ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Does Subclinical Hypothyroidism Alter the Axis of QRS and P Waves?

Subklinik Hipotiroidi QRS ve P Dalgası Aksını Değiştirir mi?

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ABSTRACT

Aim: *What changes subclinical hypothyroidism (SCH) causes on the 12-lead surface electrocardiogram (ECG) has remained elusive. We examined the relationship between subclinical hypothyroidism and cardiac electromechanics, including P wave and QRS axes on ECG and cardiac functions by 2D speckle-tracking echocardiography (2D-STE).*

Material and Method: *This cross-sectional study included 109 SCH patients who presented to the internal disease outpatient clinic between November 10, 2018, and January 30, 2019. ECG, 2D-STE images, and laboratory findings at admission were recorded for all patients. Findings were compared with a sex and age-matched control group of 74 healthy adults.*

Results: *The median age of the patients was 41 (IQR, 34–50) years, and 76.1% were female. QTc interval was significantly longer in the patient group than in the control group.[435 ms (IQR, 421–457) vs. 424 ms (IQR, 412–438), p=0.001]. The remaining ECG features, including P wave and QRS axes, were similar between the patient and control groups. There were no significant differences between the patients and control group regarding laboratory and echocardiography findings, including left ventricle global longitudinal strain.*

Conclusion: *According to our findings, individuals with SCH exhibited no change in myocardial mobility as measured by strain echocardiography. In addition, SCH may not cause significant ECG changes, except that these patients have a longer QTc interval than subjects with euthyroidism.*

Key words: *ECG; electrocardiogram; QRS axis; QTc interval; speckle-tracking echocardiography; subclinical hypothyroidism*

ÖZET

Amaç: *Subklinik hipotiroidi (SCH)'nin yüzeyel 12-lead'li elektrokardiyografi (EKG)'de yaptığı değişikler tam olarak açıklığa kavuşmamıştır. SCH ile EKG'deki P dalgası ve QRS eksenleri ve 2D speckle-tracking ekokardiyografi (2D-STE) ile incelenen kardiyak fonksiyonlar dâhil kardiyak elektromekanik arasındaki ilişkiyi araştırmayı amaçladık.*

Materyal ve Metot: *Bu kesitsel çalışmaya 10 Kasım 2018 ile 30 Ocak 2019 tarihleri arasında dâhiliye polikliniğine başvuran 109 SCH hastası dâhil edildi. Tüm hastaların başvuru anındaki EKG, 2D-STE görüntüleri ve laboratuvar bulguları kaydedildi. Bulgular, 74 sağlıklı yetişkinden oluşan cinsiyet ve yaş uyumlu kontrol grubuyla karşılaştırıldı.*

Bulgular: *Hastaların ortanca yaşı 41 (IQR, 34–50) yıl ve %76,1'i kadındı. QTc süresi hasta grubunda kontrol grubuna göre anlamlı olarak daha uzundu.[435 ms (IQR, 421–457) vs. 424 ms (IQR, 412–438), p=0,001]. P dalgası ve QRS eksenleri dâhil kalan EKG özellikleri hasta ve kontrol grupları arasında benzerdi. Sol ventrikül global longitudinal strain dâhil ekokardiyografi ve laboratuvar bulguları açısından hastalar ve kontrol grubu arasında anlamlı fark yoktu.*

Sonuç: *Çalışmamıza göre, 2D-STE ile incelendiğinde SCH hastalarının miyokard hareketinde değişiklik olmadığını görüldü. Ayrıca, bu hastaların ötiroid bireylerden daha uzun QTc süresine sahip olması dışında, önemli EKG değişikliklerine neden olmadığı ortaya kondu.*

Anahtar kelimeler: *subklinik hipotiroidi; EKG; elektrokardiyogram; speckle-tracking ekokardiyografi; QTc süresi; QRS aksı*

Introduction

Thyroid dysfunction, often observed in the general population, is closely linked with the cardiovascular system[1]. It influences the hemodynamics, cardiac mass, cardiac contractility, and autonomic cardiovascular system control via the thyroid hormone receptors, which are abundantly available in the heart[2]. Moreover, thyroid dysfunction has been widely associated with various cardiovascular disorders. It is linked with increased cardiovascular and all-cause mortality[3].

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Subclinical hypothyroidism (SCH) is characterized by elevated thyroid-stimulating hormone (TSH) without clinical alterations and with thyroxine (T4) and triiodothyronine (T3) levels within the normal range[4]. Subclinical hypothyroidism might affect up to 20% of the population, and rates vary depending on sex, age, iodine deficiency, and the TSH reference values used in each study[5,6].

12-lead surface electrocardiogram (ECG) provides crucial data related to cardiac functions[7]. The relationship between the QRS axis and many diseases such as hypertension,[8] sickle cell anemia,[9] chronic kidney disease (CKD),[10] pulmonary hypertension (PH),[11] and chronic obstructive pulmonary disease (COPD)[12] was widely revealed. Also, it was shown that an abnormal P-wave axis could be regarded as an indicator of clinical and subclinical atrial pathology, including atrial inflammation and fibrosis[13].

Thyroid disorders exert a significant impact on ECG. Reports suggest that thyroid dysfunction can lead to ECG changes and arrhythmias, including sinus bradycardia, atrioventricular blocks, atrial arrhythmias, prolonged QTc, and severe ventricular arrhythmias[3,14–16]. However, no study is available investigating the relationship between SCH and P wave and QRS axes; both could indicate some cardiac abnormalities. Thus, our purpose was to analyze the association of SCH with cardiac electromechanics, including P wave and QRS axes on ECG and cardiac functions with 2D speckle-tracking echocardiography (2D-STE). We hypothesized that SCH might alter the P wave and QRS axes on ECG.

Material and Method

Patients with SCH who presented to the internal disease outpatient clinic between November 10, 2018, and January 30, 2019, were included in this cross-sectional study. Patients withhistory of thyroid diseases, heart failure (left ventricle ejection fraction below 50%), acute coronary syndrome, renal failure (eGFR <30 ml/min/1.73 m^2), atrial fibrillation, severe cardiac valve disorders, renal failure (eGFR <30 ml/min/1.73 m^2), chronic obstructive pulmonary disease (COPD), and being under 18 years old were specified as exclusion criteria. Cases with erroneous or artifact ECG and inadequate echocardiographic images for STE analysis were also excluded.

Demographics, ECG, TTE, and laboratory findings at admission were recorded, including TSH, free T3, and T4. Electrocardiogram records were performed using Cardio-M Plus ECG device (medicalECONET GmbH, Im Erlengrund 20, D46149 Oberhausen, Germany). Electrocardiogram analysis was executed by a blinded cardiologist (M. K) using a standardized comprehensive ECG reading protocol[17]. It comprised intervals, rate, P wave, QRS axes and morphology, premature atrial and ventricular contract, and T-wave abnormalities. The corrected QT interval (QTc) was estimated using the Fridericia formula[18].

Echocardiographic images were acquired utilizing Philips Epiq7 (Philips Healthcare, Inc., Andover, MA, USA) and recorded by standard techniques per the guidelines from American Echocardiography Association[19]. For TTE, Left ventricular end-systole and end-diastolic diameters, left atrium diameter, interventricular septum thickness, left ventricular posterior wall thickness, and right atrium and ventricle diameters were recorded. Mitral valve peak early (E-wave) and late (A-wave) diastolic filling velocities were measured. E/A ratio was also calculated. Early diastolic mitral velocities peak early (E-wave) and late (A-wave) diastolic filling velocities from septal and lateral annulus (e') were calculated in the apical four-chamber view[20]. Left ventricular ejection fraction (LVEF) was calculated operating the modified Simpson's rule[21].

Left ventricular global longitudinal strain (LVGLS) was studied by an experienced cardiologist (D. I.), who was blinded to the study, using the Qlab13 (Philips Healthcare, Andover, Massachusetts) software. While the end-diastole is considered the peak R wave of the ECG, end-systole was evaluated as aortic valve closure. Left ventricular global longitudinal strain was estimated by averaging the peak longitudinal strain values of apical two-chamber, apical three-chamber, and apical four-chamber images. Automatic endocardial margins were detected at the end-systole. Manual modifications were made to ensure accurate tracking and fit left ventricle wall thickness when required. The speckle-tracking examination was conducted per the Consensus Document of the EACVI/ASE/Industry Task Force to Standardize right ventricle and LV myocardial Deformation Imaging[22,23].

Kafkas University Ethics Committee approved the study protocol (Date: January 30, 2019; Number 80576354–050–99/27)

Statistical Analysis

SPSS program (Version 20.0, SPSS, Inc., Chicago, IL, institutionally registered software) was utilized for statistical examination. The Kolmogorov– Smirnov test was conducted for the normality test. Continuous variables showing normal distribution were expressed as mean ± standard deviation. Variables with no normal distribution are represented as median (IQR).

Categorical variables were defined as a percentage. An independent t-test was used to analyze continuous data exhibiting normal distribution, Mann-Whitney U test was employed to examine variables not showing normal distribution. A p value of <0.05 was regarded as statistically significant.

Results

Demographic, laboratory, ECG, and TTE data of 119 patients were recorded. Ten cases were excluded due to exclusion criteria. The final patient group included 109 subjects [median age 41 (IQR, 34–50) years, 76.1% female]. Findings were compared with a sex and age-matched [median age 37 (IQR, 34–44) years, 68.9% female] healthy control group consisting of 74 adults. Baseline data of the study population are summarized in Table 1. Thyroid-stimulating hormone level was significantly higher in the patient group than in the Control group [5.32 (IQR, 4.98–7) vs. 2.25 (IQR, 1–3.1), p<0.001]. The levels of fT3 and fT4 were similar between the groups. Other laboratory results were similar, except for the C-reactive protein (CRP) level, which was within normal clinically (reference range, 0–5 mg/L) (Table 1).

There were no significant differences between the patients and the control group regarding demographic characteristics and comorbidities, including BMI, hypertension , diabetes (DM), smoking, and hyperlipidemia (HPL) (Table 1).

For ECG, the QTc interval was significantly higher in the patient group than in the control group.[435 (IQR, 421–457) vs. 424 (IQR, 412–438), p=0.001]. The remaining ECG features, including P wave and QRS axes, were similar between the patient and control groups (Table 2).

Regarding echocardiographic characteristics, all parameters, including left and right ventricular functions and left ventricle global longitudinal strain (LVGLS), were similar between the two groups (Table 2).

Discussion

This cross-sectional analysis of 109 patients found no association of SCH with cardiac electromechanics, which suggests no influence of SCH on axes, rhythm, conduction, and systolic and diastolic functions of the heart. The only association found was a longer QTc interval in SCH patients than in the control group.

The association of the QRS axis with diseases such as HT, sickle cell anemia, CKD, PH, and COPD was documented[8–12]. It has been suggested that the change in the axis of QRS is due to the change in the geometry of the heart. There is no study investigating the relationship between SCH and P wave and QRS axes. Our study demonstrated echocardiographically that the geometry of the heart and systolic and diastolic functions did not change in these patients. Moreover, QRS and P axis did not alter either, supporting this.

Previous reports speculated that hypothyroidism might cause PR, QRS, and QTc interval alterations[24,25]. It is yet unclear what changes SCH causes on the ECG. Some large-scale works announced conflicting data. According to a report including 132,707 participants, like our study, patients with SCH had significantly longer QTc interval than subjects with euthyroidism[25]. Another cross-sectional analysis of 13,341 individuals in a Brazilian cohort found no association of SCH with HR, rhythm alterations, or conduction disorders[26]. Further, considering the 11,795 ECGs analysis in the same study, no abnormality was associated with SCH, even in the subgroup of older adults or those with extreme TSH values.

Strain measurement using speckle-tracking echocardiography (STE) is a recently developed technique to assess cardiac function[27]. Compared with conventional echocardiography measurement, this method is a more sensitive, reliable, and reproducible modality for assessing left ventricle systolic function, particularly deducing subtle left ventricle dysfunction in the early stage of the diseases[28]. Although a few small-scale types of research showed impaired LVGLS in patients with SCH, the effect of SCH on the left ventricle has remained elusive[29,30]. We found no evidence of left ventricle dysfunction in the current research according to strain measurements and conventional TTE. This outcome showed that the impact of SCH on myocardial functions was below the limits detectable with strain measurements.

Thus, our study provided valuable data for the literature as it showed that SCH does not cause consequential deterioration of left ventricular systolic function.

The main limitations of the current study were as follows; 1) a relatively small number of patients in our study might represent a significant limitation. 2) Because this is an observational study, it is impossible to draw direct conclusions on causality regarding the findings. More studies with many patients in this field are required to reveal the relationship between SCH and cardiac electromechanics.

In conclusion, our study showed that patients with SCH had no change in myocardial movement determined by 2D-STE. In addition, SCH may not cause significant ECG changes, except that these patients have a longer QTc than subjects with euthyroidism.

Table 1. *Demographic, clinical and laboratory characteristics of the participants*

	Overall (n=183)	Patient (n=109)	Control (n=74)	P-value
Female sex, n (%)	134 (73.2)	83 (76.1)	51 (68.9)	0.278
Age (years), median [IQR]	39 [34–48]	41 [34–50]	37 [34–44]	0.113
BMI (kg/m^2) median [IQR]	26.5 [24–29.4]	27.2 [24–30]	26.2 [24–28.5]	0.351
Laboratory				
TSH (μU/mL), median [IQR]	4.85 [2.8–5.47]	5.32 [4.98–7]	2.25 [1–3.1]	**<0.001**
fT3 (ng/dl), median [IQR]	2.93 [2.48–3.2]	2.93 [2.48–3.13]	2.89 [2.48–3.2]	0.730
fT4(ng/dl), median [IQR]	1.3 [1–1.68]	1.32 [1.02–1.68]	1.3 [0.98–1.68]	0.933
Hgb (g/dL), median [IQR]	14.2 [13.5–15.2]	14.2 [13.5–15]	14.35 [13.5–15.3]	0.237
WBC (× 103/μL), median [IQR]	7.1 [6.1–8.19]	7.1 [6.15–8.21]	7.17 [6.1–8.12]	0.980
Lymphocyte (× 103/μL), median [IQR]	2.26 [1.89–2.71]	2.28 [1.85–2.73]	2.24 [1.9–2.7]	0.825
Neutrophil (× 103/μL), median [IQR]	4.2 [3.44–4.9]	4.38 [3.5–4.8]	4.11 [3.44–4.96]	0.751
PLT (× 103/μL), median [IQR]	275 [250–304]	285 [244–321]	269 [256–292]	0.143
Glucose mg/dL median [IQR]	90 [86–98]	91 [87–98]	89 [85–96]	0.198
AST	20 [17–23]	20 [17–23]	20 [17–24]	0.537
ALT	20 [16–26]	19 [16–26]	21 [17–26]	0.601
Creatinine (mg/dL), mean ± SD	0.75 [0.65–0.85]	0.7 [0.65–0.85]	0.78 [0.63–0.9]	0.286
CRP (mg/L), median [IQR]	2.8 [1.04–4.0]	3 [1.57–4.2]	2.3 [0.84–4]	**0.006**
Comorbidities				
Hypertension, n (%)	26 (14.2)	19 (17.4)	7 (9.5)	0.130
Diabetes, n (%)	17 (9.3)	11 (10.1)	6 (8.1)	0.650
Smoking, n (%)	34 (18.6)	17 (15.6)	17 (23)	0.208
Hyperlipidemia, n (%)	16 (8.7)	13 (11.9)	3 (4.1)	0.064

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CRP: C-reactive protein; fT3: free thyroxine 3; fT4: free thyroxine 4; Hgb: hemoglobin; PLT: platelet; WBC: white blood count

Table 2. *Electrocardiographic and echocardiographic characteristics of the participants*

	Overall (n=183)	Patient (n=109)	Control (n=74)	P-value
Electrocardiogram features				
Heart rate (b.p.m), median [IQR]	75 [71–84]	78 [72–85]	75 [70–80]	0.132
P wave axis (°), median [IQR]	50 [19–58]	49 [20–58]	50 [19–58]	0.995
QRS axis (°), median [IQR]	50 [28–73]	46 [28–73]	53 [28–73]	0.653
PR interval (msec) median [IQR]	144 [132–158]	144 [130–156]	144 [132–160]	0.497
QRS interval (msec) median [IQR]	92 [88–100]	90 [88–8]	94 [88–100]	0.063
QTc (msec), median [IQR]	430 [416–448]	435 [421–457)	424 [412–438]	**0.001**
T-wave change, n (%)	11 (6)	5 (4.6)	6 (8.1)	0.325
fragmented QRS, n (%)	12 (6.6)	5 (4.6)	7 (9.5)	0.191
Premature atrial/ventricular contraction, n (%)	6 (3.3)	3 (2.8)	3 (4.1)	0.627
Echocardiography features				
LVDD (mm), median [IQR]	46 [44–48]	46 [44–48]	46 [44–48]	0.860
LVSD (mm), median [IQR]	30 [28–34]	30 [28–34]	30.5 [28–34]	0.522
IVS (mm), median [IQR]	8 [8–9]	8 [8–9]	8.5 [8–9]	0.502
PW (mm), median [IQR]	8 [7–8]	7.5 [7–8]	8 [7–8]	0.207
LA (mm), median [IQR]	32 [30–34]	32 [30–34]	32 [30–34]	0.656
RV (mm), median [IQR]	32 [30–34]	32 [30–34]	32 [29–34]	0.402
RA (mm), median [IQR]	32 [31–35]	32 [31–35]	33 [31–36]	0.384
Ejection Fraction (%), median [IQR]	65 [61–67]	65 [60–66]	65 [62–68]	0.365
E/A, median [IQR]	1.2 [1–1.4]	1.14 [0.9–1.4]	1.2 [1.1–1.4]	0.158
E/E', median [IQR]	6.3 [5.3–7.6]	6.23 [5.25–7.08]	6.55 [5.6–8.2]	0.140
TAPSE, median [IQR]	21 [20–23]	21 [20–23]	21 [20–22]	0.216
R', median [IQR]	12.8 [12.1–13.8]	12.8 [12.3–13.6]	12.8 [12–14.3]	0.875
PASB, median [IQR]	9 [8–12]	9 [8–12]	8 [8–12]	0.428
LVGLS, median [IQR]	-20.1 [-21.7- -18.1]	-20.5 [-21.8– -17.9]	-19.7 [-21.7– -18.9]	0.651

A: late diastolic filling mitral velocity; E: early diastolic filling mitral velocity; LVDD: left ventricle end-diastolic diameter; LVSD left ventricle end-systolic diameter; IVS: interventricular septum thickness; LA: left atrium diameter; PASP: pulmonary arterial systolic pressure; PW: left ventricular posterior wall thickness; QTc: Corrected QT; RV: right ventricle diameter; RA: right atrium diameter; TAPSE: tricuspid annular plane systolic excursion; LVGLS: left ventricle global longitudinal strain; E': the peak early diastolic velocity of the septal mitral annulus (tissue Doppler);

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