

Investigation of the relationship of frontal QRS-T angle and digoxin use and blood digoxin level

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ABSTRACT

Objectives: Digoxin is an antiarrhythmic drug with a narrow therapeutic range and used in clinical conditions such as heart failure and atrial fibrillation. The planar frontal QRS-T angle reflects the deviations between the depolarization and repolarization of the ventricles, and it has been reported that an increase in this angle is associated with an increase in mortality. In our study, the relationship between frontal QRS-T angle and digoxin use and blood digoxin level was investigated.

Methods: The study included 105 digoxin users who used digoxin, whose levels were measured, who had an electrocardiogram (ECG) on the system, and 15 patients with similar characteristics, who had an ECG and did not use digoxin. Patients using digoxin and whose levels were measured were also divided into three groups as < 0.8 ng/mL, $0.8-1.2$ ng/mL, and > 1.2 ng/mL. The absolute value of the value obtained by subtracting the axis of the T wave from the axis of the QRS angle indicated on the paper, calculated automatically on the 12-lead ECG, was accepted as the frontal QRS-T angle value.

Results: Planar frontal QRS-T angle measured by 12-lead ECG in digoxin users was 120° ($55.5^\circ-155.5^\circ$), while it was 106° ($32^\circ-163^\circ$) in non-users, and there was no statistical difference between the two groups ($p = 0.833$). In the evaluation made according to different blood drug levels as < 0.8 ng/mL, $0.8-1.2$ ng/mL, > 1.2 ng/mL in digoxin users, no significant difference was observed between the frontal QRS-T angle between the groups (109.5° [$60.25^\circ-154.25^\circ$] for < 0.8 ng/mL, 136.5° [$48.5^\circ-158.5^\circ$] for $0.8-1.2$ ng/mL, 117° [$34^\circ-154^\circ$] for 1.2 ng/mL) ($p = 0.773$)

Conclusions: There was no significant difference in frontal QRS-T angle between digoxin users and non-users. There was no significant relationship between different blood digoxin levels and frontal QRS-T angle.

Keywords: Frontal QRS-T angle, digoxin, digoxin level, intoxication, electrocardiogram

Digoxin is an antiarrhythmic drug with positive inotropic, negative dromotropic, and chronotropic effects, used in the treatment of heart failure (HF), atrial fibrillation (AF), supraventricular tachycardia. The therapeutic range is narrow and in some cases measurement of its level may be required. Moreover, the serum drug level may reach high levels and cause intoxication. In clinical practice, measurement of

blood level is not always possible due to reasons such as laboratory conditions in the center and patient-related factors.

Planar frontal QRS-T angle can be defined as the absolute value of the number obtained by subtracting the QRS complex axis and the T wave axis, which can be calculated by superficial 12-lead electrocardiogram (ECG) [1]. The planar frontal QRS-T angle reflects

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the deviations between depolarization and repolarization of the ventricles, and an increase in this angle has been reported to be associated with increased mortality [2].

Although the effects of digoxin on the ECG have been clearly defined, its effects on the frontal QRS-T angle and the relationship between this value and the blood level have not been adequately studied. In our study, we aimed to investigate the relationship between blood digoxin level and frontal QRS-T angle.

METHODS

Study Population

This study was designed as a single-center retrospective study. A total of 400 patients who were referred to Bursa City Hospital between July 2019 and February 2022, who received oral or intravenous digoxin due to heart failure and AF, and whose blood digoxin levels were studied have been evaluated. Patients with blood digoxin levels in the system but no ECG and those with bundle branch block and pre-excitation pattern on the basal ECG and individuals under the age of 18 years were excluded from the study. Finally, 105 patients were included in the study. 15 patients with similar patient characteristics but not using digoxin were also comprised in the control group. The necessary eligibility decision was taken from the Clinical Research Ethics Committee of Bursa City Hospital (decision no: 2022-4/2). The study was conducted by the Helsinki Declaration principles.

Laboratory Evaluation

Serum digoxin levels, which were evaluated by the homogeneous immunoassay method, were recorded. Complete blood count, liver and kidney function tests, electrolytes, lipid profile, and thyroid function tests determined from the samples taken during the same period were also noted.

Electrocardiography and Echocardiography

On the day the digoxin level was studied, 12-lead surface ECG (GE Healthcare, MAC 2000 ECG System, 2063587-001) was taken in supine position at 25 mm/s paper speed and 10 mm/s voltage was evaluated. ECGs, which were transferred to personal computers afterward and magnified by 300%, were examined

under the Adobe Acrobat DC program. The QT interval was measured as the time from the beginning of the QRS complex to the end of the T wave. The corrected QT interval was calculated with Bazett's formula in patients with sinus rhythm. In AF patients, the corrected QT interval was determined by averaging 10 beats using the Bazett formula. The planar frontal QRS-T axis was found by taking the absolute value of the difference between the automatically calculated QRS complex axis and the T wave axis on the superficial 12-lead ECG. If this value was above 180, the number found by subtracting 360 was accepted as the frontal QRS-T axis.

Echocardiograms of the patients recorded in the system during the period in which digoxin levels were measured were examined. Left ventricular ejection fraction calculated using the modified Simpson method was recorded.

Other Parameters

The age and gender data of the patients were noted. Concomitant diseases such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and heart failure (HF), which required continuous drug use were detected. If there is heart failure, its etiology (ischemic/nonischemic) and NYHA class were determined. If AF was present on ECG, whether it was valvular or non-valvular and EHRA class was determined. In addition, if there are drugs used concomitantly with digoxin, it was recorded.

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the normality of the data. Normally distributed variables were expressed as mean \pm standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). The categorical variables are presented as percentages. The Chi-square test was used to assess differences in categorical variables between groups. Student's t-test or Mann Whitney U test was used to compare unpaired samples as needed. The relationships among parameters were assessed using Pearson's or Spearman's cor-

Table 1. Clinical demographic characteristics of patients in digoxin users and non-users

	Using digoxin (n = 105)	Not using digoxin (n = 15)	p value
Clinical characteristics			
Age (years)	72 ± 14.1	48.4 ± 14.0	0.292
Male, n (%)	41 (39)	8 (53.3)	0.292
HT, n (%)	58 (55.2)	12 (80)	0.069
DM, n (%)	41 (39)	4 (26.7)	0.408
HL, n (%)	1 (3.8)	0 (0)	0.582
CABG, n (%)	12 (11.5)	2 (13.3)	0.690
PCI, n (%)	17 (16.3)	6 (40)	0.03
CKD, n (%)	29 (27.6)	2 (13.3)	0.349
AF (non valvular), n (%)	69 (71.9)	13 (86.7)	0.225
HF, n (%)			
Ischemic	23 (26.4)	7 (46.7)	0.112
Nonischemic	43 (49.4)	8 (53.3)	0.780
Digoxin intoxication, n (%)	15 (14.3)	0 (0)	0.211
NYHA class	2.37 ± 0.94	2.4 ± 0.6	0.912
EHRA class	2.33 ± 0.9	2.2 ± 0.68	0.602
LVEF, (%)	43.8 ± 13.2	41 ± 12	0.443
Laboratory findings			
Hgb, g/dL	11.9 ± 2	12.4 ± 2.5	0.43
WBC, ×10 ³	9.6 ± 3.9	7 ± 2.2	0.022
PLT, ×10 ³	263 ± 125.7	220 ± 99	0.222
Urea, mg/dL	45 (31-70)	35 (29-52)	0.258
Creatinin, mg/dL	1 (0.8-1.4)	1 (0.9-1.4)	0.653
GFR (mL/min/1.73 m ²)	59.7 ± 26.7	57.4 ± 26.3	0.771
Na, mEq/L	137.3 ± 6.4	138.1 ± 3.2	0.64
K, mEq/L	4.3 ± 0.6	4.6 ± 0.5	0.176
Ca, mg/dL	9 ± 0.7	9 ± 0.4	0.794
TC, mg/dL	164.8 ± 5	133.7 ± 34.4	0.6
LDL, mg/dL	97 ± 39	79 ± 27.7	0.159
HDL, mg/dL	40.6 ± 12.2	40.5 ± 17.2	0.972
TG, mg/dL	126.5 (97.2-194.5)	73 (61.2-131)	0.017
AST, IU/L	20 (16-30)	23 (15-37)	0.762
ALT, IU/L	16 (12-24)	13 (11-22)	0.489
INR	1.3 (1.1-1.9)	1.1 (1.1-1.3)	0.192
TSH, mIU/L	1.4 (0.8-2.6)	1.1 (1.6-2.1)	0.723
Blood digoxin level, ng/mL	1.11 (0.7-1.7)	-	< 0.001
Concomitant medications			
ASA	23 (22.8)	4 (26.7)	0.739
Clopidogrel	12 (18)	3 (20)	0.407
Ticagrelor	1 (1)	0 (0)	1.000
Warfarin	27 (26.5)	0 (0)	0.021
NOAC	49 (48)	11 (73.3)	0.067
ACEi	45 (44.1)	8 (53.3)	0.584
ARB	12 (11.8)	0 (0)	0.359
BB	71 (69.6)	9 (60)	0.455
CCB	32 (31.4)	2 (13.3)	0.225
MRA	46 (45.1)	7 (46.7)	0.909
ARNI	4 (3.9)	0 (0)	0.503
Ivabradine	4 (3.9)	0 (0)	0.435
Amiodaron	12 (11.8)	2 (13.3)	0.861
SGLT-2i	6 (5.9)	0 (0)	0.335
Furosemide	77 (71.6)	9 (64.3)	0.548
Thiazide	27 (26.5)	3 (20)	0.757
Statin	14 (13.7)	2 (13.3)	0.967

Data are shown as mean ± standard deviation or n (%) or mean (minimum-maximum). HT = hypertension, DM = diabetes mellitus, HL = hyperlipidemia, CABG = coronary artery by-pass grafting, PCI = percutaneous coronary intervention, CKD = chronic kidney disease, AF = atrial fibrillation, HF = heart failure, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, EHRA = European Heart Rhythm Association, Hgb = haemoglobin, WBC = white blood cell, PLT = platelet, GFR = glomerular filtration rate, TC = total cholesterol, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglyceride, AST = aspartate aminotransferase, ALT = alanine aminotransferase, INR = international normalized ratio, TSH = thyroid stimulating hormone, ASA = acetylsalicylic acid, NOAC = novel oral anticoagulants, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist, ARNI = angiotensin receptor neprilysin inhibitor, BB = beta-blocker, CCB = calcium channel blocker, SGLT2i = sodium/glucose cotransporter-2 inhibitors

relation analysis according to the normality of the data. The significance of the difference between digoxin levels groups was evaluated using one-way ANOVA followed by Bonferroni corrected post-hoc test for normally distributed numerical parameters. Parameters that did not show normal distribution were evaluated with the Kruskal–Wallis test, and the significance between the groups was determined using the Mann–Whitney U test pairwise comparison. The significance of differences between groups for ordinal parameters was assessed by using the chi-square test. Significance was assumed at a 2-sided $p < 0.05$.

RESULTS

The clinical and demographic characteristics of the patients who used and did not use digoxin in the study are shown in Table 1. While the mean age of individuals using digoxin was 72 ± 14.1 years, it was 48.4 ± 14.0 years in those who did not use digoxin. The male sex ratio was 39% in the digoxin group. This rate was 53.3% in the group that did not use digoxin. The rate of percutaneous coronary intervention history was higher in the group that did not use digoxin. In addition, there was no statistical difference between the group's HT, DM, HL, CABG, CKD, non-valvular AF, HF. Also EHRA, NYHA class, and LVEF were similar. When the laboratory parameters were examined, no difference was found between the two groups, except that the triglyceride and WBC value was statistically higher in the group using digoxin. There was no statistical difference between the two groups in terms of drugs used other than digoxin.

The electrocardiographic findings of the patients

are given in Table 2. The corrected QRS duration was detected to be longer in the group that did not use digoxin than in those who used it. Other measurements were similar.

The clinical, demographic and electrocardiographic findings of individuals using digoxin according to blood digoxin levels are given in Table 3. The mean age was higher in the group with blood digoxin level >1.2 ng/mL than in the group with < 0.8 ng/mL (76.2 ± 11.2 years vs. 69.4 ± 13 years, $p = 0.029$). The frequency of CKD was statistically higher in the > 1.2 ng/mL group than in the other groups (16.7% for < 0.8 ng/mL, 17.9% for 0.8-1.2 ng/mL, and 40.4% for > 1.2 ng/mL, $p = 0.03$). EHRA class was statistically higher in the > 1.2 ng/mL group compared to the < 0.8 ng/mL group (2.6 ± 0.9 vs. 2 ± 0.6 , $p = 0.024$). In electrocardiographic findings the mean heart rate was found to be significantly higher in the < 0.8 ng/mL group than in the >1.2 ng/mL group (94.8 ± 27 beats/min vs. 71 ± 22.6 beats/min, $p = < 0.001$). While the QRS duration was shorter in the <0.8 ng/mL group compared to the other groups ($p = 0.033$), the QT interval was longer in the >1.2 ng/mL group than in the < 0.8 ng/mL group ($p = 0.031$). The QTc interval was longer in the 0.8-1.2 ng/mL group than in the >1.2 ng/mL group ($p = 0.046$). Urea, creatinine and GFR values, which indicate kidney functions in laboratory parameters, were statistically higher in the >1.2 ng/mL group (61.4 mg/dL, $p = < 0.009$; 1.17 mg/dL, $p = < 0.003$; 48.4 ± 23.1 mL/min/1.73 m², $p = < 0.001$, respectively). There is no significant difference in other laboratory parameters. No significant difference was observed in the drugs used, except that amiodarone was used more in the 0.8-1.2 group than in the other groups (3.4%, 25.9% and 8.7%, respectively) ($p =$

Table 2. Comparison of ECG findings of groups using and not using digoxin

	Using digoxin (n = 105)	Not using digoxin (n = 15)	<i>p</i> value
Mean HR, beat/min	82.40 ± 25.8	88.73 ± 23.5	0.372
QRS duration, ms	101.06 ± 25.5	99.4 ± 29.3	0.818
QT, ms	378.42 ± 67.8	384.93 ± 84.7	0.737
QTc, ms	426.3 ± 46.7	461.8 ± 58.6	0.009
Frontal QRS-T Axis	120 (55.5-155.5)	106 (32-163)	0.833

Data are shown as mean±standard deviation or mean (minimum-maximum). HR = heart rate, ECG = electrocardiogram, min = minute, ms = milliseconds

Table 3. Demographic and ECG characteristics of patients using digoxin according to their blood levels

	< 0.8 ng/mL (n = 30)	0.8-1.2 ng/mL (n = 28)	> 1.2 ng/ml (n = 47)	p value
Clinical characteristics				
Age (years)	69.4 ± 13 ^a	70.8 ± 11	76.2 ± 11.2 ^a	0.029
Male, n (%)	12 (40)	8 (28.6)	21 (44.7)	0.381
HT, n (%)	17 (56.7)	19 (67.9)	22 (46.8)	0.204
DM, n (%)	14 (46.7)	14 (50)	13 (27.7)	0.095
HL, n (%)	0 (0)	3 (10.7)	1 (2.1)	0.075
CABG, n (%)	2 (6.7)	6 (21.4)	4 (8.7)	0.154
PCI, n (%)	6 (20)	4 (14.3)	7 (15.2)	0.809
CKD, n (%)	5 (16.7)	5 (17.9)	19 (40.4)	0.03
AF (non valvular), n (%)	23 (85.2)	16 (64)	30 (68.2)	0.180
HF, n (%)				
Ischemic	9 (37.5)	7 (28)	7 (18.4)	0.247
Nonischemic	11 (45.8)	13 (52)	19 (50)	0.907
NYHA class	2.1 ± 0.9	2.4 ± 1	2.5 ± 0.8	0.197
EHRA class	2 ± 0.6 ^a	2.2 ± 0.9	2.6 ± 0.9 ^a	0.024
LVEF, (%)	48.2 ± 12.2	40.5 ± 14	42.6 ± 13	0.09
ECG findings				
Mean HR, beat/min	94.8 ± 27 ^a	87.8 ± 22.1	71 ± 22.6 ^a	< 0.001
QRS duration, ms	90.9 ± 19.9	106.3 ± 27.1	104.5 ± 26.4	0.033
QT, ms	354 ± 69.3 ^a	376 ± 47.5	395 ± 73 ^a	0.031
QTc, ms	426.4 ± 42.4	443.9 ± 40.4*	415.9 ± 51*	0.046
Frontal QRS-T Axis	109.5 (60.25-154.25)	136.5 (48.5-158.5)	117 (34-154)	0.773
Laboratory findings				
Hgb, g/dL	12.3 ± 2.4	12 ± 1.8	11.8 ± 2.0	0.526
WBC, ×10 ³	8.9 ± 3.9	9.9 ± 4	9.9 ± 3.9	0.569
PLT, ×10 ³	257 ± 104.5	286 ± 126	254 ± 138.1	0.53
Urea, mg/dL	38 (30-55.25)	34.4 (28.5-55.1)	61.4 (39.75-82)	0.009
Creatinin, mg/dL	0.92 (0.74-1.2)	0.98 (0.62-1.8)	1.17 (0.96-1.95)	0.003
GFR (mL/min/1.73 m ²)	69.2 ± 26.5	68.2 ± 26.2	48.4 ± 23.1	< 0.001
Na, mEq/L	138.8 ± 4.5	137 ± 9.3	136.5 ± 5.2	0.296
K, mEq/L	4.3 ± 0.6	4.3 ± 0.5	4.4 ± 0.6	0.687
Ca, mg/dL	9 ± 0.6	9.2 ± 0.7	8.9 ± 0.7	0.066
TC, mg/dL	174 ± 49	176.2 ± 63.9	151.1 ± 37.6	0.107
LDL, mg/dl	105.2 ± 37.1	106.7 ± 48.2	85.4 ± 30.4	0.062
HDL, mg/dL	43 ± 11.7	40 ± 13.2	39.6 ± 12	0.596
TG, mg/dL	140 (111-189.5)	171 (87-249)	120 (92-165)	0.153
AST, IU/L	21 (17-28)	18.5 (15-24)	21 (17-32)	0.351
ALT, IU/L	16 (12-22.75)	19 (13.5-24.5)	16 (9-25)	0.449
INR	1.28 (1.1-1.8)	1.26 (1.14-2)	1.2 (1.1-2.1)	0.924
TSH, mIU/L	1.49 (0.8-2.4)	1.6 (0.84-2.9)	1.26 (0.54-2)	0.36
Blood digoxin level, ng/mL	0.5 (0.31-0.7)	1 (0.89-1.1)	1.95 (1.54-2.84)	< 0.001
Concomitant medications				
ASA	3 (10.3)	8 (30.8)	12 (26.1)	0.151
Clopidogrel	5 (17.2)	3 (11.1)	4 (8.7)	0.531
Ticagrelor	1 (3.4)	0	0	0.281
Warfarin	8 (27.6)	7 (25.9)	12 (26.1)	0.987
NOAC	15 (51.7)	12 (44.4)	22 (47.8)	0.861
ACEi	15 (51.7)	13 (48.1)	17 (37)	0.403
ARB	3 (10.3)	4 (14.8)	5 (10.9)	0.846
BB	18 (62.1)	23 (85.2)	30 (65.2)	0.117
CCB	13 (44.8)	5 (18.5)	14 (30.4)	0.104
MRA	12 (41.4)	15 (55.6)	19 (41.3)	0.444
ARNI	0 (0)	2 (7.4)	2 (4.3)	0.354
Ivabradine	1 (3.4)	2 (7.4)	1 (2.2)	0.532
Amiodaron	1 (3.4)	7 (25.9)	4 (8.7)	0.023
SGLT-2i	1 (3.4)	3 (11.1)	2 (4.3)	0.399
Furosemide	18 (62.1)	21 (77.8)	34 (73.9)	0.383
Thiazide	10 (34.5)	6 (22.2)	11 (23.9)	0.506
Statin	5 (17.2)	3 (11.1)	6 (13)	0.788

Data are shown as mean±standard deviation or n (%) or mean (minimum-maximum). HT = hypertension, DM = diabetes mellitus, HL = hyperlipidemia, CABG = coronary artery by-pass grefting, PCI = percutaneous coronary intervention, CKD = chronic kidney disease, AF = atrial fibrillation, HF = heart failure, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, EHRA = European Heart Rhythm Association, Hgb = haemoglobin, WBC = white blood cell, PLT = platelet, GFR = glomerular filtration rate, TC = total cholesterol, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglyceride, AST = aspartate aminotransferase, ALT = alanine aminotransferase, INR = international normalized ratio, TSH = thyroid stimulating hormone, ASA = acetylsalicylic acid, NOAC = novel oral anticoagulants, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist, ARNI = angiotensin receptor neprilysin inhibitor, BB = beta-blocker, CCB = calcium channel blocker, SGLT2i = sodium/glucose cotransporter-2 inhibitors, HR = heart rate, ECG = electrocardiogram, min = minute, ms = milisecond

^ap < 0.05 between <0.8 ng/mL and < 1.2 ng/mL groups, *p < 0.05 between 0.8-1.2 ng/mL and > 1.2 ng/mL groups

0.023).

Consequently, when the results of the study were evaluated, there was no statistically significant difference in frontal QRS-T angle in digoxin users compared to non-users (120° [55.5° - 155.5°] vs. 106° [32° - 163°]), ($p = 0.833$). In addition, there was no sta-

tistical significance between blood level and frontal QRS-T angle in digoxin users (109.5° [60.25° - 154.25°] for < 0.8 ng/mL, 136.5° [48.5° - 158.5°] for 0.8 - 1.2 ng/mL, 117° [34° - 154°] for 1.2 ng/mL) ($p = 0.773$) (Figs. 1, 2 and 3).

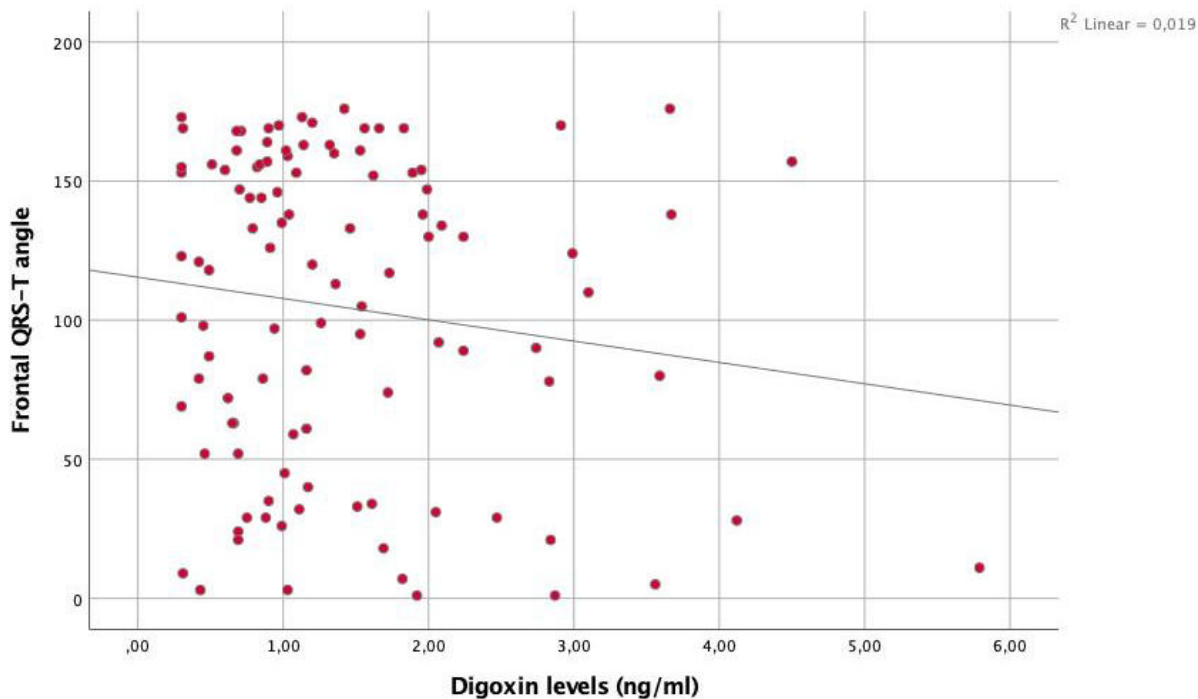


Fig. 1. Graphical representation of the relationship between digoxin level and frontal QRS-T angle.

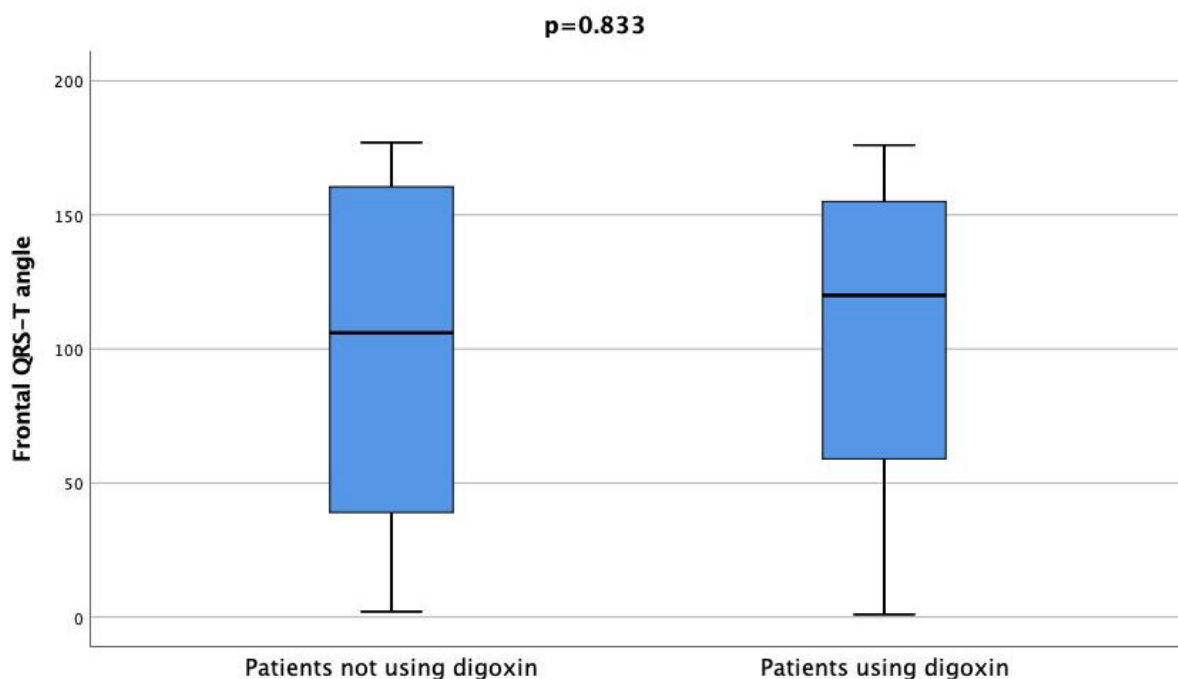


Fig. 2. Frontal QRS-T angle in digoxin and non-digoxin users.

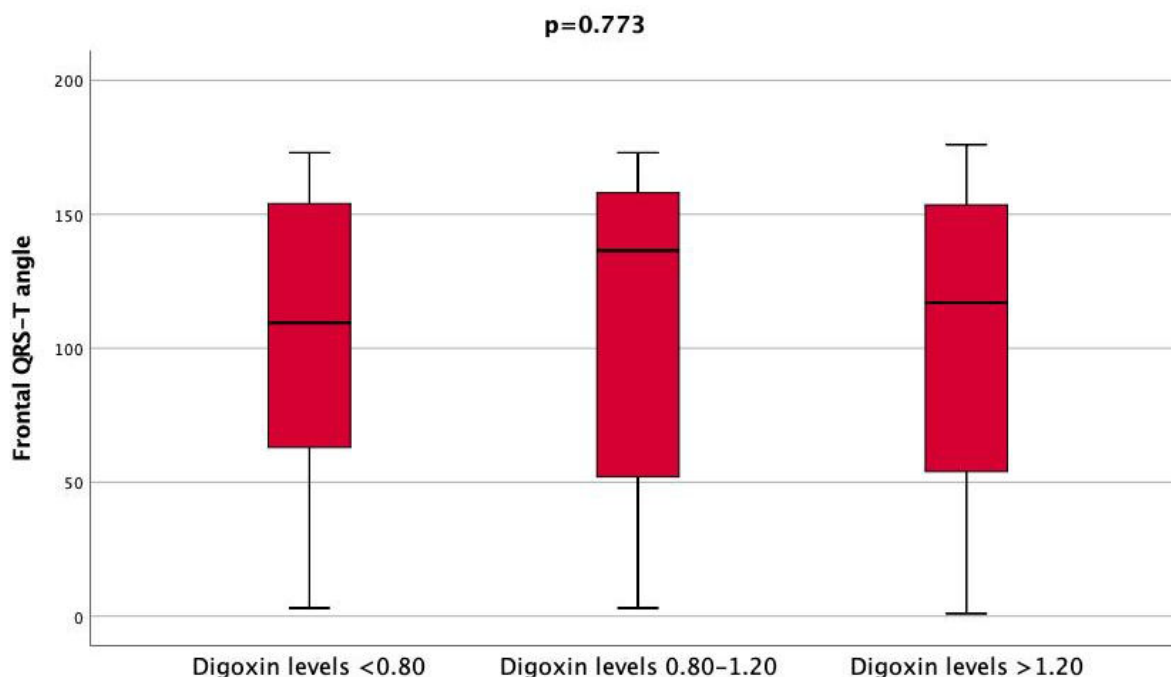


Fig. 3. Frontal QRS-T angle according to blood digoxin levels.

DISCUSSION

In our study, no significant relationship was found between frontal QRS-T angle and serum digoxin levels. Also, there was no significant relationship between drug blood levels and frontal QRS-T angle values in individuals using digoxin.

The spatial QRS-T angle can be defined as the angle between ventricular depolarization and repolarization directions and has been shown to predict cardiac death in various studies [3]. However, the spatial QRS-T angle is difficult to measure in clinical practice and requires computer-assisted electrocardiographic analysis software [4]. On the contrary, the frontal QRS-T axis is a parameter that can be obtained from a superficial 12-lead electrocardiogram (ECG) and easily calculated from automatically calculated measurements on the ECG paper and correlates well with the spatial QRS-T wave [5]. We preferred to calculate the planar frontal QRS-T angle, which we considered a more practical method in our study. Various studies have suggested different numbers regarding the cut-off values of the frontal QRS-T angle. In one study, in patients with ischemic heart disease and ICD, those with a spatial QRS-T angle less than 100° , no ventricular arrhythmia event was observed at 2-year follow-up, and its frequency was only 2% during subsequent

follow-up [6]. In another study involving the middle-aged general population, a frontal QRS-T angle of $\geq 100^\circ$ was found to increase the risk of arrhythmic death [3]. It has been stated that a wide QRS-T angle reflects structural abnormalities that affect depolarization or regional pathophysiological changes in ionic channels that change the repolarization order [3]. In our study, the frontal QRS-T angle was found to be above 100 degrees in both digoxin users and non-users, and those who used digoxin and had different blood levels. The lack of difference in frontal QRS-T angle in digoxin users may be associated with the presence of clinical conditions such as concomitant hypertension, diabetes mellitus, coronary artery disease, and the use of beta-blockers, amiodarone, and similar antiarrhythmic drugs. Therefore, the effect of digoxin on frontal QRS-T angle may not have been observed.

Digoxin is a drug with negative chronotropic and dromotropic, positive inotropic effects. It also inhibits the sodium-potassium pump (-ATPase) Na^+/K^+ , increasing the availability of calcium for contractile components or myofibrils. Digoxin increases cardiac vagal activity. The inhibition of the Na-K ATPase pump increases the intracellular Na^+ concentration and facilitates the entry of Ca^{2+} into the cell, thereby increasing cardiac inotropy [7-9]. In other words, cardiac action potential duration will be shortened in the

ventricles, and excitation-contraction coupling in the sarcomere will result in negative chronotropism and positive inotropism due to increased intracellular calcium [10]. In case of intoxication, it acts on phase 4 of the action potential [11], leading to delayed after-depolarization and increased automaticity and/or ectopic activity. As a result, atrial and ventricular tachyarrhythmias may occur [12]. The 'reverse tic' pattern in V4-V6 is the most commonly identified ECG change and can, in fact, be described as the appearance of a biphasic T wave with initial negative and terminal positive bias. These changes are due to its effect in reducing the ventricular refractory period and cause secondary repolarization abnormalities affecting the ST segment, T and U wave. As a result, the QT interval can be detected as shortened [13]. Therefore, it can be thought that the frontal QRS-T angle, which can be defined as an indicator of heterogeneity between ventricular depolarization and repolarization [14, 15], may be abnormal in digoxin users. In our study, no statistically significant difference was found between the control group and the group using digoxin in terms of frontal QRS-T. In addition, the corrected QT interval was found to be significantly longer in the group using digoxin compared to those not using digoxin, but it was within normal limits. In the evaluation made according to digoxin level, the corrected QT interval was longer in the 0.8-1.2 ng/mL group than in the > 1.2 ng/mL group. Also, the QT interval was found to be longer in the digoxin level > 1.2 ng/mL group compared to the < 0.8 ng/mL group.

In a randomized, double-blind DIG study with 6800 patients with ejection fraction < 45%, in normal sinus rhythm were divided into 2 groups with and without digoxin. As a result of approximately 40 months of follow-up, there was no decrease in total mortality, but a statistically significant decrease was found in hospitalization. In addition, there was a trend for a lower risk of death due to worsening heart failure in the digoxin group compared with the placebo group [16]. In a retrospective cohort study of patients with AF, the use of digoxin was associated with an increased risk of mortality after multivariate adjustment [17]. In a subanalysis of the AFFIRM trial, which included more than 4000 AF patients at high risk of stroke, digoxin was associated with a significant increase in mortality even after controlling for comorbidities and trend scores, regardless of gender and the presence or ab-

sence of underlying HF [18]. In another study, patients with a serum digoxin concentration ≥ 1.2 ng/mL had a 56% increased risk of mortality (adjusted HR: 1.56; 95% CI: 1.20 to 2.04) compared to those not using digoxin. When analyzed as a continuous variable, it was associated with a 19% higher adjusted hazard of death for each 0.5 ng/mL increase in serum digoxin ($p = 0.0010$) [19]. For patient safety, it has been suggested that target serum concentrations of 0.5-0.9 ng/mL, which is below the "therapeutic" range [10]. According to one study, a serum digoxin concentration of 0.5-0.9 ng/mL reduces mortality and hospitalizations in all heart failure patients, including those with preserved systolic function and high blood digoxin levels. Digoxin reduces hospitalization for heart failure, but has no effect on mortality or all-cause hospitalization. Higher blood digoxin levels were associated with increased crude all-cause mortality in patients with heart failure (0.5-0.8 ng/mL, 29.9%; 0.9-1.1 ng/mL, 38.8%, and ≥ 1.2 ng/mL, 48.0%) [20, 21]. The patient population in our study included patients with ischemic-non-ischemic heart failure and heart failure with preserved-low EF. There was no significant difference in the frontal QRS-T angles of the patients who were divided into 3 groups according to their blood digoxin levels, as < 0.8 ng/mL, 0.8-1.2 ng/mL, and > 1.2 ng/mL. In addition, there was no significant finding to predict serum digoxin levels in terms of frontal QRS-T.

In one study, it was shown that the frontal QRS-T angle remained stable until middle age, and then showed a rapid increase with a straight-line correlation [22]. In our study, no significant age-related difference was observed in the frontal QRS-T angle between the control group and digoxin group, and between the groups using digoxin. This may be related to the fact that various comorbidities and antiarrhythmic drugs affected the frontal QRS-T angle value, although there were differences in age between the control group and the groups using digoxin.

Digoxin is mostly eliminated unchanged by the kidneys. 30-50% of the daily dose is excreted within 24 hours, and enterohepatic circulation is negligible [23]. The elimination half-life is 1.5-2 days, but may be prolonged up to 4-6 days in anuric patients [21, 24, 25]. There is also an increased risk of overall mortality with digoxin therapy in end-stage renal disease requiring hemodialysis, again with the safest serum levels

<0.9 ng/mL [10, 26]. In our study, significant impairment in kidney functions (creatinine, urea, and GFR) in the group with blood levels > 1.2 ng/mL may also be associated with the decrease in digoxin renal clearance.

Limitations

There are several limitations to our study. First, the number of patients included in the study is limited. In addition, the number of patients in the control group was insufficient, although clinical and demographic characteristics were similar in both groups. Different results may be obtained with studies to be conducted in larger populations. Secondly, drugs used together with digoxin, some of which are antiarrhythmic, may have caused different values in frontal QRS-T angle. The third is the use of planar frontal QRS-T angle instead of the spatial frontal QRS-T angle, which is stated to be superior in some publications. Finally, studies involving the values and comparisons obtained before and after a certain period of starting the drug in cases where digoxin is planned to be used may reveal different results.

CONCLUSION

In our study, no significant difference was found in frontal QRS-T angles in digoxin users compared to non-users. In the evaluation of frontal QRS-T angles according to blood digoxin levels, no statistically significant correlation was found between blood digoxin levels.

Authors' Contribution

Study Conception: İZ, BU; Study Design: İZ, BU; Supervision: İZ, BU; Funding: İZ, BU; Materials: İZ, BU; Data Collection and/or Processing: İZ, BU; Statistical Analysis and/or Data Interpretation: İZ, BU; Literature Review: İZ, BU; Manuscript Preparation: İZ, BU and Critical Review: İZ, BU.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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