34.2 ± 4.6	33. 3± 3.5	0.702
LA (mm)	34.77 ± 4.83	34.07 ± 3.75	0.235
IVS (mm)	9.52± 0.8	9.46 ± 1.1	0.344
PW (mm)	9.57 ± 1.0	9.55 ± 0.8	0.389
E (cm/s)	94.6 ±12.5	98.3 ± 14.4	0.089
A (cm/s)	82.5 ± 11.7	75.3 ± 12.4	**0.009**
DT (ms)	180.9 ± 28.2	187.1 ± 27.6	0.068
E/A ratio	1.18 ± 0.16	1.33 ± 0.16	**< 0.001**
IVRT, ms	98.3 ± 23.7	81.7 ± 14.7	**< 0.001**
IVCT, ms	49.2 ± 15.3	45.9 ± 11.2	0.066
ET, ms	280.7 ± 31.2	291.8 ± 30.5	**0.020**
MPI	0.53 ± 0.07	0.41 ± 0.08	**< 0.001**
TSH (mIU/L)	7.20 ± 5.58	2.17 ± 1.10	**< 0.001**
FT3 (pmol/L)	4.32 ± 0.71	4.20 ± 0.59	0.301
FT4 (pmol/L)	11.36 ± 0.33	10.48 ± 0.34	0.402
HR (bpm)	75.1 ± 12.7	78.7 ± 13.6	0.275
PR (ms)	188.3 ± 12.8	179. 9 ± 14.6	0.457
QT (ms)	375.5 ± 31.8	365.9 ± 23.1	0.911
QTc (ms)	409.5 ± 17.3	412.4 ± 16.4	0.412
Fragmented QRS	24 (48%)	11 (22%)	**0.004**

Values are presented as mean ± standard deviation and percentages. SH: subclinical hypothyroidism, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LA: left atrium; IVS: interventricular septum diameter; PW: posterior wall, E: peak early filling velocity, A:late diastolic filling velocity, DT: E wave deceleration time,IVRT: isovolumic relaxation time, IVCT: isovolumic contraction time,ET: ejection time, MPI: myocardial performance index, TSH: thyroid stimulating hormone, FT4: free T4, FT3: free T3, HR: heart rate, QTc: QT corrected by Bazett formula.

Table II. Demographic characteristics, echocardiographic and electrocardiographic data of SH subgroups according to the presence of fragmented QRS.

Variables	fQRS (+) SH (n = 24)	fQRS (-) SH (n = 26)	*p*-value
Age (years)	44.3 ± 7.1	44.8 ± 10.4	0.805
Gender, female (%)	10 (41.6 %)	13 (50 %)	0.082
BMI (kg/m^2)	27.1 ± 4.1	27.5 ± 4.5	0.117
SBP (mmHg)	114 ± 16	118 ± 11	0.239
DBP (mmHg)	73 ± 7	70 ± 6	0.332
Creatinine (mg/dL)	1.00 ± 0.6	1.02 ± 0.8	0.109
Hemoglobin (g/dL)	13.2 ± 3.1	13.0 ± 4.1	0.221
Glucose (mg/dL)	102 ± 11.1	109 ± 14.2	0.708
LVEF (%)	60.6 ± 6.1	62.6 ± 4.1	0.543
LVED (mm)	49.4 ± 4.7	47.2 ± 6.9	0.655
LVES (mm)	36.2 ± 5.1	32.2 ± 4.8	0.652
LA (mm)	36.27 ± 5.63	33.57 ± 3.93	0.455
IVS (mm)	9.45 ± 0.8	9.60 ± 0.8	0.654
PW (mm)	9.49 ± 1.0	9.59 ± 1.0	0.549
E (cm/s)	92.9 ± 11.9	95.1 ± 12.1	0.129
A (cm/s)	83.7 ± 12.1	81.3 ± 11.9	0.211
DT (ms)	182.1 ± 26.4	181.1 ± 25.3	0.097
E/A ratio	1.17 ± 0.19	1.19 ± 0.13	0.192
IVRT, ms	105.6 ± 21.8	91.1 ± 24.4	**< 0.001**
IVCT, ms	49.1 ± 14.4	49.5 ± 16.7	0.198
ET, ms	274.2 ± 30.6	286.9 ± 32.1	0.011
MPI	0.57 ± 0.12	0.48 ± 0.06	**0.001**
TSH (mIU/L)	8.82 ± 4.58	5.73 ± 3.10	**0.003**
FT3 (pmol/L)	4.31 ± 0.56	4.34 ± 0.44	0.098
FT4 (pmol/L)	11.42 ± 0.61	11.05 ± 0.55	0.192
HR (bpm)	73.8 ± 11.9	76.3 ± 12.7	0.125
PR (ms)	188.3 ± 10.8	186. 9 ± 11.2	0.117
QT (ms)	376.2 ± 28.1	377.4 ± 29.6	0.911
QTc (ms)	410.5 ± 15.3	411.6 ± 16.7	0.732

Values are presented as mean ± standard deviation and percentages. SH: subclinical hypothyroidism, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, LVED: left ventricular end diastolic diameter, LVES: Left ventricular end systolic diameter, LA: left atrium, IVS: interventricular septum diameter, PW: posterior wall, E: peak early filling velocity, A:late diastolic filling velocity, DT: E wave deceleration time,IVRT: isovolumic relaxation time, IVCT; isovolumic contraction time, ET: ejection time, MPI: myocardial performance index, TSH: thyroid stimulating hormone, FT4: free T4, FT3: free T3, HR: heart rate, QTc: QT corrected by Bazett formula.

± 21.8 ms *vs.* 91.1 ± 24.4 ms, $p < 0.001$), while IVCT was not significantly different between the groups. Ejection time (ET) was significantly longer in the fQRS (-) SH group (274.2 ± 30.6 ms *vs.* 286.9 ± 32.1 ms, $p = 0.011$). MPI was 0.57 ± 0.12 in the fQRS (+) SH group and 0.48 ± 0.06 in the fQRS (-) SH group, which was significantly higher ($p = 0.001$). TSH was found to be 8.82 ± 4.58 mIU/L in the fQRS (+) SH group and 5.73 ± 3.10 mIU/L in the fQRS (-) SH group ($p = 0.003$). FT3 and FT4 serum levels did not make a significant difference between the groups. No significant difference was observed between the groups in electrocardiographic measurements.

In the correlation analysis, the relationships between TSH levels and other demographic characteristics, electrocardiographic and echocardiographic data are presented in Table III. It was

Table III. Correlation of TSH level with demographic characteristics, electrocardiographic and echocardiographic data.

	TSH	
Variables	r	*p*-value
Age	0.089	0.502
HR	-0.088	0.410
QTc (ms)	0.097	0.361
E/A ratio	-0.102	0.194
IVRT, ms	0.236	**0.002**
IVCT, ms	0.076	0.239
ET, ms	-0.221	**0.012**
MPI	0.302	**< 0.001**
Fragmented QRS	0.321	**< 0.001**

TSH: thyroid stimulating hormone, HR: heart rate, QTc: QT corrected by Bazett formula, IVRT: isovolumic relaxation time, IVCT: isovolumic contraction time, ET: ejection time, MPI: myocardial performance index.

determined that IVRT had a positive correlation with TSH (r: 0.236, $p = 0.002$), and ET had a negative correlation with TSH (r: -0.221, $p = 0.012$). MPI (r: 0.302, $p < 0.001$) and fQRS (r: 0.321, $p < 0.001$) were found to have a significant positive correlation with TSH.

The results of the logistic regression analysis performed to determine the independent predictors of the presence of fragmented QRS are presented in Table IV. As a result of this analysis, TSH [OR: 1.645, 95% CI: 1.322-2.067 ($p = 0.001$)], IVRT [OR: 1.502, 95% CI: 1.119-1.908 ($p = 0.003$)] and MPI [OR: 1.408, 95% CI: 0.989-1.806 ($p = 0.001$)] were found to be independent predictors of the presence of fQRS.

Discussion

In this study, we evaluated the presence and frequency of fQRS in SH patients compared to the healthy population. We evaluated whether there was a difference between SH and healthy population and within SH subgroups with and without fQRS in terms of MPI and specific echocardiographic parameters. Further, the relationship between the presence of fQRS and left ventricular dysfunction via MPI measurements was also evaluated. In our study the frequency of fQRS was higher in the SH group than in the normal population. We also found fQRS(+) SH patients had higher MPI values than fQRS(-) patients.

In clinical practice, great effort and resources are invested in identifying high risk patients for cardiovascular disease and mortality by evaluating traditional cardiovascular risk factors. For this purpose, researchers seek simple and inexpensive index or measurement techniques that can be easily adapted to clinical practice. It has always been a subject of interest for researchers to be able to comment on the risk of cardiovascular mortality and morbidity with simple indices or measurements that can be applied over the indispensable tests of cardiology clinical practice, such as electrocardiography and echocardiography.

Since systolic and diastolic disorders often coexist, it is important to consider the two as a whole rather than separately. MPI, a Doppler index, is an echocardiographic parameter used to show left ventricular systolic and diastolic dysfunction and can be easily calculated in a short period of time – approximately 10-15 minutes. While systolic and diastolic dysfunction causes myocardial relaxation abnormalities that prolong the relaxation period (isovolumic relaxation time), systolic dysfunction also causes shortening of isovolumic contraction time and ejection time. Thus, systolic and diastolic dysfunction is reflected by the prolongation of isovolumic times relative to a shortened ejection time, resulting in an increase in the value of the Doppler index[5,19]. It was found that an increase in MPI value was successful in predicting cardiovascular mortality independently of other echocardiographic parameters and traditional cardiovascular risk factors[20]. This has also been demonstrated in patients with idiopathic dilated cardiomyopathy, cardiac amyloidosis, primary pulmonary hypertension, heart failure with preserved ejection fraction, and revascularized due to acute myocardial infarction[7-9,21,22].

Table IV. Univariate analysis and independent predictors of fQRS in multiple logistic regression analysis.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.055	0.325-2.125	0.789			
HR	0.876	0.705-1.344	0.233			
QT	0.971	0.569-1.688	0.267			
QTc	1.023	0.670-2.107	0.452			
FT3	1.076	0.526-2.079	0.237			
FT4	0.986	0.622-1.679	0.345			
TSH	2.102	1.067-6.233	**0.001**	1.645	1.322-2.067	**0.001**
IVRT, ms	1.708	0.698-4.994	**0.001**	1.502	1.119-1.908	**0.003**
IVCT, ms	0.974	0.301-1.987	0.566			
ET, ms	1.102	0.422-2.635	0.221			
MPI	1.145	0.566-3.459	**0.002**	1.408	0.989-1.806	**0.001**

OR: odds ratio, CI: confidence interval, HR: heart rate, QTc: corrected QT by Bazett formula, TSH: thyroid stimulating hormone, FT4: free T4, FT3: free T3, IVRT: isovolumic relaxation time, IVCT: isovolumic contraction time, ET: ejection time, MPI: myocardial performance index.

Thyroid hormones have important effects on heart functions. They regulate the transcription of regulatory and structural proteins in the cardiovascular system, predispose to chronic inflammation, cause collagen alteration and dehydration. They cause hemodynamic changes through smooth muscles in the arterial wall and have important effects on atherosclerosis[23,24]. In the case of subclinical hypothyroidism, cardiovascular effects occur. Many studies have found that SH is associated with hypertension, hyperlipidemia, and cardiovascular diseases (CVD), and some studies have even reported that SH is an independent risk factor for CVD[4].

Fragmented QRS is defined as a variety of RSR patterns. An additional R wave (R'), notching in the R wave or in the nadir of the S wave in at least two consecutive leads corresponding a major coronary artery region. Fragmented QRS complexes represent abnormal myocardial electrical conduction due to myocardial scarring, ischemia, and fibrosis[25-27]. It has been shown that the fragmented QRS is more successful in showing the previous myocardial infarction and its localization compared to the Q wave. In fact, fQRS may be the only evidence of prior silent MI, with a significantly higher incidence in women and the elderly with atypical chest pain, diabetes mellitus, and dementia[14]. Studies have shown that the presence of fQRS is associated with increased cardiovascular mortality and morbidity in patient groups with myocardial infarction, pulmonary embolism, Brugada syndrome, and various cardiomyopathy. This relationship is thought to be related to regional myocardial fibrosis, ventricular arrhythmia, and structural heart defects[15,16,28-31].

To the best of our knowledge, our study is the first in the literature to evaluate the presence of fQRS in SH patients compared to the healthy population. We evaluated the presence of fQRS in SH patients, MPI in SH patients with fQRS, and also the predictive value of MPI in predicting the presence of fQRS in SH patients. We found that fQRS was observed at a higher rate in the SH patient group compared to the healthy participants in the control group. We observed that there is a positive correlation between TSH levels and fQRS, and that TSH is an independent predictor for the presence of fQRS. Left ventricular dysfunction is seen at a higher rate in subclinical hypothyroid patient groups and fQRS patient groups compared to control groups[4,14]. Therefore, MPI is expected to be higher in these patient groups. Previous clinical studies have shown that MPI is higher in SH patients compared to the control group and this level can be reversibly improved with levothyroxine treatment[10-13]. In our study, we found that MPI was higher in the SH patient group than in the control group, which was consistent with previous studies. In fact, we found that MPI was higher in the fQRS(+) SH subgroup compared to the fQRS(-) SH subgroup. Previous studies did not include this fQRS subgroup analysis. We found that MPI has a positive correlation with TSH levels and is another predictor of the presence of fQRS. Our study is a descriptive study, and we did not evaluate the effect of levothyroxine treatment on follow up. Studies in a prospective design can provide prognostic data and clarify the effects of medical treatment.

In patients with subclinical hypothyroidism, it is important for the clinician to be able to predict cardiac dysfunction and pathologies with a practical tool. fQRS can be obtained from routine ECG and can be added to the physical examination for this purpose. Otherwise, clinicians need a variety of advanced imaging modalities such as echocardiography, nuclear imaging, and cardiac catheterization. A cardiac risk classification can be made by demonstrating the presence of fQRS in patients with subclinical hypothyroidism without a cardiac disease history with simple ECG. With the results we obtained from this patient group, closer follow-up can be recommended for patients who have ECGs with fQRS and left ventricular dysfunction.

Limitations

There are some limitations; firstly, our study was carried out retrospectively in a relatively small population. Further, long-term clinical follow-ups of the patients in terms of mortality and morbidity were not available, therefore, the prognostic value of the results we obtained cannot be commented on.

Conclusions

A higher rate of fQRS was observed in SH patients compared to the healthy population. It was determined that MPI values were higher in fQRS (+) SH patients compared to fQRS (-) SH patients. fQRS (+) SH patients had a higher tendency to left ventricular systolic/diastolic dysfunction. TSH, IVRT, and MPI were found to be independent predictors of the presence of fQRS in SH patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID ID
Ercan Aydın: 0000-0001-8743-3762; Emre Yılmaz: 0000-0002-1656-3778; Ertan Aydın: 0000-0002-7280-5137; Sencer Çamcı: 0000-0003-2152-0470.

References

1) Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-509.
2) Bemben DA, Hamm RM, Morgan L, Winn P, Davis A, Barton E. Thyroid disease in the elderly. Part 2. Predictability of subclinical hypothyroidism. J Fam Pract 1994; 38: 583-588.
3) Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526-534.
4) Suh S, Kim DK. Subclinical hypothyroidism and cardiovascular disease. Endocrinol Metab 2015; 30: 246-251.
5) Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997; 10: 169-178.
6) LaCorte JC, Cabreriza SE, Rabkin DG, Printz BF, Coku L, Weinberg A, Gersony WM, Spotnitz HM. Correlation of the Tei index with invasive measurements of ventricular function in a porcine model. J Am Soc Echocardiogr 2003; 16: 442-447.
7) Tei C, Dujardin KS, Hodge DO, Kyle RA, Jamil Tajik A, Seward JB. Doppler index combining systolic and diastolic myocardial performance: Clinical value in cardiac amyloidisis. J Am Coll Cardiol 1996; 28: 658-664.
8) Olson JM, Samad BA, Alam M. Myocardial performance index determined by tissue doppler imaging in patients with systolic heart failure predicts poor long-term prognosis: an observational cohort study. J Card Fail 2016; 22: 611-617.
9) Kamishirado H, Hayashi T, Hatano H, Kobayashi S, Maekawa Y, Ishiyama E, Akiya K, Fujito T, Takayanagi K, Morooka S. Evaluation of restenosis after percutaneous transluminal coronary angioplasty using a Doppler index, the Tei index. J Cardiol 1999; 33: 127-133.
10) Karabulut A, Doğan A, Tuzcu AK. Myocardial performance index for patients with overt and subclinical hypothyroidism. Med Sci Monit 2017; 23: 2519-2526.
11) Gürdal A, Eroğlu H, Helvaci F, Sümerkan MÇ, Kasali K, Çetin Ş, Aksan G, Kiliçkesmez K. Evaluation of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in patients with subclinical hypothyroidism. Ther Adv Endocrinol Metab 2017; 8: 25-32.
12) Yazici M, Gorgulu S, Sertbas Y, Erbilen E, Albayrak S, Yildiz O, Uyan C. Effects of thyroxin therapy on cardiac function in patients with subclinical hypothyroidism: index of myocardial performance in the evaluation of left ventricular function. Int J Cardiol 2004; 95: 135-143.
13) Nakova VV, Krstevska B, Kostovska ES, Vaskova O, Ismail LG. The effect of levothyroxine treatment on left ventricular function in subclinical hypothyroidism. Arch Endocrinol Metab 2018; 62: 392-398.
14) Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation 2006; 113: 2495-2501.
15) Kanjanahattakij N, Rattanawong P, Riangwiwat T, Prasitlumkum N, Limpruttidham N, Chongsathidkiet P, Vutthikraivit W, Crossey E. Fragmented QRS and mortality in patients undergoing percutaneous intervention for ST-elevation myocardial infarction: Systematic review and meta-analysis. Ann Noninvasive Electrocardiol 2018; 23: e12567.
16) Qaddoura A, Digby GC, Kabali C, Kukla P, Tse G, Glover B, Baranchuk AM. Use of fragmented QRS in prognosticating clinical deterioration and mortality in pulmonary embolism: A meta-analysis. Ann Noninvasive Electrocardiol 2018; 23: e12552.
17) JU RSW, Vanderpump M. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: Reanalysis of the Whickham Surver cohort. J Clin Endocrinol Metab 2010; 95: 1734-1740.
18) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233-271.
19) Møller JE, Egstrup K, Køber L, Poulsen SH, Nyvad O, Torp-Pedersen C. Prognostic importance of systolic and diastolic function after acute myocardial infarction. Am Heart J 2003; 145: 147-153.
20) Ärnlöv J, Lind L, Andrén B, Risérus U, Berglund L, Lithell H. A Doppler-derived index of combined left ventricular systolic and diastolic function is an independent predictor of cardiovascular mortality in elderly men. Am Heart J 2005; 149: 902-907.
21) Chuwa T, Rodeheffer RJ. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function—a study in normals and dilated cardiomyopathy. J Cardiol 1995; 26: 357-366.

22) Biering-Sørensen T, Mogelvang R, Pedersen S, Schnohr P, Sogaard P, Jensen JS. Usefulness of the myocardial performance index determined by tissue Doppler imaging m-mode for predicting mortality in the general population. Am J Cardiol 2011; 107: 478-483.

23) Biondi B, Palmieri EA, Lombardi G, Fazio S. Subclinical hypothyroidism and cardiac function. Thyroid 2002; 12: 505-510.

24) Klein I. Thyroid hormone and the cardiovascular system. Am J Med 1990; 88: 631-637.

25) Gardner P, Ursell P, Fenoglio Jr J, Wit A. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985; 72: 596-611.

26) Varriale P, Chryssos BE. The RSR′ complex not related to right bundle branch block: diagnostic value as a sign of myocardial infarction scar. Am Heart J 1992; 123: 369-376.

27) Jain R, Singh R, Yamini S, K Das M. Fragmented ECG as a risk marker in cardiovascular diseases. Curr Cardiol Rev 2014; 10: 277-286.

28) Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, Dandamudi G, Mahenthiran J. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol 2008; 1: 258-268.

29) Das MK, Maskoun W, Shen C, Michael MA, Suradi H, Desai M, Subbarao R, Bhakta D. Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm 2010; 7: 74-80.

30) Canpolat U, Kabakci G, Aytemir K, Dural M, ŞAHINER L, Yorgun H, Sunman H, BARIŞ KAYA E, Tokgözoğlu L, Oto A. Fragmented QRS complex predicts the arrhythmic events in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. J Cardiovasc Electrophysiol 2013; 24: 1260-1266.

31) Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation 2008; 118: 1697-1704.