European Review for Medical and Pharmacological Sciences 2021; 25: 3028-3037

# The frontal QRS-T angle in patients with incidentally discovered nonfunctional adrenal adenomas

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**Abstract. – OBJECTIVE: Few studies have used electrocardiography (ECG) to examine nonfunctional adrenal adenomas (NFAAs). No study has investigated the QRS-T angle in NFAA patients. We analyzed the frontal QRS-T angle of patients with incidentally discovered NFAAs.**

**PATIENTS AND METHODS: Adult patients with incidentally discovered NFAAs were included. Patients with chronic diseases other than hypertension or obesity were excluded. The overnight dexamethasone suppression test was performed. Levels of plasma renin and aldosterone, as well as metanephrine fractions in 24-h urine were measured. We performed abdominal magnetic resonance imaging and computed tomography to exclude hormonal hypersecretion and nonadenomas. The frontal QRS-T angle was calculated and verified based on surface ECG. Patients were grouped in terms of QRS-T angle as normal and abnormal, and the abnormal patients were divided into positive and negative subgroups.**

**RESULTS: Of all patients (n=58), six (10.34%) had abnormal QRS-T angles. Hypertension increased the risk of an abnormal QRS-T angle six-fold (odds ratio 6.000; 95% confidence interval 0.982-36.652, *p*=0.034). The frequency of hypertension was similar between the normal, abnormally positive, and abnormally negative groups (*p*=0.086). The mean SV1+RV5 value was lower in the abnormal QRS-T angle group (*p*=0.012). Age, gender, obesity, antihypertensive medication use, prediabetes status, adenoma size or side, hyperlipidemia, and adrenal hormone levels were all not associated with the QRS-T angle.**

**CONCLUSIONS: Our study is the first to analyze the association between an abnormal QRS-T angle and NFAA. An abnormal QRS-T angle was found in a significant proportion of patients and was associated with hypertension but seemingly, not with left ventricular hypertrophy. We recommend ECG and blood pressure measurement at the time of diagnosis of an NFAA and on follow-up.**

*Key Words:*
Arrhythmia, Electrocardiography, Nonfunctioning adrenal adenoma, ECG, QRS-T angle, QRS-T axis

## Introduction

An adrenal incidentaloma (AI) is a common imaging finding evident on abdominal magnetic resonance imaging (MRI) or computed tomography (CT) scans obtained for other purposes. The prevalence of AI ranges from 0.4% to 4.4% in different series and is higher in older patients or those with obesity, type 2 diabetes mellitus, or hypertension[1-3]. An AI may be unilateral or bilateral, and malignant or benign. Although an AI is nonfunctional in most cases, a small proportion (10-15%) are hormonally active and may be diagnosed as a pheochromocytoma, adrenocortical cancer, an aldosterone-producing adenoma, or subclinical Cushing's syndrome[4,5]. Nonfunctional AIs include nonfunctioning adrenal adenomas (NFAAs) and nonadenomas, such as myelolipomas[4].

Electrocardiography (ECG) is a simple and noninvasive tool used to assess the heart rhythm in various clinical settings. The frontal (planar) QRS-T angle is an important ECG parameter and can be calculated using standard 12-lead ECG[6]. An increased frontal QRS-T angle has been shown to be associated with nonarrhythmic or sudden cardiac death in a general population and a risk of cardiovascular disease[7,8]. In the ARIC study, both mortality and coronary heart disease were found to be associated with an abnormal frontal or spatial QRS-T angle[9].

ECG findings such as atrial fibrillation (AF), T wave inversion, presence of a U wave, or a prolonged corrected QT interval have been ex-



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plored in patients with AIs, adrenal Cushing's syndrome, and pheochromocytomas[10-13]. In one study, AF was higher in patients exhibiting autonomous cortisol secretion, but not in those with nonfunctional AIs, compared to the general population[10].

Studies investigating the risk of arrhythmia in patients with NFAAs are limited. To the best of our knowledge, no study has investigated the frequency of QRS-T angle abnormality, or the clinical associations thereof, in NFAA patients. We analyzed the frequency of frontal QRS-T angle abnormality and the associations thereof with clinical, laboratory, and radiological parameters in patients with incidentally discovered NFAAs.

## Patients and Methods

### Study Population

Adult patients who were referred to the Adult Endocrinology Clinics of the Kocaeli Derince Training and Research Hospital between March 2019 and March 2020 and exhibited incidentally discovered, newly diagnosed NFAAs were included in this study. This retrospective study was approved by the Ethics Committee of our institution (University of Health Sciences, Kocaeli Derince Training and Research Hospital; approval number 2020/63) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

During the evaluation of patients with AIs, diagnoses of NFAA were made after exclusion of functional AIs and nonfunctional adrenal nonadenomas. Patients younger than 18 years of age; those with a history of diabetes mellitus, cardiovascular or chronic heart disease, chronic renal failure, chronic liver failure, chronic pulmonary disease, thyroid dysfunction, or malignancy; and those for whom data were missing were excluded. Patients who had a history of adrenal or pituitary intervention or who had been prescribed glucocorticoid or mineralocorticoid therapy, tricyclic antidepressants, antipsychotics, or other psychoactive drugs were also excluded. Hypertension and obesity were not exclusion criteria.

### Clinical, Radiological, and Laboratory Evaluation

Basic demographic information (age, sex) and clinical characteristics (height, weight, body mass index [BMI]) were recorded. Body weight (kg) and height (m) were measured with the patient barefoot and in light clothing. The BMI was calculated as the weight/square of height (kg/$m^2$). Blood pressure was measured in all patients. In participants with pre-existing hypertension, blood pressure was already being controlled with antihypertensive medications before the study. Other participants had blood pressures within normal limits as described in a previous guideline[14].

All patients who were referred with AIs discovered on abdominal or thoracic CT or MRI underwent both abdominal MRI and CT if either modality had not been employed earlier. An adrenal adenoma was diagnosed if the mass was less than 4 cm in diameter, of regular shape, exhibited sharp margins and a smooth contour, was of homogeneous density, exhibited low attenuation on unenhanced [≤10 HU (Hounsfield Unit)] and enhanced (≤30 HU) CT, evidenced contrast washout of >50% on CT at 10 min after contrast administration, was isointense with the liver on both T1- and T2-weighted MRI, and exhibited a lipid chemical shift on MRI[15,16]. We ruled out adrenocortical cancer on the basis of clinical and radiological findings[17]. We recorded the longest diameter of the NFAA based on measurements from cross-sectional MRI.

All laboratory measurements were performed in the morning after an overnight fast. Basal cortisol and adrenocorticotropic hormone (ACTH) levels were measured in all patients. Independent of the basal cortisol level, the 1-mg overnight dexamethasone suppression test (DST) was performed in all patients to exclude autonomous cortisol secretion or Cushing's syndrome. Patients with cortisol levels ≥1.8 mcg/dL after the test were excluded. To exclude primary hyperaldosteronism, plasma renin activity (PRA; ng/mL per h) and the plasma aldosterone concentration (PAC; ng/dL) were measured at 8.00 am in all patients. All patients were ambulatory. A PAC/PRA ratio of <20 ng/dL per ng/mL/h was accepted as normal, and patients with PAC/PRA values of ≥20 ng/dL per ng/mL/h were excluded[18]. If a patient was already taking any antihypertensive medication that would disturb PAC and/or PRA measurement (e.g., a beta-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonist, alpha-methyldopa, or diuretic), these medications were withdrawn and a nondihydropyridine calcium channel blocker (verapamil) and/or

an alpha blocker (doxazosin) were prescribed for at least 4 weeks to increase the reliability of PAC/PRA measurement. After such measurement, the patients returned to their previous medications. All patients were given a diet excluding food containing phenolic acids for 5 days. Then, to exclude pheochromocytoma, 24-h urine specimens were collected for the analysis of metanephrine fractions (metanephrine and normetanephrine). Levels of 24-h urinary metanephrine <400 mcg and normetanephrine <900 mcg were defined as normal[19].

Fasting blood glucose (FBG) and postprandial blood glucose (PPBG) were measured as mg/dL (mmol/L), serum creatinine (SCre) as mg/dL (μmol/L), corrected calcium (CCa) as mg/dL (mmol/L), phosphorus (P) as mg/dL (mmol/L), magnesium (Mg) as mg/dL (mmol/L), low-density lipoprotein (LDL) as mg/dL (mmol/L), high-density lipoprotein (HDL) as mg/dL (mmol/L), total cholesterol (Tchol) as mg/dL (mmol/L), and triglycerides (TG) as mg/dL (mmol/L). Serum sodium (Na) and potassium (K) were measured as mmol/L. The other measures were as follows: PAC ng/dL (pmol/L), PRA ng/mL/h ($\mu g \times h^{-1} \times L^{-1}$), urinary metanephrine μg/24-h (μmol/day), normetanephrine μg/24-h (nmol/day), fasting insulin mIU/L (pmol/L), HbA1c %, thyroid-stimulating hormone (TSH) mIU/L (mIU/L), free thyroxine (fT4) ng/dL (pmol/L), free triiodothyronine (fT3) pg/mL (pmol/L), anti-thyroid peroxidase (ATPO) IU/mL, 25 (OH)D3 ng/mL (nmol/L), ACTH pg/mL (pmol/L), cortisol mcg/dL (nmol/L), parathyroid hormone (PTH) pg/mL (ng/L), B12 pg/mL (pmol/L), and folate ng/mL (nmol/L). The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated as FBG (mg/dL) × fasting insulin (mIU/L)/405. A HOMA-IR score > 2.7 was taken to indicate insulin resistance[20]. Serum albumin (g/dL) was not analyzed per se but was used to calculate the corrected total serum Ca level using the formula: CCa=Serum Ca+0.8* (4-patient albumin). The estimated glomerular filtration rate (eGFR; mL/min per 1.73 $m^2$) was calculated using a previously defined formula[21].

Glucose was measured via a glucose oxidase method with the aid of an AU-2700 analyzer (Olympus Co. Ltd., Tokyo, Japan). TG, Tchol, and HDL were measured on the same analyzer, using enzymatic methods (Olympus Diagnostics, Hamburg, Germany) and LDL levels were calculated using Friedewald's equation. Serum electrolytes and SCre levels were measured using the same autoanalyzer. HbA1c levels were measured in National Glycohemoglobin Standardization Program (NGSP) units using high-performance liquid chromatography (HPLC). Insulin, ACTH, total cortisol, PTH, B12, folate, TSH, fT4, fT3, and ATPO levels were measured via chemiluminescence methods using a DxI 800 system (Beckman Coulter, Inc., Fullerton, CA, USA). We measured the 25 (OH)D3 level (ng/mL) using immunoassay, the PAC level using an automated immunometric technique, the PRA using radioimmunoassay, and 24-h metanephrine fractions using HPLC[22].

The participants were grouped according to age (<65 *vs.* ≥65 years), BMI (<30 *vs.* ≥30 kg/$m^2$), hypertension status (absent *vs.* present), beta-blocker use (no *vs.* yes), antihypertensive medication use other than beta-blockers (no *vs.* yes), adenoma location (right-sided *vs.* left-sided, or unilateral *vs.* bilateral), adenoma diameter (<2 *vs.* ≥2 cm), presence of prediabetes according to either the HbA1c (5.7-6.4%) or FBG (100-125 mg/dL) test, the HOMA-IR score (<2.7 *vs.* ≥2.7), hypercholesterolemia or hypertriglyceridemia status, 25 (OH)D3 level (<20 *vs.* ≥ 20 ng/mL), and ATPO positivity.

### Electrocardiography

Standard 12-lead ECG was performed with each patient in the supine position, at a paper speed of 25 mm/s and a voltage of 10 mm/mV, during the first clinical visit (before laboratory examination). The heart rate, PR interval, QRS duration, and QT interval were measured. The QT interval corrected for the heart rate was calculated using Bazett's formula. The frontal QRS-T angle, defined as the angle between the mean frontal QRS and the mean frontal T vector, was calculated in accordance with previous studies (by examining the limb leads)[6] and was verified automatically by surface ECG. The normal ranges of QRS-T angles have been defined according to age and sex[23]. Accordingly, QRS-T angles within these ranges were classified as "normal", and those out of range as "abnormal". QRS-T angles that were shifted more negatively relative to the normal range were classified as "abnormal negative", whereas those that were shifted more positively relative to the normal range were classified as "abnormal positive". The participants were grouped by QRS-T angle as normal, abnormal positive, abnormal negative, and abnormal total. Patients with complete or incomplete right or left bundle branch block (s) were excluded. We

excluded patients with left ventricular hypertrophy based on the Sokolow-Lyon criteria[24]. The summed S waves in the V1 and R waves of V5 (SV1+RV5, mV) were analyzed and compared between the two (normal *vs.* abnormal) groups. All ECG recordings were evaluated by the same cardiologist who was blinded to patient data

### Statistical Analysis

SPSS software (ver. 22.0; IBM Corporation, Armonk, NY, USA) was used for all analyses. The Shapiro-Wilk test was used to assess the normality of the data. Homogeneity of variance was evaluated using the Levene test. When comparing two independent groups in terms of quantitative measures, Mann-Whitney U-tests were used. Pearson's chi-squared tests were used to compare categorical variables. To determine the risk factors associated with abnormal QRS-T angles, we conducted univariate logistic regression analysis. Odds ratios (ORs) were calculated along with 95% confidence intervals (CIs) to examine differences in risk among the groups. Quantitative variables are reported as the means (X) ± standard deviations (SDs) in the tables. Categorical variables are reported as numbers (n) and percentages (%), and $p$-values <0.05 were taken to indicate statistical significance.

## Results

Of the total of 58 patients, 10.34% (n=6) had abnormal QRS-T angles, with 6.89% (n=4) considered "abnormal positive" and 3.44% (n=2) "abnormal negative". The mean age was 51.22 (±10.26) years. The mean SV1+RV5 voltage and FBG were significantly lower in the abnormal-total group than in the normal group ($p$=0.012 and $p$=0.049, respectively). BMI, NFAA diameter, other ECG findings, and laboratory parameters did not differ between the normal and abnormal-total groups or between the normal, abnormal-positive, and abnormal-negative groups (Table I).

Hypertension was evident in 29.31% (n=17) of the patients, and the rate was higher (66.66%) in the abnormal-total group than in the normal group ($p$=0.034). On logistic regression analysis, hypertension was associated with a six-fold greater risk of an abnormal QRS-T angle (OR 6.000; 95% CI 0.982-36.652) (not shown in the Tables). However, the frequency of hypertension was similar between the normal, abnormal-positive, and abnormal-negative groups ($p$=0.086). Obesity was found in 34.48% of the patients and prediabetes in 67.24% (Table II).

ECG parameters other than the QRS-T angle were similar between patients with or without hypertension (Table III).

## Discussion

We found that a significant proportion of the patients (10.34%) had an abnormal QRS-T angle. Hypertension and a lower FBG or SV1+RV5 voltage were shown to be related to an abnormal QRS-T angle but not with the direction (positive or negative) of the shift in QRS-T angle. Obesity, prediabetes, and hyperlipidemia were all not associated with the QRS-T angle.

In a previous study[25] analyzing the effects of antihypertensive treatment using ECG, the QRS-T angle was found to decrease with treatment but was not associated with a decrease in anatomical left ventricular hypertrophy. We found that hypertension was associated with a six-fold greater risk of an abnormal QRS-T angle. We excluded patients with left ventricular hypertrophy evident on ECG but lacked data on the duration of hypertension. Moreover, the blood pressure of participants with hypertension was already under control with antihypertensive medication (s) before the study. We also detected that the frequency of hypertension was similar in patients with positively or negatively shifted QRS-T angles. Hence, the association between hypertension and an abnormal QRS-T angle in NFAA patients was independent of left ventricular hypertrophy or antihypertensive medication use. Analysis of the spatial QRS-T angle can increase the accuracy of ECG-based assessment of left ventricular hypertrophy, but we did not perform such analysis[26]. To the best of our knowledge, our study is the first to describe the frequency of QRS-T angle abnormality and the association thereof with hypertension in NFAA patients. Aro et al[7] showed that the frequency of an abnormal QRS-T angle was 2% in a middle-aged general population. The frequency was as high as 10-14% in various studies on patients with type 2 diabetes mellitus and 11.9% in patients with polycystic ovary syndrome[27-30]. Aro et al[7] also showed that the risk of arrhythmic death increased more than two-fold in a middle-aged general population with a wide frontal QRS-T angle. In one study on primary prevention (implantation of a cardio-

**Table I.** Comparison of clinical and laboratory parameters between normal and abnormal QRS-T angle groups.

| Parameters | QRS-T angle groups | | | | | *p*-value[a] | *p*-value[b] |
|---|---|---|---|---|---|---|---|
| | | (Abnormal) | | | | | |
| | Normal (n = 52) | Abnormal positive (n = 4) | Abnormal negative (n = 2) | Abnormal total (n = 6) | Total (n = 58) | | |
| | X (±SD) | | | | | | |
| Age, year | 51.21 (10.39) | 45.75 (6.18) | 62.50 (3.53) | 51.33 (10.01) | 51.22 (10.26) | 0.171 | 1.0 |
| BMI, kg/m$^2$ | 28.28 (3.04) | 29.37 (2.41) | 28.95 (1.48) | 29.23 (1.99) | 28.38 (2.95) | 0.756 | 0.407 |
| NFAA Diameter, mm | 20.58 (7.94) | 21.80 (3.88) | 24.85 (6.85) | 22.81 (4.57) | 20.81 (7.66) | 0.723 | 0.289 |
| PR, msec | 153.30 (29.83) | 159.50 (32.75) | 162.0 (2.82) | 160.33 (25.43) | 154.03 (29.28) | 0.857 | 0.239 |
| QRS, msec | 94.32 (18.24) | 94.0 (8.48) | 108.0 (28.28) | 98.66 (15.98) | 94.77 (17.94) | 0.578 | 0.384 |
| QTc, msec | 407.48 (20.70) | 409.75 (21.60) | 423.0 (21.21) | 414.16 (20.41) | 408.17 (20.59) | 0.580 | 0.399 |
| HR, /min | 77.55 (11.02) | 80.25 (14.24) | 67.5 (13.43) | 76.0 (14.18) | 77.39 (11.24) | 0.411 | 0.929 |
| SV1+RV5, mV | 19.05 (5.87) | 14.12 (4.13) | 12.75 (1.76) | 13.66 (3.37) | 18.50 (5.88) | 0.099 | 0.012 |
| Cortisol, µg/dL | 12.75 (5.69) | 9.24 (2.17) | 20.23 (5.51) | 12.90 (6.41) | 12.76 (5.71) | 0.083 | 0.959 |
| ACTH, pg/mL | 19.35 (9.08) | 26.87 (27.11) | 21.20 (18.95) | 24.98 (22.83) | 19.93 (11.07) | 0.426 | 0.888 |
| 24-h urine metanephrine, µg/24-hour | 67.07 (56.54) | 61.47 (39.39) | 79.0 (45.25) | 67.31 (37.71) | 67.10 (54.63) | 0.936 | 0.990 |
| 24-h urine normetanephrine, µg/24-hour | 296.22 (193.80) | 371.52 (319.12) | 191.1 (118.62) | 311.38 (269.44) | 297.79 (199.98) | 0.581 | 0.959 |
| PAC, ng/dL | 10.70 (7.04) | 12.42 (10.6) | 8.05 (3.88) | 10.96 (8.69) | 10.72 (7.14) | 0.782 | 0.908 |
| PRA, ng/mL/h | 11.94 (14.03) | 10.80 (13.29) | 32.25 (9.12) | 17.95 (15.66) | 12.56 (14.18) | 0.134 | 0.358 |
| PAC/PRA | 3.91 (6.14) | 4.16 (4.07) | 0.27 (0.19) | 2.87 (3.74) | 3.80 (5.92) | 0.698 | 0.421 |
| Cortisol after 1 mg DST, µg/dL | 1.07 (0.37) | 1.25 (0.41) | 1.55 (0.34) | 1.35 (0.38) | 1.10 (0.37) | 0.149 | 0.078 |
| FBG, mg/dL | 98.79 (12.47) | 87.25 (3.59) | 96.0 (2.82) | 90.16 (5.45) | 97.90 (12.20) | 0.187 | 0.049 |
| PPBG, mg/dL | 121.23 (24.42) | 101.25 (9.14) | 132.5 (19.09) | 111.66 (19.58) | 120.24 (24.0) | 0.213 | 0.421 |
| Fasting insulin, mIU/L | 9.74 (6.32) | 18.67 (24.54) | 5.2 (2.12) | 14.18 (20.26) | 10.19 (8.58) | 0.093 | 0.436 |
| HbA1c, % | 5.72 (0.39) | 5.60 (0.49) | 5.80 (0.28) | 5.66 (0.41) | 5.71 (0.39) | 0.802 | 0.908 |
| HOMA-IR | 2.43 (1.67) | 3.91 (5.05) | 1.24 (0.53) | 3.02 (4.16) | 2.49 (2.01) | 0.248 | 0.272 |
| HDL, mg/dL | 44.04 (10.75) | 37.50 (15.0) | 44.0 (14.14) | 39.66 (13.64) | 43.59 (11.03) | 0.527 | 0.413 |
| LDL, mg/dL | 132.13 (30.61) | 101.0 (31.34) | 140.50 (34.64) | 114.16 (35.29) | 130.27 (31.27) | 0.142 | 0.197 |
| Tchol, mg/dL | 203.23 (38.53) | 169.0 (35.73) | 204.5 (31.81) | 180.83 (36.12) | 200.91 (38.60) | 0.233 | 0.164 |
| TG, mg/dL | 135.40 (82.09) | 151.50 (85.71) | 59.39 (42.0) | 134.33 (76.29) | 135.29 (80.87) | 0.769 | 0.711 |
| SCre, mg/dL | 0.78 (0.13) | 0.76 (0.05) | 0.95 (0.14) | 0.82 (0.12) | 0.78 (0.13) | 0.218 | 0.332 |
| eGFR, mL/min per 1.73 m$^2$ | 96.17 (11.01) | 98.67 (6.44) | 84.06 (14.05) | 93.80 (11.01) | 95.93 (10.94) | 0.273 | 0.619 |
| Na, mmol/L | 139.95 (2.37) | 138.5 (1.29) | 140.5 (0.70) | 139.16 (1.47) | 139.87 (2.30) | 0.449 | 0.410 |
| K, mmol/L | 4.35 (0.41) | 4.35 (0.30) | 4.50 (0.42) | 4.40 (0.30) | 4.36 (0.40) | 0.892 | 0.797 |
| CCa, mg/dL | 9.10 (0.31) | 9.05 (0.46) | 9.20 (0.028) | 9.10 (0.36) | 9.10 (0.31) | 0.862 | 0.959 |
| P, mg/dL | 3.27 (0.49) | 3.30 (0.54) | 2.90 (0.28) | 3.16 (0.48) | 3.26 (0.49) | 0.570 | 0.556 |
| Mg, mg/dL | 2.0 (0.12) | 2.05 (0.10) | 2.0 (0.14) | 2.03 (0.10) | 2.0 (0.12) | 0.756 | 0.471 |
| 25 (OH)D3, ng/mL | 15.84 (7.42) | 16.41 (12.66) | 20.33 (9.60) | 17.71 (10.90) | 16.03 (7.74) | 0.727 | 0.818 |
| PTH, pg/mL | 77.45 (28.72) | 75.05 (11.91) | 31.80 (6.92) | 60.63 (24.36) | 75.71 (28.58) | 0.084 | 0.284 |
| B12, pg/mL | 402.98 (155.75) | 294.5 (109.38) | 469.0 (296.98) | 352.66 (181.49) | 397.77 (157.58) | 0.342 | 0.180 |
| Folate, ng/mL | 8.66 (3.38) | 8.03 (2.79) | 7.91 (0.68) | 7.99 (2.18) | 8.59 (3.27) | 0.895 | 0.959 |
| TSH, mIU/L | 1.87 (1.09) | 2.24 (0.87) | 1.24 (1.10) | 1.91 (0.98) | 1.87 (1.07) | 0.568 | 0.674 |
| fT4, ng/dL | 1.14 (0.20) | 1.13 (0.16) | 1.35 (0.43) | 1.20 (0.25) | 1.14 (0.20) | 0.358 | 0.798 |
| fT3, pg/mL | 3.13 (0.41) | 3.02 (0.37) | 3.24 (0.36) | 3.09 (0.34) | 3.13 (0.40) | 0.812 | 0.818 |
| ATPO, IU/mL | 107.02 (298.29) | 347.70 (634.87) | 26.50 (2.12) | 240.63 (518.99) | 120.84 (323.91) | 0.334 | 0.765 |

[a]*p*-value indicates the significance between normal, abnormal positive and abnormal negative groups. [b]*p*-value indicates the significance between normal and abnormal total groups.

**Table II.** Comparison of categorical parameters between normal and abnormal QRS-T angle groups.

| Categorical parameters | Normal (n = 52) | QRS-T angle groups | | | Total (n = 58) | *p*-value[a] | *p*-value[b] |
|---|---|---|---|---|---|---|---|
| | | Abnormal | | | | | |
| | | Abnormal positive (n = 4) | Abnormal negative (n = 2) | Abnormal total (n = 6) | | | |
| | | n | | | | | |
| Age (<65/≥65) | 47/5 | 4/0 | 1/1 | 5/1 | 52/6 | 0.144 | 0.591 |
| Gender (female/male) | 35/17 | 3/1 | 0/2 | 3/3 | 38/20 | 0.133 | 0.398 |
| BMI (<30/≥30 kg/m$^2$) | 35/17 | 2/2 | 1/1 | 3/3 | 38/20 | 0.700 | 0.398 |
| Hypertension (absent/present) | 39/13 | 1/3 | 1/1 | 2/4 | 41/17 | 0.086 | 0.034 |
| Beta-blocker (absent/present) | 49/3 | 3/1 | 2/0 | 5/1 | 54/4 | 0.318 | 0.319 |
| Other antihypertensive (absent/present) | 42/10 | 2/2 | 1/1 | 3/3 | 45/13 | 0.231 | 0.087 |
| Laterality (unilateral/bilateral) | 41/11 | 3/1 | 2/0 | 5/1 | 46/12 | 0.751 | 0.797 |
| Right-sided adenoma (absent/present) | 23/29 | 3/1 | 1/1 | 4/2 | 27/31 | 0.491 | 0.297 |
| Left-sided adenoma (absent/present) | 18/34 | 0/4 | 1/1 | 1/5 | 19/39 | 0.317 | 0.375 |
| Prediabetes (absent/present) | 16/36 | 2/2 | 1/1 | 3/3 | 19/39 | 0.637 | 0.342 |
| Insulin resistance (<2.7/>2.7) | 38/14 | 3/1 | 2/0 | 5/1 | 43/15 | 0.694 | 0.587 |
| Hypercholesterolemia (absent/present) | 47/5 | 4/0 | 1/1 | 5/1 | 52/6 | 0.144 | 0.591 |
| Hypertriglyceridemia (absent/present) | 39/13 | 3/1 | 2/0 | 5/1 | 44/14 | 0.719 | 0.652 |
| 25 (OH)D3 (<20/≥20 ng/mL) | 38/14 | 3/1 | 1/1 | 4/2 | 42/16 | 0.768 | 0.739 |
| ATPO (absent/present) | 48/4 | 3/1 | 2/0 | 5/1 | 53/5 | 0.448 | 0.458 |

[a]*p*-value indicates the significance between normal, abnormal positive and abnormal negative groups of QRS-T angles. [b]*p*-value indicates the significance between normal and abnormal total groups of QRS-T angles.

**Table III.** Comparison of ECG parameters among the patients with or without hypertension.

| Parameters | Hypertension | | Total (n = 58) | *p*-value |
|---|---|---|---|---|
| | Absent (n = 41) | Present (n = 17) | | |
| | X (± SD) | | | |
| PR, msec | 155.75 (28.33) | 149.88 (31) | 154.03 (29.28) | 0.492 |
| QRS, msec | 93.12 (18.30) | 98.76 (16.88) | 94.77 (17.94) | 0.279 |
| QTc, msec | 405.34 (17.76) | 415.00 (25.54) | 408.17 (20.59) | 0.105 |
| HR, /min | 76.43 (11.30) | 79.70 (11.10) | 77.39 (11.24) | 0.318 |
| SV1+RV5, mV | 1.90 (0.56) | 1.71 (0.64) | 18.50 (5.88) | 0.269 |

verter-defibrillator), patients with a wide spatial QRS-T angle had a seven-fold increased risk of ventricular arrhythmia, and those with a wide planar QRS-T angle a 2.5-fold greater risk of mortality, compared to subjects with a normal angle[31]. An abnormal frontal QRS-T angle was also associated with an increased risk of AF in an elderly population and an increased risk of AF after coronary artery bypass grafting[32,33]. The spatial peak of the QRS-T angle was shown to indicate sustained ventricular arrhythmia in patients with hypertrophic obstructive cardiomyopathy[4]. The association between arrhythmia and the frontal or spatial QRS-T angle was also evident in patients with Chagas disease, those who underwent the Fontan procedure, those with systemic sclerosis, and those who underwent hemodialysis[35-38]. We showed that the frequency of an abnormal QRS-T angle was increased in patients with NFAAs, and hence, we propose that the risk of arrhythmia is also higher in this population. We recommend baseline and repeat measurements of blood pressure and the ECG-based QRS-T angle in NFAA patients. Further clinical work-up, such as echocardiography, may be performed in selected patients.

In several studies, subclinical echocardiographic changes, such as increased end-diastolic left ventricular and interventricular septal diameters and a greater left ventricular mass, were evident in nonfunctional AI patients[13,39]. We excluded patients with left ventricular hypertrophy as revealed by ECG and found that patients with an abnormal QRS-T angle exhibited a lower SV1+RV5 voltage. Interestingly, the SV1+RV5 voltage was the lowest in the "abnormal-negative" QRS-T angle group and highest in the normal QRS-T angle group. However, cardiac fibrosis may develop in the absence of left ventricular hypertrophy and cause depolarization and repolarization abnormalities. Hence, a lower SV1+RV5 voltage may not be adequate to define left ventricular hypertrophy. We did not analyze this via ECG.

The spatial QRS-T angle, independent of left ventricular hypertrophy, was higher in patients with uncontrolled hypertension than in those with controlled blood pressure[40]. An abnormal QRS-T angle was associated with hypertension in type 2 diabetes mellitus patients[28]. Nondipping hypertension has been associated with an increased frontal QRS-T angle, and it has been proposed that blood pressure elevation during sleep may affect cardiac repolarization[41]. Ambulatory blood pressure monitoring may yield additional information on the association between hypertension and the QRS-T angle in NFAA patients.

Hypertension may be more frequently observed in patients with NFAAs than in those without[42]. The frequency of hypertension was shown to be similar in patients with NFAAs and subclinical Cushing's syndrome[43]. In one study, hypertension was found in as many as 72% of patients with NFAAs, with resistant hypertension found in more than 50%[42]. Exclusion of patients with chronic diseases, which may accompany hypertension, might have contributed to the lower frequency of hypertension in our present study compared to previous reports.

Previously, a large QRS-T angle was found to be a long-term predictor of all-cause mortality or myocardial infarction in a diabetic population[27]. An abnormal QRS-T angle was associated with increased HbA1c levels in type 2 diabetes mellitus patients[28,29]. Contrasting findings[44] have also been reported. Delhey et al[45] showed that an impaired fasting blood glucose level was associated with an abnormal spatial QRS-T angle. In our present study, HbA1c, HOMA-IR, and PPBG measurements were all not associated with an abnormal QRS-T angle, but the FBG level was significantly lower in the abnormal QRS-T

angle group. We excluded patients with diabetes but even prediabetes was not associated with the QRS-T angle.

BMI is an independent factor for an abnormal QRS-T angle, but not in patients with type 2 diabetes[28,46]. Metabolic syndrome and abdominal obesity were also reported to be associated with an abnormal spatial QRS-T angle[45]. However, elevated TG and low HDL levels were associated with an abnormal QRS-T angle only in women in the cited study. Approximately one-third of our patients were obese, but obesity was not associated with the QRS-T angle. Obesity, an elevated HbA1c or fasting blood glucose level, and prediabetes or dyslipidemia were observed to be associated with an abnormal QRS-T angle in previous reports, but they did not affect the QRS-T angle in our NFAA patients.

We found no associations between an abnormal QRS-T angle and adrenal function test results (which were all within the normal range) or adenoma size or laterality.

We evaluated the frontal QRS-T angle but could not perform echocardiography or coronary angiography. Some studies cited above analyzed the frontal QRS-T angle, and some the spatial angle. Methodologically, it would be best to evaluate both the frontal and spatial QRS-T angles, and perform echocardiography, other noninvasive tests, and/or coronary angiography. We could not perform all of these tests.

### Strengths and Limitations

To the best of our knowledge, our study is the first to analyze the frequency of an abnormal QRS-T angle and the associations thereof with clinical, laboratory, and radiological findings in patients with NFAAs. We excluded patients with coronary vascular disease, diabetes, and chronic renal failure and focused only on the association between the QRS-T angle and NFAA. Limitations of our study include the relatively small number of patients and the lack of data on the duration of hypertension.

## Conclusions

We found that an abnormal QRS-T angle was common, and hence, the risk of arrhythmia was increased, in NFAA patients. The association between an abnormal QRS-T angle and hypertension was independent of the direction of the shift in QRS-T angle, left ventricular hypertrophy, and antihypertensive medication use. The QRS-T angle seems to not be related to obesity, prediabetes, or hyperlipidemia. We recommend regular follow-up (ECG and blood pressure) of patients with NFAAs; further work-up may be necessary if an abnormal QRS-T angle is detected.

### Conflict of Interest

No author has any conflicts of interest. I certify that neither I nor any of my co-authors have any conflicts of interest that would be relevant to the subject matter or materials included in this work.

### Acknowledgements

We thank all authors for their significant contributions to the study design, data collection, writing and editing of the article, and preparation of the manuscript

### Funding Acknowledgments

No funding was granted for the study, writing of the article, or preparation of the manuscript.

### Authors' Contribution

All authors played substantial roles in the study conception and design, development of the methods, investigation, data collection and analysis, writing, and manuscript preparation (details can be found in the author contribution form). The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/7grlfn.

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